UNITED STATES DISTRICT COURT
MIDDLE DISTRICT OF FLORIDA
ORLANDO DIVISION

IN RE: Seroquel Products Liability Litigation

Case No. 6:06-md-1769-Orl-22DAB

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ORDER

This cause comes before the Court for consideration of AstraZeneca's Motion to Exclude the General Causation Testimony of Plaintiffs' Generic and Case-Specific Witnesses (Doc. 1112), to which Plaintiffs responded in opposition (Doc. 1342).[1] On February 11, 2009, the Court rendered a partial decision on this motion, holding that the general causation testimony of Dr. William Wirshing is admissible. *See* Doc. 1271. The Court now considers the admissibility of the general causation testimony of Dr. Arnett.

Daubert testimony was elicited from Dr. Arnett at a hearing held on April 7, 2009. Upon consideration of the motion and memoranda, as well as the testimony set forth at the *Daubert* hearing, the Court determines that AstraZeneca's motion is due to be **DENIED** with respect to the general causation testimony of Dr. Arnett.

I. LEGAL STANDARD

AstraZeneca challenges Plaintiffs' experts' testimony under Rules 401, 402, 403, 702 and 703 of the Federal Rules of Evidence. The first two of these rules govern the admissibility of

[1] Plaintiffs' original response (Doc. 1159) was filed under seal because it contained documents designated by one or both parties as confidential. At the Court's direction, Plaintiffs later filed a redacted public version of their response (Doc. 1342).

evidence. Specifically, Rule 402 dictates that, in general, "[a]ll relevant evidence is admissible." Fed. R. Evid. 402. Rule 401 defines relevant evidence as "evidence having any tendency to make the existence of any fact that is of consequence to the determination of the action more probable or less probable than it would be without the evidence." Fed. R. Evid. 401. This rule does not stand alone, however; it must be balanced with Rule 403, which dictates that, "[a]lthough relevant, evidence may be excluded if its probative value is substantially outweighed by the danger of unfair prejudice, confusion of the issues, or misleading the jury, or by considerations of undue delay, waste of time, or needless presentation of cumulative evidence." Fed. R. Evid. 403.

Unlike Rules 401, 402, and 403, which apply to all evidence, Rules 702 and 703[2] are limited in scope to evidence involving the application of specialized expertise. Fed. R. Evid. 702 governs the admission of expert testimony at trial. The Rule states:

> If scientific, technical, or other specialized knowledge will assist the trier of fact to understand the evidence or to determine a fact in issue, a witness qualified as an expert by knowledge, skill, experience, training, or education, may testify thereto in the form of an opinion or otherwise, 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.

The Supreme Court in *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579, 592-93 (1993), laid out the standard for determining the admissibility of experts under Fed. R. Evid. 702. "The trial judge has a two-part duty to ensure that any and all scientific testimony or evidence admitted is not only relevant, but reliable."[3] *Daubert*, 509 U.S. at 589. The *Daubert* Court set forth

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[2] Rule 703, relating to the bases of expert testimony and admissibility of underlying facts or data, was nowhere addressed in AstraZeneca's motion.

[3] In *Kumho Tire Co., Ltd. v. Carmichael*, 526 U.S. 137, 149 (1999), the Supreme Court made it clear that *Daubert* applies to all types of expert testimony, scientific or not.

a non-exhaustive list of relevant factors to consider in determining whether the methodology employed is reliable. *Id.* at 593-94. The factors include whether the methods can be tested or have been subject to peer review, the potential rate of error, and whether the methods are generally accepted. *Id.* Since *Daubert*, courts have looked at additional factors, including whether an expert has properly accounted for alternative explanations (*Kumho Tire Co., Ltd. v. Carmichael*, 526 U.S. 137, 154-55 (1999)), whether the conclusions were reasoned as carefully as they would have been outside of litigation (*Norris v. Baxter Healthcare Corp*., 397 F.3d 878, 886 (10th Cir. 2005)), and whether an accepted premise is being extrapolated to unfounded claims (*Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 144-46 (1997)).

The Eleventh Circuit applied *Daubert* in *Tuscaloosa v. Harcros Chemicals, Inc*., 158 F.3d 548, 562 (11th Cir. 1998), and held that expert testimony may be admitted if three requirements are met. First, the expert must be qualified to testify competently regarding the matter he or she intends to address. *Id*. Second, the methodology used must be reliable as determined by the *Daubert* inquiry. *Id*. Third, the testimony must assist the trier of fact through the application of expertise to understand the evidence or determine a fact in issue. *Id*.

The burden of making this showing is on the party offering the expert, and admissibility must be shown by a preponderance of evidence. *McCorvey v. Baxter Healthcare Corp.*, 298 F.3d 1253, 1257 (11th Cir. 2002) (citations omitted). While "[v]igorous cross-examination, presentation of contrary evidence, and careful instruction on the burden of proof are the traditional and appropriate means of attacking shaky but admissible evidence," (*Daubert*, 509 U.S. at 596 (citations omitted)), the Court is an essential gatekeeper and in all cases "must take care to weigh the value of [expert testimony] against its potential to mislead or confuse." *U.S v. Frazier*, 387 F.3d 1244, 1263 (11th

Cir. 2004). Trial judges have considerable discretion in deciding how to evaluate expert testimony and whether it is reliable and relevant. *Kumho*, 526 U.S. at 152.

II. DISCUSSION

Plaintiffs in this MDL allege that Seroquel, an atypical antipsychotic drug approved for treatment of individuals suffering from schizophrenia and bipolar disorder, causes significant weight gain, diabetes, and other related metabolic disorders. In this *Daubert* motion, AstraZeneca seeks to exclude the testimony of three of Plaintiffs' general causation experts: a psychiatrist, an epidemiologist, and an expert specializing in pharmacology and toxicology. Each of these experts offers testimony as to whether, in general, Seroquel causes the metabolic disorders Plaintiffs complain of. AstraZeneca also seeks to prevent Plaintiffs from offering any general causation testimony by way of case-specific experts. As previously indicated, the Court has already admitted the general causation testimony of Plaintiffs' psychiatrist, Dr. William Wirshing. What follows is the Court's ruling on AstraZeneca's motion with respect to the general causation testimony of Plaintiffs' epidemiologist, Dr. Arnett.

Dr. Donna K. Arnett

Dr. Arnett, an epidemiologist, primarily proposes to testify that "Seroquel leads to clinically significant and relevant metabolic risk, including weight gain and other metabolic complications, including but not limited to hypertriglyceridemia, insulin resistance, and diabetes." *Expert Report of Donna K. Arnett, Ph.D.* (hereinafter "Arnett Am. Rep."), Doc. 1112, Ex. 17 at 3; *see also Daubert* Hr'g Tr. 14, Apr. 7, 2009 (Doc. 1404) ("Seroquel is associated with metabolic complications including but not limited to weight gain, hyperglycemia, increases in insulin levels, increases in body weight, and diabetes."). She further proposes that "the metabolic risks from Seroquel appear shortly

after treatment and throughout treatment." Arnett Am. Rep. at 3.

Dr. Arnett believes that Seroquel causes metabolic complications both by impacting glucose and insulin regulation in the body directly and by indirectly affecting the body's metabolic processes through significant and rapid weight gain. *See id.* at 3-4. With regard to her weight gain mechanism, Dr. Arnett opines that Seroquel may block histamine H1 receptors, which in turn stimulate the hypothalmic protein kinase responsible for maintaining energy balance and food intake. *Id.* at 3. In turn, according to Dr. Arnett, "weight gain is an important risk factor for diabetes development." *Id.* at 4. As support for this opinion, Dr. Arnett primarily relies on the Integrated Safety Report, which AstraZeneca submitted to the FDA in 1996 as part of the company's New Drug Application ("NDA") for Seroquel. *Id.* She observes that AstraZeneca itself concluded that the company's clinical trial data, the results of which appeared in the NDA, showed that Seroquel was associated with statistically significant weight gain. *Id.* at 5. Her independent review of the clinical data yielded the same conclusion . *Id.* at 5-6. Dr. Arnett further notes that long-term extensions of the trials included in the NDA showed that "weight gain was persistent throughout follow-up and increased with time, indicating that prolonged treatment with Seroquel could lead to substantially increased risk of metabolic toxicity." *Id.* at 6-7. Finally, Dr. Arnett points to studies conducted by AstraZeneca after the NDA was submitted, observing that they, too, "showed the consistent pattern of weight increase seen with the studies included in the NDA." *Id.* at 8. In sum, Dr. Arnett opines, the clinical data "demonstrate a large effect of Seroquel on weight gain." *Id.* at 9. Indeed, she concludes, "[b]ased on the placebo-controlled studies using doses recommended for schizophrenia, as much as 90% of the weight gain in Seroquel-treated subjects was caused by the drug." *Id.*

Dr. Arnett also believes that Seroquel can cause diabetes independent of weight gain. Arnett

Am. Rep. at 3-4 ("Seroquel affects insulin action and metabolism directly in the cell, leading to insulin resistance and alterations in lipogenesis and lipolysis, which ultimately cause progressive lipid accumulation."); *Daubert* Hr'g Tr. 14 (suggesting there may also be a "direct effect on . . . glucose and insulin mediation at the cellular level."). Dr. Arnett points to two clinical studies included in the NDA which, in her view, "clearly show the excess of glucose abnormalities in subjects randomized to Seroquel." Arnett Am. Rep. at 9. Dr. Arnett further observes that AstraZeneca's 2000 and 2007 analyses of glucose data gathered by the company during clinical trials showed elevated glucose and insulin values among Seroquel users. *Id.* at 9-10. Finally, Dr. Arnett points to several published cohort and case-control studies which showed elevated relative diabetes risk figures in Seroquel users as compared to patients receiving treatment with conventional antipsychotics. *See id.* at 10-11. At her deposition, she estimated that the relative risk of diabetes in Seroquel patients, as compared to the general population, is somewhere between 1.7 and 33, based on the observational studies she reviewed, Arnett Dep. 286:15-21, 287:3-7, and "just over 2," based on the clinical data, Arnett Dep. 286:22-25.

