IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF FLORIDA
PENSACOLA DIVISION

IN RE: ABILIFY (ARIPIPRAZOLE) PRODUCTS LIABILITY LITIGATION This Document Relates to All Cases	Case No. 3:16-md-2734 Chief Judge M. Casey Rodgers Magistrate Judge Gary Jones

DEFENDANTS' MOTION FOR SUMMARY JUDGMENT ON GENERAL CAUSATION BASED ON PLAINTIFFS' LACK OF ADMISSIBLE EXPERT TESTIMONY UNDER *DAUBERT*

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INTRODUCTION

"Law lags science; it does not lead it." *Hendrix ex rel. G.P. v. Evenflo Co.*, 609 F.3d 1183, 1194 (11th Cir. 2010). Just fifteen months ago, and two months *after* the first cases were filed here, FDA scientists concluded, after exhaustively reviewing the available literature and data, that more research was needed to clarify the "possible" relationship between Abilify® and impulse-control disorders. Yet, Plaintiffs invite this Court to decide this still-unsettled scientific question.

When FDA scientists wrote their report, they had—with one exception—all the evidence on which Plaintiffs' experts rely here: (1) case reports describing patients who took Abilify and allegedly developed pathological gambling; (2) spontaneous adverse drug event reports received by Defendants and the FDA from consumers, doctors, and often plaintiffs' lawyers; (3) statistical "disproportionality analyses" of these adverse events; and (4) literature hypothesizing a biological mechanism of action by which Abilify might cause pathological gambling. This evidence was not enough for the FDA to determine causation.

As this Court recently noted, the Eleventh Circuit has a well-developed hierarchy of "traditional evidentiary foundations that have proven reliable" to establish "medical causation." *Navelski v. Int'l Paper Co.*, 2017 WL 1132569, at *3 (N.D. Fla. Mar. 25, 2017) (Rodgers, J.). Three "methodologies" are "indispensable"—though not automatically sufficient—"to prov[e] the effect of an ingested sub-

stance": "epidemiological evidence," "dose-response," "and background risk of disease." *Chapman v. Proctor & Gamble Distrib.*, 766 F.3d 1296, 1308 (11th Cir. 2014). All other "secondary methodologies, including plausible explanations, generalized case reports, hypotheses, and animal studies are insufficient proof of general causation." *Id.*

The only new evidence to emerge since the FDA reached its conclusion in March 2016—and the only evidence in this case remotely resembling an "indispensable" methodology—is a purported epidemiological study by Dr. Mahyar Etminan. Before he even drafted the study protocol, Dr. Etminan, an enterprising plaintiff-side expert who learned of this litigation on a website called "Aboutlawsuits.com," contacted Plaintiffs' counsel to float the idea for his study.

For many reasons ultimately conceded by Dr. Etminan himself, his study is methodologically invalid and cannot serve as the science that leads this case: (1) the study purports to identify five subjects who used Abilify, but could not verify that any actually took the drug; (2) it claims that these subjects suffered from a gambling disorder, but could not verify that any actually had the disease; and (3) it purports to show that all five subjects used Abilify before developing a gambling disorder, but relies on a database that fails to identify when the disease first arose—i.e., before or after taking Abilify.

Plaintiffs experts, recognizing Etminan's limitations, ultimately revert to the FDA's 2016 report. But again, the FDA did not find causation and determined that more research was needed. No other independent scientist evaluating all the available data has found causation either. Accordingly, we ask that the Court exclude the testimony of each of Plaintiffs' experts and grant summary judgment for Defendants.

BACKGROUND

According to Plaintiffs, "Abilify injured [them], by causing harmful compulsive behaviors including compulsive gambling." Master Compl. ¶ 3. The only "experts" who have concluded that Abilify causes compulsive behaviors are paid by consultants to Plaintiffs' counsel in this litigation.

A. Abilify is approved to treat patients who suffer from serious mental health disorders—many of which are highly associated with pathological gambling.

Abilify is an "atypical" antipsychotic medication approved to treat schizophrenia, bipolar I disorder, irritability associated with autistic disorder in certain pediatric patients, Tourette's disorder, and as adjunctive therapy in treatment-resistant major depressive disorder. *See* Ex. A, Abilify Product Label. Since its introduction in 2002, tens of millions of patients worldwide have used Abilify to help manage the symptoms of these debilitating mental health conditions. *See,*

e.g., Ex. Z, Bristol-Myers Squibb Co., 1-Year Periodic Benefit Risk Evaluation Report (PBRER) #4, at 14 (2016).

As Plaintiffs' experts agree, patients who suffer from these mental health conditions have much higher rates of pathological gambling than the general population. [redacted]

The association between mental health disorders and pathological gambling is so strong that pathological gambling is considered a clinical feature of many of the mental health conditions that Abilify treats. [redacted]; Ex. F, American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders* 124 (5th ed. 2013) ("DSM-5") (listing as diagnostic criteria for bipolar mania, "ex-

cessive involvement in activities that have a high potential for painful consequences"); *see also id*. at 101 (warning that schizophrenia involves "[a]bnormalities in . . . inhibitory capacity"). In fact, these behaviors are so linked to bipolar disorder, that to diagnose gambling disorder in a bipolar patient, a doctor must rule out a manic episode as the cause. *Id.* at 589.

This has led some to believe that [redacted]. Gambling disorder also develops at a much higher rate in substance abuse patients, Ex. D, Hollander Rep. at 4, and substance abuse occurs commonly in bipolar and schizophrenic patients. Ex. F, DSM-5 at 105, 132.

This means, overall, that pathological gambling manifests at a significantly higher rate in the Abilify patient population than in the general population. *See id.* at 589. As such, any methodology examining the relationship between Abilify and gambling must account for these underlying mental health conditions as potential confounding factors.

