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Mr. Matthew Leckman
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Dear Mr. Leckman:

It is my opinion, based on a reasonable degree of medical certainty and based on my education, training, and clinical experience, as well as my review of the material referenced in this report and listed in the attached appendices, that evidence from multiple sources proves stopping Cymbalta causes withdrawal reactions in a high percentage of patients and that Cymbalta withdrawal can be severe, debilitating, and even life-threatening. Four different types of scientific evidence support this conclusion: Lilly's double-blind, placebo-controlled, randomized Cymbalta studies; data from world-wide post-marketing surveillance; published, peer-reviewed scientific studies of antidepressant withdrawal; and Cymbalta's mechanism of action.

In Lilly's studies, 40% to 50% of depressed patients stopping Cymbalta reported withdrawal side effects, and up to 17% were severe. In Lilly's short-term (eight to nine week) studies, stopping Cymbalta more than doubled the risk of withdrawal side effects by comparison with stopping placebo: the odds ratio was 2.68. In the company's longer-term (34-week) studies, stopping Cymbalta again more than doubled the risk of withdrawal symptoms: the odds ratio was 4.95. The risk of specific withdrawal symptoms—nausea, dizziness, abnormal sensations, irritability, nightmares, headaches, and vomiting—was elevated as much as 23-fold. All of these elevated risks were statistically significant, making them strong scientific evidence stopping Cymbalta causes withdrawal reactions that can be severe in a high percentage of patients. A study of the FDA's post-marketing adverse event database found reports of Cymbalta withdrawal outnumbered reports of withdrawal for all other drugs including narcotics and Valium-type antianxiety agents and sleeping pills, providing confirmatory evidence Cymbalta causes withdrawal reactions in a high percentage of patients.

Published scientific studies have established that the frequency of antidepressant withdrawal reactions directly correlates with a drug's half-life, a measure of how quickly it washes out of the body when stopped. Withdrawal symptoms are evidence of abnormal brain cell functioning in response to withdrawal of an antidepressant when there is not enough time for the brain cells to adapt. Lilly's pharmacodynamic studies found Cymbalta has an extremely short half-life, about 12 hours, exiting the body precipitously. Cymbalta's precipitous drop explains why it is one of the worst offenders when it comes to antidepressant withdrawal. Patients who inadvertently miss just one dose can experience Cymbalta withdrawal. Severe antidepressant withdrawal can be incapacitating, require hospitalization, and be life-threatening. Even with a slow taper, patients can experience severe withdrawal reactions. Stopping Cymbalta can be so difficult it takes seven months or more.

Since Cymbalta's introduction in 2004, in every version of the drug's label, Lilly has misrepresented or failed to adequately inform doctors and patients about the frequency, severity, and duration of Cymbalta withdrawal reactions. Lilly's misleading information make it impossible for any patient or physician to make an informed decision about the appropriateness of taking or prescribing Cymbalta.

Qualifications

A graduate of Harvard Medical School, I am a Clinical Instructor in Psychiatry at Harvard Medical School, was a staff psychiatrist at the Harvard Law School Health Services for twenty years, and have a private practice in Harvard Square. I am Board Certified in psychiatry by the American Board of Psychiatry and Neurology.

I am the author of two books on the side effects of psychiatric medications: *Prozac Backlash: Overcoming the Dangers of Prozac, Zoloft, Paxil, and Other Antidepressants with Safe, Effective Alternatives* published in 2000 by Simon & Schuster and *The Antidepressant Solution: A Step-by-Step Guide to Overcoming Antidepressant Withdrawal, Dependence, and "Addiction"* published by Simon & Schuster's Free Press division in January 2005.[1]

Prozac Backlash includes a chapter on antidepressant withdrawal and is annotated with over 600 footnotes from medical journals, books, and other sources. *The Antidepressant Solution* is devoted to antidepressant withdrawal and annotated with over 350 footnotes. In the title *Prozac Backlash,* I use the word "Prozac" generically to refer to the group of antidepressants known as SSRIs (selective serotonin reuptake inhibitors).

Prozac was the first of the newer antidepressants introduced in this country in the 1990s and is the best known. Cymbalta is a closely-related SNRI (selective serotonin and norepinephrine reuptake inhibitor).

I am a moderate in the debate over the risks and benefits of antidepressants. I prescribe the medications for patients whose conditions are serious enough to warrant them and have had numerous patients report their beneficial effects. But, I am a critic of the drugs being over-prescribed for mild conditions and of doctors and patients not being adequately warned of their side effects. I testified at the FDA's February 2004 and December 2006 hearings on antidepressant-induced suicidality.

I have become a national spokesperson for the appropriate, measured use of psychiatric medications. I have been interviewed on numerous national television and radio shows including NBC's The Today Show, ABC News' 20/20, ABC's Good Morning America, ABC's World News Tonight, ABC's Primetime Live, CNN, Fox News, PBS, Court TV, and National Public Radio for my expertise on antidepressants. My work has been the subject of many reviews and articles including in the *New York Times* and *The New Yorker* magazine.[2] Among the honors I have received for writing *Prozac Backlash* is the American College for Advancement in Medicine's (ACAM's) Annual Achievement Award in Medicine in May 2001. I received the award at ACAM's 2001 annual convention and delivered the convention's keynote address, the Linus Pauling Lecture. My *curriculum vitae* is enclosed with this report as Exhibit 1.

Materials Reviewed for this Report

In preparing this general causation report, I have drawn on my extensive knowledge of antidepressant withdrawal based on my education, training, and experience. I have researched the medical literature on antidepressant withdrawal symptoms. As detailed in my books, I have treated numerous patients suffering from antidepressant withdrawal. In addition, attached hereto as Exhibit 2 is a list of Lilly and other documents I reviewed or considered in forming my opinions and/or which relate to my opinions. Discovery in this case is ongoing. My understanding is that Lilly has not yet produced a number of documents I intend to review. For example, all of the Lilly Cymbalta studies discussed in this report were studies of patients with major depressive disorders. Lilly subsequently obtained FDA approval for Cymbalta for additional indications including generalized anxiety disorder (GAD), diabetic peripheral neuropathy, fibromyalgia, and chronic musculoskeletal pain.[3] Lilly's studies of these conditions are the subject of ongoing discovery. I anticipate supplementing this report once additional documents become available.

For my time doing telephone conferences, research, reviewing documents, and writing this report, I am compensated at the rate of $650 per hour. For travel and testimony, I am reimbursed at the rate of $650 per hour, with 10 hours fee for a full day and 5 hours fee for a half day. In the last four years, I have given testimony in the following cases: State of Texas ex rel. Allen Jones v Janssen on January 31, 2011, March 22, 2011, December 1, 2011, and January 18, 2012; Callahan v Jellinek on June 13, 2011; Barth v Netolicky on July 20, 2011; In re Chantix (varenicline) Products Liability Litigation on April 4, 2012, April 5, 2012, June 26, 2012, and December 13, 2012; Berry v Kinast on January 22, 2013; Brown v Forest Labs et al on March 11, 2013 and May 14, 2013; Henry v Kahnert on July 10, 2013; Elmore v Janssen on August 12, 2013; Teters v Bristol-Myers Squibb on October 25, 2013; Delahoussaye v Concepcion on November 22, 2013; Amedia v United States of America on April 15, 2014; and Muzichuck v Forest Labs on July 1, 2014.

This report is divided into eight parts:

- Section 1 discusses the evidence in Lilly's pre-approval studies that stopping Cymbalta causes withdrawal symptoms that can be severe.
- Section 2 discusses the FDA's post-approval adverse event reports (AERs) of Cymbalta causing withdrawal symptoms that can be severe.
- Section 3 reviews the evidence in published scientific studies of antidepressant withdrawal.
- Section 4 discusses the biological mechanism of Cymbalta withdrawal.
- Section 5 is a Bradford Hill causality assessment of Cymbalta's withdrawal effects.
- Section 6 explains why Lilly's label is inadequate and misleading with regard to Cymbalta withdrawal.
- Section 7 discusses Lilly's conduct.

Section 1: Lilly's Cymbalta Studies

In Lilly's placebo-controlled studies of depressed patients, stopping Cymbalta more than doubled the risk of antidepressant withdrawal reactions by comparison with stopping placebo. The increased risk was statistically significant.

The Gold Standard for Efficacy

The FDA requires pharmaceutical companies to conduct well-controlled, double-blind, randomized studies to demonstrate a new drug's efficacy for its proposed use. "Controlled" means the studies compare a group of patients receiving the test drug to a group receiving placebo (inactive) pills and/or a group receiving an established comparator drug already on the market. The FDA prefers placebo-controlled studies when feasible. "Double-blind" means the patients all receive identical pills and neither the patients nor the researchers are supposed to know who is receiving the test drug versus placebo. "Randomized" means a pool of similar patients are randomly assigned to the different treatment groups. These features are intended to remove potential bias in the studies. Pharmaceutical company studies that meet these requirements are called Randomized Clinical Trials, or RCT.

Randomized clinical trials are prospectively designed to have enough statistical power, i.e. a large enough sample size (enough patients), to detect differences in efficacy between the treatment groups. In addition, the studies are required to assess the drug's effectiveness using validated measurement scales. To measure Cymbalta's efficacy, Lilly evaluated patients weekly during treatment with Cymbalta or placebo to assess whether or not their condition improved, using detailed symptom checklist rating scales including the 17-item Hamilton Depression Rating Scale (HAMD 17), Montgomery Asberg Depression Rating Scale (MADRS), Clinical Global Impressions of Improvement scale (CGI-Improvement), Patient's Global Impressions of Improvement scale (PGI-Improvement), Hamilton Anxiety Rating Scale (HAMA), and the quality of life 36-item Short Form Health Survey (SF-36).[4]

When the studies of a new drug are completed, the results are analyzed statistically. In order for a new drug to be deemed efficacious, it not only has to outperform placebo, the difference must be statistically significant, showing that the difference was unlikely to have occurred by chance. Well-designed placebo-controlled studies are widely regarded as the gold standard for establishing a drug's efficacy. My evaluation of Cymbalta's efficacy in Lilly's studies—an important part of a risks benefits analysis—is not complete since I am awaiting documents that are the subject of ongoing discovery.

Limitations for Assessing Side Effects

Randomized clinical trials, while the gold standard for assessing efficacy, often have substantial weaknesses for assessing side effects. The studies may not be able to detect infrequent side effects, because they are not powered (i.e. they do not have enough patients) to detect differences between the drug versus placebo. While the drug's efficacy can be assessed in all the patients, an infrequent side effect may occur in just a few and the difference between the drug and placebo may not be apparent.

The problem can be compounded by the methods used to assess side effects. In many pharmaceutical company studies, detailed rating scales are *not* used to systematically assess potential side effects.[5] Instead, side effects are only recorded if patients recognize and volunteer them.[6] This unsystematic approach is called "non-probing" because the patients are not specifically asked about side effects and "spontaneous" because the patients must spontaneously volunteer them. Such spontaneous reporting is well-known to result in significant underreporting of side effects.[7]

Lilly's Cymbalta studies suffered from this shortcoming. While Lilly rigorously monitored efficacy in its Cymbalta studies, withdrawal side effects were not systematically monitored with rating scales when patients stopped the drug. Instead, according to Lilly withdrawal side effects were only assessed in a "nonprobing" manner "by means of spontaneous reports rather than a [withdrawal] symptom checklist."[8] In other words, withdrawal side effects were recorded only if the researcher recognized the patient was having a side effect or if the patient recognized a side effect as such and considered it significant enough to volunteer. Lilly-funded researchers had previously developed rating scales for systematically monitoring antidepressant withdrawal side effects.[9] Indeed, the rating scales were used in earlier Lilly-funded research on Prozac, which causes lower rates of withdrawal reactions than many other antidepressants.[10] But Lilly did not use the rating scales in its Cymbalta studies.[11] Cymbalta has an extremely short half-life, meaning it washes out of the body precipitously when the drug is stopped.[12] Therefore, Cymbalta would be expected to cause antidepressant withdrawal symptoms in a high percentage of patients.[13] Lilly has acknowledged that the company's not systematically monitoring Cymbalta side effects was one of the "main limitations" of its studies.[14] Systematically monitoring withdrawal side effects with a symptom checklist rating scale would be expected to detect higher rates of Cymbalta withdrawal.[15]

When pharmaceutical company studies are completed, statistical analyses can be conducted to compare the number and rate of side effects in patients who received the

drug versus placebo. When despite the studies' limitations, a drug statistically significantly increases the risk of a side effect, the findings are particularly compelling.[16] Indeed, the FDA has stated that statistically significant findings establish a drug causes side effects.[17] At a July 10, 2008 FDA hearing on medication-induced psychiatric side effects, the FDA's Dr. Russell Katz, the director of the agency's Division of Neuropharmacological Drugs, explained:[18]

> This is how we determine causality….If it's statistically significantly different from placebo, we say the drug caused it….I think in controlled trials, you see a signal, [if] it is statistically significantly different from placebo, that is operationally defined as causality.

