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. On June 18, 2009, the Court rendered an additional partial decision, holding that the general causation testimony of Dr. Donna Arnett is admissible. *See* Doc. 1465. The Court now considers the remainder of the motion: the admissibility of the general causation testimony of Dr. Plunkett, and the admissibility of general causation testimony offered by Plaintiffs' case-specific experts.

Daubert testimony was elicited from Dr. Plunkett at a hearing held on December 4, 2008. 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. Plunkett and **GRANTED** with respect to the general causation

[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).

testimony of Plaintiffs' case-specific experts.

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 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

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

(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 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,

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[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.

1256 (11th Cir. 2002) . 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. In addition, AstraZeneca 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. Wirshing, and Plaintiffs' epidemiologist, Dr. Arnett. What follows is the Court's ruling on AstraZeneca's motion with respect to the general causation testimony of Plaintiffs' toxicologist, Dr. Plunkett, as well as potential general causation testimony offered by Plaintiffs' case-specific experts.

Dr. Laura M. Plunkett

Dr. Plunkett, a pharmacologist and toxicologist, proposes to testify that the weight of the

scientific evidence supports a finding that Seroquel can cause "adverse metabolic effects," including weight gain, hyperglycemia, and an increased risk of diabetes. *Expert Report of Laura M. Plunkett, Ph.D., DABT* (hereinafter "Plunkett Rep."), Doc. 1112, Ex. 15 at 8-9. Dr. Plunkett opines that the exact mechanism by which Seroquel causes these adverse effects has not been established; however, she also notes that various mechanistic theories have support in the published observational literature. Plunkett Rep. at 10. For example, Dr. Plunkett believes that Seroquel may cause altered glucose metabolism by increasing the levels of glucose in the blood, affecting the transport of glucose within the body, or changing the way that fat cells respond to insulin. *Daubert* Hr'g Tr. 7-8, Dec. 4, 2008 (Doc. 1177). Dr. Plunkett also believes that Seroquel can cause statistically significant increases in weight. Plunkett Rep. at 10. In turn, she opines, "it's a generally accepted viewpoint in the medical literature" that drugs that cause significant amounts of weight gain also put patients at an increased risk for developing diabetes. *Daubert* Hr'g Tr. 62; *see also* Plunkett Rep. at 11 ("It is well-established in the medical literature that a clinically significant increase in body weight is a risk factor for diabetes.").

As noted above, Dr. Plunkett'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 she used is reliable as determined by the *Daubert* inquiry; and (3) her testimony will assist the trier of fact. The Court determines that Dr. Plunkett's general causation testimony meets each of the three requirements, as detailed in the following discussion.

A. Dr. Plunkett's Qualifications and Experience

Dr. Plunkett has advanced training, education and experience in the fields of pharmacology and toxicology. She additionally characterizes herself as an FDA regulatory specialist and expert

in human risk assessment.[4] She received a Ph.D. in pharmacology from the University of Georgia, College of Pharmacy in 1984. Thereafter, she served as a Pharmacology Research Associate Training Fellow at the National Institute of General Medical Sciences, where her research focused on the role of various brain neurochemical systems involved in the control of the autonomic nervous system and cardiovascular function.

At the conclusion of her fellowship in1986, Dr. Plunkett joined the faculty at the College of Medicine, University of Arkansas for Medical Sciences, as an Assistant Professor of Pharmacology and Toxicology. While there, she taught graduate courses in pharmacology, toxicology and neuroscience and conducted research in the areas of neuropharmacology and toxicology, as well as cardiovascular pharmacology and toxicology. Specifically, Dr. Plunkett focused on drugs that affect brain function, including antipsychotic drugs.

In 1989, Dr. Plunkett began work as a consultant at ENVIRON Corporation. At ENVIRON, Dr. Plunkett served clients in the areas of pharmacology, toxicology, risk assessment and regulatory strategy, and focused specifically on issues involving products or processes regulated by the Food and Drug Administration. In 1993, Dr. Plunkett became board-certified as a Diplomate of the American Board of Toxicology. Dr. Plunkett left ENVIRON in 1997 and continued her consulting career as owner of Plunkett & Associates from 1997 to 2001, and then as President of Integrative Biostrategies LLC from 2001 to the present. Over the course of her career as a consultant, Dr. Plunkett has assisted clients (both in the United States and Canada) with regulatory issues and strategies for their products, including designing preclinical and clinical studies for efficacy and

[4] At her deposition, she testified that she had expertise in pharmacology, toxicology, pharmacokinetics, risk assessment and "FDA regulatory matters." Plunkett Dep. 50:8-51:8.

safety, and assisting with labeling statements regarding a product's efficacy and safety. Many of her consulting projects over the years have involved a human risk assessment component.

