# The Hidden Withdrawal Epidemic of Cymbalta (Duloxetine): The Inequities of the Learned Intermediary Doctrine in Cymbalta Litigation and the Necessity of an FDA Re-Evaluation

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## I. INTRODUCTION

The World Health Organization estimates that depression affects approximately 3.8% of the world's total population, including 5% of the world's adult population.[1] In the United States alone, major depressive disorder is a leading cause of disability for individuals between the ages of fifteen to forty-four.[2] A 2022 study revealed approximately 10% of Americans suffer from depression, which is increasing at the highest rate in the teen and young adult population.[3] In 2016, the Center of Disease Control estimated that 11% to 40% of Americans suffer from chronic pain.[4]

The prevalence of chronic pain and depression is likely to increase due to the short and long-term effects of the COVID-19 pandemic.[5] In addition, and as supported by a recent clinical study noting an antidepressant may reduce the risk of COVID-19 associated hospitalization, the prescription rate of antidepressants may be primed to increase in the future.[6] In fact, Cymbalta (generic Duloxetine) is an

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1 *Depression Fact Sheet,* WORLD HEALTH ORG. [WHO] (Sept. 13, 2021), https://www.who.int/news-room/fact-sheets/detail/depression.

2 *What is Depression?*, ANXIETY & DEPRESSION ASS'N. OF AMER., https://adaa.org/understanding-anxiety/depression (last visited Nov. 6, 2022).

3 Steven Reinberg, *Depression Affects Almost 1 in 10 Americans*, U.S. NEWS (Sept. 19, 2022), https://www.usnews.com/news/health-news/articles/2022-09-19/depression-affects-almost-1-in-10-americans.

4 James Dahlhamer et al., *Prevalence of Chronic Pain and High-Impact Chronic Pain Among Adults—United States*, *2016,* 67 CTRS. FOR DISEASE CONTROL & PREVENTION MORBIDITY & MORTALITY WKLY. REP., 1001, 1001 (Sept. 14, 2018), https://www.cdc.gov/mmwr/volumes/67/wr/pdfs/mm6736a2-H.pdf.

5 *See* Heloisa Alonso-Matielo et al., *Pain in Covid Era*, FRONTIERS IN PHYSIOLOGY (Feb. 2, 2021), https://www.frontiersin.org/articles/10.3389/fphys.2021.624154/full (explaining the COVID Pandemic has increased the risk of individuals developing chronic pain "due to viral infection, pain management, or as a consequence of social isolation," and noting that "[i]t is likely that those who survive critical illnesses with COVID19 are at particular risk of developing chronic diseases such as chronic pain"); *see also* Alison Abbott, *COVID's Mental-Health Toll: Scientists Track Surge in Depression*, NATURE (Feb 3. 2021), https://www.nature.com/articles/d41586-021-00175-z (describing various reasons for the COVID-related increase in anxiety and depression increasing from 11% of US adults in January through June 2019, to around 42% of U.S. adults as of December 2020).

6 Sarah Toy, *Antidepressant Fluvoxamine Significantly Reduces Covid-19 Hospitalization*, WALL ST. J., (Oct. 28, 2021, 9:28 AM),

example of an antidepressant that is currently being used to combat long-covid symptoms.[7] Consequently, Eli Lilly's Cymbalta—a Food and Drug Administration (FDA) approved medication for depression and chronic pain—could be prescribed to significant patient populations in the U.S. and abroad.

The prevalence of depression and related mental disorders has instigated movements to destigmatize mental illnesses and encourage those experiencing depression to seek professional help, which may ultimately result in antidepressant treatment.[8] Advocating for mental health treatment to relieve the symptoms of depression is a worthy endeavor, yet, it is important to remember that antidepressants, like any other medication, have risks of which both prescribers and patients should be informed.[9] Unfortunately, and as this Comment will examine and argue below, the lack of patient and physician awareness of the potential long-term physical ramifications of certain antidepressant treatments is painfully evident from an examination of Cymbalta withdrawal litigation, which reveals a regulatory drug inadequacy overlooked by both courts and the FDA.

A cursory glance at Cymbalta litigation reveals that many individuals suffering with chronic pain and depression did seek help, but, after being prescribed Cymbalta, ultimately suffered intense withdrawal symptoms when tapering from the drug.[10] As of 2022, it has

https://www.wsj.com/articles/antidepressant-significantly-reduces-covid-19-hospitalization-11635373800.

7 *See* Priyal Taribagil et. al., *Case Report: 'Long COVID' Syndrome*, 14 BMJ JOURNALS 1, 2 (2021), https://casereports.bmj.com/content/14/4/e241485 ("Duloxetine was prescribed to improve her chronic fatigue, pain and anxiety symptoms."); *see also* Antonia Long, *Survivor Corps*, FACEBOOK (Apr. 30, 2021), https://www.facebook.com/groups/COVID19survivorcorps/posts/964123621003164/?comment_id=964576367624556 ("Started on a new medication a couple of days ago, Cymbalta, for help with my long hauler [covid] symptoms.")

8 *See* Stacy Lu, *Destigmatizing Mental Illness Needs a National Push, Report Says,* AM. PSYCH. ASS'N (July/Aug. 2016), https://www.apa.org/monitor/2016/07-08/upfront-destigmatizing (recommending the Department of Health and Human Services lead initiatives focused on reducing the stigma surrounding mental illness) (referencing Comm. on the Sci. of Changing Behav. Health Soc. Norms, *Ending Discrimination Against People with Mental and Substance Use Disorders: The Evidence for Stigma Change*, Vol. 47 No.7 at 9-10 NAT'L ACAD.'S PRESS (2016)).

9 *See, e.g.*, *Depression Medicines*, CLEVELAND CLINIC, https://my.clevelandclinic.org/health/treatments/9301-depression-medicines (last visited May 28, 2023) (describing potential physical and emotional common side effects of various types of antidepressants and that benefits should outweigh any side effects, as well as depression recovery and outlook).

10 *See, e.g.*, Hexum v. Eli Lily & Co. No. 2:13-cv-02701-SVW-MAN, 2015 U.S. Dist. LEXIS 109737 at *2 (C.D. Cal Aug. 18, 2015); s*ee also* Jena Hilliard, *Cymbalta Addiction and Abuse*, ADDICTION CTR.,

been eighteen years since FDA's approval of Cymbalta in 2004.[11] Yet, plaintiffs continue to file failure to warn lawsuits against Cymbalta manufacturer, Eli Lilly ("Lilly"), and physicians continue to prescribe Cymbalta to individuals worldwide: Cymbalta accounted for 42.1 million dollars of Lilly's U.S. revenue, and 725.6 million dollars of the company's international revenue in the fiscal year of 2020.[12]

In addition to lawsuits, individual Cymbalta withdrawal is demonstrated through online patient forums that document many patients prescribed Cymbalta have experienced, and continue to experience, devastating and prolonged effects while tapering themselves off the drug.[13] Despite the failure to warn lawsuits against Lilly and the prevalence of patient complaints, Cymbalta plaintiffs have been unsuccessful on their claims because courts have dismissed most of their failure to warn suits at the summary judgment stage due to the courts' interpretation of the learned intermediary doctrine.[14] In other words, the courts have predominately held that Lilly fulfilled its duty to warn plaintiffs of the drug's potential withdrawal effects by providing prescribers (the learned intermediary) with an FDA-approved label inclusive of potential discontinuation symptoms.[15] In so holding, courts have not only barred relief to those suffering painful withdrawal effects, but have made it possible for future patients to experience them, and for physicians to continue to prescribe this medication without sufficient knowledge of its tapering ramifications. Thus, while there is widespread evidence of suffering, there is no legal relief available. For these reasons, at least until the 2015 *Herrera v. Eli Lilly & Co*. decision,

https://www.addictioncenter.com/stimulants/antidepressants/cymbalta-addiction-abuse/ (last updated Oct. 26, 2022).

11 U.S. FOOD & DRUG ADMIN., HIGHLIGHTS OF PRESCRIBING INFORMATION, PRINTED LABELING: CYMBALTA (DULOXETINE HYDROCHLORIDE) DELAYED RELEASE TABLETS, [hereinafter CYMBALTA LABEL] https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022516lbl.pdf (last visited May 23, 2023).

12 *See Cymbalta Lawsuits*; Drugwatch (Nov. 4. 2022), https://www.drugwatch.com/cymbalta/lawsuits/; Eli Lilly & Co., Annual Report (Form 10-K) 46 (Dec. 31, 2020).

13 *See, e.g.*, Ludy v. Eli Lilly & Co., No. 1:19-cv-04606-JMS-DLP, 2020 U.S. Dist. LEXIS 113673, at *1, *6-7 (S.D. Ind. June 29, 2020); *see also* u/Bazinga1220, *How Long Did Withdrawal Symptoms Last?*, REDDIT, r/cymbaltasafetaper (Oct. 24, 2021, 1:45 PM) https://www.reddit.com/r/cymbaltasafetaper/comments/qex410/how_long_did_withdrawal_symptoms_last/ (last visited Nov. 6, 2022) ("Been weaning off of Cymbalta based on what my doctor told me. I was on 60 mg than to 30 mg then 20 mg. It's now been 2 days since I've taken it and the symptoms I'm experiencing are horrendous.").

14 *See, e.g.*, Saavedra v. Eli Lilly & Co., No. 2:12-cv-9366-SVW-MAN, 2013 U.S. Dist LEXIS 90481 at *10-12 (C.D. Cal June 13, 2013).

15 *Ludy*, 2020 US. Dist. LEXIS 113673, at *13-14*; see also* McDowell v. Eli Lilly & Co., 58 F. Supp. 3d 391, 406 (S.D.N.Y. 2014).

there seemed to be no possible change of a successful Cymbalta litigation outcome for plaintiffs.[16]

*Herrera* denied Lilly's summary judgment motion on the theory that the plaintiff had presented evidence that Lilly was aware that the rate of Cymbalta withdrawal and discontinuation symptoms was higher (indeed, much higher) than what was indicated on the label.[17] *Herrera* marked the first time a court considered evidence that Lilly failed to clarify the difference in the risk of discontinuation symptoms between discontinuing or tapering the medication.[18] The decision created an opportunity for future plaintiffs to pursue Cymbalta claims. Unfortunately, as this Comment will document below, the majority of courts have failed to follow the reasonable *Herrera* approach. Instead, courts adhered to a strict interpretation of the learned intermediary doctrine, and, thereby, precluded plaintiffs from relief by automatically accepting Cymbalta's FDA-approved withdrawal label as adequate and conclusive.

This Comment begins by examining current FDA prescription drug labeling regulations and guidelines arguing that the use of the learned intermediary doctrine is ill-suited for Cymbalta litigants suffering from withdrawal effects and should not be given credence by courts. Instead, courts should look beyond Cymbalta's FDA-approved label and analyze the drug's inherit pharmacological propensities for severe and prolonged discontinuation symptoms.

Part II of this Comment provides an overview of current federal drug labeling regulations, and the requirements and evaluation criteria the FDA considers when determining if a Risk Evaluation and Mitigation Strategy (REMS) is necessary for a prescription drug. Part III surveys the learned intermediary doctrine in prescription drug failure to warn litigation. Part IV examines Cymbalta's general usage and pharmaceutical properties, including the drug's current labeling and patient-documented discontinuation withdrawal symptoms.

Part V of this Comment contrasts opposing outcomes of two Cymbalta litigation summary judgment decisions. Part VI argues that the FDA-approved Cymbalta label does not adequately warn prescribers of the risk and extent of discontinuation and tapering side effects the patient may experience, and therefore invalidates the learned intermediary doctrine's purpose. It further contends that the *Herrera* approach should be followed by courts in future litigation. This

16 Herrera v. Eli Lilly & Co., No. 2:13-cv-02702, 2015 U.S. Dist. LEXIS 89334, at *36–38 (C.D. Cal. June 19, 2015).

17 *Id.*

18 *Id.*

Comment also argues that the FDA should, at a *minimum*, reconsider its previous approval of Cymbalta's labeling by issuing a REMS for its continued usage based on the drug's widespread tapering difficulties. In doing so, the FDA should also consider Cymbalta's inherent pharmacological design tapering flaw—that its dosage units are only available in 60, 30, and 20 mg capsule form—as evidence demonstrating the necessity of the drug's re-evaluation. This Comment further purports that the FDA should suspend Cymbalta's approval if Lilly refuses to acknowledge and resolve the drug's inherit propensity for discontinuation symptoms.

