IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF ILLINOIS

WENDY B. DOLIN, Individually and as Independent Executor of the ESTATE OF STEWART DOLIN, Deceased,	)	Case No. 1:12-cv-06403
Plaintiff,	)	
v.	)	
SMITHKLINE BEECHAM CORPORATION D/B/A GLAXOSMITHKLINE, a Pennsylvania Corporation,	)	
Defendant.	)	

DEFENDANT GLAXOSMITHKLINE LLC'S MEMORANDUM OF LAW IN SUPPORT OF ITS MOTION TO EXCLUDE THE TESTIMONY OF DR. DAVID HEALY

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Defendant GlaxoSmithKline LLC ("GSK") submits this Memorandum of Law in Support of its Motion to Exclude the Testimony of Plaintiff's expert, Dr. David Healy, pursuant to Fed. R. Evid. 104, 702 and 703, and *Daubert v. Merrell Dow Pharms. Inc.*, 509 U.S. 579 (1993), respectfully showing the Court as follows:

I. INTRODUCTION

Should a lay jury be allowed to hear the testimony of an expert who rejects bedrock principles of scientific reliability as they are stated in the *Reference Manual on Scientific Evidence*?[1] Will an expert who rejects randomized controlled trials, evidence-based medicine, and peer-reviewed literature in favor of anecdotal reports and observations assist the trier of fact? Can an expert who has testified that it is "an entirely reasonable kind of situation" for people to take violent revenge against GSK executives or editors of the *New England Journal of Medicine* be qualified to present expert testimony against GSK? These are but a few of the many questions posed by the proffered testimony of plaintiff's expert, Dr. David Healy.

Dr. Healy is a Welsh psychiatrist who proffers the general causation opinion that paroxetine[2] can cause people to become suicidal. The opinion may be unsurprising given Dr. Healy's wholesale rejection of fundamental principles of scientific reliability and his view that more than 100 commonly-used drugs -- including Lipitor, Benadryl, and Tamiflu, for example -- cause people to become suicidal and homicidal. Indeed, in direct contravention of the basic,

[1] Federal Judicial Center, *Reference Manual on Scientific Evidence* (3d. ed. 2011) (hereinafter cited as "*Reference Manual*") (Ex. 1).

[2] Paroxetine belongs to a class of antidepressants known as selective serotonin reuptake inhibitors ("SSRIs"), which also includes medications such as fluoxetine (brand name Prozac) and sertraline (brand name Zoloft), among others. GSK marketed Paxil, the brand name of the medication. At the time of his death, Mr. Dolin was allegedly taking generic paroxetine manufactured by Mylan Pharmaceuticals, Inc., a competitor of GSK; he was not taking the brand name medication manufactured by GSK. GSK preserves and does not waive its view that it had no duty in this case and should not be liable for Plaintiff's alleged injuries because it is undisputed that Mr. Dolin did not ingest GSK's Paxil. Thus, GSK owed no duty from an alleged injury stemming from use of a competitor's medicine and its product (Paxil) never injured Mr. Dolin.

immutable principles of scientific reliability, Dr. Healy rejects randomized and controlled data in favor of anecdotal case reports and clinical observations. As Dr. Healy testified in this case, "**You know, you either observe a drug causing people to become suicidal or not. Once there's an observation like that then you can say this drug can cause people to commit suicidal [acts]**."[3] Similarly, according to Dr. Healy, **"[i]f several doctors report the same thing, it becomes almost a certainty that the drug is causing the problem reported in at least some patients**."[4] In a report authored less than a month ago, Dr. Healy claims that "***no significant adverse effect of a drug . . . has been demonstrated by means of a controlled trial.*** Controlled trials are simply not the method by which adverse effects are demonstrated."[5] For ***any*** scientist, this is the functional equivalent of saying that the earth is flat. Dr. Healy also rejects elementary statistical definitions and principles that are as universally agreed-upon as basic arithmetic. *Nobody* -- not even plaintiff's other experts -- agrees with Dr. Healy on these issues.

Dr. Healy's radical rejection of the scientific method is matched by his radical advocacy and bias against GSK and the pharmaceutical industry. Over the past several years, Dr. Healy has maintained a publicly-available blog with incendiary postings directed largely at GSK and/or its CEO, Andrew Witty. In one of the more recent postings, Dr. Healy goes so far as to suggest that it would be reasonable for people who have lost loved ones due to alleged drug side effects to act on their "fantasies of **wreaking violence on the executives of GSK**" or "**to storm an editorial meeting of the New England Journal of Medicine or the British Medical Journal**

[3] Ex. 2 [Healy Dep. in *Dolin v. GSK* ("Healy Dep."] at 246:25-247:4.

[4] http://davidhealy.org/wp-content/uploads/2012/02/DBM-Draft-Position-paper-on-Antidepressants-for-Prescribers.pdf at 13(emphasis added) (Ex. 3).

[5] Ex. 67 [Healy Report in *McCraw v. GlaxoSmithKline*] at 27(emphasis in the original).

and shoot as many dead as possible."[6] At his deposition, Dr. Healy confirmed his view that "**that's an entirely reasonable kind of situation** for people if they feel part of what's happened here has come because the doctor who put their loved one on a drug hasn't been appropriately warned."[7]

Furthermore, Dr. Healy's blog -- along with other websites that generate publicity about purported side effects of SSRIs and other drugs and offer Dr. Healy's expert services -- is maintained by Dr. Healy's company, Data Based Medicine Global Ltd. ("DBMG").[8] Plaintiff's counsel, Mr. Baum, and another plaintiff's counsel in SSRI litigation are shareholders in DBMG. This symbiotic relationship between Dr. Healy and Mr. Baum tops off Dr. Healy's enormous personal bias against GSK.

Dr. Healy's radical advocacy and extreme bias against GSK, his financial relationship with plaintiff's counsel, and, most importantly, the fact that his fundamental views of scientific reliability are so wildly contrary to the scientific establishment, make clear that he cannot pass through the *Daubert* gate. His proffered testimony violates all three of the main Rule 702 requirements: he is not qualified to testify, his opinions are not the product of any reliable methodology, and his testimony will not assist the trier of fact. Notably, on the only occasion when Dr. Healy's opinions concerning what he calls SSRI-induced suicide were subjected to review by independent court-appointed experts, his testimony on general causation was excluded under *Daubert,* based on the Court's finding that "**the flaws in Dr. Healy's methodology. . . are**

[6] *See* http://davidhealy.org/war-on-civilization-what-would-happen-if-patients-radicalize/ (emphasis added) (Ex. 4).

[7] Ex. 2 [Healy Dep.] at 331:22-332:1.

[8] This is the same company that GSK paid for Dr. Healy's deposition in this case.

glaring, overwhelming and unexplained."[9] For these and numerous other reasons set forth below, Dr. Healy's causation opinions should be excluded in their entirety.

II. FACTUAL AND LEGAL BACKGROUND

GSK incorporates by reference the "Factual and Legal Background," as set forth in Point II of GSK's companion motion to exclude the testimony of Dr. Glenmullen.

III. ARGUMENT

A. DR. HEALY IS NOT QUALIFIED TO TESTIFY BECAUSE OF HIS RADICAL ADVOCACY AND EXTREME BIAS AGAINST GSK

Dr. Healy has built a career from writing and testifying about the purported side effects of SSRIs and other psychotropic medications. Since 2012, he has maintained a publicly-available blog, where he expresses his radical views about the pharmaceutical industry and purported side effects of various drugs. According to Dr. Healy, all controlled trials, all evidence-based guidelines promulgated by professional organizations, and all peer-reviewed literature is controlled by the pharmaceutical industry, and therefore, cannot be relied upon.[10] Dr. Healy also tells his audience that more than 100 commonly-used drugs -- including Lipitor, Benadryl, and Tamiflu, for example -- cause people to become suicidal and homicidal.[11]

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[9] *Miller v. Pfizer, Inc.*, 196 F. Supp. 2d 1062, 1085 (D. Kan. 2002) (emphasis added), *aff'd*, 356 F.3d 1326 (10th Cir. 2004).

[10] *See e.g.,* http://wp.rxisk.org/how-to-use-rxisk-if-you-are-not-taking-a-drug/ ("The fact of the matter is that controlled data for a number of reasons laid out on davidhealy.org is the best method ever invented for hiding the side effects of a drug.") (Ex. 5); Dr. Healy's December 4, 2012 lecture, *The End Of Medicine* (available at http://wp.rxisk.org/videos/) at 47:36-47:50. ("The guidelines by NICE and others are written on the basis of the published evidence which is controlled totally by the pharmaceutical industry which says you do this, this and this for our condition x, y and a zed. Increasingly I don't, I do the opposite."); http://davidhealy.org/shocking-the-homeland ("pretty well all the trials published in even the best journals are likely to be ghostwritten.") (Ex. 7)

[11] *See* http://davidhealy.org/left-hanging-suicide-in-bridgend/(Ex. 8); *see also* Ex. 2 [Healy Dep.] at 232:9-19 (acknowledging his statements that "in the course of a day or two, I was able to compile a list of 98 drugs that can cause you to commit suicide. It's more than that now, after the post went up I sat there thinking about a bunch more, *so it's well over a hundred different drugs that can cause you to commit suicide from antimalarial drugs to antibiotics to anti-itch drugs to a range of other drugs can all*

In numerous incendiary postings, Dr. Healy claims that the pharmaceutical industry "rapes" patients,[12] compares GSK's insistence on statistically-significant findings to sexual child abuse by Catholic priests,[13] paints GSK's CEO as Frankenstein,[14] and accuses GSK of widespread cover-up of adverse events that dwarfs the Nazis' cover-up of the Holocaust.[15] Indeed, on DavidHealy.Org, nearly forty postings since January 2012 have focused on GSK and/or its CEO, Andrew Witty.

In one of the more recent postings, authored five days after the Charlie Hebdo terrorist shootings in Paris,[16] Dr. Healy goes so far as to suggest that it would be reasonable for people who have lost loved ones due to alleged drug side effects to take violent revenge against pharmaceutical industry executives or editors of the *New England Journal of Medicine*:

> Many of those who blog or lobby – decent people – will almost certainly have had fantasies of **wreaking violence on the executives of GSK**, or Pfizer, even on paragons of data transparency such as Patrick Vaillance and Andrew Witty, when they find that in some sense these executives "knew" of the capacity of drugs like the SSRIs to cause suicide . . . **But its** [sic] **as difficult to imagine succeeding in an effort to get at a senior pharmaceutical executive** as it is to imagine getting to Barack Obama, Francois Hollande or David Cameron. **In lieu of a senior company person, what about a journal editor?** These are the people who are responsible for letting pharma have whatever they want published without having to provide data. . . . **So if one those** [sic] **who have been bereaved by the latest brand name wonder drug were to storm an editorial meeting of the New England Journal of Medicine or the British Medical Journal and shoot as many dead as possible, would we call that person a criminal, an extremist or a crazed fundamentalist?**[17]

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cause you to commit suicide, and if they can cause you to commit suicide they can cause you to commit homicide or violence also.") (emphasis added).

[12] "Pharmaceutical Rape" at http://davidhealy.org/pharmaceutical-rape/(Ex. 9).

[13] "Church of GSKology" at http://davidhealy.org/the-church-of-gskology/(Ex. 10).