Since 1982, Dr. Plunkett has authored or co-authored approximately thirty scientific publications, over forty abstracts and three book chapters. She has extensive trial experience, having testified as an expert in numerous pharmaceutical products liability cases over the last four years. *See List of Testimony for Dr. Laura M. Plunkett, Ph.D., DABT for Previous 4 Years*, Attach. to Plunkett Rep. (listing 40 cases in which she has testified as an expert witness since 2004). In view of her extensive education and experience in the fields of pharmacology and toxicology, Dr. Plunkett is qualified to opine as to whether, in general, Seroquel use is causally associated with adverse metabolic effects.

B. Reliability of Dr. Plunkett's Methodology and Supporting Data

AstraZeneca attacks Dr. Plunkett's methodology on two main fronts. First, AstraZeneca contends that Dr. Plunkett's "weight of the evidence" methodology is unreliable. Second, AstraZeneca maintains that the facts and data upon which Dr. Plunkett bases her opinion are unreliable, and, thus, insufficient to support her opinion. The Court turns to Dr. Plunkett's methodology first.

1. Dr. Plunkett's "Weight of the Evidence" Methodology

AstraZeneca contends that the "fatal flaw" in Dr.Plunkett's "weight of the evidence" methodology is that she failed to explain how and why she accepted evidence that supported her conclusion and rejected contrary evidence. In this regard, AstraZeneca points out that Dr. Plunkett only included studies in her expert report that support her opinion, while discarding or ignoring contrary evidence without proper explanation. In AstraZeneca's view, reliance on such a "biased

selection" of scientific evidence is simply not good science.

The Court agrees with AstraZeneca that an expert's failure to articulate or explain his or her process of weighing the evidence calls the expert's opinions into question. Indeed, the Court would not be able to perform an essential element of its gatekeeping function without being able to discern the expert's methods. However, here, Dr. Plunkett's methodology was made clear both during her deposition and at the *Daubert* hearing. Furthermore, the record demonstrates that Dr. Plunkett employed this methodology in these cases with the same intellectual rigor she employs in her work outside the courtroom.

At the *Daubert* hearing, Dr. Plunkett explained that she began her research by gathering what she deemed to be "the body of literature" with respect to Seroquel and diabetes: basic mechanistic studies in cell lines or animals, human clinical trial data, epidemiological data, challenge/de-challenge case reports, review articles, authoritative textbooks and the documents provided to her by Plaintiffs' counsel in relation to the litigation. *Daubert* Hr'g Tr. 15-16; *see also* Plunkett Dep. 7:19-10:10 (testifying that she typically reviews the pharmacology information on the drug, the published literature, clinical trial data and global safety information before forming her opinion in a case); Plunkett Rep. at 8-9 (indicating that she reviewed case reports, clinical data, the 2005 Seroquel product insert, a survey of adverse drug reports, epidemiological data and animal data as part of her weight of the evidence analysis). In this way, Dr. Plunkett explained, she initially considered the totality of the evidence, i.e., those studies that support her opinion and those that do not, regarding the relationship between Seroquel and diabetes. *Declaration of Laura M. Plunkett, Ph.D., DABT* (hereinafter "Plunkett Decl."), Doc. 1342, Ex. 1 at 4; Plunkett Dep. at 19:3-21:2 (testifying that she "absolutely" looks for information that both supports and contradicts her

opinion), 149:13-20 (affirming that "as any problem you look at . . . there's going to be some studies that show positive results and some studies that show negative results. What I'm looking at is what is the overall weight, what does the evidence as a whole tell me, and I have to be able to see that this evidence fits together"); *Daubert* Hr'g Tr. at 117 ("[I]n my weight of the evidence assessment I consider all of the data that's out there. I do a literature search to look for all of the available studies. And then I review each of those studies. And then from that information I form a weight of the evidence opinion."). After gathering the evidence, Dr. Plunkett employed a collection of nine guidelines commonly known as the "Bradford Hill" considerations,[5] before finally concluding that the weight of the evidence supported a conclusion that Seroquel can cause diabetes and other metabolic disorders. Plunkett Dep. 149:5-8 ("And, to me, all of that evidence put together forms this story which tells me that this drug can cause diabetes and it can cause hyperglycemia and it can cause weight gain."). Dr. Plunkett further testified that use of the Bradford Hill criteria is a "generally accepted method" that is repeatedly discussed in the scientific literature, and that she uses

[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.*

this type of assessment "as a tool every day" in her work as a human health risk assessment specialist. *Daubert* Hr'g Tr. at 8-12.

