IN THE UNITED STATES DISTRICT C OURT
FOR THE DISTRICT OF SOUTH CAROLINA
CHARLESTON DIVISION

IN RE: LIPITOR (ATORVASTATIN CALCIUM) MARKETING, SALES PRACTICES AND PRODUCTS LIABILITY LITIGATION	**MDL No. 2:14-mn-02502-RMG** **CASE MANAGEMENT ORDER NO. 76** **This Order relates to:** *Daniels v. Pfizer,* Case No. 2:14-cv-1400 *Hempstead v. Pfizer,* Case No. 2:14-cv-1879

In this MDL, Plaintiffs allege that Lipitor caused them to develop Type 2 diabetes. To carry their burden, Plaintiffs must prove both general and specific causation. *Westberry v. Gislaved Gummi AB,* 178 F.3d 257, 263 (4th Cir. 1999). Plaintiffs have disclosed two case-specific expert witnesses in these bellwether cases, Dr. David Handshoe and Dr. Elizabeth Murphy. The Court has addressed the opinion of Dr. Murphy by separate order. (CMO 55, Dkt. No. 1283).

Dr. Handshoe purports to use a differential diagnosis methodology and opines that Lipitor caused, or was a contributing factor of, Ms. Daniels and Ms. Hempstead's Type 2 Diabetes. Before the Court here is Pfizer's motion to exclude this testimony. (Dkt. No. 1004). Plaintiffs have filed a response, (Dkt. No. 1095), Defendant has filed a reply, (Dkt. No. 1129), and the Court has heard oral argument on the motion. (Dkt. No. 1206).

I. Legal Standard

Under Rule 104(a) and 702, "the trial judge must ensure that any and all scientific testimony or evidence admitted is not only relevant, but reliable." *Daubert v. Merrell Dow Pharm., Inc*., 509 U.S. 579, 589 (1993). Thus, the trial court must ensure that (1) "the testimony

is the product of reliable principles and methods," that (2) "the expert has reliably applied the principles and methods to the facts of the case," and (3) that the "testimony is based on sufficient facts or data." Fed. R. Evid. 702(b), (c), (d). "This entails a preliminary assessment of whether the reasoning or methodology underlying the testimony is scientifically valid," *Daubert,* 509 U.S. at 592-93, and whether the expert has "faithfully appl[ied] the methodology to facts." *Roche v. Lincoln Prop. Co.*, 175 F. App'x 597, 602 (4th Cir. 2006)

Factors to be considered include "whether a theory or technique . . . can be (and has been) tested," "whether the theory or technique has been subjected to peer review and publication," the "known or potential rate of error," the "existence and maintenance of standards controlling the technique's operation," and whether the theory or technique has garnered "general acceptance." *Daubert,* 509 U.S. at 593-94; *accord United States v. Hassan*, 742 F.3d 104, 130 (4th Cir. 2014). However, these factors are neither definitive nor exhaustive, *United States v. Fultz*, 591 F. App'x 226, 227 (4th Cir. 2015), *cert. denied*, 135 S. Ct. 2370 (2015), and "merely illustrate[] the types of factors that will bear on the inquiry." *Hassan*, 742 F.3d at 130. Courts have also considered whether the "expert developed his opinions expressly for the purposes of testifying," *Wehling v. Sandoz Pharm. Corp.*, 162 F.3d 1158 (4th Cir. 1998), or through "research they have conducted independent of the litigation," *Daubert v. Merrell Dow Pharm., Inc.*, 43 F.3d 1311, 1317 (9th Cir. 1995) (on remand), and whether experts have "failed to meaningfully account for . . . literature at odds with their testimony." *McEwen v. Baltimore Washington Med. Ctr. Inc.*, 404 F. App'x 789, 791-92 (4th Cir. 2010).

Rule 702 also requires courts "to verify that expert testimony is 'based on sufficient facts or data.'" *E.E.O.C. v. Freeman*, 778 F.3d 463, 472 (4th Cir. 2015) (quoting Fed. R. Evid. 702(b)). Thus, "trial judges may evaluate the data offered to support an expert's bottom-line

opinions to determine if that data provides adequate support to mark the expert's testimony as reliable." *Id.* The court may exclude an opinion if "there is simply too great an analytical gap between the data and the opinion offered." *Id.* "The proponent of the [expert] testimony must establish its admissibility by a preponderance of proof." *Cooper v. Smith & Nephew, Inc.*, 259 F.3d 194, 199 (4th Cir. 2001).

The Court is mindful that the *Daubert* inquiry involves "two guiding, and sometimes competing, principles." *Westberry v. Gislaved Gummi AB*, 178 F.3d 257, 261 (4th Cir. 1999). "On the one hand, . . . Rule 702 was intended to liberalize the introduction of relevant expert evidence," *id.*, and "the trial court's role as a gatekeeper is not intended to serve as a replacement for the adversary system." *United States v. Stanley*, 533 F. App'x 325, 327 (4th Cir. 2013) *cert. denied*, 134 S. Ct. 1002 (2014). On the other, "[b]ecause expert witnesses have the potential to be both powerful and quite misleading, it is crucial that the district court conduct a careful analysis into the reliability of the expert's proposed opinion." *United States v. Fultz*, 591 F. App'x 226, 227 (4th Cir.) *cert. denied*, 135 S. Ct. 2370 (2015); *accord Westberry*, 178 F.3d at 261.

II. The Role of Relative Risk in General and Specific Causation

Before addressing Dr. Handshoe's opinions, it is helpful to review the difference between general and specific causation and how each is proven. "[I]n order to carry the burden of proving a plaintiff's injury was caused by exposure to a specified substance," a plaintiff must demonstrate general and specific causation. *Westberry v. Gislaved Gummi AB*, 178 F.3d 257, 263 (4th Cir.1999); *Zellers v. NexTech Ne., LLC*, 533 F. App'x 192, 196 n.6 (4th Cir. 2013) *cert. denied*, 134 S. Ct. 911 (2014). "General causation is whether a substance is capable of causing a particular injury or condition in the general population and specific causation is whether a

substance caused a particular individual's injury." *Norris v. Baxter Healthcare Corp.*, 397 F.3d 878, 881 (10th Cir. 2005). "Plaintiff must first demonstrate general causation because without general causation, there can be no specific causation." *Id.*; *accord Knight v. Kirby Inland Marine Inc.*, 482 F.3d 347, 351-52 (5th Cir. 2007).

The parties agree that epidemiologists use a two-step process for establishing general causation. (Dkt. No. 972 at 27-28; Dkt. No. 1053 at 13); *see also Ambrosini v. Labarraque*, 101 F.3d 129, 136 (D.C. Cir. 1996). First, studies must establish an association or correlation between two variables, here, Lipitor and diabetes. If two variables correlate, the incidence of one variable (diabetes) changes with the incidence of another (Lipitor). In other words, one variable (Lipitor) increases the risk of the other (diabetes). Once an association is established, epidemiologists apply the "Hill factors" to evaluate whether an association is causal. Reference Manual on Scientific Evidence (RMSE) 600 (3d ed. 2011); *In re Zoloft (Sertraline Hydrochloride) Products Liab. Litig.*, 26 F. Supp. 3d 449, 454-55 (E.D. Pa. 2014), *recon. denied*, 2015 WL 314149 (E.D. Pa. Jan. 23, 2015).

However, even if Plaintiffs establish that there is an association between Lipitor and diabetes (i.e., that Lipitor increases the risk of diabetes) and that Lipitor is capable of causing diabetes, it does not necessarily follow the Lipitor caused the development of diabetes in a particular plaintiff. For specific causation, the plaintiff must "demonstrate[] that the substance actually caused injury in her particular case." *Guinn v. AstraZeneca Pharm. LP*, 602 F.3d 1245, 1249 n.1 (11th Cir. 2010). Under a preponderance-of-evidence burden, a plaintiff must show, more likely than not, the substance caused, or was a substantial contributing factor to, her particular injury.

