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U.S. DISTRICT COURT
N.D. OF ALABAMA

UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF ALABAMA
SOUTHERN DIVISION

IN RE: CHANTIX (VARENICLINE) PRODUCTS LIABILITY LITIGATION

Master File No.: 2:09-CV-2039-IPJ
MDL No. 2092

This Order Relates To:

ALL CASES

MEMORANDUM OPINION and ORDER

This cause comes before the court on defendant's motions to exclude certain general causation and liability opinions offered by various plaintiffs' experts (doc. 578), and numerous briefs and evidence filed in support of and in opposition to said motions. Specifically, defendant challenges plaintiffs' designated experts Dr. Richard E. Olmstead, Dr. Curt Furberg, Dr. Shira Kramer, Dr. Antoine Bechara, Dr. Joseph Glenmullen, and Dr. Jon Wesley Boyd. In support of this motion, defendant filed one-hundred fifty-four exhibits (docs. 580 and 589), a brief titled "Introduction and Statement of Facts Relevant to all *Daubert* Motions" (doc. 582), and specific memoranda of points and authorities in support of its motion in regard to each of the six plaintiffs' experts they challenge under *Daubert* (docs. 583-588). The plaintiffs filed an "Omnibus Memorandum of Facts and Law" in opposition to defendant's motion (doc. 601), briefs in opposition to the motion in regard to each challenged expert (docs. 603-608), and approximately two hundred and fifteen exhibits (doc. 609). Thereafter, the defendant filed an additional thirteen exhibits and four more

depositions (docs. 618, 626), an introductory statement relevant to all of its reply memoranda (doc. 619), and reply memoranda in support of its motion to exclude specific experts of plaintiffs (docs. 620-625). The court has read all of the above pleadings and other submissions.

The defendant's motion was set for hearing on July 24, 2012, and a hearing was held at that time at which the defendant was present by and through its counsel of record and the plaintiffs were present by and through their designated counsel of record. The court heard argument in support of the defendant's motion and in opposition to said motion from the plaintiffs. Having carefully considered all of the filed pleadings, the exhibits and other evidence, the arguments of counsel and the relevant law, the court finds as follows:

RELEVANT FACTUAL BACKGROUND

As the court set forth in its Memorandum Opinion and Order of July 23, 2012, this is a multidistrict product liability action concerning the drug Chantix,[1] touted by defendant as a medication to aid in smoking cessation. The Food and Drug Administration (FDA) approved Chantix for sale in the United States in May 2006. Master Consolidated Complaint (doc. 36), at ¶ 17. Chantix works by reducing nicotine cravings in smokers trying to quit both by blocking nicotine from

[1]The generic name of the drug is varenicline.

reaching receptors in the brain and also by causing a steady release of dopamine in the brain. *Id.*, ¶ 26.

According to the plaintiffs, Chantix causes depression and other psychiatric disorders, some so severe that reports of suicide and attempted suicide from Chantix use have been made. Master Consolidated Complaint, ¶¶ 31-32. The plaintiffs allege defendant either knew or should have known about such side effects, but for defendant's intentional failure to design studies which were reflective of their targeted population. Master Consolidated Complaint, ¶¶ 27-31, 33-38. The defendant denies there is any merit to such allegations, and asserts that numerous studies show the side effects of Chantix to be in line with those of other nicotine replacement therapies (NRTs), such as nicotine patches.

As well explained by the District Court of Massachusetts,

> In order to prevail in a pharmaceutical personal injury case, a plaintiff must establish two types of causation: general and specific. *In re Bextra and Celebrex Mktg. Sales Practices and Prod. Liab. Litig.*, 524 F.Supp.2d 1166, 1171-72 (N.D.Cal.2007) (consumers alleging cardiovascular injury in a products liability suit against drug manufacturer); *In re Rezulin Prods. Liab. Litig.*, 369 F.Supp.2d 398, 401-02 (S.D.N.Y.2005) (diabetes patients alleging liver injuries in products liability actions against drug manufacturer). As explained in the Federal Judicial Center's *Reference Manual on Scientific Evidence,* "General causation is established by demonstrating, often through a review of scientific and medical literature, that exposure to a substance *can* cause a particular disease.... Specific, or individual, causation, however, is established by demonstrating that a given exposure *is the* cause of an individual's disease...." Mary Sue Henifin et al., *Reference Guide on Medical Testimony*, in *Reference Manual on Scientific*

> *Evidence* 439, 444 (Fed. Judicial Ctr. 2nd ed.2000) (hereinafter "Reference Guide on Medical Testimony"). Only general causation -whether Neurontin is capable of causing suicide-related events-is at issue in this motion.

In re Neurontin Marketing, Sales Practices, and Products Liability Litigation, 612 F.Supp.2d 116, 123 (D.Mass.2009) (emphasis in original). Similarly, for purposes of the pending motion and this opinion, the court considers only whether Chantix is capable of causing the adverse neuropsychiatric events alleged.

As set forth in greater detail below, the plaintiffs' challenged experts each offer an opinion about either the reasons Chantix allegedly causes depressive or suicidal symptoms, the method by which these side effects could occur, or whether defendant should have recognized this drug had the potential to cause the alleged side effects. Defendant's challenge to each of the six experts in question can be summarized as a challenge to the expert's methodology in reaching certain conclusions, or a challenge to the reliability of those conclusions, for a variety of reasons, as set forth in detail herein.

The parties do not dispute, and the court has previously found that in November 2007 the "adverse reactions" section of the label was updated to reflect post-marketing reports of depression, agitation, changes in behavior, suicidal ideation and suicide in patients taking Chantix. *See* defendant ex. 2 (doc. 590-2). In January 2008 the label was again updated, this time adding a "warnings" section

which reflected "[s]erious neuropsychiatric symptoms have occurred in patients being treated with Chantix." Defendant ex. 3 (doc. 590-3) at 10. The warning continued that people taking Chantix "should be observed for ... changes in behavior, agitation, depressed mood, suicidal ideation and suicidal behavior." *Id.* That label also warned that such symptoms had been reported in patients taking Chantix, that individuals with serious psychiatric illnesses were excluded from pre-marketing studies of Chantix, and that the safety of Chantix had not been established in individuals with such pre-existing illnesses. *Id.* The label was again strengthened in May 2008 to state that patients taking Chantix who develop neuropsychiatric symptoms should stop taking the drug and contact their health care provider immediately. Defendant ex. 4 (doc. 590-4) at 10.

In addition to the black box warning added in July 2009, a "Medication Guide" was added to the package inserts at the same time, to inform patients that "[s]ome people have had changes in behavior, hostility, agitation, depressed mood, and suicidal thoughts or actions while using CHANTIX ..." and that if "you [or] your family" notice such symptoms or changes in behavior, "stop taking CHANTIX and call your healthcare provider right away..." Defendant ex. 5 (doc. 590-5), at 1. The "black box warning" and the Medication Guide have remained unchanged since July 2009.

In October 2011 the FDA released a Safety Announcement which reported that the FDA reviewed two FDA-sponsored studies evaluating the risk of neuropsychiatric injury from Chantix. Defendant ex. 6 (doc. 590-6). That Announcement states

> Neither study found a difference in risk of neuropsychiatric hospitalizations between Chantix and ...NRT.... However, both studies had a number of study design limitations, including only assessing neuropsychiatric events that resulted in hospitalization, and not having a large enough sample size to detect rare adverse events .... Although these two studies did not suggest an increased risk of neuropsychiatric events that result in hospitalization, they do not rule out an increased risk of other neuropsychiatric events with Chantix.

Id., at 1 of 3. That Announcement further states that "[o]verall, FDA has determined that the current warnings in the Chantix drug label, based on post-marketing surveillance reports, remain appropriate." *Id*., at 2 of 3.

The court ruled that the July 2009 label change is sufficient as a matter of law for warnings regarding neuropsychiatric injuries, thus the court considers the pending motion to exclude certain of plaintiffs' experts in light of its prior ruling on the label sufficiency.

STANDARD OF REVIEW

Rule 702, Federal Rules of Evidence, as construed by the United States Supreme Court in *Daubert v. Merrell Dow Pharmaceuticals, Inc*., 509 U.S. 579, 113 S.Ct. 2786, 125 L.Ed.2d 469 (1993), requires expert scientific evidence to be

both reliable and relevant pursuant to Rule 702, such that it appropriately assists the trier of fact. *See e.g., United States v. Henderson*, 409 F.3d 1293, 1302 (11th Cir.2005). Rule 702 requires that such evidence or testimony "assist the trier of fact to understand the evidence or to determine a fact in issue." *Daubert*, 509 U.S. at 591, 113 S.Ct. at 2795. The Rule, in respect to all such matters, "establishes a standard of evidentiary reliability." *Id*., 509 U.S., at 590, 113 S.Ct. at 2795. It "requires a valid ... connection to the pertinent inquiry as a precondition to admissibility." *Id*., 509 U.S. at 592, 113 S.Ct. at 2796. In other words, the evidence must be relevant to issues in the case.

Where such testimony's factual basis, data, principles, methods, or application is called sufficiently into question, the trial judge must determine whether the testimony has "a reliable basis in the knowledge and experience of [the relevant] discipline." *Kumho Tire Co., Ltd. v. Carmichael*, 526 U.S. 137, 149, 119 S.Ct. 1167, 1175 (1999) (citing *Daubert,* 509 U.S. at 592, 113 S.Ct. 2786). Faced with a proffer of expert scientific testimony, the trial judge must determine at the outset whether the expert is proposing to testify to (1) scientific knowledge that (2) will assist the trier of fact to understand or determine a fact in issue. This entails a preliminary assessment of whether the reasoning or methodology underlying the testimony is scientifically valid and of whether that reasoning or methodology properly can be applied to the facts in issue. *Daubert*, 509 U.S. at 592-593, 113

S.Ct. at 2796. This primary assessment required by courts has become known as a "gatekeeping function" in which the court should admit testimony only if it is reliable and relevant. *Rink v. Cheminova, Inc.*, 400 F.3d 1286, 1291 (11th Cir.2005).

Because the plaintiffs' experts' methodology is challenged by the current motion, the burden falls to the plaintiffs to establish that their experts' testimony will be reliable. To make this determination, the court must consider whether (1) the expert is qualified to testify competently regarding the matter he intends to address; (2) the methodology through which the expert reached his conclusion is sufficiently reliable as determined by the inquiries mandated by *Daubert*; and (3) the testimony will assist the trier of fact, through the application of scientific expertise, to understand the evidence or determine a fact in issue. *See United States v. Douglas*, 489 F.3d 1117, 1124-25 (11th Cir.2007). Even given these considerations, the inquiry required by *Daubert* is meant to be a "flexible one," and expert testimony which does not meet all or most of the *Daubert* factors may still be admissible based on the specific facts of a particular case. *United States v. Brown*, 415 F.3d 1257, 1267-68 (11th Cir.2005).

> Our emphasis on the word "may" thus reflects *Daubert's* description of the Rule 702 inquiry as "a flexible one." 509 U.S., at 594, 113 S.Ct. 2786. *Daubert* makes clear that the factors it mentions do not constitute a "definitive checklist or test." *Id.*, at 593, 113 S.Ct. 2786. And *Daubert* adds that the gatekeeping inquiry must be "'tied to the

> facts'" of a particular "case." *Id*., at 591, 113 S.Ct. 2786 (quoting *United States v. Downing*, 753 F.2d 1224, 1242 (3rd Cir.1985)).