Dr. Plunkett agreed both at her deposition and at the *Daubert* hearing that there are some studies that do not support her opinion. Plunkett Dep. 267:1-9 ("I agree with you that there's some studies that show a statistically significant association and some studies that do not. But, to me, the weight of the evidence leans toward the statistically significant association."); *Daubert* Hr'g Tr. 115 (indicating that "there were studies that have hazard ratios that are statistically significant and there are some that don't"). She also testified that she only cited studies in the text of her report that she believes are supportive of her opinion. Plunkett Dep. 34:13-35:7; *Daubert* Hr'g Tr. at 109 (testifying that she listed in her expert report studies that she relied on to support her opinion but indicating that she had "reviewed many other studies"). She clarified in her declaration, however, that although she did not cite or give "detailed rebuttals" of studies that do not support her opinion, she reviewed them, included them in her reference list and was prepared to discuss the reasons she rejected them at her deposition. Plunkett Decl. at 4.

On the record before the Court, it is clear that Dr. Plunkett employed a reliable process for gathering and assessing the scientific evidence used in rendering her opinions on general causation. Dr. Plunkett began her causation inquiry by reviewing the totality of the literature on the association between Seroquel and diabetes, hyperglycemia and weight gain, including studies in which the authors found no evidence of a causal connection. At her deposition and in her declaration, Dr. Plunkett demonstrated a familiarity with the studies that contradicted her position, and was able to articulate why she did not rely on them in forming her opinion. Plunkett Dep. 205:21-209:6 (testifying that she had reviewed "Melkersson 2005" and explaining why she did not include it in

her report), 246:16-250:24 (testifying that she had reviewed "the Miller paper" but disagreed with it because "the weight of the evidence is a large group of papers which teach the opposite of this paper"), 382:18-388:24 (discussing why she did not cite the "Gianfresco 2003 study" in her report), 416:10-429:14 (discussing why she did not rely on a 2004 paper published by Cohen), 473:18-478:23 (discussing why she did not rely on Henderson's 2006 study), 554:20-568:6 (discussing Stroup 2006); Plunkett Decl. 9-10 (discussing her reasons for rejecting Henderson 2006 and Melkersson 2005). Finally, Dr. Plunkett applied a generally-accepted set of guidelines to the evidence before her, thereby arriving at her conclusion that the weight of the evidence supported a causal connection. Therefore, Dr. Plunkett's employment of a "weight of the evidence" methodology was a reliable means of assessing causation in these cases.

2. Dr. Plunkett's Supporting Data

Aside from the company's concerns about Dr. Plunkett's methodology, AstraZeneca also challenges Dr. Plunkett's opinion because she "places significant stock" in facts and data that are unreliable. In this regard, AstraZeneca asserts that Dr. Plunkett impermissibly relies on the following "hollow bricks" of evidence: (a) studies involving other atypical antipsychotic drugs; (b) case reports and case series; (c) animal studies; and (d) confounded data. AstraZeneca further argues that Dr. Plunkett's failure to come forward with evidence of the physiological process by which Seroquel allegedly causes diabetes, as well as evidence of dose-response, renders her opinion speculative and, thus, inadmissible.

a. Dr. Plunkett's Alleged "Hollow Bricks"

As an initial matter, the Court is unconcerned by Dr. Plunkett's reliance on confounded epidemiologic data. As she testified at the *Daubert* hearing, "every epidemiologic study has

limitations and confounders," and she "would never perform a causation assessment only looking at epi data," for the very reason that "every one of these studies if you want to, you could find some limitation that you have to admit is there." *Daubert* Hr'g Tr. at 121. She further affirmed that "[y]ou need to have more pieces to the puzzle," i.e, "biologic information, the mechanistic data, the clinical trial data," and "what you have to look at, as a scientist, is across several studies of different designs and different authors" to discern whether there is consistency across those studies even considering each study's limitations. *Id.*