Some courts have held that one way that a plaintiff can meet her burden of production on specific causation is to have an expert witness testify to specific causation based on epidemiologic studies that find a relative risk of injury of 2.0 or higher and what is referred to as "the logic of the effect of doubling of the risk." RMSE at 612; *see also Marder v. G.D. Searle & Co.*, 630 F. Supp. 1087, 1092 (D. Md. 1986) ("In epidemiological terms, a two-fold increased risk is an important showing for plaintiffs to make because it is the equivalent of the required legal burden of proof–a showing of causation by the preponderance of the evidence or, in other words, a probability of greater than 50%.").

The relative risk ratio is the risk of disease or injury among people exposed to an allegedly harmful substance divided by the risk of the disease among those not exposed to the substance. RMSE at 627. For instance, if the risk of developing diabetes while on Lipitor is 6% and the risk of developing diabetes not on Lipitor (i.e., in a placebo group) is 4%, then the relative risk of developing diabetes associated with Lipitor is 6/4 or 1.5.[1] A relative risk of 1.0 indicates no difference between the two groups in risk. The risk in the two groups is the same (e.g., 5% divided by 5% or 20% divided by 20%).

Assuming no confounding factors, bias, etc., a statistically significant relative risk ratio between 1.0 and 2.0 can be used, in conjunction with the "Hill factors," to establish general causation but cannot be used, by itself, to establish specific causation. A relative risk ratio in this range suggests that while some people exposed to the substance developed the disease due to exposure (i.e., there is the potential for the substance to cause the disease), most would have

[1] Absolute risk is the risk in a particular population without relation to another group. Here, the absolute risk in the Lipitor group is 6%, the absolute risk in the placebo group is 4%, and the difference in the absolute risk is 2%.

developed the disease anyway. Take the example above with a relative risk ratio of 1.5,[2] where 4% of the placebo group and 6% of the Lipitor group develop diabetes. In a group of 100 people all taking Lipitor, six of them will develop diabetes. Four of these people (4% of 100) would have developed diabetes regardless, as in the placebo group. The other two diabetics (2% of 100) would not have developed diabetes but for Lipitor. In other words, two-thirds of the people who take Lipitor and develop diabetes would have done so regardless, and one-third of people who take Lipitor and develop diabetes would not have developed diabetes but for the Lipitor. For this minority (the one-third), Lipitor is a substantial contributing factor to their diabetes. Thus, to establish specific causation with a relative risk between 1.0 and 2.0, an expert—utilizing a valid methodology, applying it reasonably and relying on sufficient data to support her opinions—must opine to a reasonable degree of medical certainty that the particular plaintiff is in the minority of those that developed the disease due to exposure to a particular drug or substance rather than in the majority that would have developed the disease regardless.

A relative risk ratio greater than 2.0, however, suggests that of the people exposed to a substance who developed the disease, most of them developed the disease *due* to the exposure. For example, if the relative risk of diabetes due to Lipitor were 3.0,[3] then two-thirds of those on Lipitor who develop diabetes would not have developed diabetes but for the drug. An example of this would be if, in a randomized study, 6% of the Lipitor group developed diabetes and 2% of the placebo group developed diabetes. In this example, six out of a hundred people on Lipitor

[2] Other ways to state this relative risk of 1.5 are (a) someone on Lipitor is 1.5 times as likely to develop diabetes as someone not on Lipitor, (b) Lipitor increases the risk of diabetes by 50%, or (c) Lipitor increases the risk of diabetes by half.

[3] Other ways of stating this relative risk of 3.0 are (a) there is a threefold increase in risk or (b) a 300% increase in risk.

would develop diabetes. Of these six, two would have done so regardless and four would develop diabetes only because they took Lipitor.

Thus, for a relative risk ratio above 2.0, there is a "probability of greater than 50%" that the substance at issue caused the disease or injury. *Marder*, 630 F. Supp. at 1092. In other words, it is more likely than not that the substance caused the injury or disease. This logic does have its limitations. It relies on studies "identifying a genuine causal relationship and a reasonably reliable measure of the increased risk." RMSE at 612. If confounding factors, bias or random error is the source of the association, rather than a true causal relationship, the logic falls apart. *Id.* at 612-13. Thus, a finding of statistical significance is very important, and observational studies with the potential for confounding and bias may not be sufficient for this theory of specific causation. Randomized controlled trials may be required to show an actual doubling of the risk exists (i.e., to show a valid relative risk ratio).

Turning to the cases at hand, Dr. Handshoe testifies that the best estimate of the relative risk ratio for diabetes associated with statin use is 1.25. (Dkt. No. 1004-6 at 238-39). Thus, using his estimate of relative risk, most of the people who develop diabetes while on Lipitor would have done so anyway, and he cannot use the logic of "doubling the risk" to provide a specific causation opinion. Regardless, Dr. Handshoe does not claim to use this logic. Using the estimated relative risk ratio of 1.25, 80% of the people who take Lipitor and develop diabetes would have done so *in the absence of Lipitor*, whereas 20% of the people who take Lipitor and develop diabetes did so only because they took Lipitor. The question then becomes how does

Dr. Handshoe conclude that Ms. Daniels and Ms. Hempstead are in the 20% that develop diabetes due to Lipitor, rather than the 80% that would have done so regardless.[4]

III. Dr. Handshoe's Opinion in *Daniels*

Dr. Handshoe is a medical doctor that practices in the areas of internal medicine, pulmonary diseases, critical care medicine, and sleep disorders. (Dkt. No. 1004-7 at 2). He is board certified in these four areas and has twenty-two years of clinical experience. (*Id.*).

A. Ms. Daniels' Medical History and Diagnosis of Diabetes

In September of 1997, Ms. Daniels had a total cholesterol of 466, with an LDL of 364, an HDL of 44, and triglycerides of 288.[5] (Dkt. No. 1004-7 at 3). A few weeks later, her physician diagnosed her with hyperlipidemia and prescribed 40 mg of Lipitor. (*Id.*). At this time, she weighed 158 pounds, and with a height of 5'3", had a BMI of 28.[6] (*Id.*). At the time, Ms. Daniels also had hypertension and was on the diuretic HCTZ. (*Id.*). She was 49 years old. Her blood draw taken in September of 1997 showed a blood glucose level of 108 mg/dL.[7]

---

[4] Dr. Handshoe testifies that studies show a relative risk associated with statins "up to" 1.87. (Dkt. No. 1004-42 at 115). Using this relative risk ratio, 53.5% of the people who take Lipitor and develop diabetes would have done so in the absence of Lipitor, whereas 46.5% of the people who take Lipitor and develop diabetes did so only because they took Lipitor.

[5] Normal levels for these lipid measurements are less than 200 md/dL for total cholesterol; less than 130 mg/dL for LDL; between 35 and 150 md/dL for HDL; and less than 200 mg/dL for triglycerides. (Dkt. No. 1064-7 at 29).

[6] BMI is a measurement based on height and weight that is used as an indicator of body fat and is method of screening for weight category, such as underweight, normal or healthy weight, overweight and obesity. Centers for Disease Control and Prevention, http://www.cdc.gov/healthyweight/assessing/bmi/adult_bmi/index.html (last visited May 4, 2016). A BMI of 25.0-29.9 is considered overweight and a BMI of 30.0 or above is considered obese. *Id.; accord* U.S. Department of Health &and Human Services, National Heart, Lung, and Blood Institute, http://www.nhlbi.nih.gov/health/educational/lose_wt/BMI/bmicalc.htm (last visited May 4, 2016).

[7] The parties generally agree that fasting blood glucose of $\leq$ 100 mg/dL is normal, multiple fasting blood glucose levels between 100 mg/dL and 125 md/dL is diagnostic for pre-diabetes,

Approximately 11 months later, in September of 1998, Ms. Daniels had symptoms "consistent with hyperglycemia and/or diabetes," namely urinary frequency and increased thirst. (*Id.*). Lab tests showed non-fasting or "random" glucose levels of 169 mg/dL and 143 mg/dL and an HbA1c of 6.1%, and she was diagnosed with "borderline diabetes," which the parties appear to agree means she was pre-diabetic. (*Id.*). During the same 11-month period from the time Ms. Daniels started taking Lipitor until she was diagnosed as borderline diabetic, Ms. Daniels also gained 23 pounds. (*Id.*). Thus, at the time she was diagnosed as borderline or pre-diabetic she weighed 181 pounds with a BMI of 32.1, making her "obese." (*Id.*). She was 50 years old. (*Id.*). Her LDL had dropped from 364 to 113, and her total cholesterol had dropped from 466 to 212. (*Id.*).