Kumho Tire Co., Ltd. v. Carmichael, 526 U.S. 137, 150, 119 S.Ct. 1167, 1175 (1999).

In determining the reliability of a particular scientific expert opinion, the court must consider, to the extent possible: "(1) whether the expert's theory can be and has been tested; (2) whether the theory has been subjected to peer review and publication; (3) the known or potential rate of error of the particular scientific technique; and (4) whether the technique is generally accepted in the scientific community." *Quiet Tech. DC-8, Inc. v. Hurel-Dubois UK Ltd.*, 326 F.3d 1333, 1341 (11th Cir.2003) (citing *McCorvey v. Baxter Healthcare Corp*., 298 F.3d 1253, 1256 (11th Cir.2002)). "Notably, however, these factors do not exhaust the universe of considerations that may bear on the reliability of a given expert opinion, and a federal court should consider any additional factors that may advance its Rule 702 analysis." *Id.* (citing *Kumho Tire Co.*, 526 U.S. at 150, 119 S.Ct. 1167). The court's focus is solely on the principles and methodology, not on the conclusions they generate. Therefore, whether the proposed testimony is scientifically correct is not a consideration for this court, but only whether or not the expert's testimony, based on scientific principles and methodology, is reliable. *Allison v. McGhan Medical Corp.*, 184 F.3d 1200, 1312 (11th Cir.1999). A "district court's gatekeeper role

under *Daubert* 'is not intended to supplant the adversary system or the role of the jury.'" *Maiz v. Virani*, 253 F.3d 641, 666 (11th Cir.2001) (quoting *Allison*, 184 F.3d at 1311). "[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." *Allison*, 184 F.3d at 1311 (quoting *Daubert*, 509 U.S. at 596, 113 S.Ct. 2786).

The correctness of an expert's conclusions is thus left to the trier of fact to determine. *See e.g., U.S. v. Brown*, 415 F.3d at 1267, citing *U.S. v. Copeland*, 20 F.3d 412, 413 (11th Cir.1994). Accordingly, a district court may not exclude an expert because it believes one expert is more persuasive than another expert. *Rink*, 400 F.3d at 1293. In evaluating the reliability of an expert's method, however, a district court may properly consider whether the expert's methodology has been contrived to reach a particular result. *Rink,* 400 F.3d at 1293; citing *Joiner*, 522 U.S. at 146, 118 S.Ct. at 519 (affirming exclusion of testimony where the methodology was called into question because an "analytical gap" existed "between the data and the opinion proffered").

In sum, the court may admit relevant expert testimony if it finds that (1) the expert is qualified to testify about the matters he or she intends to address; (2) the methodology used by the expert to reach his or her conclusions is sufficiently reliable; and (3) the expert's testimony will assist the trier of fact through the

application of scientific, technical, or specialized expertise, to understand the evidence or to determine a fact in issue. *McCorvey v. Baxter Healthcare Corp*., 298 F.3d 1253, 1257 (11th Cir.2002) (citing *Maiz v. Virani*, 253 F.3d 641, 644 (11th Cir.2001)). See also *Rink*, 400 F.3d at 1291-1292 (citing *City of Tuscaloosa v. Harcros Chems, Inc.*, 158 F.3d 548, 562 (11th Cir.1998).

LEGAL ANALYSIS

The defendant challenges five of the contested plaintiffs' experts[2] based on the argument that he or she "has no reliable basis to conclude that there is a statistical association between the use of Chantix and serious neuropsychiatric events and no reliable basis to conclude that any such association reflects a causal relationship." *See* doc. 578. In other words, the defendant challenges the methodology and hence the reliability of these experts' opinions. Defendant also seemingly expects the plaintiffs to prove their case at this juncture, framing many of their arguments for excluding plaintiffs' experts in terms of alleged failures to establish that Chantix ***did*** cause the injuries in question. However, the court finds the relevant question for purposes of a *Daubert* inquiry to be whether Chantix ***can*** cause the injuries in question.

[2]The defendant does not challenge the opinions of Dr. Antoine Bechara on these particular grounds.

Daubert offers four non-exclusive factors that courts may consider in evaluating the reliability of an expert's testimony: (1) testability; (2) error rate; (3) peer review and publication; and (4) general acceptance. 509 U.S. at 593–95; *J & V Development, Inc. v. Athens-Clarke County*, 387 F.Supp.2d 1214, 1223 (M.D.Ga. 2005). However, the trial court has "considerable leeway" in deciding which tests or factors to use to assess the reliability of an expert's methodology. *See Kumho Tire*, 526 U.S. at 150–52.

A. Dr. Richard E. Olmstead

Defendant complains that Dr. Olmstead "has no reliable basis to conclude that his analyses demonstrate a valid statistical association between Chantix and depression." *See* doc. 583 at 1. Specifically, the defendant asserts that Dr. Olmstead's methodology failed to account for the background risk of suicide among smokers, without consideration of Chantix, that his analyses are based on unreliable methods, and that he used a test that is not generally accepted within the scientific community. *Id*., at 1-2. Although defendant faults Dr. Olmstead's methods in arriving at his opinions, the defendant does not challenge Dr. Olmstead's qualifications as an expert in his field, specifically psychometrics and applied statistics, nor does defendant challenge Dr. Olmstead's claim of eighteen years

experience with clinical trials involving nicotine and tobacco research.[3] Expert Report of Dr. Olmstead, plaintiff ex. 016189 (submitted as doc. 609-167), at 2.

The plaintiffs respond that Dr. Olmstead will assist the jury in understanding data from defendant's clinical program for Chantix testing, as well as testify regarding whether Chantix is causally associated with an increased risk of depression and depressed mood, and when reasonable evidence of this association existed, based on the clinical trial data Pfizer had at various points in time. Plaintiff's response (doc. 608) at 1-2. In fact, plaintiffs stress that Dr. Olmstead has taken the very data defendant submitted to the Food and Drug Administration (FDA) to have Chantix approved, and analyzed it.

Of the four factors suggested by *Daubert* for a court to consider when evaluating reliability, the defendant does not suggest that Dr. Olmstead's analysis is not testable, has a high rate of error based on the data he used, was not subjected to peer review or is not based on generally accepted methods. Rather, the defendant complains that Dr. Olmstead did not use all of the data available (doc. 583 at 5). According to the plaintiffs, Dr. Olmstead focused on the very data defendant used as its "Primary Safety Cohort." Plaintiffs' response (doc. 608), at 11, citing

[3]Defendant asserts Dr. Olmstead is not a professor and does not hold a medical degree, Dr. Olmstead is an Associate Research Psychologist at UCLA, holding dual Bachelor of Science degrees in Mathematics and Psychology, and a Ph.D. in Psychology with a specialization in Psychometrics. He has taught statistics and research methods at universities at the undergraduate and graduate levels, and acts as a consultant with companies for research methods and designs, particularly pharmaceutical and medical device companies. Additionally, he has co-authored publications in the area of nicotine dependence and others. Expert Report of Olmstead, at 1.

Summary of Clinical Safety, plaintiff ex. 000112 (doc. 609-25). Clearly, the defendant's argument goes to the weight a jury should afford Dr. Olmstead's testimony, and not its admissibility. "Vigorous 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, 113 S.Ct. 2786.

The defendant challenges Dr. Olmstead's methodology as well, asserting that his combining of data from controlled and uncontrolled trials somehow "tainted" that data (doc. 583 at 7). Again, the argument goes to the weight of his testimony, not its admissibility. Although the defendant offers that other studies excluded the data relied on by Dr. Olmstead in counting depression-related events, the defendant may argue this on cross-examination.[4] Nothing inherent in the defendant's objections to Dr. Olmstead's methodology addresses the reliability of his findings. The fact that no other researcher combined data in the manner Dr. Olmstead did does not make Dr. Olmstead's data necessarily flawed. Rather, these and the other objections defendant has to Dr. Olmstead's report are matters of credibility, not reliability, and are strictly within the province of the jury.[5] *See e.g. Quiet Tech DC-*

[4]Defendant also argues that because Dr. Olmstead combined open label data with placebo controlled data, his results were erroneous. However, as pointed out by plaintiffs at oral argument, Dr. Olmstead used this method because the defendant not only did so, but used the published results of such methodology to support its application for FDA approval.

[5]Also in this category is defendant's complaint that Dr. Olmstead used data predating 2007 and did not consider later, larger studies. Given that the plaintiffs offer Dr. Olmstead in

8, Inc. v. Hurel-Dubois UK, Ltd., 326 F.3d 1333, 1341 (11th Cir.2003). *See also Kumho Tire,* 526 U.S. at 153, 119 S.Ct. 1167 (stating that if an expert's testimony is within "the range where experts might reasonably differ," the jury, not the trial court, should be the one to "decide among the conflicting views of different experts."

The defendant also complains that Dr. Olmstead and other of plaintiffs' experts failed to consider background risk, *i,e.*, the fact that people not trying to quit smoking also suffer from depression and/or commit suicide. However, the case defendant relies on for this proposition, *In re Trasylol Products Liability Litigation*, 2010 WL 4052141 (S.D.Fla.2010), actually found the expert's opinion in question there admissible, noting such issues were matters for a jury to consider. *Id*., at 2 The language from this case defendant cites in support of its proposition that the failure to consider background risk made expert testimony inadmissible, was quoted by the *In re Trasylol* court in a footnote. *Id.*, n. 4. Specifically, the court quoted it directly from the defendant's brief, before finding such argument to be without

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part to testify when reasonable evidence of the alleged Chantix-neuropsychiatric injury existed, based on the clinical trial data Pfizer had at various points in time, logic dictates that Dr. Olmstead would consider defendant's clinical data at specific points in time. Defendant argues that later data does not support an earlier finding, but again, this is an issue of credibility left for consideration by a jury. Defendant also, and somewhat contradictingly, argues that rates of depression reports are higher in the more recent Chantix trials which Dr. Olmstead did not consider. *See* doc. 583, at 14. At any rate, because Dr. Olmstead is offered for the purpose of what defendant should have known from its own data, defendant's assertion that Dr. Olmstead "cherry-picked" data is without merit.

merit.[6] Defendant also relies on *McClain v. Metabolife Intern., Inc*., for the proposition that "courts in the Eleventh Circuit routinely exclude expert opinions that rely on uncontrolled data and fail to take background risk into account. As stated above, the *Trasylol* court simply did not do so. In *McClain*, the Eleventh Circuit cautioned that

> A reliable methodology should take into account the background risk. The background risk is not the risk posed by the chemical or drug at issue in the case. It is the risk a plaintiff and other members of the general public have of suffering the disease or injury that plaintiff alleges *without* exposure to the drug or chemical in question.

McClain, 401 F.3d 1233, 1243 (11th Cir.2005) (emphasis in original). Dr. Olmstead's methodology satisfies this requirement. He states he considered the data used by defendant to reach his conclusion that "the incidence of certain neuropsychiatric symptoms including depressed mood disorders and disturbances ... should have merited additional scrutiny and concern by Pfizer..." Expert Report of Olmstead (plaintiff ex. 016189), at 6. He then sets forth the data sets considered by him, which compared side effects from Chantix to placebo for a variety of psychiatric and other disorders. *Id.* at 6-15. In fact, Dr. Olmstead sets forth the various methodologies he employed to calculate the increase in risk of various

[6]The court did state, however, that "Bayer's arguments in favor of exclusion are either misdirected or directed at the weight of the opinions rather than their admissibility: vigorous cross-examination and the presentation of contrary evidence will be the appropriate means of attacking them." *In re Trasylol*, 2010 WL 4052141, at 5, (citing *Quiet Tech*., 326 F.3d at 1341). Defendant's representation that this case supports a proposition otherwise is simply incorrect. *See* defendant's memorandum of points (doc. 583) at 23.

neuropsychiatric injuries from taking Chantix as compared to placebo. Thus, he accounted for background risk in the identical manner the defendant did.[7] Unlike the expert before the court in *McClain*, Dr. Olmstead is not analogizing from one drug to another to establish negative reactions from a medication. *See McClain*, 401 F.3d at 1246.