B. In 2010, a small number of unsubstantiated case reports emerged suggesting a possible link between Abilify and pathological gambling.

The first published reports suggesting a possible link between Abilify and pathological gambling appeared in the published literature in 2010, and all authors concluded there was insufficient evidence to establish causation and a case-control study was required. One report described an Australian schizophrenic patient with a pre-existing gambling habit who "developed an irresistible urge to gamble" six months after her physician increased her dose of Abilify. *See* Ex. G, Roxanas (2010). This resolved one month after switching to another antipsychotic. *See id*. Three other reports describing the experiences of eight schizophrenic patients in France and the UK appeared in 2010 and 2011. *See* Ex. H, Gavaudan et al. (2010); Ex. I, Cohen et al. (2011); Ex. J, Smith et al. (2011). One report acknowledged that the data showed "higher rates of pathological gambling in schizophrenic patients," which of course is a confounding factor. Ex. I, Cohen et al. (2011) at 51. Another noted "the need for additional research" on the issue. Ex. J, Smith et al. (2011) at 159.

In 2014, a French scientist, Dr. Louise Gaboriau, decided to analyze the existing literature to see if the cases were caused by Abilify. She authored a paper describing eight patients at her clinic who experienced pathological gambling while taking Abilify and also evaluated previously published case reports. *See* Ex.

K, Gaboriau et al. (2014). "[T]o explore this potential adverse drug reaction," Dr. Gaboriau and her co-authors applied the "Naranjo scale" to both their eight cases and the nine cases previously reported by Roxanas (2010), Gavaudan et al. (2010), Cohen et al. (2011) and Smith et al. (2011). *Id.* at 563-564. The Naranjo scale analyzes "various components that must be assessed to establish a causal association between drug(s) and adverse events." *Id*. at 563. The scale assigns a score ranging from -3 to +12, with 0 or less deemed "doubtful," 1 to 4 deemed "possible," 5 to 9 deemed "probable" and 10 to 12 deemed "definite." Ex. L, Naranjo et al. (1981).

Although the Naranjo scale cannot be used to establish general causation, Gaboriau et al. found none of the 17 published cases met the criteria for "definite" or even "probable" under this scale. Ex. K, Gaboriau et al. (2014) at 564. The authors noted that "[m]ost of the patients were already gambling before aripiprazole was instituted" and cautioned that pathological gambling was strongly associated with the underlying conditions for which Abilify was prescribed:

> Although there is both a clinical and pharmacological range of arguments that suggest aripiprazole is involved in the occurrence of [pathological gambling], it is important to underline that it is less obvious when [an adverse drug reaction] is a chronic problem. Moreover, it is possible that other factors may have been involved, such as regular gambling (Currie et al., 2006), history of mood, psychotic or substance use disorders (Kessler et al., 2008). A subgroup of pathological gamblers display high levels of psychopathology, in particular depression, anxiety and alcohol dependence (Blaszczynski & Nower, 2002). In these individuals, called "emotionally dis-

> turbed," ***psychiatric or addictive comorbid disorders are primary conditions and constitute an important risk factor for the development of pathological gambling. These primary conditions would precisely justify the prescription of aripiprazole, in some cases***.

Id. at 565 (emphasis added). Given this, the authors concluded that "the causal part of aripiprazole should be confirmed by a case-control study conducted on a psychiatric population treated by aripiprazole." *Id*.

C. In 2014, Plaintiffs' expert published a disproportionality analysis finding elevated adverse event rates for Parkinson's disease medications; the study mentioned Abilify in passing, noting that it had a weaker signal.

In November 2014, Plaintiffs' expert Dr. Joseph Glenmullen, prior to being retained, published a disproportionality analysis examining the rate of spontaneous adverse event reports of impulse control disorders for six Parkinson's disease drugs. Ex. M, Moore et al. (2014). The entirety of the report—the background, methods, discussion, conclusions, and the corresponding tables and graphs—mentions only those six Parkinson's drugs. The only reference to Abilify is a single sentence noting that the authors "found a weaker signal for aripiprazole" than the six drugs under study. *Id.* at 1932.

As the authors further acknowledged, a disproportionality analysis does not constitute an epidemiological study of causation: "Our data share the limitations of spontaneous adverse event reports that are not collected systematically: an individual report does not itself prove a causal relationship, only that such a relation-

ship was suspected." *Id.* Additionally, "insufficient data were available to investigate dose or treatment duration." *Id.* at 1933. The authors could not determine whether the risk of pathological gambling increases with the dose or length of exposure of the Parkinson's drugs at issue, and noted that the same was true for Abilify.

D. In March 2016, the FDA reviewed all available science—and found only a "possible causal relationship" between Abilify and pathological gambling, noting that additional study was needed.

In March 2016, the FDA conducted a comprehensive Pharmacovigilance Review of all available evidence to examine the possible association between Abilify and impulse control disorders. *See* Ex. N, FDA, Center for Drug Evaluation and Research, Pharmacovigilance Review (March 10, 2016) ("FDA Review"). *Id.* The FDA discussed Abilify's putative mechanism of action, reviewed case reports, and conducted a disproportionality analysis. *Id.* Ultimately, the FDA concluded only that there is "an association between aripiprazole and ICDs" and detailed remaining open questions. *Id.* at 28. The FDA explained that "[t]his association confirms the sponsor's conclusions that there is a possible causal association between aripiprazole use and pathological gambling." [1]

[1] As FDA noted, around the same time, Defendants conducted a review of the same evidence and reached a similar conclusion as FDA of a "possible causal association" between Abilify and pathological gambling. This phrase is a term of art in Pharmacovigilance: [redacted]

As to mechanism of action, the FDA noted that Abilify "action at the D3 receptor is not well defined in the literature," and cautioned that "[m]ore research on the subject is needed before any conclusive statements can be made" about biological plausibility." *Id.* at 28-29. Significantly, the FDA noted that Abilify's action at the D3 receptors was "of particular interest," because D3 receptor-activation is implicated in addiction and associated with impulse-control disorders in Parkinson's disease patients receiving dopamine-replacement therapy. *Id*. at 28.