In November of 2003, at 55 years of age, Ms. Daniels had an HbA1c of 6.9%, which is past the diagnostic threshold (6.5%) for diabetes. (*Id.* at 5). While there does not appear to be a weight for this exact date, her weight two months later was 203 pounds, which put her at a BMI of 36. (Dkt. No. 1095-14).

B. Dr. Handshoe's Differential Diagnosis

Dr. Handshoe first confirms that Ms. Daniels took Lipitor and that Ms. Daniels had glucose levels and symptoms consistent with a diagnosis of diabetes. (Dkt. No. 1004-7 at 4-5). He then rules out the possibility that Ms. Daniels developed Type 1 Diabetes or Maturity Onset Diabetes of the Young. (*Id.* at 6). As he states, "[t]he true question is whether Ms. Daniels Developed Type 2 Diabetes Mellitus as a result of genetic and environmental factors or whether

---

and multiple fasting blood glucose levels > 125 mg/dL is diagnostic for diabetes. (*See* Dkt. No. 972 at 12, Dkt. No. 1047 at 10, 12). There is no indication in the record that this particular glucose measurement was fasting.

her use of Lipitor was a substantial contributing factor, without which she would not have developed . . . diabetes." (*Id.* at 7).

Dr. Handshoe then reviewed medical literature, concluding that there is an increased risk of developing Type 2 diabetes in patients taking statins, including Lipitor. (*Id.* at 7-8). In other words, he "ruled in" Lipitor as a potential cause of Ms. Daniels' diabetes. There are certain risk factors for Type 2 diabetes that Dr. Handshoe rules out as significant risk factors in Ms. Daniels' case: race/ethnicity at a higher risk of developing diabetes, gestational diabetes during her pregnancies, a diagnosis of Polycystic Ovary Syndrome, age, and the diuretic HCTZ. (*Id.* at 9).

1. BMI and Family History

Dr. Handshoe's report lists two risk factors, other than Lipitor, that he did not rule out as contributing risk factors in Ms. Daniels' case: weight and family history. (Dkt. No. 1004-7 at 9). Dr. Handshoe testifies that did not rule out Ms. Daniels' obesity as a cause of her diabetes. (Dkt. No. 1004-6 at 199). In his report, Dr. Handshoe does not discuss Ms. Daniels' BMI at the time of diagnosis, which was above the threshold considered obese, but states that "when she first began taking Lipitor in October 1997, her body mass index (BMI) was 28, which is only slightly overweight," and "Ms. Daniels . . . led an active life." (Dkt. No. 1004-7 at 9).

The entirety of Dr. Handshoe's analysis of Ms. Daniels family history of diabetes is:

> Ms. Daniels does have a positive family history of diabetes with two brothers and a daughter. However, due to the temporal relationship of her high-dose Lipitor ingestion, I believe that her pre-diabetes was caused by her Lipitor ingestion and not her family history.

(*Id.* at 11). In deposition, Dr. Handshoe agrees that according to the National Health and Nutrition Examination Survey, adults with a family history of diabetes have four times the odds of having diabetes themselves compared with individuals without a family history. (Dkt. No.

1004-6 at 223-24). He agrees that this risk is "much higher" than the risk associated with statin use. (*Id.* at 224-25).

2. Other Risk Factors Not Considered in Dr. Handshoe's Report

In deposition, Dr. Handshoe agrees that he has not ruled out Ms. Daniels' weight gain as a cause of her diabetes. (Dkt. No. 1004-6 at 199). Ms. Daniels gained a total of 23 pounds in the 11 months from the time she started taking Lipitor until she was diagnosed with borderline diabetes. (Dkt. No. 1004-7 at 3). Dr. Handshoe does not discuss this weight gain as a risk factor for diabetes anywhere in his report, but only discusses Ms. Daniels weight and BMI at the time she started taking Lipitor. (Dkt. No. 1004-7 at 9). In deposition, Dr. Handshoe admits that this weight gain, which placed Ms. Daniels' BMI in the category of obese, increased her risk of developing diabetes. (Dkt. No. 1004-6 at 196, 198). When asked why he did not diagnose Ms. Daniels with weight induced diabetes in addition to statin induced diabetes, Dr. Handshoe replied in *ipse dixit* fashion, "[d]iabetes is diabetes. I believe her diabetes was caused by ingestion of the Lipitor." (Dkt. No. 1004-6 at 199).

In his deposition, Dr. Handshoe also testifies that Ms. Daniels has other risk factors for diabetes, but these additional risk factors are not mentioned anywhere in his report. He testifies that among the "best recognized and most significant risk factors for diabetes" are "hypertension, hypolipidemia, [and] the metabolic syndrome."[8] (Dkt. No. 1004-6 at 118-19). However, Dr. Handshoe does not mention these factors as risk factors for diabetes in his report. He states that "Ms. Daniels' medical history includes ***two*** risk factors for Adult Onset Type 2 Diabetes (weight and family history)." (Dkt. No. 1004-7 at 9 (emphasis added)). While he acknowledges these other factors as risk factors in his deposition, he still provides no explanation for how he

[8] With these three, Dr. Handshoe also listed obesity, physical inactivity, increased waist circumference, family history, ethnicity, and advancing age. (*Id.*).

considered them, if at all, but simply notes that these are risk factors as well and concludes in *ipse dixit* fashion that "it's more probable than not her diabetes causes—was caused by administration of the statin drug." (Dkt. No. 1004-6 at 238; *see also id.* at 214 ("She had all these other risk factors. The statin caused her to have diabetes.")).

Finally, Ms. Daniels smoked a pack of cigarettes a day for 32 years, from the time she was 15 years-old until she was 47. (Dkt. No. 1004-22 at 133-34). Dr. Handshoe initially testified that he did not consider her smoking in his report because it was "not germane to diabetes." (Dkt. No. 1004-6 at 228). When asked whether he was familiar with the Unites States Surgeon General's statements on smoking, he stated "I know they list it as a risk factor for diabetes, but I don't think it's a risk factor for diabetes." (*Id.* at 230). In response to follow-up questions, he states he has "not see any data" on the issue. (*Id.* at 231). The night between his depositions in the *Daniels* case and *Hempstead* case, Dr. Handshoe researched the issue. (Dkt. No. 1004-42 at 147). He summed up his night's research as: "There is [sic] some studies that suggest that it does [cause diabetes]. There are some studies that suggest it doesn't. The association of women is quite – is much smaller than men." (Dkt. No. 1004-42 at 147-48). He stated that "based on [Ms. Hempstead's] smoking history of a few cigarettes a week, I would say this is completely insignificant." (*Id.* at 148). However, he never addressed the issue further with regard to Ms. Daniels.

3. Comparison of Risk Factors

Notably, Dr. Handshoe did not consider and compare the various magnitudes of the risks associated with these various risk factors:

> Q. If I understand correctly, you don't actually look at the relative risk or odds ratio that's been reported for statins and compare it to the relative risk or odds ratio that has been reported for any of the other risk factors that are present in the patient?

A. No.

Q. You don't do that?

A. I did not do that.

(Dkt. No. 1004-6 at 178). Indeed, he was unaware of the relative risk of various risk factors. When he was asked whether statin use was as potent a risk factor as other risk factors like hypertension and weight gain, he responded, "[n]obody knows." (Dkt. No. 1004-6 at 133). Counsel then pointed out, and Dr. Handshoe agreed, that studies indeed have quantified the risk associated with statins and the risk associated with other factors. (*Id.* at 133-34). However, he did not seem to know the relative risk associated with these factors. For instance when asked whether adult weight gain without reaching obesity was a risk factor for diabetes, Dr. Handshoe stated "I actually don't know that data, so I will reserve comment." (Dkt. No. 1004-42 at 109). When asked whether the risk of developing diabetes associated with metabolic syndrome is higher than the risk associated with statin use, Dr. Handshoe replied, "given that I told you that I don't know the absolute number, I have no way to answer that." (Dkt. No. 1004-6 at 237).