As noted above, Dr. Arnett's testimony may be admitted if the following three requirements are met: (1) she is qualified to testify competently regarding the matter she intends to address; (2) the methodology used is reliable as determined by the *Daubert* inquiry; and (3) the testimony will assist the trier of fact. AstraZeneca does not directly contest Dr. Arnett's qualifications to testify as to general causation, nor does the company suggest that her testimony, if admitted, would not be helpful to the jury. The bulk of AstraZeneca's motion, and thus the bulk of this order, focuses on the second of the above requirements: the reliability of Dr. Arnett's methodology.

A. Dr. Arnett's Qualifications and Experience

Dr. Arnett considers herself an expert in chronic disease epidemiology, genetic epidemiology, pharmacogenetics and study design. Arnett Dep. 8:25-9:4. She received her Master's degree in Public Health from the University of South Florida in 1987, and a Ph.D. in Epidemiology from the University of North Carolina in 1991. Thereafter she acquired a position as a postdoctoral fellow at the University of North Carolina until 1994, when she became an assistant professor of epidemiology at the school. In 1998, Dr. Arnett left North Carolina for the University of Minnesota, where she took a position first as an associate professor of epidemiology and later as the Mayo Professor of Epidemiology. In 2004, Dr. Arnett took a position as Chair and Professor of Epidemiology at the University of Alabama at Birmingham, where she remains to this day.

She is a member of several state and national professional organizations and committees, including the American Heart Association, the Society for Epidemiologic Research and the American Public Health Association. In addition, she currently holds editorial positions with several scientific journals, and routinely reviews epidemiologic research studies for publication in other respected peer-reviewed journals. She has authored or co-authored approximately 255 published peer-reviewed articles, numerous book chapters, and has served on several National Institutes of Health review panels for epidemiologic research. Given her extensive education and experience in the field of epidemiology, Dr. Arnett possesses the qualifications necessary to render a general causation opinion in this case.

B. Reliability of Dr. Arnett's Methodology

AstraZeneca attacks Dr. Arnett's methodology on numerous fronts. First, AstraZeneca contends that Dr. Arnett reached her opinion before reviewing the relevant scientific evidence, and, thereafter, cherry-picked data supporting her opinion. Next, AstraZeneca criticizes Dr. Arnett's

reliance on statistically insignificant study results and confounded data. AstraZeneca also argues that Dr. Arnett reached conclusions about observational data that are prohibited by the studies' authors. Finally, AstraZeneca contends that Dr. Arnett failed to identify reliable evidence of dose-response and physiological mechanism. Thus, AstraZeneca contests both the reliability of Dr. Arnett's process of gathering data and forming her opinion, as well as the reliability of the data upon which she ultimately based her opinion. The Court first turns to Dr. Arnett's process of gathering and evaluating the available scientific data.

1. Dr. Arnett's Accumulation and Evaluation of the Scientific Data

AstraZeneca complains that Dr. Arnett formed her opinions and drafted her expert report before she had reviewed all of the relevant scientific evidence. Instead, AstraZeneca points out, Dr. Arnett spent considerable time *after* submitting her first report reviewing additional evidence she had not previously had time to look over. In AstraZeneca's view, Dr. Arnett's attempt to later "shore up" her opinions is "a telltale sign of an opinion that does not meet scientific standards and should be excluded." Doc. 1112 at 31.

AstraZeneca also maintains that Dr. Arnett cherry-picked evidence that was favorable to her opinion while rejecting unfavorable studies without explanation. In this regard, AstraZeneca claims that Dr. Arnett cited only one observational study in her first expert report,[4] and then later cherry-picked nine other observational studies to include in her amended report, all without bothering to explain why she rejected a large body of contrary evidence. In AstraZeneca's view, Dr. Arnett's

[4] Dr. Arnett submitted her first expert report on September 11, 2008. A few days prior to her October 6, 2008 deposition, she submitted an amended report which contained an expanded discussion of the observational data with respect to Seroquel's alleged direct effects on blood-glucose. The remainder of the amended report was virtually identical to the first report.

alleged failure to consider and explain away contrary data is fatal to her opinions.

The Court agrees with AstraZeneca's general contention that the reliability of an expert's opinion should be seriously questioned when it is shown that the expert formed his or her opinion prior to reviewing scientific evidence, and, thereafter, merely cherry-picked evidence favorable to that opinion. *See Perry v. U.S.*, 755 F.2d 888, 892 (11th Cir. 1985) ("A scientist who has a formed opinion as to the answer he is going to find before he even begins his research may be less objective than he needs to be in order to produce reliable scientific results."); *Claar v. Burlington N. R. Co.*, 29 F.3d 499, 502-03 (9th Cir. 1994) ("Coming to a firm conclusion first and then doing research to support it is the antithesis of [the scientific] method."); *In re Bextra and Celebrex Mktg. Sales Practices and Prod. Liab. Litig.*, 524 F. Supp. 2d 1166, 1176 (N.D. Cal. 2007) (excluding expert's testimony where it was found that the expert "reache[d] his opinion by first identifying his conclusion . . . and then cherry-picking observational studies that support his conclusion and rejecting or ignoring the great weight of the evidence that contradicts his conclusion."). However, there is no evidence in this case that Dr. Arnett employed such a flawed methodology.

Dr. Arnett stated in her expert report that her opinion was based on her "education, training, research, experience, and review of the Seroquel New Drug Application (NDA) to the Food and Drug Administration, internal Astra Zeneca documents, the peer-reviewed medical literature, and other publicly available documents concerning Seroquel and its relationship to weight gain and other metabolic risks." Arnett Am. Rep. at 3. She further stated that she relied "primarily" on the following: "the Astra Zeneca NDA application and the related published literature, published cohort and nested case-control studies, and meta-analyses of published studies." *Id.*; *see also* Arnett Dep. 32:13-20 (testifying that she reviewed the NDA and "several other studies" published on

AstraZeneca's website in preparation for her first report). In all, Dr. Arnett spent approximately 15 hours reviewing the relevant literature before agreeing to become an expert, Arnett Dep. 64:3-8, "over 80 hours" reviewing documents and literature prior to issuing her first report, Arnett Am. Rep. at 3, and an additional 25 hours reviewing published literature after submitting her first report, Arnett Dep. 68:19-69:14.

As guidance for her review of the evidence, Dr. Arnett turned to nine principles known in the scientific community as the Bradford Hill criteria[5]. Arnett Dep. 16:20-17:11; *Daubert* Hr'g Tr. 9. Dr. Arnett described these principles as "the standard methodology used by epidemiologists and clinicians." *Daubert* Hr'g Tr. 9. Specifically, Dr. Arnett evaluated the evidence with the following considerations in mind: experimental design, strength of association, dose-response, temporality, analogy, consistency, and biological plausibility. *Daubert* Hr'g Tr. 11-14. She additionally affirmed that she was a "thorough scientist who looked at all the data available" to form her opinion, Arnett Dep. 72:22-73:4, and, thus, she reviewed "many more documents" than ultimately were cited in her

[5] The Bradford Hill considerations, enunciated by Sir Austin Bradford Hill in a 1965 speech before the Royal Society of Medicine, are a collection of "nine different viewpoints" from which to "study association before we cry causation." Hill, A.B., *The Environment and Disease: Association or Causation?* PROC R SOC MED 58(5):295-99 (May, 1965). These nine "viewpoints" are as follows: (1) strength of the association; (2) consistency (whether the association has been repeatedly observed "by different persons, in different places, circumstances and times"); (3) specificity (whether there are alternative causes of a condition); (4) temporality (whether the condition followed the exposure to the agent); (5) biological gradient (whether a dose-response relationship exists); (6) plausibility (whether the association is biologically plausible); (7) coherence (whether the association "seriously conflict[s] with the generally known facts of the natural history and biology of the disease"); (8) experiment (whether the condition improves upon removal of the hypothesized causative agent); and (9) analogy. *Id.* Sir Austin Bradford Hill additionally cautioned that "[n]one of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a *sina qua non*." *Id.* at 299. That is, Hill's viewpoints were not intended to be "hard-and-fast rules of evidence that *must* be obeyed before we accept cause and effect." *Id.*

expert report, *id.* at 89:12-14.