As to the case reports and other available evidence, the FDA recognized that a "possible confounding variable in all of our cases is the underlying psychiatric conditions for which aripiprazole is indicated." *Id.* at 29. The FDA "attempted to minimize" this background incidence by "only including cases that documented a positive challenge, as well as excluding cases in which concurrent mania or symptoms of mania, and active substance abuse disorder were reported." *Id.* 28-29. But even this did not satisfy the FDA.

The agency therefore concluded that a "case-control study" was necessary to "help clarify the association between ICDs and aripiprazole, and further minimize

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[redacted] In other words, given the available evidence and the clear link between pathological gambling and the conditions Abilify treats, Defendants could not rule out underlying disease as the cause of the reported adverse events. For a discussion of these analyses, see our motion to exclude Plaintiffs' expert Dr. Glenmullen.

underlying disease as a confounder." *Id.* at 29. The FDA then noted that, "until such a study is conducted, it would be prudent to warn HCPs and the public of the potential for new onset ICDs associated with aripiprazole treatment." *Id.*

The FDA Review recommended that the product label add a warning describing the risk as follows: "case reports suggest that patients can experience intense urges, particularly for gambling." *Id.* at 30. The FDA did not recommend a more substantial warning (or any language indicating a causal relationship) because the science did not support one. The warning in the Abilify label currently states:

> Post-marketing case reports suggest that patients can experience intense urges, particularly for gambling, and the inability to control these urges while taking aripiprazole. Other compulsive urges, reported less frequently include: sexual urges, shopping, eating or binge eating, and other impulsive or compulsive behaviors. Because patients may not recognize these behaviors as abnormal, it is important for prescribers to ask patients or their caregivers specifically about the development of new or intense gambling urges, compulsive sexual urges, compulsive shopping, binge or compulsive eating, or other urges while being treated with aripiprazole. It should be noted that impulse-control symptoms can be associated with the underlying disorder. In some cases, although not all, urges were reported to have stopped when the dose was reduced or the medication was discontinued. Compulsive behaviors may result in harm to the patient and others if not recognized. Consider dose reduction or stopping the medication if a patient develops such urges.

Ex. A, Abilify Product Label at §5.7.

Previously, both the European Medicines Agency ("EMA") and Health Canada reviewed the association between aripiprazole and pathological gambling and found that, while a warning was prudent, a causal link could not be proven. An EMA Rapporteur explained that [redacted] Health Canada's recommendation was merely to [redacted]

Thus, as late as 2016, no independent scientist evaluating all available data on Abilify and pathological gambling had found causation. And at least three sources (FDA, EMA, and Gaboriau) had called for further study, including a case-control epidemiological study.

E. In 2017, Plaintiffs' consultant, Dr. Etminan, published a purported epidemiology study "to quantify the risk" of Abilify with pathological gambling and ICDs, but he admits the study is flawed and litigation-driven.

Shortly after the FDA's analysis, Dr. Mahyar Etminan purported to conduct an epidemiological study addressing the issue raised by the FDA.

A plaintiff-side expert in this and other pharmaceutical product liability cases, Dr. Etminan learned of this lawsuit from the website "AboutLawsuits.com." *See* Ex. O, Etminan Dep. at 108:12-15. He then contacted Plaintiffs' counsel to discuss an "epidemiological study" on Abilify and pathological gambling. *Id.* at 105:7-11. As Plaintiffs' own expert, Dr. Russell Luepker, testified, this approach lacks scientific integrity:

[redacted]

Dr. Etminan admitted that he understood such a study could help Plaintiffs here, given the limited scientific evidence on causation. Ex. O, Etminan Dep. at 105:7-13. He also agreed that case reports, spontaneous adverse event reports, and disproportionality analyses "on their own cannot demonstrate a link with aripiprazole," and "large epidemiologic studies are lacking" yet "are needed to quantify this risk simultaneously controlling for potential confounding issues." Ex. P,

Etminan et al. (2017) at 1. Dr. Etminan never disclosed to his co-authors that he had contacted Plaintiffs' counsel. *See* Ex. O, Etminan Dep. at 119:23-120:1.

The Etminan Study relied on a random sample of six million patients from an insurance claims database called LifeLink. That database captures information on prescriptions, physician visits, and hospitalizations through codes submitted with health insurance claims. Ex. P, Etminan et al., at 1. The underlying data is generated "for insurance reimbursement reasons," not scientific research. *See* Ex. O, Etminan Dep. at 21:4-6. While presumably suitable for its purpose, the database suffers from well-known data entry and miscoding errors, and diagnosis codes are frequently inaccurate. *Id.* at 83:12-84:4.

Notwithstanding these database limitations, the authors identified cases of "gambling disorder" by searching for a particular code ("ICD-9-CM code 312.31"). Ex. P, Etminan et al., at 1. But the study authors did not have access to corresponding medical records and thus could not verify the accuracy of any diagnosis. *See* Ex. O, Etminan Dep. at 93:16-24. Nor could they ascertain the actual onset of the disease. *Id.* at 94:10-14. Moreover, the authors of the study were not experts in gambling disorder, and failed to consult an expert to understand disease-diagnosis and potential confounders.

From this admittedly flawed data set, the authors identified exposure to Abilify based on a patient's single prescription in the year before the first diagnosis

of gambling disorder. However, by relying on prescription information—instead of usage information—the study authors could not confirm whether any of the individuals *actually ingested Abilify*. This is not a superficial distinction. Dr. Etminan recognized that psychiatric patients have high noncompliance rates, making it very likely that some (if not all) the patients either did not take Abilify or took it long after it was dispensed. Validation could have confirmed exposure, but there was no validation. *See* Ex. O, Etminan Dep. at 35:15-21, 39:19-22.