[14] "Persecution: Brand Fascism" at http://davidhealy.org/persecution-brand-fascism/(Ex. 11).

[15] "Magna Pharma" at http://davidhealy.org/magna-pharma/(Ex. 12).

[16] Ex. 2 [Healy Dep.] at 327:4-23.

[17] *See* http://davidhealy.org/war-on-civilization-what-would-happen-if-patients-radicalize/ (emphasis added) (Ex. 4).

Remarkably, at his deposition, Dr. Healy acknowledged that his blogs are, in part, *aimed at people whose loved ones had committed suicide while on SSRIs*[18] and testified that "it is entirely reasonable" for these people to become murderous:

> Of people who have been left behind, yes, when they come to the conclusion that a drug has caused the problem, that the person -- their son or husband or wife or whatever -- has ended up dead because of use of one of these drugs, they become very unhappy **and potentially murderous. I think we should all recognize that that's an entirely reasonable kind of situation** for people if they feel part of what's happened here has come because the doctor who put their loved one on a drug hasn't been appropriately warned.[19]

Incomprehensibly, Dr. Healy asserted at his deposition that his blogging to this audience about "wreaking violence" on GSK executives and journal editors was actually likely to reduce the risk of such an occurrence![20]

Dr. Healy's animus toward GSK is further compounded by his belief that GSK (i) had an influence on his loss of a faculty position at the University of Toronto[21] and (ii) may be behind his current investigation by the General Medical Council, which could result in the loss of his license to practice medicine.[22] Although he was unable to cite any support for this speculation, Dr. Healy claimed that he hasn't "ruled out in [his] mind that GSK could have a role in the whole thing."[23]

To top off this enormous personal bias against GSK, Dr. Healy is also a business partner of plaintiff's counsel, Michael Baum, and another plaintiff's counsel in SSRI litigation, Andy Vickery. Dr. Healy is the founder and main shareholder of DBMG, a UK for-profit Company.[24]

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[18] Ex. 2 [Healy Dep.] at 158:3-159:10.
[19] Ex. 2 [Healy Dep.] at 331:15-332:1.
[20] *Id.* at 353:4-10.
[21] *Id.* at 449:8-450:22.
[22] *Id.* at 447:7-449:11.
[23] *Id.* at 449:8-11.
[24] Ex. 13 [Healy Report in *Dolin v. GSK* ("Healy Report")] at Healy C.V. p. 3; Ex. 14 [Data Based Medicine Limited ("DBML" is the predecessor to DBMG) 2011 Annual Return]; Ex. 15 [DBMG

Mr. Baum and Mr. Vickery are also shareholders in DBMG, although their names are misspelled in DBMG's corporate filings, obscuring their identities.[25] DBMG operates RxISK.org, a website that contains information about purported side-effects of specific SSRIs and other pharmaceuticals.[26] This information is based solely on adverse event data, rather than any controlled studies.[27] In Dr. Healy's words, "when it comes to working out whether a drug cause [sic] a problem, the RxISK data will be a much better bet than the Clinical Trial literature."[28]

The website invites the users to use its RxISK eConsult service by consulting with Dr. Healy and his colleagues about the purported side effects for a fee or retaining him as an expert witness.[29] The website notes that "[y]our counsel may wish to retain us directly to have legal privilege protection."[30] Moreover, Dr. Healy has referred claimants with potentially drug-induced side-effects to Mr. Baum and Mr. Vickery.[31] Finally, RxISK hosts Dr. Healy's blog, and SSRI Stories, a website which "focuses primarily on problems caused by selective serotonin reuptake inhibitors (SSRIs)."[32] These websites generate publicity about purported side effects of SSRIs and other drugs and promote RxISK eConsult, thereby promoting the financial interests of Dr. Healy, Mr. Baum, and Mr. Vickery.

Company Check Shareholder's Summary]; Ex. 16 [DBMG Datalog Company Overview]; Ex. 2 [Healy Dep.] at 85:20-86:15, 93:11-97:22, 119:7-121:19.

[25] Ex. 14 [DBML 2011 Annual Return]; Ex. 15 [DBMG Company Check Shareholder's Summary]; Ex. 2 [Healy Dep.] at 121:20-124:7.

[26] http://wp.rxisk.org/about/(Ex. 17); Ex. 2 [Healy Dep.] at 93:11-94:10.

[27] Ex. 2 [Healy Dep.] at 166 ("Q: Now, your website provides adverse event data compiled by the FDA. A: There's adverse event data compiled by FDA, there's also Health Canada data and there's also RxISK data."); Ex. 18 [Healy Dep. in *Kuykendall v. Forest Labs. Inc.*] at 271:19-22 ("Q. What is RxISK.org? A. RxISK.org is an adverse event reporting website. It's a website that makes available the FDA's adverse event data. . . .").

[28] Ex. 2 [Healy Dep.] at 175.

[29] https://econsult.rxisk.org/how-does-it-work/(Ex. 19).

[30] *Id.*

[31] Ex. 2 [Healy Dep.] at 34:10-36:19.

[32] http://ssristories.org (Ex. 20); Ex. 2 [Healy Dep.] at 98:2-100:23.

In short, on top of Dr. Healy's extreme animus against GSK, his financial and other interests are so aligned with those of Mr. Baum and the plaintiff as to be virtually indistinguishable. Courts have excluded expert testimony under far less compelling circumstances. As Judge Posner explained, the court must be vigilant in precluding testimony from "expert witnesses who are 'often the mere paid advocates or partisans of those who employ and pay them, as much so as the attorneys who conduct the suit.'"[33] Indeed, both Judges Posner and Easterbrook have repeatedly affirmed decisions excluding experts who were biased advocates for their clients rather than objective witnesses; and Judge Posner has even cautioned that such behavior may render an expert unfit to testify in *any* future case.[34]

Similarly, as emphasized by several district courts, "**where an expert becomes an advocate for a cause, he therefore departs from the ranks of an objective witness, and resulting testimony would be unfairly prejudicial and misleading**."[35] Thus, where, as here, an expert becomes "a mere proxy for a party in [the] case . . . his extreme partisanship renders

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[33] *Olympia Equip. Leasing Co. v. Western Union Tel. Co.*, 797 F.2d 370, 382 (7th Cir. 1986) (reversing the trial judge's refusal to grant defendant judgment notwithstanding a jury verdict where an expert's testimony was unsound and plainly biased in favor of plaintiff), *quoting Keegan v. Minneapolis & St. Louis R.R.*, 78 N.W. 965, 966 (Minn. 1899); *accord Miller v. Lenz*, No. 08-773, 2010 WL 252287, at *2 (N.D. Ill. Jan. 20, 2010) *citing Olympia*, 797 F.2d at 382.

[34] *See Emerald Invs. Ltd., P'Ship v. Allmerica Fin. Life Ins. and Annuity Co.*, 516 F.3d 612, 617-18 (7th Cir 2008) (Posner, J.) (affirming exclusion of expert who had "demonstrated a willingness to abandon the norms of his profession in the interest of his client. Such a person cannot be trusted to continue as an expert witness in the case in which he has demonstrated that willingness, and perhaps not in other cases either"); *Mid-State Fertilizer Co. v. Exchange Nat'l Bank of Chicago*, 877 F.2d 1333, 1340 (7th Cir. 1989) (Easterbrook, J.) (sustaining trial court's decision to disregard expert affidavit "because ukase in the guise of expertise is a plague in contemporary litigation . . . [and the expert here] cast aside his scholar's mantle and became a shill for [plaintiff]"); *Minasian v. Standard Chartered Bank*, PLC, 109 F.3d 1212, 1216 (7th Cir. 1997) (Easterbrook, J.) (affirming trial court's refusal to admit expert affidavit that "exemplifies everything that is bad about expert witnesses in litigation. It is full of vigorous assertion . . . carefully tailored to support plaintiffs' position…").

[35] *Viterbo v. Dow Chem. Co.*, 646 F. Supp. 1420, 1425-26 (E.D. Tex. 1986) (emphasis added), *citing Johnston v. United States*, 597 F. Supp. 374 (D. Kan. 1984); *accord In re Air Crash Disaster at Detroit Metro. Airport on Aug. 17, 1987*, 737 F. Supp. 427, 430 (E.D. Mich. 1989) (quoting *Viterbo* and excluding the opinions of an expert who was "an ardent supporter and a leader of the Right to Life movement, and, as such, his opinion regarding the viability of a fetus cannot be accepted as objective").

any testimony that he could provide unhelpful . . . . [and he] is not qualified to serve as an expert witness."[36]

The decision in *Johnston v. United States* is particularly apposite. There, another district court excluded two experts who proffered testimony about dangerous radiation levels in a case alleging that plaintiffs developed cancers from radiation exposure.[37] The court found that the experts held views that ran counter to "the vast majority of competent, respected scientists in this field" and refused to accept "the consensus reports of [relevant scientific] committees as reliable authorities."[38] In precluding the experts because they "have become advocates for a cause and have therefore departed from the ranks of objective witnesses," the court emphasized both the experts' vociferous advocacy (in their professional careers and in litigation) for their minority opinion and their contempt for scientists and professional organizations with contrary views.[39]

The court recounted with concern that one expert "claims that the recognized authorities such as [UN and governmental scientific committees] are all wrong because the scientists serving on these committees have some vague connection with government grants," while the other expert claims certain reports from committees formed by the National Academy of Sciences are a "'shocking mishandling of scientific evidence,'" "arbitrary and 'without scientific foundation'" and are "'seriously flawed,'" with procedures that "'can be rejected out of

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[36] *In re Comm'l Money Ctr., Inc.*, 737 F. Supp. 2d 815, 844 (N.D. Ohio 2010); *see also Borgognone v. Trump Plaza*, No. 98-6139, 2000 WL 341135, at *4 (E.D.N.Y. Mar. 9, 2000) (excluding expert whose claim calls "into serious question his objectivity, and strongly suggests instead that [he] has abandoned his obligation under Rule 702 to 'assist the trier of fact' in favor of partisan advocacy on behalf of the plaintiff's cause"). *C.f. Conde v. Velsicol Chem. Corp.*, 804 F. Supp. 972, 984 (S.D. Ohio 1992) (permitting plaintiff to testify as expert where, among other things, there was no evidence he had "preconceived notions before the litigation commenced") *differentiating Viterbo,* 646 F. Supp. at 1425-26 and *In re Air Crash*, 737 F. Supp. at 430.

[37] *Johnston,* 597 F. Supp. at 409-15.

[38] *Id.* at 410-11.

[39] *Id.* at 411.

hand.'"[40] The court found that this "**dramatic conflict with all of the world's radiation experts creates a bias in him which destroys his credibility as an objective expert witness in radiation cases. His obsession blinds his objectivity!**"[41]

Dr. Healy's extreme bias against GSK and his financial ties to plaintiff's counsel make it impossible for him to proffer any objective testimony in this case. Thus, he should be precluded from testifying on this basis alone.