Finally, this Comment argues that Cymbalta litigation and patient complaints reveal that the FDA has inadequately considered the potential effects of antidepressant-related discontinuation effects. The federal opioid regulations provide an interesting foil here because they provide substantial guidelines for tapering.[19] By contrast, there are currently little correspondingly detailed guidelines for antidepressant tapering.[20] Therefore, as this Comment ultimately concludes below, while like opioids, Cymbalta is prescribed for pain, its users do not enjoy the inherit protection of the FDA-promoted physician awareness regulations that pertain to opioids. The FDA needs to address this issue.

As this Comment explains, patients who wish to discontinue antidepressants often find that their prescribers are unaware of how to successfully stop or taper the drugs without the user suffering severe withdrawal symptoms. [21] This results in individual self-tapering,

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19 *See, e.g.*, *FDA Identifies Harm Reported from Sudden Discontinuation of Opioid Pain Medicines and Requires Label Changes to Guide Prescribers of Gradual, Individualized Tapering*, *FDA Drug Safety Communication*, U.S. FOOD & DRUG ADMIN. (Apr. 9, 2019), https://www.fda.gov/drugs/drug-safety-and-availability/fda-identifies-harm-reported-sudden-discontinuation-opioid-pain-medicines-and-requires-label-changes.

20 *See* Anders Sørensen et. al, *Clinical practice guideline recommendations on tapering and discontinuing antidepressants for depression: a systematic review*, 12 THER. ADV. PSYCHOPHARMACOLOGY, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8841913/pdf/10.1177_20451253211067656.pdf (last visited May 23, 2023) (analyzing multiple clinical practice guidelines and concluding that while 71% of guidelines recommend that antidepressants should be tapered gradually, the quality of the guidelines was "low" as they do not provide guidance on "specific dose reductions, how to distinguish withdrawal symptoms from relapse or how to manage withdrawal symptoms").

21 *See, e.g.*, *How To Stop Duloxetine (Cymbalta) Without Withdrawal Symptoms*, THE PEOPLE'S PHARMACY (Jan. 18, 2022), https://www.peoplespharmacy.com/articles/how-to-stop-duloxetine-cymbalta-without-withdrawal-symptoms ("Based on what we hear from readers of our syndicated newspaper column and visitors to this website, most patients are not warned about how to stop duloxetine (Cymbalta). Perhaps the prescriber assumes that they will need to take this antidepressant for the rest of their lives. Or perhaps there is a reluctance to mention anything negative about a new

without doctor supervision, which creates a cycle of widespread suffering. [22] This suffering has resulted in what this comment refers to as a "hidden epidemic" of vulnerable Cymbalta users suffering from withdrawal effects, without the hope of any likely relief.

## II. FDA PRESCRIPTION DRUG LABELING HISTORY AND REQUIREMENTS

### *A. 21 CFR § 201.56 and 21 CFR § 201.57*

The Pure Food and Drug Act defines drugs as "any substances . . . intended to be used for the cure, mitigation, or prevention of disease of either man or other animals."[23] In 1938, Congress enacted the Food, Drug, and Cosmetic Act, which authorized the FDA to regulate food and drug products to ensure their safety for their intended uses.[24] The FDA then promulgated prescription drug labeling guidelines, which specify the information required on prescription drugs as set forth in 21 C.F.R. §§ 201.56-201.57.[25]

Federal labeling requirements for prescription drugs demand a summary of the "essential scientific information" needed for "safe and effective drug use" that is "informative and accurate, and neither promotional in tone nor false and misleading in any particular [manner]."[26] Furthermore, drug labeling "must be based whenever possible on data derived from human experience" and may not contain implied claims or suggestion of drug use without adequate evidence of safety and effectiveness.[27] Labels must describe "clinically significant adverse reactions," including those that are potentially fatal and serious, as well as other hazards, such as the expected side effects of that drug's pharmacological class that may result from drug interactions, limitations imposed by the safety hazards, and steps that should be taken if those safety hazards occur, such as dose modifications.[28]

Once the FDA approves a drug, the manufacturer must notify the agency of any labeling changes necessary to "reflect newly acquired

prescription. Whatever the motivation, a lot of people are not adequately warned that they must *never* stop duloxetine suddenly.").

22 *See, e.g.*, *id*. ("Getting off of Cymbalta was the hardest physical thing I've ever done in my life. Many doctors don't realize how difficult it is or that you have to taper—mine did not.").

23 Pure Food and Drug Act, ch. 3915, § 88, 34 Stat. 768, 768-72 (1906) (repealed 1938).

24 *See* Dorsett v. Sandoz, Inc., 699 F. Supp. 2d 1142, 1146 (9th Cir. 2010) (citing 21 U.S.C. § 393(b)(1)–(b)2)).

25 21 C.F.R. § 201.56 (2022); 21 C.F.R. § 201.57 (2022).

26 21 C.F.R. §§ 201.56(a)(1)–(a)(2) (2021).

27 21 C.F.R. § 201.56(a)(3).

28 21 C.F.R. § 201.57(c)(6)(i).

information." [29] Such updates include, but are not limited to, information that would add or strengthen: (1) a drug's contraindication, warnings, adverse reactions or precautions, (2) a statement about drug abuse, dependence, psychological effect, or overdosage, or (3) a statement about dosage and administration intended to increase the drug's safe use, or (4) to delete false, misleading or unsupported indications for use or claims for effectiveness.[30] Under "other special care precautions," the warning and precaution section must contain information outlining care to be exercised by the practitioner for safe and effective use of the drug—precautions that are not required under any other specific subsection.[31] Court application of this section becomes particularly important in the Cymbalta litigation.

The FDA also provides specific guidelines for categorizing adverse reactions. Each reaction must be categorized by body system, severity, or in order of decreasing frequency, or a combination of these methods, as appropriate.[32] Data regarding adverse effects during clinical trials must be listed if they occur "at or above a specified rate appropriate to the safety database."[33]

Clinical trial data regarding adverse reactions must include the occurrence rate of a reaction, with comparators (placebos) presented, unless this data cannot be determined.[34] If the reaction rates cannot be reliably determined, adverse reactions should be listed within appropriately specified frequency ranges in the drug's safety database, such as "adverse reactions occurring at a rate of less than 1/100, adverse reactions occurring at a rate of less than 1/500."[35] Where adverse reactions have "significant clinical indications," the data must be supplemented with detail regarding withdrawal, including the nature, frequency, and severity of the reaction, its relationship to the drug dose, and relevant demographic characteristics.[36] Drug abuse and dependence data must be included in the label, consisting of "characteristic effects" resulting from the drug's psychological and physical dependence.[37] Details of the adverse effects must also be provided, along with the effects of abrupt withdrawal, and necessary

29 21 C.F.R. § 601.12 (f)(2)(i).
30 21 C.F.R. §§ 601.12 (f)(2)(i)(A)–(D).
31 21 C.F.R. § 201.57 (c)(6)(ii) (2021).
32 *Id.* § 201.57 (c)(7)(ii) (2021).
33 *Id.* § 201.57 (c)(7)(ii)(A) (2021).
34 *Id.*
35 *Id.*
36 *Id.*
37 21 C.F.R. § 201.57 (c)(10)(iii) (2021).

procedures to diagnose the dependent state and ways of treating the effects of abrupt withdrawal.[38]

*B. FDA Labeling Draft Guidance: Drug Abuse and Dependence*

Federal regulations are not the only source of information that prescription drug manufacturers consider. The FDA has issued guidelines associated with the label's drug abuse and dependence section that warrant further mention. In 2019, the FDA Office of Medical Policy in the Center for Drug Evaluation and Research, in cooperation with the Center for Biologics Evaluation and Research, issued draft guidance listing the general principles, format, and information that should be considered when drafting the drug label's Drug Abuse and Dependence section.[39] While legally nonbinding, this guidance provides insight into what the FDA considers as adequate prescription drug labeling.[40]

The purpose of the Drug Abuse and Dependence section is to provide information regarding the drug's "potential for abuse, misuse, addiction, physical dependence, and tolerance" to assist the prescriber and "facilitate the safe and effective use of prescription drug products."[41] For increased prescriber awareness of possible ramifications, the FDA stresses that the abuse and dependence section ought to be written clearly and accurately and include information that "accurately summarizes" the drug's signs and symptoms of withdrawal, and potential for abuse, to provide the drug's effective and safe use, and deter overall abuse and misuse.[42]

The FDA defines abuse as the "intentional, non-therapeutic use of a drug, even once, for its desirable physiological or psychological effects."[43] The draft guidelines state that the abuse section should explain the types of abuse that can occur with the drug, the pertinent adverse reactions to using the drug, any particularly susceptible patient populations, and the risks specific to the drug's particular formulation.[44]

Misuse is defined as "the intentional use, for therapeutic purposes, of a drug by an individual in a way other than prescribed by a health care

38 *Id.*

39 U.S. DEP'T OF HEALTH & HUMAN SERVS. FOOD & DRUG ADMIN., DRUG ABUSE AND DEPENDENCE SECTION OF LABELING FOR HUMAN PRESCRIPTION DRUG AND BIOLOGICAL PRODUCTS—CONTENT AND FORMAT GUIDANCE FOR INDUSTRY DRAFT GUIDANCE (2019), https://www.fda.gov/media/128443/download [hereinafter FDA GUIDANCE FOR INDUS.].

40 FDA GUIDANCE FOR INDUS., *supra* note 39, at 1.

41 FDA GUIDANCE FOR INDUS., *supra* note 39, at § II General Principles.

42 FDA GUIDANCE FOR INDUS., *supra* note 39, at § II General Principles.

43 FDA GUIDANCE FOR INDUS., *supra* note 39, at § III(B)(1) Information on Abuse.

44 FDA GUIDANCE FOR INDUS., *supra* note 39, at § III(B)(1) Information on Abuse.

provider or for whom it was not prescribed."[45] The dependence section must contain information related to the drug's potential for physical dependence, withdrawal, and tolerance as well as describe both the effects resulting from dependence and the amount of the drug necessary to lead to potential tolerance or dependence over a period of time.[46] Once a dependent state is identified, the label should provide procedures to diagnose the dependent state and treat or mitigate the effects of abrupt withdrawal.[47] Most relevant to the Cymbalta litigation, a drug's label should include concrete measures that should be taken to manage withdrawal symptoms.[48]

*C. FDA REM Rationale*

The FDA's issuance of a REMS evidences acknowledgment that an approved drug can require additional monitoring and controls to be used safely. The REMS program was first established through the Food and Drug Administration Amendments Act that created section 505-1 of the Food, Drug and Cosmetic Act.[49] This Act provides that the FDA Secretary may determine that a REMS is necessary to ensure that a drug's benefits outweigh its risks.[50] The Act also authorizes the FDA to use various strategies that ensure effective drug use, such as: including patient medication guides, patient package inserts, and a communication plan that informs healthcare providers about the REMS and encourages its implementation.[51]

A REMS communication plan may require sending letters to health care providers, disseminating information about REMS strategy to encourage implementation by health care providers, or explaining certain safety protocols.[52] If information dissemination is insufficient to overcome the drug's potential risks, the FDA may require further

45 FDA GUIDANCE FOR INDUS., *supra* note 39, at § III (B)(2) Information on Misuse.

46 FDA GUIDANCE FOR INDUS., *supra* note 39, at § III (C) Dependence.

47 FDA GUIDANCE FOR INDUS., *supra* note 39, at § III(C)(1) Information on Physical Dependence and Withdrawal.

48 FDA GUIDANCE FOR INDUS., *supra* note 39, at § III(C)(1) Information on Physical Dependence and Withdrawal (stating, as a suggestion, "[d]iscontinue DRUG-X by gradual taper over a 2-week period to reduce the risk of symptoms of withdrawal").

