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Hepatic Outcomes Among Adults Taking Duloxetine in a US Health Care Claims Database

FINAL Report
(Revised with Addendum Describing Post-hoc Review of Case Etiology)

Prepared for Eli Lilly

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Introduction to Revisions in this Report

Optum issued this revision on 16 August 2013 (with additional minor revisions on 06 May 2013) to record two modifications to previous versions of the report. First, we changed the interpretative comments in the Discussion sections of the Executive Summary and main text. The revised language was agreed on by scientists at Eli Lilly and Optum after ongoing discussion and is marked with italicized text. The second modification was the inclusion of an addendum that explains a *post hoc* re-review of selected cases of hepatic injury regarding the existence of alternate etiologies (cases with documented alternate etiologies were excluded from the primary case series per protocol). This addendum exists wholly in Appendix VII.

1. Executive Summary

Background

Duloxetine (Cymbalta®) is a serotonin-norepinephrine reuptake inhibitor (SNRI) manufactured and marketed by Eli Lilly and Company that is approved for the treatment of: major depressive disorders, generalized anxiety disorder, diabetic peripheral neuropathic pain, stress urinary incontinence (in European Union), fibromyalgia, and musculoskeletal pain (in some geographies). An earlier assessment performed using the Optum Research Database (formerly the Normative Health Information database) suggested higher incidence rates of hepatic injury of lesser severity among duloxetine users relative to propensity score-matched venlafaxine and nondepressed comparators, but not selective serotonin reuptake inhibitor (SSRI) comparators. For serious liver injury (such as hepatic failure and hepatic condition-related death), duloxetine did not differ from other antidepressants and showed an overall hepatic safety profile similar to that of the currently widely prescribed SSRIs, albeit with modest statistical power. We conducted a retrospective matched cohort study to evaluate the association of clinically significant hepatic injury and exposure to duloxetine, with specific definitional and methodological enhancements to focus on potential drug-related associations. These enhancements included expansion of the study accrual period, focus on cases of potentially drug-induced liver injury confirmed through review of medical records that occurred while exposed to a drug of interest or up to 15 days after last drug availability, and the exclusion of patients with baseline hepatic disorders.

Objectives

The primary study objective was to estimate the absolute and relative incidence of clinically significant hepatic events (hepatic-related death, liver failure, other clinically significant liver injury, hepatic-related death and liver failure combined, all clinically significant hepatic injury categories combined) among patients with depression who initiated duloxetine relative to each of 3 propensity score-matched comparison cohorts: patients with depression who initiated venlafaxine, patients with depression who initiated SSRIs, and patients with a diagnosis of depression who did not receive treatment. Secondary objectives addressed a range of potential alternative explanations for the observed results (e.g., residual confounding).

Methods

Eligible patients included adults (18+ years of age) who: initiated at least one study antidepressant (duloxetine, venlafaxine, or SSRI) between 01 August 2004 and 31 September 2010, or who had a diagnosis of depression without an antidepressant medication; were members of a commercial health plan that allows access to medical records for research purposes, with complete medical coverage and pharmacy benefits; met 12 months prior continuous enrollment criteria, and had a claim for diagnosis of depression during the 12-month baseline period. Initially-eligible patients were excluded if they had claims evidence of a diagnosis for hepatic conditions during the baseline period. Patients were identified and followed for the occurrence of clinically significant hepatic events during the study period of 01 August 2004 to 30 September 2010, with follow-up through 31 December 2010.

We matched duloxetine initiators to each of the 3 comparator cohorts (venlafaxine, SSRI, untreated) using a multivariable technique (propensity score analysis and matching) that can

achieve a high degree of balance between comparison groups. Propensity score matching produces groups that have similar patterns of presence or absence of a large number of key variables. Propensity scores were estimated by unconditional logistic regression analyses that incorporated potential demographic, medical, and healthcare utilization-related predictors of therapy (as captured in the claims data) as independent variables in the regression, and group status (duloxetine or comparator) as the dependent variable.

The primary outcomes were cases of clinically significant hepatic injury (hepatic-related death, liver failure, other clinically significant hepatic injury, hepatic-related death or liver failure combined, and all clinically significant hepatic categories combined). The secondary outcome was non-serious asymptomatic hepatic enzyme elevation. Potential cases were identified on the basis of diagnosis codes and/or procedure codes associated with inpatient or outpatient encounters in the claims data, and were verified through review of medical records.

Patients were followed separately for each of the hepatic outcomes, and for 2 composite outcomes (hepatic-related death or liver failure combined, and all clinically significant hepatic outcomes combined). Follow-up was restricted to 3 specified exposure windows: time from cohort entry through 15 days following discontinuation of treatment; time from cohort entry through 30 days following discontinuation of treatment; and time restricted to the 1st 90 days following cohort entry.

Incidence rates were calculated as the number of cases divided by the relevant person-time. We also estimated 95% confidence intervals (CIs) of the IRs for the duloxetine initiator and comparator cohorts. Rate ratios (RR) and associated 95% CIs were estimated for duloxetine initiators compared with each of the 3 propensity score-matched comparator cohorts. We performed an analysis using proportional hazards regression that estimated the relative hazard of study outcome events comparing duloxetine initiators with each of the 3 propensity score-matched comparator cohorts.

An additional analysis involving a case-control study nested within the cohort study was planned to further address potential confounding factors through supplementary data collection from medical records for all cases and controls. However, due to the small number of confirmed hepatic events observed in the study, it was infeasible to conduct a nested case control analysis with sufficient statistical power to be informative. In place of the case-control study, a descriptive tabulation of claims-based and chart-based characteristics was performed for the cases eligible to enter the planned analysis.

Results

From 01 August 2004 through 30 September 2010, a total of 30,844 duloxetine initiators, 29,243 venlafaxine initiators, 166,236 SSRI initiators, and 311,338 patients with pharmacologically untreated depression met initial eligibility criteria. Of these patients, 21,000 venlafaxine initiators, 28,479 SSRI initiators, and 22,714 patients with pharmacologically untreated depression were matched to an equal number of duloxetine initiators on the estimated propensity scores. The matching substantially improved balance within the matched study cohorts across a wide range of demographic factors and baseline claims-identified comorbidities, medications, and health services.

Across all the cohorts, 0 cases of hepatic-related death and 0 cases of liver failure were confirmed. For the outcome, other clinically significant hepatic injury, the IR among

duloxetine initiators was 0.7 per 1,000 person-years (95% CI: 0.2, 1.5) among those matched to venlafaxine compared to 0.0 per 1,000 person-years (95% CI: 0.0, 0.3) among venlafaxine initiators, and was 0.4 per 1,000 person-years (95% CI: 0.1, 1.0) among those matched to SSRI compared to 0.0 per 1,000 person-years (95% CI: 0.0, 0.3) among SSRI initiators. IRs were similar among duloxetine initiators and the matched untreated cohort (0.5 per 1,000 person-years [95% CI: 0.1, 1.3] among duloxetine initiators vs. 0.5 per 1,000 person-years [95% CI: 0.1, 1.5] among untreated comparators). Due to the absence of other clinically significant hepatic events in the venlafaxine and SSRI cohorts, RRs and 95% CIs estimated from Cox proportional hazards models were not available for the duloxetine-venlafaxine or duloxetine-SSRI comparisons; as such, incidence rate ratios (IRR) and exact 95% CIs were estimated for these comparisons. Varying the length of the exposure (through restriction to the 1st 90 days following cohort entry, or expansion to include time on therapy through 30 days following treatment discontinuation) produced substantively similar results as the primary analysis.

Discussion

Using data from the Optum Research Database, this propensity score-matched retrospective cohort study quantified the absolute and relative risk of clinically significant hepatic events associated with duloxetine initiation compared to initiators of venlafaxine or SSRI, and patients with depression who remained pharmacologically untreated. In our study, 0 confirmed cases of hepatic-related death or hepatic failure were identified in the duloxetine and the 3 comparator cohorts. The risk of other clinically significant hepatic outcomes in the duloxetine initiators was higher than among the propensity score-matched venlafaxine and SSRI cohorts, however these differences were not statistically significant. Overall, the number of confirmed clinically significant hepatic events was small, resulting in wide confidence limits.

This study has several limitations and considerations. As an observational study, the patients who receive duloxetine may differ from those who do not. If these differences are associated with risk for hepatic injury, then the comparison of duloxetine users to comparators may be confounded. While matching on propensity score achieved good balance among the cohorts for claims-based covariates included in the propensity score model, prevalence estimates of selected baseline characteristics derived from abstracted medical records in a random sample of patients suggests that some differences may remain (e.g., smoking, pain-syndromes). Risk for hepatotoxicity is noted in the precautions and warnings section of the product label for Cymbalta, and there is the potential that differential rates of diagnosis of hepatic injury may arise from differences in monitoring for the hepatic conditions in users of duloxetine relative to comparators.

The strengths of this study include the use of propensity score methods to rigorously account for potential confounding and further mitigation of potential confounding from the presence of pre-existing hepatic disease through restriction of the study population to patients without baseline hepatic disorders (on the basis of the health care claims) in order to focus on potential drug-related associations. In addition, this study focused on clinically significant potentially drug-induced liver injury events, validated by medical record review, occurring while exposed to a drug of interest for up to 15 days after last drug availability to evaluate the risk of idiosyncratic drug-induced liver injury at the typical time of its occurrence.