Because of uncertainty about exposure and disease-onset, the authors could not scientifically determine if the supposed cause (Abilify) preceded or, in fact, followed effect (gambling). Ex. O, Etminan Dep. at 9:21-30:1. Despite these flaws, the authors identified five cases (out of millions of patients) purporting to link gambling disorder and Abilify exposure—and from those five cases concluded that "users of aripirazole demonstrated an increased risk of pathological gambling . . . and impulse control disorder." Etminan et al., at 1-2. Dr. Etminan himself admitted that in at least one, and perhaps two, of these cases causation was unlikely. Ex. O, Etminan Dep. at 78:7 – 79:19.

Plaintiffs' biostatistician expert, Dr. Madigan, has criticized this type of database study, [redacted]

[redacted] Moreover, the Etminan study fails to compute a calibrated *p*-value [redacted]

[redacted]

[redacted]; Ex. AE, Schuemie et al. (2014) at 210.

ARGUMENT

II. EXPERT TESTIMONY ON GENERAL CAUSATION MUST BE BASED ON VALID SCIENTIFIC METHODS.

Federal Rule of Evidence 702 governs the admissibility of expert testimony and "compels the district courts to perform the critical 'gatekeeping' function concerning the admissibility of expert scientific evidence." *United States v. Frazier*, 387 F.3d 1244, 1260 (11th Cir. 2004) (en banc) (emphasis omitted) (citing *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579 (1993)).

The Eleventh Circuit application of *Daubert* is particularly rigorous. *First*, the court has repeatedly explained that "[t]he courtroom is not the place for scientific guesswork, even of the inspired sort. Law lags science; it does not lead it." *Hendrix ex rel. G.P.*, 609 F.3d at 1194; *see McClain*, 401 F.3d 1233, 1247 (11th Cir. 2005) (same). Courts must therefore guard against "speculative, unreliable expert testimony" "reach[ing] the jury under the mantle of reliability that accompanies the appellation 'expert testimony.'" *Rink v. Cheminova, Inc.*, 400 F.3d 1286, 1291 (11th Cir. 2005) (quotations omitted). The Eleventh Circuit has cautioned courts "not to admit speculation, conjecture, or inference that cannot be supported by sound scientific principles." *Hendrix ex rel. G.P.*, 609 F.3d at 1194.

Second, the Eleventh Circuit considers three "methodologies" "indispensable" to proving general causation: "epidemiological evidence," "dose-response," "and background risk of disease." *Chapman*, 766 F.3d at 1308. Without one of those, any "secondary methodologies, including plausible explanations, generalized case reports, hypotheses, and animal studies are insufficient proof of general causation." *Id.* And absent epidemiology, the court's review of other evidence "must be that much more searching." *Kilpatrick*, 613 F.3d at 1337 n.9; *see also Goldstein v. Centocor, Inc*., 310 F. App'x 331, 332 (11th Cir. 2009). Courts routinely find expert opinions relying on the same collection of secondary sources unreliable to establish general causation. In *Chapman*, the court affirmed the exclusion of experts who, lacking knowledge of "dose-response, epidemiological evidence, and background risk of disease," had only "secondary methodologies" of biological plausibility, animal studies, and case reports. 766 F.3d 1296, 1308. Similar conclusions have been reached in *McClain v. Metabolife Int'l*, 401 F.3d 1233 (11th Cir. 2005), and *Rider v. Sandoz Pharm. Corp*., 295 F.3d 1194 (11th Cir. 2002). *See also Wells v. SmithKline Beecham Corp*., 601 F.3d 375, 381 (5th Cir. 2010) (affirming summary judgment for manufacturer in pathological gambling litigation where plaintiffs' expert's opinions, relying on case studies, internal company data, and warning label changes, were scientifically unreliable).

III. PLAINTIFFS' EXPERTS HAVE NO RELIABLE EVIDENCE ON GENERAL CAUSATION.

Attempting to meet their burden of proof, Plaintiffs designated five experts, each of whom relies—to varying degrees—on the same evidence. This includes, in its totality, the evidence described above: one supposed epidemiological study (the Etminan Study), several case reports published in the literature, including a handful showing dechallenge or rechallenge data, a disproportionality analysis by Moore and Glenmullen, post-marketing adverse event reports, preclinical data on potential mechanisms of action, and analyses of this same data by the FDA, other health authorities, and Defendants. Under Eleventh Circuit jurisprudence, this is not enough.

A. Plaintiffs' experts have no reliable epidemiology.

As a threshold matter, because there is no valid epidemiological study, "more searching" scrutiny is required of Plaintiffs' remaining evidence. *Id.* Epidemiology "concerns itself with finding the causal nexus between external factors and disease." *Rider*, 295 F.3d at 1198. "In cases involving toxic substances," "epidemiology is the best evidence of causation." *Chapman*, 766 F.3d at 1307. A proper epidemiological study has four characteristics: (1) it precisely identifies onset of the disease; (2) it precisely identifies exposure; (3) it establishes that cause

preceded effect; and (4) it accounts for confounding variables of disease.[2] Here, the Etminan Study—the sole "pharmacoepidemiological study" that purports to link Abilify with pathological gambling—does none of these. The study is so riddled with flaws as to be inherently unreliable.

***First*, the study design did not allow the authors to confirm onset of pathological gambling.** The study authors relied on a review of diagnosis records from a massive insurance database. Ex. P, Etminan et al. (2017) at 1. The authors identified cases of "gambling disorder" by searching for a particular diagnosis code. But as Dr. Etminan admitted, the limitations of this insurance database made it impossible for the authors to identify the onset of pathological gambling or impulse control disorder. *See* Ex. O, Etminan Dep. at 29:21-30:1, 57:5-9, 72:19-24.