49 *See FDA's Role in Managing Medication Risks, U.S. Food & Drug Ass.,* https://www.fda.gov/drugs/risk-evaluation-and-mitigation-strategies-rems/fdas-role-managing-medication-risks (last visited May 28, 2023*)*; Food & Drug Admin. Amends. Act, Pub. L. No. 110–85 § 505-1(a)(1), 121 Stat. 823, 926-39 (2007) (codified at 21 U.S.C. § 355-1).

50 21 U.S.C. § 355-1.

51 *Id.* at §§ 505-1(e)(2)–(3).

52 *Id.* at §§505-1(e)(3)(A)–(C).

restrictive measures titled Elements To Assure Safe Use ("ETASU").[53] These elements may require that prescribers, pharmacies, and health care settings have special training or experience in the drug, require that the drug be dispensed with evidence or other documentation of safe-use conditions, and that using the drug be subject either to certain monitoring or enrollment in a registry.[54]

While this system may seem elaborate and limited to a small class of drugs, this is not the case. The FDA has issued an REMS for sixty-one drugs, 92% of which require clinicians or health care settings to become certified prior to prescribing and to participate in additional REMS activities such as patient counseling, physician training, and monitoring.[55]

The FDA has also issued a REMS for the antidepressant Spravato, a prescription oral antidepressant nasal spray for adults with treatment-resistant depression and major depressive disorder.[56] The FDA issued a REMS due to Spravato's risk of "serious adverse outcomes" resulting from disassociation, sedation, and the potential likelihood of drug abuse and misuse.[57] Spravato's REMS requires prescribers to become certified to dispense the drug, to counsel patients on the drug's pertinent risks, and to continuously monitor patients for sedation and disassociation symptoms before prescribing the drug.[58] The FDA also issued a REMS for the antidepressant Zyprexa, used to treat bipolar disorder and schizophrenia.[59] Zyprexa's REMS guidelines include patient counseling prior to initial treatment, patient enrollment in the REMS program, and continuous patient monitoring to evaluate patients for post-injection delirium sedation syndrome.[60]

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53 *See id.* at §§ 505-1(f)(1)–(3).

54 *Id.* at §§ 505-1(f)(3)(A)–(F).

55 *Approved Risk Evaluation and Mitigation Strategies (REMS*), U.S. FOOD & DRUG ADMIN., https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=RemsData.page (last visited Nov. 13, 2022) [hereinafter *Approved REMS*].

56 *See Approved Risk Evaluation and Mitigation Strategies (REMS): Spravato (esketamine),* U.S. FOOD & DRUG ADMIN., https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=IndvRemsDetails.page&REMS=386 (last visited Aug. 2, 2023).

57 *Id.*

58 *Id.*

59 *Approved Risk Evaluation and Mitigation Strategies (REMS): Zyprexa*, U.S. FOOD & DRUG ADMIN., https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=IndvRemsDetails.page&REMS=74 (last visited Aug. 2, 2023).

60 *Id.*

*D. REMS Criteria*

The FDA considers multiple factors when deciding whether REMS is necessary, including: (1) the population size expected to use the drug; (2) the seriousness of the disease the drug treats; (3) the drug's expected benefit; (4) the drug's expected or actual treatment duration; (5) the severity of any "known or potential" adverse events in the population likely to use the drug, and (6) "[w]hether the drug is a new molecular entity[.]"[61] Notably, the fifth factor, which includes the risk of a serious and irreversible adverse event such as one that causes a permanent disability or persistent incapacity, "may be particularly likely to have a favorable benefit-risk profile . . . in the presence of a REMS that . . . minimize[s] drug exposure and the associated occurrence of the adverse event."[62]

The FDA also considers "whether information about managing the particular risk is widely available and whether risk management measures are being widely implemented."[63] The FDA factors the specialties of the healthcare providers who may prescribe, dispense, or administer the drug, and whether approaches to mitigate the risk standard are well-known by such health care professions when determining whether a REMS is needed.[64]

A relatively well-known example of FDA REM involves opioids. In 2012, the FDA developed a unique Opioid Analgesic REMS after identifying the need for a "comprehensive pain education" plan as a result of studies revealing that over eleven million Americans misused a prescription pain reliever.[65] The opioid strategy considers tapering and acknowledges that health care providers should be knowledgeable as to how to safely and effectively taper opioids, including how to "recognize and manage" the symptoms of opioid withdrawal.[66] Evidence of the success of this opioid REMS is that many physicians, patients, and the overall public are more likely to be informed and aware of the potential ramifications of being prescribed an opioid drug.[67]

61 *REMS: FDA's Application of Statutory Factors in Determining When a REMS Is Necessary*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/media/100307/download (last visited Aug. 2, 2023).

62 *Id.*

63 *Id.*

64 *Id.*

65 U.S. FOOD & DRUG ADMIN., FDA'S OPIOID ANALGESIC REMS EDUC. BLUEPRINT FOR HEALTH CARE PROVIDERS INVOLVED IN THE TREATMENT AND MONITORING OF PATIENTS WITH PAIN, 1–3, https://www.fda.gov/media/99496/download (Sept. 2018).

66 *Id.* at 11.

67 *Id.* at 5 (stating that after completing Opioid REMS trainings, providers "should be knowledgeable of how to safely and effectively manage patients on opioid analgesics in

## III. THE LEARNED INTERMEDIARY DOCTRINE IN PRESCRIPTION DRUG CASES

The average patient may not be aware that a drug's manufacturer will most likely succeed in disclaiming liability from any potential adverse drug effects by claiming the drug's prescriber was warned of such possible effects by the product's labeling. This is because the majority of courts evaluate drug manufacturer's failure-to-warn liability by assessing whether the drug's warning label was sufficient to satisfy the learned intermediary doctrine.[68] The purpose of the learned intermediary doctrine is to alter the general liability principle that a manufacturer must warn the user of known risks and hazards associated with the drug.[69] In practice, this doctrine relieves the drug manufacturer of liability if the drug's label warns the plaintiff's prescriber of the risks associated with the drug, and, as a result, manufacturers only have the duty to warn the prescriber or the "learned intermediary," not the user, of the risks associated with a drug.[70] This doctrine's rationale is that a prescriber can make a more knowledgeable assessment of medical risks of the drug than a typical patient and is in a more advantageous position to assess said risks and warn the patient—unlike the manufacturer who has no knowledge of the patient's particular susceptibilities and needs.[71]

Thus, the learned intermediary doctrine is often used by manufacturers as a liability "shield."[72] The Lexapro failure-to-warn case, in which plaintiffs alleged the drug manufacturer did not warn of the drug's inherit suicidal ideations that resulted in a suicide, serves as an example.[73] There, the plaintiff's estate sued the drug manufacturer on a wrongful death claim and the manufacturer, in turn, argued that the summary judgment motion should be granted because it provided an adequate warning to the plaintiff satisfying the learned intermediary doctrine.[74] The court recognized the doctrine and granted the manufacturer's motion.[75]

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the acute and chronic pain settings", including initiating therapy, titrating, and discontinuing use of opioid analgesics).

68 *See* Frumer & Friedman, 5 Products Liability *Prescription Drug Warnings* § 50.04.

69 *See* Ludy v. Eli Lilly & Co., No. 1:19-cv-04606-JMS-DLP, 2020 U.S. Dist. LEXIS 113673 at *10 (D. Ind. June 29, 2020) (citing Dietz v. Smithkline Beecham Corp., 598 F.3d 812, 815 (11th Cir. 2010)).

70 *Id.* at *10–11 (citing McCombs v. Synthes, 587 S.E.2d 594, 595 (Ga. 2003)).

71 *Id.*

72 Sheryl Calabro, Note, *Breaking the Shield of the Learned Intermediary Doctrine: Placing the Blame Where It Belongs*, 25 CARDOZO L. REV. 2241, 2248–49 (2004).

73 Shah v. Forest Labs, Inc., No. 10 C 8163, 2015 U.S. Dist. LEXIS 67554 at *3–4 (N.D. Ill. May 26, 2015).

74 *Id.* at *17–21.

75 *Id.* at *34.

However, the learned intermediary doctrine is not without exceptions. Several courts have developed exceptions involving mass-vaccine immunization and direct mass marketing to consumers because prescribers have a "diminished" role as decision-makers in these situations.[76]

States that do not utilize the learned intermediary doctrine, such as Wisconsin, have varying outcomes with regard to drug manufacturer liability. In *Forst v. Smithkline Beecham Corp.*, plaintiff sued Paxil's manufacturer after a patient using the drug attempted suicide.[77] Plaintiff alleged that the drug's label did not warn against increased risk of suicidal tendencies.[78] The manufacturer claimed it was not liable based on the learned intermediary doctrine.[79]

In response, the Wisconsin federal district court recognized that the doctrine has not been adopted by all states, and that no Wisconsin court had applied the doctrine to prescription drug manufacturers.[80] The court found a material issue of fact regarding a link between inadequate warnings and the prescriber's decision to prescribe Paxil, and evidence that had the physician known about the suicidal risks of Paxil, he may not have prescribed it.[81] Thus, the court denied the manufacturer's summary judgment motion.[82]

### *A. FDA Prescription Drug Labeling and the Learned Intermediary Doctrine*

Because the FDA closely regulates prescription drug label warnings, and most courts have adopted the learned intermediary doctrine, plaintiffs are unlikely to succeed on a failure to warn claims against drug manufacturers, so long as the drug label includes an adequate FDA-approved warning.[83] Yet, as discussed below, some courts refuse to equate a manufacturer's compliance with FDA labeling requirements with an adequate warning for tort law purposes.[84]

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76 *See, e.g.*, Perez v. Wyeth Corp, 734 A.2d 1245, 1253 (N.J. 1999) (holding a consumer mass-advertising campaign for contraceptive drug interfered with the traditional premise of the learned intermediary doctrine as it damaged the integrity of the relationship between doctors and patients).

77 Forst v. Smithkline Beecham Corp., 602 F. Supp. 2d 960, 963 (E.D. Wis. 2009).

78 *Id.*

79 *Id.* at 968.

80 *Id.*

81 Forst v. Smithkline Beecham Corp., 602 F. Supp. 2d 960, 968 (E.D. Wis. 2009).

82 *Id.* at 976.

83 *See, e.g.*, Ebel v. Eli Lily & Co, 536 F. Supp 2d. 767, 782 (S.D. Tex. 2008) (granting defendant's failure to warn summary judgment claim for antipsychotic Zyprexa).

84 *See, e.g.*, Motus v. Pfizer, 127 F. Supp. 2d 1085 (C.D. Cal 2000).

In *Motus v. Pfizer*, Pfizer argued conflict claim preemption in a failure-to-warn claim arising from a suicide because the FDA did not require the inclusion of detailed suicide warnings on the drug's labeling.[85] The court, however, determined that the FDA labeling requirements were mere minimum standards.[86] It further found that the FDA never implied it would be impermissible to state *additional* discretionary warnings because the pertinent labeling provisions indicate only the warnings that are *required* to be included in the labeling.[87]

Similarly, a plaintiff sued Roche Laboratories under a failure-to-warn claim after developing inflammatory bowel disease from the use of the acne medication Accutane.[88] The court recognized that, because FDA approved the drug's warning, New Jersey's Product Liability Act provides a rebuttable presumption of adequacy.[89] While the court dismissed the case, it also stated that an FDA-approved label is not dispositive of manufacturer liability because it "may grow stale" based on new information received by the manufacturer about a "clinically significant hazard" associated with the drug, and that "[*p*]*rior FDA approval of a label's warning is not a license for a manufacturer to withhold updating and revising that warning*."[90] The court explained that the rebuttable presumption could be overcome if the plaintiff proves one of the following: (1) a "deliberate concealment or nondisclosure" of later acquired knowledge of harmful effects, (2) an economic manipulation of the post-market regulatory process, or (3) clear and convincing evidence that the warnings were inadequate because Federal labeling regulations required updates.[91] Thus, an FDA-approved label does not preclude a drug manufacturer's liability where there is clear evidence that the manufacturer was aware of, or hid, differing data regarding harmful effects.