Dr. Arnett began her review of the evidence by sifting through thousands of pages of AstraZeneca's own clinical data in search of studies examining the effects of Seroquel on body weight, glucose metabolism, and other metabolic abnormalities. Specifically, Dr. Arnett testified that she "went through about a third of the beginning of all the NDA documents," from which she ultimately pulled the integrated efficacy report and integrated safety report, documents which enabled her to examine data that was otherwise spread throughout "7700 different documents within the NDA itself." Arnett Dep. 87:11-19. In addition, Dr. Arnett stated that she evaluated randomized controlled trial study summaries posted on AstraZeneca's website, which confirmed her initial conclusions from the NDA regarding the correlation between Seroquel use and clinically relevant weight gain. *Declaration of Donna K. Arnett, Ph.D., M.S.P.H.* (hereinafter "Arnett MDL Decl."), Doc. 1342, Ex. 3 at 3.

Dr. Arnett did not review publications stemming from the NDA, for a few reasons. First, she observed that much of the data was "not readily available in the published literature." Arnett MDL Decl. at 3; *see also Daubert* Hr'g Tr. 74-5 ("The only metabolic attribute published in the literature from the NDA was regarding body weight, and it was the last entry in the result section of every published study."). Second, as an epidemiologist, Dr. Arnett preferred to review the actual clinical data produced by AstraZeneca. In this regard, she testified: "[A]s an epidemiologist, I'm used to looking at data. And having the actual data unfiltered by any . . . author or peer-reviewed mechanism lets you see the data in its totality." *Daubert* Hr'g Tr. 77. Having concluded that the published studies stemming from the NDA were not helpful to her, Dr. Arnett returned to the NDA to investigate the "actual data that was produced during these trials." *Id.* at 75.

As pointed out by AstraZeneca, Dr. Arnett did not review every piece of clinical trial data available to her. *See, e.g.*, Arnett Dep. 91:7-24 (testifying that she did not review a large clinical trial data hard drive at all, and was able to review only "about the first 500 files" on a smaller NDA hard drive);166:1-4 (testifying that she hadn't reviewed any of AstraZeneca's clinical study reports);177:23-178:2 (admitting that there were "many more" clinical trial synopses than she was able to review on AstraZeneca's website). In her declaration, Dr. Arnett defended her failure to examine all of the evidence. There, she explained that she reviewed only a portion of the clinical trial synopses on AstraZeneca's website because she was merely using that information as confirmation of her findings with respect to the NDA. Arnett MDL Decl. at 6-7. She also stated that she did not review individual clinical study reports produced by AstraZeneca because they were "nearly impossible to identify" within the data provided to her by counsel; however, she averred that any safety data contained within those reports would also have been contained within the NDA's integrated safety report, which she reviewed in detail. *Id.* at 7. At the *Daubert* hearing she confirmed these statements, adding that she "didn't find [the clinical study reports] necessary given how I approached an assessment of causality in this particular case," *Daubert* Hr'g Tr. 66, and "didn't see [the] utility in pursuing [the remaining trial synopses] further, given the consistency of weight gain findings across the portfolio," *id.* at 68.

Though the NDA provided Dr. Arnett with ample data with respect to weight gain, her investigation of the NDA with respect to glucose abnormalities was less fruitful. Indeed, Dr. Arnett testified at her deposition that she hadn't found any AstraZeneca clinical studies in which glucose

metabolism was a primary endpoint of the study.[6] Arnett Dep. 211:24-212:9. Likewise, at the *Daubert* hearing, Dr. Arnett testified that she did not recall seeing any glucose data reported in the NDA. *Daubert* Hr'g Tr. 137 (indicating that glucose data "w[ere] collected in every study" but "were not included" in the NDA). She further observed that AstraZeneca did not publish any glucose data in the peer-reviewed literature. *Id.* at 74. Aside from the NDA, Dr. Arnett evaluated two of AstraZeneca's more recent submissions to the FDA in which the company looked more closely at Seroquel's impact on glucose regulation. *See* Arnett Am. Rep. at 9 (discussing AstraZeneca's 2000 submission evaluating "disturbances in glucose regulation in their Phase I-III program as well as post-marketing surveillance," and a 2007 clinical overview submitted by AstraZeneca to support changes to the "Core Data Sheet"). Although Dr. Arnett drew conclusions from these documents, she acknowledged that "the randomized studies were not large enough to identify diabetes as an outcome, nor were they designed to do that." *Daubert* Hr'g Tr. at 169. She thus explained that although she generally preferred to make causation conclusions based on randomized clinical trial data, "in the question regarding diabetes as a unique characteristic, the only data that I could conclusively rely on were the observational studies." *Id.*

Having concluded that the clinical trial data was largely unavailing on the question of whether Seroquel exerts direct effects on blood-glucose levels, Dr. Arnett derived the relevant published literature on the association between Seroquel and diabetes using PubMed to search for the terms "Seroquel" and "diabetes" in the paper's title or abstract. Arnett MDL Decl. at 9. In her initial report, Dr. Arnett cited only one observational epidemiologic study as support for her opinion

[6] Dr. Arnett did discuss the results of two NDA clinical trials, Studies 126 and 127, in which glucose homeostasis was a "secondary aim." Arnett Am. Rep. at 9.

that Seroquel causes diabetes. *See Expert Report of Donna K. Arnett, Ph.D.* (hereinafter "Arnett First Rep."), Doc. 1112, Ex. 16 at 10. In her amended report, and after spending 25 more hours reviewing the peer-reviewed literature, Arnett Dep. 68:19-69:14, Dr. Arnett cited nine additional studies in support of her opinion. *See* Arnett Am. Rep. at 10-11.

At the *Daubert* hearing, Dr. Arnett agreed that there are approximately twenty observational epidemiologic studies on the association between Seroquel and diabetes in the published literature, and that she cited only ten. *Daubert* Hr'g Tr. 183. Dr. Arnett explained that her report was limited to discussing studies in which Seroquel was compared to conventional antipsychotics because "[i]t's the only [comparator] that had a sufficient number of studies to report on." *Id.* at 186; *see also* Arnett Dep. 302:15-21 (testifying that her summary of the observational data with respect to Seroquel and diabetes risk only included relative risk data for Seroquel as compared to conventional antipsychotics, "because that's what's available in the literature."). She additionally explained that she rejected other studies, both those using conventional antipsychotics as comparators and those using other comparators, because she had concerns about the sample size, study design, or methodology employed by the study authors. *Daubert* Hr'g Tr. 182-184, 254-257. Though she also admitted that the fact that she limited her PubMed search to the title or abstract "was one of the reasons" some of the observational studies involving Seroquel and diabetes were not included in her report, she affirmed at the *Daubert* hearing that she had read all twenty observational studies and was prepared to discuss them. *Id*. at 188.

In sum, the record does not support AstraZeneca's contention that Dr. Arnett employed a flawed methodology in gathering and reviewing the scientific evidence on the association between Seroquel and metabolic disease. Contrary to AstraZeneca's assertions, Dr. Arnett did not approach

the evidence with a preconceived conclusion on causation. Indeed, she testified that she spent fifteen hours reviewing data even before agreeing to testify as an expert for Plaintiffs. Arnett Dep. 64:3-8. She further testified that her opinions evolved over the 80 or so hours she spent preparing her first report. *Id.* at 64:11-13. Furthermore, the record demonstrates that Dr. Arnett conducted a reasonably thorough review of the clinical data prior to issuing her first report.[7] Clearly, AstraZeneca generated an enormous amount of clinical data during its development of Seroquel. *See id.* at 87:18-19 (testifying that she believed there were 7700 different documents within the NDA itself); 91:7-10 (wherein defense counsel indicated that an "NDA Documents" hard drive provided to Dr. Arnett contained "over 28,000 documents."). Given the sheer volume of the clinical trial data produced by AstraZeneca, and the format in which they were produced,[8] Dr. Arnett's reliance on documents summarizing the results of the individual clinical trials, rather than the individual clinical study reports or synopses themselves, was not unreasonable. From there, Dr. Arnett appears to have properly focused on the studies that were based on the most reliable design, then reviewed individual clinical trial synopses for consistency, and then drawn her conclusions accordingly. *Id.* at 32:1-8 (affirming that she "would not look at the totality of all data," but instead would focus on "the data with the best design that carries the most evidence."); *Daubert* Hr'g Tr. 60 (testifying that she

[7] Dr. Arnett's amended report did not contain any new discussion of the clinical data, demonstrating that she completed her review of the NDA prior to submitting her opinions via her first expert report.

[8] Dr. Arnett twice mentioned in her declaration the difficulties she had with the format in which the clinical data was provided to her. *See* Arnett MDL Decl. at 6 (indicating that the data were provided by AstraZeneca "in a format which did not include an index of the files included, making the task much more difficult than it needed to be."), 7 ("Because of the method in which the data were provided to me through AZ it was nearly impossible to identify the individual clinical study reports.").

reviews studies that she deems the most reliable from their design "[a]s a first starting point").