The literature is replete with warnings about the limitations of database studies. The database owners themselves warn that "coding … is not always accurate, especially at the fourth or fifth digit." *Id.* at 83:12-84:4 (quoting IMS, LifeLink Health Plan Claims Database: Overview and Study Design Issues 45 (2010)). The

[2] *See* Bert Black & David E. Lilienfeld, *Epidemiological Proof in Toxic Tort Litigation*, 52 Fordham L. Rev. 732, 752 (1984); *id.* at 755("[I]n an epidemiologic study, one seeks to observe the effect of *exposure to a single factor* upon the incidence of disease in two otherwise identical populations." (emphasis added)); *Barrow v. Bristol-Myers Squibb Co.*, 1998 WL 812318, at *22 (M.D. Fla. Oct. 29, 1998), *aff'd*, 190 F.3d 541 (11th Cir. 1999).

gambling and impulse control disorder codes Dr. Etminan used, however, were "the diagnosis at the fourth and fifth digits." *Id.* at 84:5-9.

Dr. Etminan readily conceded that he could not determine whether a "gambling disorder" code was the result of a coding error. *Id.* at 69:10-15. Plaintiffs' expert Dr. Luepker also confirmed that administrative databases, such as LifeLink, [redacted]

In addition, the study authors were not able to verify the medical accuracy of any diagnosis. *See* Ex. O, Etminan Dep. at 69:10-15, 93:12-94:8. They did not have access to any of the underlying medical records. *See id.* at 23:18-24:16. They therefore had no way to determine whether any diagnosis of gambling disorder was real, merely suspected (and subsequently rejected), or confirmed. *See id.* at 22:15-19, 63:12-64:1, 77:7-10. They had no way to confirm whether any diagnosis actually satisfied the required diagnostic criteria or whether any particular code was the result of a practitioner's mistake. *See id.* at 80:20-81:1.

Dr. Etminan confirmed that this is not merely a theoretical problem. According to the study, the average time between Abilify prescriptions and diagnosis of gambling disorder was just *20 days*. *See* Ex. P, Etminan et al. (2017) at 2. But

gambling disorder under the DSM criteria takes up to *twelve months* to develop into a disease. Ex. O, Etminan Dep.at 72:10-18. In other words, if each diagnosis actually followed the DSM criteria, the symptoms of gambling disorder must have "been there for at least a year prior to that actual diagnosis." *Id.* at 73:8-12, 23-24. That means gambling disorder would have started long before the Abilify use.

To avoid this conclusion, Dr. Etminan suggested that a diagnosis might be proper "even if one or two of the[] [DSM] conditions are there"—even though the DSM requires at least four of nine criteria. *Id.* at 66:19-20; *see* DSM-5 at 585. But who is to know? Certainly not Dr. Etminan, who reviewed no records, does not practice as a physician, has never diagnosed someone with pathological gambling and consulted no experts in pathological gambling. *See id.* at 67:11-16. He admits that, for all five cases of gambling disorder, it was possible that the "disorder had been diagnosed a year after the disorder began"—long before any of the patients took Abilify. *Id.* at 73:1-6.

***Second*, the LifeLink database does not permit the authors to identify when—or even if—patients were exposed to Abilify.** The study authors defined exposure to Abilify as "the use of 1 prescription in the year before" the first diagnosis of gambling disorder. Ex. P, Etminan et al. (2017) at 1-2. But the date a patient fills a prescription is *not* the same as the date he takes the drug, especially considering (as Dr. Etminan testified), psychiatric patients have higher noncompli-

ance rates than other patients. *See* Ex. O, Etminan Dep. at 35:15-21, 39:19-22. Dr. Etminan further testified that the study authors could not confirm whether any of the patients actually ingested Abilify (*id*. at 36:14-37:5, 56:23-57:3) or, assuming they had, *when* that ingestion occurred (*id*. at 33:20-34:9, 56:23-57:3, 77:14-20).

Adding to its unreliability, the study did nothing to account for this issue. In past studies, Dr. Etminan has used a "buffer" around the prescription date, accounting for the time it takes patients to fill a prescription, take the medication, and develop the disease. *Id.* at 45:6-46:10. In another published article, Dr. Etminan used *two* prescriptions as a proxy for exposure because a second prescription increases the likelihood of ingestion. *See* Ex. Q, Etminan (2004) at 1106. In this case, however, Dr. Etminan and his co-authors used no method to verify use. This is a startling omission considering the risk of noncompliance.

***Third*, the database provided no way to tell whether cause (Abilify exposure) preceded effect (pathological gambling).** The study authors could determine the date of a supposed diagnosis. *See* Ex. O, Etminan Dep. at 72:19-24. But they could not determine when "the true onset" of gambling disorder occurred. *Id*. at 29:21-30:1. Dr. Etminan admitted that "the database study did not allow [him to] determine when the patient developed pathological gambling as opposed to when they were diagnosed with it." *Id*. at 57:5-9. As a result, the study authors

had no way to confirm whether the onset of symptoms preceded or followed Abilify use, assuming use occurred at all.

***Fourth*, the authors did not account for confounders that are known risk factors for pathological gambling.** None of the Etminan Study authors is an expert in pathological gambling. Dr. Etminan, the lead author, did not know the DSM definition of pathological gambling and could not recall if he had looked at the definition when writing the study.[3] Nor did the authors "speak to any expert in pathological gambling" regarding "what risk factors should be controlled for." *Id.* 55:19-56:1. While the authors purported to control for some confounders, such as bipolar disorder and substance abuse disorder, they did nothing to control for a number of others, such as "depressive disorders, anxiety disorders, and personality disorders." Ex. F, DSM-5 at 589.