Using data from the Optum Research Database, this propensity score-matched retrospective cohort study quantified the absolute and relative risk of clinically significant hepatic events associated with duloxetine initiation compared to initiation of venlafaxine or SSRI, and patients with depression who were pharmacologically untreated. The statistical power of this study to evaluate relative risks was limited due to the rarity of these outcomes. We observed no cases of hepatic-related death or liver failure in the duloxetine or the 3 comparator cohorts, and the study is inconclusive regarding their association with duloxetine use. This study does offer insights into the association between duloxetine use and the incidence of other clinically significant hepatic events among a cohort of patients without evidence of pre-existing hepatic conditions. Our study identified a statistically non-significant elevated risk for other clinically significant hepatic outcomes in the duloxetine initiators compared with the propensity score-matched venlafaxine cohort and a lower statistically non-significant increase compared with the SSRI cohort in the protocol-specified and post-hoc analyses. These differences are not statistically significant and remain consistent with chance, and therefore an elevated risk cannot be ruled in or out. Similar rates of clinically significant hepatic outcomes were observed when comparing the duloxetine and untreated comparator cohorts. Overall, the number of confirmed clinically significant hepatic events was small, resulting in wide confidence limits.

2. Introduction

Duloxetine (Cymbalta®) is a serotonin-norepinephrine reuptake inhibitor (SNRI) manufactured and marketed by Eli Lilly and Company(1) that is approved for the treatment of:

- Major depressive disorders
- Generalized anxiety disorder
- Diabetic peripheral neuropathic pain
- Stress urinary incontinence (in European Union)
- Fibromyalgia
- Musculoskeletal pain (in some geographies)

Hepatic injury with a hepatocellular, cholestatic or mixed pattern has been reported rarely in association with duloxetine during the post-marketing period. Lilly previously contracted with OptumInsight Epidemiology (formerly i3 Drug Safety) to conduct Study FIJ-MC-B021 (Study B021), a pharmacoepidemiologic study to estimate the incidence rate of serious hepatic events among patients with depression who received duloxetine and in 6 comparison populations: depressed patients treated with one of 4 other antidepressants or antidepressant classes, depressed patients receiving no pharmacologic antidepressant treatment, and a population without a depression diagnosis.

Study B021, covering data from the first 2 years following duloxetine launch in the US, was designed to include all patients initiating an antidepressant of interest, including those with baseline hepatic risks and active disease; the study also considered all hepatic outcomes regardless of time since last exposure. The results of that study revealed that for hepatic injury of lesser severity such as elevated transaminases, duloxetine was associated with a higher incidence rate relative to the venlafaxine and nondepressed cohorts, but not relative to the SSRI cohort. However, for serious liver injury (such as hepatic failure and hepatic condition-related death), duloxetine did not differ from other antidepressants and showed an overall hepatic safety profile similar to that of the currently widely prescribed SSRIs, albeit with modest statistical power.

As part of Committee for Medicinal Products for Human Use (CHMP) feedback on the duloxetine Risk Management Plan 5, Lilly was requested to consider extending Study B021. This request was the basis for a meeting with the Rapporteur (May 2009), during which a number of updates to the protocol were discussed and agreed upon, including a greater sample size with a minimum of 5 years' worth of observational US data since duloxetine launch.

The current study is a follow-up study focusing specifically on clinically significant potentially drug-induced hepatic events, with specific definitional and methodological enhancements over Study B021 and an analytic expansion to include a nested case-control analysis. This follow-up study included the following:

- Accrual of additional patients and follow-up of eligible patients through December 2010

- Focus on concrete diagnoses of potentially drug-induced liver injury, i.e., all hepatic events, properly validated against the medical record, occurring while exposed to a drug of interest or up to 15 days after last drug availability

- Exclusion of patients with baseline hepatic disorders, in order to focus on potential drug-related associations. This exclusion mitigated potential confounding from the presence of pre-existing hepatic disease.

- Extension of the sensitivity analysis for unmeasured confounding by increasing the number of patients whose medical records were evaluated in detail.

- Inclusion of clinically significant variables that may have remained unbalanced across cohorts following propensity-score matching in the Cox regression models

- Addition of a nested case-control analysis conducted within the propensity score matched cohorts, augmented with data ascertained from review of medical records for the cases and all controls as a means to further address potential confounding

3. Objectives

The primary study objective was to estimate the absolute and relative incidence of clinically significant hepatic events among patients with depression who initiated duloxetine relative to each of the following propensity score-matched comparison cohorts: patients with depression who initiated venlafaxine, patients with depression who initiated SSRIs, and patients with a diagnosis of depression who did not receive treatment. The outcomes of interest were:

- Hepatic-related death
- Liver failure
- Other clinically significant liver injury
- Hepatic-related death and liver failure combined
- All clinically significant hepatic categories combined (hepatic-related death, liver failure, and other clinically significant liver injury)

The secondary objectives were:

- To estimate the absolute and relative incidence of non-serious, asymptomatic hepatic enzyme elevations among patients with depression who initiated duloxetine and in the following 3 comparison cohorts: patients with depression who initiated venlafaxine, patients with depression who initiated SSRIs, and patients with a diagnosis of depression who did not receive treatment

- To estimate absolute and relative incidence of the outcome categories as specified in the primary objective occurring within 90 days from first drug exposure

- To estimate the association between all clinically significant hepatic events combined (hepatic-related death, liver failure, or other clinically significant liver injury) and duloxetine exposure within a nested case-control study that would account for potential confounding variables derived from medical records

- To conduct a sensitivity analysis for unmeasured confounding of the relative occurrence of all clinically significant hepatic events combined (hepatic-related death, liver failure, or other clinically significant liver injury) based on medical record review of sampled charts from each of the 4 analytic cohorts: patients with depression who initiated either duloxetine, venlafaxine, SSRIs, and patients with a diagnosis of depression who did not receive pharmacologic treatment

4. Methods

4.1. Overview of Study Design

We conducted a retrospective cohort study of individuals with depression who initiated duloxetine and contemporaneous comparators (depressed initiators of venlafaxine or SSRIs, and people with a depression diagnosis who did not receive antidepressant medication) in a large US health care claims database in order to estimate and compare the incidence of clinically significant hepatic injury. Individuals were identified and followed for the occurrence of clinically significant hepatic events during the study period of 01 August 2004 to 30 September 2010, with follow-up through 31 December 2010. The study included primary comparisons between duloxetine initiators and each of the comparator cohorts. Secondary analyses addressed a range of potential alternative explanations for the observed results (e.g., residual confounding). Propensity score matching was performed to address numerous potential confounding variables.

The cohort study consisted of as-matched analyses, including an analysis that censored follow-up at 90 days following drug initiation to evaluate the risk of idiosyncratic drug-induced liver injury at the typical time of its occurrence. In addition, a sensitivity analysis was performed to assess the impact of potential unmeasured confounding on the effect estimates.

An additional analysis involving a case-control study nested within the cohort study design was planned to further address potential confounding factors through supplementary data collection from medical records for all cases and controls. However, due to the small number of confirmed clinically significant hepatic events observed in the study, it was infeasible to conduct a nested case control study with sufficient statistical power to be informative. In place of the case-control study, a descriptive tabulation of claims-based and chart-based characteristics was performed for the cases eligible to enter the planned analysis.

4.2. Institutional Review Board / Privacy Board Approvals

This observational study was designed as an analysis of the insurance claims data from a large US population with health insurance. There was no active enrollment or active follow-up of patients, and no data were directly collected from patients. To comply with Health Insurance Portability and Accountability Act (HIPAA) Privacy Regulations, OptumInsight, Epidemiology Division obtained approval from the New England Institutional Review Board (NEIRB) and a waiver of authorization approval from the Privacy Board of the NEIRB, as this study involves the use of protected health information (PHI) in order to access medical records for abstraction and to link to death certificate data using a National Death Index (NDI) search. OptumInsight study investigators analyzed the data, and no individually identifiable patient information was provided to Lilly.

4.3. Data Source

We derived the study cohorts from a large, geographically diverse population of health insurance enrollees included in the proprietary Optum Research Database (ORD, formerly Normative Health Information (NHI) database). The ORD contains enrollment data, medical claims, and pharmacy claims dating back to 1993. Enrollment in 2010 included approximately 12 million members. The data undergo regular audits and quality control procedures by the insurer and are updated monthly. The insured population from which we draw the data comprises approximately 3 to 4% of the US population.

The records of the ORD are organized into a medical file containing claims from providers and facilities, a pharmacy file with outpatient pharmacy dispensing records, and an enrollment file that provides demographic data and dates of insurance eligibility for persons included in the database. An encrypted identifier links all of these files at the individual level. Data are only re-identified following approval by an appropriate institutional review board.

4.4. Study Population

Adults (18 years of age or older) in the ORD who met the following criteria were eligible to enter the study:

- Valid record of age and gender
- Member of a commercial health insurance plan that allows access to medical records for research purposes, with complete medical coverage and pharmacy benefits
- Initiated at least one study antidepressant (duloxetine, venlafaxine, or SSRI) between 01 August 2004 and 30 September 2010, or had a diagnosis of depression between 01 August 2004 and 30 September 2010 without an antidepressant medication
- Continuously enrolled for at least 12 months prior to initiation of the study drug
- Had no prior dispensing of the initiating drug during the baseline period
- Had a claim for diagnosis of depression during the baseline period

From this pool of initially-eligible individuals, individuals with a claim for hepatic conditions occurring during the baseline period were excluded. We additionally excluded patients from the Louisiana and Mississippi regions whose index dates occurred prior to 01 September 2006, as the availability of medical records during this period was likely to be affected by disruptions following Hurricane Katrina. For patients who were eligible for 2 or more initiator cohorts, cohort assignment was based on the earliest study drug initiated during the study period. If a patient was an initiator of more than one study drug on the same date, cohort assignment was based on the following order of priority: (1) if one of the initiated drugs was duloxetine, the patient was assigned to the duloxetine cohort; or (2) if none of the initiated drugs was duloxetine, the patient was randomly assigned to one of the initiated study drug cohorts (i.e., venlafaxine or SSRI).