In consideration of the foregoing, the motion to exclude is **DENIED** as to Dr. Olmstead.

B. Dr. Curt Furberg

Dr. Furberg is both a medical doctor, albeit admitted to practice in Sweden, and holds the equivalent of a Ph.D. from a Swedish University. Expert Report of Dr. Furberg, ¶ 1, submitted as plaintiff ex. 016174. More importantly, Dr. Furberg worked for the National Institute of Health ("NIH") in Maryland, including serving as the Chief of the National Heart, Lung and Blood Institute of the NIH from 1979 to 1985. *Id.* Thereafter, he served as Professor of Medicine at Wake Forest University School of Medicine. Upon establishment of the Department of Public Health Sciences in 1989, he was appointed Chairman of it. During his tenure, that

[7]Again, the cases defendant offers in support of its proposition that Dr. Olmstead's methodology was unreliable are wholly distinguishable. For example, in *Sumner v. Bioment*, Inc., 434 Fed.Appx. 834, 842 (11th Cir.2011), the Court affirmed the trial court's disallowance of an expert because the expert himself testified that he had never read of an instance in the scientific literature which supported his theory because one had never been written about or studied. That is a far cry from the evidence before this court. *Jaquillard v. Home Depot U.S.A, Inc.*, 2012 WL 527421 (S.D.Ga.2012), concerned expert testimony regarding the safety of watering plants at a time customers were present in a store. The court disallowed the testimony because it was based on a "Safety Hierarchy" that had no known application to slip and fall cases.

Department grew to include separate sections for Epidemiology, Biostatistics and Social Sciences and Health Policy. Dr. Furberg remains as a Professor at Wake Forest. *Id*., at ¶¶ 3-4. He is a past charter member of the FDA Drug Safety and Risk Management Advisory Committee, has testified as an expert on drug safety on two occasions before Congress, has authored numerous publications on clinical trials, has co-authored a text book about clinical trials and written hundreds of articles and book chapters on other topics. *Id*., at ¶ 6-16.

Defendant asserts this court should exclude Dr. Furberg's opinions about whether defendant misled the FDA, "similar to the district court in the *Rezulin* litigation. *See In re Rezulin Prods. Liab.Litig*., 309 F.Supp.2d 531, 543 n. 32, 560 (S.D.N.Y.2004) (excluding Dr. Furberg's 'personal opinion[s] about what standards [he] believes should apply to pharmaceutical company conduct' as speculative)." Defendant's memorandum to exclude (doc. 584) at 1. That court was considering Dr. Furberg's proposed testimony concerning what standards the FDA should impose on pharmaceutical companies, an issue not before this court. *In re Rezulin*, 309 F.Supp.2d at 560 (where "Dr. Furberg admitted that the efficacy data for Rezulin met FDA standards ... [b]ut he proposes to testify that the FDA should 'go beyond' this criterion to require that diabetes drugs should be shown to "reduce macrovascular complications...," holding that such testimony would not help the fact-finder to determine a fact issue in that litigation).

According to defendant's memorandum concerning Dr. Furberg, he considered primarily adverse event reports. *See* doc. 584 at 4. According to the plaintiffs, this is simply untrue. *See* plaintiffs' memorandum in opposition to defendant's motion to exclude (doc. 605), at 10, reciting a variety of studies, reports and materials considered by Dr. Furberg. According to Dr. Furberg, he considered "various clinical studies and materials" before concluding that pre-FDA approval clinical trials were small and involved carefully selected patients. Expert Report of Furberg, at ¶¶ 30-31. Specifically, Dr. Furberg opined that

> The exclusionary criteria resulted in underestimating the overall risk of serious neuropsychiatric adverse events. As a result, the initial drug label was misleading and failed to highlight or provide adequate information about the harmful effects that may be associated with varenicline. Not surprisingly, soon after the drug was marketed, there was a dramatic increase in serious neuropsychiatric adverse events reported for varenicline.

Id., at ¶ 31. As Dr. Furberg explains this, by excluding the segment of the population with prior psychiatric conditions, defendant underestimated the overall risk of neuropsychiatric adverse events, causing the initial drug label to be misleading. *Id.* After the drug entered the market, the European regulatory agency (EMEA) informed the FDA that the EMEA had concerns over side effects of varenicline. *Id.,* at ¶ 32. Hence, Dr. Furberg considered reports of adverse events, studies linking suicidal behavior and smoking cessation treatments, and FDA's reviews, to conclude that Chantix causes adverse neuropsychiatric symptoms such

as suicidal behavior, depression, and violence. *Id.*, at ¶¶ 33-38, 48. He asserts this "serious adverse drug effect was known to Pfizer prior to regulatory approval of varenicline by the FDA" and that Pfizer failed to inform the FDA of the same. *Id.*, at ¶ 48.

Much of the defendant's criticism of Dr. Furberg stems from his failure to discuss matters favorable to the defendant in his expert report. For example defendant asserts Dr. Furberg "does not discuss the analysis of the European Medicines Agency (EMA) ... and its finding that the clinical trial data 'does not support a causal link' between Chantix use and serious neuropsychiatric events." Defendant's memorandum (doc. 584) at 5. In support of this statement defendant cites its own Statement of Facts (doc. 582), at I.F. While defendant did state this in its Statement of Facts, omitted from the defendant's argument on this point is any recognition that the CHMP, part of the EMA , thereafter asked defendant to conduct a study in smokers with active, major depression.[8]

[8]Similarly, in their reply brief (doc. 621) the defendant asserts the court should exclude Dr. Furberg's testimony because the efficacy of Chantix "is demonstrated by the fact that FDA approved Chantix as a safe and effective aid to smoking cessation, citing its efficacy and "significant potential benefit to public health." Doc. 621, at 23. Approval by the FDA is not evidence of the safety of a medication. The court takes judicial notice of such things as that at one time, thalidomide was used for morning sickness in pregnant women. Unfortunately, 10,00 children were born with birth defects from it before it was banned. And 50 years elapsed before doctors understood why thalidomide caused limbs to disappear. *See e.g.* http://www.nytimes.com/2010/03/16/science/16limb.html?pagewanted=all. Similarly, the fact that the FDA at one time approved Vioxx did not prevent the same being removed from the market due to growing concerns that it increased the risk of heart attacks and strokes. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsand Providers/ucm103420.htm. Hence, initial approval by the FDA is not proof of the safety of a medication.

The defendant asserts that "[t]o establish causation, Dr. Furberg must demonstrate a valid statistical association between Chantix and serious neuropsychiatric events." Defendant's memorandum (doc. 584), at 14. The defendant misses the point of *Daubert*. Plaintiffs must establish that their experts opinions "are based on sufficient facts or data" and will help the jury "to understand the evidence." Rule 702, Fed.R.Evid. What the plaintiffs do not have to do at this juncture is prove their case.[9] As so well stated by another district court, "[t]he line between methodology and conclusion can be subtle and even elusive in some cases." *Tucker v. SmithKline Beecham Corp*., 701 F.Supp.2d 1040, 1055 (S.D.Ind.2010). The court in *Tucker* continued

> In evaluating the soundness of the expert's analysis, the court should avoid passing judgment on the "factual underpinnings of the expert's analysis and correctness of the of the expert's conclusions," a role better left to the fact finder.

Tucker, 701 F.Supp.2d at 1055 (quoting *Smith v. Ford Motor Co.*, 215 F.3d 713, 718 (7th Cir.2000); accord *Daubert*, 509 U.S. at 595, 113 S.Ct. 2786 (court must focus on the methodology, not on the conclusions generated by the methodology).

[9]Defendant's argument in this regard focuses on the fact that plaintiffs' experts reach different conclusions than defendant's experts. The defendant seemingly fails to recognize that if the parties agreed on relevant evidence and conclusions therefrom, there would be no need for a trial. In other words, the fact that plaintiffs' experts simply disagree with defendant's experts is not a valid basis to exclude plaintiffs' experts. The issue of a "valid statistical association" between Chantix and adverse neuropsychiatric events is no different that the ultimate issue in this case – specifically, does Chantix cause the injuries plaintiffs have suffered?

The court finds defendant seeks to have Dr. Furberg's conclusions excluded, although under the guise of objections to his methodology.

While the defendant repeatedly harps on the importance of statistically significant data, the United States Supreme Court recently stated that "[a] lack of statistically significant data does not mean that medical experts have no reliable basis for inferring a causal link between a drug and adverse events .... medical experts rely on other evidence to establish an inference of causation." *Matrixx Initiatives, Inc. v. Siracsano*, 131 S.Ct. 1309, 1319 (2011). The Court further recognized that courts "frequently permit expert testimony on causation based on evidence other than statistical significance." *Id;* citing *Wells v. Ortho Pharmaceutical Corp.*, 788 F.2d 741, 744-745 (11th Cir.1986). Hence, the court does not find the defendant's argument that Dr. Furberg "cannot establish a valid statistical association between Chantix and serious neuropsychiatric events" to be a persuasive reason to exclude his opinion, even if the court found the same to be true. *See* defendant's memorandum (doc. 584) at 13.

The *Matrixx* Court recognized that the FDA often considers a variety of factors in determining whether to take regulatory action, stating that the FDA "does not apply any single metric for determining when additional inquiry or action is necessary." *Matrixx*, 131 S.Ct. at 1320. The Court continued

> Not only does the FDA rely on a wide range of evidence of causation, it sometimes acts on the basis of evidence that suggests, but does not prove, causation.... the FDA may make regulatory decisions against drugs based on postmarketing evidence that gives rise to only a suspicion of causation.

Matrixx, *id*. The court declines to hold the plaintiffs' experts to a more exacting standard as the defendant requests.[10] Dr. Furberg and others may testify as to "postmarketing evidence that gives rise to only a suspicion of causation," *supra,* as such testimony goes to the weight the evidence is entitled to get, and not its admissibility.[11] In light of these considerations, the defendant's objections to Dr. Furberg's testimony, in large part, are matters of credibility for the jury, and not bases on which to exclude the testimony completely.

To some extent, the defendant's arguments to exclude Dr. Furberg's opinions miss the point for which he is offered. Plaintiffs have put forth Dr. Furberg as an expert on how to conduct clinical trials, an area in which he has extensive expertise. *See e.g.*, plaintiffs' memorandum (doc. 605), at 15-16. Defendant does not dispute his expertise in that area.

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[10]In essence, in support of its motion to exclude each of the six plaintiff experts in question, the defendant asserts that the plaintiffs have no proof that Chantix causes neuropsychiatric injuries or suicide, so all testimony that suggests causation is inadmissible. That is simply not what *Daubert* requires. Of course, if the plaintiffs' experts could definitively prove that Chantix caused neuropsychiatric injuries, to the satisfaction of the defendant, the court would not need to consider *Daubert* motions, or hold a trial.