Finally, Dr. Arnett's later supplementation of her first report with more extensive observational data does not necessarily indicate that Dr. Arnett did not conduct a reliable review of the available published literature before rendering her opinion. Dr. Arnett's deposition testimony makes clear that she reviewed more studies than were ultimately cited in her first report, but simply did not have time to add citations and a discussion of these studies before the report was due. *See* Arnett Dep. 180:16-23 (testifying that she reviewed observational studies other than those cited in her first report but ran out of time to include a discussion of those studies, which was why she submitted the supplemental report), 283:10-14 (indicating that she had read studies other than the one cited in her first report, she "just hadn't cited them yet"). Though the Court does not condone Dr. Arnett's failure to be complete in her first report, her subsequent testimony satisfactorily explains why she felt a supplemental report was necessary.

In sum, the record demonstrates that Dr. Arnett did not form her opinions first, and then do the research to back it up later, as AstraZeneca argues. Instead, Dr. Arnett did a reasonably thorough review of the clinical and observational data, assessing both those data that showed a causal association and those that did not, and formed her opinions over the course of that review. Moreover, Dr. Arnett confirmed that the expanded discussion of the observational data in her amended report reflected only her desire to be more complete, not her failure to review the observational studies prior to forming her opinions. Therefore, the Court cannot say that Dr. Arnett's process of reviewing the available scientific evidence on the causal connection between Seroquel ingestion and adverse metabolic effects was unreliable.

2. Dr. Arnett's Data

Aside from its criticisms of Dr. Arnett's process of gathering and reviewing the available scientific evidence, AztraZeneca criticizes the reliability of the evidence she submitted in support of her opinion as to both the physiological mechanism by which Seroquel causes diabetes and other metabolic disorders, and the dose-response relationship between the drug and these disorders. Specifically, AstraZeneca contests Dr. Arnett's reliance on confounded studies and statistically insignificant relative risk measurements, as well as her willingness to draw conclusions from studies that even the study authors themselves do not draw. Though these arguments raise important reliability considerations, none of them are sufficient to render Dr. Arnett's opinions inadmissible, as the following discussion demonstrates.

a. Mechanism

In her expert report, Dr. Arnett stated that she believes Seroquel causes diabetes both indirectly, i.e., by encouraging clinically significant weight gain, and directly, i.e., by impacting insulin action and metabolism directly in the cell. Arnett Am. Rep. at 3-4. At the *Daubert* hearing, Dr. Arnett testified as to three mechanisms she believes could be responsible for the increased incidence of metabolic disorders in Seroquel users: (1) weight gain via inhibition of H1 receptors; (2) impairment of glucose transport via effect on GLUT 1 receptors; and (3) increased glucagon secretion. *Daubert* Hr'g Tr. 207-208. AstraZeneca argues that Dr. Arnett's failure to demonstrate that medical science understands and accepts the mechanism by which Seroquel causes metabolic disorders renders her opinion speculative and, thus, inadmissible.

The Court rejects AstraZeneca's suggestion that Dr. Arnett must demonstrate a generally accepted mechanism by which Seroquel leads to diabetes and other metabolic disorders in order to raise her opinion above the speculative level. Drawing on dicta from the Eleventh Circuit's opinion

in *McClain v. Metabolife International, Inc.*, 401 F.3d 1233, 1253 (11th Cir. 2005) (citing expert's failure to offer "a reliable explanation of the physiological process by which Metabolife causes heart attacks and ischemic strokes" as one among many grounds for exclusion of his general causation opinion), AstraZeneca essentially demands that the causal mechanism be known and accepted in the medical community. However, as the *Reference Manual on Scientific Evidence* recognizes, causation can still be established even when the causal mechanism is unknown:

> Particularly in toxic tort cases, proving causation raises numerous complicated issues because the mechanisms that cause certain diseases and defects are not fully understood. Consequently, the proof of causation may differ from that offered in the traditional tort case in which the plaintiff details and explains the chain of events that produced the injury in question. In toxic tort cases in which the causal mechanism is unknown, establishing causation means providing scientific evidence from which an inference of cause and effect may be drawn.

Margaret Berger, *The Supreme Court's Trilogy on the Admissibility of Expert Testimony*, *in* REFERENCE MANUAL ON SCIENTIFIC EVIDENCE 32 (Federal Judicial Center, 2d ed. 2000).

Here, Dr. Arnett has ample scientific evidence demonstrating a cause and effect relationship between Seroquel ingestion and weight gain and diabetes. Furthermore, she offers plausible explanations of the physiological process by which Seroquel causes these metabolic conditions—explanations that have been tested and published in the scientific literature.

Weight-Mediated Mechanism

The majority of Dr. Arnett's discussion of mechanism in her expert report was devoted to weight gain. There, she opined that "[t]here is unequivocal and consistent evidence that Seroquel treatment leads to clinically and statistically significant increases in weight,"and, in turn, that "weight gain is an important risk factor for diabetes development." Arnett Am. Rep. at 4; *see also Daubert* Hr'g Tr. 51-52 (testifying that Seroquel causes weight gain and that weight gain, in turn,

causes diabetes). At her prior deposition, she testified that she generally believes that any drug that causes weight gain increases a patient's risk for diabetes, Arnett Dep. 116:18-22, and that "increased weight leads to an increased risk for diabetes across a continuum of increasing weight," Arnett Dep. 108:11-14. She was confident in this conclusion, testifying that the association between weight gain and diabetes risk is "well established" and "an accepted scientific observation." *Id.* at 111:17-112:18. She further acknowledged that it is common knowledge in the medical community that weight gain is a risk factor for diabetes. *Id.* at 115:3-6. Although she could not precisely identify the amount of weight gain necessary to trigger an increased risk of diabetes, stating that "[i]t's variable depending on the person," *id.* at 108:25-109:3, Dr. Arnett did testify that weight gain and diabetes risk increase "on a continuous graded scale. So the more weight they gain, the greater the risk," *id.* at 110:22-3.

Dr. Arnett formed her opinion about the causal association between Seroquel and clinically significant weight gain based in large part on the placebo-controlled randomized studies conducted by AstraZeneca as part of the NDA. Arnett MDL Decl. at 2. She relied heavily on these studies because placebo-controlled randomized studies are "the most optimal design to test causal hypothesis." *Id.* at 3. In her report, Dr. Arnett discussed the results of nine clinical studies from the NDA, and eleven studies conducted by AstraZeneca after the NDA was submitted, which, in her view, demonstrate that Seroquel caused significant weight gain in study participants. *See* Arnett Am. Rep. at 4-9. AstraZeneca attacks Dr. Arnett's reliance on several of these studies because they produced statistically insignificant increased relative risks.[9] The company believes that Dr. Arnett's

[9] At the *Daubert* hearing, AstraZeneca also launched a vigorous attack on Dr. Arnett's use of data derived from adverse event reports. Specifically, with respect to four clinical studies Dr. Arnett

acceptance of such studies as proof of causation "cannot be squared with accepted principles of epidemiology nor with the position of numerous courts . . . that have rejected reliance on statistically insignificant results." Doc. 1112 at 32.

Dr. Arnett understands the role of statistical significance in drawing a causal connection between a drug and a disease. She testified at her deposition that "[i]n assessing the findings of any epidemiologic study, one would want to evaluate the probability of making one of two errors in claiming an association is statistically significant. So one is to avoid a type one error, which is called statistical significance. But counterbalanced with that is the goal to avoid the type two error, which is related to statistical power. They're two interrelated concepts." Arnett Dep. 19:18-20:1. She further stated that she draws causal inferences from statistically insignificant study results when

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reported as showing a statistically significant increased risk for clinically significant weight gain in Seroquel users, it was revealed that she had relied on data compiling adverse event reports for weight gain, not data reflecting the actual number of pounds gained by each patient. Arnett Dep. 192:25-195:6 (Study 105); *Daubert* Hr'g Tr. 112-116 (Study 39); *Daubert* Hr'g Tr. 116-119 (Study 100); *Daubert* Hr'g Tr. 119-120 (Study 135). Dr. Arnett defended her use of the adverse event reports in these studies, explaining that these particular reports likely derived from patients confined to assisted living facilities, in which weight was routinely monitored by nursing staff. *Daubert* Hr'g Tr. 115. Thus, in her view, the adverse event reports were likely to accurately reflect actual weight gain in the patients studied. *Id.* She further clarified that she did not deem adverse event reporting reliable in the NDA studies involving outpatient schizophrenic patients, due to their perceived inability to accurately self-report weight gain. *Id.* at 108-9.