Patients were eligible for cohort entry starting on 01 August 2004, with follow-up as available through 31 December 2010. As determined following review of the Baseline Assessment Report (dated 03 August 2011) by Eli Lilly and OptumInsight, Epidemiology

Division, a baseline period of 12 months was used to identify the study cohorts for this study.*

It should be noted that it was not possible to map to specific thresholds delineated in the study protocol for certain lab-related baseline study exclusion criteria on the basis of the claims data alone. Per agreement with Lilly, we used available ICD-9 codes as appropriate to serve as proxies to capture these exclusions. A listing of the claims-based codes used to apply the study eligibility criteria is provided in Appendix I.

4.4.1. Initiators of Duloxetine

Patients who met study eligibility criteria described in Section 4.4 and who had at least one pharmacy claim for duloxetine between 01 August 2004 and 30 September 2010 were eligible to enter the cohort of duloxetine users. The date of cohort eligibility (index date) was set as the date of the first dispensing of duloxetine within the study timeframe, with no dispensing of duloxetine during the 12 months prior to the index date and with a diagnosis of depression during the 12-month baseline period (including the index date).

4.4.2. Initiators of Venlafaxine or SSRIs

In a similar fashion, we identified cohorts of patients who initiated therapy with a comparison drug (venlafaxine or SSRI). Eligible patients with a dispensing for a comparison antidepressant between 01 August 2004 and 30 September 2010 without a dispensing for the same drug class (venlafaxine or SSRI) in the 12 months prior to their index date and who met the study eligibility criteria were eligible to enter these cohorts.

4.4.3. Cohort of Patients with Depression who were Not Receiving Pharmacologic Treatment

Eligible patients with a claim for diagnosis of depression between 01 August 2004 and 30 September 2010 but without any pharmacological treatment for depression in the 12 months prior to or including their index date, and who met the study eligibility criteria described in Section 4.4 were included in this cohort. The date of cohort eligibility was a randomly chosen outpatient physician office visit with a claim for depression during the study period.

* As a preparatory step to conducting this safety study, OptumInsight performed an assessment of the impact of use of baseline periods of varying lengths (6 months, 9 months, or 12 months) on sample size/power and the capture of important study exclusion and confounder information. Lengthening of the baseline period from 6 months to 12 months was associated with an approximately 23% reduction in the size of the duloxetine population. Use of a shorter baseline period, however, may have also led to underascertainment of baseline hepatic exclusions, though the amount of relative underascertainment appeared to be consistent across the study cohorts. Following review of the Baseline Assessment Report (dated 03 August 2011), it was determined by Eli Lilly that removal of sources of heterogeneity through restriction of the study population (i.e., to assess the risks associated with duloxetine use among a population without pre-existing hepatic conditions) and enhanced capture of important confounder information through the use of the 12-month baseline period was the preferred approach. As such, a baseline period of 12 months was applied to identify the study cohorts for the main safety study.

4.5. Potential Confounders / Covariates

We identified potential confounders using a priori knowledge and an empirical approach, all derived from diagnosis, procedure, and medication codes associated with the claims data from the ORD from each subject's 12-month baseline period.

4.5.1. A Priori-Defined Covariates

Using claims and membership data, a wide range of baseline covariates that may be associated with the decision to begin therapy with duloxetine were ascertained during the 12 months prior to and including the index date, including but not limited to the following:

- Demographics
  - Age (at index date)
  - Gender
  - Region of the country
  - Calendar time

- Hepatic Risks (informed by criteria in Chalasani 2008(2) and de Abajo 2004(3))
  - Hypercholesterolemia/dyslipidemia
  - Hyperglycemia
  - Albuminuria
  - Diabetes mellitus
  - Cytomegalovirus (CMV) infection
  - Epstein-Barr virus (EBV) infection
  - Claims indicating liver ultrasound scans
  - Obesity
  - Nonsteroidal anti-inflammatory drug (NSAID) use (with diclofenac specifically identified as a subset)
  - Other known or suspected hepatotoxic drugs (isoniazid, phenytoin, valproic acid, nitrofurantoin, propylthiouracil, rifampin, fluconazole, chlorpromazine, interferon beta, amiodarone, statins)
  - Naloxone, naltrexone, disulfiram, acamprosate (as potential markers for alcohol use)

- History of
  - Seizure
  - Hypertension
  - Stroke
  - Myocardial infarction (MI)
  - Angina
  - Suicide attempts

- Use of specified health services (number of unique diagnoses, number of different drugs dispensed, use of intensive care and critical care services, prior hospitalization, number of health care visits to a psychiatrist or psychologist, number of visits to other physicians, number of emergency department visits, health care costs)

While the protocol stated that laboratory-related measures were a priori-specified covariates, it was not possible to map to specific laboratory thresholds on the basis of the claims data alone. As described in Section 4.4, these laboratory-related measures were

also included as part of the study exclusion criteria, and per agreement with Lilly, we used available ICD-9 codes as proxies for exclusion variables. As a result of applying the ICD-9 codes as study exclusion criteria, the prevalence of these laboratory-based characteristics within the study cohorts was zero; as such, the protocol-specified laboratory-related baseline covariates were not used in propensity score modeling.

4.5.2. Empirical Covariates

We empirically identified additional baseline covariates by listing the 100 most frequent drug classes dispensed to the duloxetine initiator cohort during the baseline period, along with the most frequent diagnoses (at the 3-digit International Classification of Diseases, 9th edition (ICD-9) level) and procedures (based on Current Procedural Terminology (CPT) codes).

4.6. Propensity Score Development and Matching

A priori and empirically-identified baseline characteristics among the initial pool of duloxetine initiators and each of the comparator cohorts were assessed using a multivariable technique to estimate each patient's predicted probability of initiating duloxetine conditional on the observed covariates (propensity score).(4-6) The propensity score is each person's predicted probability of duloxetine initiation, given membership in one of the cohorts and his or her baseline characteristics. Propensity score analysis is especially helpful in situations with few outcomes as it summarizes covariate information in a single variable by modeling the more common exposure.(7)

Variables for inclusion in the propensity models were chosen based on a priori considerations of clinical plausibility, prevalence of the variable, statistical significance of the variable, and discrimination between duloxetine initiators and non-initiators (area under the receiver operating characteristic curve).

The propensity score was estimated by unconditional logistic regression analyses that incorporated selected potential predictors of therapy as independent variables in the regression model and group status (duloxetine initiator or comparator) as the outcome. The following variables were forced into the propensity score model:

- Age group
- Sex
- Region
- Months of preceding continuous health plan membership
- Days between starting date of each calendar block and individual index date
- Depressive disorder, not elsewhere classified
- Episodic mood disorders (diagnoses with depressive component and diagnoses without depressive component included separately)
- Adjustment reaction
- Anxiety, dissociative and somatoform disorders
- Anticonvulsant use
- Fluconazole use
- Number of visits to a psychiatrist/psychologist
- Number of visits to other physicians
- Number of unique ICD-9 diagnosis codes

- Number of different drugs dispensed
- Number of emergency room visits
- Use of intensive care and critical care services
- Any hospitalization
- Number of psychiatric hospitalizations
- Number of liver scans
- Any liver enzyme test
- Any test for bilirubin
- Total costs
- Total patient pharmacy costs (i.e., out-of-pocket pharmacy costs) and non-patient pharmacy costs (i.e., health plan paid pharmacy costs) (included separately)
- Total facility costs
- Prescriber specialty (psychiatrist/psychologist, other)

We applied a stepwise selection of the remaining a priori and empirical variables to improve the discrimination of the propensity score model. The stepwise criteria were a p-value of 0.2 for model entry and 0.3 for retaining variables. Each person's predicted probability of initiating duloxetine relative to not initiating duloxetine use was their propensity score.

To account for potential calendar time trends in duloxetine prescribing, the propensity score models were developed within each of 6 calendar blocks of time (01 August 2004 – 30 June 2005; 01 July 2005 – 30 June 2006; 01 July 2006 – 30 June 2007; 01 July 2007 – 30 June 2008; 01 July 2008 – 30 June 2009; 01 July 2009 – 30 September 2010).

Duloxetine initiators were then matched to each of the comparison cohorts on the estimated propensity score of receiving duloxetine treatment. Matching was performed using a standard matching algorithm.(8) The final comparison cohorts were selected as a 1:1 match for each duloxetine patient, with the comparison cohort member selected at random from all potential comparators who matched sufficiently closely to the duloxetine patient. The actual number of duloxetine initiators matched to each of the other comparison cohorts differed as a function of the amount of overlap in the propensity score distributions of the duloxetine cohort and comparison groups.