B. DR. HEALY'S WHOLESALE REJECTION OF BEDROCK PRINCIPLES OF SCIENTIFIC RELIABILITY SHOWS THAT HIS METHODOLOGY IS FUNDAMENTALLY UNRELIABLE AND HIS TESTIMONY CANNOT ASSIST THE TRIER OF FACT

The *Reference Manual on Scientific Evidence* (the "Manual") provides guidelines to federal judges in evaluating the reliability of scientific evidence. In doing so, the Manual describes certain basic principles of scientific evidence that are plainly *beyond dispute* in the scientific community. As shown by way of some examples below, Dr. Healy's views are completely contrary to these bedrock scientific principles described in the Manual, which are meant to guide this Court in evaluating the reliability of scientific testimony:

Reference Manual on Scientific Evidence	**Dr. Healy**
"This type of study, called a randomized trial, clinical trial, or true experiment, is considered the gold standard for determining the relationship of an agent to a health outcome or adverse side effect."[42] "Randomized controlled experiments are ideally suited for demonstrating causation"[43]	"Clinical trials are the gold standard way to hide adverse events."[44] "The repetition that RCTs [randomized controlled trials] are a gold standard for everything and good case reports are anecdotes is deliberate propaganda."[45]

[40] *Id.* at 411-12.
[41] *Id.* (emphasis added).
[42] Ex. 1 [*Reference Manual*] at 555.
[43] *Id.* at 218.
[44] Ex. 2 [Healy Dep.] at 281:20-282:6
[45] http://davidhealy.org/cri-de-coeur/(Ex. 21).

"There are, however, some basic questions to ask when appraising causal inferences based on empirical studies: • Was there a control group? *Unless comparisons can be made, the study has little to say about causation*."[46] "In summary, data from a treatment group without a control group generally reveal very little and can be misleading. ***Comparisons are essential.***"[47]	"The fact of the matter is that controlled data for a number of reasons laid out on DavidHealy.org is the best method ever invented for hiding the side effects of a drug. . . . When it comes to working out whether a drug causes a problem, the RxISK data [i.e., uncontrolled adverse event data] will be a much better bet than Clinical Trial literature."[48] ". . .but in terms of determining whether the problem happens or not, that's a different issue and case studies can definitely be more -- conclusive than controlled trials can be."[49] "***In fact, no significant adverse effect of a drug, birth defect or otherwise, has been demonstrated by means of a controlled trial.*** Controlled trials are simply not the method by which adverse effects are demonstrated."[50]
"[U]nsystematic clinical observations or case reports" are "at the bottom of the evidence hierarchy."[51] "Anecdotal evidence usually amounts to reports that events of one kind are followed by events of another kind. Typically, the reports are not even sufficient to show association, because there is no comparison group."[52]	"If several doctors report the same thing, it becomes almost a certainty that the drug is causing the problem reported in at least some patients."[53] "You know, you either observe a drug causing people to become suicidal or not. Once there's an observation like that then you can say this drug can cause people to commit suicidal [acts]."[54]
"If the relative risk is less than 1.0, the risk in exposed individuals is less than the risk in unexposed individuals. There is a negative association, which could reflect a protective or	"Well, you see, what we're looking at is an issue here where I've outlined to you earlier today on a few occasions, more than one occasion, that the relative risk could be 0.5 and

[46] Ex. 1 [*Reference Manual*] at 222 (emphasis added).
[47] *Id.* at 220 (emphasis added).
[48] Ex. 2 [Healy Dep.] at 175:12-16; http://wp.rxisk.org/how-to-use-rxisk-if-you-are-not-taking-a-drug/(Ex. 5).
[49] *Id.* at 272:3-9.
[50] Ex. 67 [Healy McCraw Report] at 27 (emphasis in the original).
[51] Ex. 1 [*Reference Manual*] at 724.
[52] *Id.* at 218.
[53] http://davidhealy.org/wp-content/uploads/2012/02/DBM-Draft-Position-paper-on-Antidepressants-for-Prescribers.pdf at 13 (Ex. 3).
[54] Ex. 2 [Healy Dep.] at 246:25-247:4.

curative effect of the agent on risk of disease."[55]	I could think that the data was still consistent with the antidepressant in question, that has a relative risk, an odds ratio of 0.5, causing people to commit suicide."[56]
Where the confidence interval does not include 1.0, the results are statistically significant.[57]	"It's not —I mean the fact that—that the 90 percent—95 percent confidence interval does not include one—does not include 1.0 should not be taken—should not be read as saying that this—that it is statistically significant."[58]
"Large **p**-values are consistent with the null hypothesis; small *p*-values undermine the null hypothesis. . . . If *p* is smaller than 5%, the result is statistically significant."[59]	"The p-value is immaterial."[60] "[Statistical significance] actually provides no useful information at all."[61]

In short, Dr. Healy turns the scientific method on its head -- elevating uncontrolled anecdotal case reports over randomized controlled clinical trials, and failing to subscribe to universally-agreed upon definitions of risk estimates and statistical significance. *Nobody* -- not even plaintiff's other experts -- agrees with Dr. Healy on these issues. It is axiomatic that an expert whose fundamental views of scientific reliability are so wildly contrary to the scientific establishment is using an unreliable methodology and cannot assist the trier of fact. He should not be allowed to testify before a lay jury.[62] This is the very purpose of Rule 702 and yet another reason why Dr. Healy's testimony must be excluded.

[55] Ex. 1 [*Reference Manual*] at 567.
[56] Ex. 22 [Healy Dep. in *In re Celexa Prods. Liab. Litig.*] at 176:6-12.
[57] Ex. 1 [*Reference Manual*] at 581.
[58] Ex. 22 [Healy Dep. in *In re Celexa*] at 227:4-8.
[59] Ex. 1 [*Reference Manual*] at 291.
[60] Ex. 23 [Healy Dep. in *Tucker v. SmithKline Beecham*] at 346:4.
[61] Ex. 24 [Healy Dep. in *Ebel v. Eli Lilly and Co.*] at 261:11-12.
[62] *Johnston,* 597 F. Supp. at 411-12 (excluding expert with radical views contrary to the scientific establishment; "This Court cannot believe that all of the most eminent radiation scientists in this country and the entire world are as incompetent as Dr. Gofman claims, and that only Dr. Gofman has been able to define the true risks of radiation.")

C. DR. HEALY'S OPINION THAT PAXIL CAN CAUSE ADULTS TO COMMIT SUICIDE IS NOT BASED ON SUFFICIENT DATA AND IS NOT THE PRODUCT OF ANY RELIABLE METHODOLOGY

1. Dr. Healy Admits There Are No Epidemiological Studies Showing A Statistically Significant Association Between Paroxetine And Suicide

In Dr. Healy's words, **"I agree that there isn't a single controlled study that shows a statistically significant increased risk of completed suicide on Paxil."**[63] This admission is especially powerful given the overwhelming body of clinical trial data examined for such an association. This includes:

(1) GSK's New Drug Application ("NDA") submitted to the FDA in 1989 (analysis of 2963 paroxetine patients and 544 placebo patients)[64]

(2) GSK's April 29, 1991 suicidal ideation and behavior report to the FDA [65]

(3) The FDA's June 19, 1991 Safety Review of the 1989 Paxil NDA[66]

(4) GSK's May 2002 "apples to apples" analysis of the original NDA dataset, looking only at data from the randomized phase of placebo-controlled trials[67]

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[63] Ex. 23 [Healy Dep. in *Tucker v. SmithKline Beecham*] at 77:17-20; *see also id*. at 76:20-82:19, 235:18-237:3, 239:1-25, 241:3-7, 259:2-7; Ex. 2 [Healy Dep.] at 401:4-402:15; Ex. 25 [Healy Dep. in *Van Dyke v. GlaxoSmithKline*] at 71:15-73:25; Ex. 26 [Healy Dep. in *Kohler/Thompson v. SmithKline Beecham Corp.*] at 228:15-229:5. Dr. Glenmullen has made the same concession. Ex. 27 [Glenmullen Dep. in *Mason v. SmithKline Beecham Corp.*] at 98:9-16; Ex. 28 [Glenmullen Dep in *Kohler v. SmithKline Beecham Corp*.] at 57:15-58:7, 67:10-68:14.

[64] Ex. 29 [NDA Submission] at 183-202c. As disclosed to FDA in the original NDA, and in a subsequent April 1991 report on suicidal behavior and ideation, the two placebo suicides occurred during the placebo run-in period, a one or two-week period prior to randomization when patients are typically taken off other drugs and given placebo pills. Ex. 29 [NDA submission] at 183, 184, 202b, 202c; Ex. 30 [4/29/91 Report] at 1, 16. The run-in issue is discussed further in Point III.C.3 *infra*. Whether one counts the run-ins or not, there is no statistically significant association between paroxetine and suicide, even using Dr. Healy's improper "apples to oranges" analysis comparing controlled placebo data to a mixture of controlled and uncontrolled paroxetine data. *See id.*

[65] Ex. 30 [4/29/91 Report] at 1, 16. This contains the same suicide data as the NDA submission referenced above.

[66] Ex. 31 [6/19/91 FDA Safety Review] at 23-25. This also contains the same suicide data as the NDA submission.

(5) GSK's April 2002 analysis of a larger data set involving 6927 paroxetine patients and 4757 placebo patients[68]

(6) GSK's 2003 -2004 analyses of the paroxetine clinical trials data at the request of the European Agency for the Evaluation of Medicinal Products ("EMEA") involving 8481 paroxetine patients and 5808 placebo patients[69]

(7) GSK's 2006 analyses of its paroxetine clinical trials data involving 8958 paroxetine patients and 5953 placebo[70]

(8) The FDA's 2006 analyses of 372 clinical trials involving almost 100,000 patients for 11 antidepressants, including paroxetine.[71]

Dr. Healy's report ignores this large body of clinical trial data and literature, including his own 2005 article, which analyzed data pertaining to 36,445 patients in 345 antidepressant clinical trials and concluded that "[i]n comparing fatal suicide attempts, **we did not detect any differences between SSRIs and placebo**."[72] In fact, the article acknowledged that "estimates for patients with major depression favoured a **decrease** in suicides with SSRIs."[73]

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[67] Ex. 32 [5/10/02 Analysis], Section A (finding 0 suicides in both the paroxetine and placebo arms of the NDA placebo-controlled trials).

[68] Ex. 33 [4/2/02 Analysis] (finding 2 paroxetine and 1 placebo suicide, yielding an obviously non-significant p-value of 1.00).

[69] Ex. 34 [January 2004 EMEA submission] at 59-62, Appendix 6 (citing 1 paroxetine and 3 placebo suicides).

[70] Ex. 35 [4/5/06 GSK analysis (Briefing Document)] at 7 & fn. (citing no paroxetine or placebo suicides in the paroxetine trials for MDD patients. There was one paroxetine suicide in an SAD trial.)

[71] Ex. 36 [11/17/06 FDA analysis (Stone & Jones Clinical Review)] at 42, Table 30. For all of the SSRIs studied, the odds ratio for suicide was 0.86. The table cited 1 paroxetine and 0 placebo suicides in the paroxetine placebo-controlled trials, obviously not a significant difference. The one patient in the paroxetine trials who committed suicide was a 23 year old man being treated for social phobia. Ex. 35 [4/5/06 GSK analysis] at Appendix VII, p. 18.

[72] Ex. 37, Fergusson et al., Association between suicide attempts and selective serotonin reuptake inhibitors: systematic review of randomised controlled trials, BMJ 2/19/05; 330:1-7 at 4 (emphasis added).