In addition to statistically significant findings, there are other widely used measures for assessing causality including the Bradford Hill criteria discussed below.

What Lilly's Short-Term, Placebo-Controlled Cymbalta Studies Found

Despite their limitations, Lilly's randomized, double-blind, placebo-controlled studies of depressed patients demonstrated that Cymbalta more than doubled the risk of withdrawal reactions when the drug was stopped.[19] The elevated risk was statistically significant.[20] To win FDA approval for Cymbalta, Lilly conducted a number of short-term (eight to nine week) studies of patients with major depressive disorder (MDD), comparing treatment with Cymbalta to treatment with placebo. In Table 1, which reproduces a table from a Lilly article published in 2005 in the *Journal of Affective Disorders*, the first six studies are short-term, placebo-controlled studies.[21] A total of 870 patients participated in the six studies; 490 received Cymbalta while 380 received placebo.

Table 1

Summary of Lilly's MDD Cymbalta Studies

Table 1
Summary of clinical trials

Study	Study design	Treatments (*N*)	Weeks of treatment
1	Parallel, double-blind, placebo-controlled, randomized, fluoxetine-controlled	Placebo (70) Duloxetine 20–60 mg BID[a] (70) Fluoxetine 20 mg QD (33) Total (173)	8
2	Parallel, double-blind, placebo-controlled, randomized, fluoxetine-controlled	Placebo (75) Duloxetine 20–60 mg BID[a] (82) Fluoxetine 20 mg QD (37) Total (194)	8
3	Parallel, double-blind, placebo-controlled, randomized	Placebo (122) Duloxetine 60 mg QD (123) Total (245)	9
4	Parallel, double-blind, placebo-controlled, randomized	Placebo (139) Duloxetine 60 mg QD (128) Total (267)	9
5	Parallel, double-blind, placebo-controlled, randomized, paroxetine-controlled	Placebo (90) Duloxetine 20 mg BID (91) Duloxetine 40 mg BID (84) Paroxetine 20 mg QD (89) Total (354)	8
6	Parallel, double-blind, placebo-controlled, randomized, paroxetine-controlled	Placebo (89) Duloxetine 20 mg BID (86) Duloxetine 40 mg BID (91) Paroxetine 20 mg QD (87) Total (353)	8
7	Parallel, double-blind, placebo-controlled, randomized, paroxetine-controlled	Placebo (93) Duloxetine 40 mg BID (93) Duloxetine 60 mg BID (95) Paroxetine 20 mg QD (86) Total (367)	8; +26-week extension phase
8	Parallel, double-blind, placebo-controlled, randomized, paroxetine-controlled	Placebo (99) Duloxetine 40 mg BID (93) Duloxetine 60 mg BID (103) Paroxetine 20 mg QD (97) Total (392)	8; +26-week extension phase
9	Open-label	Duloxetine 40–60 mg BID (1279)	52

In all these studies, the observation period for DEAEs is 2 weeks; BID=twice daily; QD=once daily.
[a] Forced titration to 120 mg/day.

As seen in Table 1, some of the six short-term studies also had active comparators, including Prozac (fluoxetine) and Paxil (paroxetine). At the end of the eight to nine week studies, patients' active drugs (Cymbalta, Prozac, or Paxil) were stopped with double-blind placebo substitution for one to two additional weeks in what Lilly called a "placebo lead-out" phase, also known as a placebo wash-out phase.[22] The placebo group simply continued on placebo during this post-active treatment phase. Table 2 reproduces another Lilly table, listing the most common withdrawal side effects reported by at least 2% of patients whose Cymbalta was stopped.[23] In Table 2, "discontinuation-emergent adverse effects" is Lilly's term for symptoms of antidepressant withdrawal.

Table 2

Antidepressant Withdrawal Side Effects in Lilly's Cymbalta Studies

Table 2
Discontinuation-emergent adverse events after acute treatment reported by at least 2% of duloxetine-treated patients who entered the lead-out phase of studies 1, 2, 3, 4, 5 and 6

Event	Placebo (N=380; n (%))	Duloxetine (N=490; n (%))
Patients with ≥ 1 event	87 (22.9)	217 (44.3)*
Dizziness	3 (0.8)	61 (12.4)*
Nausea	1 (0.3)	29 (5.9)*
Headache NOS	3 (0.8)	26 (5.3)*
Paraesthesia	1 (0.3)	14 (2.9)*
Diarrhea NOS	3 (0.8)	11 (2.2)
Vomiting NOS	2 (0.5)	12 (2.4)*
Irritability	1 (0.3)	12 (2.4)*
Insomnia	2 (0.5)	10 (2.0)
Nightmare	0 (0.0)	10 (2.0)*

NOS=not otherwise specified.
* P<0.05 vs. placebo, Fisher's Exact Test.

As seen in Table 2, in Lilly's studies Cymbalta withdrawal reactions were common: 44% of patients stopping the drug experienced one or more characteristic symptoms of antidepressant withdrawal. Since Lilly did not systematically assess Cymbalta withdrawal side effects in the studies, systematic monitoring would be expected to detect even higher rates.[24]

The most common withdrawal symptoms were dizziness, nausea, headaches, paraesthesias (abnormal sensations such as electric shock-like sensations in the brain), diarrhea, vomiting, irritability, and nightmares, all classic symptoms of antidepressant withdrawal. Many of the withdrawal symptoms were reported within a day of stopping Cymbalta.[25]

Table 3 analyzes Lilly's Cymbalta data in Table 2, providing the odds ratios, confidence intervals, and p-values for the risk of patients experiencing withdrawal symptoms when stopping Cymbalta versus placebo.[26]

Table 3
Statistical Significance Calculations
Based on Lilly's Data in Table 2

Withdrawal Symptoms	Placebo N=380	Cymbalta N=490	OR	p-Value	CI
Patients with ≥1 symptom	87 (22.9%)	217 (44.3%)	2.68	<0.001	1.98 - 3.65
Dizziness	3 (0.8%)	61 (12.4%)	17.87	<0.001	5.74-89.59
Nausea	1 (0.3%)	29 (5.9%)	23.84	<0.001	3.91 - 976.20
Headache NOS	3 (0.8%)	26 (5.3%)	7.04	<0.001	2.13 - 36.57
Paraesthia	1 (0.3%)	14 (2.9%)	11.15	0.004	1.68 - 472.60
Vomiting NOS	2 (0.5%)	12 (2.4%)	4.75	0.041	1.05 - 43.84
Irritability	1 (0.3%)	12 (2.4%)	9.51	0.012	1.39 - 406.7
Nightmares	0 (0.0%)	10 (2.0%)	8.71	0.020	1.25 – 376.00

As seen in Table 3, stopping Cymbalta more than doubled the risk of withdrawal symptoms by comparison with stopping placebo: the odds ratio was 2.68.[27] The increased risk was statistically significant: the p-value was less than 0.001.[28] The risk of individual withdrawal symptoms was elevated even more: By comparison with stopping placebo, stopping Cymbalta statistically significantly elevated the risk of nausea 23-fold, dizziness 17-fold, paraesthias 11-fold, irritability 9-fold, nightmares 8-fold, headaches 7-fold, and vomiting 4-fold.

These statistically significant findings in Lilly's short-term, placebo-controlled, randomized studies of depressed patients constitute strong scientific evidence that stopping Cymbalta causes withdrawal reactions in a high percentage of patients. The findings for multiple, classic symptoms of antidepressant withdrawal provide evidence of a broad range of Cymbalta withdrawal reactions.

Confirmatory Evidence from Lilly's 34-Week Studies

The findings in Lilly's short-term studies were confirmed by two 34-week placebo-controlled studies the company conducted, studies 7 and 8 in Table 1.[29] These two longer term studies consisted of initial 8-week studies followed by 26-week extension phases, for a total of 34 weeks. A total of 343 patients in the studies were treated with either 80 milligrams a day of Cymbalta (118 patients); 120 milligrams a day of Cymbalta (124 patients); or placebo (101 patients). At the end of active treatment, the patients' Cymbalta was stopped with double-blind placebo substitution in a two week placebo lead-out phase.[30] The placebo group continued on placebo for two additional weeks.

Lilly again did not systematically monitor withdrawal side effects in these studies, only recording them if patients spontaneously reported them.[31] Nevertheless, in the longer-term studies, stopping Cymbalta again more than doubled the risk of antidepressant withdrawal reactions by comparison with stopping placebo: the odds ratio was 4.95.[32] The increased risk was statistically significant: the p-value was 0.023.[33] Thus, in Lilly's longer-term placebo-controlled studies, stopping Cymbalta significantly increased the risk of withdrawal reactions almost 5-fold by comparison with stopping placebo.

Confirmatory Evidence from
Lilly's 52-Week Longer-Term Study

Lilly also conducted a longer-term, 52-week study of Cymbalta for depressed patients, study 9 in Table 1. This study was not placebo-controlled; it was open label. A total of 553 patients participated in the study. In this longer-term study, too, Lilly did not systematically monitor Cymbalta withdrawal side effects, only recording them if patients spontaneously reported them.[34] Notwithstanding the absence of systematic monitoring, 50.8% of Cymbalta patients *still* reported antidepressant withdrawal reactions upon discontinuing the drug.[35] Had Lilly used systematic monitoring, one would expect the rate to be even higher.[36] Table 4 reproduces another Lilly table listing the withdrawal side effects reported by patients after a year of treatment with Cymbalta.[37]

Table 4

Cymbalta Withdrawal Side Effects
in Lilly's Longer-Term 52-Week Study

Table 4
Discontinuation-emergent adverse events after long-term treatment for which the incidence was at least 2%

Event	Duloxetine (N=553; n (%))
Patients with ≥ 1 DEAE	281 (50.8)
Dizziness (excluding vertigo)	106 (19.2)
Anxiety NEC	55 (9.9)
Nausea	54 (9.8)
Headache NOS	40 (7.2)
Insomnia	37 (6.7)
Irritability	33 (6.0)
Vomiting NOS	24 (4.3)
Nightmare	16 (2.9)
Paraesthesia	16 (2.9)
Tinnitus	16 (2.9)
Crying	15 (2.7)
Depressed mood	15 (2.7)
Depression NOS	15 (2.7)
Anorexia	14 (2.5)
Diarrhea NOS	14 (2.5)
Myalgia	13 (2.4)
Tremor	12 (2.2)
Nervousness	11 (2.0)

NEC=not elsewhere classified; NOS=not otherwise specified.

As seen in Lilly's list in Table 4, the side effects of antidepressant withdrawal include characteristic physical side effects (such as dizziness, nausea, headaches, vomiting, parathesias [abnormal sensations such as electric shock-like sensations in the brain], diarrhea, and tremors) as well as characteristic psychiatric side effects (including anxiety, depression, insomnia, irritability, nightmares, and crying).