[11]As the Supreme Court aptly noted, "[t]his is not a case about a handful of anecdotal reports, as Matrixx suggests..... Matrixx received information that plausibly indicated a reliable causal link between Zicam and anosmia." *Id*., at 1322.

According to his report, Dr. Furberg will testify that pre-approval clinical trials for Chantix were small, with modest positive results after one year, and that individuals with psychiatric conditions were excluded from these trials, resulting in underestimating the overall risk of adverse psychiatric events. Furberg Report, at 14-15. Because of these pre-approval trial flaws, the initial drug label was misleading about possible harmful side effects to those with preexisting psychiatric conditions and, after Chantix was placed on the market, the number of reported adverse neuropsychiatric reactions was high. *Id.*, at 15. Defendant's arguments concerning reasons to exclude Dr. Furberg, asserting he bases his opinion on uncontrolled post-marketing adverse event reports, do not reflect his opinions from his expert report. Rather, defendant directs the court back to its own Statement of Facts, wherein defendant sets forth its argument as to why uncontrolled post-marketing adverse event reports are unreliable. *See* defendant memorandum (doc. 584), at 14, citing SOF § II.A.4.

Defendant further argues that the court should exclude Dr. Furberg's opinions about what Pfizer "knew" or that Pfizer misled the FDA. Defendant memorandum, at 23. The court agrees, as such opinions are necessarily based on speculation. Said motion to exclude is **GRANTED** to the extentd that Dr. Furberg may not testify about what Pfizer "knew" or that Pfizer "misled" the FDA. Dr. Furberg may testify

as to what Pfizer "should have known" and to what information Pfizer provided to the FDA. The remainder of said motion in regard to Dr. Furberg is **DENIED.**

C. Dr. Shira Kramer

Defendant seeks to have the court exclude Dr. Kramer on the same grounds as Drs. Olmstead and Furberg: that she based her opinions on uncontrolled data, that she cannot establish a statistical association, that she failed to consider the principle of statistical significance, that she ignores studies that benefit defendant, and that she failed to consider the presence or absence of a dose-response relationship.[12] Defendant memorandum (doc. 585), at 1, 20.

Dr. Kramer is an epidemiologist, having received a Ph.D. in the same from the Johns Hopkins School of Public Health in 1979. Expert Report of Kramer, submitted as plaintiff ex. 016185, at 6. "Epidemiology, a field that concerns itself with finding the causal nexus between external factors and disease, is generally considered to be the best evidence of causation in toxic tort actions." *Rider v. Sandoz Pharmaceuticals Corp*., 295 F.3d 1194, 1198 (11th Cir.2002). In *Rider,* the Eleventh Circuit added that "[t]his Court has long held that epidemiology is not required to prove causation in a toxic tort case." *Id.*, at 1199; citing *Wells v. Ortho Pharm. Corp*., 788 F.2d 741, 745 (11th Cir.1986) (holding that "a cause-effect relationship need not be clearly established by animal or epidemiological studies.").

[12]The court discusses dose-response relationship separately, in section G, *infra.*

Although she performed no independent studies of her own, Dr. Kramer considered all evidence concerning Chantix, from whatever source, and whatever result, in performing a Weight of Evidence analysis. Kramer Report, at 12. She notes that determinations about the weight of evidence are "subjective interpretations" based on "various lines of scientific evidence. *Id.*, at 9. She also recognizes that each scientist "brings a unique set of experiences, training and expertise .... Philosophical differences exist between experts.... Therefore, it is not surprising that differences of opinion exist among scientists. Such differences of opinion are not necessarily evidence of flawed scientific reasoning or methodology, but rather differences in judgment between scientists." *Id.*, at 11.

Based on her Weight of Evidence approach, Dr. Kramer concludes that (1) defendant designed its trials inadequately to evaluate neuropsychiatric safety; that (2) varenicline is causally associated with increased risks of adverse neuro-psychiatric events; and that (3) defendant had data which reflected safety concerns with Chantix as early as 2005, before the drug was placed on the market. Kramer Report, at 19. Not surprisingly, the defendant asserts that Dr. Kramer's testimony should be excluded. Again, the defendant does not challenge Dr. Kramer's qualifications or whether her testimony will assist the trier of fact, but focuses solely on Dr. Kramer's methodology. *See e.g.*, defendant memorandum (doc. 585) at 6. In spite of defendant's assertion otherwise, Dr. Kramer considered many of

defendant's clinical trials in reaching her conclusions.[13] *See* Kramer Report, Tables A1, A2, A3, A4, A5, A6, A7. The fact that Dr. Kramer did not credit certain studies with the same weight as defendant is "not necessarily evidence of flawed scientific reasoning or methodology, but rather differences in judgment between scientists." Kramer Report, *supra,* at 11. Why Dr. Kramer chose to include or exclude data from specific clinical trials is a matter for cross-examination, not exclusion under *Daubert.* Dr. Kramer's expert report and its attachments simply does not reflect defendant's version of Dr. Kramer's report.[14]

Defendant also c[14]omplains that Dr. Kramer's findings are inconsistent with findings of the FDA. Defendant memorandum, at 17. Such allegations are simply untrue, and based on creative rewording of what the FDA Report in question actually says. For example, the defendant asserts that the FDA found Chantix to

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[13]*See* defendant memorandum (doc. 585) at 7. Although defendant cites back to its own Statement of Facts to support its assertion that Dr. Kramer ignored trials where rates of depression reported were lower for patients assigned to Chantix, Dr. Kramer notes that in many of the published versions of Pfizer's clinical trials, defendant chose to only report adverse events which occurred with a frequency of more than five percent, or more than ten percent. Kramer Report, at 47.

[14]Similarly, her deposition testimony does not reflect what defendant represents to this court that Dr. Kramer states in her deposition (submitted as defendant ex. 41). For example, the defendant cites to her deposition at 165-168 in support of its statement "because suicide and depression-related events occur regularly among people not taking Chantix – and at even higher rates among smokers trying to quit – a control group is needed to determine whether the rates of such events in patients taking Chantix are distinguishable from the rates in smokers trying to quit without Chantix." Defendant memorandum (doc. 585), at 21. Dr. Kramer's testimony at the cited pages actually states that control groups are useful, but whether one is needed or desirable depends on "the context of the trial, the nature of the question that you're asking and what you're trying to control for." Kramer depo. at 165-169.

have a lower proportion of suicide attempts and completions than other nicotine replacement therapies (NRTs). *Id*. The FDA report[15] states in relevant part:

> ....Varenicline had a higher proportion of cases for suicidal ideation (76%) vs. bupropion (61%) or nicotine (47%) and a lower proportion of suicide (attempted and completed) or other self injurious behavior (24%) than the other drugs.... Depression was the most commonly co-reported psychiatric event in all the cases (varenicline 45%, bupropion 35%, nicotine 15%).
> ....
>
> Suicidal events were reported in patients with (varenicline 50%, bupropion 24%, and nicotine 65%) or without (varenicline 26%, bupropion 32%, and nicotine 3%) psychiatric history. Bupropion case series had the most cases with no concomitant psychiatric medications reported (33%) followed by varenicline (21%) and nicotine (9%)....
> ....
>
> In conclusion, [t]he AERS data suggest a possible association between suicidal events and the use of varenicline and bupropion, given that there were postmarketing cases of positive dechallenge, close temporal relationship between the event and drug use, and the occurrence of suicidal events in patients without any psychiatric history....
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> ....
>
> **OVERALL CONCLUSION**
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> ....
>
> • Clinical trial data is not adequate to either rule in or rule out an association between suicidal behaviors and varenicline treatment, owing to the small number of such events reported in the trials.

[15]The FDA Report is based largely on adverse event reporting. Pollack, et al., FDA Office of Surveillance and Epidemiology, *Suicidality*, July 16, 2008 (submitted as defendant ex. 52).

> • Reporting of suicidal events proportional to prescriptions dispensed during the first two calendar years of marketing has been higher for varenicline than for bupropion, and considerably higher for varenicline than for transdermal nicotine. Given that there was a substantial increase in the number of such reports for varenicline during the final months of 2007 that was not accompanied by an increase in prescriptions, its seems likely that stimulated reporting accounts for this recent increase....

Pollack, et al., FDA Office of Surveillance and Epidemiology, *Suicidality*, July 16, 2008 (submitted as defendant ex. 52), at 3-6.

The defendant also claims that Dr. Kramer "ignores the importance of statistical significance." Defendant memorandum (doc. 585), at 23. For the same reasons the court found this argument not persuasive in regard to Dr. Furberg, the court does not find this argument persuasive in regard to Dr. Kramer. Additionally, here the defendant's argument is faulty for another reason. The defendant's argument assumes that Dr. Kramer relied on only uncontrolled data, but an examination of the evidence underlying her weight of evidence analysis clearly shows that she considered controlled and uncontrolled studies as well as meta-analyses and other data.[16] Thus, while "courts regularly exclude experts who rely

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[16]The *Neurontin* court summarized that

> Oftentimes, epidemiological studies lack the statistical power needed for definitive conclusions, either because they are small or the suspected adverse effect is particularly rare. *Id*. [Michael D. Green et al., *Reference Guide on Epidemiology*, in *Reference Manual on Scientific Evidence* 333, 335 (Fed. Judicial Ctr.2d ed.2000) (hereinafter "*Reference Guide on Epidemiology*")]. at 380; *see, e.g.*, *Giles*, 500 F.Supp.2d at 1058 (noting that, "[a]s a rare event, studying [suicide] for purposes of causation requires a huge number of participants"). The technique of meta-analysis, where study results are pooled "to arrive at a single figure to represent the totality of the studies reviewed," was developed to address

on statistically non-significant results," (defendant's memorandum at 26), the court finds Dr. Kramer did not do so. The court also finds that the defendant places undue emphasis on statistical significance.[17] For example, in *In re Prempro Products Liability Litigation,* the court stated

> We agree that statistical significance, by itself, should not mechanically control whether an epidemiological analysis is sufficiently reliable to be admissible. But as many federal courts observe, if an expert places undue emphasis on statistically insignificant evidence, it may indicate that the expert's methods are unreliable. *See, e.g., Wells v. SmithKline Beecham Corp*., 601 F.3d 375, 380 & n. 23 (5th Cir.2010); *Pritchard v. Dow Agro Sciences*, 705 F.Supp.2d 471, 489–90 (W.D.Pa.2010); cf. *General Elec. Co. v. Joiner*, 522 U.S. 136, 145–47, 118 S.Ct. 512, 139 L.Ed.2d 508 (1997) (ruling that, where expert opinion was founded on statistically insignificant data and other doubtful evidence, the district court did not abuse its discretion by excluding the opinion).

> such situations. *Reference Guide on Epidemiology, supra*, at 380. Meta-analysis "systematiz[es] the time-honored approach of reviewing the literature" and provides a "standardized framework with quantitative methods for estimating risk." *Id.* Meta-analysis is "most appropriate[ly]" used to pool randomized experimental trials, but "if carefully performed it may also be helpful for observational studies." *Id*. at 361 n. 76.

In re Neurontin, 612 F.Supp.2d at 126.