4.7. Chart Abstraction for Confounding Sensitivity Analysis

Insurance claims might incompletely capture covariates or exclusions, including those related to hepatic injury (e.g., hepatic enzyme elevations documented in laboratory test results). Baseline comparability of the propensity score-matched cohorts on the basis of medical record review of potential confounders, which were unavailable from insurance claims, was therefore assessed to elucidate the magnitude of residual confounding that might be present in claims-based analyses.

We sampled patients at random from each of the 4 cohorts and sought medical records from physician office visits around the time of cohort-defining drug initiation (or analogous index date for the pharmacologically untreated cohort). Information abstracted from the medical record included patient history, such as past hepatitis, alcohol use, etc., and other aspects of patient status, such as recent laboratory tests (especially liver function tests), from the 12-month baseline period that might not be ascertained from insurance claims. To optimize the recording and assessment of the risk factors of interest, OptumInsight preferentially selected medical records from a specialist (e.g., psychiatrist) where feasible.

For this assessment, a goal of obtaining medical records for 200 patients per cohort was specified in the study protocol. Based on chart retrieval rates of 60%-69% observed for a similar assessment in the previous safety study of duloxetine conducted by OptumInsight, we assumed an approximately 64% success for chart retrieval and randomly sampled 315 patients from each of the study cohorts for a total of 1,260 charts.

4.8. Outcome Definition and Assessment

The outcomes of interest were the occurrence of incident cases of clinically significant hepatic injury. Potential cases were identified by a search of the claims database. This yielded a pool of potential claims-based cases, which were further screened by a review of the chronological listings of all claims for each person (profile review), and then confirmed via medical record review.

4.8.1. Claims-Based Identification of Potential Outcomes of Interest

For each patient, potential clinically significant hepatic events were identified on the basis of ICD-9 diagnosis codes or procedure codes resulting in inpatient or outpatient encounters through an initial screening of the claims data (see Appendix II for the list of claims codes used to identify potential hepatic events). Each potential case was assigned a potential outcome date corresponding to the date of the diagnosis or procedure that represented the most severe outcome coded on a claim during an episode of care (e.g., a date associated with a claim for hepatic failure was preferentially selected over the claim date for elevated liver transaminases within an episode of care). Multiple associated symptoms, features at presentation, or clinical entities in the pathway within an episode of care were not considered potential outcomes themselves. For example, if a patient had a claim for a diagnosis of hepatitis and a few days later there was also a claim for elevated liver transaminases, the 2 codes still constituted one potential event/outcome of hepatitis. Similarly, outcome events representing a diagnostic cluster (e.g., hepatic failure including encephalopathy, coma, coagulopathies) were grouped as a single outcome. Operationally, diagnosis and procedure codes that occurred within 30 days following a previous eligible claims code were considered part of the same episode of care as the previous encounter.

For the primary study analyses, potential events were required to have occurred while the patient was exposed or within 15 days of last exposure to the antidepressant drug of interest. For patients in the untreated depression cohort, each patient was assigned a proxy "treatment discontinuation" date corresponding to the date of treatment discontinuation of their matched duloxetine comparator.

4.8.2. Profile Review: Identification of Medical Records for Abstraction

A review of a chronological listing of claims data (claims profile) of the potential case of clinically significant hepatic injury was performed by an independent clinical consultant. Profile review was done prior to medical record abstraction to determine the most likely medical site for abstraction. An independent clinician reviewed detailed chronological listings of claims for services and treatments from the period prior to the claims-based potential outcome date and extending for an additional period following the potential outcome date, and identified the provider claim associated with the diagnosis or procedure representing the most severe outcome coded on a claim during the episode of care and most likely to provide relevant information for adjudication.

4.8.3. Medical Record Abstraction

Medical record abstraction of claims-based hepatic events was undertaken to adjudicate clinically significant hepatic injury case status as selected through profile review. OptumInsight trained abstractors in the collection of information from medical records, using a standardized instrument. The trained abstractors then contacted the place of the patient's care corresponding to the outcome event and requested relevant information from the medical record. Abstracted medical records were blinded to antidepressant drug exposure and provided to expert clinicians for outcome adjudication. For some potential cases, medical records were not available for abstraction and adjudication (e.g., provider refusal to provide records, unavailable due to administrative reasons); these cases were classified as non-cases for the study analyses.

4.8.4. Adjudication of Outcomes

Patient information drawn from medical records for each potential case was independently reviewed by 2 hepatologists. The clinical consultants adjudicated case status and identified the most severe hepatic event confirmed for the episode of care, determined whether an alternate etiology for a confirmed hepatic event was explicitly identified, and identified the date of diagnosis based on the clinical data in the medical record.

The standard case definitions for hepatic injury used in this study were informed by criteria in Chalasani 2008(2) and de Abajo 2004(3), and are provided below:

- All fatalities where the underlying or any of the contributory causes of death in the death certificate was a hepatic event, or in the absence of a death certificate, where there is evidence of an underlying hepatic event in relation to the death. This was based on a linkage to the NDI along with health insurance claims. The NDI is an electronic repository of death records based on state vital statistics, with data available on deaths at the time of this study. Death data from NDI were available for subjects who died prior to December 31, 2010, the end of the study period.

  To determine vital status for subjects who disenrolled from the health plan and identify deaths related to hepatic conditions during the study period, an NDI search was performed. We searched the NDI for all patients in the cohorts who disenrolled from the health plan during the study period without subsequent reenrollment and those who died during follow-up. We retained deaths with a high probability of a true match, according to NDI algorithms.(9) Among all defined death cases from the NDI data, deaths with underlying disease as hepatic events were determined based on the presence of the hepatic-related ICD-10 codes (see Appendix II-B) in any of the NDI search results for cause of death (ICD-10), entity-axis conditions, or record-axis conditions.[†] Cases of

  [†] As described in the National Death Index Users Guide, with regard to entity-axis conditions: "The original scheme for coding conditions contained on the death certificate was designed with two objectives in mind. First, to facilitate etiological studies of the relationships among conditions, it was necessary to reflect accurately in coded form each condition and its location on the certification in the exact manner given by the certifier. Secondly, the codification needed to be carried out in a manner by which the underlying cause of death could be assigned through computer applications. The approach was to suspend the linkage provisions of ICD for the purpose of condition coding and to code each entity with minimum regard to other conditions present on the certification. This general approach is hereafter called entity coding." With regard to

death with an underlying hepatic event and an identified date of death between cohort entry and the end of the current therapy (plus 15- or 30-day extension) period were included in the analysis, with the NDI date of death set as their case date.

- Liver failure, not resulting in death, defined by the following conditions, only in the absence of explicit identification of an alternative etiology (e.g., acute or chronic viral hepatitis, autoimmune hepatitis, alcoholic hepatitis, acute congestive hepatopathy, chronic liver disease, malignant neoplasm, cholecystitis, alcoholism, alcoholic cirrhosis, congestive heart failure, hemochromatosis, Wilson Disease, Budd-Chiari syndrome, or other well-defined pathology affecting the liver, etc).
    - Hepatic failure
    - Fulminant hepatitis (non-infectious)
    - Hepatic encephalopathy
    - Hepatic coma
    - Liver transplant or renal and liver transplant
    - When explicitly associated with acute liver disease:
    - Acquired coagulation factor V deficiency due to liver disease (factor V level <30%)
    - Acquired hypoprothrombinemia
    - International normalized ratio (INR) >1.5, prothrombin time >16 seconds
- Other clinically significant liver injury in the absence of explicit identification of an alternative etiology, as defined by:
    - ALT > 500 IU/ml or ≥ 10x ULN, with any of the following:
        - Incident toxic hepatitis
        - Incident acute hepatitis
        - Incident hepatic necrosis
        - Incident toxic liver disease
        - Incident toxic hepatitis
    - ALT > 250 IU/mL or > 5x ULN with any of the following:
        - Nausea/vomiting
        - Abdominal pain
        - Weakness
        - Fatigue

record-axis conditions, as described in the National Death Index Users Guide: “The Division of Vital Statistics creates from the original set of entity codes a new code set called record-axis multiple cause data. Essentially, the axis of classification is converted from an entity basis to a record (or person) basis. The record-axis codes are assigned in terms of the set of codes that best describe the overall medical certification portion of the death certificate.”

- ALT > 3x ULN with any of the following:
  - Jaundice/icterus when alkaline phosphatase < 2x ULN
  - Ascites
  - A combination of ALT > 3x ULN with Total Bilirubin > 2x ULN (Hy's rule) and alkaline phosphatase < 2x ULN

- Non-serious hepatic enzyme elevation in the absence of explicit identification of an alternative etiology, as defined by:
  - A combination of all the following, provided patient is asymptomatic:
    - 5x ULN < ALT < 10x ULN
    - T bilirubin < 2x ULN
    - Any ICD-9 hepatic code, validated by medical record review, when no symptoms were associated with it and in absence of any codes for hepatic failure or serious hepatic injury (hepatic coma, jaundice, ascites, etc.)

The outcome entity of interest upon medical chart review and adjudication was the most severe diagnosis documented during an episode of care, however many visits it may have entailed. Multiple associated symptoms, features at presentation, or clinical entities in the pathway were not considered outcomes themselves. Similarly, events representing a diagnostic cluster (e.g., hepatic failure including encephalopathy, coma, coagulopathies) were grouped as a single outcome.