[73] *Id.* at 5 (emphasis added).

Dr. Healy's admission that there is no statistically significant association between paroxetine and suicide -- particularly in the face of a large body of clinical data examined for such an association -- means that the very first step in his causation analysis is lacking. His testimony should be excluded on this basis alone.[74]

2. Dr. Healy's Disregard Of Statistical Significance And Reliance On Case Reports And Investigator "Relatedness" Assessments As Evidence Of Causation Is Contrary To Any Reliable Methodology

Given the absence of data showing a statistically significant increased risk of completed suicide on paroxetine, it is not surprising that, as repeatedly acknowledged by Dr. Healy, **no regulatory or scientific body in the world has concluded that paroxetine causes suicide in adults (or anyone else)**.[75] Dr. Healy is nonetheless able to reach this very conclusion because he is admittedly "not awfully concerned about things being statistically significant."[76] In his report, he states "whether a risk is demonstrated through a statistically significant degree is simply irrelevant."[77] Dr. Healy has even gone so far as to state that statistical significance "provides no useful information at all."[78] Because he eschews this fundamental premise of

[74] *See, e.g., Caraker v. Sandoz Pharms. Corp.*, 188 F. Supp. 2d 1026, 1033-34 (S.D. Ill. 2001) (rejecting opinions relying on statistically insignificant data); *Miller,* 196 F. Supp. 2d at 1080 (excluding the testimony of Dr. Healy in part because of his failure to "rely on studies which yield results that are statistically significant regarding the causal relationship at issue in this case"), *aff'd* 356 F. 2d 1326 (10th Cir. 2004); *Norris v. Baxter Healthcare Corp.*, 397 F.3d 878, 887 (10th Cir. 2005) ("[The Court] cannot allow the jury to speculate based on an expert's opinion… in the absence of [evidence] showing consistent, statistically significant association between breast implants and systemic disease."); *Siharath v. Sandoz Pharms. Corp.*, 131 F. Supp. 2d 1347, 1358 (N.D. Ga. 2001), *aff'd sub nom, Rider v. Sandoz Pharms. Corp.,* 295 F.3d 1194 (11th Cir. 2002); *Gen. Elec. v. Joiner*, 522 U.S. 136, 145 (1997); *In re TMI Litig.*, 193 F.3d 613, 711 (3d Cir. 1999), *amended* 199 F.3d 158 (3d Cir. 2000).

[75] Ex. 25 [Healy *Van Dyke* Dep.] at 72:16-73:25; Ex. 23 [Healy *Tucker* dep.] at 268:6-270:15; Ex. 2 [Healy Dep.] at 401:4-402:15. He has similarly testified that there is no regulatory or scientific body anywhere in the world that concluded SSRIs can cause suicide in adults. Ex. 25 [Healy *Van Dyke* Dep.] at 72:16-73:19; Ex. 23 [Healy *Tucker* dep.] at 269:15-269:19; Ex. 2 [Healy Dep.] at 401:4-402:9..

[76] Ex. 23 [Healy *Tucker* dep.] at 202:24-203:21; *see also id.* at 346:2-8; Ex. 25 [Healy *Van Dyke* Dep.] at 404:8-13; Ex. 26 [Healy Kohler/Thompson Dep.] at 362:3-11.

[77] Ex. 13 [Healy Report] at 16.

[78] Ex. 24 [Healy *Ebel* Dep.] at 261:11-12.

epidemiology, Dr. Healy claims that any risk estimate that exceeds 1.0 (and, indeed, even any risk estimate that is below 1.0), *regardless of statistical significance*, constitutes evidence that Paxil causes suicidality.[79] This approach is contrary to the fundamental principles of scientific reliability.[80]

Dr. Healy's rejection of statistical significance is especially remarkable given that his general causation opinions have previously been excluded for exactly this reason. In *Miller*, much like here, Dr. Healy proffered the opinion that exposure to the SSRI Zoloft can cause suicide by inducing akathisia.[81] Finding his analytical methods unreliable, the court admonished that to satisfy *Daubert*: "Dr. Healy . . . **must rely on studies which yield results that are statistically significant regarding the causal relationship at issue** in this case."[82] Because of his failure to require statistical significance (among other things), the court excluded Dr. Healy's general causation opinions, finding that the "flaws in Dr. Healy's methodology . . . [were] **glaring, overwhelming and unexplained** . . . ."[83]

Even Dr. Healy's fellow plaintiff experts here disagree with his rejection of statistical significance. Dr. Grimson has stated, "**if you want to reach a conclusion about causation, you have to have, as a minimum, a statistically significant association.**"[84] Dr. Glenmullen has

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[79] *See, e.g.*, Ex. 22 [Healy *Celexa* Dep.] at 174:24-176:12, 224:16-227:8.

[80] *See, e.g.*, Ex. 1 [*Reference Manual*] at 291, 567, 581.

[81] Akathisia is a syndrome described as a state of subjective or inner restlessness that is accompanied by objective motor restlessness that manifests as fidgety movements (particularly in the legs), rocking from foot to foot, pacing, or an inability to sit or stand still. *See Stedman's Medical Dictionary*, (25th ed. 1989) (Ex. 39).

[82] *Miller*, 196 F. Supp. 2d at 1080 (emphasis added). Significantly, the court's independent experts emphasized that because "even strong associations may turn out to be false . . . statistical significance – as expressed by confidence intervals, P values or both – is important in determining the stability of [an association]." *Id*. at 1079.

[83] *Id.* at 1085 (emphasis added).

[84] Ex. 40 [Grimson Dep. in *Knipe v. SmithKline Beecham Corp.*] at 23:19-22 (emphasis added). See *also* Ex. 41[Grimson *Kohler/Thompson* Dep.] at 214:21-215:13.

similarly opined that, if there is no statistically significant difference in incidence, then any numerical difference could be the result of mere chance.[85]

At the same time that he turns his back on statistical significance, Dr. Healy relies, in significant part, on case reports.[86] Case reports and case series are simply published reports of a physician's uncontrolled clinical observations in the treatment of a single patient or a series of patients. It is universally recognized in the medical and scientific communities that case reports and case series do not constitute proof of a causal relationship between ingestion of a drug and a subsequent adverse event.[87]

Unlike his peers in the scientific community, Dr. Healy apparently believes that uncontrolled challenge, de-challenge, re-challenge case reports[88] make his conclusions about

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[85] Ex. 42 [Glenmullen Dep. in *Williams v. SmithKline Beecham Corp.*] at 82:8-15; Ex. 43 [Glenmullen *Tucker* Dep.] at 58:7-13.

[86] *E.g.* Ex. 13 [Healy Report] at 6, 13-14, 34.

[87] *See In re Diet Drugs (Phentermine, Fenfluramine, Dexfenfluramine) Prods. Liab. Litig.*, MDL No. 1203, 2001 WL 454586, at *15 (E.D. Pa. Feb. 1, 2001); *McClain v. Metabolife Int'l, Inc.,* 401 F.3d 1233, 1251-54 (11th Cir. 2005) (excluding expert report, in part, because it was based on adverse event reports, which the court noted "offer[] one of the least reliable sources to justify opinions about both general and individual causation" and "[s]imply stated, case reports raise questions; they do not answer them"); *Hollander v. Sandoz Pharms. Corp.*, 289 F.3d 1193, 1209-12 (10th Cir. 2002); *Glastetter v. Novartis Pharms. Corp.*, 252 F.3d 986, 989-90 (8th Cir. 2001); *Caraker v. Sandoz Pharms. Corp.*, 188 F. Supp. 2d 1026, 1035 (S.D. Ill. 2001) ("this Court rejects the plaintiffs' experts' opinions inasmuch as they rely on these case reports"); *Miller*, 196 F. Supp. 2d at 1085 ("heavy reliance on case reports is not an accepted methodology for determining the strength of association between Zoloft and suicide. The Court therefore has no alternative but to sustain Pfizer's motion to prohibit Dr. Healy's testimony on the subject of general causation . . ."); *DeLuca v. Merrell Dow Pharms., Inc.*, 791 F. Supp. 1042, 1051 (D.N.J. 1992), *aff'd*, 6 F.3d 778 (3d Cir. 1993), *cert. denied*, 510 U.S. 1044 (1994) (adverse event reports "are not of a type of data that are reasonably relied upon by experts in the fields of epidemiology and public health to make a determination of [a] causal relationship . . . ."); *Soldo v. Sandoz Pharms. Corp.*, 244 F. Supp. 2d 434, 542 (W.D. Pa. 2003) ("plaintiff's experts' reliance on anecdotal case reports to support their causation opinions is contrary to both good scientific practice and the *Daubert* case law"); *Fabrizi v. Rexall Sundown, Inc.*, No. 01-289, 2004 WL 1202984, at *10 (W.D. Pa. June 2, 2004) (excluding general causation testimony because expert based opinion on case reports, which are not "an acceptable and/or sufficient basis for showing causation"); *Hall v. Baxter Healthcare Corp.*, 947 F. Supp. 1387, 1411 (D. Or. 1996) ("[C]ase reports and case studies are universally regarded as an insufficient scientific basis for a conclusion regarding causation because case reports lack controls.")

[88] This refers to a situation in which an individual patient's symptoms are observed when the patient is given a drug ("challenge"), taken off the drug ("de-challenge), and put back on the drug ("re-

SSRI-induced suicidality "well supported" "according to the normal canons of scientific method."[89] Dr. Healy is wrong. First, as noted in *McClain* and *Miller*, challenge-de-challenge-re-challenge experiments are still case reports and cannot offer reliable conclusions as to causation.[90] Second, Dr. Healy testified that he is not aware of any published cases of challenge-dechallenge-rechallenge with Paxil and suicidality.[91]

Dr. Healy also attempts to elevate individual investigator "relatedness" assessments from the paroxetine clinical trials into admissions of causation by GSK.[92] Such assessments are essentially nothing more than individual case reports in which the blinded investigator makes his "best guess" concerning the possible relationship between exposure and outcome and cannot reliably determine causation.[93] Moreover, Dr. Healy's methodology fails because, as he well knows,[94] numerous events occurring in patients who were taking ***placebo*** (*i.e.*, a sugar pill) were also rated as "probably related." This demonstrates the lack of reliability of such assessments -- those adverse events were obviously not caused by placebo sugar pills. Not surprisingly, the

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challenge"). Such uncontrolled observations are anecdotal, and cannot provide the type of reliable information one would get from a randomized controlled trial.

[89] Ex. 13 [Healy Report] at 13.

[90] *See McClain*, 401 F.3d at 1254-55; *Miller*, 196 F. Supp. 2d at 1076-77; *See also Glastetter,* 252 F.3d at 989; *Haggerty v. Upjohn Co.*, 950 F. Supp. 1160, 1164 (S.D. Fla. 1996), *aff'd,* 158 F.3d 588 (11th Cir. 1998); *Hall,* 947 F. Supp. at 1411; *Soldo*, 244 F. Supp. 2d at 442; *Brumbaugh v. Sandoz Pharms. Corp.*, 77 F. Supp. 2d 1153, 1156 (D. Mont. 1999); *Jones v. United States*, 933 F. Supp. 894, 899 (N.D. Cal. 1996), *aff'd,* 127 F. Supp. 3d 1154 (9th Cir. 1997); *In re Breast Implant Litig.*, 11 F. Supp. 2d 1217, 1230 (D. Colo. 1998); *Casey v. Ohio Med. Prods.*, 877 F. Supp. 1380, 1385 (N.D. Cal. 1995).