The Supreme Court affirmatively agreed with the Seventh Circuit's proposition in *Wyeth v. Levine*, where the court held an FDA-approved label does not automatically preempt manufacturer liability.[92] There, the plaintiff sued Wyeth for damages after an IV-push of the drug

85 *Id.* at 187.

86 *Id.* at 1092.

87 *Id.* at 1096.

88 *In re* Accutane Litigation, 194 A.3d 503, 505–06 (2018).

89 *Id.* at 506 (citing N.J. STAT. ANN. § 2A:58C-4).

90 *Id.* at 530 (emphasis added).

91 *Id.* at 531 (citing Perez v. Wyeth Lab'ys Inc., 734 A.2d 1245, 1259 (N.J. 1999); McDarby v. Merck & Co., 949 A.2d 223, 256 (N.J. App. Div. 2008); 21 C.F.R. § 314.70(c)).

92 Wyeth v. Levine, 555 U.S. 555, 570 (2009).

Phenergan resulted in the amputation of her arm due to gangrene.[93] The plaintiff claimed that Phenergan's label failed to provide physicians with a clear warning that the drug should not be administered via the IV-push method due to its corrosiveness.[94]

In evaluating this contention, the Supreme Court explained that manufacturers need not wait for FDA approval where the proposed label change "adds or strengthens a contraindication, warning, precaution, or adverse reaction" under the FDA's "changes being effected" (CBE) regulations.[95] The Court rejected Wyeth's argument that manufacturers can only update the label to "reflect newly acquired information."[96] In so doing, it explained that "newly acquired information" was not limited to new data, but included "new analyses of previously submitted data," and "[t]he rule accounts for the fact that risk information accumulates over time and that the same data make take on a different meaning in light of subsequent developments."[97]

In holding the manufacturer liable, the Supreme Court relied on the central premise that the manufacturer, not the FDA, bears ultimate responsibility for drug labeling, and is "charged with crafting an adequate label and with ensuring that its warnings remain adequate as long as the drug is on the market."[98] The Court explained that Wyeth *could* have drafted a stronger warning label regarding the drug's administration, and there was no evidence that the FDA would have rejected this increased warning.[99] In other words, the Court did not view prescribers as "informed" intermediaries simply because the FDA had—at some point—approved the drug's label. This holding is particularly relevant when analyzing recent Cymbalta withdrawal litigation because it undermines Lilly's argument that FDA-approved Cymbalta warning label is inherently satisfactory under the learned intermediary doctrine.

## IV. CYMBALTA DISCONTINUATION SYNDROME, LABELING, AND GENERAL

93 *Id.* at 559.

94 *Id.* at 560.

95 *Id.* at 591.

96 *Id.*

97 *Wyeth,* 555 U.S. at 569.

98 *Id.* at 571.

99 *Id.* at 593 (noting that the FDA's approval "is not a guarantee that the drug's label will never need to be changed and nothing in the text of the statutory or regulatory scheme necessarily insulates Wyeth from liability under state law simply because the FDA has approved a particular label").

INFORMATION

### *A. Documented Antidepressant Discontinuation Syndrome in Cymbalta*

Withdrawal effects from antidepressants, including serotonin and norepinephrine reuptake inhibitors (SNRIs) known as "second generation" antidepressants, are a well-documented phenomenon.[100] For these reasons, physicians should advise patients not to abruptly discontinue the medication without monitoring.[101] Studies reveal that antidepressants with relatively short "half-lives" may be more likely to result in severe or continued symptoms.[102] As it turns out, Cymbalta has a half-life that is notoriously shorter than other comparable antidepressants.[103]

In a general antidepressant guideline, Harvard School of Medicine advises that, should discontinuation symptoms occur after a reduction, a dosage may need to be added, and the patient should "continue from there with smaller reductions."[104] Harvard, however, fails to either mention or acknowledge the potential serious withdrawal effects about which many patients complain when attempting to taper Cymbalta, even while under a physician's care. Many of these patients claim to experience extreme, sometimes life-altering discontinuation symptoms, that are beyond the typically expected discontinuation withdrawal effects, and suffer from reactions, including severe electric shock sensations, known as "debilitating brain zaps," nausea, dizziness, memory loss, and sleep disturbances.[105]

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100 Emma Wilson et. al, *A Review of the Management of Antidepressant Discontinuation Symptoms*, 5 THERAPEUTIC ADVANCES IN PSYCHOPHARMACOLOGY 357, 357–68 (2015).

101 *See, e.g.*, Kirsten Weir, *How hard is it to Stop Antidepressants?*, AMER. PSYCH. ASS'N (Apr. 1, 2020), https://www.apa.org/monitor/2020/04/stop-antidepressants (noting that professional guidelines advise patients to not stop antidepressants abruptly and recommend tapering).

102 Wilson*, supra* note 100100, at 87 ("The syndrome is believed to be dependent on the elimination half-life of the administered drug and the patient's rate of metabolism, occurring most frequently following the withdrawal of agents with shorter half-lives.").

103 Christopher H. Warner et. al, *Antidepressant Discontinuation Syndrome*, 73 AMER. FAMILY PHYSICIAN 499, 449-456 (2006), https://www.aafp.org/afp/2006/0801/p449.html?utm_medium=email&utm_source=transaction (describing Cymbalta as an "atypical" antidepressant with a half-life of eleven to sixteen hours, compared to antidepressants such as Prozac that have a half-life of eighty-four to one hundred forty-four hours).

104 *Diseases and Conditions, How to Taper Off Your Antidepressant*, HARVARD HEALTH PUBL'G, HARVARD MED. SCH. (Jan. 29, 2020), https://www.health.harvard.edu/diseases-and-conditions/how-to-taper-off-your-antidepressant.

105 Tom Lamb, *Some Patients Who Stopped Taking Cymbalta Have Suffered From Extended And Severe Withdrawal Reactions Without Warning*, DRUG INJ. WATCH (Oct. 27,

*B. Cymbalta Discontinuation Labeling and General Information*

Cymbalta (generic Duloxetine) is one of several selective serotonin/norepinephrine reuptake inhibitors, commonly characterized as an antidepressant to treat mood disorders like anxiety and depression.[106] Cymbalta's FDA-approved label is available for viewing on the FDA's website, and states as follows regarding discontinuation syndrome:

> [d]iscontinuation 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; headache; paresthesia, fatigue, vomiting; irritability, insomnia, diarrhea, anxiety, and hyperhidrosis.[107]

The label then highlights the tendency for withdrawal effects in antidepressants, making special note that these effects are particularly likely to occur when the drug is abruptly discontinued.[108] The FDA website also states that patients who discontinue Cymbalta should be "monitored" for these discontinuation symptoms, recommending whenever possible "[a] gradual reduction in the dose" as opposed to "abrupt cessation."[109]

Unlike other antidepressants that are prescribed for mental health only, Cymbalta is indicated for chronic pain management, and, as such, is FDA-approved to treat fibromyalgia, diabetic peripheral neuropathic pain and chronic musculoskeletal pain in adults.[110] In the mid-2000s, before developing Cymbalta, Lilly was renowned for its antidepressant

2014), https://www.drug-injury.com/druginjurycom/2014/10/cymbalta-withdrawal-reactions-side-effects-lawsuits-eli-lilly-misrepresentations-warnings-failure.html?cid=6a00d8341c89dd53ef0240a490c6f2200c#comment-6a00d8341c89dd53ef0240a490c6f2200c.

106 CYMBALTA LABEL, *supra* note 1111, at 5.

107 CYMBALTA LABEL, *supra* note 1111, at 8 (emphasis added).

108 CYMBALTA LABEL, *supra* note 1111, at 8 (stating that "[t]here 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., paresthesia such as electric shock sensation), anxiety, confusion, headache, lethargy, emotional lability, insomnia, tinnitus, and seizures").

109 CYMBALTA LABEL, *supra* note 1111, at 8.

110 CYMBALTA LABEL, *supra* note 1111, at 6.

Prozac but was concerned about that drug's potential and likely patent expiration in December 2003.[111]

Fearful of losing a substantial part of its Prozac revenue to cheaper generic competitors, Lilly established a special research and development team to research a new medication to replace Prozac.[112] In pursuit of a superior Prozac replacement, the researchers analyzed several "comorbidities" associated with depression, including chronic pain, as a Lilly neuropharmacologist was testing Cymbalta's pain effects on animals at the time, and believed the drug's effects could block pain.[113] Additional studies revealed a connection between imbalances in serotonin and norepinephrine and reduced pain thresholds.[114] To increase the drug's marketability, Lilly decided to research whether Cymbalta could treat pain in general, including osteoarthritis, rheumatoid arthritis, and fibromyalgia, apart from depression, given that the primary pain relievers at the time were either non-steroidal anti-inflammatory drugs or addictive opioids.[115]

While Cymbalta's future revenue is yet to be determined, its generic active ingredient, duloxetine, is currently listed as a treatment for nerve and muscle myofascial and musculoskeletal pain resulting from "long-haul" Covid-19 neurology-related symptoms.[116] Thus, the drug's prevalence in the marketplace has the potential to dramatically increase in coming years.

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111 Elie Ofek & Ron Laufer, *Eli Lilly: Developing Cymbalta*, HARVARD BUS. SCH. (Jul. 30, 2008), https://d1wqtxts1xzle7.cloudfront.net/51428760/Eli_Lilly_Developing_Cymbalta71451-with-cover-page-v2.pdf?Expires=1629901186&Signature=fyhrpO5Ju82ddYkpmuQdL96KevJnYQx—XdVhOpzQEB36DzG2uEqxNITcgtcVX8pSBFmSlDjs~RqAbMpihk9d0vn0y2J0FZU1CZIoUbVQW-B-5NZMowA5SXRM7XfGv5hcEUgq2iGUv~sucYBU8kCx~vaBx~QzyXT6xN273lHtcRGoV2~YOewMRiTYJimJFlqhvb3fX~LAFjBMPLJq8bKHtxuBrTDawSW9y4HlZxSZOm7WmYJz3-Ep4gOybThE7nUlO1eSZtN2ctsGgmYenuILkA7XGtj4Qu5DdFTNx2wb6ZVwsrflCwoOyHlm~1VvSTuhu-eM7h9kve7j~eU6FusPQ__&Key-Pair-Id=APKAJLOHF5GGSLRBV4ZA.

112 *See id.*

113 *Id.*

114 *Id.*

115 *Id.*

116 ANTHONY CHENG MD ET AL., *Clinical Guidelines: Long COVID-19*, OSHU (2021), https://www.ohsu.edu/sites/default/files/2021-04/Long-COVID-19-Clinical-Guidelines-English-April-21-2021.pdf.; *see also* Colleen Stinchcombe, *How Doctors Are Treating COVID-19 Long-Haulers*, MED. BAG (Dec. 18, 2020), https://www.medicalbag.com/home/features/how-doctors-are-treating-covid-19-long-haulers/.