Dr. Handshoe's deposition also calls into question his ability to interpret and apply such data. In his deposition, Dr. Handshoe was presented with a peer-reviewed article published in the Annals of Internal Medicine in 1995 that used data from the Nurses Health Study and looked at weight gain as a risk factor for diabetes in women. Dr. Handshoe agreed that based on this study, Ms. Daniels' relative risk for the development of diabetes, based solely on her age and BMI, was 40.3. (Dkt. No. 1004-6 at 208). This is a forty-fold increased risk or an increased risk of almost 4000% percent. Dr. Handshoe said he had no reason to dispute "the validity of these numbers." (*Id.* at 209).

However, Dr. Handshoe interpreted the relative risk ratio of 40.3 to mean that 40.3% of these women got diabetes and 60% of them did not. (*Id.* at 210). In other words, he interpreted this number as an *absolute* risk, not a *relative* risk.[9] (*See id.* at 211-12). Dr. Handshoe was then asked to compare this increased risk of diabetes due to age and BMI to the increased risk of diabetes from statins as reported by the Waters study analyzing the SPARCL data. Dr. Handshoe opined that "[t]hey're pretty equivalent, 37, 40." (*Id.* at 217). The respective relative risk ratios are 40.3 and 1.37. Dr. Handshoe is off by two orders of magnitude. The risk is dramatically different. Defendant raised this point in its initial brief, and Plaintiffs have made no attempt to address it.

This mistake was not an isolated incident. When shown data regarding the relative risk of developing diabetes associated with metabolic syndrome, Dr. Handshoe testified that a relative risk of 3.0 translates into an increased risk of 30 percent. (Dkt. No. 1004-6 at 239). Counsel had to inform Dr. Handshoe that a relative risk of 3.0 actually translates into a 300 percent increase in risk. (*Id.* at 240).

In sum, Dr. Handshoe did not rule out all other causes of Ms. Daniels' diabetes; nor did he consider and compare the relative risk ratios for Ms. Daniels' various diabetes risk factors. Indeed, his testimony indicates that he may lack the expertise to do so.

4. Reliance on Temporal Relationship

So how did Dr. Handshoe determine that Lipitor was a substantial contributing factor of Ms. Daniels' diabetes? He testifies that all women with pre-existing risk factors for diabetes and who take a statin and are then diagnosed with diabetes probably have "statin induced diabetes."

---

[9] If the absolute risk of developing diabetes in the control group was 2%, then a relative risk ratio of 40.3 would mean that absolute risk of developing diabetes for the women in this group was 2% * 40.3 or 80.6%. The relative risk ratio, as its name suggests, is a ratio of risks in the two groups, not the absolute risk for a single group.

(Dkt. No. 1004-6 at 166; *accord id.* at 161 ("She would have to have the right clinical risk factors, the right gender, be prescribed the drug, then develop diabetes or prediabetes."), 175 ("She has multiple risk factors for diabetes, did not have diabetes prior to ingestion of the drug and subsequently developed diabetes."), 176 ("[M]y methodology–in other words, she had multiple risk factors for diabetes as we discussed. She was exposed to the statin drug. She subsequently developed diabetes.")).

As he readily admits, Dr. Handshoe's logic/methodology is solely based on the temporal relationship of developing diabetes after taking a statin:

> Q. So regardless of what her risk factors are, how many there are or how strong they are, am I correct that what you're really focusing on is the temporal relationship between statin use and diagnosis of diabetes?
>
> A. That's correct.
>
> Q. So here's Ms. Daniels, she has a number of independent powerful risk factors for diabetes, but essentially, your logic is she didn't–she had those but didn't have diabetes until after she began taking the statin?
>
> A. That's correct.
>
> Q. Therefore, under your method, it is statin induced diabetes?
>
> A. Correct.
>
> Q. Am I missing any other critical fact or critical logical step in your methodology?
>
> A. No.

(Dkt. No. 1004-6 at 201; *see also id.* at 225 ("Q: [W]hy wouldn't you call her diabetes genetically induced diabetes? A. Because she did not have diabetes, she took the medication and developed diabetes."); *id.* at 200 ("Those are all risk factors for diabetes. She did not have diabetes until she took the drug for a year. So the way I look at this and put it together, again, she had statin induced diabetes.").

C. Discussion

"[S]imply because a person takes drugs and then suffers an injury does not show causation. Drawing such a conclusion from temporal relationships leads to the blunder of the *post hoc ergo propter hoc* fallacy." *McClain v. Metabolife Int'l, Inc.*, 401 F.3d 1233, 1243 (11th Cir. 2005); *see also Roche v. Lincoln Prop. Co.*, 278 F. Supp. 2d 744, 752 (E.D. Va. 2003) ("Dr. Bernstein's reliance on temporal causation as the determinative factor in his analysis is suspect because it is well settled that a causation opinion based solely on a temporal relationship is not derived from the scientific method and is therefore insufficient to satisfy the requirements of Rule 702.") (internal quotes omitted).

Plaintiffs note that in *Westberry*, the Fourth Circuit held that "depending on the circumstances, a temporal relationship between exposure to a substance and the onset of a disease or a worsening of symptoms can provide compelling evidence of causation." *Westberry v. Gislaved Gummi AB*, 178 F.3d 257, 265 (4th Cir. 1999). However, *Westberry* also states that "[o]f course, the mere fact that two events correspond in time does not mean that the two necessarily are related in any causative fashion" *Id.* There are circumstances where temporal proximity is particularly compelling. *See, e.g., Cavallo v. Star Enter.*, 892 F. Supp. 756, 774 (E.D.Va. 1995) (explaining that "there may be instances where the temporal connection between exposure to a given chemical and subsequent injury is so compelling as to dispense with the need for reliance on standard methods of toxicology," for example, if one were exposed to a substantial amount of "chemical X and immediately thereafter developed symptom Y").

However, this is not always the case. *See Moore v. Ashland Chem. Inc.*, 151 F.3d 269, 278 (5th Cir. 1998) ("In the absence of an established scientific connection between exposure and illness, or compelling circumstances such as those discussed in *Cavallo*, the temporal

connection between exposure to chemicals and an onset of symptoms, standing alone, is entitled to little weight in determining causation."). In *Westberry*, it was "undisputed that inhalation of high levels of talc irritate[d] mucous membranes" and that the plaintiff's sinus disease began shortly after he started as a gasket cutter where he "worked in clouds of talc . . . that covered him and his clothes." 178 F.3d at 265. Every time the plaintiff stayed out of work, his sinuses improved. *Id.* Every time he returned, they worsened. The Fourth Circuit found these particular circumstances compelling, but they are not analogous to facts here. In this matter, there was no immediate response to the Lipitor that disappeared when Lipitor exposure was removed. Ms. Daniels' diagnosis of borderline diabetes occurred 11 months after she began Lipitor.

Furthermore, during these same 11 months, Ms. Daniels also gained 23 pounds. To the extent that her diabetes "immediately" followed her exposure to Lipitor, it also "immediately" followed Ms. Daniels' weight gain and "immediately" followed Ms. Daniels progression from being "slightly overweight," as Dr. Handshoe states in his report, to being obese. *Westberry* has no such admittedly obvious confounding factors. This situation is a far cry from the temporal proximity and factual situations in *Westberry* and *Cavallo*.