[17]In examining the issue of "statistical significance," the court in *In re Neurontin* noted

> A study found to have "results that are unlikely to be the result of random error" is "statistically significant." *Reference Guide on Epidemiology*, *supra,* at 354. Statistical significance, however, does not indicate the strength of an association found in a study. *Id*. at 359. "A study may be statistically significant but may find only a very weak association; conversely, a study with small sample sizes may find a high relative risk but still not be statistically significant." *Id.* To reach a "more refined assessment of appropriate inferences about the association found in an epidemiologic study," researchers rely on another statistical technique known as a "confidence interval." *Id*. at 360 (defining a confidence interval as "a range of values calculated from the results of a study, within which the true value is likely to fall").

In re Neurontin, 612 F.Supp.2d at 127.

In re Prempro Products Liability Litigation, 738 F.Supp.2d 887, 892 (E.D.Ark. 2010).

The defendant's argument is flawed in two other respects. First, the defendant incorrectly asserts that "the FDA has never said that Chantix causes or increases the risk of events such as suicide or depression." Secondly, the defendant asserts "[w]here, as here, an event occurs frequently in the general population, the medical and scientific communities rely on statistical significance...." Defendant's memorandum (doc. 585), at 29. The court is unsure if the defendant is referring to suicide or depression as "an event occurring frequently."[18]

In the FDA's Media Briefing surrounding the 2009 label change for Chantix, Dr. Curtis Rosenbraugh, Director of Drug Evaluation II in the Center for drug Evaluation and Research at FDA, stated that the FDA was requiring Chantix to carry a new box warning to highlight the risk of serious mental health symptoms. Defendant ex. 11 to defendant motion for summary judgment (doc. 590-11). He added that such warning was to "highlight symptoms including changes in behavior, hostility, agitation, depressed mood, suicidal thoughts and behavior and attempted

[18]In its reply brief focusing on Dr. John Wesley Boyd, the defendant states "Suicidality is a distinct adverse event from depression, mania, psychosis, or aggression." Defendant's reply (doc. 625) at 6. The court agrees with this statement, as suicide is certainly distinct from other forms of neuropsychiatric events. However, such a recognition necessarily implicates a significant limitation of the Department of Veteran Affairs study, which solely considered hospitalizations, upon which defendant also relies. *See* defendant Statement of Facts (doc. 582), at 55. Specifically, in considering the discharge reasons for hospitalizations in patients treated with Chantix, the study authors found no difference in admissions on this basis. In highlighting this study, the defendant overlooks the fact that very few completed suicides require hospitalization.

suicide." *Id*. He noted that such symptoms "have occurred in patients with and without a history of psychiatric illness..." *Id.* Distinguishing these symptoms from nicotine withdrawal, Dr. Rosenbraugh pointed out that the FDA had received reports of such symptoms in patients still smoking, eliminating the possibility that symptoms were withdrawal related.[19] *Id*.

Similarly, Dr. Rosenbraugh noted that "We really don't know what the rate of these reactions are. We think they're very rare and we don't know that there – whether there is a subgroup that is at particular risk or not and that is part of the purpose of the trial we're going to require the sponsors to do." *Id*. As the plaintiffs repeatedly allege, the defendant failed to screen for these types of reactions in their clinical trials, thus the greatest abundance of adverse data to date has come from doctor's observations and self-reporting. *See e.g.*, plaintiffs' memorandum (doc. 607) at 18, and citations therein.

As to defendant's concern that Dr. Kramer was considering events which "occur[] frequently in the general population..." (defendant's memorandum (doc. 585) at 29), the court notes that neither suicide nor attempted suicide are recognized as "frequently" occurring events. Rather, as the *In re Neurontin* court recognized

[19]Throughout each of their motions to exclude, the defendant asserts that many of the neuropsychiatric effects alleged to be caused by Chantix are actually symptoms of nicotine withdrawal. Dr. John Wesley Boyd, one of the plaintiffs' experts discussed *infra,* testified at his deposition that psychosis, mania, major depression and/or suicidal ideation are not symptoms of nicotine withdrawal. Boyd depo. (submitted as defendant ex. 31) at 283. Upon further questioning, he reiterated that major depression is not a symptom of nicotine withdrawal, Boyd depo. at 282-289.

in regard to suicide, "epidemiological studies lack the statistical power needed for definitive conclusions, either because they are small or the suspected adverse effect is particularly rare. [*Reference Guide on Epidemiology*], at 380; *see, e.g., Giles*, 500 F.Supp.2d at 1058 (noting that, "[a]s a rare event, studying [suicide] for purposes of causation requires a huge number of participants"). The technique of meta-analysis, where study results are pooled "to arrive at a single figure to represent the totality of the studies reviewed," was developed to address such situations. *In re Neurontin*, 612 F.Supp.2d at 126. Similarly, the court in *Tucker v. SmithKline Beecham Corp*. observed that

> The study of suicide is rife with both ethical and practical difficulties. Meaningful studies require large numbers of participants. Thankfully, suicide is a rare act. Not only that, but to conduct a placebo-controlled study, some patient-participants already at risk necessarily would be treated with a placebo. For practical and ethical reasons, "suicidality itself has rarely if ever been studied in large, randomised placebo-controlled double-blind epidemiological studies .... the trials upon which the FDA based its 2006 meta-analysis 'were not designed to specifically detect suicidality.'" *Giles v. Wyeth, Inc*., 500 F.Supp.2d 1048, 1058 (S.D.Ill.2007) (admitting testimony of Dr. Glenmullen on general causation in Effexor suicide case), quoting Marc Stone & M. Lisa Jones, *Clinical Review: Relationship Between Antidepressant Drugs and Suicidality in Adults*, 43 (Nov. 17, 2006).

Tucker v. SmithKline Beecham Corp., 701 F.Supp.2d 1040, 1060-1061 (S.D.Ind. 2010). Defendant's concerns are thus misplaced.

Similarly, although defendant accuses Dr. Kramer (and plaintiffs' other experts) of "cherry picking" data (defendant's memorandum (doc. 585) at 29-30),

Dr. Kramer did no such thing. Rather, she reviewed all of the information, including the studies and trials defendant chose not to publish.[20] The fact that some of the studies Dr. Kramer considered may have weaknesses is not a basis to exclude her testimony. "Vigorous cross-examination, presentation of contrary evidence, and careful instruction on the burden of proof are traditional and appropriate means of attacking shaky but admissible evidence." *Daubert,* 509 U.S. at 596. The district court's gatekeeper role, "is not intended to supplant the adversary system or the role of the jury." *Allison*, 184 F.3d at 1311; citing *Daubert*, 509 U.S. at 596. In contrast to defendant's claim that Dr. Kramer "ignore[s] ... the totality of data available

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[20]Defendant harps on the weight to which its randomized, placebo controlled clinical trials should be entitled. *See e.g.,* defendant memorandum (doc. 585), at 28-29. As noted by one publication in rejecting publication of the results of a study,

> Following recent reports of the exacerbation of psychiatric disorders in patients receiving varenicline ... and the FDA's public health advisories regarding the drug's behavioral sequelae, the authors present data from a series of premarketing studies funded by the drug's manufacturer....
>
> The studies exclude subjects with serious or unstable psychiatric disease. On page 7, the authors note that subjects receiving treatment for depression at study initiation or within the prior 12 months were excluded (curiously a diagnosis of depression not requiring treatment was not an exclusion). Also excluded were subjects with "a past or present history of panic disorder, psychosis, bipolar disorder or who had alcohol or drug abuse/dependency within the past year." In short, the data do not address the population which has prompted the concern– those with pre-existing major psychiatric disorders.
>
> Table 3 shows a distressing incidence of sleep dysfunction with varenicline (and buproprion). This may be critical to the exacerbation of pre-existing psychiatric disorders. Disrupting the integrity of sleep in those with psychiatric illness is certainly a risk-factor regarding decompensation or recrudescence of psychiatric symptomology....
>
> .... Likewise, the effort to attribute depressive symptoms solely to nicotine withdrawal falls short."

Plaintiffs' ex. 004017.

today" (defendant's memorandum (doc. 585) at 31), Dr. Kramer asserts she considered all of the data available in reaching her conclusions.[21]

Additionally, as pointed out by the plaintiffs, defendant's attempt to isolate individual pieces of evidence as a basis to exclude all of Dr. Kramer's testimony has been rejected by other courts. *See* plaintiff's memorandum, at 27, citing *In re Phenylpropanolamine (PPA) Products Liability Litigation*, 289 F.Supp.2d 1230, 1242 (W.D.Wash.2003). That court stated

> Defendants isolate these sources, rather than considering the whole. Non-epidemiological sources are frequently utilized by experts in rendering scientific opinions and, under *Daubert*, should be considered by the court in assessing the reliability of those opinions. *See, e.g., Kennedy*, 161 F.3d at 1228–31 (finding trial court abused its discretion by excluding expert testimony based on, inter alia, peer-reviewed articles, clinical trials and product studies conducted by the manufacturer, and a state health department's review of reported cases of adverse reactions); *Hopkins v. Dow Corning Corp*., 33 F.3d 1116, 1124–25 (9th Cir.1994) (upholding trial court's admission of expert testimony based on, inter alia, clinical experience and studies, medical literature, and general scientific knowledge about drug's properties established by animal studies and biophysical data).
>
> In considering the non-epidemiological evidence relied upon by plaintiffs' experts, the court finds significant the sheer volume of case reports, case series, and spontaneous reports associating PPA with hemorrhagic stroke in women. *See, e.g., Rider v. Sandoz Pharms. Corp*., 295 F.3d 1194, 1202 (11th Cir.2002) (noting that the district court identified the types of evidence that would have been considered reliable, including, inter alia, "a very large number of case reports.")

[21]Defendant relies on *Norris v. Baxter Healthcare Corp*. in support of its conclusion that Dr. Kramer's methods were flawed. In that case, the Tenth Circuit noted that the expert at issue there relied solely on "differential diagnosis and case studies." *Id.*, 397 F.3d 878, 885 (10th Cir.2005). Dr. Kramer did not fall prey to such an error.

> While not conclusive, the multitude of textbooks and treatises including PPA as a risk factor for stroke adds to the reliability of plaintiffs' experts' opinions. *See Daubert*, 509 U.S. at 594, 113 S.Ct. 2786 ("Widespread acceptance can be an important factor in ruling particular evidence admissible[.]") The non-epidemiological evidence also gains added legitimacy from the fact that several of plaintiffs' experts base their opinions, in part, on independent PPA-related research. *See Daubert II*, 43 F.3d at 1317.

Id. By extension, Dr. Kramer's weight of evidence methodology is persuasive.

Defendant also repeatedly harps on the assertion that its ongoing trials, performed at the request of the FDA, "ethically could not be performed if it were established that Chantix causes serious neuropsychiatric events." Defendant's memorandum at 32, citing its SOF § III.A.4. However, as stated earlier by the court, the FDA has required a "black box warning" on Chantix's label addressing just these types of events. *See* 21 C.F.R. § 201.57(c)(6)(i) (requiring revision to product label "about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug."). And logically, was there no suspicion of a connection between Chantix and neuropsychiatric injuries, the FDA would not have required further studies of just such events.[22] Defendant also

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[22]The court has considered defendant's argument that FDA actions are not evidence because the FDA tends to err on the side of caution. Defendant's memorandum at 36. In *Rider*, the court came to that conclusion, as well, noting that

> The district court concluded that the language in the FDA statement itself undermined its reliability as proof of causation. In the statement, the FDA did not purport to have drawn a conclusion about causation. Instead, the statement merely states that possible risks outweigh the limited benefits of the drug. This risk-utility analysis involves a much lower standard than that which is demanded by a court of law. A regulatory agency such as the FDA may choose to err on the side of caution. Courts, however, are required by the *Daubert* trilogy to engage in

criticizes Dr. Kramer on the basis that her findings are inconsistent with findings of the FDA. Defendant memorandum (doc. 585), at 17. Thus, the defendant asks this court to both ignore and consider the FDA's statements, an impossible task at best.