When questioned about whether she considered the confounding factors of the studies she reviewed in forming her opinion, she responded that, "certainly when I review the studies, looking at factors that confound or don't confound is something I apply during my assessment of the literature." *Id.* at 119; *see also id.* at 27 (testifying that the presence of confounding factors is "something that I look for and it's something I consider in my analysis"); Plunkett Dep. 241:18-22 (agreeing "that you should consider the confounding factors when you interpret any study"). Indeed, she testified, judging the extent to which the studies she reviewed were confounded was made simple by the authors themselves. *See Daubert* Hr'g Tr. 27 (testifying that "in all the studies that I'm aware of in this case, the authors of the studies themselves discuss [confounding factors]. They talk about the limitations of their studies. They talk about the fact that they may or may not have been able to control, for example, for family history of diabetes.").

The Court also does not consider Dr. Plunkett's reliance on analogy studies, case reports and animal studies a threat to the reliability of her testimony. Dr. Plunkett herself stressed that each of these pieces of evidence cannot, taken on its own, constitute proof of causation. *Daubert* Hr'g Tr. at 144 ("By itself, animal data would not be evidence of causation."); Plunkett Dep. 299:2-11 ("[I]n

general, I would agree case reports by themselves would not be enough to prove causation."), 299:24-300:3 (testifying that adverse event reports by themselves should not be considered evidence of causation). However, Dr. Plunkett explained, viewed in the aggregate, and in conjunction with the other epidemiologic and clinical studies, these data help to form a clearer picture of causation. Indeed, Dr. Plunkett urged, each of these forms of evidence is critical to an assessment of the weight of the evidence under the Bradford Hill criteria. Plunkett Decl. at 4-5.

For example, Dr. Plunkett stated that data drawn from compounds that are chemically similar to Seroquel, e.g., Zyprexa and clozapine, assisted her in her evaluation of the Bradford Hill criterion of "analogy." *Id.* at 6-8. She acknowledged that drugs that are structurally similar often do not operate in the same way; however, she believed that extrapolation from data involving chemically-similar compounds is a valid part of her methodology, Plunkett Dep. 473:15-16, because "it's one of the first principles of pharmacology. The structural similarity can be predictive, and so you can start there," Plunkett Dep. 183:12-17. Thus, in her view, although data on chemically similar compounds is not conclusive evidence of causation, it can be useful when considered as part of the body of evidence on causation. Plunkett Decl. at 7-8.

Dr. Plunkett also believes that case reports serve an important role among the totality of the evidence "because often that's the first piece of information that's going to appear in the medical literature." *Daubert* Hr'g Tr. 17. Dr. Plunkett views case reports involving challenge/dechallenge data[6] as particularly important to her consideration of the Bradford Hill criteria of temporality,

[6] According to Dr. Plunkett, challenge/dechallenge data are developed when an individual shows symptoms after exposure to an agent, and those symptoms appear to resolve once exposure to the agent is discontinued. *Daubert* Hr'g Tr. 17-18.

consistency and specificity. *Id.* at 18-22 (discussing case reports in which two Seroquel patients exhibited challenge/dechallenge responses to Seroquel).

Dr. Plunkett further believes that animal studies are "the foundation for pharmacology and toxicology" and are "extremely important" and "very valid" when considered as part of the body of evidence. *Id.* at 76. While she concedes that animal studies may not be good indicators of the magnitude of the response in humans, she believes they can still serve as reliable qualitative indicators of an effect in humans. *Id.* at 76-78 ("[R]ats aren't humans, humans aren't rats. But again, qualitatively, usually you can see some synergy between the types of effects you see in humans and then when you investigate in animals."). She additionally opines that animal studies are often used to investigate the mechanism by which a drug has already shown a particular effect in humans. *Id.* at 78.