All told, Dr. Etminan and his co-authors could not determine whether any individual actually developed pathological gambling, ever took Abilify, developed pathological gambling before taking Abilify, or developed pathological gambling as a result of a confounder. Even assuming one could extract such information from the database—which is not possible—the study results are nonsensical. In

[3] Dr. Etminan suggested he "kind of relied on" the opinion of one of his coauthors, a neuropsychopharmacologist, who "would know about gambling," but admitted that this coauthor was not an expert in pathological gambling. *Id.* at 29:2-6; 38:11-15.

the identified cases, the average time between Abilify use (prescription date) and the diagnosis of gambling disorder (recorded in the database) is just twenty days. *See* Ex. P, Etminan et al. (2017) at 2. The shortest time gap is just three days. Ex. O, Etminan Dep. at 41:24-42:4. That means the individual must have been prescribed Abilify, taken Abilify, become a pathological gambler, and been diagnosed with pathological gambling, within three days. *Id.* at 43:21-44:10. Such a "diagnosis" would not survive the diagnostic criteria, and Dr. Etminan himself admitted the scenario was "unlikely." *Id.* at 78:3-79:7.

This slipshod methodology is not surprising given the study's genesis. Dr. Etminan learned about Abilify litigation via the website "AboutLawsuits.com," which he considers "a good source of topics for drug safety researchers like [him]self." Ex. O, Etminan Dep. at 105:3-6; 108:12-15; 112:10-15. Upon learning about the litigation, Dr. Etminan called Plaintiffs' counsel to see what he thought. *Id.* at 105:7-11. In making that initial call, Dr. Etminan believed it was "a given" that his study could help Plaintiffs' counsel. *Id.* at 105:7-11. By the time of his deposition, Dr. Etminan was officially consulting for Plaintiffs' counsel and considered himself part of the team. *Id.* at 9:7-9.

This is a replay of the *Mirena IUD* litigation, in which the plaintiffs relied on an Etminan article to support their general causation arguments. In that article, Dr. Etminan analyzed the FAERs database and found a higher-than-expected propor-

tion of the disease at issue associated with Mirena as compared to other products. Although his article disclosed "no conflict of interest in preparing th[e] article," Dr. Etminan later executed an affidavit revealing that throughout the litigation he had been on the Mirena plaintiffs' payroll and recanting the results of his study. Ex. R, Etminan Aff. ¶ 12; Ex. S, Etminan et al. (2015) at 113 (2015).

The publishing of the Etminan study in a peer-reviewed journal does not save it from these fatal flaws, nor is it any assurance of reliability or sound methodology. Although "peer review increases the likelihood that substantive flaws in methodology will be detected, scrutiny by one's peers does not insure admissibility." *Allison v. McGhan Med. Corp.*, 184 F.3d 1300, 1316 (11th Cir. 1999). And "[p]eer review and publication mean little if a study is not based on accurate underlying data." *In re Viagra Products Liab. Litig.*, 658 F. Supp. 2d 936, 945 (D. Minn. 2009)). The same concerns ring true here.

B. Plaintiffs' experts fail to establish a dose-response relationship.

A further, fundamental problem with Plaintiffs' proposed expert testimony here is their failure to demonstrate the dose-response relationship. For purposes of general causation, dose-response is assessed at the population level. David L. Eaton, *Scientific Judgment and Toxic Torts – A Primer in Toxicology for Judges and Lawyers*, 12 J.L. Pol'y 5, 15 (2003). A dose-response relationship is one "in which a change in amount, intensity, or duration of exposure to an agent is associ-

ated with a change—either an increase or decrease—in risk of disease." *McClain*, 401 F.3d at 1241-42 (quotations and brackets omitted). This "relationship between dose and effect (dose-response relationship) is the hallmark of basic toxicology." *Id.* (citation omitted). "The expert who avoids or neglects this principle of toxic torts without justification casts suspicion on the reliability of his methodology." *McClain*, 401 F.3d at 1242; *see Kilpatrick*, 613 F.3d at 1339.

None of Plaintiffs' experts attempt to "determine how much [Abilify] must be used for how long to increase the risk of [impulse control disorder]." *Chapman*, 766 F.3d 1296, 1307 (11th Cir. 2014). Nor do they address "the dose or level of exposure at which [Abilify] causes harm." *McClain*, 401 F.3d at 1241. Instead, the experts resort to anecdotal evidence of individual patients exhibiting a temporal relationship between a change in dose and the presence or severity of symptoms. This might be relevant to specific causation, but it ignores the threshold general causation question: "What degree of risk is associated with chemical exposure at any given dose?" Ex. T, Goldstein et al. (2011) at 637.

At best, perhaps Plaintiffs' experts might believe that Abilify causes impulse control disorders no matter what the dose" and no matter how briefly. *In re Accutane Prods. Liab.*, 511 F. Supp. 2d 1288, 1302 (M.D. Fla. 2007). But that is not enough to satisfy "the basic methodology that scientists use to determine causation—the dose-response relationship." *McClain*, 401 F.3d at 1242.

C. None of the other evidence Plaintiffs' experts cite is reliable to prove general causation under Eleventh Circuit law.

In addition to the Etminan Study, Plaintiffs' experts point to five additional sources of evidence: (1) published case reports, (2) spontaneous adverse event reports, (3) disproportionality analyses, (4) preclinical data on mechanism of action and (5) the analyses of health authorities. None of these "secondary" sources, however, show causation under Circuit precedent.

1. None of the study authors cited by Plaintiffs' experts found that Abilify causes pathological gambling.

It is "axiomatic that causation testimony is inadmissible if an expert relies on studies or publications, the authors of which were themselves unwilling to conclude that causation has been proven." *Huss v. Gayden*, 571 F.3d 442, 459 (5th Cir. 2009); *see Happel v. Walmart Stores, Inc.*, 602 F.3d 820, 826 (7th Cir. 2010) (same). An expert betrays "the speculative nature of his opinions" when he "draw[s] overreaching conclusions from self-limiting medical articles." *McClain*, 401 F.3d at 1247.