However, for the same reasons the court set forth in its discussion of Dr. Furberg, the court will not allow Dr. Kramer to testify to what defendant "knew." Because Dr. Kramer cannot testify to what Pfizer "knew," by extension she cannot testify to any labeling changes she believes would have been appropriate based on that knowledge.

Having considered the argument of the defendant and the response of the plaintiffs, the court is of the opinion that the motion to exclude is **DENIED** as to Dr. Kramer, in all respects, **EXCEPT** said motion is **GRANTED** to the extent that Dr. Kramer may not testify as to what defendant "knew," nor to labeling changes based on that knowledge.

> objective review of evidence to determine whether it has sufficient scientific basis to be considered reliable. The district court did not abuse its discretion in concluding that the FDA actions do not, in this case, provide scientific proof of causation.

Rider, 295 F.3d at 1201. Here, neither Dr. Kramer nor the court has "relied" on the FDA's action. Rather, it is but one piece of evidence that the plaintiffs' expert has used to support her conclusions. In *Rider,* the court was faced with evidence that attempted to analogize the injury suffered to other compounds, not the drug in question itself. *See id.* ("The district court, after a detailed review of the properties of ergot alkaloids, concluded that plaintiffs failed to come forward with even a theory as to why the mechanism that causes some ergot alkaloids to act as vasoconstrictors would more probably than not be the same mechanism by which bromocriptine acts to cause vasoconstriction.").

D. Dr. Joseph Glenmullen

Dr. Glenmullen is a medical doctor, a clinical instructor in psychiatry at Harvard Medical School, has a private psychiatry practice and is Board Certified in psychiatry. Expert Report of Dr. Glenmullen (submitted as plaintiff ex. 016178), at 2. He has authored two books on the side-effects of psychiatric medications and co-authored three peer-reviewed published studies on Chantix. *Id.* Dr. Glenmullen is offered as a general causation expert, who plans to testify that Chantix causes "abnormal dreams, depression, suicidality, aggression, violence, and psychosis." Report of Glenmullen, at 1.

According to defendant, Dr. Glenmullen relies on the same data set as Dr. Olmstead. Defendant's memorandum (doc. 587) at 7-8. For the same reasons the court found this data a reliable basis for Dr. Olmstead's testimony, the court reaches the same conclusion here. Defendant also asserts that Dr. Glenmullen lacks any training in pharmacoviligance (defendant's memorandum (doc. 587) at 6). The plaintiffs respond that Dr. Glenmullen is a specialist in psychopharmacology.[23] Plaintiffs' memorandum (doc. 606), at 5. Indeed, a number of courts have so recognized Dr. Glenmullen. See e.g., *Shuman v. Spencer*, 636 F.3d 24 (1st Cir.2011); *Tucker v. SmithKline Beecham Corp.*, 701 F.Supp.2d 1040, 1062-1063

[23]The former is the pharmacological science relating to the detection, assessment, understanding and prevention of adverse effects, particularly long term and short term side effects of medicines; the latter is the scientific study of the actions of drugs and their effects on mood, sensation, thinking, and behavior.

(S.D.Ind.2010) ("Given Dr. Glenmullen's uncontested expertise, his 'review of experimental, statistical or other scientific data gathered by others may suffice as a reasonable methodology upon which to base an opinion'"); *Giles v. Wyeth, Inc.*, 500 F.Supp.2d 1048, 1058 (S.D.Ill.2007) (admitting testimony of Dr. Glenmullen on general causation in Effexor suicide case).

As with plaintiffs' other expert witnesses, the defendant complains that Dr. Glenmullen did not consider the best available data.[24] For reasons stated previously, the court is of the opinion this is a credibility matter for cross-examination and determination by the trier of fact. According to the defendant, Dr. Glenmullen considered the Halperin 2009 study, the Harrison-Woolrych 2011 study (also referred to as the New Zealand study), adverse event reports, FDA analyses of adverse reports, and FDA warnings. Defendant memorandum (doc. 587) at 9-12. A review of the extensive citations of evidence considered by him demonstrate that Dr. Glenmullen relied on much more than those particular studies identified by defendant. See Report of Glenmullen (plaintiff ex. 016178).

Dr. Glenmullen opines that it is biologically plausible that Chantix can cause mild to severe psychiatric side effects in a vulnerable subset of patients and that

[24]In fact, each of defendant's arguments concerning Dr. Glenmullen has been covered in regard to plaintiffs' other experts, *i.e.*, he should have considered the randomized controlled data, he cherry-picked data, etc. The court finds the same reasoning set forth as to the other experts' opinions applies equally to defendant's arguments regarding Dr. Glenmullen. The court declines to go through the academic exercise of repeating its legal analysis here.

those side effects would differ in different people.[25] Report of Glenmullen, at 50. Dr. Glenmullen sets forth an in-depth explanation of the role of dopamine in the brain, and known side-effects of altering dopamine releases and receptors. *Id*. He states

> ... brain cells are not passive in the face of drugs like Chantix; in response the cells change over time, through processes such as desensitization and up-regulation. Because of genetic and physiological diversity, one would expect different people to be affected in different, idiosyncratic ways. Indeed, since it alters dopamine signals – and apparently serotonin signals – Chantix would be expected to have profound effects on mood and behavior....
>
> What is known, is that dopamine plays a role in the pathogenesis, symptomatology, and/or treatment of a wide range of conditions including schizophrenia, psychosis, depression, anxiety, attention deficit disorder, Alzheimer's disease, and Parkinson's disease. Indeed, the leading hypothesis for the biochemical basis of schizophrenia is called the "dopamine hypotheses of schizophrenia," since drugs that increase dopamine signals in the brain can cause psychosis, while drugs that block dopamine are used to treat schizophrenia and other forms of psychosis.
> .....
>
> The risks of altering dopamine signals in the brain have long been recognized. Dopaminergic drugs typically have serious psychiatric side effects. The evidence I have reviewed proves Chantix shares this undesirable property common to other drugs active in dopamine pathways....

Report of Glenmullen (plaintiff ex. 016178), at 51, 53.

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[25]Biological plausibility is a criteria which depends on existing knowledge about the mechanisms by which the disease in question develops. Green, et al., *Reference Guide on Epidemiology*, in *Reference Manual on Scientific Evidence*, 604 (Fed.Judicial Ctr. 3rd ed.2011). When biological plausibility exists, it lends credence to an inference of causality. *Id*.

Defendant attacks Dr. Glenmullen in piecemeal fashion, asserting he only holds a medical degree. Hence, defendant argues Dr. Glenmullen is not qualified to offer opinions about epidemiological data because he is not an epidemiologist; not qualified to offer opinions about adverse event data because he is not trained in the field of pharmacovigilence; he has no degree in pharmacology, chemistry or neuroscience, has never conducted animal or laboratory research, and never worked for a pharmaceutical company or the FDA. Defendant's memorandum (doc. 587), at 16-17. None of the above is relevant to Dr. Glenmullen's testimony.[26]

Similarly, defendant argues that Dr. Glenmullen relied on Dr. Olmstead's statistical analysis, but then argues that Dr. Glenmullen relied on a single, uncontrolled observational study, and further complains that Dr. Glenmullen should not have relied on adverse event reports. Defendant's memorandum at 22-24. In reality, Dr. Glenmullen considered a wide variety of evidence from a wide variety of sources in reaching his opinion. The fact that defendant does not like the conclusions drawn from that evidence is not a basis for exclusion under *Daubert.* The court may consider only if the methodology was valid and based on reliable evidence. *See e g., Quiet Tech*, 326 F.3d 1341. The credibility or persuasiveness of those opinions is firmly within the province of the jury. *Id.*

[26]Defendant argues Dr. Kramer is not qualified as expert as to her opinions because she is an epidemiologist, not a medical doctor. With Dr. Glenmullen, defendant complains that he is a medical doctor, and not an epidemiologist.

Not surprisingly, the defendant dislikes Dr. Glenmullen's "biological mechanism hypotheses." Defendant's memorandum, at 28. Defendant asserts that Dr. Glenmullen's "biological mechanism hypothesis rests on a scattered list of speculative, unfounded analogies to other substances. After noting that Chantix stimulates the release of dopamine ... Dr. Glenmullen claims that '[m]any prescription and street drugs that affect dopamine can produce undesireable, often dangerous, psychiatric side effects." Defendant memorandum, at 29. However, defendant does not dispute either part of Dr. Glenmullen's conclusion, specifically (1) affecting dopamine can produce undesireable psychiatric side effects, and (2) Chantix is known to affect dopamine.[27]

The defendant's motion to exclude is therefore **DENIED** as to Dr. Glenmullem on all bases set forth, except that said motion is **GRANTED** to the extent that Dr. Glenmullen may not testify as to what defendant "knew" or that defendant "misled" the FDA.

E. Dr. Jon Wesley Boyd

The defendant moves this court to exclude the opinion of Dr. Boyd on the basis that he is not qualified to offer opinions about epidemiology or drug safety.

[27]Defendant also faults Dr. Glenmullen for his lack of ability to identify who will have severe psychiatric side-effects. Defendant's memorandum at 30. The court assumes that if Dr. Glenmullen, or anyone else were indeed so omniscient, the defendant would hire such an individual immediately. Expecting such abilities is akin to expecting someone to identify who will get cancer from smoking, or from exposure to a myriad of other harmful substances. The court does not find Dr. Glenmullen's lack of ability to predict who will fall prey to side-effects entitled to any consideration in relation to the *Daubert* standards.

Defendant's memorandum (doc. 588), at 1. Dr. Boyd is a medical doctor with Board Certification in psychiatry. Expert Report of Boyd (plaintiff ex. 016165), at 1. He specializes in treating individuals who suffer from addictions, including tobacco. *Id.*

In forming the opinions he holds regarding Chantix, Dr. Boyd considered a wide range of studies, reports, and articles. *See e.g*,. Expert Report of Boyd, at 3-7. The defendant complains about specific studies cited by Dr. Boyd, but does so with the suggestion that those studies are all Dr. Boyd considered. *See* defendant's memorandum, at 3-5. Such assertion is belied by the extensive number of studies to which Dr. Boyd refers in his expert report. Report of Boyd, at 3-7. Clearly, there is extensive literature which supports Dr. Boyd's opinions that Chantix is linked to psychiatric symptoms, that pre-marketing clinical trials excluded certain individuals, and that defendant should have disclosed these exclusions at the time of marketing. Report of Boyd, at 2-3. Similarly, there are multiple studies which supports defendant's assertion that a link between Chantix and psychiatric symptoms has not been conclusively identified. *See e.g.*, defendant's memorandum (doc. 588), at 6-13. This divergence of opinion is not a basis to exclude either point of view, but rather is a matter for a jury to consider. This court's role is only to "'ensur[e] that an expert's testimony both rests on a reliable foundation and is relevant to the task at hand.'" *Kumho* Tire, 526 U.S. at 141 (quoting *Daubert*, 509

U.S. at 597, 113 S.Ct. 2786). See also *Quiet Tech*, 326 F.3d at 1344-45 (where appellant argued that the expert used incorrect data or was missing data, and such flawed the analysis, the Court held that such an attack goes more to the weight of the evidence than to its admissibility, noting that "is precisely the role of cross-examination."); *In re Prempro Products Liability Litigation,* 586 F.3d 547, 567 (8th Cir.2009) ("Wyeth and Upjohn had the opportunity to expose the testimony's weaknesses through vigorous cross-examination and the presentation of contrary evidence.") (citing *Larson v. Kempker*, 414 F.3d 936, 941 (8th Cir.2005) (stating the factual basis of an expert opinion is assessed by the jury)); *In re TMI Litig*., 193 F.3d 613, 692 (3rd Cir.1999) ("So long as the expert's testimony rests upon 'good grounds,' it should be tested by the adversary process – competing expert testimony and active cross-examination – rather than excluded from jurors' scrutiny for fear that they will not grasp its complexities or satisfactory [sic] weigh its inadequacies." (quoting *Ruiz-Troche v. Pepsi Cola of Puerto Rico Bottling Co.*, 161 F.3d 77, 85 (1st Cir.1998)); *Wilmington v. J.I. Case Co.*, 793 F.2d 909, 920 (8th Cir.1986) ("Virtually all the inadequacies in the expert's testimony urged here by [the defendant] were brought out forcefully at trial .... These matters go to the weight of the expert's testimony rather than to its admissibility.").