Section 2: Post-Marketing Adverse Event Reports (AERs) of Cymbalta Withdrawal

Once a drug is on the market and prescribed to millions of patients, postmarketing surveillance adds additional safety information to what was learned in pre-approval pharmaceutical company studies.[38] In this country, the FDA's system for postmarketing surveillance is called the Adverse Event Reporting System, or AERS. Healthcare professionals know the system by the name MedWatch. Healthcare professionals and consumers can report side effects to the FDA or the pharmaceutical company, which collects the information, writes the case reports, and submits them to the FDA. Pharmaceutical companies write 94% of the reports and forward them to the FDA.[39] The FDA relies on postmarketing surveillance for its regulatory decisions. The system is voluntary, or spontaneous, not mandatory. The FDA receives about 500,000 side effect reports a year, which are estimated to represent 1% to 10% of all side effects that actually occur.[40] The report rate for any particular side effect may vary by drug, side effect, and over time.

The technical term for these side effect reports is adverse event reports or adverse drug event reports (ADERs). According to the FDA and pharmacoepidemiology textbooks, adverse drug reports are the essential, core data of postmarketing surveillance.[41] The consensus in the field is that the reports imply the drug caused the side effect—the healthcare provider or consumer who reported the event thought it was related to the drug.[42] The reports can include details such as the patient's age, gender, diagnosis, concomitant medications, dates of exposure, and the dates of the drug reaction. They also include a narrative section in which the reporter can describe in some detail what the patient experienced. The narratives provide a descriptive picture of the side effect that complements more matter-of-fact information.

The important role of postmarketing surveillance has been summarized in an article by Dr. Janet Woodcock, the director of the FDA's Center for Drug Evaluation and Research, and two of her colleagues at the agency. The article, entitled the "Role of Postmarketing Surveillance in Contemporary Medicine," was published in the August 2010 issue of the *Annual Review of Medicine.*[43] According to Woodcock:[44]

> Even well-controlled randomized controlled clinical trials cannot uncover every safety problem, nor are they expected to do so. In most cases, clinical trials are not large enough, diverse enough, or long enough in duration to provide all the information on a product's performance and safety. Additionally, clinical trials of the size and scope typically

> supported by our current system are unlikely to reliably detect serious adverse events [side effects] that are rare, that occur with long latency, or that happen in subpopulations who have not participated (or had small representation) in clinical studies.
>
> Once a new medical product enters the market, it can be expected to be used in a patient population that is much larger and more heterogeneous than those studied in preapproval clinical trials. The real-world population has a broader range of comorbidities, uses a wide variety of concomitant medications, has genetic diversity that can affect drug metabolism, and may be treated for conditions that have not been studied. For all these reasons, postmarketing surveillance plays a critical role in identifying medication risks that were previously unknown.
>
> For the past 40 years, spontaneous reporting has been the cornerstone of FDA's postmarketing drug safety monitoring. The spontaneous reporting system is based on the public—both healthcare professionals and their patients—voluntarily reporting adverse events, errors, and quality problems they observe during the use of a product to either manufacturers or FDA.… Substantial underreporting of adverse events is widely acknowledged. Moreover, the reports submitted are a highly selective sample of the events observed in practice. Despite these limitations, well-documented observations made at the point of care—reported either to manufacturers, who are required by law to report to FDA, or directly to FDA—are an invaluable component of the drug safety surveillance system.

The FDA makes postmarketing surveillance data publicly available for research, so independent scientists can also examine and evaluate the data. So do many foreign drug regulators. Personal information that might reveal the patient's identity is redacted. The FDA makes adverse event report data publicly available four times a year, on a quarterly basis, for independent scientists to examine and analyze.

The Institute for Safe Medication Practices is one such group of independent scientists who evaluate and analyze adverse event reports to the FDA.[45] The Institute is a nonprofit organization dedicated to educating the healthcare community and patients about safe medication practices.[46] Four times a year, the Institute publishes an analysis of adverse event reports called *QuarterWatch: Monitoring FDA MedWatch Reports*.[47] According to the Institute:[48]

> QuarterWatch…monitors all domestic, serious adverse drug events reported to the FDA. We analyze computer excerpts from the FDA Adverse Event Reporting System. These voluntary reports (best known as MedWatch reports) are a cornerstone of the nation's system for monitoring the safety of prescription drugs after FDA marketing approval.

The October 3, 2012 issue of *QuarterWatch* reported that in the first quarter of 2012 reports to the FDA of Cymbalta withdrawal outnumbered reports of withdrawal for all other drugs:[49]

> We observed a signal for serious drug withdrawal symptoms associated with Cymbalta, a widely used antidepressant that is also approved to treat arthritis and back pain, anxiety, and fibromyalgia….Cymbalta was notable in the first quarter of 2012 because reports of serious drug withdrawal effects (n=48) outnumbered all other regularly monitored drugs, including an opioid treatment for narcotics addiction, buprenorphine-naloxone (Suboxone) (n=43) and the potent synthetic opioid fentanyl (Duragesic) (n=34)….The specific symptoms spanned a wide range of disorders. They included physical and neurological symptoms such as dizziness, paresthesia, and abnormal sweating. But psychiatric symptoms were also reported such as crying, anger, suicidal ideation, hallucinations, and personality change.

Thus, the reports to Lilly and the FDA included severe, life threatening cases of Cymbalta withdrawal. Indeed, according to *QuarterWatch*:[50]

> Several cases involved hospitalization….[and] all of the…cases were coded as serious….

The FDA defines serious side effects as those that result in death, inpatient hospitalization or prolongation of a hospitalization, significant or persistent incapacity, or birth defects.[51] *QuarterWatch* described Cymbalta withdrawal as a "major drug safety issue":[52]

> We document a serious lapse in the system that ought to be providing complete information and clear warnings for patients and health professionals about the extensive withdrawal effects of the antidepressant Cymbalta. The Medication Guide for patients gives no hint that withdrawal symptoms can affect half of those discontinuing Cymbalta,

> and that many cases may be severe, persistent, or both. The prescribing information for physicians and pharmacists does not provide realistic schedules for dose tapering or a clear picture of the likely incidence of these reactions….Excessive and unnecessary long-term use [of anti-depressants] is another likely consequence of serious withdrawal effects without adequate warnings. Patients try to discontinue, encounter severe symptoms, and discover that these problems disappear quickly if they resume the drug. While antidepressants are not classified as drugs of abuse, they share the risk of withdrawal symptoms with the opioids and benzodiazepines [Valium-type drugs]. Given that antidepressant drugs were tested primarily in short-term trials of six to nine weeks, the fact that that 60% of the large population taking antidepressants had done so for two years or more moves this issue onto the short list of major drug safety issues.

The strong signal of serious Cymbalta withdrawal reactions seen in post-marketing adverse event reports to the FDA—a larger number of reports than for any other drugs including opiates or Valium-type medications—provides strong supporting evidence Cymbalta causes withdrawal reactions that can be severe. As discussed later in this report, I agree with the *QuarterWatch* scientists that the information Lilly provides doctors and patients in its Cymbalta label is inadequate and that Cymbalta withdrawal is a serious drug safety issue.

Section 3: The Evidence in Published Scientific Studies of Antidepressant Withdrawal

Published studies have established that antidepressants cause withdrawal reactions.[53] Indeed, a study and reviews calling attention to withdrawal with newer SSRI antidepressants were funded and published by Eli Lilly when the company was marketing its earlier antidepressant, Prozac.[54] In the study, Lilly-funded researchers systematically monitored withdrawal side effects using checklist rating scales to compare the frequency of withdrawal reactions in patients stopping Prozac, Zoloft and Paxil.[55] The study was conducted in the mid-1990s before Lilly began marketing Cymbalta in 2004. A subsequent study by some of the same researchers evaluated withdrawal reactions in patients stopping the SNRI-type antidepressant Effexor.[56] Table 5 summarizes the results of the studies.[57]

Table 5
Frequency of Antidepressant Withdrawal Reactions

Antidepressant	Half-Life	Frequency of Withdrawal Reactions
Effexor	5 hours	78%
Paxil	21 hours	66%
Zoloft	26 hours	60%
Prozac	4-6 days	14%

As seen in Table 5, 78% of patients stopping Effexor, 66% of patients stopping Paxil, 60% of patients stopping Zoloft, and 14% of patients stopping Prozac experienced withdrawal symptoms in the studies.

The Role of an Antidepressant's Half-Life

As shown in Table 5, the frequency of withdrawal reactions directly correlates with an antidepressant's half-life, a measure of how quickly the antidepressant washes out of the body. A medication's half-life is the length of time it takes for half the drug to be excreted from the body after a patient stops taking it. If an antidepressant's half-life is twenty-four hours, then twenty-four hours after the last dose—the next day—half the antidepressant is eliminated. Another twenty-four hours later, half again—a total of 75% of the drug—has been eliminated. By contrast, if the antidepressant's half-life is seven days, then it takes a week—instead of a day—for half of it to be gone, and two

weeks—instead of two days—for three quarters of it to be gone. Obviously, this is a significant difference in how precipitously or gradually the level of the antidepressant drops and therefore how much time brain cells have to adapt to the change. Withdrawal reactions are evidence of abnormal brain cell functioning in response to insufficient time for the cells to gradually adapt to withdrawal of the drug. Even after an antidepressant is gone, withdrawal reactions can persist because the brain cells are still distressed, trying to cope with the drop in the drug's level.

Another standard measure of how quickly antidepressants wash out of the body is the time it takes for 90% of the drug to be eliminated, which is about five half-lives. With its extremely short half-life, Effexor washes out of the body in about a day. With their short half-lives, Paxil and Zoloft are eliminated within about four to five days. By contrast, Prozac takes about 25 days to be eliminated, providing an automatic, gradual taper. Like Effexor, Cymbalta has an extremely short half-life of about 12 hours.[58] Thus, Cymbalta washes out of the body precipitously in about two and a half days. Because Cymbalta's half-life (12 hours) is between Effexor's (5 hours) and Paxil's (21 hours), if Lilly had systematically monitored withdrawal side effects in its Cymbalta studies, one would expect to find between 66% and 78% of patients experienced Cymbalta withdrawal.

Worst Offenders

Table 6 lists the half-lives, 90% elimination times, and typical time of onset of withdrawal side effects of SSRIs, SNRIs, and other newer antidepressants.[59] In Table 6, the antidepressants are listed from those with the shortest half-lives—Effexor and Cymbalta—to those with the longest half-lives—Remeron, Celexa, and Prozac. The half-lives of the antidepressants span a wide range from five hours to four to six days. As seen in Table 6, two of the worst offenders are Cymbalta and Effexor with their extremely short half-lives. Because of their extremely short half-lives, patients on Cymbalta or Effexor can experience withdrawal side effects if they inadvertently miss just one dose.[60]

Table 6
The Half-Lives, Elimination Times, and Typical Onset
of Withdrawal Symptoms after Stopping Antidepressants

Antidepressant	Half-Life	90% Eliminated	Typical Onset of Withdrawal
Effexor, Effexor XR	5 hours	1 day	Day 1-2
Cymbalta	12 hours	2.5 days	Day 2-3
Luvox	15.6 hours	3.3 days	Day 2-3
Serzone	11-24 hours	3.6 days	Day 2-3
Paxil CR	15-20 hours	3.6 days	Day 2-3
Paxil	21 hours	4.4 days	Day 2-3
Wellbutrin, Wellbutrin SR, Wellbutrin XL	21 hours	4.4 days	Day 2-3
Zoloft	26 hours	5.4 days	Day 3-4
Lexapro	27-32 hours	6.1 days	Day 3-5
Remeron	20-40 hours	6.3 days	Day 3-5
Celexa	35 hours	7.3 days	Day 3-6
Prozac	4-6 days	25 days	2-3 weeks

Characteristic Symptoms of
Antidepressant Withdrawal

More than 50 symptoms of antidepressant withdrawal have been reported.[61] Withdrawal symptoms are broadly divided into two main categories: psychiatric symptoms and physical symptoms.[62] The psychiatric symptoms of antidepressant withdrawal include depressed mood, anxiety, insomnia, nightmares, irritability, agitation, impulsivity, or suicidal and violent urges. The characteristic physical symptoms include dizziness that can be disabling, imbalance, flu-like aches and pains, nausea, vomiting, headaches, tremors, tingling sensations, and electric shock-like "zaps" in the brain. Table 7 reproduces the checklist of withdrawal symptoms used in the Lilly-funded Prozac study.[63] Thus, Table 7 is the Lilly-sponsored list of side effects characteristic of antidepressant withdrawal.