The Court finds Dr. Arnett's reporting of the data in her expert report somewhat misleading; her summaries of Studies 105, 39, 100 and 135 do not mention that the data reflects adverse event reports, not actual weight measurements. Nonetheless, Dr. Arnett's subsequent explanation of her process of accepting or rejecting adverse event reports as reliable evidence of weight gain suggests that her omission of the basis for her stated results was not intended to deceive. Furthermore, even excluding these four studies from Dr. Arnett's report, there is still ample reliable clinical study evidence supporting her opinion that Seroquel leads to clinically significant weight gain. Finally, the adequacy of these four studies bears on the weight of Dr. Arnett's testimony, not its admissibility. *See Quiet Technology DC-8, Inc. v. Hurel-Dubois UK Ltd.*, 326 F.3d 1333, 1345 (11th Cir. 2003) (quoting *Hemmings v. Tidyman's Inc.*, 285 F.3d 1174, 1188 (9th Cir. 2002)). Therefore, her reliance on these studies is more appropriately tested by AstraZeneca on cross-examination.

writing her own peer-reviewed articles. *Id.* at 20:6-13. In her November declaration, she asserted that statistical significance is not an "exclusive requisite for evaluation of causation." Arnett MDL Decl. at 8. Indeed, she indicated that "accepted epidemiologic methods" require more than just an assessment of a single p-value, but rather incorporate an evaluation of the confidence limits around a point estimate. *Id.* ("[T]he confidence limits around a point estimate must be interpreted with respect to the point estimate, namely points nearer to the center of the range are more compatible to the data . . . than points farther away from the center."). The *Reference Manual on Scientific Evidence* supports her assertion:

> The two main techniques for assessing random error are statistical significance and confidence intervals. A study that is statistically significant has results that are unlikely to be the result of random error, although the level of significance used entails a somewhat arbitrary determination. A confidence interval provides both the relative risk found in the study and a range (interval) within which the true relative risk resides within some (arbitrarily chosen) level of confidence.
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> . . . .
>
> There is some controversy among epidemiologists and biostatisticians about the appropriate role of significance testing. To the strictest significance testers, any study whose *p*-value is not less than the level chosen for statistical significance should be rejected as inadequate to disprove the null hypothesis. Others are critical of using strict significance testing, which rejects all studies with an observed *p*-value below that specified level. Epidemiologic studies have become increasingly sophisticated in addressing the issue of random error and examining the data from studies to ascertain what information they may provide about the relationship between an agent and a disease, without the rejection of all studies that are not statistically significant.
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> Calculation of a confidence interval permits a more refined assessment of appropriate inferences about the association found in an epidemiologic study. A confidence interval is a range of values calculated from the results of a study, within which the true value is likely to fall; the width of the interval reflects random error. The advantage of a confidence interval is that is displays more information than significance testing. What a statement about whether a result is statistically significant does not provide is the magnitude of the association found in the study or an indication of how statistically stable that association is. A confidence interval

> for any study shows the relative risk determined in the study as a point on a numerical axis. It also displays the boundaries of relative risk consistent with the data found in the study based on one or several selected levels of alpha or statistical significance.

Mary Sue Henefin, et al., *Reference Guide on Epidemiology*, *in* REFERENCE MANUAL ON SCIENTIFIC EVIDENCE 354-62 (Federal Judicial Center, 2d ed. 2000)(footnotes omitted).

The Court agrees with AstraZeneca's general premise that the reliability of an expert's opinion should be seriously questioned, and perhaps even excluded altogether, when the expert can point to *no* evidence showing a statistically significant increased risk of disease. *See Dunn v. Sandoz Pharms. Corp.*, 275 F. Supp. 2d 672, 680-81 (M.D. N.C. 2003) (rejecting expert's reliance on one epidemiologic study that showed statistically insignificant results, where the parties agreed there were no other "controlled, blinded, and statistically valid" epidemiologic studies); *Soldo v. Sandoz Pharms. Corp.*, 244 F. Supp. 2d 434, 533-34 (W.D. Pa. 2003) (finding medical experts' general causation opinions unreliable because none of the epidemiologic studies upon which they relied showed a statistically significant positive association between the drug and the disease at issue). However, here, Dr. Arnett cited several clinical studies that showed a statistically significant increased relative risk of weight gain in Seroquel users. *See, e.g.*, Arnett Am. Rep. at 5 (discussing a combined summary of Studies 4, 6, 8 and 13, which showed that the risk of clinically significant weight gain was more than three times greater in Seroquel patients than placebo-treated participants, a statistically significant relative risk). These studies were randomized placebo-controlled trials, "the optimal design for testing a hypothesized association between an exposure (or treatment) and disease . . . ." *Id.* at 1. Therefore, not only did Dr. Arnett rely on studies that show a statistically significant increased relative risk of clinically significant weight gain in Seroquel patients, these

studies were of the optimal design for testing Dr. Arnett's weight-mediated mechanism.

Dr. Arnett acknowledged that some of the clinical studies upon which she relied did not produce statistically significant relative risks. *See, e.g.*, Arnett Dep. 153:14-155:6, 164:4-165:4. However, her opinion need not be excluded on this basis, in light of the existence of other studies showing a statistically significant increased relative risk for clinically significant weight gain in Seroquel patients. The more prudent measure for testing Dr. Arnett's reliance on these studies is cross-examination.

Direct Effect Mechanism

Dr. Arnett also spent some time in her expert report discussing the evidence supporting her opinion that Seroquel causes diabetes independently of weight gain. She cited both clinical data and published observational data as support for her direct mechanism theories. Though AstraZeneca raised some notable objections to this evidence, the Court finds that Dr. Arnett's reliance on the evidence is not so unreliable as to render her opinions inadmissible.

As an initial matter, Dr. Arnett observed that "limited data were provided in the NDA related to glucose, insulin, or other biochemical indices of metabolic risk." Arnett Am. Rep. at 9. Thus, she testified that the observational data was the only source of evidence she could "conclusively rely on." *Daubert* Hr'g Tr. 169. Nonetheless, Dr. Arnett discussed the clinical glucose data contained in Studies 126,[10] 127, 135, and AstraZeneca's 2000 and 2007 submissions to the FDA, which, in her

[10] AstraZeneca criticizes Dr. Arnett's reliance on AstraZeneca's Study 126, which was later published by Vieta, E., et al., *Efficacy and Safety of Quetiapine in Combination with Lithium or Divalproex for Maintenance of Patients with Bipolar I Disorder*, J. AFFECTIVE DISORDERS 109(3):251-8 (2008). In the Vieta paper, the authors indicated that the study "was not designed to identify or confirm the emergence of diabetes" and "[g]iven the absence of definitive diagnostic testing within the design of this study, reliable and accurate determination of incidence and risk for

view, demonstrated an increased risk for diabetes independent of weight gain. Arnett Am. Rep. at 9-10 (discussing Studies 126, 127 and the 2000 and 2007 FDA submissions); *Daubert* Hr'g Tr. at 43-44 (testifying that Study 135 showed rapid increases in blood-glucose over the short term). Specifically, Dr. Arnett opined that AstraZeneca's 2000 FDA submission showed Seroquel patients were at a two- to five-fold increased risk of heightened blood-glucose over patients treated with placebo. Arnett Am. Rep. at 9-10 (noting relative risk of 1.93 (p=0.12) for heightened glucose versus placebo group and relative risk of 4.87 (p=0.116) for glucose values in excess of 200 mg/dL in short-term placebo-controlled trials). Dr. Arnett also opined that the clinical data contained within AstraZeneca's 2007 FDA submission demonstrated a two-fold increased risk of diabetes in Seroquel patients as compared to patients treated with placebo. Arnett Am. Rep. at 10 ("Not unexpectedly, given these differences in glucose and insulin resistance, the relative risk for diabetes was 2.02 (p=0.49), 95% CI 0.31-12.04).").

AstraZeneca pointed out at the *Daubert* hearing that all three of Dr. Arnett's relative risk calculations with respect to glucose values contained in the clinical data were not statistically significant. Dr. Arnett agreed, but also indicated that the studies evaluating glucose changes were not sufficiently powered[11] to detect statistical significance. *Daubert* Hr'g Tr. 129 (testifying that

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diabetes for patients enrolled in this study *is not possible*." Vieta 2008, at 260 (emphasis added). AstraZeneca claims that Dr. Arnett's independent analysis of the data gleaned from Study 126, and subsequent opinion that the results showed a positive association between Seroquel use and diabetes, impermissibly disregards the limitations cited by the study authors. The Court agrees. Dr. Arnett's use of the glucose data from the study "expands the application [of Study 126] beyond good science." *McClain*, 401 F.3d at 1247. However, this fact does not render Dr. Arnett's opinion inadmissible, as there was other reliable evidence to support her opinion.

[11] The *Reference Manual on Scientific Evidence* explains the concept of "power" as follows:

"with only one case in the placebo group [in AstraZeneca's 2007 clinical overview], it would be impossible to find statistical significance"); *id.* at130 ("[AstraZeneca's 2007 clinical overview] was not powered. So, in – every time I'm asked this and every time I respond, I will come back to the point that there was not power, which means if the effect is real, our ability to detect it is tiny. We just don't have power to detect it. It doesn't mean that it's not real."); *id.* at150-152 (testifying that the power for the studies in the 2000 FDA submission was "quite low actually"). Therefore, according to Dr. Arnett, the data "cannot be interpreted as insignificant given the power that was available to test that hypothesis." *Id.* at153-154.