The defendant also seeks to have the court exclude Dr. Boyd's opinion that Chantix causes neuropsychiatric symptoms through dopamine excess and depletion. Defendant memorandum (doc. 588), at 26-27. Dr. Boyd testified that

> ... varenicline, as you know, is a partial agonist of the nicotonic receptor. It in turn by stimulating the receptor at a level of 35 to 60 percent of nicotine causes the brain to increase dopamine, and dopamine at increased levels is associated with mania and psychosis, probably agitation as well.

Boyd depo. (submitted as defendant ex. 31) at 45. Later, he states that "a continuous release of dopamine could be stimulating and could directly cause the symptoms." *Id*., at 336. He further explains that if "individuals who take Chantix and develop psychiatric side effects such as mania or psychosis, I would say and do say that it is the dopamine, the overabundance of dopamine that is the reason for those symptoms." *Id.* However, Dr. Boyd admits there are no direct studies in humans that demonstrate the same. *Id.*, at 337.

Having considered the arguments of the parties on this issue, the court finds this is more a question of ***why*** side effects could occur than whether Chantix ***could*** cause those side effects. Whether or not Chantix actually does cause those effects is left to the trier of fact. "It is axiomatic that questions regarding proximate cause are 'undeniably a jury question' and may only be determined by the courts 'in plain and undisputed cases.'" *Sanders v. Lull Intern., Inc.,* 411 F.3d 1266, 1271 (11th Cir.2005) (quoting *Ontario Sewing Mach. v. Smith,* 275 Ga. 683, 572 S.E.2d 533,

536 (2002)). As the plaintiffs assert, this court is not charged with determining which theory of the various experts is correct, but only ensuring that the testimony offered to the jury is reliable. *See* plaintiff's response (doc. 604) at 27. Dr. Boyd puts forth his dopamine depletion theory as just that, a theory. The court finds no basis on which a jury may be confused into thinking such a theory is established fact.

In consideration of the foregoing, the motion to exclude is **DENIED** as to Dr. Boyd.

F. Dr. Antoine Bechara

Unlike plaintiffs' other experts, Dr. Bechara is offered for the purpose of explaining why Chantix causes the alleged neuropsychiatric effects.[28] Dr. Bechara is a Professor of Neuroscience and Psychology at University of Southern California, a Professor of Psychiatry at McGill University, and a Professor of Neurology at the University of Iowa. Expert Report of Dr. Bechara (plaintiff ex. 016162), at 2. His research focuses on the neurobiological mechanisms of behavioral addiction, including addition to nicotine. *Id*. The court notes that Dr. Bechara's background and research in neurobiology clearly render him an expert in his field, and the defendant does not assert otherwise. Rather, the defendant claims that Dr. Bechara

[28]As stated s*upra*, Dr. Boyd touches on the biological plausibility of dopamine depletion as the cause, but also states in his deposition that he would defer to Dr. Bechara on this.

does not have a medical degree, is not a psychiatrist, and is not a pharmacologist. Defendant memorandum (doc. 586), at 4. The court finds that, as Dr. Bechara has not been offered as a medical doctor, psychiatrist, or pharmacologist, these criticisms by the defendant are without relevance.

Dr. Bechara offers that Chantix causes neuropsychiatric symptoms because of dopamine depletion. Report of Bechara, at 6-7. Dr. Bechara postulates that because Chantix causes a sustained release of dopamine, there is an initial excess in the synapses, allowing more dopamine to be metabolized and leaving less available for reabsorption. Report of Bechara, at 11. According to Bechara, an excess of dopamine leads to mania type behaviors. *Id*. Because the brain is then using more dopamine than it is creating, dopamine deficiency ensues. *Id.* Dopamine deficiency is thought to be a cause of major depression. *Id*. Dr. Bechara further offers that similar neuropsychiatric side effects to Chantix are not seen with nicotine replacement therapy ("NRT") because NRTs utilize nicotine as opposed to a synthetic substance. Report of Bechara, at 12.

Defendant asserts that the above theory is based on cocaine and amphetamine research, and that there is no basis for attributing such a mechanism to Chantix. Defendant's memorandum, at 6-8. In fact, defendant secured an expert report from one of the dopamine depletion theory authors, who states that the theory would not apply to Chantix. *See e.g.*, defendant memorandum (doc. 586), at 8.

The court does not again delve into the same arguments by defendant it has addressed for each of the other challenged plaintiffs' experts. Rather, the court focuses solely on whether it will allow Dr. Bechara to testify as to his dopamine depletion theory as it relates to Chantix. The validity of the dopamine depletion theory itself is not being challenged by defendant. Rather, the application of the theory to Chantix is the focus of defendant's objections. The defendant asserts that Dr. Bechara's adaptation of this theory is extrapolated solely from animal studies, where animals given high dosages of Chantix had an increase in dopamine receptors, which would indicate dopamine depletion. *See* defendant's memorandum at 10-11; Report of Bechara at 13-14. Thus, in Dr. Bechara's rebuttal report (submitted as plaintiff ex. 016049), he states

> A common theme among several experts for the defendant.... was the dismissal of the dopamine depletion mechanism for varenicline on the grounds that there were no cited scientific studies that directly link varenicline to dopamine depletion....However, as an expert in the field, it is within my professional capacity to rely on basic scientific principles, and the current state of knowledge to show the plausible biological mechanism that exists to a reasonable degree of scientific certainty. The dopamine excess/depletion mechanism rests on solid basic scientific principles....

Id., at 2.

Dr. Bechara's support for his theory – that an increase in dopamine receptors reflects a decrease in overall dopamine and that this is what Chantix does – is based in part on animal studies where mice and rats received doses many times in excess

of what is actually used for humans. In explaining the basis for his theory, Dr. Bechara explained that

> One study indicates that in the rat's nucleus accumbens, varenicline has an inverted U-shaped dose response curve, i.e., it can initially increase dopamine release, but then it starts to decrease it at a higher dose. Other investigations show that while the effects of nicotine on dopamine release in the nucleus accumbens are brisk and short, the effects of varenicline are more sustained. Both pieces of evidence signal a change in dopamine release in the nucleus accumbens that is fundamentally different from nicotine. Certainly these changes do reflect the fact that varenicline can substitute for nicotine reward, but the sustained nature of dopamine release by varenicline should have alerted investigators to potential neuropsychiatric adverse events.

Expert Report of Bechara (plaintiff ex. 016162), at 14.

The defendant asserts that the above findings are not a basis to extrapolate to humans because Dr. Bechara cites no support for his assertion that an increase in dopamine receptors is evidence that dopamine is depleted, and because not all animal studies may be extrapolated to humans. Defendant's memorandum, at 25-26.

In deposition, Dr. Charles Dackis, defendant's expert for purposes of dopamine depletion theory, states that

> ... with a lower level of dopamine, the reuptake sites would be much more able to engage the dopamine and bring it back into the neuron for recycling than with a very high level, which would flood the dopamine reuptake sites. They would be incapable and that would be flushed through metabolism by COMT.

Dackis depo. (submitted as defendant ex 32), at 160. Dr. Dackis, like Dr. Bechara, also bases his postulation on "30 years of experience with dopamine systems and neurochemistry and dopamine shunts and how dopamine depletion might reasonably occur...." (Dackis depo. at 161), rather than citation to a specific reference work.

Unlike Dr. Bechara, Dr. Dackis is of the opinion dopamine depletion cannot occur with varenicline. Dackis depo. at 161. He testified that "I don't think it's plausible to say that just because there is a somewhat elevated level of dopamine in the synapse that there is going to be dopamine depletion because you still have reuptake involved." Dackis depo. at 191. He further disputes Dr. Bechara's conclusion that increased dopamine would lead to increased metabolism – specifically that "increased demand for dopamine synthesis may exert a burden on the synthesizing enzyme tyrosine hydroxylase" – stating that Dr. Bechara is "reaching when he says this." Dackis depo. at 192. He adds that such a conclusion is "highly speculative and I think untrue." *Id*., at 193. Dr. Dackis could cite no literature which either supported or refuted Dr. Bechara's conclusions. *Id*., at 194. He did, however, dispute the findings of every study, article, and publication which supported Dr. Bechara on the basis that he either did not agree with it, thought others were overreaching, or, in one instance, announced the study authors were "confused" by their own findings. Dackis depo. at 195-230.

Clearly, there is debate in the scientific community as to whether Dr. Bechara's dopamine depletion theory for Chantix can explain major depression and other neuropsychiatric injuries. However, debate is not a basis for exclusion. Reversing a district court for just such a mistake, the First Circuit explained:

> The court's analysis repeatedly challenged the factual underpinnings of Dr. Smith's opinion, and took sides on questions that are currently the focus of extensive scientific research and debate—and on which reasonable scientists can clearly disagree. In this, the court overstepped the authorized bounds of its role as gatekeeper. "The soundness of the factual underpinnings of the expert's analysis and the correctness of the expert's conclusions based on that analysis are factual matters to be determined by the trier of fact." *Smith*, 215 F.3d at 718. "When the factual underpinning of an expert's opinion is weak, it is a matter affecting the weight and credibility of the testimony—a question to be resolved by the jury." *Vargas*, 471 F.3d at 264 (quoting *Int'l Adhesive Coating Co. v. Bolton Emerson Int'l*, 851 F.2d 540, 545 (1st Cir.1988)) (internal quotation marks omitted); see also *Quiet Tech. DC–8, Inc. v. Hurel–Dubois UK Ltd.*, 326 F.3d 1333, 1345 (11th Cir. 2003); *Amorgianos v. Nat'l R.R. Passenger Corp.*, 303 F.3d 256, 267 (2nd Cir.2002).