Table 7

Antidepressant

Withdrawal Side Effects

Appendix. Discontinuation-Emergent Signs and Symptoms

Symptom
1. Nervousness or anxiety
2. Elevated mood, feeling high
3. Irritability
4. Sudden worsening of mood
5. Sudden outbursts of anger ("anger attacks")
6. Sudden panic or anxiety attacks
7. Bouts of crying or tearfulness
8. Agitation
9. Feeling unreal or detached
10. Confusion or trouble concentrating
11. Forgetfulness or problems with memory
12. Mood swings
13. Trouble sleeping, insomnia
14. Increased dreaming or nightmares
15. Sweating more than usual
16. Shaking, trembling
17. Muscle tension or stiffness
18. Muscle aches or pains
19. Restless feeling in legs
20. Muscle cramps, spasms, or twitching
21. Fatigue, tiredness
22. Unsteady gait or incoordination
23. Blurred vision
24. Sore eyes
25. Uncontrollable mouth/tongue movements
26. Problems with speech or speaking clearly
27. Headache
28. Increased saliva in mouth
29. Dizziness, lightheadedness, or sensation of spinning (vertigo)
30. Nose running
31. Shortness of breath, gasping for air
32. Chills
33. Fever
34. Vomiting
35. Nausea
36. Diarrhea
37. Stomach cramps
38. Stomach bloating
39. Unusual visual sensations (lights, colors, geometric shapes, etc.)
40. Burning, numbness, tingling sensations
41. Unusual sensitivity to sound
42. Ringing or noises in the ears
43. Unusual tastes or smells

Patient was asked, "During the past 7 days, have you experienced any changes in the following symptoms." Patient chose one of four responses (new symptom; old symptom, but worse; old symptom, but improved; old symptom, but unchanged or symptom not present).

Similar side effects were seen in Lilly's later Cymbalta studies (compare Table 7 from Lilly's Prozac study to Table 4 from Lilly's Cymbalta studies). Table 4 is a shorter list than Table 7 because Lilly did not systematically monitor withdrawal side effects in its Cymbalta studies, as was done in the Prozac study. In addition, Table 4 does not list all of the Cymbalta withdrawal side effects spontaneously reported by patients; it only lists side effects that were reported by two percent or more of patients.

Table 8 reproduces another table of characteristic symptoms of antidepressant withdrawal from *The Antidepressant Solution: A Step-by-Step Guide to Safely Overcoming Antidepressant Withdrawal Dependence, and "Addiction"*.[64] Table 8 lists a total of 58 side effects characteristic of antidepressant withdrawal that have been reported in the medical literature. Table 8 breaks this large number of withdrawal side effects down into smaller, easier to recognize clusters of characteristic side effects of antidepressant withdrawal. The characteristic psychiatric side effects are divided into depressive symptoms, anxiety symptoms, irritability and aggression, confusion and memory problems, mood swings, hallucinations, and dissociation. The characteristic physical side effects are divided into flu-like symptoms, gastrointestinal symptoms, dizziness, headache, tremor, and abnormal sensations.

Table 8

Symptoms of

Antidepressant Withdrawal

Psychiatric Symptoms	Medical Symptoms
Depressive Symptoms 1. Crying spells 2. Worsened mood 3. Low energy (fatigue, lethargy, malaise) 4. Trouble concentrating 5. Insomnia or trouble sleeping 6. Change in appetite 7. Suicidal thoughts 8. Suicide attempts *Anxiety Symptoms* 9. Anxious, nervous, tense 10. Panic attacks (racing heart, breathless) 11. Chest pain 12. Trembling, jittery, or shaking *Irritability and Aggression* 13. Irritability 14. Agitation (restlessness, hyperactivity) 15. Impulsivity 16. Aggressiveness 17. Self-harm 18. Homicidal thoughts or urges *Confusion and Memory Problems* 19. Confusion or cognitive difficulties 20. Memory problems or forgetfulness *Mood Swings* 21. Elevated mood (feeling high) 22. Mood swings 23. Manic-like reactions *Hallucinations* 24. Auditory hallucinations 25. Visual hallucinations *Dissociation* 26. Feeling detached or unreal *Other* 27. Excessive or intense dreaming 28. Nightmares	*Flu-Like Symptoms* 29. Flu-like aches and pains 30. Fever 31. Sweats 32. Chills 33. Runny nose 34. Sore eyes *Gastrointestinal Symptoms* 35. Nausea 36. Vomiting 37. Diarrhea 38. Abdominal pain or cramps 39. Stomach bloating *Dizziness* 40. Disequilibrium 41. Spinning, swaying, lightheaded 42. Hung over or waterlogged feeling 43. Unsteady gait, poor coordination 44. Motion sickness *Headache* 45. Headache *Tremor* 46. Tremor *Sensory Abnormalities* 47. Numbness, burning, or tingling 48. Electric zap-like sensations in the brain 49. Electric shock-like sensations in the body 50. Abnormal visual sensations 51. Ringing or other noises in the ears 52. Abnormal smells or tastes *Other* 53. Drooling or excessive saliva 54. Slurred speech 55. Blurred vision 56. Muscle cramps, stiffness, twitches 57. Feeling of restless legs 58. Uncontrollable twitching of mouth

The Characteristic Time Course of Antidepressant Withdrawal

In addition to characteristic symptoms, antidepressant withdrawal typically follows a characteristic time course. Patients stopping antidepressants with short half-lives like Cymbalta typically develop withdrawal side effects within one to five days after stopping the drugs.[65] Indeed, in Lilly's Cymbalta studies, many patients reported withdrawal side effects within one to two days.[66] Because of Cymbalta's extremely short half-life, patients who inadvertently miss just one dose can experience withdrawal reactions.[67] The close temporal relationship between lowering the dose of Cymbalta and the abrupt development of symptoms is characteristic of antidepressant withdrawal.[68] By contrast, depressive relapse (a return of the patient's original depression) occurs gradually, one to two months or more after stopping an antidepressant.[69]

Mild, Moderate, and Severe Withdrawal Reactions

Antidepressant withdrawal side effects can be categorized as mild, moderate, or severe.[70] This is a global, or overall, assessment based on the patient's worst symptoms and their effect on the patient's ability to function. Mild withdrawal side effects are noticeable but not terribly uncomfortable and do not affect the patient's ability to function. Moderate withdrawal is sufficiently uncomfortable that it negatively affects the patient's ability to think clearly and/or function normally. Severe withdrawal reactions are characterized by one or more debilitating side effects that:

- include suicidal thoughts, suicidal behavior, harm to the patient or others, hallucinations, or manic-like symptoms
- make it impossible for the patient to function normally for all or part of the day
- necessitate resuming the antidepressant or putting the dose back up to stop the withdrawal symptoms
- require tapering the antidepressant so painstakingly slowly that it takes more than four months to safely discontinue the drug

According to Lilly, in the company's short-term, placebo-controlled Cymbalta studies of depressed patients, 9.6% of Cymbalta withdrawal side effects were severe.[71] In the company's year-long study, 17.2% of withdrawal side effects were severe.[72]

Severe withdrawal reactions can be incapacitating, leaving patients bedridden and unable to work.[73] Because antidepressant withdrawal reactions can be severe and even life-threatening, antidepressants should not be stopped abruptly, with rare exceptions such as modest doses of Prozac with its automatic, slow, built-in taper. Instead, the drugs should be tapered, i.e. the dose should be lowered gradually over an extended period of time. How long it takes a patient to taper off an antidepressant depends on a number of factors including the particular drug, how long the patient has been on it, the dose, and the patient's vulnerability to withdrawal symptoms. Some patients are extremely sensitive to antidepressant withdrawal reactions. There are reports of people who could not stop using their antidepressant because of severe withdrawal reactions.[74]

Antidepressant tapering schedules need to be individualized for patients.[75] When a patient has severe withdrawal reactions, one tries to adjust the reductions until they are small enough that the patient can tolerate them relatively comfortably. One aims for the patient to only have mild to moderate withdrawal side effects that typically peak within seven to ten days and subside over the course of two to three weeks. If this pattern has been achieved, the patient's dose can be lowered about once a month. But especially with worst offenders like Cymbalta and Effexor, even when the drug is tapered slowly, patients may experience severe withdrawal reactions and require seven or more months to get off the drug. Unfortunately, many doctors are unaware of antidepressant withdrawal and how slowly antidepressants need to be tapered for some patients.

Physical Dependency

In medicine, physical dependency is the term for when patients are forced to go back on a drug that has been stopped (or back up on the dose that has been lowered) in order to suppress intolerable or debilitating withdrawal side effects. Thus, when patients experience moderate to severe antidepressant withdrawal and are forced to resume taking the drug and/or take longer to taper off, they are physically dependent on the antidepressant to prevent unpleasant or debilitating withdrawal reactions.

Differentiating Withdrawal from Relapse

When doctors and patients are misinformed about antidepressant withdrawal, there is a danger that they will mistake withdrawal side effects for a return of the patients' underlying psychiatric condition. On the other hand, when doctors and patients know what to look for, in most instances it can become easier for the physician to distinguish withdrawal from relapse. The characteristics that typically set withdrawal apart from

depressive relapse are: the timing of the onset of symptoms; the presence of physical symptoms of withdrawal; the characteristic time course for withdrawal side effects to peak and fade; and the dramatic disappearance of withdrawal side effects if they are intolerable and the prior antidepressant dose is reinstated.

Unfortunately, when doctors and patients are misinformed about antidepressant withdrawal they can mistake withdrawal for relapse of the patients' original psychiatric condition. In this antidepressant catch-22, the drug may be reinstated—often for years—needlessly exposing patients to the side effects and long-term risks of antidepressants. In many instances, not only is the drug restarted, the dose is increased and additional drugs—additional antidepressants, mood stabilizers, antianxiety agents, and sleeping pills—are added to "treat" withdrawal that has been misdiagnosed as a relapse of the patients' prior psychiatric condition. In the process, patients get the false impression their psychiatric conditions and prognoses are far worse than they really are.

Section 4: The Biological Mechanism of Cymbalta Withdrawal

Stopping Cymbalta or lowering the dose can cause withdrawal reactions because of the drug's mechanism of action. When the Cymbalta dose is lowered, brain cells may not have sufficient time to adapt to the sudden change. Withdrawal symptoms are evidence of abnormal brain cell functioning in response to precipitous withdrawal of an antidepressant, not enough time for the cells to gradually adjust.

Brain cells are not passive, in response to medications including antidepressants like Cymbalta. Instead, brain cells actively adapt, or change, in response to drugs. The adaptations are typically in the direction of reversing or counteracting the effects of drugs. Lilly promotes Cymbalta as increasing serotonin and norepinephrine levels in the brain.[76] Serotonin and norepinephrine are two of the chemical signals brain cells use to communicate with one another. These chemicals target serotonin and norepinephrine receptors on the surfaces of brain cells. In response to increased serotonin and norepinephrine signals, brain cells decrease the sensitivity of their receptors to the signals in a process called "down regulation."[77] Since the serotonin and norepinephrine receptors are made of proteins, within the cells changes occur in protein synthesis, which involves changes in the instructions given by the cells' DNA, the master code regulating cellular function.[78] The process takes weeks or months. Some of the changes the cells make are believed to be responsible for the drugs' therapeutic effects. When doctors prescribe antidepressants like Cymbalta, we often tell patients the drugs take about a month to work, because the changes in brain cells take time to occur. Other changes in the brain cells are believed to be responsible for the side effects of antidepressants.