[91] Ex. 2 [Healy Dep.] at 249:10-15 ("Q. . . . And, by the way, do you know of any published cases of challenge-dechallenge-rechallenge with Paxil and suicidality or violence? A. As I sit here today I don't have any that I can give you. . . .").

[92] Ex. 13 [Healy Report] at 14.

[93] *See, e.g., Soldo*, 244 F. Supp. 2d at 545-546; *In re Accutane Prods. Liab. Litig.*, 511 F. Supp. 2d 1288, 1296 (M.D. Fla. 2007); *In re Accutane Prods. Liab. Litig., MDL No. 1626*, 2007 WL 1288354, at *5 (M.D. Fla. May 2, 2007).

[94] See Ex. 26 [Healy *Kohler/Thompson* Dep.] at 240:4-9.

FDA's view of such investigator assessments is that "[t]hese analyses are generally not expected to provide much useful information in assessing causality."[95]

Dr. Healy also devotes much pagination in his report and appendix 1 to so-called "healthy volunteer" studies,[96] yet he does not claim that a single suicide-related event occurred in the paroxetine healthy volunteer trials.[97] Nor could he, since, as noted in GSK's August/September 2003 submission to the EMEA, there were no possibly suicide-related or self-harm events in any of the paroxetine healthy volunteer trials.[98]

In short, Dr. Healy's causation opinions based on non-statistically-significant data, case reports, and investigator "relatedness" assessments are based on an unreliable methodology and must be excluded.

3. Dr. Healy's "Apples To Oranges" Re-analysis Of The Pre-1991 NDA Data Is Not A Scientifically Reliable Methodology

Even if it was not inherently suspect, Dr. Healy's "re-analysis" of the paroxetine pre-1991 NDA data could not pass muster under *Daubert* because it employs a flawed methodology. To begin with, it focuses on a small fraction of the available clinical trial data regarding paroxetine and suicidality, while ignoring the much more robust analyses of the entire clinical trials database flatly refuting his claims. The pre-1991 NDA data cited in Dr. Healy's report included 921 paroxetine and 554 placebo patients in placebo-controlled trials (2963 paroxetine

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[95] Ex. 44 [2/05 FDA Reviewer Guidance] at 9.

[96] Healthy Volunteer Studies are the first, or "Phase I", human studies conducted in connection with a New Drug Application. As their name implies, they include persons who are "healthy," i.e. who do not have the disease that the medication is being developed to treat. Their main purpose therefore is not to determine whether the drug is efficacious in treating the disease. *See* 21 C.F.R. § 312.21.

[97] He claims only that one volunteer committed suicide many months "following the study." Ex. 13 [Healy Report] at 11. The FDA has concluded that suicides even within 30 days following the conclusion of a clinical trial are too confounded to be considered related to the medication. Ex. 36 [11/17/06 FDA analysis] at 47; Ex. 70 (11/17/06 Levenson & Holland Statistical Evaluation] at 54-55.

[98] Ex. 45 [August/September 2003 EMEA submission] at 19.

and 554 placebo in both controlled and uncontrolled trials).[99] The 2006 FDA analysis includes 9951 paroxetine and 7005 placebo patients, *i.e.* over 11 times the number of NDA patients in placebo-controlled trials.[100]

Most importantly, Dr. Healy's re-analysis" is a fundamentally flawed "apples to oranges" analysis of the original pre-1991 NDA data, removing placebo run-in events from the equation because they did not occur during a randomized trial phase, but leaving in numerous paroxetine events that similarly occurred during non-randomized phases of clinical trials. Thus, Dr. Healy included in the paroxetine count events that occurred not only in placebo-controlled trials (as FDA and GSK have done), but also those occurring in active-controlled and uncontrolled paroxetine trials, where there were no patients taking placebo.[101] In fact, the overwhelming majority of possibly suicide-related events in Dr. Healy's re-analysis (35 of 40 Paxil "suicide attempts" and all 5 of the paroxetine suicides) occurred outside of the placebo-controlled clinical trials.[102]

No regulator, academic, or other objective expert has ever employed such methodology. Dr. Glenmullen has admitted that he is not aware of anyone else applying this methodology.[103] As also noted in Point III.A.5 in GSK's motion to exclude Dr. Glenmullen, the generally accepted "best way" to make the comparison between paroxetine and placebo, as acknowledged

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[99] *See, e.g.*, Ex. 13 [Healy Report] at 18-20.

[100] *See, e.g.*, Ex. 36 [11/17/06 FDA analysis (Stone & Jones Clinical Review)] at 42, Table 30.

[101] *See, e.g.*, Ex. 13 [Healy Report] at 18-20; Dr. Glenmullen has acknowledged that such an analysis comparing all events on paroxetine "whether that was in placebo -controlled-, comparator-controlled or uncontrolled versus patients on placebo" involves "comparing apples and oranges." Ex. 27 [Glenmullen *Mason* Dep.] at 252:18-253:7.

[102] Ex. 69 [2/6/02 GSK analysis] (showing 5 paroxetine and 1 placebo suicide attempts in placebo controlled studies in the 1991 NDA data); Ex. 32 [5/10/02 Analysis] (showing 0 suicides on either paroxetine or placebo in the placebo-controlled studies in the 1991 data).

[103] Ex. 46 [Glenmullen *Dolin* Dep.] at 318:24-319:4, 363:6-22. *See DeLuca,* 791 F. Supp. at 1057 ("[T]he fact that [a] methodology has not been used non-judicially weighs against its admissibility.") (*citations omitted*).

by Dr. Grimson and numerous district courts, is to conduct an "apples to apples" analysis of data only from placebo-controlled trials, rather than the unbalanced mixture of controlled and uncontrolled data that Dr. Healy employs in his analyses.[104] These same principles were emphasized by the district court in the *Diet Drugs* litigation:

> A fundamental premise of epidemiology is the use of controls or comparison groups in scientific studies. Control groups are an essential component to epidemiological studies because many diseases occur in persons who have not been exposed to a particular drug or substance under study. . . . Epidemiologists compare rates of disease in various populations to determine whether there is an increased risk of disease in those who used a particular substance in comparison to non-users. **Thus, without utilizing a control group for comparison purposes, a conclusion that a substance caused a particular condition is scientifically unreliable.** [105]

Similarly, the *Manual* states in relevant part:

> There are, however, some basic questions to ask when appraising causal inferences based on empirical studies:
>
> - Was there a control group? **Unless comparisons can be made, the study has little to say about causation**.[106]

Indeed, when assessing the possible risk of suicidality from SSRIs, FDA has relied exclusively on data from randomized, double-blind placebo-controlled trials for more than a decade. As FDA scientists stated before FDA conducted a meta-analysis of suicidality data for anti-depressants, including Paxil, in 2006: "Rates based on the pooling of data from both randomized controlled trials (RCTs) and open-label extension trials are subject to bias and could lead to misleading conclusions."[107] For this very reason, FDA requested antidepressant

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[104] *See* Ex. 38 [Grimson *Williams* Dep.] at 197:4-198:15, 203:23-204:19, 213:6-15, 426:8-17; Ex. 57 [Grimson O'Neal Dep.] at 110:11-15; Ex. 40 [Grimson *Knipe* Dep.] at 218:6-9; *see also Jones,* 933 F. Supp. at 899 (noting that using uncontrolled study to prove general causation was "not based on good science" and a "fallacious method of arriving at causation.").

[105] *In re Diet Drugs*, 2000 WL 962545, at *6

[106] *Reference Manual* at 222 (emphasis added) (Ex. 1).

[107] Ex. 68. Hammad, TA, et al., Suicide Rates in Short-term Randomized Controlled Trials of Newer Antidepressants, J. Clinical Psychopharmacology April 2006; 26(2):203-207 at 204; *see also*

manufacturers, including GSK, to submit data only from randomized, double-blind placebo-controlled trials: "As noted, we are requesting information from placebo controlled trials only. Please do not submit data from active control only studies, uncontrolled extensions of placebo controlled studies or combination drug studies."[108]

Dr. Healy's own report here acknowledges the necessity for placebo-controlled data to reach causation conclusions. He gives an example of a study of subjects with influenza who improve after taking a vitamin. "Taking this to mean that the vitamin led to a benefit in influenza would be mistaken; ***without a placebo control it is simply not possible to say***."[109] He further states: "***Uncontrolled before-and-after comparison studies are considered pre-scientific and not usually published by the better science journals***."[110] Dr. Healy then quotes FDA's Dr. Robert Temple's statement concerning an article by Simon as follows:

> He explained that the "new study doesn't have an untreated group. They have no information at all about what would have happened to those people had they not been treated. *It simply sheds no light at all on the particular point raised in the labeling or the analysis of those trials*."[111]

Thus, when it suits him, Dr. Healy advocates for placebo-controlled data. But when he needs to reach a litigation-driven opinion about paroxetine, that concern goes out the window.[112]

In sum, Dr. Healy's recalculation of data from a 26-year-old dataset based on an "apples to oranges" comparison of controlled and uncontrolled data is not a scientifically reliable

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Mason v. SmithKline Beecham Corp., 596 F.3d 387, 394 n.8 (7th Cir. 2010) ("Having a control group is important when analyzing suicidal behavior data because suicidal behavior is a symptom of depression and related diseases.").

[108] Ex. 36 [11/17/06 FDA analysis] at 50.

[109] Ex. 13 [Healy Report] at 43 (emphasis added).

[110] *Id.*

[111] *Id.* at 44 (emphasis in original).

[112] For example, at his deposition here, he stated that "controlled data . . . is the best method ever invented for hiding the side effects of a drug." Ex. 2 [Healy Dep.] at 175:13-15, 257:8-21. Continuing his double-speak, he also claimed that "case studies can definitely be more . . . conclusive than controlled trials can be." *Id.* at 272:5-9. As noted elsewhere, these assertions are flatly inconsistent with generally accepted methodology.

methodology.[113] Moreover, Dr. Healy fails to mention that *even with his unreliable manipulation, 5 paroxetine suicides (none of which occurred in placebo-controlled trials) versus 0 placebo suicides is still not statistically significant.*[114]

D. DR. HEALY'S RELIANCE ON AND EXTRAPOLATION FROM DATA FOR OUTCOMES OTHER THAN SUICIDE IS SCIENTIFICALLY UNRELIABLE

1. Dr. Healy's Opinion That Paxil Can Cause Suicidality Is Irrelevant, Not Based On Sufficient Data, And Is Not the Product Of Any Reliable Methodology

Perhaps implicitly acknowledging the difficulties of showing that Paxil can cause completed suicide, Dr. Healy's report repeatedly claims that Paxil can cause suicidality (a composite of suicidal ideation and suicidal behavior, including attempts and completed suicides) in adult patients.[115] Apart from its lack of relevance to the issue in this case, this claim has been repeatedly tested in numerous controlled studies that have failed to find a statistically significant association between the two.