Milward v. Acuity Specialty Products Group, Inc. 639 F.3d 11, 22 (1st Cir.2011). See also *Kuhn v. Wyeth, Inc.*, – F.3d –, 2012 WL 3030730, 5 (8th Cir. July 26, 2012) ("Proponents of expert testimony need not demonstrate that the assessments of their experts are correct, and trial courts are not empowered 'to determine which of several competing scientific theories has the best provenance.'") (citing *Milward,* 639 F.3d at 15)); *Ambrosini v. Labarraque,* 101 F.3d 129, 134 (D.C.Cir.1996) ("Even if the burden placed on the 'gatekeeper' may seem heavy at times, *see, e.g.,*

Daubert, 509 U.S. at 600–01, 113 S.Ct. at 2800 ... there is nothing in *Daubert* to suggest that judges become scientific experts, much less evaluators of the persuasiveness of an expert's conclusion. Rather, once an expert has explained his or her methodology, and has withstood cross-examination or evidence suggesting that the methodology is not derived from the scientific method, the expert's testimony, so long as it 'fits' an issue in the case, is admissible under Rule 702 for the trier of fact to weigh.").

Hence, the court is of the opinion that Dr. Bechara may testify as to his theory, Dr. Dackis may testify as to why Dr. Bechara's theory is mistaken, and the trier of fact may determine which of these dueling experts' conclusions is more correct.

The court next turns to the defendant's other contention, that not all animal studies may be extrapolated to humans. Defendant's memorandum (doc. 586), at 26-27. Dr. Dackis stated that he was not aware of any data on humans showing "what dopamine does in response to Varenicline treatment, whether it's acute or steady." Dackis depo. at 163. He asserted that the applicability of rat studies to humans was limited. As to this type assertion, the Sixth Circuit has ruled

> Animal studies often comprise the backbone of evidence indicating biological hazards, and their legal value has been recognized by federal courts and agencies. *See, e.g., International Union, UAW v. Johnson Controls, Inc.*, 499 U.S. 187, 111 S.Ct. 1196, 1215, 113 L.Ed.2d 158 (White J., concurring) (citing *Industrial Union Dep't v.*

> *American Petroleum Institute*, 448 U.S. 607, 657 n. 64, 100 S.Ct. 2844, 2871 n. 64, 65 L.Ed.2d 1010 (1980)); *Environmental Defense Fund, Inc. v. EPA*, 548 F.2d 998, 1006-07 (D.C.Cir.1976); Proposed Guidelines for Assessing Female Reproductive Risk, 53 Fed.Reg. 24,834, 24,836-39 (1988) (discussing the use of animal studies to identify and assess reproductive hazards for human females); Proposed Guidelines for Assessing Male Reproductive Risk, 53 Fed.Reg. 24,850, 24,853-60 (1988) (discussing the use of animal studies to identify and assess reproductive hazards for human males).

Turpin v. Merrell Dow Pharmaceuticals, Inc., 959 F.2d 1349, 1360 (6th Cir .1992).

More recently, another district court held that

> "The extent to which animal and cell experiments accurately predict human responses to chemical exposures is subject to debate." Fed. Judicial Ctr., *Reference Manual on Scientific Evidence,* 405 (2000). Nonetheless, animal studies can be a necessary second-best way to show causation. Because it "is often unethical to experiment on humans by exposing them to known doses of chemical agents, animal toxicological evidence often provides the best scientific information about the risk of disease from a chemical exposure." *Id.* "In qualitative extrapolation, one can usually rely on the fact that a compound causing an effect in one mammalian species will cause it in another species." *Id*. at 410. An expert should review similarities and differences between the animal species and humans. *Id*. at 419.

In re Zicam Cold Remedy Marketing, Sales Practices, and Products Liability Litigation, 2011 WL 798898, 8-9 (D.Ariz.2011). Hence, nothing inherent in the fact that these studies were conducted on animals requires this court to exclude either the studies or the extrapolations therefrom. Rather, this again is a basis for cross-examination.

Defendant further argues that biological plausibility is not proof of causation. Defendant's memorandum, at 17. Absent is any argument that the plaintiff must prove the biological means of injury, because no such requirement exists.[29] See e.g., *In re Traylsol Products Liability Litigation*, 2010 WL 4102247, *4 (S.D.Fla.2010) ("biological plausibility is a factor to be considered in making this determination, and that a causal relationship can be established even when the mechanism of action is unknown."); citing *In re Seroquel Prods. Liab. Litig.*, 2009 WL 3806435, at *8–9 (M.D. Fla. June 23, 2009); *In re Accutane Prods. Liab.*, 511 F.Supp.2d 1288, 1295–96 (M.D.Fla.2007)). Although the plaintiffs must prove specific causation, to the satisfaction of the trier of fact, this is not analogous to proving the specific bodily interaction or mechanism which underlies that causation. More importantly,

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[29]The Tenth Circuit recognized this, stating:

> [W]e do not believe that a medical expert must always cite published studies on general causation in order to reliably conclude that a particular object caused a particular illness. The first several victims of a new toxic tort should not be barred from having their day in court simply because the medical literature, which will eventually show the connection between the victims' condition and the toxic substance, has not yet been completed. If a properly qualified medical expert performs a reliable differential diagnosis through which, to a reasonable degree of medical certainty, all other possible causes of the victims' condition can be eliminated, leaving only the toxic substance as the cause, a causation opinion based on that differential diagnosis should be admitted.

Turner v. Iowa Fire Equip. Co., 229 F.3d 1202, 1209 (8th Cir.2000) (internal quotation marks omitted); see also *Westberry*, 178 F.3d at 262 (holding that a reliable differential diagnosis alone may provide a valid foundation for a causation opinion, even when no epidemiological studies, peer-reviewed published studies, animal studies, or laboratory data are offered in support of the opinion).

Hollander v. Sandoz Pharmaceuticals Corp., 289 F.3d 1193, 1211-1212 (10th Cir.2002).

at this juncture, the plaintiffs must only demonstrate general causation. "General causation is established by demonstrating, often through review of scientific and medical literature, that exposure to a substance *can* cause a particular disease." *In re Neurontin*, 612 .F.Supp.2d 123 (citations omitted). *See also*, Green, et al., *Reference Guide on Epidemiology*, in *Reference Manual on Scientific Evidence*, 604 (Fed.Judicial Ctr. 3rd ed.2011).

Having considered the foregoing, the court will allow Dr. Bechara to testify about the increase in dopamine receptors in rats following administration of high doses of Chantix. The defendant may cross-examine on this subject. Hence, the defendant's motion is **DENIED** as to Dr. Bechara.

G. Dose-Response Relationship

Dose-response relationship refers to the concept that the greater the exposure, the greater the risk of disease from that exposure. See *Reference Guide on Epidemiology* (3rd ed.), at 603.[30] For several of plaintiff's experts,[31] the defendant asserts that the expert in question ignores evidence of dose-response relationships, relying heavily on the Eleventh Circuit's opinion in *McClain* and on *In re Accutane*

[30]As noted in the *Reference Guide*, the concept of the "dose makes the poison," a central tenet of toxicology, is attributed to Paracelsus, in the sixteenth century. *See Reference Guide on Epidemiology* at 603, n. 160. That note clarifies that a dose-response relationship "does not mean that any agent is capable of causing any disease if an individual is exposed to a sufficient dose." *Id.* Similarly, some causal agents do not exhibit a dose-response relationship. *Id.*, at 603.

[31]These include Dr. Olmstead, Dr. Furberg, Dr. Glenmullen, Dr. Boyd, and Dr. Bechara.

Products Liability, 511 F.Supp.2d 1288, 1293 (M.D.Fla.2007). The court disallowed the testimony in question in *In re Accutane* because the point at which a dose-response relationship was seen in dogs was higher than the dose prescribed for humans and because the authors of that study concluded the dosage prescribed for humans would not have a similar side effect. *Id.,* at 1293.

However, as addressed by plaintiffs' counsel at oral argument, evidence of a dose-response relationship does exist, and is included in their experts' reports and testimony. The fact that reports of depression did not increase with a higher dose of Chantix is less concerning in the numerous studies this court has examined than the number of dechallenge-rechallenge reports also contained in the literature, and which are also evidence of a dose-response relationship. The court in *In re Accutane* recognized the limits of the study relied on by the expert in question there, stating, "[h]e also has no explanation as to why his conclusion differs from the conclusion of the study itself, to wit: there is a dosage threshold below which there is no adverse effect once the drug is withdrawn." *Id.*, 511 F.Supp.2d at 1294. The expert testimony before this court has no similar shortcomings.

Similarly, the inability of the experts to identify how long an individual must take Chantix for the adverse effects to occur, or to identify to whom they will occur, are not bases for exclusion of these experts' opinions. The court notes only that

these are issues more akin to specific causation, *i.e.* that Chantix did in fact cause a particular plaintiff's injury.

H. Labeling

Defendant seeks to exclude plaintiffs' experts from testifying that the Chantix label was inadequate in anyway. This portion of the defendant's motion is directed specifically to proposed testimony of Dr. Kramer and Dr. Glenmullen. For the reasons set forth in defendant's memorandum in support of its motion to exclude the testimony of Dr. Kramer (doc. 585), the motion to exclude is **GRANTED** as to Dr. Kramer testifying concerning the adequacy of the Chantix label, as no such opinions were set forth in her expert report.

The defendant also seeks to have this court bar Dr. Glenmullen from testifying as to his opinion that the Chantix label was misleading because it did not disclose the number of patients who experienced psychiatric side effects after taking Chantix, and did not list other known side effects of Chantix. As stated previously, the court will not allow any of the plaintiffs' experts to testify to what defendant "knew." However, this is not the same as opinions on what defendant "should have known." Plaintiffs' experts may testify as to what defendant should have known and, by extension, what defendant should have disclosed on its label.

Clearly, the evidence before the court supports a reasonable jury being able to find that defendant should have known, prior to July 1, 2009, that Chantix was

suspected of causing various neuropsychiatric injuries, and in fact had numerous reports of the same before it. *See e.g.,* plaintiffs' exhibits 000751; 000875; 000891; 001266; 001430; 001461; 001715 001839 (stating "[w]hen you concede that your drug has these very serious side effects, such as suicide, the game is up in the area of public safety"); 001949; 001978; 002090; 002144; 002184 (noting number of adverse event reports); 002585 (in email from FDA stating "[t]he phrase 'While it is not known whether they are directly related to the use of the drug' was deleted because we don't want to be overly reassuring and there were at least some cases that appeared to be clearly related to use of Chantix and not to nicotine withdrawal or some other factor").

Federal regulations do not prohibit drug manufacturers from strengthening their warnings prior to FDA approval to reflect new developments and to comply with state laws. *Wyeth v. Levine*, 555 U.S. 555, 568-569, 129 S.Ct. 1187, 1196-97 (2009); citing 21 C.F.R. §§ 314.70(c)(6)(iii)(A), (C). The Supreme Court stated "it has remained a central premise of federal drug regulation that the manufacturer bears responsibility for the content of its label at all times. It is charged both with crafting an adequate label and with ensuring that its warnings remain adequate as long as the drug is on the market."). *Id*. at 555 U.S. at 570-571, 129 S.Ct. at 1197-98. Clearly, for this statement to have any meaning, what the manufacturer knew or should have known relative to what was on the label is necessarily at issue.

CONCLUSION

For the reasons set forth herein, it is **ORDERED** by the court that the defendant's motion to exclude (doc. 578) is **GRANTED IN PART** and **DENIED IN PART**. Said motion is **GRANTED** to the extent that none of plaintiffs' experts may testify as to what defendant "knew." It is further **GRANTED** to the extent that none of the plaintiffs' experts may testify to whether defendant "intentionally misled the FDA." The remainder of said motion is **DENIED**.

DONE and **ORDERED** this 21st day of August, 2012.

INGE PRYTZ JOHNSON
U.S. DISTRICT JUDGE