Two Seroquel cases are instructive. In *Guinn v. AstraZeneca Pharm. LP*, 602 F.3d 1245 (11th Cir. 2010), the plaintiff claimed that Seroquel caused her to develop diabetes. The district court excluded the case-specific expert testimony and granted summary judgment, and the Eleventh Circuit upheld both decisions. In *Guinn*, the expert admitted that "other risk factors alone were sufficient to explain the onset of [plaintiff's] diabetes" and that "she knew of no methodology for ruling out alternative causes and thus had not attempted to do so." *Id.* at 1249-50. Recognizing the problem with this opinion, the expert submitted a supplemental declaration stating that "she believed other potential causes were not solely responsible because [plaintiff]

had gained weight and developed diabetes soon after taking Seroquel when [plaintiff's] other risk factors remained constant." *Id.* at 1254. However, even assuming the plaintiff's risk factors for diabetes remained constant,[10] the Eleventh Circuit rejected this argument as a reliable methodology: "Dr. Marks' reliance on the temporal proximity of the introduction of an additional risk factor, however, does not satisfy the requirement that a differential diagnosis consider possible alternative causes on the facts of this case." *Id.* at 1254.

First, "[t]emporal proximity is generally not a reliable indicator of a causal relationship. . . . [and] several factors make it especially unreliable in this case." *Id.* Second, and more importantly, the expert "does not explain why having a stable risk profile makes it unlikely that preexisting factors caused [plaintiff's] diabetes when such factors put her at an extremely high risk for diabetes." *Id.* Plaintiffs "numerous other risk factors for diabetes make it hard to draw any inferences from the temporal proximity." *Id.* The *Guinn* decision is in accord with *Westberry*'s statement that temporal proximity can be compelling in particular circumstances; those circumstances are just not present here:

> After considering the nature of the temporal relationship at issue in this case, we conclude Dr. Marks did not adequately consider possible alternative causes simply by noting the temporal proximity between Guinn's ingestion of Seroquel and subsequent development of diabetes. *We do not hold that a temporal relationship can never be used to consider alternative causes of a plaintiff's injury; instead, we merely find that temporal proximity is not sufficient on the facts of this case.*

Id. at 1255 (emphasis added).

Next, the expert in *Guinn* provided a second explanation of how she considered alternative causes–by testifying that all the risk factors work together. This is Dr. Handshoe's explanation: "Again, you have this risk, you have that risk, I think the risks are additive. I mean,

[10] As the Eleventh Circuit noted in *Guinn*, "one important risk factor—[plaintiff's] age—did not remain constant." *Id.* at 1254. Here, Ms. Daniels' weight and BMI also did not remain constant.

how can you tease out that only one thing caused somebody's diabetes . . ." (Dkt. No. 1004-6 at 134; *see also id.* at 224 ("The family history, her BMI, her triglyceride levels, all her risk factors. You just can't take one thing, it's the totality."); *id.* at 177 ("I think it's a totality of the risk factors. I don't look at one thing of family history or hypertension or weight.")). The Eleventh Circuit also rejected this reasoning as a valid methodology, holding that "[a]n expert, however, cannot merely conclude that all risk factors for a disease are substantial contributing factors in its development." *Id.* at 1255.

> The fact that exposure to [a substance] may be a risk factor for [a disease] does not make it an actual cause simply because [the disease] developed." *Cano v. Everest Minerals Corp.*, 362 F.Supp.2d 814, 846 (W.D.Tex.2005). "[A]lthough the differential diagnosis technique is well accepted ... [, a finding] that all possible causes are causes does not appear to have gained general acceptance in the medical and scientific communities." *Id.* While multiple factors can work together to cause diabetes, Dr. Marks was still required to provide some analysis of why she concluded that, more likely than not, Seroquel substantially contributed to Guinn's weight gain and such weight gain was among the factors that substantially contributed to her diabetes.

Id.

As in *Guinn*, Dr. Handshoe cannot simply opine that all present risk factors are "substantial contributing factors." Risk factors are *potential* causes of diabetes. Identifying potential causes is the work of general causation and, without more, does not suffice for a specific causation opinion. *See Norris v. Baxter Healthcare Corp.*, 397 F.3d 878, 881 (10th Cir. 2005) ("General causation is whether a substance is capable of causing a particular injury or condition in the general population and specific causation is whether a substance caused a particular individual's injury."); *see also Viterbo v. Dow Chem. Co.*, 826 F.2d 420, 424 (5th Cir. 1987) (If a patient's "symptoms could have numerous causes," the expert cannot "simply pick[] the cause that is most advantageous to [the plaintiff's] claim"). "While multiple factors can work together to cause diabetes, [Dr. Handshoe is] still required is still required to provide some

analysis of why []he concluded that, more likely than not, [Lipitor] substantially contributed to [Ms. Daniels'] . . . diabetes." *Guinn*, 602 F.3d at 1255.

Haller v. AstraZeneca Pharm. LP, 598 F. Supp. 2d 1271 (M.D. Fla. 2009) is another Seroquel case where the plaintiff claimed the drug caused her weight gain and diabetes. The court excluded both case-specific causation experts. *Id.* at 1276. The endocrinologist expert in *Haller* "agreed that the complications from diabetes that he described in his report could have been solely caused by pre-existing obesity, years of smoking, metabolic syndrome, and uncontrolled hypertension that preceded [plaintiff's] ingestion of Seroquel" and "made crystal clear at his deposition that the sole basis for his opinion that Seroquel caused the development of diabetes in [plaintiff] was the temporal relationship between [plaintiff's] taking Seroquel and his subsequent weight gain, and the weight gain's temporal relationship with the development of diabetes." *Id.* at 1278, 1278-79. The expert "made equally clear that [plaintiff] would have developed diabetes at some point even if he had never taken Seroquel. His opinion was that Seroquel somehow accelerated the development of diabetes," but he did not attempt to quantify the acceleration. *Id.* at 1279. Even though the plaintiff's risk factors in *Haller* are more extreme than Ms. Daniels', the court's conclusions are still instructive:

> Standing alone, the first factor–temporal connection–is legally insufficient. *McClain*, 401 F.3d at 1243. The second listed ground–that other risk factors had not yet caused diabetes–is also unpersuasive. This observation is largely temporal proximity in disguise. It posits that arguably the last additive factor–Seroquel–is necessarily the one that caused or substantially contributed to causing the disease. This overlooks Dr. Tulloch's own testimony regarding the slow progression of diabetes and the additive nature of the factors that can cause it. Moreover, it is equally plausible that the additive effects of, or an incremental increase in, one or more of the other risk factors was the actual tipping point. The third and fourth factors–biologically plausible mechanism and literature demonstrating a connection between Seroquel and diabetes–relate to *general* causation and carry little if any relevance to the question of whether Seroquel caused diabetes in Haller's *specific* case.

Id. at 1297-98 (emphasis in original). As in *Haller*, Dr. Handshoe readily admits that there is nothing in Ms. Dnaiels' medical presentation or the course of her disease that is inconsistent with the development and diagnosis of diabetes in persons who never took statins. (Dkt. No. 1004-6 at 163-64). Dr. Handshoe relies solely on temporal proximity and general causation evidence, without any other explanation for his conclusion that Lipitor caused diabetes *in this instance*.

Plaintiff argues that because Dr. Handshoe utilized the differential diagnosis methodology and that methodology has been recognized as scientifically valid, the Court must accept Dr. Handshoe's opinions as sufficient to meet *Daubert* standards. Under the traditional differential diagnosis approach, a physician, after clinically evaluating the patient, identifies "the cause of a medical problem by eliminating the likely causes until the most probable one is isolated." *Westbury*, 178 F.3d at 262. Courts have recognized that the differential diagnosis approach, sometimes referred to also as "differential etiology,"[11] may be permissible even where the physician has not examined the patient or where all possible causes of the patient's medical problems have not been ruled out. *See Cooper v. Smith & Nephew, Inc.*, 259 F.3d 194, 202 (4th Cir. 2001) ("A medical expert's opinion based upon differential diagnosis normally should not be excluded because the expert has failed to rule out every possible alternative cause of a plaintiff's illness."); *Kannankeril v. Terminix Int'l, Inc.*, 128 F.3d 802, 807 (3d Cir. 1997), *as amended* (Dec. 12, 1997) ("Depending on the medical condition at issue and on the clinical information already available, a physician may reach a reliable differential diagnosis without himself performing a physical examination, particularly if there are other examination results available."). But courts have made clear that regardless of what the methodology may be called,

[11] "Technically, differential diagnosis refers to a method of determining which of two diseases a patient suffers from, whereas differential etiology is a term used to describe the process by which the cause of an injury is determined." *Guinn*, 602 F.3d at 1253. However, the trend among federal courts is to "use the term differential diagnosis to refer to both concepts." *Id.*

it must meet the standards of Rule 702—an expert must use a valid methodology, the methodology must be reliably applied, and her opinions must be supported by sufficient facts and data. *Cooper,* 259 F.3d at 201; *see also McClain* at 401 F.3d at 1253 ("[A]n expert does not establish the reliability of his techniques or the validity of his conclusions simply by claiming that he performed a differential diagnosis on a patient.").