### *C. Cymbalta's Unique Pharmaceutical Properties*

Cymbalta is currently manufactured in twenty, thirty, and sixty-milligram doses in delayed-release capsules, the contents of which are weighted beads.[117] The capsule must be swallowed whole, and cannot be crushed, chewed, or opened.[118] The drug's dosage requirements vary according to the targeted ailment: the maximum dose is sixty milligrams a day for diabetic nerve pain and chronic musculoskeletal pain, whereas the maximum dose is one-hundred-twenty milligrams a day for Generalized Anxiety Disorders ("GAD") and major depressive disorders.[119]

## V. DIFFERING COURT INTERPRETATIONS REGARDING CYMBALTA LITIGATION

### *A. Lilly Summary Judgment Motion Granted: McDowell v. Eli Lilly & Co.*

To date, Lilly has prevailed in most of its Cymbalta litigation at the summary judgment stage by arguing its FDA-approved label provides adequate warning of potential discontinuation symptoms to prescribing doctors and patients, such as in *McDowell v. Eli Lilly Co*.[120]

In *McDowell*, a nurse practitioner prescribed Cymbalta to plaintiff for anxiety, depression, sleep disturbances, and migraines, after he was prescribed several other antidepressants that failed to relieve his symptoms and resulted in undesired side effects.[121] Plaintiff was continuously prescribed Cymbalta for the next four years, but, upon medication discontinuance, suffered severe brain zaps, insomnia, headaches, dizziness, and suicidal thoughts, which lasted several months.[122]

Plaintiff initiated a lawsuit against Lilly alleging negligence, breach of implied warranty, negligent misrepresentation, fraud, and violation of state consumer laws.[123] Plaintiff acknowledged the Cymbalta label included a "Discontinuation of Treatment" section, which warned that discontinuation symptoms may occur "at a rate of one or more percent," but argued however, that such labeling was inherently misleading due to Lilly's knowledge of a then-recent scientific study that indicated the percentage of individuals suffering from Cymbalta-related

117 CYMBALTA LABEL, *supra* note 1111, at 1.
118 CYMBALTA LABEL, *supra* note 1111, at 9.
119 CYMBALTA LABEL, *supra* note 1111, at 6–7.
120 McDowell v. Eli Lilly & Co., 58 F. Supp. 3d 391, 393 (S.D.N.Y. 2014).
121 *See id.* at 396–97.
122 *See id.*
123 *Id.* at 393.

discontinuation syndrome *may be significantly higher* than the 1% or more reported on the label.[124]

Plaintiff's claim relied on scientific data from a 2005 Journal of Affective Disorders ("JAD") article describing data from nine clinical duloxetine trials, funded by Lilly, that "assess[ed] the efficacy and safety of duloxetine in the treatment of major depressive disorder."[125] The JAD article explained the parameters of the trials, that involved the discontinuation of either Cymbalta or a placebo followed by a lead out phase of one to two weeks, which allowed for the collection of discontinuation-emergent adverse events ("DEAEs").[126] These studies reported that "significantly more" patients treated with Cymbalta (44.3%) in an "acute treatment" setting reported at least one discontinuation symptom than placebo-treated patients (22.9%), with dizziness being the most common symptom.[127] Out of the DEAEs reported, 39% were mild, 50.6% were moderate and 49.6% were severe.[128] While a higher incidence of DEAEs involved patients tapered from a 120 milligrams per day dose, (e.g., the maximum dose for major depressive disorder), the overall relationship between dose and DEAEs was not "linear as similar incidences were reported for patients taking forty, sixty, or eighty milligrams a day, who also reported significantly more DEAEs than patients treated with placebo," and the study classified 53.7% of the adverse event as "unresolved" prior to final contact with patients.[129]

The fifty-two-week study reported similar results, in which 793 DEAEs were reported among the 281 patients who reported at least one DEAE, with 46.3% classified as moderate and 17.2% as severe.[130] The study concluded by noting that "reassurance by the clinician may be all that is required for most patients," but, "for more severe symptoms, the *prescribing clinician may wish to consider reinstating the original dose* and slowing the rate of taper."[131]

Given the study results, McDowell claimed that Lilly had "uncontested knowledge of the 44-50% withdrawal rate in Cymbalta," but deliberately manufactured a misleading label that assured

124 *Id.* at 395 (emphasis added).

125 David Perahia et. al, *Symptoms Following Abrupt Discontinuation of Duloxetine Treatment in Patients with Major Depressive Disorder*, 89 J. AFFECTIVE DISORDERS, 207, 207 (2005).

126 *Id.* at 208.

127 *Id.* at 210.

128 *Id.*

129 *Id.* at 209.

130 *Id*. at 210.

131 Perahia, *supra* note 125, at 211.

physicians that the risk of withdrawal was only "1% or greater."[132] The Southern District of New York completely rejected this argument, finding Lilly's discontinuance warning adequate as a matter of law, because it "provide[d] specific detailed information on the risks of the drug" and "information regarding 'the precise malady incurred' [by plaintiff] was communicated."[133]

In reaching that result, the court noted that it "consider[s] factors including 'whether the warning is accurate, clear, consistent on its face, and whether it portrays with sufficient intensity the risk involved in taking the drug.'"[134] It further reasoned that a discontinuation warning "should also be evaluated as a whole and not through nitpicking prism of an interested legal advocate," as any "vagueness may be overcome if, when read as a whole, the warning conveys a meaning as to the consequences that is unmistakable."[135] In sum, the court was satisfied that Lilly's discontinuation symptoms label was inclusive of both the "important fact that the [withdrawal] rate was significantly higher in Cymbalta patients than patients on placebo" as well as specific potential symptoms upon discontinuation, including those symptoms McDowell alleged that he suffered.[136] The court also explained that the "at a rate greater than or equal to 1%" withdrawal warning was adequate because it comported with the "accepted practice of identifying such individual adverse events observed at or above a specified threshold and in accord with FDA regulations and guidance, directing that the label' list the adverse reactions identified in clinical trials that occurred at or above a specified rate appropriate to the safety database.'"[137] McDowell's claim also failed because the court accorded importance to the prescriber's testimony that she did not rely on the withdrawal information on the label in her decision to prescribe the drug.[138] Under New York law, failure to warn plaintiffs are required to demonstrate that the physician would not have prescribed the drug in the same manner, or would have prescribed a different drug had a different, more accurate warning been given.[139]

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132 Perahia, *supra* note 125125, at 208; McDowell v. Eli Lilly & Co., 58 F. Supp. 3d 391, 403 (S.D.N.Y 2014).

133 *See McDowell*, 58 F. Supp. 3d at 402–03 (first quoting Martin v. Hacker, 628 N.E.2d 1308, 1312 (N.Y. 1993); then quoting Alston v. Caraco Pharm., Inc., 670 F. Supp. 2d 279, 284 (S.D.N.Y. 2009)).

134 *Id.* at 403 (quoting Martin v. Hacker, 628 N.E.2d 1308, 1313 (N.Y. 1993)).

135 *Id*.

136 *Id.* at 403–04.

137 *Id.* at 404 (quoting 21 C.F.R. § 201.57(c)(7) (2014)).

138 *See id.* at 408–09.

139 *McDowell*, 58 F. Supp. 3d at 408.

*B. Lilly Summary Judgment Motion Denied: Herrera v. Eli Lilly & Co.*

Like in *McDowell*, the plaintiff in *Herrera* alleged that Lilly failed to adequately warn of the risk and severity of discontinuation side effects upon discontinuing Cymbalta, which the plaintiff had been prescribed for five years.[140] Plaintiff was initially prescribed Cymbalta for depression by her general practitioner, who allegedly did not discuss future or potential Cymbalta tapering or discontinuation with her.[141] However, after suffering from lethargy, weight gain, depression and anxiety, plaintiff decided to discontinue Cymbalta, and a different doctor provided her with a "tapering" schedule that changed her current sixty-milligram dose to a thirty-milligram dose for thirty days before completely discontinuing the medication.[142]

Two days after the discontinuation of the medication plaintiff felt withdrawal effects, which consisted of brain zaps, muscle spasm, suicidal ideations, hot flashes, memory loss, and skin irritation, among others.[143] Her doctor suggested that she resume taking the thirty-milligram tablet, which plaintiff did not want to do.[144] The prescribing physician interpreted the label's warning, "the following symptoms occurred at a rate greater than or equal to 1 percent," as conveying an uncertain message because it meant "exactly what it says, that it could be equal to 1 percent rate or much higher."[145] The physician also stated that he was surprised by the varying results of the JAD article and opined that if "Lilly was aware that the risk of discontinuation side effects was between 44 and 50 percent, then he believes Lilly should have disclosed [that] information."[146]

*Herrera's* approach of evaluating information apart external to the label was unique in recognizing the dosage and tapering flaw in Cymbalta was sufficient to preclude summary judgment.[147] The court

140 Herrera v. Eli Lilly & Co., No. 13-cv-02702, 2015 U.S. Dist. LEXIS 89334, at *16 (C.D. Cal. June 19, 2015).

141 *Id*. at *10–14.

142 *Id.* at *16.

143 *Id.* at *17.

144 *Id.* at *18.

145 *Id.* at *14.

146 *Herrera*, No. 13-cv-02702, 2015 U.S. Dist. LEXIS 89334, at *15.

147 *See id*. at *38 (C.D. Cal. June 19, 2015) ("Moreover, in light of the newly uncovered evidence, the Court finds this case distinguishable from both *McDowell* and *Carnes*. Both of those courts relied, in relevant part, on the prescribing physicians' knowledge of the risks of *abrupt* withdrawal. Additionally, neither court considered the possibility that there was no difference in the risk of discontinuation symptoms from discontinuing Cymbalta abruptly or tapering. On this record, Plaintiffs' evidence is sufficient to raise a triable issue of fact and Lilly fails to show that it is entitled to summary judgment under Rule 56.").

considered, among other things, Lilly's internal documents, including employee emails implying that tapering may not be effective in reducing Cymbalta discontinuation syndrome.[148] It also reviewed a report that referred to a two-week taper Cymbalta study, which found "no statistical significance among the study drug stopping method (taper compared with abrupt) during the drug-tapering phase."[149] The court used this evidence to evaluate Cymbalta's label warning adequacy and held that, while the label recommends tapering, it failed to "provide specific parameters—such as timeframe or dosage increments—for designing an appropriate taper regime[,]" and Cymbalta's label states that the drug "should be swallowed whole and should not be chewed or crushed, nor [ . . . ] be sprinkled on food or mixed with liquids."[150] Because the label makes it clear that one should not open the tablet, it prohibits a physician from prescribing a tapering regime that involves doses lower than twenty milligrams, which is Cymbalta's lowest available dosage. The court accorded weight to the internal Lilly emails and insinuated that tapering may not improve withdrawal tolerability.[151] The court subsequently mentioned the prescribing physician's claim that a revised warning label regarding withdrawal effects may have impacted his decision to prescribe the medication.[152]

For these reasons, and because the plaintiff provided substantial evidence that Lilly was aware that discontinuation symptoms may be severe, regardless of whether the patient abruptly discontinues or tapers off the medication, the court distinguished *Herrera* from *McDowell*, and concluded that *McDowell* erred by not considering the possibility that there was no difference in the risk of discontinuation symptoms between abrupt withdrawal or tapering.[153]

## VI. LILLY NEEDS TO RESOLVE THIS TAPERING ISSUE, OR CYMBALTA SHOULD BE

148 *Id.* at *20 (referring to internal Eli Lilly email stating: "I don't think we're in a position to make a data-driven recommendation with regard to dose tapering, although our 'official' position is to obviously recommend tapering").

149 *Id.* at *21.

150 *Id.* at *6.

151 *Id.* at *22 (referring to email stating: "[n]one of the individual studies specifically designed to look at this (SUI or GAD) have shown a benefit to tapere [sic] compared with abrupt discontinuation. I just believe the sentence that concludes the first paragraph is not accurately reflecting the lack of benefit (or lack thereof) of tapering in studies designed to look at this specifically . . . overall it strongly implies that tapering substantially improves tolerability, which does not represent the data accurately").

152 Herrera v. Eli Lilly & Co., No. 13-cv-02702, 2015 U.S. Dist. LEXIS 89334, at *37 (C.D. Cal. June 19, 2015)

153 *Id.* at *37–38.

REMOVED FROM THE MARKET

Physicians continue to prescribe Cymbalta to individuals and the individuals continue to suffer from the adverse effects of withdrawal. Those individuals, however, are unlikely to succeed on failure-to-warn withdrawal claims because of the learned intermediary doctrine and the court and FDA's refusal to acknowledge Cymbalta's inherent pharmacological properties that make dependence inevitable.