Here, the scientific community has "demonstrated the intellectual rigor in this field of science" by "not leap[ing] to specific conclusions about causation or toxicity from incomplete evidence or broad principle." *McClain*, 401 F.3d at 1248. As confirmed by the FDA's 2016 analysis, the independent scientists who meaningfully considered data on the relationship between Abilify and compulsive gam-

bling concluded that they needed additional case-controlled epidemiological evidence to draw any conclusions about causation. *See* Ex. K, Gaboriau et al.; Ex. N, FDA Review at 29.[4]

Plaintiffs' experts act as though these independent study authors determined causation, when they did not. But when an expert "draws unauthorized conclusions from limited data—conclusions the authors of the study do not make"—he shows a "lack of scientific rigor." *McClain v.*, 401 F.3d at 1248. In *McClain*, the court faulted an expert for relying on a study that "has the limitation of being an observational study and as such does not definitively establish the relationship between [use of the drug] and the risk of adverse … events.'" (alteration in original)). *Id*. The same principle applies here.

[4] One article in the West Indian medical journal that reports on two case reports contains a "summary," which states: "Due to the use of aripiprazole, pathological gambling behavior occurs quickly and with discontinuation of aripiprazole it ended completely. In spite of its very low therapeutic drug monitorization (TDM) level, aripiprazole may cause this. Aripiprazole causes pathological gambling by forming hyperdopaminergic condition in the mesolimbic dopaminergic way." Mehmet Ceylan, Pathological Gambling Due to Aripirazole Two Cases, West Indian Medical Journal, Nov. 2015. However, when discussing the mechanism of action in the body of the article, the authors make no definitive statement of causation: "Aripiprazol may cause pathological gambling due to its act as a partial dopamine agonist in mesolimbic pathway." Both cases in the article involved a history of gambling, and one involved a history of alcohol abuse. This article does not contain a meaningful analysis of available data, and the FDA did not include in its comprehensive analysis.

2. The "secondary" sources cited by Plaintiffs' experts are insufficient to establish general causation.

Even if the authors of the underlying articles had found causation, the evidence would be insufficient under Eleventh Circuit law. Where, as here, an expert "fail[s] to demonstrate the primary methods for proving" general causation, "secondary methodologies, including plausible explanations, generalized case reports, hypotheses, and animal studies are insufficient proof of general causation." *Chapman*, 766 F.3d at 1308. This "latter evidence could mislead the jury by causing it to consider testimony that was insufficient by recognized primary methodologies." *Id.* The Eleventh Circuit has repeatedly and consistently excluded expert testimony on general causation that fails to consider or demonstrate the primary, indispensable methodologies of epidemiological evidence, dose-response relationship, and background risk. *See, e.g.*, *id.*; *Kilpatrick*, 613 F.3d at 1336-43; *McClain*, 401 F.3d at 1240-54; *Rider*, 295 F.3d at 1198-1202.

a. Case reports cannot show general causation.

Plaintiffs' experts rely on case studies and case reports, which are simply published descriptions of what happened after individuals took a given drug. They are literally anecdotes. Case reports—including dechallenge/rechallenge re-

ports[5]—"are merely accounts of medical events. They reflect only reported data, not scientific methodology." *Rider*, 295 F.3d at 1199. "Case studies and clinical experience, used alone and not merely to bolster other evidence, are [] insufficient to show general causation." *Hendrix*, 609 F.3d at 1197.

"Some case reports are a very basic form report of symptoms with little or no patient history, description of course of treatment, or reasoning to exclude other possible causes." *Id.* Even "more detailed case reports, however, are not reliable enough, by themselves, to demonstrate causa[tion] … because they report symptoms observed in a single patient in an uncontrolled context." *Id.* In other words, case reports "do not rule out the possibility that the effect … is simply idiosyncratic or the result of unknown confounding factors." *Id.* "Simply stated, case reports raise questions; they do not answer them." *McClain*, 401 F.3d at 1254.

b. Adverse event reports cannot show causation.

Plaintiffs' experts rely on spontaneous adverse events reported to Defendants by physicians, patients and lawyers. The Eleventh Circuit has held, however, that adverse events are "[o]ne of the least reliable sources" to prove causation. *McClain*, 401 F.3d at 1250. "Under the adverse events reporting system, consumers call in to describe medical problems that they think they are experiencing from

[5] "A test is a 'dechallenge' test when a drug that is suspected of causing a certain reaction is withheld to see if the reaction dissipates. The drug may then be reintroduced in a 'rechallenge' to see if the reaction reoccurs." *Rider*, 295 F.3d at 1199.

taking a product," and "[t]hese complaints provide the basis for the AERs." *Id*. Because these reports "reflect complaints called in by product consumers without any medical controls or scientific assessment," they are even less reliable than case studies, and they "do not prove causation." *Id*.

The FDA itself cautions that AERs "may not be used to calculate incidences or estimates of drug risk." Ex. U, FDA, Annual Adverse Experience Drug Report: 1996 at 2 (Oct. 30, 1997). Adverse event reports lack controls and "are subject to a variety of reporting biases," and the underlying "data may be affected by … reporting stimulated by publicity or litigation." Ex. V, Center for Biologics Evaluation and Research (CBER) & Center for Drug Evaluation and Research (CDER), FDA, Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment 9 (2005).