In sum, the Court concludes that Dr. Plunkett's general causation opinion is based on more than just "hollow bricks" of evidence. It is clear from the record that Dr. Plunkett relied on the types of data criticized by AstraZeneca only as confirmatory pieces of the totality of the evidence she reviewed, and did not consider any of the case studies, animal studies or analogy studies as individual evidence that Seroquel can cause diabetes. Furthermore, both at her deposition and at the *Daubert* hearing, Dr. Plunkett demonstrated a familiarity with the influence of confounding factors on the data she relied upon and ably described her reasons for accepting the data anyway. Finally, any alleged flaws in the individual studies upon which Dr. Plunkett relied, such as failure to control for various diabetes risk factors, go to the weight of the evidence, not the validity of Dr. Plunkett's methods. *See Quiet Technology DC-8, Inc. v. Hurel-Dubois UK Ltd.*, 326 F.3d 1333, 1345 (11th Cir. 2003) ("[I]n 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.")(quoting *Hemmings v. Tidyman's Inc.*, 285 F.3d 1174, 1188 (9th Cir. 2002)). Therefore, although AstraZeneca aptly identifies many of the limitations of the studies on which Dr. Plunkett relies, it appears that Dr. Plunkett appropriately took all of these limitations into account when evaluating the universe of evidence regarding the association between Seroquel and adverse metabolic conditions. AstraZeneca will have a full opportunity to explore the limitations of these studies during Dr. Plunkett's trial testimony.

b. Mechanism

Next, AstraZeneca argues that Dr. Plunkett's failure to demonstrate the physiological process by which Seroquel allegedly causes diabetes renders her opinion speculative and, thus, inadmissible. 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 suggests that *Daubert* requires an expert to show that the mechanism by which a drug induces harm is known and accepted in the medical community. However, as the *Reference Manual on Scientific Evidence* recognizes, causation can 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 acknowledged that the exact mechanism by which Seroquel carries out its harmful effects has not been established. Plunkett Rep. at 10; Plunkett Dep. 150:14-18. Yet, she offered ample scientific evidence demonstrating a cause and effect relationship between Seroquel ingestion and weight gain and diabetes. *See* Plunkett Rep. at 8 (citing five case reports, eight clinical study publications, one survey of adverse event reports, ten epidemiologic studies and one animal study as examples of the body of evidence supporting her opinion that Seroquel causes increased body weight, diabetes and "other metabolic effects"). Furthermore, she offered plausible explanations of the physiological process by which Seroquel causes these metabolic conditions—explanations that have been tested and published in the scientific literature.

Dr. Plunkett believes that Seroquel causes diabetes and other metabolic disorders both indirectly, i.e., through induction of clinically significant weight gain,[7] and by exerting a direct effect on various pathways in the body, independent of weight gain. With respect to her weight gain mechanism, Dr. Plunkett indicated in her expert report that she believes there is evidence that Seroquel causes weight gain by acting on the neurotransmitter systems in the brain that affect mood and appetite, thereby increasing caloric intake and decreasing energy expenditure. Plunkett Rep. at 10-11; Plunkett Dep. 166:11-167:18. In turn, she says, "[i]t is well established in the medical

[7] The fact that Dr. Plunkett could not predict the amount of weight gain generally attributable to Seroquel does not render her methodology unreliable, as AstraZeneca claims. Dr. Plunkett made clear that she believes that Seroquel can cause *clinically significant* weight gain, i.e., a gain of at least seven percent of an individual's body weight. Certainly, the actual amount of weight considered clinically significant varies widely among individuals depending on their baseline weight. Thus, Dr. Plunkett's methodology is not rendered unreliable merely because the amount of weight attributable to Seroquel cannot be reduced to a generally-applicable number of pounds.

literature that a clinically significant increase in body weight is a risk factor for diabetes." Plunkett Rep. at 11.

In addition to the two studies cited in her report, Dr. Plunkett discussed two additional studies underlying her weight gain mechanism at the *Daubert* hearing. The first study, published by Cope, et al.,[8] explored the effects of Seroquel on weight in mice. Dr. Plunkett explained that the authors found that Seroquel administration produced significant weight gain in mice, which was tied to increased caloric intake. *Daubert* Hr'g Tr. 75-6; Plunkett Decl. at 11. Dr. Plunkett also pointed to the results of the Vestri study,[9] a study conducted using adipocytes (fat cells). Dr. Plunkett explained that the study demonstrated Seroquel's ability to block the insulin response in fat cells, which then prevented the cells from breaking down, thereby contributing to weight gain. *Daubert* Hr'g Tr. 79-80; Plunkett Decl. at 12.