Adjudicators reviewed and approved the case definitions and suggested approach for managing hepatic outcome validation at an initial meeting prior to commencing with the adjudication (see Appendix IV for the adjudication algorithm). The adjudicators retained final responsibility for the case definition and cases not meeting the criteria were adjudicated by reviewers using clinical judgment.

Discrepancies were resolved by consensus, with the OptumInsight Epidemiology senior scientist serving as tiebreaker if needed. This process aimed to balance the sensitivity of the initial case ascertainment through the broad initial screen with specificity through application of a standardized case definition. Following the final consensus meeting, the 2 reviewers had 100% agreement regarding classification as case or non-case for potential outcome events and regarding whether an alternate etiology was identified. For cases where the 2 reviewers indicated case dates that fell within 5 days of one another, the reviewers agreed that these cases would be considered concordant and the earlier case date would be selected for the analysis. Following application of this 5-day rule, the 2 reviewers had 100% agreement regarding determination of the case date for each confirmed event.

4.9. Analysis

In the analyses, we estimated the effect of duloxetine exposure compared to each of 3 comparator cohorts on the risk of clinically significant hepatic injury separately (hepatic-related death, liver failure, other clinically significant hepatic injury), and for 2 composite outcomes (the composite occurrence of hepatic-related death or liver failure combined, the composite occurrence of hepatic-related death, liver failure, or other clinically significant

hepatic injury combined). The data were analyzed as an as-matched analysis, based on the original exposure classifications at the time of cohort entry.

4.9.1. Follow-up

Patients in the matched cohorts were followed from the day after the index date until the earliest of discontinuation of the study drug (or, for the non-treated comparator cohort, initiation of a study drug), disenrollment from the health plan, occurrence of the first confirmed hepatic outcome event, or the end of the study (31 December 2010).

Patients were followed for the occurrence of each outcome separately (hepatic-related death, liver failure, other clinically significant hepatic injury, non-serious hepatic enzyme elevation). As the presence of an ICD-9 diagnosis code in the claims data is not proof positive that a condition is present, it is possible that a claim code for hepatic failure or hepatic-related death may not meet the protocol-specified definitions of either of these two categories but could meet the definition of another clinically significant hepatic outcome. Therefore, claims codes indicative of hepatic-related death, hepatic failure, or other clinically significant hepatic injury were used to screen for potential other clinically significant hepatic injury events. Similarly, confirmation of non-serious hepatic enzyme elevation relied on meeting specified lab measure thresholds and the presence of any ICD-9 hepatic code validated through medical record review without associated symptoms and in absence of any codes for hepatic failure or serious hepatic injury. It was considered possible that a claim code for clinically significant hepatic injury may not meet the protocol-specified definitions of any of the 3 clinically significant hepatic injury categories but could meet the definition for non-serious hepatic enzyme elevation. Therefore, claims codes indicative of hepatic-related death, hepatic failure, or other clinically significant hepatic injury were used to screen for potential non-serious hepatic enzyme elevations. For individuals with more than one claims-identified hepatic event, the first claims-identified event was retained for the analysis of the other clinically significant hepatic injury and the non-serious hepatic enzyme elevation outcome categories. Similarly, for the composite case definitions (hepatic-related death or liver hepatic failure combined; all clinically significant hepatic categories combined), such patients contributed only the case and corresponding person-time associated with the first claims-identified event. Patients for whom the first claims-identified event was not confirmed via medical record review were censored on the date of the claims-identified event.

Each study drug exposure during follow-up was characterized on the basis of recorded pharmacy dispensings, including date of dispensing and amount supplied. For the purposes of assessing the effect of current therapy on risk of clinically significant hepatic injury, three exposure windows were defined:

- Current therapy plus 15-day extension. The primary definition for current exposure was the time extending from cohort entry until the 15th day following the end of continuous antidepressant supply, consistent with consensus criteria for acute liver injury from the Roussel Uclaf Causality Assessment Method (RUCAM).(10) Follow-up for each person was classified according to current use of each of the study drugs, allowing for apparent gaps in therapy of up to 15 days (days supplied plus an additional 15 days). In a scenario where a continued antidepressant supply period was followed by a greater than 15-day gap until the subsequent dispensing, follow-up was censored after the 15th day following end of supply. This follow-up definition ensured that all study outcomes

occurring during or within 15 days of the end of exposure to the initiated antidepressant (current exposure person-time to a study antidepressant) were identified.

- Current therapy (15-day extension) restricted to first 90 days following cohort entry. To address the timing of duloxetine exposure relative to hepatic events, we conducted an additional analysis of incidence rates and relative hazards for person-time and outcomes occurring within 90 days from first exposure.

- Current therapy plus 30-day extension. As a sensitivity analysis, current exposure was defined as extending from cohort entry until the 30th day following the end of the continuous antidepressant supply to test the robustness of the study results with respect to the censoring after 15 days following discontinuation of duloxetine or comparison drugs.

For the depressed untreated patients, we utilized the follow-up durations among their duloxetine initiators to inform the length of follow-up. Among them, follow-up extending from the previously defined cohort entry date through censoring was considered unexposed to antidepressants.

Patients eligible for inclusion in the study who dropped out during follow-up were characterized on the aggregate, by cohort. In addition, a tabulation of baseline covariates was created to describe the characteristics of people who dropped out from follow-up, by cohort, within the first 90-day follow-up window. These tabulations were intended to inform inference about bias potentially introduced by differential loss to follow-up.

4.9.2. Baseline Descriptive Analyses

Baseline characteristics, including demographics, medical history, and prescription drug history identified on the basis of claims comparing initiators of duloxetine, venlafaxine, SSRIs, and patients with depression who did not receive pharmacologic treatment were tabulated for the cohorts prior to matching, within the matched cohorts, and for duloxetine initiators who remained unmatched. Frequencies and proportions are presented for categorical variables. Means and standard deviations are presented for continuous variables.

To assess whether potential imbalances remained after propensity score matching, we calculated the absolute standardized differences for covariates included in the propensity score model (difference between the 2 mean values divided by the standard deviation).(11, 12)

4.9.3. Cohort Study

4.9.3.1. As-Matched Analysis

The as-matched analysis was based on data from the 3 pairs of propensity score-matched cohorts (duloxetine vs. venlafaxine, duloxetine vs. SSRI, and duloxetine vs. untreated) and involved estimating the IRs per 1,000 person-years for clinically significant hepatic injury as the number of incident events divided by the total person-time. Exact Poisson 95% confidence intervals (CIs) for the IRs were calculated.

Kaplan-Meier plots were generated to depict the unadjusted cumulative probability of event-free time among the propensity score-matched cohorts, and Cox regression models were fit to calculate crude and adjusted relative hazard and 95% CIs among the propensity score-matched cohorts. Diagnostics were conducted to assess proportionality assumptions for the Cox regression models in this analysis.

For adjusted analyses, variables representing demographic characteristics and hepatic risk factors were evaluated for inclusion in outcome models, as feasible given the number of observed outcomes.(13) In addition, other potential confounders that had an absolute standardized difference >0.1 between the duloxetine cohort and the relevant comparator after propensity score matching were evaluated for a confounding effect through their addition into the Cox regression models, with the intent of retaining variables that produced a greater than 10% change in the hazard ratio of the duloxetine effect as feasible given the number of observed outcomes.

The modeling constraint of approximately one covariate per 10 outcomes in a logistic regression model was used.(13) The rarity and distribution of the confirmed study outcomes across the study cohorts precluded simultaneous adjustment for covariates beyond the primary study drug exposure variables and the performance of diagnostics to assess proportionality assumptions for the Cox regression models in the analysis. Given the small number of confirmed study outcomes, incidence rate ratios (IRR) and exact 95% CIs were estimated, in addition to performing the protocol-specified Cox proportional hazards regression.

4.9.3.2. Cohort Sensitivity Analysis for Unmeasured Confounding

To assess the potential for spurious associations between duloxetine and hepatic outcomes categories, we conducted an array sensitivity analysis(14) anchored on the observed prevalence and medical record-derived unadjusted odds ratios of associations between duloxetine and each imbalanced potential unmeasured confounder and the outcome, all clinically significant hepatic categories combined. The range of prevalences of potential confounding variables for these analyses were based on medical records data from the randomly selected subset of patients from each of the matched comparison cohorts described in Section 4.7. The sensitivity analyses define the magnitude of potential spurious effects on observed study associations potentially accounted for by an unmeasured confounder across a range of values for this potential unmeasured confounder.

The potential identification of baseline exclusions among the baseline medical records reviewed allowed for a sensitivity analysis with respect to the effect of inclusion of cohort members who should have been excluded. In the present study, the magnitude of residual confounding due to unmeasured confounders is assessed using data on medical record-confirmed baseline characteristics, including prevalence (P_C) and the association between these factors and exposure status (OR_{EC}), from among the randomly sampled duloxetine initiators and comparators. Since these approaches are based on binary confounding variables, continuous variables as confounders were evaluated across a range of cut-points. For all the analyses, the prevalence of duloxetine (P_E) is set to be 50% by design due to the 1:1 matching of duloxetine and comparator cohorts.