AstraZeneca accuses Dr. Arnett of using the power of the studies to "magically allow" herself to rely on them as proof of causation.[12] Doc. 1112 at 34. However, it is clear from her expert

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> When a study fails to find a statistically significant association, an important question is whether the result tends to exonerate the agent's toxicity or is essentially inclusive with regard to toxicity. The concept of power can be helpful in evaluating whether a study's outcome is exonerative or inconclusive.
>
> The power of a study expresses the probability of finding a statistically significant association of a given magnitude (if it exists) in light of the sample sizes used in the study. The power of a study depends on several factors: the sample size; the level of alpha, or statistical significance, specified; the background incidence of disease; and the specified relative risk that the researcher would like to detect. Power curves can be constructed that show the likelihood of finding any given relative risk in light of these factors. Often power curves are used in the design of a study to determine what size the study populations should be.

Mary Sue Henefin, et al., *Reference Guide on Epidemiology*, *in* REFERENCE MANUAL ON SCIENTIFIC EVIDENCE 362 (Federal Judicial Center, 2d ed. 2000) (footnotes omitted).

[12] AstraZeneca also contested Dr. Arnett's failure to conduct precise power calculations for the studies she criticized for their low power. Dr. Arnett responded to this criticism in her MDL Declaration by indicating that her education and experience had equipped her with a "solid understanding of the factors that contribute to statistical power," and, as such, she was able to discern whether certain studies were not adequately powered without conducting precise calculations. Arnett

report and her subsequent testimony that Dr. Arnett was well aware that these studies, by themselves, could not constitute proof of causation. For example, in her expert report she stated that "[s]ince most of the participants in the randomized clinical trials were treated for a short period of time, the actual person-time contributed is small, and may have not yielded sufficient power to detect the excess risk of diabetes associated with Seroquel." Arnett Am. Rep. at 10. She further acknowledged in her November declaration that she looked at the clinical data on glucose "[i]n light of the totality of statistically significant data" discussed in her expert report and at her deposition. Arnett MDL Decl. at 8. Finally, at the *Daubert* hearing, Dr. Arnett acknowledged that her relative risk calculations were "one piece of a large portfolio of research findings" in her report, *Daubert* Hr'g Tr. 130, and that she could not rule out chance as an explanation for the results, "[w]hich is why, as epidemiologists, we look at multiple ways to infer causality," *id.* at 154.

As mentioned before, Dr. Arnett testified that she was unable to find sufficiently reliable clinical studies evaluating the direct effect of Seroquel on blood-glucose levels. Indeed, her failure to find a statistically significant relative risk from these data, and her observation that the studies were not adequately powered to detect statistical significance, is entirely consistent with this testimony. Thus, her attempted analysis of the clinical data on blood-glucose appears to be submitted as more of an illustrative point, rather than as direct support for her opinion. After all,

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MDL Decl. at 8. Later, in a Delaware state court declaration filed by Plaintiffs as a supplement to their response to AstraZeneca's motion in this litigation, Dr. Arnett conducted the power calculations cited by AstraZeneca, "at the request of plaintiff's counsel." *Declaration of Donna K. Arnett, Ph.D, M.S.P.H.* (hereinafter "Arnett Del. Decl."), Ex. 1 to Doc. 1339 at 8-9. Her calculations confirmed the low power of the studies. *Id.* Thus, the Court is confident that Dr. Arnett's education and experience enable her to reliably opine about the power of a study without conducting a precise power calculation.

her testimony at the *Daubert* hearing was clear: "[I]n the question regarding diabetes as a unique characteristic, the only data that I could conclusively rely on were the observation[al] studies." *Daubert* Hr'g Tr. 169.

As was previously noted, Dr. Arnett cited only one observational epidemiologic study in her first report: Guo, J.J. et al., *Risk of Diabetes Mellitus Associated with Atypical Antipsychotic Use Among Medicaid Patients with Bipolar Disorder: A Nested Case-Control Study*, PHARMACOTHERAPY 27(1):27-35 (2007).[13] In her amended report she added nine more. *See* Arnett Am. Rep. at 10-11.

As a general matter, AstraZeneca maintains that the observational studies upon which Dr. Arnett relies suffer from various degrees of confounding, and Dr. Arnett offers no explanation as to why she relies on the studies despite this confounding. The *Reference Manual on Scientific Evidence* explains:

> Even when an association exists, researchers must determine whether the exposure causes the disease or whether the exposure and disease are caused by some other confounding factor. A confounding factor is both a risk factor for the disease and a factor associated with the exposure of interest. . . . When researchers find an association between an agent and a disease, it is critical to determine whether the association is causal or the result of confounding. Some epidemiologists classify confounding as a form of bias. However, confounding is a reality–that is, the observed association of a factor and a disease is actually the result of an association with a third, confounding factor. Failure to recognize confounding can introduce a bias–error–into the findings of the study.

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[13] She also cited a case study published by Koller, et al, *A Survey of Reports of Quetiapine-Associated Hyperglycemia and Diabetes Mellitus*, J CLIN PSYCHIATRY 65:857-63 (2004). She acknowledged that case studies are "the lowest form of scientific evidence," and should never be used alone to establish causality; however, "[t]hey can be used . . . with evidence from other studies that have consistency of findings with respect to, say, risk factors or weight gain . . . They help build the case for causation." Arnett Dep. 94:4-15; *see also Daubert* Hr'g Tr. 50 ("You have to evaluate [case studies] in the totality of all of the other clinical trial evidence . . . and the observational evidence.").

Mary Sue Henefin, et al., *Reference Guide on Epidemiology*, *in* REFERENCE MANUAL ON SCIENTIFIC EVIDENCE 369-70 (Federal Judicial Center, 2d ed. 2000).

Through her testimony, Dr. Arnett has shown that she understands the concept of confounding, and appropriately considered it during her review of the observational data. For example, at her deposition, Dr. Arnett demonstrated a working knowledge of the various risk factors for diabetes that may contribute to confounding. *See* Arnett Dep. at 10:17-18 (family history), 28:11-13 (obesity), 101:6-11 (listing age, family history and obesity as "the three major" risk factors for diabetes), 101:20-103:4 (sedentary lifestyle, ethnicity, history of gestational diabetes, smoking, hypertension, schizophrenia, chronic sleep loss, stress and mood changes), 107:4-6 (alcohol abuse). Dr. Arnett also ably identified the limitations of the observational epidemiologic data upon which she relied in forming her opinions. *Id.* at 305:18-306:22 (citing sample size, length of study, reliance on administrative databases, failure to compare with non-treatment, failure to adjust for BMI, and failure to adjust for use of other drugs as potential confounders). Thus, the record demonstrates that Dr. Arnett acknowledged that the observational data were confounded, knew which other risk factors might have contributed to confounding, and evaluated the studies with these confounders in mind. Her methodology in this regard is reliable.

At the *Daubert* hearing, Dr. Arnett specifically discussed three studies in support of her opinion that Seroquel may exert a direct effect on glucose transport and insulin action in the body. The Dwyer study[14] investigated the effects of various antipsychotic drugs, including Seroquel, on glucose transport in mice. According to Dr. Arnett, the study showed that Seroquel inhibited

[14] Dwyer, D.S. and Donohoe, D., *Induction of Hyperglycemia in Mice With Atypical Antipsychotic Drugs That Inhibit Glucose Uptake*, PHARMACOL BIOCHEM BEHAV 75:255-60 (2003).

glucose transport, causing the body's cells, particularly in the liver, to "mistakenly start generating glucose in response to that blockage of glucose entering the cell," thereby leading to significant hyperglycemia. *Daubert* Hr'g Tr. 39-40.

Dr. Arnett also discussed the Smith study,[15] a rat study designed to investigate whether second generation antipsychotics, like Seroquel, have an acute effect on glucose metabolism apart from insulin resistance associated with obesity. Dr. Arnett described the results as follows: "[E]ssentially they found that these drugs ultimately lead to hepatic synthesis of glucose that leads to the hyperglycemia and that it was independent of body weight." *Daubert* Hr'g Tr. 41. She further noted that the study authors attempted to "evaluate doses that would be comparable to drug doses . . . taken by people." *Id.* at 213.

Finally, Dr. Arnett discussed the Guo study.[16] Dr. Arnett described this study as "probably the best designed study" showing diabetes in Seroquel patients in the absence of weight gain. *Daubert* Hr'g Tr. 46. Indeed, according to Dr. Arnett, the study showed a statistically significant 2.5-fold increased risk of diabetes in Seroquel patients in the absence of weight gain. *Id.* at 47. Although there was no examination of the mechanism by which the observed phenomenon occurred, Dr. Arnett believes that the study clearly demonstrates a weight-independent cause and effect relationship between Seroquel and diabetes.

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[15] Smith, G.C., et al., *Atypical Antipsychotic Drugs Induce Derangements in Glucose Homeostatis By Acutely Increasing Glucagon Secretion and Hepatic Glucose Output in the Rat*, DIABETOLOGIA 51:2309-17 (2008).

[16] Guo, J.J., et al., *Risk of Diabetes Mellitus Associated With Atypical Antipsychotic Use Among Medicaid Patients With Bipolar Disorder: A Nested Case-Control Study*, PHARMACOTHERAPY 27(1):27-35 (2007).