Although Dr. Plunkett believes that weight gain "is an overriding driving factor that in many individuals could be part of the reason for why you're seeing development of diabetes," *Daubert* Hr'g Tr. 147, she also sets forth a number of studies that suggest other plausible scientific theories for how Seroquel acts to produce adverse metabolic effects independent of weight gain. *See* Plunkett Rep. at 12 (citing, e.g., 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) (inhibition of glucose transport in mice); Ardizzone, T.D. *et al.*, *Inhibition of*

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[8] Cope, M.B. et al. *Antipsychotic Drug-Induced Weight Gain: Development of an Animal Model* INT. J. OBESITY 29:607-14 (2005).

[9] Vestri H.S. et al. *Atypical Antipsychotic Drugs Directly Impair Insulin Action in Adipocytes: Effects on Glucose Transport, Lipogenesis, and Antilipolysis* NEUROPSYCHOPHARMACOLOGY 32:765-72 (2007)

Glucose Transport in PC12 Cells by the Atypical Antipsychotics Drugs Risperidone and Clozapine, and Structural Analogs of Clozapine, BRAIN RES 923:82-90 (2001) (inhibition of glucose transport in rats); Newcomer, J.W. *et al.*, *Abnormalities in Glucose Regulation During Antipsychotic Treatment of Schizophrenia* ARCH GEN PSYCHIATRY 59:337-45 (2002) (weight-independent alteration of glucose regulation in humans with schizophrenia); Ebenbichler, C.F. *et al.*, *Olanzapine Induces Insulin Resistance: Results From a Prospective Study* J CLIN PSYCHIATRY 65:1436-39 (2003) (weight-independent insulin resistance in humans)); Plunkett Decl. at 11-13 (citing, e.g., Savoy, Y.E. *et al. Differential Effects of Various Typical and Atypical Antipsychotics on Plasma Glucose and Insulin Levels in the Mouse: Evidence for the Involvement of Sympathetic Regulation*, SCHIZOPHR BULL (Aug 14, 2008) (inhibition of insulin secretion in mice)). Dr. Plunkett discussed some of these studies at length, first in her declaration and then at the *Daubert* hearing. For instance, the Dwyer and Donohoe study[10] was a mouse study in which the authors looked at the effects of Seroquel and other antipsychotic medications on blood-glucose levels. *Daubert* Hr'g Tr. 81-2. According to Dr. Plunkett, the study demonstrated a significant increase in plasma glucose with exposure to Seroquel. *Id.* at 82. Dr. Plunkett also discussed another mouse study, the Savoy study,[11] which showed both plasma glucose level increases and an impaired insulin response in mice treated with Seroquel. *Id.* at 82-3.

In sum, Dr. Plunkett's acknowledgment that the mechanism by which Seroquel causes

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[10] 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).

[11] Savoy, Y.E. *et al. Differential Effects of Various Typical and Atypical Antipsychotics on Plasma Glucose and Insulin Levels in the Mouse: Evidence for the Involvement of Sympathetic Regulation*, SCHIZOPHR BULL (Aug 14, 2008).

certain adverse metabolic effects is yet unknown does not, by itself, render her testimony unreliable. As previously discussed, Dr. Plunkett 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. Plunkett 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. Plunkett'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 opinion into question.")(citing *Daubert v. Merrell Dow Pharms., Inc.*, 43 F.3d 1311 (9th Cir. 1995)).

c. Dose-Response

AstraZeneca additionally attacks Dr. Plunkett'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 development of diabetes. 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.*

Dr. Plunkett made no mention of dose-response in her expert report. *See generally* Plunkett Rep. She further confirmed at her deposition that she had not formed an opinion as to whether there was a dose-response relationship between Seroquel and weight gain or increases in blood-glucose, and that she hadn't studied it in preparing her expert report, either. Plunkett Dep. 214:9-216:6. At that time, she explained: "I don't know that we have enough . . . dose response data to be able to say that there's definitely or not a relationship." *Id.* at 214:18-20; *see also id.* at 53:24-54:1 ("I can't do [a] quantitative dose response assessment because I don't have the data that allows me to determine the threshold of events . . . ."). She added that, "to be able to dissect out dose effect might be very difficult" because "[w]hen you measure weight gain in studies, there's a lot of things you'd really need to control for in order to determine if it's a specific drug effect only." *Id.* at 214:22-215:3.