4.9.4. Nested Case Control Study

To address additional potential unmeasured confounding, we had planned to conduct a nested case-control study within the matched, treated cohorts only. This nested case-control study would include as cases all confirmed clinically significant hepatic events occurring within the exposed study cohorts, and would draw patients with appendectomy as concurrent controls from the at-risk person-time within the pool of treated study participants. The choice of appendectomy/appendicitis as controls was based on it being a condition that is likely unrelated to hepatic injuries but with similar levels of detail with respect to patient medical history. Appendectomy/appendicitis would represent an almost random event occurring within the study cohorts (few known risk factors). In addition, in order for the controls to have medical records with similar levels of covariate details to the cases, we proposed to sample the controls from cohort members with frequency matching with respect to hospitalization or outpatient visits. Since it might be possible for a case to be only seen in the outpatient setting and the aim is to have a similar covariate ascertainment, we proposed that the records for a similar number of controls be chosen from outpatient settings, likely appendectomy follow-up visits.

Cases and controls would be assessed for baseline exclusions, characterized based on baseline insurance claims, and further characterized using additional data obtained from the medical records used to confirm the hepatic outcomes. Cases and controls with any medical record-based evidence of an exclusion condition would be excluded from the case-control analysis. In order for the controls to have medical records with similar levels of covariate details to the cases, the protocol proposed to sample the controls from cohort members with frequency matching up to a 4:1 control-to-case ratio with respect to setting of the encounter (hospitalization or outpatient visit) and within blocks of calendar time, with the aim of achieving a similar level of covariate ascertainment. Conditional logistic regression was planned to estimate the association between current duloxetine use and hepatic outcomes as an odds ratio representing the incidence rate ratio for current duloxetine use, relative to current exposure to comparison agents (since the controls are sampled from the person-time giving rise to the cases), allowing for cross-classification by exposure categories, with adjustment for claims-derived characteristics as well as baseline characteristics obtained from the medical records. To account for missing data among covariates obtained from medical records, we proposed to use a multiple imputation technique based on Markov chain Monte Carlo methodology to estimate values of missing data in the chart-derived covariates. (15, 16)

During the course of this study, only 5 cases of clinically significant hepatic injury without alternate etiology were confirmed among the treated cohorts during the current therapy (plus 15 day) exposure window through review of the medical records. Based on these findings, it was determined that the planned nested case control analysis would not have sufficient statistical power to provide informative results. As such, the nested case control analyses were not performed and instead, a descriptive tabulation of chart- and claims-derived covariates of the 5 confirmed cases is provided in this report.

4.9.5. Characterization of Risk Profiles of Cases and Case Detail Listing

Time to onset of hepatic events was tabulated according to patient age and gender within the matched and comparator cohorts. For additional characterization, anonymized cases of hepatic injury confirmed through review of medical records or NDI search were described in the format of a case-level line listing. Listed characteristics included demographics, select

baseline conditions and select medications dispensed during the 45 days prior to the case date based on the health care claims, exposure information including initiation drug, and time from exposure onset to case date for select medications. In addition, we provided information on the most recent antidepressant dose based on the dispensing of the antidepressant proximal to the case date and case characteristics including outcome claims codes identified from the health care claims or confirmed by medical record review or NDI search, and year of diagnosis. Cases occurring in the 16 to 30 days following discontinuation of duloxetine or comparison drugs and therefore included in the sensitivity analysis on the time of censoring relative to drug discontinuation are listed separately.

The array sensitivity analyses were conducted using an Excel (Microsoft) spreadsheet (available at http://www.hdpharmacoepi.org). All other data analyses were performed using SAS version 9.2 (SAS Institute, Cary, North Carolina).

5. Results

5.1. Study Population

Table 1a describes the flowchart of study inclusion and exclusion criteria, and the associated number of individuals involved at each step.

From 01 August 2004 to 30 September 2010, a total of 156,682 patients who received at least 1 dispensing of duloxetine, 231,793 patients who received at least 1 dispensing of venlafaxine, and 1,314,147 patients who received at least 1 dispensing of an SSRI were accrued in the Life Sciences Research Database. From this initial pool of patients, restriction by study inclusion and exclusion criteria yielded cohorts of 30,844 initiators of duloxetine, 29,243 initiators of venlafaxine, and 166,236 initiators of SSRI prior to propensity score matching.

During the same accrual period, a total of 1,577,784 patients who had a diagnosis of depression and who were not present in the treated initiator cohorts were accrued in the Life Sciences Research Database. Of this initial pool of patients, 311,338 patients met all inclusion and exclusion criteria for entry into the pharmacologically untreated depression cohort.

Of the 30,844 eligible duloxetine initiators, the following numbers (and percentages) were matched in a 1:1 ratio to each of the other groups on the basis of estimated propensity scores: 21,000 (68.1%) matched to venlafaxine initiators, 28,479 (92.3%) matched to SSRI initiators, and 22,714 (73.6%) matched to patients with a claim for diagnosis of depression who did not receive antidepressant drug therapy. Conversely, 21,000 out of 29,243 (71.8%) venlafaxine initiators, 28,479 out of 166,236 (17.1%) SSRI initiators, and 22,714 out of 311,338 (7.3%) patients in the pharmacologically untreated cohort were matched to duloxetine initiators on the basis of estimated propensity scores.

5.1.1. Claims-Based Baseline Characteristics Across Study Cohorts Prior to and After Propensity Score Matching

Table 1b describes the claims-based baseline characteristics of the duloxetine initiators and 3 comparator cohorts prior to propensity score matching.

Among the pool of duloxetine initiators eligible for matching, approximately 31% of patients were between 41-50 years old and another 31% were 51 years of age or older; nearly 73% were female. Approximately 47% of patients had a baseline claim with a diagnosis code for depressive disorder, not elsewhere classified, 36.7% had a diagnosis code for episodic mood disorder with a depressive component, and over half had a diagnosis code for anxiety, dissociative and somatoform disorder.

Prior to propensity score matching, duloxetine initiators were more likely to be older compared to the other 3 comparator cohorts, and were more likely to be female compared to the SSRI and pharmacologically untreated depression cohorts.

Duloxetine initiators also had a higher prevalence of baseline claims across a wide range of a priori-defined characteristics representing baseline neuropsychological comorbidities, hepatic risk factors, medication use, and health services utilization. Of note, compared to the 2 treated comparator cohorts, duloxetine initiators had a higher prevalence of baseline claims for episodic mood disorders with a depressive component (36.7% vs. 28.5% vs. 19.6% for the duloxetine, venlafaxine, and SSRI cohorts, respectively), psychotic disorders (41.6% vs. 32.9% vs. 23.8%), fibromyalgia (15.2% vs. 7.0% vs. 4.9%), and back pain (18.5% vs. 11.6% vs. 9.8%), and a lower prevalence of baseline claims for anxiety disorders (51.3% vs. 56.0% vs. 58.4%). Duloxetine initiators also had a higher baseline prevalence for a number of a priori-defined medications, including: NSAIDs excluding diclofenac (31.3% vs. 24.6% vs. 21.1%); anticonvulsants (33.8% vs. 21.3% vs. 13.9%); anxiolytics or sedative hypnotics (53.2% vs. 44.4% vs. 40.1%); antihistamines (23.1% vs. 19.7% vs. 15.3%); antipsychotics (10.1% vs. 6.8% vs. 3.7%); and narcotic analgesics (52.4% vs. 40.7% vs. 35.0%). Finally, as expected, duloxetine initiators had higher baseline use of venlafaxine compared with SSRI initiators (11.7% vs. 3.9%), a higher baseline use of SSRIs compared with venlafaxine initiators (39.7% vs. 35.4%); and a higher baseline use of other antidepressants compared to both venlafaxine initiators and SSRI initiators (42.0% vs. 33.1% vs. 30.8%).

Comparison of duloxetine initiators with a cohort of depressed but pharmacologically untreated patients generally showed similar or greater differences across these baseline characteristics.

Table 2a describes the distribution of dosage among the duloxetine and treated comparator cohorts prior to propensity score matching and within the propensity-score matched cohorts.

Table 2b compares the distribution of dosage among the duloxetine initiators who were matched to comparators on propensity score, stratified by matched cohort.

Among initiators of study drugs prior to propensity score matching, the modal daily dose was 60 mg for duloxetine and 75 mg for venlafaxine; modal dose was calculated separately for each drug in the SSRI cohort. Prior to propensity score matching, 5.5% of duloxetine initiators were prescribed duloxetine at above the modal dose, 62.7% initiated duloxetine at the modal dose, and 31.7% initiated duloxetine at below the modal dose. Prior to propensity score matching, a higher proportion of individuals in the venlafaxine cohort (37.8%) and SSRI cohorts (18.0%) initiated their respective cohort-defining drug above the modal dose compared to duloxetine initiators. Among the propensity scorematched cohorts, the distributions of dosage observed remained similar to those in the cohorts prior to matching.

Tables 3a through 3c describe the baseline characteristics of the duloxetine initiators compared with each of the comparator cohorts (venlafaxine initiators, SSRI initiators, and pharmacologically untreated depression comparators, respectively) among the matched cohorts only and among the unmatched duloxetine initiators. These tables include variables that were included in the final propensity score models, as well as variables that were not retained in the final propensity scores following the stepwise regression but which may be considered clinically relevant.

Matching on propensity score resulted in matched duloxetine initiator and comparator cohorts that were well-balanced for most of the measured baseline characteristics retained in the final propensity score models. Some residual imbalances were observed (e.g., healthcare costs among the duloxetine-venlafaxine and duloxetine-SSRI matched cohorts), though these differences were generally quite small. Standardized difference scores did not exceed the threshold of >0.1 for any of the variables included in the propensity scores.