A review of clinical trial studies and patient complaints examined above makes it clear that Cymbalta's label fails to adequately warn physicians or patients of the high potential of prolonged discontinuation withdrawal effects upon tapering. Cymbalta's current discontinuation warning also fails to satisfy the FDA regulatory standards concerning discontinuation labeling, and for these reasons, the *McDowell* court erred in holding that the drug label's warning was adequate.[154]

Cymbalta's current discontinuation warning, which states that "1% or greater" of the adult placebo-controlled clinical trials have experienced discontinuation symptoms "following abrupt or tapered discontinuation," is both misleading and inaccurate.[155] As previously noted, the 2005 JAD study reported as many as 44.3% of patients experienced Cymbalta discontinuation symptoms, with almost half of these symptoms classified as severe.[156] Thus, the "1% or greater" withdrawal symptom rate "warning" gives the false impression that the rate of individuals experiencing discontinuation syndrome is near one percent—or possibly two or three percent. The scientific data gathered by the JAD study, however, indicates that the actual discontinuation symptom rate is *much* higher than one percent and about 42% higher than what the label indicates.[157] This violates 21 CFR 201.56's prohibition on labeling that is "misleading" and "promotional in tone."[158] This very high discontinuation symptom rate is "essential scientific information" that should have been included in the drug's warning according to federal labeling regulations.[159]

The *McDowell* court reasoned that Cymbalta's labeling was adequate because it recited the same withdrawal symptoms that the plaintiff experienced and the drug's withdrawal rate was higher than that of patients on placebo, and labeling vagueness could be overcome if it otherwise conveyed a meaning as to the drug's unmistakable

154 McDowell v. Eli Lilly & Co., 58 F. Supp. 3d 391, 406 (S.D.N.Y. 2014).

155 *See* CYMBALTA LABEL, *supra* note 1111, at 8.

156 David Perahia et. al, *supra* note 125, at 207.

157 *See* David Perahia et. al, *supra* note 125, at 207.

158 21 C.F.R. § 201.56 (a)(2) (2021).

159 *Id.* at § 201.56(a)(1).

consequences.[160] This reasoning, however, completely disregards the essential purpose of drug labeling requirements—to make the drug safe for its intended use.[161] Prescribers and patients may very well conclude that a higher incidence of withdrawal symptoms is a significant factor when evaluating the risks and benefits associated with a particular drug. If, for example, an individual has been prone to adverse drug reactions, drug sensitivity, or has experienced drug withdrawal effects in the past, a prescriber may be less likely to prescribe a drug with a high rate of documented discontinuation symptoms.

Cymbalta's label also violates FDA's guidance to notify prescribers and patients about the potentiality of drug dependence and abuse.[162] This suggests the FDA would likely consider certain prevalent Cymbalta tapering methods, such as opening the capsule and removing a small number of beads at a time, to try to deal with the drug's troubling withdrawal effects as a classic example of drug abuse.[163]

Cymbalta's label does not even mention the possibility that tapering off the lowest available dosage may be required, and, to accomplish that end, the capsule must be opened, and its contents removed. It also fails to convey this substantial risk of abuse to prescribers. In addition, when Cymbalta patients use self-help taper guidelines by, for example, slowly removing the capsule's beads on a regimented schedule, they are also inherently misusing the drug by intentionally taking a different dose than what was prescribed for therapeutic purposes.[164] By failing to acknowledge the withdrawal symptoms that could occur upon Cymbalta discontinuation, and that effective tapering strategies can lead to inherent abuse and misuse of the drug, Lilly is neglecting its obligation to provide the prescriber with information related to the "characteristic effects" likely to result from the physical dependence of the drug under FDA labeling guidelines.[165]

Perhaps most importantly, Lilly is in violation of its regulatory obligation to describe the principles of treating or mitigating the effects of abrupt withdrawal.[166] The Cymbalta label does *not* provide a suggested tapering schedule. [167] The label's only suggestion is that a

160 *McDowell*, 58 F. Supp. 3d at 403.

161 21 C.F.R. § 201.56(a)(1) (2021).

162 FDA GUIDANCE FOR INDUS., *supra* note 39, at 6.

163 *See* Clare Wilson, *People are Hacking Antidepressant Doses to Avoid Withdrawal*, NEW SCIENTIST (July 7, 2017), https://www.newscientist.com/article/2140106-people-are-hacking-antidepressant-doses-to-avoid-withdrawal/.

164 FDA GUIDANCE FOR INDUS., *supra* note 39, at 8.

165 FDA GUIDANCE FOR INDUS., *supra* note 3939, at 10.

166 21 C.F.R. § 201.57(c)(10)(iii) (2022).

167 *See* CYMBALTA LABEL, *supra* note 11, at 8.

gradual, as opposed to abrupt, cessation of the drug is recommended, but does not explain how one can possibly gradually reduce a twenty-milligram capsule that cannot be opened.[168] This does not provide prescribers with concrete criteria as to how to slow tapering—which, after the patient is prescribed twenty milligrams, is technically impossible, unless the patient defies labeling instructions and opens the capsule, which many patients have done to try to avoid withdrawal symptoms.[169]

For all these reasons, Cymbalta's current labeling reads as a poorly executed "choose your own adventure" novel. A prescriber will likely review section 2.4 "Discontinuing Cymbalta" when considering the withdrawal risks associated with the drug's discontinuation and determining how to discontinue its use.[170] Section 2.4 states the following: "[s]ymptoms associated with discontinuation of Cymbalta and other SSRIs and SNRIs have been reported . . . [a] gradual reduction in the dose rather than abrupt cessation is recommended whenever possible."[171] Prescribers who follow these instructions will see that section 5.6 again describes the potential discontinuation syndrome.[172] Regarding treatment for discontinuation syndrome, however, section 5.6 merely rephrases section 2.4 and then directs the prescriber back to that section.[173]

168 *See* CYMBALTA LABEL, *supra* note 11, at 8.

169 u/Oddsciencegirl, r/cymbaltasafetaper, REDDIT (Dec. 3, 2021) https://www.reddit.com/r/cymbaltasafetaper/comments/r7q6sc/anyone_do_okay_going_off_cymbalta/ (last visited Aug. 2, 2023) ("Yes, my psychiatrist told me to go off it cold Turkey from 30 mg. It was a horrible experience. I followed advice from cymbalta hurts worse on Facebook on safe tapering. I've been off cymbalta since July and I have no brain zaps. But it took me over a year to wean off of it safely. I would reinstate the lowest dose that doesn't give you the brain zaps/side effects. There is a website that also helps you determine a safe tapering, you will find it if you google it or find that Facebook group. You need to count the beads in your capsule, then every 2 weeks, drop a percentage that works for you (no side effects), and keep doing this every two weeks. If you drop too fast, you will know. Never drop beads when you have a side effect."); *see* Crystal Lindell, *How I Finally Took Myself Off Cymbalta*, PAIN NEWS NETWORK (Sept. 16, 2015) https://www.painnewsnetwork.org/stories/2015/9/15/how-i-finally-took-myself-off-cymbalta (last visited Aug. 2, 2023) ("My doctor never told me NOT to go off Cymbalta cold turkey. Ever. Not one time . . . I decided to call Dr. Google. And I found out that some people were just opening the capsules and pouring a little more out each day until they got down to nothing. I decided to do the same thing.").

170 CYMBALTA LABEL, *supra* note 1111, at 21.

171 CYMBALTA LABEL, *supra* note 1111, at 21.

172 CYMBALTA LABEL, *supra* note 1111, at 8.

173 CYMBALTA LABEL, *supra* note 1111, at 8 ("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,

Thus, reviewing the label text evidences that while prescribers are told to reduce Cymbalta at a gradual rate, they are provided no guidance as to how to gradually reduce dosage to treat discontinuation syndrome. The FDA should not consider the drug manufacturer's suggestion of resuming the previous dosage as an effective way of "treating or mitigating the effects" of discontinuation syndrome.[174] Because there are no clear tapering guidelines on the label, many individuals prescribed Cymbalta must choose between enduring endless, painful withdrawal symptoms, or taking the drug indefinitely—as evidenced by posts in the online community.[175] As such, the *McDowell* court's reasoning was flawed when it concluded that Lilly designed an adequate label despite withholding uncontested knowledge of the 44 to 50% withdrawal symptom rate.[176]

*McDowell* is also flawed insofar as it determined that the current label is "in accord with FDA regulations and guidance directing that the label' list the adverse reactions identified in clinical trials that occurred at or above a specified rate appropriate to the safety database."[177] This is because the court failed to apply 21 C.F.R. § 314.70(c)(6), which requires drug manufacturers to update labels when presented with new information regarding the drug's safety and effectiveness.[178] The 2005 JAD study finding that around 44 to 50% of patients in a controlled experiment suffered from withdrawal affects was published seventeen years ago and has not been disputed by Lilly. Yet, Lilly has still not updated its label accordingly. Surely such a large disparity in the rate of individuals suffering discontinuation effects warrants "adding or

then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate.").

174 FDA GUIDANCE FOR INDUS., *supra* note 3939, at 10.

175 *See, e.g.*, *User Reviews for Duloxetine to Treat Pain*, DRUGS.COM (Aug. 12. 2014), https://www.drugs.com/comments/duloxetine/for-pain.html (stating in a patient review that "I'd been taking Cymbalta for about 2 years when I decided that I didn't want to pay $30/mo [sic] anymore, so I decided that I would wean myself off. I tried and I started getting the brain zaps, like lightening in my head. So, I started back, slowly I just started missing a dose here and there until I was able to stop them without the side effects. I've been off for several months now and I've noticed that I've been in more pain and everything that was hurting me before has compounded. So needless to say, I'm starting them back. Appears that I'm not going to be able to do without it").

176 McDowell v. Eli Lilly & Co., 58 F. Supp. 3d 391, 406 (S.D.N.Y. 2014).

177 *Id.* at 404.

178 *See* 21 C.F.R § 314.70 (c)(6) ("Changes in the labeling to reflect newly acquired information, except for changes to the information required in § 201.57(a) of this chapter (which must be made under paragraph (b)(2)(v)(C) of this section), to accomplish any of the following . . . [t]o add or strengthen a statement about drug abuse, dependence, psychological effect, or overdosage.").

strengthening" a discontinuation warning as required by the regulation.[179]

### *A. The Learned Intermediary Doctrine is Ill-Suited to Cymbalta Withdrawal Litigation*

Cymbalta's discontinuation label is misleading and fails to adequately inform prescribers or patients of the significant and debilitating symptoms that may occur upon drug discontinuation. Failure to warn plaintiffs have previously argued that the learned intermediary doctrine provides drug manufacturers with an unnecessary, automatic defense.[180] Cymbalta's inherent qualities (including that its lowest available dosage is a twenty-milligram capsule that cannot be opened) presents a stronger case as to why this doctrine should be limited.

It is no coincidence that the average Cymbalta patient is unaware of the likelihood of physical withdrawal effects that may occur, or the extreme methods they may need to resort to in order to successfully discontinue the drug, which may include being prescribed another antidepressant only as a method to transition off Cymbalta.[181]

The essential rationale of the learned intermediary doctrine is that drug manufacturers only have a duty to warn prescribers—the learned intermediaries—of potential drug side effects. Its theory is that the provider has the duty to then warn the patient. Such is not feasible, however, with Cymbalta because there is strong evidence that prescribers are unaware of the potential, prolonged withdrawal effects that occur either upon tapering or discontinuation and how to help individuals who are struggling to stop the drug. This is why many individuals struggling to discontinue antidepressants turn to internet forums for non-medical self-help.[182]

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179 *See* 21 C.F.R. § 314.70 (c)(6).

180 *See, e.g.*, Susan A. Casey, C*omment: Laying an Old Doctrine to Rest: Challenging the Wisdom of the Learned Intermediary Doctrine*, 19 WM. MITCHELL L. REV. 931, 960 (1993).

181 *The Cymbalta/Duloxetine Tapering Handbook*, CYMBALTA WITHDRAWAL, https://cymbalta-withdrawal.com/cymbalta-tapering-handbook/ (last visited Aug. 2, 2023) ("Switching to Prozac or 'bridging' is another well-known method when tapering off an SNRI . . . [m]any doctors suggest a normal dose of Cymbalta, then switch to 10 mg Prozac with a week overlap. Meaning, you will take both medications for a week and then drop the Cymbalta on day 8 and continue taking Prozac.").