When patients lower the dose or stop taking Cymbalta, brain cells need sufficient time to undo the adaptations they made to living with the drug. The cells need to readapt to living with less Cymbalta or to living without the drug. Whereas the cells down regulated in response to Cymbalta, now they need to "up regulate" in response to less of the drug. Once again, the process takes weeks or months. When the Cymbalta dose is lowered, the brain cells may not have sufficient time to adapt. The stress on the cells produces abnormal brain cell activity, resulting in the symptoms of Cymbalta withdrawal.

Lowering the dose of Cymbalta too abruptly is like driving a car at sixty miles per hour and suddenly putting it in reverse. Instead, one needs to slow the car down gradually,

and only put it in reverse once it has stopped. Similarly, one needs to gradually taper Cymbalta to allow the brain cells sufficient time to adjust.

This biological model explains why putting the dose of Cymbalta back up suppresses withdrawal symptoms: If the brain cells have not had enough time to readapt to a drop in Cymbalta levels, putting the dose back up reestablishes the level with which the brain cells are comfortable.

This biological model also explains why an antidepressant's half-life correlates with the frequency of withdrawal reactions. The shorter an antidepressant's half-life, the more quickly it washes out of the body and the more likely patients are to experience withdrawal reactions. Even before Lilly studied Cymbalta in patients, the company knew from pharmacodynamic studies Cymbalta had an extremely short half-life and would be expected to cause withdrawal reactions in a high percentage of patients. This biological mechanism explains the high rate of Cymbalta withdrawal reactions seen in patients in Lilly's studies.

Section 5: Bradford Hill Causality Assessment
Cymbalta Withdrawal

Taken together as a whole, the available evidence satisfies the Bradford Hill criteria for concluding that stopping Cymbalta can cause characteristic withdrawal reactions that can be severe. Introduced in 1965 by Bradford Hill, the criteria have become widely used in medicine to provide a formal structure for evaluating causality; for example, for evaluating whether or not a drug causes specific side effects.[79] The nine Bradford Hill criteria for evaluating causality are: experiment, strength of association, consistency, temporality, biological gradient, specificity, plausibility, coherence, and analogy.[80] Not all of the criteria need to be satisfied to conclude a drug causes a side effect; instead, the criteria provide a framework for comprehensively evaluating the available evidence.

Experiment

According to the Bradford Hill criteria, "experimental evidence is the most compelling evidence of causation."[81] In the case of Cymbalta withdrawal, this criteria is met: In Lilly's short-term, placebo-controlled studies stopping Cymbalta more than doubled the risk of withdrawal symptoms by comparison with stopping placebo: the odds ratio was 2.68.[82] The increased risk was statistically significant: the p-value was less than 0.001.[83] The risk of specific withdrawal side effects was elevated even more: By comparison with stopping placebo, stopping Cymbalta significantly elevated the risk of nausea 23-fold, dizziness 17-fold, parasthias 11-fold, irritability 9-fold, nightmares 8-fold, headaches 7-fold, and vomiting 4-fold.[84] Among the Cymbalta withdrawal side effects, 50.6% were moderate and 9.6% were severe.[85]

These results were confirmed in Lilly's longer-term, 34-week placebo-controlled studies. In the longer-term studies, stopping Cymbalta again more than doubled the risk of antidepressant withdrawal reactions by comparison with stopping placebo: the odds ratio was 4.95.[86] The elevated risk was statistically significant: the p-value was 0.023.[87]

The results of Lilly's short and longer-term placebo-controlled studies were confirmed by the company's 52-week open label study in which about 51% of patients reported withdrawal reactions when stopping Cymbalta after one year of treatment.[88] Among the Cymbalta withdrawal side effects, 46.3% were moderate and 17.2% were severe.[89]

The evidence from Lilly's Cymbalta studies has also been confirmed and elaborated upon by the FDA's post-marketing adverse event surveillance data. In the first quarter of 2012, reports of serious Cymbalta withdrawal reactions outnumbered reports for all

other regularly monitored drugs including narcotic (opiate-type) drugs and Valium-type (benzodiazepine) drugs.[90]

The evidence from Lilly's Cymbalta studies is also supported by Lilly's earlier Prozac study investigating the comparative rates of withdrawal reactions in patients stopping Prozac, Paxil, and Zoloft. In that study, with their short half-lives, stopping Paxil and Zoloft caused withdrawal reactions in 66% and 60% of patients respectively.[91] With its long half-life, stopping Prozac caused withdrawal reactions in a lower percentage of patients, 14%.

Supporting evidence also comes from Lilly's pharmacokinetic studies of Cymbalta. Cymbalta's extremely short 12 hour half-life is consistent with Cymbalta causing withdrawal reactions in a high percentage of patients stopping the drug: 40 to 50% in Lilly's studies.[92]

Taken together, this substantial body of experimental results provides convincing scientific evidence that stopping Cymbalta can cause withdrawal reactions in a high percentage of patients and that the withdrawal reactions can be severe.

Strength of Association

Strength of association refers to the degree to which a drug is associated with side effects. A statistically significant association is a strong association. In Lilly's studies, Cymbalta statistically significantly increased the risk of withdrawal reactions. In Lilly's short-term, placebo-controlled studies, Cymbalta increased the risk of withdrawal reactions 2.68-fold.[93] In Lilly's longer-term, 34-week placebo-controlled studies, Cymbalta increased the risk of withdrawal reactions 4.95-fold.[94] The risk of specific withdrawal symptoms was elevated as much as 23-fold.[95] These statistically significantly elevated risks demonstrate a strong association between Cymbalta and withdrawal side effects.

Consistency

Consistency refers to whether or not additional studies have replicated or confirmed a drug's association with side effects. Lilly's short-term, placebo-controlled studies; Lilly's longer-term, 34-week placebo-controlled studies; and Lilly's 52-week open label study have consistency demonstrated Cymbalta increases the risk of withdrawal side effects in a high percentage of patients. Lilly's pharmacodynamic studies of Cymbalta's short

half-life and the FDA's postmarketing adverse event surveillance data are also consistent with high rates of Cymbalta withdrawal reactions.

Temporality

Temporality refers to the temporal relationship between a drug and its side effects. According to the Bradford Hill criteria, in order to conclude that A causes B, A must occur before B. This criteria is met in the case of Cymbalta withdrawal side effects because in pharmaceutical company studies, the FDA requires that only treatment emergent signs and symptoms can be recorded as side effects.[96] Side effects are only recorded after the baseline, when patients begin treatment with the study drug or, as in the case of withdrawal side effects, in the phase of the study monitoring side effects after active treatment has stopped. Thus, all the incidents of Cymbalta withdrawal side effects in Lilly's studies occurred in the first week or two after the patients stopped taking Cymbalta, having taken the drug for at least two months.

Biological Gradient

A biological gradient refers to a dose-dependent relationship between a drug and side effect: that is, the higher the dose, the more frequent the side effect. A dose-dependent relationship provides additional evidence a drug causes a side effect. In Lilly's short-term, placebo-controlled studies, the patients on Cymbalta received 40, 60, 80, or 120 milligrams a day.[97] The rates of withdrawal reactions when patients stopped the different doses were 42.4%, 39.2%, 36.9%, and 62.1% respectively. Thus, a higher rate of Cymbalta withdrawal reactions was seen in patients who had taken 120 milligrams a day by comparison with the lower doses. Among the three lower doses, the dose-response relationship was not linear; the lower doses had similar rates of Cymbalta withdrawal reactions. In Lilly's longer-term 34-week placebo-controlled studies, a higher percentage of the patients who had taken 120 milligrams a day of Cymbalta experienced withdrawal reactions than those who had taken 80 milligrams a day.[98] Thus, in Lilly's studies the highest Cymbalta dose resulted in the highest rates of withdrawal side effects, providing support for a biological gradient, although the lower doses did not have a linear relationship. It is important to note that patients vary widely in their sensitivity to antidepressant withdrawal. Some patients experience severe withdrawal after stopping low doses of antidepressants while other patients experience milder withdrawal side effects after stopping higher doses of antidepressants.

Specificity

Bradford Hill defines two types of specificity: (1) agents producing a specific result not caused by other agents or conditions, or caused by few others, or (2) specificity in the magnitude of the association. One of Cymbalta's withdrawal side effects satisfies the first definition: electric shock-like sensations in the brain. These brain "zaps" are characteristic of antidepressant withdrawal. Cymbalta's other withdrawal side effects do not satisfy the first definition, since side effects like dizziness, nausea, vomiting, headaches, irritability, and nightmares can be caused by a wide range of drugs and medical conditions. But, Cymbalta's withdrawal side effects satisfy the second definition: based on the magnitude of the association. In Lilly's placebo controlled studies, Cymbalta increased the risk of withdrawal side effects between 2.86-fold and 23-fold by comparison with placebo, a very strong association. The magnitude of the association suggests a Cymbalta-specific effect, despite the fact that other drugs or conditions can cause similar symptoms. The magnitude of the association satisfies the Bradford Hill criteria for specificity.

Plausibility

Plausibility refers to a plausible biological hypothesis for how Cymbalta can cause withdrawal side effects. Lilly's studies dating back to the company's Prozac study comparing Prozac to Paxil and Zoloft have demonstrated stopping antidepressants can cause withdrawal reactions, and antidepressants with short half-lives can cause particularly high rates of withdrawal in 40%-50% of patients or more. Cymbalta has an extremely short half-life of about 12 hours. When the Cymbalta dose is lowered, brain cells need sufficient time to re-adapt, for example through a process called "down regulation," which takes weeks to months. When the dose is lowered, the brain cells may not have sufficient time to adapt to the sudden change. The stress on the cells produces abnormal brain cell activity, resulting in the symptoms of Cymbalta withdrawal. With its extremely short half-life Cymbalta is one of the worst offenders: its precipitous exit from the body and the stress on brain cells trying to adapt to the sudden change in their environment is a plausible biological mechanism for Cymbalta withdrawal.

Coherence

Coherence refers to whether or not our knowledge of Cymbalta withdrawal is consistent with previous knowledge. Other classes of drugs acting on the central nervous system including opiates, Valium-type (benzodiazepine) antianxiety agents and sleeping pills are also known to cause withdrawal reactions when stopped. Earlier

classes of antidepressants such as tricyclic antidepressants have also been shown to cause withdrawal reactions. And studies of earlier SSRI and SNRI-type antidepressants including Prozac, Zoloft, Paxil and Effexor have demonstrated that these so-called "newer" antidepressants can cause withdrawal reactions. Thus, our current knowledge of Cymbalta's withdrawal side effects is consistent with previous knowledge of these other drugs.

Analogy

Analogy is similar to coherence and refers to whether or not Cymbalta's withdrawal side effects are analogous to those of other drugs or conditions. Cymbalta's withdrawal side effects are analogous to the similar side effects of drugs such as Prozac, Zoloft, Paxil, and Effexor that are also promoted as increasing serotonin or norepinephrine signals in the brain. Like Cymbalta, these drugs can also cause withdrawal reactions when stopped. Cymbalta being one of the worst offenders is analogous to Effexor, which also has an extremely short half-life.

Summary

In conclusion, the available data demonstrates that the Bradford Hill criteria for establishing causality are met in the case of Cymbalta withdrawal side effects. The Bradford Hill criteria provide a structure for analyzing causality in medicine. The results of the above Bradford Hill analysis support my opinion that Cymbalta frequently causes withdrawal reactions that can be severe.

Section 6: Lilly's Label is Inadequate and Misleading with Regard to Cymbalta Withdrawal

For prescribing doctors like myself and for patients, an antidepressant's likelihood of causing withdrawal symptoms and, ultimately, physical dependency is an important factor in deciding whether to prescribe or take a particular antidepressant versus an alternative medication. The degree of risk of withdrawal symptoms associated with a particular antidepressant must be considered by any doctor who might prescribe the drug, and any patient who might take it.