Plaintiffs' experts also rely on "disproportionality analyses," also known as "data mining," which use adverse event databases to compare the reporting rate of a particular adverse event for one drug (*e.g.*, the proportion of Abilify adverse event reports that report pathological gambling) to all other drugs (*e.g.*, the proportion of adverse event reports for all other drugs that report pathological gambling). But as Plaintiffs' expert Dr. Glenmullen has noted, disproportionality analyses "share the limitations of spontaneous adverse event reports." Ex. M, Moore et al.(2014) at 132. Given this limitation, it is a textbook principle that "the use of

data mining is for signal detection — that is, for hypothesis generation — and that further work is needed to evaluate the signal." Ex. W, *Pharmacoepidemiology* 147 (5th ed. 2012). Accordingly, federal courts have held "mining [adverse event] data is not the scientific method; rather, it is rife with bias and variability." *Wells*, 601 F.3d at 381 n.30.

c. Plaintiffs' experts ignore the placebo effect.

The reliance by Plaintiffs' experts on anecdotal, spontaneous reports suffers from an additional flaw in this context. Although Plaintiffs' experts make much of the reported "dechallenge" and "rechallenge" events, the experts ignore the well-established literature describing a particularly "robust placebo response" among individuals with pathological gambling, with responses ranging from over 30% to close to 50% in placebo-controlled, double-blind, randomized trials. *See* Ex. X, Potenza Rep. ¶ 101 (collecting literature). In other words, based on this literature, an individual's knowledge of a treatment/intervention (*e.g.*, either the administration *or* removal of a medication) could easily cause them to alter their gambling behavior. And even Plaintiffs' experts do not seriously dispute this point or the underlying literature demonstrating it.

d. A proposed mechanism of action does not show general causation.

Finally, lacking any other reliable primary or secondary methodologies to prove general causation, Plaintiffs' experts fall back on theories about a purported

mechanism of action by which Abilify causes pathological gambling. Evidently, Plaintiffs assume that they can show causation by demonstrating *how* the drug works, at least theoretically. But *Chapman* makes clear that "plausible explanations" are an inferior secondary methodology. *Chapman*, 766 F.3d at 1308.

Plaintiffs' experts rely on four possible theories—three speculating as to over-activation of D3 receptors and one hypothesizing an impairment of learning from mistakes. But a biological plausibility is "not proof of causation;" it merely "lends credence to an inference of causality." *In re Accutane*, 511 F. Supp. 2d at 1296. Furthermore, to get to causation even hypothetically, that inference must be connected to and supported by scientific fact, not just "the *ipse dixit* of the expert." *General Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997). Plaintiffs' experts fail to make that connection here.

Moreover, for their mechanism of action opinions, Plaintiffs' experts rely on *in vitro* and animal studies. Neither, however, can show general causation. *First*, it is inherently uncertain how *in vitro* results transfer to human subjects. *See* Defs. Motion to Exclude Bechara at 12-13. *Second*, animal studies are also "insufficient proof of general causation," *Chapman*, 766 F.3d at 1308, because "at most" they "suggest[] a connection between" a drug and effect in the particular animal tested—but "[t]his does not equate to a conclusion of direct causation (or a connection

of any degree)," *Kilpatrick*, 613 F.3d at 1338. Plaintiffs' expert opinions that improperly rely on such studies should be excluded.

IV. GIVEN THE LACK OF RELIABLE EXPERT TESTIMONY, SUMMARY JUDGMENT IS WARRANTED.

As shown here, and in detail in our *Daubert* motions, Plaintiffs lack admissible expert testimony on general causation. This calls for summary judgment, which "is proper if the movant shows 'there is no genuine dispute as to any material fact and the movant is entitled to judgment as a matter of law.'" *Chapman*, 766 F.3d at 1312 (quoting Fed. R. Civ. P. 56(a)). It is well-settled that Plaintiffs must "have *Daubert*-qualified, general and specific-causation-expert testimony that would be admissible at trial to avoid summary judgment," *Id.* at 1316; *see also, e.g.*, *Kilpatrick*, 613 F.3d 1334 n.4 (same); *In re Lipitor (Atorvastatin Calcium) Marketing, Sales Practices & Prod. Liab. Litig.*, No. MDL214MN02502RMG, 2017 WL 87067, at *13 (D.S.C. Jan. 3, 2017) (surveying case law from all fifty states, the District of Columbia, and Puerto Rico, and concluding that "all jurisdictions require expert testimony" on general causation in pharmaceutical products liability cases), *appeal filed*, No. 17-1189 (4th Cir. Feb. 10, 2017).

"Evidence inadmissible at trial cannot be used to avoid summary judgment," and "[t]he burden for laying the proper foundation for admission of expert testimony is on the party offering the expert." *Chapman*, 766 F.3d at 1312-13 (quotation marks omitted). "If the nonmoving party fails to make a sufficient showing on an

essential element of her case with respect to which she has the burden of proof, the moving party is entitled to summary judgment." *U.S. v. Four Parcels of Real Prop. in Greene & Tuscaloosa Ctys. In State of Ala.*, 941 F.2d 1428, 1438 (11th Cir. 1991) (citation omitted); *Chapman*, 766 F.3d at 1312. That is the situation here.

CONCLUSION

Plaintiffs' experts cannot use a courtroom to change the current scientific knowledge; they must follow it. For all these reasons, and those stated in our individual *Daubert* briefs, we respectfully request that the Court exclude Plaintiffs' expert opinions on general causation and enter summary judgment for Defendants.

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE WITH LOCAL RULE 7.1(B)

Pursuant to Local Rule 7.1(B), counsel for Defendants certify that they contacted counsel for Plaintiffs regarding the relief requested in the foregoing motion. Plaintiffs do not consent to the relief requested.

CERTIFICATE OF COMPLIANCE WITH LOCAL RULE 7.1(F)

I HEREBY CERTIFY that this brief complies with the word limit of Local Rule 7.1(F) and contains 7,969 words, excluding the parts exempted by that Rule.

/S/ Larry Hill
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