With respect to the Guo study, AstraZeneca points out that the authors wrote that they believed it was unclear whether the results they found linking certain atypical antipsychotics, including Seroquel, to diabetes could be attributed to the drugs themselves or other various characteristics of the study participants, such as low socioeconomic status, poor overall physical health and poor access to health care services. AstraZeneca maintains that Dr. Arnett's citation of the study in support of her opinion that Seroquel causes diabetes is "a strong indicator of unreliability." Doc. 1112 at 38.

Indeed, the reliability of an expert's opinion is properly scrutinized when the expert "draws unauthorized conclusions from limited data–conclusions the authors of the study do not make." *McClain*, 401 F.3d at 1248; *see also In re Accutane Prods. Liab.*, 511 F. Supp. 2d 1288, 1291 (M.D. Fla. 2007) ("When an expert relies on the studies of others, he must not exceed the limitations the authors themselves place on the study."). However, the Court disagrees with AstraZeneca's narrow assessment of the Guo study. Dr. Arnett testified at the *Daubert* hearing that all observational studies have limitations, and that authors have to acknowledge these limitations in order to publish their studies in the literature. *Daubert* Hr'g Tr. 233-34. Dr. Arnett further pointed out that, despite the stated limitations of the Guo study, the authors still concluded that Seroquel and other atypical antipsychotics were "consistently associated" with increased diabetes risk. *Id.* at 234. Dr. Arnett has not drawn any "overreaching conclusions" from the Guo study; rather, her use of the study as one among several studies demonstrating consistent conclusions[17] appears to be "consistent with the

[17] *See, e.g.*, Sacchetti, E., et al., *Incidence of Diabetes in a General Practice Populations: A Database Cohort Study on the Relationship With Haloperidol, Olanzapine, Risperidone or Quetiapine Exposure*, INT CLIN PSYCHOPHARMACOL 20:33-37, 35 (2005) (concluding that, despite study limitations, "after an antipsychotic drug-free interval, the groups treated with haloperidol, olanzapine,

principles of good science." *McClain*, 401 F.3d at 1247.

In sum, Dr. Arnett's inability to demonstrate the precise mechanism by which Seroquel causes certain adverse metabolic effects does not, by itself, render her testimony unreliable. As previously discussed, Dr. Arnett provided reliable scientific evidence supporting an inference of cause and effect. Further lending to the reliability of her opinion, the various mechanistic theories suggested by Dr. Arnett have been tested and their results peer-reviewed and published in the scientific literature. *See Daubert*, 509 U.S. at 594 ("[S]ubmission to the scrutiny of the scientific community is a component of 'good science,' in part because it increases the likelihood that substantive flaws in methodology will be detected."). Dr. Armett's inability to identify one of these mechanisms as *the* mechanism does not render her opinion unreliable. *See Allison v. McGhan Med. Corp.*, 184 F.3d 1300, 1312 (11th Cir. 1999) ("[T]he proponent of the testimony does not have the burden of proving that it is scientifically correct, but that by a preponderance of the evidence, it is reliable."); *In re Phenylpropanolamine (PPA) Prods. Liab. Litig.*, 289 F. Supp. 2d 1230, 1247 (W.D. Wash. 2003) ("The fact that the mechanism remains unclear does not call the reliability of the

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risperidone or quetiapine monotherapy shared a higher risk for new-onset diabetes compared to untreated subjects.");Guo, J.J., *Risk of Diabetes Mellitus Associated With Atypical Antipsychotic Use Among Patients With Bipolar Disorder; A Retrospective, Population-Based, Case-Control Study*, J CLIN PSYCHIATRY 67(7):1055-61, 1060 (2006) (concluding that "some atypical antipsychotics like clozapine, olanzapine, risperidone and quetiapine are consistently associated with a clinically important increased risk of diabetes mellitus in bipolar patients after adjustment for relevant risk factors."); Sernyak, M.J., *Association of Diabetes Mellitus With Use of Atypical Neuroleptics in the Treatment of Schizophrenia*, AM J PSYCHIATRY 159:561-66, 565 (2002) (concluding that although their study did not definitively demonstrate a causal relationship between atypical antipsychotic use and diabetes, the results were "strongly suggestive of such a relationship."); Citrome, L., et al., *Relationship Between Antipsychotic Medication Treatment and New Cases of Diabetes Among Psychiatric Inpatients*, PSYCHIATR SERV 55(9):1006-1013, 1012 (2004) (concluding that their study "lends support to the hypothesis that an association exists between second-generation antipsychotic use and the development of diabetes mellitus.").

opinion into question.")(citing *Daubert v. Merrell Dow Pharms., Inc.*, 43 F.3d 1311 (9th Cir. 1995)).

b. Dose-Response

AstraZeneca additionally attacks Dr. Arnett's opinion on the basis that she failed to come forward with reliable evidence of a dose-response relationship between exposure to Seroquel and subsequent weight gain and diabetes. AstraZeneca additionally accuses Dr. Arnett of pursuing an unreliable "no-threshold theory" with respect to the dose at which Seroquel causes harm. The *Reference Manual on Scientific Evidence* provides the following guidance on this issue:

> A dose-response relationship means that the more intense the exposure, the greater the risk of disease. Generally, higher exposures should increase the incidence (or severity) of disease. However, some causal agents do not exhibit a dose-response relationship when, for example, there is a threshold phenomenon (i.e., an exposure may not cause disease until the exposure exceeds a certain dose). Thus, a dose-response relationship is strong, but not essential, evidence that the relationship between an agent and disease is causal.

Mary Sue Henefin, et al., *Reference Guide on Epidemiology, in* REFERENCE MANUAL ON SCIENTIFIC EVIDENCE 377 (Federal Judicial Center, 2d ed. 2000).

The importance of the dose-response relationship is additionally highlighted in the Eleventh Circuit's opinion in *McClain v. Metabolife International, Inc.*, 401 F.3d 1233 (11th Cir. 2005), which makes clear that "the link between an expert's opinions and the dose-response relationship is a key element of reliability in toxic tort cases." *Id.* at 1241 n.6. Indeed, the *McClain* court stressed that "[w]hen analyzing an expert's methodology in toxic tort cases, the court should pay careful attention to the expert's testimony about the dose-response relationship." *Id.* at 1241. This is important because "[i]n toxic tort cases, scientific knowledge of the harmful level of exposure to a chemical plus knowledge that plaintiff was exposed to such quantities are minimal facts necessary to sustain the plaintiff's burden . . . ." *Id.* (quoting *Allen v. Pa. Eng'g Corp.*, 102 F.3d

194, 199 (5th Cir. 1996))(internal quotations omitted). The court, thus, cautioned that "[t]he expert who avoids or neglects [the dose-response relationship] without justification casts suspicion on the reliability of his methodology." *Id.* at 1242.

In *McClain*, the Eleventh Circuit reviewed a district court's admission of testimony by a pharmacology expert that Metabolife, an herbal weight loss supplement, caused heart attacks and strokes. In reversing the district court's ruling, the appeals court found that the expert "offered no testimony about the dose of Metabolife required to injure Plaintiffs or anyone else. He could not say how much is too much." *Id.* at 1241. Instead, the expert "said that any amount of Metabolife is too much," which, in the court's mind, "clearly contradict[ed] the principles of reliable methodology." *Id.* at 1243. Therefore, the expert's failure to offer any evidence about the dose or level of exposure at which Metabolife caused harm seriously compromised the reliability of his testimony. *Id.*

The Court rejects AstraZeneca's attempts to liken Dr. Arnett's testimony to that of the expert in *McClain*. Here, Dr. Arnett cited and discussed at least three clinical studies evaluating the magnitude of Seroquel's impact on weight and blood-glucose according to dose. For example, Dr. Arnett pointed to Study 13, the results from which she calculated that the relative risk of weight gain on Seroquel was significantly higher in patients on higher doses (300 and 600 milligrams) than for those on lower doses (75 and 100 milligrams). Arnett Am. Rep. at 5 ("In comparing low dose Seroquel (75 or 100 mg) versus placebo, the relative risk of weight gain was 3.54 (p=.06, 95% CI .95-16.1), and contrasting high dose (the dose recommended for schizophrenia), the relative risk of weight gain versus placebo was 4.77 (p=.012, 95% CI 1.34-18.2)."). Though it was revealed at the *Daubert* hearing that she likely had made mathematical errors in calculating these relative risks, Dr.