Doctors like myself prescribe medicines such as Cymbalta relying on the accuracy of the drug's label (i.e., the prescribing information contained in the package insert and published in the Physicians' Desk Reference, the so-called "PDR"). Rarely do we perform our own clinical studies or have time to research what other studies have been performed on a particular medication. Although we have access to other sources of information, such as pharmaceutical representative detailing, recommendations by fellow physicians, and medical journal publications, treating physicians rely on the label as an ultimate authority of a drug's safety and efficacy.

The original 2004 Cymbalta label stated:[99]

> Discontinuation of Treatment with Cymbalta – Discontinuation symptoms have been systematically evaluated in patients taking Cymbalta. Following abrupt discontinuation in placebo-controlled clinical trials of up to 9-weeks duration, the following symptoms occurred at a rate greater than or equal to 2% and at a significantly higher rate in duloxetine-treated patients compared to those discontinuing from placebo: dizziness; nausea; headache; paresthesia; vomiting; irritability; and nightmare.

Lilly's list of withdrawal side effects that occurred in significantly more Cymbalta patients is the same as the list in Table 3 in this report of the side effects that occurred at significantly higher rates in Lilly's original short-term studies of depressed patients. In 2005, Lilly added "MDD" before "placebo-controlled clinical trials" so the label read (the change is highlighted in bold):[100]

> Discontinuation of Treatment with Cymbalta – Discontinuation symptoms have been systematically evaluated in patients taking Cymbalta. Following abrupt discontinuation in **MDD** placebo-controlled clinical

> trials of up to 9-weeks duration, the following symptoms occurred at a rate greater than or equal to 2% and at a significantly higher rate in Cymbalta-treated patients compared to those discontinuing from placebo: dizziness; nausea; headache; paresthesia; vomiting; irritability; and nightmare.

After that, the label stayed essentially the same for several years until 2008. In 2008, Lilly took out "trials of up to 9-weeks duration," changed the percentage withdrawal rate from 2% to 1%, and added additional withdrawal symptoms that occurred at significantly higher rates in Lilly's later Cymbalta studies:[101]

> Discontinuation of Treatment with Cymbalta – Discontinuation symptoms have been systematically evaluated in patients taking **duloxetine**. Following abrupt discontinuation in placebo-controlled clinical trials, the following symptoms occurred at a rate greater than or equal to 1% and at a significantly higher rate in duloxetine-treated patients compared to those discontinuing from placebo dizziness; nausea; headache; paresthesia; vomiting; irritability; nightmares; **insomnia, diarrhea, anxiety, hyperhidrosis and vertigo**.

In 2009, Lilly added "or tapered" to the label and "fatigue" to the list of Cymbalta's withdrawal side effects:[102]

> Discontinuation of Treatment with Cymbalta – Discontinuation symptoms have been systematically evaluated in patients taking duloxetine. Following abrupt **or tapered** discontinuation in placebo-controlled clinical trials of up to 9-weeks duration, the following symptoms occurred at a rate greater than or equal to 1% and at a significantly higher rate in duloxetine-treated patients compared to those discontinuing from placebo: dizziness; nausea; headache; **fatigue**; paresthesia; vomiting; irritability; nightmares; insomnia, diarrhea, anxiety, hyperhidrosis and vertigo.

In 2012, Lilly changed "at a rate greater than or equal to 1%" to "at 1% or greater," altered the sequence of the withdrawal side effects and removed "nightmares" so the label read:[103]

> Discontinuation of Treatment with Cymbalta – Discontinuation symptoms have been systematically evaluated in patients taking duloxetine. Following abrupt or tapered discontinuation in

> placebo-controlled clinical trials, the following symptoms occurred **at 1% or greater** and at a significantly higher rate in duloxetine-treated patients compared to those discontinuing from placebo: dizziness; nausea, headache, paresthesia, fatigue, vomiting, irritability, insomnia, diarrhea, anxiety, and hyperhidrosis.

Since entering the market, Lilly's label for Cymbalta has failed to provide accurate and/or sufficient information about the frequency, severity, and duration of those symptoms caused by stopping Cymbalta, i.e., Cymbalta withdrawal.

Lilly's label uses the phrases "Discontinuation of Treatment with Cymbalta" and "discontinuation symptoms," euphemisms for Cymbalta withdrawal. In my opinion, Lilly's label should use the plain English phrases "Cymbalta Withdrawal" and "withdrawal symptoms" so doctors and patients readily understand Cymbalta can cause withdrawal reactions. In contrast to Lilly's Cymbalta label in the United States, in Europe Lilly's Cymbalta label explicitly uses the phraseology "withdrawal symptoms," instead of the euphemism discontinuation symptoms.[104]

Lilly's label asserts withdrawal "symptoms have been systematically evaluated in patients taking Cymbalta" in the company's studies. But, as discussed earlier in this report, in its Cymbalta studies Lilly did *not* systematically monitor withdrawal reactions with the symptom checklist rating scale used in the earlier Lilly-sponsored study comparing stopping Prozac with stopping Paxil or Zoloft.[105] Instead, in Lilly's Cymbalta studies, withdrawal side effects were only recorded if patients recognized and volunteered them.[106] Lilly's unsystematic approach is called "non-probing" because the patients were not specifically asked about side effects.[107] This unsystematic approach is also called "spontaneous" reporting because patients must spontaneously volunteer the side effects.[108] Spontaneous reporting of side effects is well-known to result in significant underreporting.[109] Lilly's Cymbalta label misleadingly suggests withdrawal side effects were more rigorously and sensitively evaluated in the company's studies than was the case.

With regard to the frequency of Cymbalta withdrawal reactions, Lilly's Cymbalta label gives the misimpression that the frequency of withdrawal reactions is low, approximately 1% to 2% of patients. These percentages suggest that when it comes to withdrawal reactions, Cymbalta is one of the *best* antidepressants with a low rate of withdrawal side effects and therefore relatively little difficulty getting off the drug when, in fact, the opposite is true: Cymbalta is one of the *worst*. This language in Cymbalta's label misrepresents Lilly's own clinical data. As described in Section 1 of this report, in Lilly's six short-term, double-blind placebo controlled Cymbalta studies,

involving a combined total of 870 patients, 44% of patients stopping Cymbalta experienced withdrawal side effects.[110] In Lilly's year-long, open label study involving 1,279 patients, about 51% of patients experienced Cymbalta withdrawal symptoms.[111] As explained earlier in this report, the true percentage is likely much higher since Lilly did not systematically assess Cymbalta withdrawal side effects in the studies. Cymbalta increased the risk of some withdrawal symptoms, for example nausea, as much as 23-fold by comparison with placebo. The 1% to 2% figures in Lilly's Cymbalta label fail to convey the magnitude and seriousness of the problem of Cymbalta withdrawal. In contrast to Lilly's Cymbalta label in the United States, in Europe, Lilly's Cymbalta label informs doctors and patients that in the company's studies "approximately 45% of patients treated with Cymbalta" reported withdrawal side effects.[112] Lilly's United States label fails to inform doctors in this country that Cymbalta is one of the worst antidepressants with high rates of withdrawal reactions documented in Lilly's own studies, one of the most difficult antidepressants to comfortably and safely taper off.

With regard to the severity of Cymbalta withdrawal, Cymbalta's labeling fails to indicate how severe Cymbalta withdrawal can be. Specifically, in Lilly's six short-term, placebo-controlled Cymbalta studies, among the 44% of patients who experienced withdrawal symptoms, 50.6% of withdrawal side effects were moderate and 9.6% were severe.[113] In Lilly's larger year-long, open-label study, among the roughly 51% of patients experiencing withdrawal side effects, approximately 46% of the side effects were moderate and 17% were severe.[114] It is important to note that the FDA's black box and accompanying warnings regarding antidepressant-induced suicidality state that dosage changes, including tapering or stopping the drugs, are among the most vulnerable times for antidepressants to induce suicidal thinking and behavior. Physical symptoms of withdrawal, such as severe nausea, vomiting, disequilibrium, or electric shock-like sensations in the brain can be incapacitating and make patients bed-ridden. Lilly's label fails to explain that severe withdrawal reactions can be debilitating or even life-threatening.

Regarding the duration of Cymbalta withdrawal, Cymbalta's labeling does not provide any indication of the duration patients can expect to experience withdrawal symptoms following the discontinuation of Cymbalta. In Lilly's short-term, placebo-controlled Cymbalta studies, 53.7% of patients who reported withdrawal symptoms continued to experience withdrawal reactions after two weeks.[115] In Lilly's longer-term, 34-week studies, 64.7% of the patients who reported withdrawal symptoms continued to experience symptoms after two weeks.[116] In the year-long, open-label study, 55.2% of the patients who reported withdrawal symptoms continued to experience symptoms after two weeks.[117] Since Lilly did not monitor or record withdrawal symptoms beyond two weeks in any of these studies, there is no indication of how long the patients

continued to experience withdrawal symptoms. When patients attempt to go off antidepressants with extremely short half-lives like Cymbalta, seven or more months may be required to painstakingly taper off the drug. Lilly's label fails to inform doctors and patients it can be so difficult to discontinue Cymbalta. In contrast to Lilly's Cymbalta label in the United States, in Europe Lilly's label acknowledges Cymbalta withdrawal reactions "may be prolonged (2-3 months or more)."[118]

Throughout the years, the Cymbalta label also stated that:[119]

> During marketing of *other* SSRIs and SNRIs (Serotonin and Norepinephrine Reuptake Inhibitors), there have been *spontaneous* reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. *Although these events are generally self-limiting, some have been reported to be severe.*
>
> Patients should be monitored for these symptoms when discontinuing treatment with Cymbalta. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate [emphasis added].

Lilly's use of "other SSRIs or SNRIs" is misleading because it suggests antidepressants are more or less the same with regard to withdrawal reactions, and that Cymbalta is just another typical SSRI or SNRI, when this is not the case. Antidepressants are not the same; they vary widely in their half-lives and likelihood of causing withdrawal reactions. With its extremely short half-life and high rates of withdrawal reactions, Cymbalta is an outlier, one of the worst. Doctors and patients need to be properly informed of the risk of Cymbalta withdrawal so they understand it is one of the most difficult antidepressants to get off. Lilly's use of "generally self-limiting" suggests withdrawal is uncommon and that severe reactions are rare, neither of which is true. In addition, Lilly's statement that there have been "spontaneous" reports upon discontinuation "during marketing" of these "other SSRIs or SNRIs" misleadingly obscures the more specific data from Lilly's own Cymbalta studies. In addition to the

high rates of patients who reported withdrawal side effects in Lilly's Cymbalta studies, a high percentage were severe.

Lilly's information on gradually reducing the dose is also inadequate. Lilly fails to mention that patients who inadvertently miss just one dose of Cymbalta may experience withdrawal reactions (which Lilly's European label again discloses); fails to provide recommended dosage reductions; fails to explain dosage reductions need to be customized to the individual patient; fails to mention that even with a gradual taper, patients may experience severe withdrawal reactions because of Cymbalta's extremely short half-life; and again fails to inform doctors and patients that Cymbalta is one of the worst offenders.[120] While Lilly's label recommends gradually tapering Cymbalta, Lilly only manufactures and makes available 20, 30, and 60 milligram delayed release capsules.[121] Lilly's label explicitly instructs patients: "Cymbalta should be swallowed whole and should not be chewed or crushed nor should the contents be sprinkled on food or mixed with liquids."[122] So, for a patient complying with the product labeling, the only available taper regimen would involve a minimum dose of 20 milligrams a day, with no smaller doses available. In addition to a limited selection of Cymbalta dosages, Lilly has never given physicians or consumers any specific instructions on the appropriate taper regimen and has never warned that a patient might still experience severe withdrawal even with a painstakingly gradual taper regimen. Lilly's pill design and its generalized warnings, especially in light of the company's clinical trial data on Cymbalta, is grossly inadequate.