Compared with duloxetine initiators who were successfully matched to venlafaxine initiators, duloxetine initiators who remained unmatched were more likely to be older and to have a higher prevalence of baseline claims for: episodic mood disorder (with depressive component); psychotic disorders; fibromyalgia; back pain; hypercholesterolemia/ dyslipidemia; and hypertension (Table 3a). Unmatched duloxetine initiators were less likely to have a baseline claim for anxiety, dissociative and somatoform disorders. The unmatched duloxetine initiators also had a higher prevalence of baseline claims indicating prior use of NSAIDs, statins, venlafaxine, SSRI, bupropion, other antidepressants, anticonvulsants, antihistamines, antipsychotics, and narcotic analgesics, were more likely to have had a visit with a psychiatrist/psychologist on the index date, and had a heavier burden of comorbidities as evidenced by a greater number of unique ICD-9 codes and greater number of different drugs dispensed, and a higher prevalence of prior hospitalization.

Compared with duloxetine initiators who were successfully matched to SSRI initiators, duloxetine initiators who remained unmatched were more likely to be older, female, and to have a higher prevalence of baseline claims for episodic mood disorders (with depressive component); psychotic disorders; fibromyalgia; back pain; hypercholesterolemia/ dyslipidemia; and hypertension (Table 3b). They were more likely to have had a visit with psychiatrist/psychologist on the index date and were less likely to have a baseline claim for anxiety, dissociative and somatoform disorders. The unmatched duloxetine initiators also had a higher baseline prevalence of use of NSAIDs, statins, venlafaxine, SSRI, bupropion, other antidepressants, anticonvulsants, anxiolytics, antipsychotics, and narcotic analgesics, were more likely to have claims representing a greater number of unique ICD-9 codes and greater number of different drugs dispensed during the baseline period, and were more likely to have been hospitalized during the baseline period.

Compared to duloxetine initiators who were successfully matched to pharmacologically untreated patients, duloxetine initiators who remained unmatched were more likely to be older, female, and to have a higher prevalence of baseline claims for: depressive disorder, not elsewhere classified; episodic mood disorders (with depressive component); psychotic disorders; fibromyalgia; and back pain (Table 3c). They were also more likely to have claims representing baseline use of NSAIDs, venlafaxine, SSRIs, bupropion, other antidepressants, anticonvulsants, anxiolytics or sedative hypnotics, antipsychotics, narcotic analgesics, and sedative-hypnotics (non-barbiturate). They were also more likely to have higher health care utilization in the baseline period, as evidenced by claims representing a

greater number of unique ICD-9 codes, a greater number of different drugs dispensed during the baseline period, and prior hospitalization.

5.1.2. Medical Record Validation of Baseline Comparability

Of the 315 individuals randomly selected from the duloxetine cohort, medical records were available for 213 (68%); of these, 158 represented duloxetine initiators matched to venlafaxine, 203 represented individuals matched to SSRI, and 150 represented individuals matched to the untreated cohort (subgroups not mutually exclusive). Of the 315 individuals randomly selected from each of the matched comparator cohorts, medical records were abstracted for 212 (67%) individuals from the venlafaxine cohort, 223 (71%) individuals from the SSRI cohort, and 212 (67%) individuals from the untreated cohort.

Table 4 describes the chart-based baseline characteristics for the sample of duloxetine initiators for whom charts were abstracted, overall and by subgroup according to the comparator cohort to which the duloxetine initiators were matched. The mean propensity score among duloxetine initiators in the sample who were matched to venlafaxine was higher compared to duloxetine initiators in the sample who matched to SSRI comparators and to untreated comparators (0.52 vs. 0.30 vs. 0.29), while the prevalences of measured chart-based characteristics were quite similar across the subgroups. Overall, approximately 3.8% of duloxetine initiators with abstracted medical records had documented abnormal liver enzymes and 1.4% had documented chronic liver disease during the 12-month baseline period, suggesting that the hepatic-related study exclusions were largely but not completely captured in the health care claims.

Tables 5a through 5d describe the baseline comparability of the propensity score-matched duloxetine and comparator cohorts, among the patients for whom charts were successfully abstracted. The mean propensity scores for the sample of patients with abstracted medical records were similar to the mean propensity scores for the overall matched cohorts, suggesting that they were a representative sample of the matched cohorts.

Compared to venlafaxine initiators with abstracted medical records, individuals in the matched duloxetine sample had a lower baseline prevalence of anxiety disorders (35.5% vs. 48.3%) and a higher prevalence of fibromyalgia (6.3% vs. 1.4%) based on information in the medical records (Table 5b). While alcohol use/abuse was less frequently documented among the duloxetine initiators (5.1% vs. 8.5%), current smoking was more frequently documented among duloxetine initiators (21.5% vs. 16.5%) compared with venlafaxine initiators. Approximately 3.8% of duloxetine initiators and 4.7% of venlafaxine initiators had a record of abnormal liver enzymes, while 1.3% of duloxetine initiators and 0.5% of venlafaxine initiators had chronic liver disease documented in the medical records.

Compared to SSRI initiators with abstracted medical records, individuals in the matched duloxetine sample were more frequently identified as a current smoker (20.7% vs. 11.2%), and had a higher baseline prevalence of fibromyalgia (7.4% vs. 2.7%) and diabetes neuropathy (2.0% vs. 0.0%) documented in the medical records (Table 5c). Duloxetine initiators also had a slightly higher prevalence of documented obesity (21.2% vs. 18.8%) and alcohol use/abuse (6.4% vs. 3.1%) compared with SSRI initiators. SSRI and duloxetine initiators had a similar prevalence of documented abnormal liver enzymes (3.5% vs. 3.6%) and chronic liver disease (1.5% vs. 0.9%).

Compared to untreated individuals with abstracted medical records, individuals in the matched duloxetine sample had a lower prevalence of past smoking (3.3% vs. 8.5%) and a higher prevalence of documented fibromyalgia (7.3% vs. 2.4%) (Table 5d). Duloxetine initiators were also slightly more likely to have documented alcohol use/abuse (6.7% vs. 3.8%) and a record of abnormal liver enzymes (4.7% vs. 2.8%) compared to the untreated sample.

5.2. Validation of Hepatic Outcomes

5.2.1. Validation of Claims-Identified Hepatic Events

Table 6a presents the results of the clinical adjudication of the potential clinically significant hepatic injury events prior to restrictions to the specified windows of exposure. Table 6b characterizes the non-confirmed cases with respect to the adjudication diagnostic criteria. The corresponding Figure 1 provides a visual representation of the results from the medical record abstraction and adjudication described in Tables 6a and 6b.

The initial screening of the claims identified a total of 969 potential cases of clinically significant hepatic injury for 962 individuals among the propensity score-matched cohorts (9 hepatic-related deaths, 32 liver failure events, and 928 other clinically significant hepatic injury events). Of these, a total of 716 charts (74% chart retrieval; 6 hepatic-related deaths, 25 liver failure events, and 685 other clinically significant hepatic injury events) representing 712 individuals were abstracted for review by the clinical consultants. Overall episode-level chart retrieval across the matched cohorts was as follows: duloxetine vs. matched venlafaxine: 73% vs. 77%; duloxetine vs. matched SSRI: 72% vs. 76%; duloxetine vs. matched untreated: 73% vs. 71%).

Through the medical records review, 54 out of the 716 abstracted potential events were confirmed as either a clinically significant or a non-serious asymptomatic hepatic injury. This represented a total of 53 unique events, as in the case of one individual, 2 potential events were identified (1 claims-identified hepatic death and 1 other clinically significant hepatic injury) but were classified by the clinical adjudicators as a single case of other clinically significant hepatic injury.

Exclusion of confirmed hepatic events for which an alternate etiology was identified reduced the overall number of hepatic events from 53 to 18 (0 hepatic-related death, 0 liver failure, 12 other clinically significant hepatic injury, 6 non-serious hepatic enzyme elevation), representing a decrease of 66%.

Figure 2 describes the impact of successive restrictions of follow-up to the 3 specified windows of exposure (current therapy plus 30 days, current therapy plus 15 days, first 90 days following cohort entry), and the associated number of subjects and/or events involved at each stage.

5.2.2. Identification of Hepatic-Related Deaths Using the National Death Index

A total of 24,406 study individuals from the 4 study cohorts who disenrolled from the health plan before 31 December 2010 and who did not have a record of re-enrollment were sent for an NDI search. The NDI search matched 27,331 records to individuals, of which we retained 2,281 records with a high probability of a true match according to NDI algorithms. Eighty-five death records (representing 58 unique patients) were identified as having a

potential underlying hepatic condition. When we restricted the potential hepatic-related deaths to those with a date of death within the specified exposure windows, 0 death records remained for inclusion in the analyses.

5.3. As-Matched Analysis

5.3.1. Primary Analysis: IRs and RRs (95% CI) for Hepatic Outcomes: Current Therapy Plus 15-Day Exposure Window

Table 7a describes the IRs and 95% CIs of the hepatic outcome categories among the matched duloxetine initiator and comparator cohorts. There were 0 hepatic-related deaths and 0 liver failures in the duloxetine and 3 comparator cohorts. For the outcome, other clinically significant hepatic injury, a total of 8 events were confirmed (5 duloxetine, 0 venlafaxine, 0 SSRI, 3 untreated). Figures 3a-1 through 3c-6 describe the time to event survival curves for the 6 study outcome categories (hepatic-related death, liver failure, other clinically significant hepatic injury, hepatic-related death or liver failure combined, all clinically significant hepatic injury categories combined, and non-serious asymptomatic hepatic enzyme elevation). These curves provide little additional information because the outcomes are rare.