Under Fourth Circuit law, an expert need not rule out every possible alternative cause of a disease in a differential diagnosis. *Westberry*, 178 F.3d at 265. However, he must offer an explanation as to why these other recognized causes, alone, are not responsible for the disease in a particular plaintiff. *Cooper*, 259 F.3d at 202; *see also Westberry*, 178 F.3d at 265.

In this case, Dr. Handshoe admitted that Plaintiff had a number of statistically significant risk factors for diabetes beyond ingestion of Lipitor, including her BMI, weight gain, family history, hypertension, hypolipidemia, and metabolic syndrome. However, he has provided no explanation as to why these other admitted risk factors, alone or combination, do not solely account for Ms. Daniels' diabetes, i.e., why Lipitor is also a substantial contributing factor.

Tellingly, Dr. Handshoe acknowledges that "statins do not cause diabetes in every patient who takes them," and that "there are patients who have taken statins that are then diagnosed with diabetes, but in whom the statin played no role in causing diabetes." (Dkt. No. 1004-6 at 164). But he "couldn't tell one way or another who those were." (*Id.* at 164).

Q. Could you walk into a room of 100 patients with diabetes and pick out the ones who have what you call statin induced diabetes versus the non-statin induced diabetics?

A. No.

Q. Could you even do that if there were ten people in the room?

A. No.

Q. Could you do it between two people?

A. No.

Q. Is there any validated test or procedure that you could perform that would distinguish what you call statin induced diabetes from non-statin induced diabetes?

A. No.

(Dkt. No. 1004-6 at 163). Here, Dr. Handshoe acknowledges he has no methodology for determining whether a particular patient has statin-induced diabetes. His opinion that Ms. Daniels' diabetes is statin-induced is nothing but unacceptable *ipse dixit*. *See Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997) ("Nothing 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.").

Turning to factors of reliability, Dr. Handshoe's purported methodology is not published, (Dkt. No. 1004-6 at 160-61, 173), has not been validated, (*id.* at 173), has no known potential rate of error because it has only been applied once, in this case, (*id.* at 174), has never been used by Dr. Handshoe in his clinical practice, (*id.* at 166-67), has never been used by another doctor, (*id.* at 184), and has only been applied by Dr. Handshoe in the context of litigation. (*Id.* at 185)

Dr. Handshoe does not use a reliable methodology to determine whether Lipitor is a substantial contributing factor to Ms. Daniels' development of diabetes. None of the *Daubert* factors indicating reliability are present. Dr. Handshoe developed the methodology solely for this litigation and has never used it in his clinical practice. To the extent that Dr. Handshoe is using the differential diagnosis methodology, his application of it is unreliable because he utterly fails to consider some alternative causes, not even mentioning them in his report, and fails to provide any explanation as to why these causes and other alternative causes mentioned in his

report are not solely responsible for Ms. Daniels' development of diabetes. Furthermore, the gap between the available scientific evidence and Dr. Handshoe's opinions are too great to survive a Rule 702 review. *See Viterbo v. Dow Chem. Co.*, 826 F.2d 420, 424 (5th Cir. 1987) (If a patient's "symptoms could have numerous causes," the expert cannot "simply pick[] the cause that is most advantageous to [the plaintiff's] claim"); *In re Prempro Products Liab. Litig.*, No. 3:05CV00078-WRW, 2010 WL 8357351, at *2 (E.D. Ark. Sept. 26, 2010) ("Mentioning some risk factors and moving on to a conclusion, without a specific explanation, is not a proper differential diagnosis. . . . [it] is simply a recitation of facts—this does not help the jury."). Therefore, the Court excludes Dr. Handshoe's specific causation opinion in the *Daniels* case.

IV. Dr. Handshoe's Opinion in Hempstead

A. Ms. Hempstead's Medical History and Diagnosis of Diabetes

Juanita Hempstead began seeing primary care physician Dr. Lou Sabih in January of 1998. (Dkt. No. 1275-1 at 9). In March of 1998, Dr. Sabih ordered a lipid panel, which showed that Ms. Hempstead had total cholesterol of 243 mg/dL, LDL of 151 mg/dL, HDL of 41 mg/dL, and triglycerides of 255 mg/dL. (*Id.*). In response to these labs, Dr. Sabih diagnosed Ms. Hempstead with hyperlipidemia and prescribed 20 mg of Lipitor daily. (Dkt. No. 1004-40 at 3; *id.*). Because of apparent concerns about possible liver toxicity, Ms. Hempstead did not start taking Lipitor at that time. (*Id.*; Dkt. No. 1004-40 at 3).

Over a year later in June of 1999 (and after adjustments to her blood pressure medication), Ms. Hempstead had another lipid panel, which showed Ms. Hempstead had a total cholesterol of 250 mg/dL, LDL of 175 mg/dL, HDL of 46 mg/dL, and triglycerides of 142 mg/dL. (Dkt. No. 1275-1 at 10). Ms. Hempstead weighed 176 lbs at the time and had a body mass index (BMI) of 26.4. (Dkt. No. 1004-40 at 3). Her only chronic condition at the time was

hypertension. (*Id.*). Ms. Hempstead was again prescribed 20 mg of Lipitor daily. (Dkt. No. 1275-1 at 10). Ms. Hempstead took Lipitor inconsistently over the next year. (*Id.*). Pharmacy records indicate that she did not refill the prescription at all between January and July of 2000. (*Id.*).

In July of 2000, Ms. Hempstead began taking Lipitor regularly. (Dkt. No. 1275-1 at 11). In the fall of 2000, Dr. Michael Ausmus became Ms. Hempstead's primary care physician. (*Id.* at 10-11). Two years later, in September of 2002, a lipid panel showed Ms. Hempstead had total cholesterol of 179 md/dL, LDL of 111 mg/dL, HDL of 40 mg/dL, and triglycerides of 139 mg/dL. (*Id.* at 10). She had an abnormal glucose reading of 114 mg/dL. (*Id.*). She had gained a total of 13 pounds since starting Lipitor in 1999, resulting in a total weight of 184 and a BMI of 27.57. (*Id.*).

In the fall of 2003, Ms. Hempstead stopped taking Lipitor for three weeks due to abdominal pain. (Dkt. No. 1275-1 at 11). A lipid panel taken after being off Lipitor for approximately three weeks showed Ms. Hempstead's blood lipid levels had risen. She had total cholesterol of 258 mg/dL, LDL of 173 mg/dL, HDL of 46 mg/dL, and triglycerides of 194 mg/dL. (*Id.* at 10). Her glucose reading after three weeks off Lipitor was 122 mg/dL. (*Id.*). Three months later, after resuming Lipitor, her lipid levels came back down, with total cholesterol of 176 mg/dL, LDL of 103 mg/dL, HDL of 37 mg/dL, and triglycerides of 179 mg/dL. (*Id.* at 10, 11).

In February of 2004, Ms. Hempstead was seen in the emergency room and diagnosed with colitis. (Dkt. No. 1275-1 at 11). She had a random blood glucose reading of 214 mg/dL, but there was no diagnosis of diabetes. (*Id.*). On May 14, 2004, Ms. Hempstead was admitted to the hospital with a blood glucose level of 613 mg/dL and HbA1c of 12.2% (Dkt. No. 1004-40 at

3). She exhibited multiple symptoms consistent with diabetes and was diagnosed with Type 2 diabetes. (*Id.*). At the time, she weighed 191 pounds, making her BMI 28.6. (*Id.*). She was 59 years old. (*Id.*).