Since Cymbalta's entry onto the United States market, in each and every version of the drug's label, Lilly misrepresented or failed to adequately inform prescribing physicians and patients in this country about the frequency, severity, and duration of withdrawal symptoms that can be caused by the discontinuation of Cymbalta. Lilly's label contains material misstatements related to the frequency, severity, and duration of Cymbalta withdrawal. Lilly's misrepresentations and omissions make it impossible for any patient or physician to make an informed decision about the appropriateness of taking or prescribing Cymbalta.

Section 7: Lilly's conduct

Lilly's label minimizing the risk of Cymbalta withdrawal is particularly egregious given that in the mid-1990s, while marketing Prozac, Lilly mounted a campaign to call attention to Paxil, in particular, as one of the worst offenders when it comes to antidepressant withdrawal.[123] In the late 1980s, Lilly introduced Prozac as the first of the newer antidepressants in this country. By the mid-1990s, Paxil and Zoloft had entered the market and were a threat to Prozac sales. With its campaign to call attention to antidepressant withdrawal, Lilly sought a market advantage for Prozac as an antidepressant with a long half-life and therefore a relatively low frequency of withdrawal reactions. Then in 2004, Lilly did an about face, minimizing and obscuring the risk with its new antidepressant with an extremely short half-life, Cymbalta.

In the 1990s, Lilly funded the study discussed earlier in this report comparing withdrawal reactions in patients taking Prozac against its competitors at the time, Paxil and Zoloft.[124] The study was headed by Dr. Jerold Rosenbaum, a paid Lilly consultant.[125] In the study, the patients' antidepressants were stopped abruptly for five to eight days and withdrawal side effects were systematically monitored using a symptom checklist rating scale.[126] Rosenbaum and one of his colleagues published the study with three Lilly employees in 1998 in the journal *Biological Psychiatry*.[127] The conclusion of the study was that Paxil had the highest level of withdrawal, Zoloft to a lesser degree, and there were "few symptoms seen with Prozac."[128] The authors reasoned that Prozac did not cause as frequent or severe withdrawal reactions as Paxil and Zoloft because Prozac had a substantially longer half-life than the other drugs. Rosenbaum subsequently became a public spokesperson commenting on antidepressant withdrawal with SSRI-type antidepressants.[129]

Also in the mid-1990s, Lilly paid for a group of key opinion leader psychiatrists, so-called KOLs, to meet at a resort in Phoenix, Arizona to discuss antidepressant withdrawal.[130] After the meeting, Lilly provided financial assistance for the opinion leaders, many of them prominent academic psychiatrists like Rosenbaum, to publish eight papers on antidepressant withdrawal.[131] The eight papers were published in 1997 as a supplement to the *Journal of Clinical Psychiatry*.[132] The bound supplement was mailed free of charge to doctors across the country. As is typical of journal supplements, the papers were not peer reviewed. Instead, they were effectively Lilly-funded infomercials when the company was trying to promote Prozac as causing less withdrawal than its competitors.

In another article by Rosenbaum and Dr. Alan Schatzberg (both paid Lilly consultants), the authors point out that, in patients stopping Effexor (which has an extremely short half-life like Cymbalta), withdrawal reactions "occur dramatically and commonly."[133]

Internal GlaxoSmithKline memos and sales training materials document Lilly's campaign.[134] A May 1, 1997 GlaxoSmithKline memo states: "Lilly has initiated a new campaign focused on discontinuation symptoms associated with cessation of SSRI" antidepressants.[135] Another report suggests: Lilly has created a "marketing campaign focusing on the higher incidence of withdrawal symptoms associated with Paxil compared to Prozac" because "Lilly has seen a precipitous drop in their market share over the past two years while Paxil market share has been soaring."[136] And a June 5, 1997 memo from GlaxoSmithKline's public relations firm, Ruder Finn, describes the steps it is taking on behalf of the pharmaceutical giant to refute "what Rosenbaum [the paid Lilly consultant] et al. state or allege."[137] Indeed, in the late 1990s, GlaxoSmithKline went to considerable effort to train its sales force to counter Lilly's campaign pointing a finger at Paxil as one of the worst offenders.[138]

Thus, Lilly was aware of the risks associated with antidepressant withdrawal and its relationship to a drug's half-life. And, Lilly was making an issue of antidepressants with short half-lives being the worst offenders when this was to the company's advantage promoting Prozac. Since Cymbalta's half-life is considerably shorter than Paxil's—indeed, Cymbalta's is the second shortest after Effexor's—Lilly must have recognized the risk of Cymbalta withdrawal was substantial compared to other newer antidepressants, as confirmed by its own clinical data. However, rather than being forthcoming about the degree of the Cymbalta risk, Lilly chose to obscure the degree of risk by using misleading language in Cymbalta's label once the company was marketing its own antidepressant with an extremely short half-life.

In 2005, Lilly published the results of its Cymbalta studies in the *Journal of Affective Disorders* in an article entitled "Symptoms Following Abrupt Discontinuation of Duloxetine Treatment in Patients with Major Depressive Disorder."[139] The article disclosed that 40%-50% of patients stopping Cymbalta reported withdrawal side effects.[140] While the article acknowledged Cymbalta caused statistically significantly more withdrawal side effects than placebo, Lilly failed to provide the odds ratios and p-values showing that Cymbalta increased the risk of withdrawal side effects as much as 23-fold.[141]

At the time of its publication, like many psychiatrists, I was not a subscriber to the *Journal of Affective Disorders* (nor am I a subscriber now) and only became aware of the article once I began to more closely investigate the Cymbalta risk at issue in this

litigation. The *Journal of Affective Disorders* is published out of the Netherlands. According to a search of the Scientific Journal Research medical journal ranking database, in 2005 when Lilly published the Perahia article, the *Journal of Affective Disorders* was not on the list of 87 journals ranked in the United States in psychiatry and mental health, in other words, it appears readership in the United States was too low to make it onto this list.[142] Like myself, many American doctors would have been unaware of the article, whereas doctors are aware of and rely on a drug's label. Indeed, doctors generally rely on a drug's label as the ultimate authority on a drug's safety and efficacy. In fact, in an instance such as this, where a medical journal article gives a very different impression from a drug's label, physicians generally would consider the label more authoritative than the publication since the label is FDA approved.

In the 1990s, Lilly tried to use antidepressant withdrawal to its advantage when marketing Prozac. But since 2004, Lilly has minimized and obscured Cymbalta withdrawal in its label. Lilly's Cymbalta label misleads doctors and patients in this country, and seriously sets back the effort to properly inform patients and the medical community of the risks of antidepressant withdrawal. It is my understanding that Lilly's Prozac promotional and sales training material targeting Paxil and other antidepressants is the subject of forthcoming discovery. When I review these documents, I reserve the right to supplement my report.

All of the opinions in this report are expressed to a reasonable degree of medical certainty. Of course, my opinions are subject to change based on additional discovery.

Sincerely yours,

Joseph Glenmullen, MD

Attachments:
Exhibit 1 (CV)
Exhibit 2 (List of Documents Reviewed)

[1] J. Glenmullen, *Prozac Backlash* (New York: Simon & Schuster, 2000); J. Glenmullen, *The Antidepressant*

Solution (New York: Free Press Division of Simon & Schuster, 2005). Please note that in academic and professional journals, the chemical rather than the commercial names for drugs are typically used. For example, Cymbalta is referred to as duloxetine. When these journals are quoted in the text, for readability the well-recognized commercial names of the drugs have been substituted for their chemical names. In addition, abbreviations and shorthand commonly used in medical records have also been spelled out, again, for readability.

[2] J. Maslin, "Exploring a Dark Side of Depression Remedies," *The New York Times*, June 29, 2000. Acocella, J. "The Empty Couch: What is lost when psychiatry turns to drugs?" *The New Yorker*, May 8, 2000, pg. 112.

[3] http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022516lbl.pdf

[4] Eli Lilly Clinical Study Synopses, Clinical Trials (CT) Registry ID numbers 3327A, 3327B, 4689A, 4689B, 4091A, 4091B, 4298A, 4298B, 4092.

[5] J. Glenmullen. *Prozac Backlash*. New York, NY: Simon & Schuster, 2000, pp. 119-121.

[6] D.G. Perahia, D.K. Kajdasz, D. Desaiah, P.M. Haddad, "Symptoms following abrupt discontinuation of duloxetine treatment in patients with major depressive disorder," *Journal of Affective Disorders* 2005 Dec; 89(1-3):207-12.

[7] J. Glenmullen. *Prozac Backlash*. New York, NY: Simon & Schuster, 2000, pp. 119-121.

[8] D.G. Perahia, D.K. Kajdasz, D. Desaiah, P.M. Haddad, "Symptoms following abrupt discontinuation of duloxetine treatment in patients with major depressive disorder," *Journal of Affective Disorders* 2005 Dec; 89(1-3):207-12.

[9] J.F. Rosenbaum, M. Fava, S.L. Hoog, R.C. Ascroft, W.B. Krebs, "Selective serotonin reuptake inhibitor discontinuation [withdrawal] syndrome: a randomized clinical trial," *Biological Psychiatry* 1998;44(2):77-87

[10] Ibid.

[11] D.G. Perahia, D.K. Kajdasz, D. Desaiah, P.M. Haddad, "Symptoms following abrupt discontinuation of duloxetine treatment in patients with major depressive disorder," *Journal of Affective Disorders* 2005 Dec; 89(1-3):207-12.

[12] *Physicians' Desk Reference* (59th ed.). Montvale, NJ: Thomson PDR, 2005, pp. 3430-3435.

[13] J.F. Rosenbaum, M. Fava, S.L. Hoog, R.C. Ascroft, W.B. Krebs, "Selective serotonin reuptake inhibitor discontinuation [withdrawal] syndrome: a randomized clinical trial," *Biological Psychiatry* 1998;44(2):77-87; M. Fava, R. Mulroy, J. Alpert, A.A. Neirenberg, J.F. Rosenbaum, "Emergence of adverse events following discontinuation [withdrawal] of treatment with extended-release venlafaxine [Effexor]," *American Journal of Psychiatry* 1997; 154(12):1760-2.

[14] D.G. Perahia, D.K. Kajdasz, D. Desaiah, P.M. Haddad, "Symptoms following abrupt discontinuation of duloxetine treatment in patients with major depressive disorder," *Journal of Affective Disorders* 2005 Dec; 89(1-3):207-12.

[15] T.B. Newman, "A black box warning for antidepressants in children," *New England Journal of Medicine* 2004 Oct. 14;351(16):1595-1598.

[16] Ibid.

[17] In addition to statistically significant findings, there are other widely used measures for assessing causality including the Bradford Hill criteria. R. Van Reekum , D.L. Streiner , and D.K. Conn , "Applying Bradford Hill's criteria for causation to neuropsychiatry," *The Journal of Neuropsychiatry & Clinical Neurosciences* August 2001;13:318-325; Hofler, "The Bradford Hill considerations on causality: a counterfactual perspective," *Emerging Themes in Epidemiology* 2005;2(11).

[18] Transcript of the Joint Meeting of the Food and Drug Administration's Peripheral and Central Nervous System Drugs Advisory Committee (PCNS) and the Psychopharmacologic Drugs Advisory Committee (PDAC), July 10, 2008.

[19] D.G. Perahia, D.K. Kajdasz, D. Desaiah, P.M. Haddad, "Symptoms following abrupt discontinuation of

duloxetine treatment in patients with major depressive disorder," *Journal of Affective Disorders* 2005 Dec; 89(1-3):207-12.

[20] Report of Dr. Roger Grimson.

[21] Ibid.

[22] Eli Lilly Clinical Study Synopses, Clinical Trials (CT) Registry ID numbers 3327A, 3327B, 4689A, 4689B, 4091A, 4091B, 4298A, 4298B, 4092.

[23] D.G. Perahia, D.K. Kajdasz, D. Desaiah, P.M. Haddad, "Symptoms following abrupt discontinuation of duloxetine treatment in patients with major depressive disorder," *Journal of Affective Disorders* 2005 Dec; 89(1-3):207-12.