Perhaps recognizing the importance of the dose-response relationship to her expert testimony after AstraZeneca filed its *Daubert* motion, Dr. Plunkett submitted a responsive declaration, explaining why she had not previously formed an opinion on the dose-response relationship between Seroquel and diabetes and offering new evidentiary support. Dr. Plunkett began by explaining that there is little epidemiologic literature on dose-response in Seroquel patients "due to the fact that design of such a study would require enormous resources in order to recruit patients at both low and high doses of the drug, across diseases." Plunkett Decl. at 13. Therefore, Dr. Plunkett maintained, dose-response information "is generally not available." *Id.*

After recognizing that epidemiologic data on dose was limited, Dr. Plunkett then indicated that clinical trial data developed by AstraZeneca could be used to examine dose-response. Plunkett Decl. at 14. For example, she observed that AstraZeneca's Study 15 revealed a dose-response effect

on weight gain across Seroquel doses of 75, 300 and 600 milligrams. *Id.* She additionally noted that there is at least one peer-reviewed study in the scientific literature demonstrating that a mean Seroquel dose of only 80 milligrams is associated with a statistically significant increase in the risk for development of diabetes. *Id.* at 16 (citing Buse, J.B. *et al. A Retrospective Cohort Study of Diabetes Mellitus and Antipsychotic Treatment in the United States,* J. CLIN. EPIDEMIOL. 56:164-70 (2003)).

At the *Daubert* hearing, Dr. Plunkett further discussed the role of AstraZeneca's clinical trial data in determining a dose-response relationship. On direct examination, she reiterated her prior observations with regard to evidence of dose-response in Study 15, *Daubert* Hr'g Tr. at 70- 72, and further discussed AstraZeneca's 2008 FDA submission documents, which contained "additional evidence for what you have already seen in the epidemiology data, that this drug can increase fasting glucose levels in individuals across different doses," *id.* at 96. Dr. Plunkett also discussed two case reports in which patients experienced adverse blood-glucose changes at doses of 400 milligrams and 600 milligrams, respectively. *Id.* at 19-22 (discussing Domon, S.E. & Cargile, C.S., *Quetiapine-Associated Hyperglycemia and Hypertriglyceridemia,* J. AM. ACAD. CHILD ADOLESC. PSYCHIATRY 41(5):495-96 (May 2002) and Marlowe, K.F. et al., *New Onset Diabetes with Ketoacidosis Attributed to Quetiapine*, SOUTH MED J 100(8):829-31 (August 2007)).

In the ordinary toxic tort case, in which the parties often have only a few months to evaluate the expert testimony proffered by the opposing side prior to trial, Dr. Plunkett's failure to promptly form and voice an opinion on dose-response, "a key element of reliability," would likely result in exclusion of her testimony. However, the circumstances of this MDL counsel against such a result. Here, the parties have had many months to develop and examine the testimony of Plaintiffs' general

causation experts. Thus, though Dr. Plunkett's dose-response opinions were not apparent until she filed her declaration in late November 2008, AstraZeneca was able to test these opinions at the *Daubert* hearing in December, and will have ample time to prepare a response to the opinions before her trial testimony is taken.[12] This is not to say that the Court condones Dr. Plunkett's submission of new opinions and supporting evidence on dose-response two months after submitting her expert report; however, AstraZeneca suffered no apparent prejudice, as counsel for the company had ample opportunity to question Dr. Plunkett about these new opinions at the *Daubert* hearing.

Furthermore, it is worth noting that Dr. Plunkett's failure to form an opinion as to dose-response prior to her deposition may bear only on the reliability of her testimony as an expert witness in this litigation, not the reliability of her methods as a practiced pharmacologist and toxicologist. From her testimony, it is clear that in her ordinary practice, dose-response is not a "key element" of reliability, but is simply one of nine considerations that work together to inform her opinions as to causation. *See Daubert* Hr'g Tr. at 112 ("I don't like to say [dose-response is] one of the key [criteria] but certainly it's one of the nine that you must consider when you do this evaluation . . . ."). Inasmuch as she considered dose-response in this context, the Court is confident that she will "employ[] in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field." *Kumho Tire*, 526 U.S. at 152.