For example, in June 2003, FDA expressly addressed concerns that paroxetine might induce suicidality in adults, stating: "Extensive analyses of the data from studies of Paxil in adults and from post-marketing adverse event reports **have not revealed an increase in rate**

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[113] *See In re Baycol Prods. Litig.*, 495 F. Supp. 2d 977, 991-94 (D. Minn. 2007) (excluding two of plaintiffs' experts' recalculations of prior study where recalculations involved statistical readjustments and inclusion of uncontrolled adverse event reports); *Carnegie Mellon Univ. v. Hoffmann-LaRoche, Inc.*, 55 F. Supp. 2d 1024, 1039 (N.D. Cal. 1999) (calling expert's manipulation of previously-published data to achieve results at odds with those in the publications an "armchair analysis" that does not qualify as science).

[114] Similarly, when GSK performed an "apples to apples" analysis of the NDA data in 2002 comparing only randomized placebo-controlled data for both paroxetine and placebo, there were 0 suicides in each patient group and 5 paroxetine "attempts" versus 1 placebo attempt. Neither comparison was statistically significant. Ex. 32 [5/10/02 Analysis] (showing 0 suicides on either paroxetine or placebo in the placebo-controlled studies in the 1991 data); Ex. 69 [2/6/02 GSK analysis] (showing 5 paroxetine and 1 placebo suicide attempts in placebo controlled studies in the 1991 NDA data). When Dr. Healy presents a similar "apples to apples" analysis of combined suicides and suicide attempts using only placebo-controlled data, the results, based both on numbers of patients and numbers of years exposed, are not significant. Ex. 13 [Healy Report] at 20.

[115] *See, e.g.,* Ex. 13 [Healy Rep.] at 1, 3, 5, 6, 8-9, 11-13, 15-20, 23, 26-27, 30-31, 33, 40, 46, 50.

[sic] of suicidal thoughts or suicide attempts compared to placebo."[116] This conclusion was reiterated in 2004 during hearings held to assess pediatric suicidality findings.[117]

Similarly, the data from the FDA's 2006 analyses on suicidality (the primary endpoint) illustrate **an overall protective effect for paroxetine compared to placebo**, with an odds ratio of 0.93, and a confidence interval of 0.62 to 1.42 (p=0.75).[118] This was also true for antidepressants as a whole, which had an odds ratio of 0.83, confidence interval of 0.69 to 1.00 (p=0.05).[119] On the basis of these results, FDA concluded that "the pooled estimates of studies of the adult population support the null hypothesis of **no treatment effect on suicidality**" and that antidepressants (including paroxetine) appear to be "protective for suicidality for adults . . . ."[120] These findings also prompted FDA to mandate new class labeling for paroxetine and other SSRIs, which states: "Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24."[121]

GSK's own findings are in accord. Specifically, GSK's 2003 EMEA[122] analysis found no difference in the incidence of even possibly suicide-related events between paroxetine and placebo. In fact, in every category studied, including the overall data and multiple individual indications such as depression, the odds ratios pointed in a protective direction, i.e. <1.0.[123] The company's more comprehensive 2006 analyses of the paroxetine clinical trial data (involving both MDD and non-MDD studies) likewise showed no significant difference on the primary

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[116] Ex. 47 [6/19/03 FDA Q&A] (emphasis added).
[117] Ex. 48 [9/13/04 Adcom transcript] at 187-89.
[118] Ex. 36 [11/17/06 FDA analysis] at 24, Table 15.
[119] *Id.*
[120] *Id.* at 44 (emphasis added).
[121] Ex. 49 [5/07 FDA labeling requirements].
[122] GSK's submission to the European Agency for the Evaluation of Medicinal Products.
[123] Ex. 45 [August/September 2003 EMEA submission] at 24, Table 2.4.

outcome -- suicidality (defined there as "definitive suicidal behavior and ideation").[124] In fact, both the overall analysis and the analysis for Mr. Dolin's age group pointed in a **protective** direction for this outcome.[125]

In sum, all of these data point to only one reasonable conclusion: after repeated testing, there is simply no reliable basis to conclude that paroxetine can cause even suicidality (let alone suicide) in 57-year-old patients such as Mr. Dolin, or, for that matter, any adult patient of any age. Dr. Healy's report does not cite any data to the contrary to support his conclusions. Thus, as in *General Electric Co. v. Joiner,* there is "simply too great an analytical gap between the data and the opinion proffered."[126]

2. As Acknowledged By Plaintiff's Other Causation Experts, Dr. Healy's Extrapolation From Data Regarding Suicidal Behavior Is Scientifically Unreliable

Faced with the lack of any evidence of a significant association between paroxetine and suicide or even suicidality, Dr. Healy next attempts to extrapolate from data pertaining to suicidal behavior (a composite of preparatory acts, suicide attempts, and completed suicide that was a secondary endpoint of the 2006 GSK and FDA analyses). However, as admitted by plaintiff's other experts, it is ***necessary*** to consider data for completed suicide (as opposed to suicidal thinking or behavior) to determine whether paroxetine is associated with suicide.[127]

While lay persons might assume that suicide and suicidality or suicide attempts are sufficiently similar to allow extrapolation from one to the other, that notion has been repeatedly rejected by the scientific community. As one authoritative treatise on suicidology states, "Clinicians need to be extremely careful not to generalize inappropriately from their partially

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[124] Ex. 35 [4/5/06 GSK analysis], Table 2.01 (all indications)
[125] *Id.* Table 2.01 (all indications), Table 2.08 (all indications).
[126] 522 U.S. at 146.
[127] Ex. 27 [Glenmullen *Mason* Dep.] at 325:1-3; Ex. 57 [Grimson Dep. in *O'Neal v. SmithKline Beecham*] at 150:3-13.

self-destructive patients to completed suicides … There are many important differences between completed suicides and nonfatal suicide attempts."[128] Other experts agree.[129]

Dr. Healy himself stated in his deposition in this case:

> . . . I think **in terms of looking at the clinical trial data for the purposes of trying to work out what contribution the clinical trial data may make to an assessment of whether the drugs cause a problem or not, it's much better to go on the clear behavior, that is acts of completed suicides** . . . .[130]

Similarly, Dr. Healy's fellow expert, Dr. Glenmullen, has stated: **". . . you can't equate suicide with a suicide attempt, let - let alone starting to act on a plan."**[131] Dr. Grimson agrees that "in a case involving a completed suicide, the most important comparison would be Paxil patients versus placebo patients who committed suicide. . . . "[132] Even more directly, Dr. Grimson acknowledged that **"any evaluation of whether Paxil is associated with completed suicides would require looking at data of completed suicides**."[133] Indeed, Drs. Grimson and Glenmullen have even testified that they do not dispute FDA's conclusion that the data in the

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[128] Maris RW, Berman AL, Silverman MM, Comprehensive Textbook of Psychiatry, at 5 (Guilford Press 2000) (Ex. 50).

[129] *See,* Ex. 51 [Simon, GE, et al., Suicide Risk During Antidepressant Treatment, Am J Psychiatry 2006; 163:41–47] at 45-46 ("We still found that suicide attempts and suicide deaths are quite distinct phenomena. . . . We urge caution in using data regarding suicidal ideation or suicide attempts to make predictions regarding risk of suicide death."); Ex. 52 [Reith, DM, et al., Assessing the Role of Drugs in Suicidal Ideation and Suicidality, CNS Drugs 2007; 21(6):463-72] at 468 ("The progression from suicidal ideation to self-harm and then to suicide is by no means absolute . . . . Hence, suicidal ideation and behaviours should be analysed as a separate outcome to suicide."); Ex. 53 [Kessler, RC, et al., Trends in Suicide Ideation, Plans, Gestures, and Attempts in the United States, 1990-1992 to 2001-2003, JAMA 2005, 293(20):2487-2495] at 2487; Ex. 55 [Safer, DJ, et al., Do antidepressants reduce suicide rates?, Public Health 2007, 121:274-77] at 275. *See also* Appendix 1 to GSK's motion to exclude Dr. Glenmullen; *see generally* Ex. 54 [Klein, DF, The Flawed Basis for FDA Post-Marketing Safety Decisions: The Example of Anti-Depressants and Children, Neuropsychopharmacology 2005:1-11].

[130] Ex. 2 [Healy Dep.] at 370:18-24 (emphasis added). Dr. Healy has also testified that the "most robust" data is "clearly completed suicides." Ex. 56 [Healy Dep. in *Moote v. Eli Lilly and Co.*] at 199:2-3.

[131] Ex. 27 [Glenmullen *Mason* Dep.] at 325:1-3 (emphasis added).

[132] Ex.40 [Grimson *Knipe* Dep.] at 286:5-9; *see also id.* at 299:14-18.

[133] Ex. 57 [Grimson *O'Neal* Dep.] at 150:9-13 (emphasis added); *accord* Ex. 58 [*Grimson Dep. in Forst v. SmithKline Beecham Corp.*] at 146:6-12.

adult trials of antidepressants "**was not sufficient to reach any conclusion about drug effect on suicide.**"[134]

Thus, Dr. Healy's extrapolation from data pertaining to suicidal behavior is scientifically unreliable.

3. Even if Dr. Healy's Extrapolation Were Appropriate (Which It Is Not), The Suicidal Behavior Data Fail To Support the Conclusions Dr. Healy Draws

a) 2006 GSK Analysis

Dr. Healy selectively relies on the 6.7-fold increased risk (Odds Ratio or "OR") from GSK's 2006 meta-analysis, which is a single result for a secondary outcome (suicidal behavior) in a subpopulation of a subpopulation of patients (patients with major depressive disorder, within the larger subpopulation of patients with depression). This reliance is inappropriate for the following reasons.

First, Dr. Healy ignores the primary outcome of the analysis (suicidality) as well as the data for completed suicide, the only outcome relevant in this case. [135] As noted in Point III.D.1, *supra*, the results for the primary outcome for the overall data actually pointed in a protective, though non-statistically significant, direction.[136] As to suicide, in the entire clinical trials database analyzed in 2006, there was one suicide by a paroxetine patient (out of 8958) versus 0 suicides on placebo (out of 5953), also a non-significant difference.[137] As this Court has emphasized, "such selective use of facts fail[s] to satisfy the scientific method and *Daubert*."[138]

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[134] Ex. 27 [Glenmullen *Mason* Dep.] at 68:4-11; Ex. 41 [Grimson *Kohler/Thompson* Dep.] at 30:18-31:6; Ex. 59 [paroxetine label] at 12 (emphasis added).

[135] Ex. 13 [Healy Report] at 16-17

[136] Ex. 35 [4/5/06 GSK analysis] at Table 2.01 (all indications).