Arnett's impromptu revised calculations, and her acceptance of the revised calculations of defense counsel, still showed a more than two-fold increased risk of weight gain across all five doses studied.[18]

Dr. Arnett also pointed to Study 15 in her expert report, which evaluated the magnitude of weight gain across doses of 75, 300 and 600 milligrams. Arnett Am. Rep. at 6. She explained that AstraZeneca itself concluded from the study that the percentage of Seroquel patients who experienced clinically significant weight gain increased with increasing Seroquel dose. *Id.* Dr. Arnett additionally noted that this upward trend was statistically significant. *Id.*

In addition to her opinion that Seroquel patients experience a dose-dependent increase in body weight, Dr. Arnett believes that there is also a dose-response relationship between Seroquel and blood-glucose abnormalities. Arnett Dep. 210:22-211:1. At the *Daubert* hearing, Dr. Arnett explained the results of Study 135, which examined Seroquel's effects on blood-glucose at 300 and 600 milligram doses. *Daubert* Hr'g Tr. 45. Dr. Arnett remarked that Study 135 was "a shorter study, only eight weeks, conducted for bipolar disease. And within that short eight-week study, there was not only a large increase in glucose during the trial, but that glucose increase was dose dependent." *Id.* at 44. Specifically, the study showed that the mean increase in blood-glucose was

[18] Dr. Arnett's miscalculations appear to have stemmed from a misreading of the data with respect to the number of patients who experienced clinically significant weight gain after ingesting a placebo. *Daubert* Hr'g Tr. 104-105 (testifying that she could find no basis for her assertion in her expert report that only 2 of the 51 patients taking a placebo experienced significant weight gain, where the clinical study report showed that number as 3 out of 51). Using data from the clinical study report, Dr. Arnett agreed to trust defense counsel's math for revised relative risk calculations of 2.36 for the lower doses (75 and 150mg), and 2.17 for the higher doses (300, 600 and 750 mg). *Id.* at 104-108. With the new calculations in mind, Dr. Arnett admitted that the relative risk for the higher doses was actually numerically lower than that for the lower doses, but couldn't be sure whether the two relative risks were "statistically different." *Id.* at 108.

higher among patients on 600 milligrams than those on 300 milligrams, and was "more than double the placebo" for both doses. *Id.* at 44-45.

On the record, it is clear that Dr. Arnett neither avoided nor neglected the dose-response relationship between Seroquel and weight gain and diabetes. Unlike the expert in *McClain*, who offered *no* evidence of the dose or level of exposure at which the herbal supplement caused harm, Dr. Arnett reliably opined that Seroquel causes harm at doses varying from as low as 75 milligrams to as high as 750 milligrams. The inaccuracy of a few of Dr. Arnett's relative risk calculations does not negate an otherwise reliable methodology; rather, "in most cases, objections to the inadequacies of a study are more appropriately considered an objection going to the weight of the evidence rather than its admissibility." *Quiet Technology DC-8, Inc. v. Hurel-Dubois UK Ltd.*, 326 F.3d 1333, 1345 (11th Cir. 2003) (quoting *Hemmings v. Tidyman's Inc.*, 285 F.3d 1174, 1188 (9th Cir. 2002)).

Furthermore, nothing about Dr. Arnett's testimony supports AstraZeneca's contention that Dr. Arnett is pursuing a "no-threshold" theory with respect to the metabolic effects of Seroquel treatment. She has not offered testimony that Seroquel is harmful in *any* amount. Indeed, when asked at her deposition whether Seroquel was harmful to patients at doses of 12.5 and 25 milligrams, Dr. Arnett declined even to speculate because she had not seen any studies evaluating doses that low. Arnett Dep. 157:13-158:16; 211:2-6. Therefore, Dr. Arnett's inability to reliably establish a dose-response curve for the metabolic effects of Seroquel does not render her methodology irreparably flawed, as AstraZeneca charges; it simply reflects the limitations of the existing data. Moreover, Dr. Arnett's testimony should not be excluded simply because it does not cover all possible dosing regimens in the thousands of cases in this MDL. Effective cross-examination is the more appropriate method to test the limitations of Dr. Arnett's opinions on dose.

C. General Acceptance

Finally, AstraZeneca argues that Dr. Arnett's opinion should be excluded because it is not generally accepted in the scientific community. On this point, AstraZeneca proposes that the views of the FDA and the ADA Consensus Panel represent the "generally accepted wisdom of the medical community," on whether Seroquel causes diabetes. Doc. 1112 at 21. In this regard, AstraZeneca observes that neither entity has concluded that the scientific evidence establishes that Seroquel causes diabetes, and, accordingly, Dr. Arnett's view that there is a causal connection "stand[s] far from the mainstream scientific community." *Id.*

The Court notes that neither the FDA nor the ADA Consensus Panel has concluded that Seroquel does *not* cause diabetes. Indeed, it is apparent from Seroquel's label that the FDA believes that "the relationship between atypical antipsychotic use and hyperglycemia-related adverse reactions *is not completely understood*." Doc. 1112, Ex. 13 at 3 (emphasis added). Likewise, the ADA Consensus Panel concluded in 2004 that "[t]he risk [of diabetes] in patients taking . . . [Seroquel] is less clear; some studies show an increased risk for diabetes, while others do not." Doc. 1112, Ex. 1 at 3 (American Diabetes Association, et al., *Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes*, Diabetes Care 27:2 (Feb. 2004)(further characterizing data on the risk of diabetes in Seroquel users as "discrepant")).

Although *Daubert* suggests that "[w]idespread acceptance can be an important factor in ruling particular evidence admissible," 509 U.S. at 594, in this instance the Court gives minimal consideration to this factor in light of that fact that there appears to be no general scientific consensus as to the extent of the association between Seroquel and diabetes.

D. Assistance to the Jury

As the final step in this *Daubert* analysis, the Court must inquire as to whether Dr. Arnett's testimony would assist the jury. AstraZeneca makes no specific argument in this regard, and the Court can find no reason to exclude Dr. Arnett's testimony on this basis. The scientific evidence in these cases is complex, and likely cannot be read and understood without expert assistance. In particular, Dr. Arnett's testimony will help jurors assess the voluminous clinical trial data generated by AstraZeneca over the years. These data are central to the general causation issue, and likely cannot be evaluated by the average juror unassisted. Thus, Dr. Arnett's testimony will assist the jury.

E. Admissibility Determination

The admissibility of Dr. Arnett's general causation testimony is a close question. AstraZeneca exposed several notable weaknesses in both in Dr. Arnett's methodology and the data upon which she relied. Furthermore, AstraZeneca and the Court contended with several revised versions of Dr. Arnett's opinions, each version setting forth new supporting evidence and new insight into her methodology. The Court recognizes that the science on the relationship between atypical antipsychotic drugs and various metabolic disorders continues to evolve; however, Dr. Arnett's amendments to her opinion went beyond merely addressing new science. Indeed, as AstraZeneca pointed out, Dr. Arnett appeared to use her amended report and subsequent declarations to "shore up" her opinions after she was made aware of potential weak spots. This is not how *Daubert* is supposed to work.

In an ordinary case, an expert offers opinions and explains his or her methodology in an expert report. Then, the expert is deposed on those opinions, and a *Daubert* motion is filed by opposing counsel, if appropriate. In this case, Dr. Arnett, under an apparent time crunch, offered

preliminary opinions, and little explanation of her methodology, in her first expert report, and then sought to supplement those opinions with new data in an amended report, which was served on opposing counsel only a few days before she was deposed. *See* Arnett Dep. 69:17-71:22 (testifying that she completed her amended report at 2:00 pm the Friday afternoon before her Monday deposition). Furthermore, after the deposition had taken place, and counsel for AstraZeneca had filed the *Daubert* motion, Dr. Arnett submitted two responsive declarations (one in the MDL in November and one in a Delaware state court in February) in which she articulated additional new data supporting her opinions and further explained various aspects of her methodology.

In the end, Dr. Arnett's numerous amendments to her opinion do not appear to have caused serious harm to AstraZeneca, as the company was given a full opportunity to question Dr. Arnett about any new information contained within her declarations at the April *Daubert* hearing. In addition, the Court finds that any weaknesses in Dr. Arnett's methodology bear on the weight of her testimony, not its ultimate admissibility. Thus, AstraZeneca's attacks on Dr. Arnett's opinions should be assessed by a jury, not this Court. Accordingly, the Court concludes that Dr. Arnett's proposed general causation testimony is admissible, and, as such, she may testify at trial as to her opinion that Seroquel can cause a variety of adverse metabolic effects, including weight gain, hyperglycemia, and diabetes.

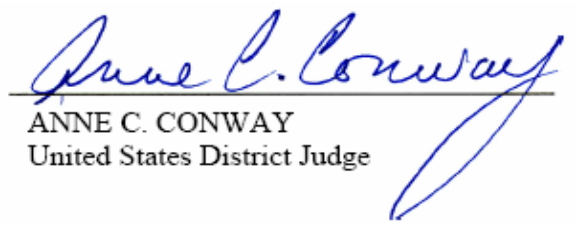
III. CONCLUSION

Based on the foregoing, it is **ORDERED** as follows: AstraZeneca's Motion to Exclude the General Causation Testimony of Plaintiffs' Generic and Case-Specific Witnesses (Doc. 1112) is **DENIED** with respect to Dr. Arnett, who shall be permitted to offer general causation testimony consistent with this opinion. The Court reserves ruling on the remainder of the motion for another day.

DONE and **ORDERED** in Chambers, in Orlando, Florida on June 18, 2009.

Copies furnished to:

Counsel of Record



ANNE C. CONWAY
United States District Judge