182 Adele Framer*, What I Have Learnt from Helping Thousands of People Taper Off Antidepressants and Other Psychotropic Medications*, 11 THERAPEUTIC ADVANTAGES IN PSYCHOPHARMACOLOGY 1, 3 (2021) ("We would very much prefer to refer people to knowledgeable medical providers, but website members have been unable to find them. Many experienced painfully unsuccessful tapers following a physician's recommendations, restarted the drug, and, having lost confidence in their prescribers,

The learned intermediary doctrine grants immunity to a manufacturer in a failure to warn case if the prescriber cannot testify a "more adequate" warning would have persuaded them to choose a different drug.[183] This is an almost impossible hurdle for a Cymbalta plaintiff to overcome because it requires inherent speculation. Moreover, prescribers' preference to avoid potential liability incentivizes them to testify that the at-issue drug's benefits outweighed its risks, and that a more accurate warning would not have factored into any decision to prescribe the drug. Thus, the intermediary doctrine provides pharmaceutical manufacturers with an additional shield: the prescribers fear of potential personal liability, reputation, and ego.

*B. The Herrera Court Adopted the Best Approach*

*Herrera* considered factors beyond the drug's FDA-approved label, and in doing so, determined that the intermediary doctrine is not a fit-all approach.[184] The court ruled that a warning that was FDA-approved and provided general information about discontinuation symptoms is not automatically determinative in satisfying the manufacturer's duty to warn the prescriber, especially if there are factors that the manufacturers did not consider or simply ignored.[185] This is the best approach, for several reasons.

Once the FDA approves a drug, it is difficult to continuously monitor the drug's potential defects.[186] While the FDA's center for Drug Evaluation and Research does require manufacturers to submit post-market studies and report adverse events,[187] a study conducted by the United States Government Accountability Office revealed that the FDA nevertheless lacks "reliable, readily accessible data" on current post-market studies and other safety issues.[188] The study noted that this lack

want finally to stop it. Others mistrust prescriber uncertainty about tapering. All fear withdrawal symptoms.").

183 *See, e.g.*, *McDowell*, 58 F. Supp. 3d at 408–09.

184 *See* Herrera v. Eli Lilly & Co., No. 13-cv-02702, 2015 U.S. Dist. LEXIS 89334, at *38 (C.D. Cal. June 19, 2015) (denying Lilly's summary judgment motion.)

185 *See id*. at *38 (distinguishing its reasoning from *McDowell* in that *McDowell* did not consider "the possibility that there was no difference in the risk of discontinuation symptoms from discontinuing Cymbalta abruptly or tapering").

186 *See In re* Accutane Litigation, 235 N.J. 229, 273 (2018).

187 *FDA Adverse Event Reporting System (FAERS) Public Dashboard,* U.S. FOOD AND DRUG ADMIN, https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard (last visited Aug. 2, 2023).

188 U.S. GOV'T ACCOUNTABILITY OFF., GAO-16-192, DRUG SAFETY: FDA EXPEDITES MANY APPLICATIONS, BUT DATA FOR POST APPROVAL OVERSIGHT NEED IMPROVEMENT (2015), https://www.gao.gov/assets/gao-16-192.pdf (stating "CDER's evaluation also found

of information resulted in the delay of the FDA publishing required reports on safety issues in a timely manner, making it less effective for FDA to monitor post-market drug safety.[189]

The *Herrera* court subtly acknowledged the possibility of outdated, unreliable data when it denied Lilly's summary judgment motion based on evidence that the drug tapering does not improve discontinuation symptoms and the prescriber's testimony that he would have been more alert to the fact that the patient is likely to experience withdrawal symptoms, with a more detailed warning.[190] *Herrera* was correct to consider the unique pharmacological makeup of Cymbalta, noting that tapering off the lowest dosage of a twenty-milligram capsule that cannot be opened creates a "cliff" that makes it inherently difficult for a patient to painlessly taper.[191]

The *Herrera* court ultimately denied plaintiff's design defect claim on the basis that she failed to provide sufficient evidence that the twenty-milligram "cliff" caused her harm because the plaintiff was never prescribed the twenty-milligram dose.[192] Accordingly, the court did not rule out the "cliff" argument in general, and implied it would not necessarily preclude a design defect claim should a plaintiff who was (1) prescribed twenty milligrams and (2) attempted to taper presented evidence that the Cymbalta twenty milligram "cliff" inherently caused withdrawal symptoms.[193] Acknowledgment of this dosing nuance would benefit failure-to-warn or design defect flaw claims of those who experienced severe withdrawal symptoms after stopping the ttwenty-milligramdose, and would also explain why many individuals have resorted to defying manufacturer instructions and opening the capsule to slowly taper to achieve some relief, resulting in a prolonged, bizarre, and visibly painful tapering schedule that involves counting or weighing a daily dose of beads using various methods, such as a jewelry scale.[194]

inaccuracies in the post-market study data, such as statuses recording as pending or ongoing that should have been recorded as delayed, as well as delays in data entry").

189 *Id.*

190 *Herrera*, 2015 U.S. Dist. LEXIS 89334, at *36–38.

191 *Id.* at 39.

192 *Id.* at 39–40 (noting her physician told her to take thirty milligrams of Cymbalta for thirty days, and then completely stop the medication).

193 *Id.*

194 *See The Scale Method*, CYMBALTA HURTS WORSE, https://www.healingamericanow.com/chw-the-scale-method/ (last visited Aug. 2, 2023) (listing a detailed tapering method using a jewelry scale: "[g]et all your equipment together (scale, empty capsules, Cymbalta capsules, funnel, tweezers or spatula, dishes, capsule holder). Sit in a place where you will be comfortable, out of a draught, away from children and pets. You need a level surface and plenty of space for all your equipment. Sitting at a table is best. Working on your lap will affect the scale. Turn on

While *Herrera* did recognize the learned intermediary doctrine as a potential defense to manufacturer liability,[195] patients attempting to slowly taper off Cymbalta using these bizarre methods would certainly argue that their physician was not adequately warned that this extreme method may be the only way to discontinue the drug. Based on the bizarre attempted self-help methods and the vague Cymbalta label statement regarding discontinuation symptoms, there is no logical way that this warning, read in conjunction with the discontinuation rate text of "1% or more," fulfills the federal regulatory requirement to provide prescribers with the "essential scientific information needed for safe and effective" drug use and "clinically significant adverse reactions."[196]

### *C. The FDA Needs to Issue a REMS for Cymbalta*

Cymbalta patients have described their pain and suffering while attempting to taper from the drug, and their fear and frustration regarding their inherent dependency, about which they were not informed by their prescribers, in online communities.[197] This raises serious issues as to whether the potential benefits of Cymbalta—its antidepressant effects and pain relief—outweighs its risk of severe withdrawal effects, prolonged tapering, or dependence. The FDA issues a Risk Evaluation and Mitigation Strategy ("REMS") on drugs it believes need additional guidelines and monitoring to ensure their safety based

your scale. Calibrate it according to your scale instructions. Do this the very first time you use the scale, then every 4-5 uses afterwards to keep it as precise as possible. Place the Scale Dish on the scale, press TARE. Make sure your display shows 0.000g. Open your Cymbalta capsules, pour all the beads into a dish (the Bead Dish). Place the longer half of the empty capsule / vegetarian capsule into your capsule holder. Carefully move the beads from your Bead Dish onto the Scale Dish, until you reach the weight for your new taper capsule. Once you reach that weight, use the funnel to tip the beads from your Scale Dish into the empty taper capsule. Pick up the taper capsule with the beads in it very carefully, place the other end on top and push till it clicks shut").

195 Herrera v. Eli Lilly & Co., No. 13-cv-02702, 2015 U.S. Dist. LEXIS 89334, at *31–32 (C.D. Cal. June 19, 2015).

196 21 C.F.R. §§ 201.56(a)(1)–(a)(2) (2021).

197 *See, e.g.*, *How to Stop Duloxetine (Cymbalta) Without Withdrawal Symptoms*, THE PEOPLE'S PHARMACY, https://www.peoplespharmacy.com/articles/how-to-stop-duloxetine-cymbalta-without-withdrawal-symptoms ("I was on Cymbalta for about a year to treat pain in in my shoulder and neck. When it was diagnosed as a torn rotator cuff, the doctor said I could get off the drug. He gave me 30 mg for a week and said I would be fine. I had been on 60 mg. I did as I was told. Once I finished that week of 30mg doses, I was pretty sick. I had horrible stomach pain, diarrhea, and headaches. I felt so nauseated and dizzy I was miserable.").

on an evaluation of a drug's benefits versus its inherent risks.[198] It is clear that the FDA should issue a REMS for Cymbalta.

As discussed above, Cymbalta's label fails to provide physicians with a tapering schedule, and only suggests tapering the drug via a "gradual reduction" or resume the previously prescribed dose if discontinuation symptoms present.[199] Prescribers, therefore, are provided no guidance as to how to safely taper the drug once patients decide they no longer wish to take it.[200] As a result, many patients believe self-help is their own option and have resorted to amateur tapering websites, where they attempt to taper without a doctor's supervision.[201]

Self-tapering without a doctor's supervision is an impractical and dangerous way to discontinue mediation. The FDA, therefore, should issue a REMS for Cymbalta that includes a communication plan regarding the inherent withdrawal risks associated with the drug. This is a good start, but still insufficient because many physicians do not know how to taper Cymbalta to avoid withdrawal symptoms.[202] As such, the Cymbalta REMS should include an "Elements to Assure Safe Use" requirement, which would require that physicians who prescribe the drug are "specially certified" and have special training or experience in safely tapering patients from this medication.[203]

The FDA should also require that Cymbalta patients be enrolled in a special program where they are continuously monitored by medical professionals, both during their regular dosage and during their tapering, should the patients ultimately decide to stop taking the drug.

198 *Risk Evaluation and Mitigation Strategies ("REMS"),* U.S. FOOD & DRUG ADMIN., https://www.fda.gov/drugs/drug-safety-and-availability/risk-evaluation-and-mitigation-strategies-rems (last visited Aug. 2, 2023).

199 CYMBALTA LABEL, *supra* note 1111, at § Discontinuation.

200 u/thelauryngotham, REDDIT, "So I've been trying to quit taking Cymbalta for over six months now. Every time, the withdrawals have been horrific and I've ended up having to take it again. I've tried what my doctor recommended . . . halving my dose for several weeks and then stopping. That did nothing so tried opening the capsules and measuring out 1/4th and even 1/8th doses. Regardless what I do, the symptoms are equally bad when trying to stop." (last visited Aug. 2, 2023). https://www.reddit.com/r/cymbalta/comments/ycrnih/tapering_off_this_stuff/.

201 *See* Crystal Lindell, *How I Finally Took Myself Off Cymbalta*, PAIN NEWS NETWORK (Sept. 16. 2015), https://www.painnewsnetwork.org/stories/2015/9/15/how-i-finally-took-myself-off-cymbalta (last visited Aug. 2, 2023) ("My doctor never told me NOT to go off Cymbalta cold turkey. Ever. Not one time . . . I decided to call Dr. Google. And I found out that some people were just opening the capsules and pouring a little more out each day until they got down to nothing. I decided to do the same thing.").

202 *See generally id.*

203 U.S. FOOD & DRUG ADMIN. AMEND. ACT, Sec. 505-1 Risk Evaluation and Mitigation Strategies.

This requirement would compel Lilly to carefully consider discontinuation issues and develop safe tapering criteria. If the only way to painlessly taper off the twenty-milligram dose, or from one dose to a lower dose, is to open the capsule and slowly reduce the number of beads a patient ingests, Lilly should acknowledge this in the label and provide this information to all health care providers. Lilly must address the question whether a physician must advise patients to either stop taking the medication abruptly at the lowest available dosage and suffer painful withdrawal symptoms or continue taking the drug for the indefinite future to avoid debilitating withdrawal symptoms.