In sum, Dr. Plunkett's tentative approach to the issue of dose-response in this litigation does not mandate exclusion of her testimony altogether. Indeed, Dr. Plunkett acknowledged that the data

[12] The Court will facilitate preservation of the trial testimony of general causation experts by video beginning in September 2009. The parties will be notified of specific dates and times by separate order.

on dose-response were limited, and did not venture to speculate on the effect of Seroquel doses other than those specifically examined in clinical and observational studies. Furthermore, she considered dose-response as support for causation in this litigation just as she would consider dose-response in her everyday work as a toxicologist: by looking at it in the context of eight other equally important considerations. Finally, the limitations of the evidence on dose go more to the weight of Dr. Plunkett's testimony, rather than its admissibility. Any gaps in her dose-response opinion can adequately be tested through cross-examination during her trial testimony.

C. General Acceptance

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. Plunkett's view that there is a causal connection "stand[s] far from the mainstream scientific community." *Id.*

In addition, 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

AstraZeneca did not contest Dr. Plunkett's general causation testimony on the ground that it would not assist the jury, and the Court can likewise find no reason to exclude it on this basis. Indeed, the available scientific data on the relationship between Seroquel and diabetes is highly technical and, in the Court's view, could not possibly be fairly evaluated by a jury of ordinary citizens without expert assistance. Therefore, Dr. Plunkett's proposed testimony would undoubtedly be helpful to the jury on the issue of general causation.

E. Admissibility Determination

In view of the above discussion, the Court concludes that Dr. Plunkett's proposed general causation testimony is admissible, and, as such, she may present trial testimony as to her opinion that Seroquel can cause a variety of adverse metabolic effects, including weight gain, hyperglycemia, and diabetes. Accordingly, AstraZeneca's motion must be denied with respect to Dr. Plunkett.

Plaintiffs' Case-Specific Experts

Finally, AstraZeneca challenges the general causation opinions of Plaintiffs' case-specific experts, "to the extent Plaintiffs may attempt to rely upon opinions of those witnesses to bolster the flawed general causation opinions of Drs. Arnett, Plunkett and Wirshing." Doc. 1112 at 41-2. In a footnote in their response in opposition to AstraZeneca's motion, Plaintiffs indicated that they

addressed AstraZeneca's contention in their response to the company's Motion to Exclude the Specific Causation Testimony of Plaintiffs' Case-Specific Causation Witnesses. *See* Doc. 1342 n.114.[13] However, upon review of that response (Doc. 1335), the Court was unable to find any discussion in support of the admissibility of any general causation opinions that may be offered by case-specific experts. Indeed, it is unclear whether Plaintiffs intend even to elicit general causation testimony from these experts.

As previously discussed, the burden of establishing the admissibility of expert testimony is on the party offering the expert, and admissibility must be shown by a preponderance of evidence. *McCorvey*, 298 F.3d at 1256. Plaintiffs have failed to uphold this burden. Therefore, AstraZeneca's motion must be granted as to Plaintiffs' case-specific experts.

III. CONCLUSION

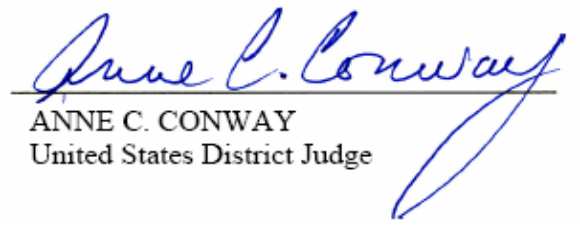
Based on the foregoing, it is **ORDERED** as follows: AstraZeneca's Motion to Exclude the General Causation Testimony of Plaintiffs' Generic and Case-Specific Witnesses (Doc. 1112) is **GRANTED** in part and **DENIED** in part. The motion is **DENIED** as to Dr. Plunkett, who shall be permitted to offer general causation testimony consistent with this opinion. The motion is **GRANTED** as to Plaintiffs' case-specific experts; Plaintiffs shall not employ case-specific experts to establish general causation at trial.

DONE and **ORDERED** in Chambers, in Orlando, Florida on June 23, 2009.

[13] Plaintiffs' original response in opposition to the present motion (Doc. 1159) was filed under seal because it contained documents designated by one or both parties as confidential. Plaintiffs later filed a redacted public version of their response (Doc. 1342) at the request of the Court.

Copies furnished to:

Counsel of Record



ANNE C. CONWAY
United States District Judge