B. Dr. Handshoe's Differential Diagnosis

As with Ms. Daniels, Dr. Handshoe first confirms that Ms. Hempstead took Lipitor and that she had glucose levels and symptoms consistent with a diagnosis of diabetes. (Dkt. No. 1004-40 at 4-5). He then rules out the possibility that Ms. Hempstead developed Type 1 Diabetes or Maturity Onset Diabetes of the Young. (*Id.* at 5, 6-7). As he states, "[t]he true question is whether Ms. Hempstead Developed Type 2 Diabetes Mellitus as a result of genetic and environmental factors or whether her use of Lipitor was a substantial contributing factor in causing her to become resistant to insulin and causing a decreased production of insulin from beta cells, thereby leading to her diabetes." (*Id.* at 7).

Then, as he did with Ms. Daniels, Dr. Handshoe reviewed medical literature, concluding that there is an increased risk of developing Type 2 diabetes in patients taking statins, including Lipitor. (*Id.* at 7-8). In other words, he "ruled in" Lipitor as a potential cause of Ms. Hempstead's diabetes. Dr. Handshoe rules out several other possible risk factors: the diuretic HCTZ, Polycystic Ovary Syndrome, gestational diabetes, and her "remote, light smoking history." (*Id.* at 6, 10).

Dr. Handshoe notes that Ms. Hempstead did not experience an abnormal lab value prior to taking Lipitor, that her level of physical activity should have offered her a protective benefit, and that Ms. Hempstead took 20 mg of Lipitor over multiple years, and opines that all of these factors support a diagnosis of statin-induced diabetes. (Dkt. No. 1004-40 at 9, 10-11).

1. BMI

In his report, Dr. Handshoe states that just prior to her diagnosis, Ms. Hemptead's BMI of 28.6 is "only slightly overweight," but does not otherwise address BMI as a risk factor or state whether Ms. Hempstead's BMI substantially contributed to her diabetes. (Dkt. No. 1004-40 at 9). In deposition, Dr. Handshoe testifies that he "felt it was not clinically significant given that . . . she had multiple normal blood sugars even with this weight . . ." (Dkt. No. 1004-42 at 109). Thus, he ruled this risk factor out as a substantial contributing factor to her diabetes. (*Id.* at 114). He also noted that Ms. Hempstead's weight gain occurred slowly but could not point to any medical literature supporting his proposition that weight gain does not increase the risk for diabetes if it occurs slowly over time. (*Id.* at 116).

Dr. Handshoe agrees that, according to the Colditz article, the age-adjusted relative risk ratio for Ms. Hempstead's BMI is 15.8, and he has no reason to disagree with this assessment of risk. (Dkt. No. 1004-42 at 113-15). He testifies that he is not aware of any medical literature that reports an association between Lipitor use and the development of diabetes "anywhere near the range of a relative risk of an odds ratio of 15." (*Id.* at 115). He testifies that range of relative risk ratios for statin use are "up to" 1.87. (*Id.*).

2. Weight Gain

Adult weight gain, as a risk factor separate from BMI, is not discussed in Dr. Handshoe's report. (*See* Dkt. No. 1004-40; *see also* Dkt. No. 1004-42 at 109-10). From the time that Ms. Hempstead started taking Lipitor until her diagnosis with diabetes (1999-2004), she gained 15 pounds. (Dkt. No. 1004-42 at 107). Ms. Hempstead gained a total of 55 pounds as an adult, over 25 years. (*Id.* at 108). Dr. Handshoe testified that he did not know the data with regard to whether adult weight gain put a patient at an increased risk for diabetes and, therefore, did not

consider it in preparing his opinions. (*Id.* at 109, 110). However, he also testified in the *Daniels* case, that weight gain would increase the risk of diabetes in and of itself. (Dkt. No. 1004-6 at 197).

3. Family History

Ms. Hempstead's father was diabetic. (Dkt. No. 1004-40 at 9). Because her father was not diagnosed until his eighties and because Ms. Hempstead's siblings are not diabetic, Dr. Handshoe opines that "the evidence more clearly points to the development of statin-induced Type 2 Diabetes." (*Id.* at 9-10). In other words, he ruled out family history as a risk factor in Ms. Hempstead's case. (Dkt. No. 1004-42 at 121-22).

4. Race/Ethnicity

Dr. Handshoe addresses this risk factor in a single sentence in his report: "Ms. Hempstead is African American, and, while this racial category has been shown to be associated with a slightly-increased risk of developing diabetes, I believe that her statin use put her at a greater risk than her race or ethnic background." (Dkt. No. 1004-40 at 10). He provides no data whatsoever to support this opinion and provides no analysis. (*Id.*).

In deposition, Dr. Handshoe testifies that while Ms. Hempstead self identifies as African American, she testified, and he knew, that her father was mostly Choctaw Native American and her mother had some French heritage as well as African American. (Dkt. No. 1004-42 at 139). However, he did not mention Ms. Hempstead's Choctaw heritage in his report, nor did he do any investigation into the incidence of diabetes in Choctaw Native Americans. (*Id.* at 140, 142). He testifies that "based on my clinical experience of working in rural Mississippi where the Choctaw Nation is from, I did not see an increase incidence of diabetes in Choctaw Indians." (*Id.*). However, when confronted with a peer-reviewed study that reported the incidence of diabetes in

Choctaw Native Americans in Mississippi to be 6.5 times the incidence of diabetes in the United States, Dr. Handshoe admitted that the study showed an increased rate of diabetes in Choctaw Native Americans and retreated, pointing out that Ms. Hempstead was only partially Choctaw. (*Id.* at 206-208). Dr. Handshoe testifies that he does not rely on any medical literature for his opinion that Ms. Hempstead's racial and ethnic background is not a contributing factor to her diabetes, but only relies on his "clinical judgment." (*Id.* at 142).

5. Age

Dr. Handshoe provides no analysis or data in his report regarding this risk factor, but simply states in a conclusory fashion: "Ms. Hempstead was fifty-nine years old at the time of her diabetes diagnosis. Her age was not a substantial contributing factor for developing diabetes." (Dkt. No. 1004-40 at 10).

In deposition, Dr. Handshoe testifies that "advancing age is a risk factor for diabetes, but at age 59 I felt that it was not significant." (Dkt. No. 1004-42 at 143). Dr. Handshoe "surf[ed] on the internet" and found a chart that stated a person at age 59 has "some risk." (*Id.* at 144). He did not do anything else to investigate Ms. Hempstead's increased risk of diabetes due to age. (*Id.*). Despite the fact that this chart on the internet showed an increased risk for diabetes, Dr. Handshoe testifies that "in my clinical judgment, I felt it was not the major driver of her diabetes." (*Id.*).

6. Hypertension, Elevated Triglycerides, and low HDL

Dr. Handshoe testifies that hypertension is a well-established independent risk factor for diabetes. (Dkt. No. 1004-42 at 181). Dr. Handshoe did not address this risk factor at all in his differential diagnosis. (*Id.*; *see also* Dkt. No. 1004-40).

Similarly, Dr. Handshoe testifies that high triglycerides and low HDL are also risk factors for diabetes and that he did not consider these risk factors in his differential diagnosis with regard to Ms. Hempstead. (Dkt. No. 1004-42 at 194; *see also* Dkt. No. 1004-40).

7. Comparison of Risk Factors

Dr. Handshoe makes no attempt to compare the relative risks associated with Ms. Hempstead's various risk factors for diabetes. (*See* Dkt. No. 1004-40). In Ms. Hempstead's case, he also does not testify that the risk factors are additive as he did in Ms. Daniels' case. Instead, he testifies that any and all changes in Ms. Hemstead's blood sugar are due to Lipitor; "it is the only factor." (Dkt. No. 1004-42 at 235, 236). He acknowledges that Ms. Hempstead had other risk factors, and then simply states "I felt that they were not significant to my clinical judgment." (*Id.* at 237).