[137] *Id.* at appendices IV and VII

[138] *Holden Metal & Aluminum Works, Ltd*., No. 00C 0191 2003 WL 1797844, at *2 (N.D. Ill. Apr. 3, 2003) (Zagel, J.); *see also Lust by and Through Lust v. Merrell Dow Pharms., Inc.*, 89 F.3d 594, 596 (9th Cir. 1996) (excluding an expert whose methodology was to "pick and ch[o]ose from the

Second, Dr. Healy fails to mention that this secondary outcome in this subpopulation was analyzed in two different ways, and the analysis that was based on the methodology previously employed by FDA yielded a clearly non-significant odds ratio ("OR") of 1.6 (CI 0.6,4.2, p=0.363).[139] Similarly, while Dr. Healy cites the other analysis of this outcome which yielded a 6.7 OR, that result is not statistically significant by standard convention, as it bears a p-value of .058.[140]

Third, the odds ratio for MDD suicidal behavior relied upon by Dr. Healy was but one of numerous calculations of secondary endpoints[141] in multiple subpopulations contained in the GSK analysis. Yet Dr. Healy made no adjustment for the multiple comparisons, contrary to

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scientific landscape and present the Court with what he believes the final picture looks like. This is hardly scientific."); *In re Zoloft (Sertraline Hydrochloride) Prods. Liab. Litig.*, 26 F. Supp. 3d 449, 460-62 (E.D. Pa. 2014) ("The Court finds that the expert report prepared by Dr. Bérard does selectively discuss studies most supportive of her conclusions, as Dr. Bérard admitted in her deposition, and fails to account adequately for contrary evidence, and that this methodology is not reliable or scientifically sound."); *Cano v. Everest Minerals Corp.*, 362 F. Supp. 2d 814, 850 (W.D. Tex. 2005) ("[Expert's] methodology for ruling in the radiation exposure in relation to each of the Plaintiff's cancers is not reliable.… [R]ather than truly evaluating the studies that he listed as supporting his conclusions, [expert] simply sifted through the literature to pick and choose positive relative risks between ionizing radiation (of any type, source, and dose) and a particular Plaintiff's cancer."); *Caraker*, 188 F. Supp. 2d at 1033-34; *Newton*, 243 F. Supp. 2d at 680-81.

[139] Ex. 35 [4/5/06 GSK analysis] at Table 2.04.

[140] As the authors of the analysis noted, GSK referred to this result as "statistically significant" because the confidence interval did not include one, even though (i) the p-value exceeded 0.05 and (ii) the OR was not adjusted for multiple comparisons performed. Thus, the odds ratio was non-significant by conventional criteria, even without adjusting the p-value for multiple comparisons. Ex. 60 [Kraus, J., et al., *Clinical features of patients with treatment-emergent suicidal behavior following initiation of paroxetine therapy*, Journal of Affective Disorders 2010; 120:40-47] at 42, 44. Dr. Glenmullen, plaintiff's other general causation expert, has acknowledged that it is a convention that one must have a p-value of less than .05 in order to be statistically significant. Ex. 43 [Glenmullen *Tucker* Dep.] at 58:7-13 Dr. Grimson, another plaintiff's expert, states that, if there is an inconsistency between the p-value and the confidence interval, he would determine significance based on the p-value. Specifically, if he had a p-value that was higher than 0.05 but the confidence interval did not include 1.0, he would consider that to be a non-significant result. Ex. 40 [Grimson *Knipe* Dep.] at 112:19-114:9, 279:3-282:15. Accordingly, Dr. Grimson would agree that the 2006 GSK analysis result for definitive suicidal behavior for the MDD sub-population is not statistically significant at the conventional 0.05 level. Ex. 58 [Grimson *Forst* Dep.] at 178:4-180:19; Ex. 41 [Grimson *Kohler/Thompson* Dep.] at 60:1-17.

[141] Every analysis of clinical trial data has a primary outcome, or "endpoint," which is the principal focus of the analysis, be it a measure of efficacy or safety. Analyses also typically have "secondary" outcomes, or endpoints, which look at other measures of efficacy or safety.

generally accepted methodology as recognized by the FDA, the *Manual*, and plaintiff's own expert statistician, Dr. Grimson.[142] Indeed, Dr. Healy has admitted that he cannot identify a biological mechanism that would cause him to believe that paroxetine increases the risk of suicidal behavior in MDD patients but not in patients taking it for other indications.[143] This concession further highlights the likelihood that a single (arguably) nominally significant odds ratio found only in the MDD subpopulation is likely an artifact of multiple comparisons, rather than some suicidal effect of paroxetine that applies only to MDD patients.

Fourth, Dr. Healy fails to mention that the majority of the attempts for paroxetine (8 of 11) were in younger adults aged 18-30, not in Mr. Dolin's age group.[144] As emphasized by another district court under identical circumstances, "[i]t is therefore misleading to lump individuals aged 18 to 30 years in the 25–to–64 age group."[145] As described in more detail *infra*, that case -- *Vanderwerf v. SmithKline Beecham Corp* -- involved a claim (albeit by a different expert) that paroxetine caused an adult male to commit suicide based upon data *identical* to those relied by Dr. Healy in this case. That court correctly concluded that the 6.7 OR can be construed

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[142] *See* Point II.C.4 -- "Is the Association An Artifact of Multiple Comparisons?" -- of GSK's motion to exclude the testimony of Dr. Glenmullen. *See also Boughton v. Cotter Corp.,* 65 F.3d 823, 835 n. 20 (10th Cir. 1995) (Even if the elevated levels of lung cancer for men had been statistically significant, a court might well take account of the statistical "Texas Sharpshooter" fallacy in which a person shoots bullets at the side of a barn, then, after the fact, finds a cluster of holes and draws a circle around it to show how accurate his aim was…. With independent variables, one would expect one statistically significant reading in every twenty categories at a 95% confidence level purely by random chance.")

[143] Ex. 26 [Healy *Kohler/Thompson* Dep.] at 113:16-114:23.

[144] Ex. 35 [4/5/06 GSK analysis] at 6, 9. Dr. Healy admits that there is no there is no published placebo-controlled study or analysis in the worldwide literature showing a statistically significantly increased risk of **suicide attempts** on Paxil in adults over the age of 30. Ex. 2 [Healy Dep.] at 403:4-404:3. The elevated, though not statistically significant, odds ratio for the secondary outcome of suicidal behavior in the MDD subpopulation is also inconsistent with (1) the failure to find any difference between Paxil and placebo on the primary outcome, (2) the protective trend with respect to rating scale identified emergent or worsening suicidality, (3) the fact that this finding was not replicated in the larger adult clinical trials database, and (4) none of the suicide "attempts" in this population was successful. Ex. 61 [Rothschild Report] at 23.

[145] *Vanderwerf v. SmithKline Beecham Corp,* 529 F. Supp. 2d 1294, 1307 (D. Kan. 2008).

"at most" as showing that "Paxil *may* increase the risk of suicidal behavior and suicide in adult patients between the ages of 18 and 30 (emphasis in the original)."[146]

Fifth, Dr. Healy's methodology also fails to assess that:

- GSK noted that a causal relationship could not be concluded, and both GSK and FDA stated that the data should be interpreted with caution due to the small incidence and absolute number of events; [147] and that GSK further advised caution in light of the retrospective nature of the meta-analysis, and the potential for confounding by the fact that the events of interest are a symptom of the psychiatric illness themselves.[148]

- It was also reported that most (9 of 11) of the paroxetine-treated patients had an identified social stressor at the time of the suicide attempt.[149]

For all of these reasons, even if this observed association could be viewed as real, it would be insufficient to establish a cause and effect relationship in any adult, much less in an adult above the age of 30. As the *Vanderwerf* court put it, under identical circumstances, **"such a conclusion would be sheer speculation."**[150]

b) 2006 FDA Analysis

Dr. Healy similarly selectively relies on a single finding from the FDA's 2006 analysis, yielding a nominally statistically significant 2.76 "relative risk" pertaining to the secondary outcome of suicidal behavior.[151] Dr. Healy's reliance on this finding as evidence of an association is not scientifically reliable for the following reasons:

First, Dr. Healy again ignores the primary outcome of suicidality and the discussion of completed suicide. As noted in Point III.D.1, *supra,* the primary outcome yielded an odds ratio (0.93) for paroxetine pointing in a protective, though not statistically significant, direction.[152]

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[146] *Id.* at 1308.
[147] Ex. 62 [GSK Dear Healthcare Professional Letter]; Ex. 63, FDA Safety Alert.
[148] *Id.*.
[149] Ex. 35 [4/5/06 GSK analysis] at 7.
[150] *Vanderwerf*, 529 F. Supp. 2d at 1308 (emphasis added).
[151] Ex. 13 [Healy Report] at 17.
[152] Ex. 36 [11/17/06 FDA analysis] at 24, Table 15.

Additionally, the assessment of completed suicide showed one suicide out of 9951 Paxil patients compared to 0 out of 7005 placebo patients in the Paxil trials, a non-significant difference.[153]

Second, Dr. Healy fails to mention FDA's caution that "although the values for some individual drugs are statistically significant at the 0.05 level, the significance of those findings ***must be discounted*** for the large number of comparisons being made."[154] The *Vanderwerf* court emphasized this fact in concluding that plaintiff's expert's failure to "discount" this finding as mandated by the FDA rendered his methodology scientifically unreliable.[155] The court emphasized that "repeated testing complicates interpretation of significance levels; if enough comparisons are made, *random error almost guarantees that some will yield significant findings, even when no real effect*."[156] Moreover, Dr. Healy himself has previously acknowledged that "[w]hen large data sets are handled, there are corrections that often need to be made because findings can be thrown up by chance."[157]

Third, Dr. Healy conveniently ignores the FDA's ultimate conclusion from this analysis that "**the net effect appears to be neutral on suicidal behavior but possibly protective for suicidality for adults between the ages of 25 and 64**."[158] **Indeed, Dr. Healy has testified that he does not dispute this conclusion.**[159] Thus, there is no basis for Dr. Healy to claim that there is an increased risk of suicidal behavior in an adult of Mr. Dolin's age.[160] The *Vanderwerf* court

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[153] *Id*. at 42, Table 30.
[154] *Id.* at. 23 (emphasis added).
[155] *Vanderwerf*, 529 F. Supp. 2d at 1308.
[156] *Id.* (emphasis added; citing to the *Reference Manual*).
[157] Ex. 26 [Healy *Kohler/Thompson* Dep.] at 90:17-19.
[158] Ex. 36 [11/17/06 FDA analysis] at 44 (emphasis added).
[159] Ex. 25 [Healy *Van Dyke* Dep.] at 235:23-239:23 ("I don't particularly actually disagree with the statement . . . .")
[160] To the extent that Dr. Healy might claim that the "net" effect is neutral because paroxetine caused suicidal behavior in some and prevented it in others, this is (i) nothing but rank speculation and (ii) is contradicted by Dr. Healy's recent claim that antidepressants confer *no benefit* on suicidal outcomes. David Healy, *Pharmageddon* 223 (Univ. of Cal. Press 2012) ("In the case of the antidepressants, even the

similarly emphasized that "the FDA specifically rejected any association between suicidality or suicidal behavior in adults age 25 or older" in criticizing plaintiff's expert's reliance on the FDA 2006 analysis.[161]

4. The Decision In *Tucker v. SmithKline Beecham* Is Inapposite Due To Subsequent Statements And Critical Admissions By Plaintiff's Experts, As Well As Contrary Precedent

GSK anticipates that plaintiff will point out that a *Daubert* motion to exclude Dr. Healy's testimony in another case involving allegations of a Paxil-induced suicide was denied, in 2010, in *Tucker v. Smithkline Beecham Corp.*[162] Plaintiff's reliance on this decision is entirely inapposite because it preceded (and therefore could not account for) subsequent critical admissions and other statements by plaintiff's experts.[163]

First, the *Tucker* court did not consider Dr. Healy's radical advocacy and extreme bias against GSK, which has become apparent in Dr. Healy's writings on his blog over the past few years.