The REMS evaluation criteria that estimates the size and population likely to use the drug involved, the seriousness of the disease treated by the drug, and the seriousness of known or potential adverse events that may be related to the drug demonstrate that a REMS is necessary for Cymbalta. Given Cymbalta's antidepressant qualities, and corresponding posts from the internet community, it is apparent that many individuals are prescribed this drug, and that number has a potential to increase in the future. These facts, along with the documented prevalence of withdrawal side effects, as seen in the JAD clinical study and the myriad of patient complaints, should compel the FDA to re-evaluate its approval of the drug. It is painfully ironic that Cymbalta tapering has caused patients widespread physical and mental suffering given that the drug is intended to treat depression and pain.

Finally, because the FDA is supposed to consider the specialties of the healthcare providers who prescribe the drug, "and whether approaches to mitigate the risk are . . . well known by the health care professionals,"[204] it should re-evaluate Cymbalta, and issue a REMS. While antidepressants are usually prescribed by psychiatrists who are likely to have a knowledge in antidepressant tapering, Cymbalta is also prescribed by rheumatologists and general practitioners for its alleged fibromyalgia and neuropathy treatments since it is FDA-approved as both an antidepressant and a chronic pain medication.[205] Because many individuals suffer from chronic pain,[206] Cymbalta is likely prescribed to a large number of individuals who may suffer severe withdrawal effects upon discontinuation.

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204 U.S. FOOD & DRUG ADMIN., REMS: FDA'S APPLICATION OF STATUTORY FACTORS IN DETERMINING WHEN A REMS IS NECESSARY: GUIDANCE FOR INDUSTRY (Apr. 2019).

205 CYMBALTA LABEL, *supra* note 11, at Indications and Usage.11

206 *See* Philip J. Mease et. al., *Evaluation of Duloxetine for Chronic Pain Conditions,* PAIN MANAGE, FUTURE SCI. GROUP (2011) (finding chronic pain affects fifty to ninety million people in the United States alone).

### *D. FDA's Issuance of a Cymbalta REMS Will Enhance Public Health Awareness of Antidepressant Withdrawal*

An FDA REMS is needed for Cymbalta due to the prevalence of individuals expressing discontent with their antidepressant withdrawal symptoms and their prescribers' inability to ease their associated pain and suffering.[207] While the FDA has provided guidelines for opioid usage and tapering, and promulgated awareness of potential opioid abuse, which includes managing the symptoms of opioid withdrawal,[208] it has not provided equivalent guidelines for antidepressants. The courts' usage of the learned intermediary doctrine, which accepts Cymbalta's drug labeling as adequate as a matter of law without considering its inherent defects, provides undeserved immunity to Lilly. The company continues to manufacture and mass-market the drug to prescribers who are uninformed and ill-equipped to treat its discontinuation ramifications.

## VII. CYMBALTA MUST BE MANUFACTURED IN SMALLER DOSAGES TO ASSIST TAPERING

Cymbalta must be manufactured in smaller doses because the drug has an inherit design flaw: its lowest available dosage is a twenty-milligram delayed-release capsule, that, according to its own label, should not be opened. As demonstrated in online forums, numerous individuals have defied Cymbalta's label instructions and have slowly removed the enclosed beads in an attempt to stop the medication experience withdrawal symptoms associated with discontinuing the twenty-milligram dose.[209] This method of tapering is neither

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207 *See* Edward White et. al., *The Role of Facebook Groups in the Management and Raising of Awareness of Antidepressant Withdrawal: is Social Media Filling the Void Left by Health Services?* 11 THERAPEUTIC ADVANCES IN PSYCHOPHARMACOLOGY 1, 1–18 (2021) (attributing the amount of Cymbalta and other antidepressant "self-help" withdrawal groups to physicians who are unaware of or unprepared to treat patients suffering from withdrawal effects).

208 U.S. FOOD AND DRUG ADMIN., FDA'S OPIOID ANALGESIC REMS EDUC. PRINT FOR HEALTHCARE PROVIDERS INVOLVED IN THE TREATMENT AND MONITORING OF PATIENTS WITH PAIN (Sept. 2018).

209 *See, e.g.*, *Withdrawal at 20 Mg*, Cymbalta Withdrawal Forums, https://www.cymbaltawithdrawal.com/topic/9818-withdrawal-at-20mg (last visited Aug 2., 2023) ("I am looking for any advice whatsoever . . . [m]y doctor slowly lowered me from 90 mg to 60 mg in three months, then finally 30 mg to 20 mg with the final 3 months. I have been on 20 mg for an additional three months and I have recently seen her. She told me to stop taking them cold turkey . . . I'm currently on day 5 of being cold turkey and it feels like my world has been turned upsidedown [sic]. I feel so out of it, almost as if there are clouds in my mind. I'm also experiencing brain zaps . . . I called her and told her this . . . [s]he basically told me my only option was to ride out the withdrawal symptoms. Honestly, I don't know what to do—I cannot feel this way

recommended nor acknowledged by Lilly and implies that there is currently no safe way to discontinue a twenty-milligram dose. In fact, it appears that the only way to avoid discontinuation symptoms associated with a twenty-milligram dose is to either resume the dose, as Lilly recommends,[210] or to resort to a non-medically approved method of tapering off the dose. Because Lilly does not acknowledge that patients attempting to taper are opening the capsules and slowly removing beads, it has not provided physicians with any studies documenting potentially adverse physical and or psychological effects associated with this tapering method. Given that the label specifically states that the capsules should not be opened, or their contents crushed,[211] it implies there may be potential adverse effects related to removing beads.

The effects of discontinuing a psychotropic medication have been thoroughly documented.[212] In order to address this significant issue, the FDA should require Lilly to both manufacture its capsules in smaller dosages (possibly 15 milligram, 10 milligram, 5 milligram, etc.) and provide physicians with detailed and complete tapering schedules. This would assist individuals experiencing discontinuation symptoms to safely taper the drug without opening the beads, a cumbersome and almost impossible task.

Scientific evidence, such as the JAD study noted above, reveals that Cymbalta is an antidepressant highly prone to discontinuation withdrawal symptoms.[213] Because of Lilly's blatant refusal to acknowledge the actual extent of individuals suffering from discontinuation symptoms—fostered by court decisions—and the FDA's lack of oversight regarding antidepressant tapering in general, combined with the previous failure of Cymbalta-related lawsuits primarily due to the learned intermediary doctrine, Cymbalta continues to be mass marketed. Physicians continue to mass-prescribe this drug,

anymore . . . I opened a 20mg capsule last night and divided the beads into two piles and took half. I am already feeling better than yesterday. . . I just got off the phone with my doctor . . . she advised me to go back onto 20mg which I don't want to do. I want to continue to count beads, because I eventually want nothing to do with this medication.").

210 *See* CYMBALTA LABEL, *supra* note 1111, at 8.

211 CYMBALTA LABEL, *supra* note 1111, at 9.

212 *See, e.g.*, Giovanni A. Fava, *Symptoms After Serotonin-Noradrenaline Reuptake Inhibitor Discontinuation: Systematic Review*, J. PSYCHOTHERAPY & PSYCHOSOMATICS (2018) (concluding studies "indicate that withdrawal symptoms may occur after discontinuation of any type of SNRI . . . withdrawal symptoms included a wide range of clinical manifestations (Table 1), regardless of whether gradual or abrupt discontinuations were implemented, and they were similar to those observed after discontinuation of SSRI").

213 *See* David Perahia et. al, *supra* note 125, at 207.

even though they are ignorant of, and ill-equipped, to treat its eventual discontinuation problem.

The learned intermediary doctrine is particularly inappropriate in Cymbalta withdrawal litigation. Its essential premise—that the manufacturer is immune from patient liability based on previous label warnings given to the physician—does not and should not apply regarding the duty to warn about Cymbalta's adverse withdrawal effects because physicians have not been properly warned of this drug's discontinuation effects. This unawareness is manifested in an inability to adequately treat these patients suffering from withdrawal symptoms. That is, the physicians are not truly "learned" or informed of Cymbalta's tapering requirements.[214]

There is an obvious disconnect between physician knowledge of Cymbalta's tapering requirements, so that they could inform their patients of its potential ramifications, and the knowledge that their patients are provided upon medication initiation. The negative ramifications of this problem are extensive and can potentially impact anyone who was prescribed Cymbalta. It is inherently dangerous for an individual to be "addicted" to a medication, in that they are compelled to either continue its use or misuse it just to avoid devastating withdrawal symptoms. Based on Cymbalta's short half-life and the dual severity and insidiousness of its documented discontinuation symptoms, a simple accidentally missed dosage, a pregnancy requiring the termination of its use,[215] or the loss of access to the medication due to insurance discontinuation or other reasons could potentially cause a patient to develop severe withdrawal effects, as has been documented in online patient forums.[216]

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214 *See, e.g.*, *User Reviews for Cymbalta Oral*, WEBMD, https://www.webmd.com/drugs/drugreview-91491-cymbalta?drugid=91491 (last visited Aug. 2, 2023) ("My Doctor said that Cymbalta is a very safe drug with very little side-effects; he didn't mention anything about the withdrawal side-effects (I'm not sure if he really even knew the full extent of the withdrawal symptoms). Now, in 2022, my Arthritis is under control, so I am happy to gradually wean off the Cymbalta. A couple of weeks into weaning off this medication, I was already going through hell, and I haven't even taken it for a long period like some of the poor people who have commented in the last few years. . . If I knew how bad the withdrawal side effects were, I would 'NEVER' have taken Cymbalta, I would have tried another drug for my RA."); *see also* Benedict Carey & Robert Gebeloff, *Many People Taking Antidepressants Discover They Cannot Quit*, N.Y. TIMES (Apr. 7, 2018), https://www.nytimes.com/2018/04/07/health/antidepressants-withdrawal-prozac-cymbalta.html.

215 *See* CYMBALTA LABEL, *supra* note 11, at 20 (stating that pregnant and nursing mothers should only use it if the potential benefit justifies the risk to the fetus or child).

216 *See* u/TheArtBug, REDDIT, https://www.reddit.com/r/IAmA/comments/pka0a/i_am_currently_going_through_w

An undercurrent of desperate individuals, compelled to inherently abuse the drug, and who are understandably disillusioned with both antidepressants and their prescribing physicians, has emerged as a result.[217] Simply put, this needs to end. Both the court and FDA should acknowledge that this drug is being prescribed to a subset of a population that is arguably already physically and mentally vulnerable—those suffering from depression and chronic pain. That these same users will be most likely be compelled to suffer prolonged physical withdrawal effects should they choose to taper its usage defies reason and should evoke a public outcry. Courts need to re-evaluate their handling of Cymbalta litigation, and the FDA should suspend future prescriptions of this drug until Lilly resolves the problems that continue to adversely affect the lives of thousands of vulnerable patients that Cymbalta was designed to improve.

ithdrawals_from/_(last visited Aug. 2, 2023) (describing symptoms resulting from accidentally missing a dosage due to insurance issues: "[m]y insurance company requires a prior authorization on this particular medication because it is incredibly expensive. Every 6 months the prescription runs out and my doctor must resend an authorization in. This particular time it snuck up on me (college, work, midterms, etc.) and I am now experiencing severe withdrawals . . .")).

217 *See, e.g.*, *Cymbalta Reviews*, EVERYDAY HEALTH, https://reviews.everydayhealth.com/drugs/cymbalta (last visited Aug. 2, 2023) ("Cymbalta was poison to me from day one. I took it for fibromyalgia. I ballooned in weight, even though I spent hrs [sic]vomiting every day, after I crawled up the stairs due to vertigo. I was constantly overheated, even if it was -30 degrees. I was on 60 mgs. I was in and out of the er [sic] and Dr's. I was treated as a drug seeker, even though I never took nor asked for pain meds. I was slowly dying. My mental health suffered as well. I tapered off of it very slowly, the withdrawal is horrible. 4 yrs [sic] later and the long-term effects leave me in agony every day. I have pulse pounding headaches 24/7, use a walker, have cognitive issues and my eyesight is deteriorating rapidly. I still have zaps from head to toe and many other issues. I'm 57 and may as well be 97. Poison! Should not be on the market, the long-term effects are just becoming known and they aren't good. Do your research. Dr's [sic] weren't even aware of what they were prescribing, or the kickbacks were so good they ignored the danger.").