8. Reliance on Temporal Relationship

Dr. Handshoe's opinion that Lipitor was the sole contributing factor to Ms. Hempstead's blood glucose changes and development of diabetes is based only on a temporal relationship. As Dr. Handshoe testified:

> Q. So what you relied you relied on was the fact that she took Lipitor and developed diabetes after taking Lipitor?
>
> A. That's correct.
>
> Q. And that's really the same reason that you ruled out all these other risk factors that we've talked about, isn't it?
>
> A. Yes.

(Dkt. No. 1004-42 at 145-46 (objection omitted); *see also id.* at 239 ("[I]n Ms. Hempstead's case, she did not have diabetes, she was given the drug and then developed diabetes. To me it's pretty clear that she had a statin induced diabetic process.")).

C. Discussion

Dr. Handshoe's purported differential diagnosis is unreliable. In the *Daniels* case, Dr. Handshoe testified that risk factors were additive. (Dkt. No. 1004-6 at 134). However, here, he takes a different approach, testifying that he has ruled out all other risk factors in Ms. Hempstead's case, leaving Lipitor as the sole contributing cause to her increased glucose levels and diabetes. (Dkt. No. 1004-42 at 235, 236). There are two major problems with this approach. First, Dr. Handshoe fails to consider several risk factors at all, namely hypertension, elevated triglycerides, low HDL, and weight gain. (Dkt. No. 1004-42 at 109, 110, 181). "A differential diagnosis that fails to take serious account of other potential causes may be so lacking that it cannot provide a reliable basis for an opinion on causation." *Westberry v. Gislaved Gummi AB*, 178 F.3d 257, 265 (4th Cir. 1999).

Second, "there is simply too great an analytical gap between the data and the opinion offered." *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997). Dr. Handshoe readily admits that Ms. Hempstead's BMI places her at a risk of developing diabetes and that the risk of developing diabetes due to statins is not anywhere near the risk of developing diabetes due to her BMI. (Dkt. No. 1004-42 at 113-15). He also admits that her racial and ethnic background put her at an elevated risk, but provides no explanation for ruling this risk out as a contributing factor to her diabetes. (Dkt. No. 1004-40 at 10; *see also* Dkt. No. 1004-42 at 206-208). He readily admits he did not investigate the risk posed by her racial and ethnic background and does not rely on any medical literature for his opinion in ruling this factor our as a contributory cause. (*Id.* at 142). He also readily admits that Ms. Hempstead's age put her at an increased risk of diabetes, but simply concluded this risk was "not clinically significant" without explanation and with his only research consisting of "surfing the internet." (Dkt. No. 1004-42 at 143-44). Dr. Handshoe also

testifies that hypertension is a well-established independent risk factor for diabetes, but he simply chose not to address it at all. (Dkt. No. 1004-42 at 181).

Despite the fact that Dr. Handshoe admits published, peer-reviewed literature finds each of these factors increases a person's risk of diabetes, he rules them all out based only on his "clinical judgment" and the fact that Ms. Hempstead did not develop diabetes until after taking Lipitor. (*See, e.g.*, Dkt. No. 1004-42 at 109, 142, 144, 145-46, 237-38). In this case, Dr. Handshoe's clinical judgement is nothing more than unacceptable *ipse dixit* testimony. *See Joiner*, 522 U.S. at 146. When relying on his experience, an expert must "explain how his experience leads to the conclusion reached, why his experience is a sufficient basis for the opinion, and how his experience is reliably applied to the facts." *United States v. Wilson*, 484 F.3d 267, 274 (4th Cir. 2007). Dr. Handshoe makes no attempt to do this.

Furthermore, his opinion runs contrary to the published literature, and Dr. Handshoe makes no attempt to reconcile his opinion with that literature. *See McEwen v. Baltimore Washington Med. Ctr. Inc.*, 404 F. App'x 789, 791-92 (4th Cir. 2010) (upholding exclusion of expert testimony where experts "failed to meaningfully account for . . . literature at odds with their testimony"). For example, Dr. Handshoe admits that one peer reviewed article found that Ms. Hempstead's BMI increased her risk of diabetes by a factor of 15.8 and that no published literature puts the risk of diabetes due to statins anywhere close to that number. (Dkt. No. 1004-42 at 113-15). Yet without explanation, Dr. Handshoe concludes Ms. Hempstead's BMI played no role whatsoever in her development of diabetes.

Dr. Handshoe's opinion in the *Hempstead* case is also counter to his opinion in the *Daniels* case, where he testified that risk factors are additive. Dr. Handshoe himself testified: "you have this risk, you have that risk, I think the risks are additive. I mean, ***how can you tease***

out that only one thing caused somebody's diabetes . . ." (Dkt. No. 1004-6 at 134 (emphasis added). Yet, this is precisely what Dr. Handshoe purportedly did in Ms. Hempstead's case.

Finally, the reliability of Dr. Handshoe's opinion that Lipitor is the sole cause of Ms. Hempstead's diabetes is also undermined by his testimony that Ms. Hempstead may have developed diabetes even if she had not taken statins and his testimony that the risk factors he "ruled out" in Ms. Hempstead's can culminate in a diagnosis of Type 2 Diabetes absent statin exposure in some people. (Dkt. No. 1004-42 at 239). When asked, "if risk factors that Ms. Hempstead had can be sufficient to cause diabetes in some people, why do you believe that they were not sufficient to cause diabetes in her," Dr. Handshoe replied with the temporal relationship: "[b]ecause she had a normal blood sugar, she was prescribed Lipitor, she was active and exercising and ***it was only after she was exposed to this drug that she developed diabetes***." (*Id.* (emphasis added)).

The Court has address Dr. Handshoe's sole reliance on the temporal relationship above and does not reiterate it here. However, the Court notes that the temporal relationship here is even more attenuated than in *Daniels*. Two years after Ms. Hempstead began taking Lipitor, it had no apparent effect on her glucose levels, (Dkt. No. 1275-2 at 205), and Ms. Hempstead did not develop diabetes until almost five years after starting Lipitor. (Dkt. No. 1275-1 at 10).

Again, Dr. Handshoe's purported methodology for diagnosing statin-induced diabetes is not published, (Dkt. No. 1004-6 at 160-61, 173), has not been validated, (*id.* at 173), has no known potential rate of error because it has only been applied once, in this MDL, (*id.* at 174), has never been used by Dr. Handshoe in his clinical practice, (*id.* at 166-67), has never been used by another doctor, (*id.* at 184), and has only been applied by Dr. Handshoe in the context of litigation. (*Id.* at 185; *see also* Dkt. No. 1004-42 at 19 (testifying that he used the same

methodology in *Daniels* and *Hempstead*). Furthermore, Dr. Handshoe acknowledges that "statins do not cause diabetes in every patient who takes them," and that "there are patients who have taken statins that are then diagnosed with diabetes, but in whom the statin played no role in causing diabetes." (Dkt. No. 1004-6 at 164). But, even with his methodology, he "couldn't tell one way or another who those were." (*Id.* at 164).

In sum, Dr. Handshoe does not use a reliable methodology to determine whether Lipitor is a substantial contributing factor to Ms. Hempstead's development of diabetes. To the extent that Dr. Handshoe is using the differential diagnosis methodology, his application of it is unreliable because he utterly fails to consider some alternative causes, not even mentioning them in his report, and fails to provide any explanation as to why these causes and other alternative causes mentioned in his report are not solely responsible for Ms. Hempstead's development of diabetes. Instead, he opines in *ipse dixit* fashion that in his "clinical judgment," Lipitor is the sole cause of Ms. Hempstead's diabetes. In addition to not being based on a reliable methodology, the gap between the available scientific evidence and this opinion is simply too great to survive a Rule 702 review. Therefore, the Court excludes Dr. Handshoe's specific causation opinion in the *Hempstead* case.

V. Conclusion

For the reasons stated above, Pfizer's Motion to Exclude the Expert Testimony of David K. Handshoe, M.D. (Dkt. No. 1004) is **GRANTED**.

AND IT IS SO ORDERED.

Richard Mark Gergel
United States District Court Judge

May 11, 2016
Charleston, South Carolina