Second, the *Tucker* court did not consider Dr. Healy's wholesale rejection of bedrock principles of scientific reliability, an issue not raised in *Tucker* and brought into focus by Dr. Healy's more recent documents, testimony, and blog writings.

Third, critical concessions by plaintiff's experts *subsequent to Tucker* render moot the *Tucker* court's conclusions that Dr. Healy's extrapolation from suicidal behavior data to

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FDA had doubts about whether the drugs worked. There was absolutely no evidence they reduce suicides -- all the clinical evidence pointed to an increase in risk . . . .") (Ex. 64).

[161] *Vanderwerf*, 529 F. Supp. 2d at 1308.

[162] 701 F. Supp. 2d 1040 (S.D. Ind. 2010).

[163] Dr. Grimson was not one of the plaintiff's experts in *Tucker*.

completed suicide was scientifically reliable.[164] Specifically, Drs. Glenmullen and Grimson have conceded that:

(i) it is ***necessary*** to consider data for completed suicide (as opposed to suicidal thinking or behavior) to determine whether paroxetine is associated with suicide,[165] and

(ii) they do not dispute FDA's conclusion that the data produced by FDA's 2006 analysis of some 372 antidepressant clinical trials involving approximately 100,000 adults, "***was not sufficient to reach any conclusion about drug effect on suicide.***"[166]

Simply put, given these admissions, plaintiff's experts' opinions can no longer satisfy *their own standards of reliability*.[167]

Fourth, shortly after the *Daubert* briefing in *Tucker*, the district court in *Vanderwerf* rejected the same contentions as those proffered by Dr. Healy in this case. As mentioned, *supra*, *Vanderwerf*[168] involved a claim (albeit by a different expert) that paroxetine caused an adult male to commit suicide based upon data *identical* to those relied by Dr. Healy in this case. Much like in *Tucker*, the *Vanderwerf* plaintiff claimed that "GSK has admitted general causation" in its DHCP letter.[169] Yet, unlike the *Tucker* court, the *Vanderwerf* court concluded that:

> [T]he DHCP letter does not say that Paxil increases the risk of suicidal behavior, let alone suicide and suicide precursors, across all psychiatric disorders for adults of all ages with major depressive disorder. It discloses a 'possible' risk in adult patients, states that the risk is likely limited to

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[164] The *Tucker* court found that the statistical significance prong of Dr. Healy's causation opinion was met because GSK acknowledged, in its Dear Health Care Provider (DCHP) letter, "that the 2006 analysis of the GSK clinical trials database revealed a statistically significant increase in suicidal behavior in adult patients with major depressive disorder being treated with Paxil compared to those administered a placebo." *Tucker*, 701 F. Supp. 2d at 1061. As shown below, the nominally statistically significant finding related to this secondary endpoint disappears when appropriately adjusted for multiple comparisons and is not even nominally significant when the latest analytical methods are applied.

[165] Ex. 27 [Glenmullen *Mason* Dep.] at 325:1-3; Ex. 57 [Grimson Dep. in *O'Neal v. SmithKline Beecham*] at 150:3-13.

[166] Ex. 27 [Glenmullen *Mason* Dep.] at 68:4-11; Ex. 41 [Grimson Dep. *in Kohler/Thompson v. SmithKline Beecham Corp.*] at 30:18-31:6.

[167] *Soldo,* 244 F. Supp. 2d at 561 ("Because consistency is a hallmark of the scientific method, *plaintiff's experts must be required to satisfy their own standards of reliability*") (emphasis added).

[168] 529 F. Supp. 2d 1294.

[169] *Id.* at 1307-08.

> younger adults between the ages of 18 and 30, and emphasizes that it is difficult to conclude a causal relationship because of (1) the small incidence and absolute number of events, (2) the retrospective nature of the metaanalysis and (3) the fact that the risk of suicidal behavior is a symptom of the underlying psychiatric illnesses . . . . Therefore, even giving plaintiffs the benefit of all favorable inferences, GSK has at most admitted that Paxil *may* increase the risk of suicidal behavior and suicide in adult patients between the ages of 18 and 30. (emphasis in the original).[170]

Thus, the *Vanderwerf* court rejected the very same misinterpretation of the DHCP letter that was the lynchpin of the *Tucker* court's decision to admit Dr. Healy's causation opinion. Moreover, given Dr. Healy's recent claims that "***no significant adverse effect of a drug . . . has been demonstrated by means of a controlled trial***" and that "[c]ontrolled trials are simply not the method by which adverse effects are demonstrated," his reliance on a misinterpretation of GSK's controlled trial data is contrary to his own (warped) standards of reliability.[171]

Fifth, the only federal court that has appointed independent scientific experts to consider Dr. Healy's claim that SSRIs cause people to commit suicide, wholly excluded Dr. Healy's testimony under *Daubert* in a well-known decision that (unlike *Tucker*) was affirmed by a federal Court of Appeals. In *Miller*,[172] the court and its independent experts soundly rejected Dr. Healy's opinion that Zoloft, another SSRI, causes suicide, finding that the defects in his methodology were "glaring, overwhelming and unexplained."[173] Among other methodological shortcomings that similarly plague Dr. Healy's opinions here, the *Miller* court held that, while Dr. Healy "must rely on studies which yield results that are statistically significant regarding the causal relationship at issue," the independent experts were not able to derive statistically

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[170] *Id.*
[171] Ex. 67 [Healy *McCraw* Report] at 27 (emphasis in the original).
[172] 196 F. Supp. 2d 1062.
[173] *Miller*, 196 F. Supp. 2d at 1085.

significant results from the materials which Dr. Healy provided.[174] The court further emphasized Dr. Healy's failure to acknowledge "the large body of research from [randomized controlled trials] with placebo controls which refute or fail to support his opinions."[175]

E. DR. HEALY HAS CONCEDED THAT HE DOES NOT KNOW OF ANY PLACEBO-CONTROLLED DATA SHOWING THAT SUICIDES, SUICIDALITY, OR AKATHISIA CAN BE CAUSED BY PAROXETINE AT A DOSE EQUIVALENT TO THE DOSE ALLEGEDLY TAKEN BY MR. DOLIN.

Last week, the Seventh Circuit affirmed the exclusion of experts whose causation opinions failed to account for the dose of vinyl chloride to which plaintiffs were exposed.[176] While recognizing that vinyl chloride is a well-known human carcinogen, the Seventh Circuit found that the experts' extrapolation from studies involving much higher doses and/or longer durations of exposure was unreliable.[177] Similarly, the *Manual* recognizes that "all chemical agents are intrinsically hazardous - whether they cause harm is only a question of dose. Even water, if consumed in large quantities, can be toxic."[178] Accordingly, to establish general causation in a pharmaceutical product liability case, a plaintiff must demonstrate at what dose the substance in question causes injury.[179] Similarly, it is well-established that "where an expert relies on a study of a high dose to determine adverse effects of a lower dose, without supplying a

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[174] *Id.* at 1080.

[175] *Id.* at 1081.

[176] *C.W. ex rel Wood v. Textron*, No. 14-3448, 2015 WL 5023926, at *2-8 (7th Cir. Aug. 26, 2015).

[177] *Id.* at *3-4, 6-8.

[178] Ex. 1, *Reference. Manual* at 636; *see also In re W.R. Grace & Co.*, 355 B.R. 462, 486 n.99 (Bankr. D. Del 2006) (*quoting Reference Manual*) .

[179] *See*, e.g., *McClain*, 401 F.3d at 1241 (excluding experts who "could not say how much is too much."). *See also Mitchell v. Gencorp, Inc.*, 165 F.3d 778, 781 (10th Cir. 1999) (in order to "carry [her] burden" to recover in a toxic tort case, "a plaintiff must demonstrate 'the levels of exposure that are hazardous to human beings generally as well as the plaintiff's actual level of exposure to the defendant's toxic substance before he or she may recover'") *quoting Wright v. Willamette Indus., Inc.*, 91 F.3d 1105, 1106 (8th Cir. 1996); *Abuan v. Gen. Elec. Co.*, 3 F.3d 329, 333 (9th Cir. 1993)) (holding that expert opinion that could not show a dose-response relationship to product exposure was "of no utility in the context of this lawsuit"); *Westberry v. Gislaved Gummi AB*, 178 F.3d 257, 263 (4th Cir. 1999).

method to substantiate this inference, courts often rule that such extrapolations are unreliable."[180] Such extrapolation is particularly egregious where, as here, *the data indicate that, at a 10 mg dose of paroxetine (a dose sub-therapeutic for depression) the rate of suicide-related adverse events was lower than on placebo*.[181]

Dr. Healy has specifically conceded that he knows of no placebo-controlled data showing a statistically significant increased risk of suicide, suicide attempt, suicidality, or even akathisia, at a dose of 10 mg per day of paroxetine.[182] Thus, to the extent that Dr. Healy attempts to extrapolate from data with higher doses, such extrapolation is unsupported and unreliable. This is yet another independent reason why Dr. Healy's general causation opinion should be excluded under *Daubert* and Rule 702.

[180] *In re Prempro Prods. Liab. Litig.*, 738 F. Supp. 2d 887, 895 (E.D. Ark. 2010) (excluding expert for not "specify[ing] what level of exposure increases the risk of adverse health effects"); *see also Sutera v. Perrier Group*, 986 F. Supp. 655, 667 (D. Mass. 1997) (rejecting reliance on epidemiological studies that involved exposures higher than that experienced by the plaintiff); *In re Bextra and Celebrex Mktg. Sales Practices and Prod. Liab. Litig.*, 524 F. Supp. 2d 1166 (N.D. Cal. 2007)(in opinion containing an exhaustive analysis of the law, the trial court excluded expert testimony on general causation at a particular drug dosage because "plaintiffs have not presented scientifically reliable evidence that Celebrex causes heart attacks or strokes when ingested at the 200 milligram a day dose").

[181] Ex. 61 [Rothschild Report] at 18; Ex. 45 [August/September 2003 EMEA submission] at 19 at 86-87.

[182] Ex. 23 [Healy *Tucker* Dep.] at 258:23-260:4; *see also* Ex. 2 [Healy Dolin Dep.] at 285-86. Dr. Glenmullen, another plaintiff's expert here, has made similar concessions. Ex. 43 [Glenmullen *Tucker* Dep.] at 193:5-21, 206:16-207:2; Ex. 65 [Glenmullen Dep. in *Gruder v. SmithKlineBeecham Corp.*] at 272:17-274:10.

IV. CONCLUSION

For the foregoing reasons and based on the record as a whole, GSK respectfully requests that the Court grant its Motion to exclude Dr. Healy from offering opinion testimony in this case.

Dated: September 2, 2015

Respectfully submitted,

By: /s/ Alan S. Gilbert

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CERTIFICATE OF SERVICE

It is hereby certified that on September 2, 2015, I electronically filed the foregoing **DEFENDANT GLAXOSMITHKLINE LLC'S MEMORANDUM OF LAW IN SUPPORT OF MOTION TO EXCLUDE PLAINTIFF'S EXPERT DR. DAVID HEALY** with the Clerk of the Court using the CM/ECF system which will send notification of such filing to registered parties.

/s/ Alan S. Gilbert
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