[24] T.B. Newman, "A black box warning for antidepressants in children," *New England Journal of Medicine* 2004 Oct. 14;351(16):1595-1598.

[25] D.G. Perahia, D.K. Kajdasz, D. Desaiah, P.M. Haddad, "Symptoms following abrupt discontinuation of duloxetine treatment in patients with major depressive disorder," *Journal of Affective Disorders* 2005 Dec; 89(1-3):207-12.

[26] Report of Dr. Roger Grimson.

[27] Ibid.

[28] Ibid.

[29] D.G. Perahia, D.K. Kajdasz, D. Desaiah, P.M. Haddad, "Symptoms following abrupt discontinuation of duloxetine treatment in patients with major depressive disorder," *Journal of Affective Disorders* 2005 Dec; 89(1-3):207-12.

[30] Eli Lilly Clinical Study Synopses, Clinical Trials (CT) Registry ID numbers 3327A, 3327B, 4689A, 4689B, 4091A, 4091B, 4298A, 4298B, 4092.

[31] D.G. Perahia, D.K. Kajdasz, D. Desaiah, P.M. Haddad, "Symptoms following abrupt discontinuation of duloxetine treatment in patients with major depressive disorder," *Journal of Affective Disorders* 2005 Dec; 89(1-3):207-12.

[32] Report of Dr. Roger Grimson

[33] Ibid.

[34] D.G. Perahia, D.K. Kajdasz, D. Desaiah, P.M. Haddad, "Symptoms following abrupt discontinuation of duloxetine treatment in patients with major depressive disorder," *Journal of Affective Disorders* 2005 Dec; 89(1-3):207-12.

[35] Ibid.

[36] T.B. Newman, "A black box warning for antidepressants in children," *New England Journal of Medicine* 2004 Oct. 14;351(16):1595-1598.

[37] Ibid.

[38] J. Woodcock, R.E. Behrman, and G.J. Dal Pan, "Role of postmarketing surveillance in contemporary medicine," *Annual Review of Medicine* 2011;62:1-10.

[39] Ibid.

[40] B.L. Strom, Ed., *Pharmacoepidemiology* 4th ed., England: John Wiley & Sons Ltd., 2005, p. 136; J. Woodcock, R.E. Behrman, and G.J. Dal Pan, "Role of postmarketing surveillance in contemporary medicine," *Annual Review of Medicine* 2011;62:1-10; D. A. Kessler, "Introducing MedWatch: a new approach to reporting medication and device adverse effects and product problems," *Journal of the American Medical Association* (JAMA) 1993 June 2;269(21):2765-2768.

[41] B.L. Strom, Ed., *Pharmacoepidemiology* 4th ed., England: John Wiley & Sons Ltd., 2005, p. 153; J. Woodcock, R.E. Behrman, and G.J. Dal Pan, "Role of postmarketing surveillance in contemporary medicine," *Annual Review of Medicine* 2011;62:1-10.

[42] Report of CIOMS Working Group V, *Current Challenges in Pharmacovigilance: Pragmatic Approaches,* Geneva: Council for International Organizations of Medical Sciences, CIOMS, 2001; FDA Code of Federal Regulations (CRF), Part 21 (g), adverse reactions.

[43] J. Woodcock, R.E. Behrman, and G.J. Dal Pan, "Role of postmarketing surveillance in contemporary medicine," *Annual Review of Medicine* 2011;62:1-10.

[44] Ibid.

[45] http://www.ismp.org/

[46] Ibid.

[47] Ibid.

[48] Ibid.

[49] Ibid.

[50] Ibid.

[51] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=314.80

[52] Eli Lilly Clinical Study Synopses, Clinical Trials (CT) Registry ID numbers 3327A, 3327B, 4689A, 4689B, 4091A, 4091B, 4298A, 4298B, 4092.

[53] J.F. Rosenbaum, M. Fava, S.L. Hoog, R.C. Ascroft, W.B. Krebs, "Selective serotonin reuptake inhibitor discontinuation [withdrawal] syndrome: a randomized clinical trial," *Biological Psychiatry* 1998;44(2):77-87; M. Fava, R. Mulroy, J. Alpert, A.A. Neirenberg, J.F. Rosenbaum, "Emergence of adverse events following discontinuation [withdrawal] of treatment with extended-release venlafaxine [Effexor]," *American Journal of Psychiatry* 1997; 154(12):1760-2; A.F. Schatzberg, "Introduction: antidepressant discontinuation [withdrawal] syndrome: an update on serotonin reuptake inhibitors," *Journal of Clinical Psychiatry* 1997;58(suppl 7):3-4; A.F. Schatzberg, P. Haddad, E.M. Kaplan, M. Lejoyeux, J.F. Rosenbaum, A.H. Young, J. Zajecka, "Serotonin reuptake inhibitor discontinuation [withdrawal] syndrome: hypothetical definition," *Journal of Clinical Psychiatry* 1997;58(suppl 7):5–10; Schatzberg et al., "Serotonin reuptake inhibitor discontinuation [withdrawal] syndrome; M. Lejoyeux and J. Adés, "Antidepressant discontinuation [withdrawal]: a review of the literature," *Journal of Clinical Psychiatry* 1997;58(suppl 7):11-16; P. Haddad, "Newer antidepressants and the discontinuation [withdrawal] syndrome," *Journal of Clinical Psychiatry* 1997;58(suppl 7):17-22; A.F. Schatzberg, P. Haddad, E.M. Kaplan, M. Lejoyeux, J.F. Rosenbaum, A.H. Young, J. Zajecka," Possible biological mechanisms of the serotonin reuptake inhibitor discontinuation [withdrawal] syndrome," *Journal of Clinical Psychiatry* 1997;58(suppl 7):23-27; A.H. Young and A. Currie, "Physicians' knowledge of antidepressant withdrawal effects: a survey," *Journal of Clinical Psychiatry* 1997;58(suppl 7):28-30; E.M. Kaplan, "Antidepressant noncompliance as a factor in the discontinuation [withdrawal] syndrome, *Journal of Clinical Psychiatry* 1997; 58(suppl 7):31-36; J.F. Rosenbaum and J. Zajecka, "Clinical management of antidepressant discontinuation [withdrawal]," *Journal of Clinical Psychiatry* 1997;58(suppl 7):37-40. Please note that these citations are a representative sample of studies and articles regarding antidepressant withdrawal in the medical literature. These are not meant to be an exhaustive or complete list of all the studies and articles I am familiar with and have relied upon in forming my opinions.

[54] J.F. Rosenbaum, M. Fava, S.L. Hoog, R.C. Ascroft, W.B. Krebs, "Selective serotonin reuptake inhibitor discontinuation [withdrawal] syndrome: a randomized clinical trial," *Biological Psychiatry* 1998;44(2):77-87; A.F. Schatzberg, "Introduction: antidepressant discontinuation [withdrawal] syndrome: an update on serotonin reuptake inhibitors," *Journal of Clinical Psychiatry* 1997;58(suppl 7):3-4; A.F. Schatzberg, P. Haddad, E.M. Kaplan, M. Lejoyeux, J.F. Rosenbaum, A.H. Young, J. Zajecka, "Serotonin reuptake inhibitor discontinuation [withdrawal] syndrome: hypothetical definition," *Journal of Clinical Psychiatry* 1997;58(suppl 7):5–10; Schatzberg et al., "Serotonin reuptake inhibitor discontinuation [withdrawal] syndrome; M. Lejoyeux and J. Adés, "Antidepressant discontinuation [withdrawal]: a review of the literature," *Journal of Clinical Psychiatry* 1997;58(suppl 7):11-16; P. Haddad, "Newer antidepressants and the discontinuation [withdrawal] syndrome," *Journal of Clinical Psychiatry* 1997;58(suppl 7):17-22; A.F. Schatzberg, P. Haddad, E.M. Kaplan, M. Lejoyeux, J.F. Rosenbaum, A.H. Young, J. Zajecka," Possible biological mechanisms of the serotonin

reuptake inhibitor discontinuation [withdrawal] syndrome," *Journal of Clinical Psychiatry* 1997;58(suppl 7):23-27; A.H. Young and A. Currie, "Physicians' knowledge of antidepressant withdrawal effects: a survey," *Journal of Clinical Psychiatry* 1997;58(suppl 7):28-30; E.M. Kaplan, "Antidepressant noncompliance as a factor in the discontinuation [withdrawal] syndrome, *Journal of Clinical Psychiatry* 1997; 58(suppl 7):31-36; J.F. Rosenbaum and J. Zajecka, "Clinical management of antidepressant discontinuation [withdrawal]," *Journal of Clinical Psychiatry* 1997;58(suppl 7):37-40.

[55] J.F. Rosenbaum, M. Fava, S.L. Hoog, R.C. Ascroft, W.B. Krebs, "Selective serotonin reuptake inhibitor discontinuation [withdrawal] syndrome: a randomized clinical trial," *Biological Psychiatry* 1998;44(2):77-87

[56] M. Fava, R. Mulroy, J. Alpert, A.A. Neirenberg, J.F. Rosenbaum, "Emergence of adverse events following discontinuation [withdrawal] of treatment with extended-release venlafaxine [Effexor]," *American Journal of Psychiatry* 1997; 154(12):1760-2.

[57] J.F. Rosenbaum, M. Fava, S.L. Hoog, R.C. Ascroft, W.B. Krebs, "Selective serotonin reuptake inhibitor discontinuation [withdrawal] syndrome: a randomized clinical trial," *Biological Psychiatry* 1998;44(2):77-87; M. Fava, R. Mulroy, J. Alpert, A.A. Neirenberg, J.F. Rosenbaum, "Emergence of adverse events following discontinuation [withdrawal] of treatment with extended-release venlafaxine [Effexor]," *American Journal of Psychiatry* 1997; 154(12):1760-2.

[58] *Physicians' Desk Reference* (59th ed.). Montvale, NJ: Thomson PDR, 2005, pp. 3430-3435.

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EXHIBIT 1

JOSEPH GLENMULLEN, M.D.

Curriculum Vitae

Academic Appointments

1988 to present: Clinical Instructor in Psychiatry, Harvard Medical School, in the Department of Psychiatry, Cambridge Hospital, Cambridge, MA
1988-89: Associate Director, Medical Student Education, Cambridge Hospital/Harvard Medical School, Cambridge, MA
1987-89: Instructor, Psychiatry 700 Course, Harvard Medical School

Clinical Practice

Clinical Practice
1986 to present: Private practice in Harvard Square, Cambridge, MA
1988 to 2008: Psychiatrist, Harvard Law School Health Services, Cambridge, MA

Forensic Practice
2001 to present: Expert witness and forensic consulting
2002-present: Member, Program in Psychiatry and the Law, Harvard Medical School

Teaching and Awards

Teaching
1988-present: Supervision of social work interns, psychology fellows, and psychiatry residents at the Cambridge Hospital/Harvard Medical School.

Awards:
May, 2001: Annual Achievement Award in Medicine, American College for Advancement in Medicine (ACAM), and delivered the keynote address, the Linus Pauling Lecture, at ACAM's annual convention.

Education and Training

Education

1984: MD, Harvard Medical School, Boston, MA

1972: BA, magna cum laude, Brown University, Providence, RI

Postdoctoral Training

1987-88: Psychiatry Fellow, Harvard University Health Services, Cambridge, MA

1987-88: Chief Resident, Outpatient Department, Department of Psychiatry, Cambridge Hospital/Harvard Medical School, Cambridge, MA

1986-88: Residency, Department of Psychiatry, Cambridge Hospital/Harvard Medical School, Cambridge, MA

1984-85: Internship, Department of Medicine, Cambridge Hospital/Harvard Medical School, Cambridge, MA

Board Certification

1990: Board certified in psychiatry by the American Board of Psychiatry and Neurology

Licensure

1985 to present: Medical License, Massachusetts Board of Registration in Medicine

Board Membership/Professional Organizations

2008-present: Member, Board of Directors, Boston Chapter of the American Foundation for Suicide Prevention

2008-present: Member, American Association of Suicidology

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