For the outcome, other clinically significant hepatic injury, the IR among duloxetine initiators was 0.7 per 1,000 person-years (95% CI: 0.2, 1.5) among those matched to venlafaxine compared to 0.0 per 1,000 person-years (95% CI: 0.0, 0.3) among venlafaxine initiators, and was 0.4 per 1,000 person-years (95% CI: 0.1, 1.0) among those matched to SSRI compared to 0.0 per 1,000 person-years (95% CI: 0.0, 0.3) among SSRI initiators. IRs and 95% CI were similar among duloxetine initiators and the matched untreated cohort (0.5 per 1,000 person-years [95% CI: 0.1, 1.3] among duloxetine initiators vs. 0.5 per 1,000 person-years [95% CI: 0.1, 1.5] among untreated comparators). Due to the absence of other clinically significant hepatic events in the venlafaxine and SSRI cohorts, relative hazards and 95% CIs were not available for the duloxetine-venlafaxine or duloxetine-SSRI comparisons using Cox proportional hazards regression models. In instances in which the incidence rate ratio was undefined (e.g., when there was 0 events in the referent group), the lower limit for the 95% CI was calculated according to exact methods. The IRRs and exact 95% CIs of other clinically significant hepatic injury for duloxetine was undefined (95% CI: 1.1, ∞) when compared with venlafaxine, undefined (95% CI: 0.6, ∞) when compared with SSRI, and 1.0 (95% CI: 0.2, 6.7) when compared with untreated comparators. As expected, the IRRs and exact 95% CIs of all clinically significant hepatic categories combined were consistent with those for the single outcome, other clinically significant hepatic injury.

For the outcome, non-serious hepatic enzyme elevations, a total of 3 events were confirmed among the study cohorts (1 duloxetine, 2 SSRI), corresponding to an IR of 0.1 per 1,000 person-years (95% CI: 0.0, 0.5) among duloxetine initiators and an IR of 0.2 per 1,000 person-years (95% CI: 0.0, 0.7) among SSRI initiators.

The small number of confirmed hepatic events did not allow for multivariable adjustment, and only unadjusted rate ratios and associated 95% CI are provided.

5.3.2. Secondary Analysis: IRs and RRs (95% CI) for Hepatic Outcomes Within 1st 90 Days Following Cohort Entry

When follow-up was restricted to the first 90 days following cohort entry, a total of 8 cases remained for all 4 study cohorts combined: 0 hepatic-related deaths, 0 liver failures, 6 other clinically significant hepatic injury events, 2 non-serious hepatic enzyme elevations.

Table 7b describes the IRs and 95% CIs of the hepatic outcomes occurring within the first 90 days following cohort entry among the matched duloxetine initiator and comparator cohorts. For the outcome, other clinically significant hepatic injury, results were consistent with the primary analysis, albeit with further reduced statistical power.

For the outcome, non-serious hepatic enzyme elevations, both confirmed events occurred in the SSRI cohort (IR: 0.4; 95% CI: 0.0, 1.4).

As with the primary analysis, the small number of confirmed hepatic events did not allow for multivariable adjustment, and only unadjusted rate ratios are provided for all analyses.

5.3.3. Sensitivity Analysis: IRs and RRs (95% CI) for Hepatic Outcomes: Current Therapy Plus 30-Day Exposure Window

Expansion of the current therapy exposure window from 15 days to 30 days following treatment discontinuation resulted in the inclusion of only one additional non-serious hepatic enzyme elevation case.

Table 8 describes the IRs and 95% CIs of the hepatic outcome categories among the matched duloxetine initiator and comparator cohorts. Results for the clinically significant hepatic outcomes were consistent with results from the primary analysis.

For the outcome, non-serious hepatic enzyme elevations, a total of 4 events were confirmed among the study cohorts (1 among duloxetine initiators, 1 among venlafaxine initiators, and 2 among SSRI initiators). The IRs and 95% CIs among duloxetine initiators were comparable to their matched comparator cohorts (duloxetine vs. venlafaxine: 0.1 [95% CI: 0.0, 0.7] vs. 0.1 [95% CI: 0.0, 0.6]; duloxetine vs. SSRI: 0.1 [95% CI: 0.0, 0.5] vs. 0.2 [95% CI: 0.0, 0.7]; duloxetine vs. untreated: 0.1 [95% CI: 0.0, 0.6] vs. 0.0 [95% CI: 0.0, 0.5]).

5.3.4. Cohort Sensitivity Analysis of Unmeasured Confounding

In the as-matched analysis, the IRR of all clinically significant hepatic categories combined comparing duloxetine to the untreated cohort was 1.0 (Table 7a). For all clinically significant hepatic events combined comparing duloxetine to venlafaxine initiators and to SSRI initiators, 0 cases were observed in the venlafaxine and the SSRI comparator cohorts, such that the IRRs comparing duloxetine initiators to these comparator groups were undefined (IRs among duloxetine vs. venlafaxine initiators: 0.7 [95% CI: 0.2, 1.5] vs. 0.0 [95% CI: 0.0, 0.3];IRs among duloxetine vs. SSRI initiators: 0.4 [95% CI: 0.1, 1.0] vs. 0.0 [95% CI: 0.0, 0.3]). As such, an array sensitivity analysis could not be conducted.

5.4. Nested Case Control Analysis

Only 5 cases of clinically significant hepatic injury without alternate etiology were confirmed among the treated cohorts in the primary analysis (current therapy plus 15 days). Based on this finding, it was determined that the planned nested case control analysis would not have sufficient statistical power to provide informative results, and the nested case control analysis was not performed. A descriptive tabulation of selected chart- and claims-derived characteristics of the 5 confirmed cases is provided in Table 9. Cases were well-distributed across age groups and by gender. Four out of 5 cases had a calendar year of cohort entry between 2008 and 2010. All 5 cases were exposed to duloxetine on the event date, while 1 case was also exposed to an SSRI within 45 days prior to the event date. The presence of other conditions within the 45 days preceding the event date, as identified on the basis of the health care claims, was infrequent (1 case each identified with acute viral infection, chronic liver disease, cirrhosis, or fibrosis, use of chlorpromazine).

5.5. Characteristics of Confirmed Cases of Clinically Significant Hepatic Injury and Case Detail Listing

Table 10 describes the distribution of claims-identified characteristics during the 12-month baseline period among cases of hepatic events combined across the matched duloxetine cohort and comparator cohorts. The mean number of days from index date to onset of the hepatic event was 67.1 (standard deviation: 80.2) among cases of other clinically significant hepatic injury and 110.3 (standard deviation: 95.8) among cases of non-serious hepatic enzyme elevation, where 5 out of 8 cases of other clinically significant hepatic injury and 1 out of 3 cases of non-serious hepatic enzyme elevation were identified as current users of duloxetine at the date of onset of the hepatic event on the basis of the health care claims. Among the 8 cases of other clinically significant hepatic injury, cases were well-distributed across age groups, 5 were female, and 7 entered the study cohorts between 2008 and 2010. Zero out of 8 cases had a baseline claim for a liver ultrasound and 1 case had a baseline claim for an ALT/ASP/ALP test. At the same time, the majority of cases had claims indicative of high comorbidity burden, as evidenced by the high number of unique ICD-9 codes and number of different drugs dispensed during the baseline period.

Tables 11a through 11c describe the time to onset of hepatic events according to select claims-based characteristics during the 12-month baseline period within the PS-matched duloxetine and comparator cohorts. The small number of confirmed cases limits robust comparisons of the prevalence of baseline comorbidity and medication use between cases and limits the summarization of potential differences in time to onset of hepatic events according to selected characteristics.

A case-level tabulation of all confirmed hepatic cases is presented in Appendix IV to allow for more detailed evaluation of each case with regard to baseline characteristics, antidepressant exposure information, and case characteristics. For some cases, a screening of the health care claims during the 45 days prior to the confirmed case date identified the presence of claims suggestive of potential alternate causes for hepatic injury (e.g., acute viral infection; chronic liver disease, cirrhosis, or fibrosis). However, review of the medical records by the independent adjudication committee failed to confirm documentation of the presence of alternate etiologies; in such instances, the case was determined by the clinical adjudicators to be a possible drug-induced, other clinically significant hepatic injury event.

5.6. Assessment of Potential Differential Loss to Follow-Up

Patterns of cohort-specific attrition for each matched comparison are described in the Number Remaining at Risk tables in Figures 3a-1 through 3c-6. In each of the treated cohorts, a distinct drop in the number of initiators remaining in the study was apparent at 7 to 8 weeks following the initial dispensing of the study antidepressant. Compared with venlafaxine initiators, only slightly more duloxetine users were censored at 8 weeks following cohort entry, a small effect that persisted through follow-up. Differences in attrition between duloxetine and SSRI initiators were even slighter. Pharmacologically untreated comparators exhibited a similar pattern of attrition as their matched duloxetine initiators which was expected by design, as the durations of on-therapy exposure windows among duloxetine initiators had been used to inform analogous windows of "non-exposure" for the untreated cohort (described in Section 4.9.1).

To assess the potential for bias introduced by differential loss to follow-up, patients eligible for inclusion in the study who were censored during follow-up either (1) due to treatment discontinuation or who were censored on the date of a non-confirmed hepatic event (administratively censored patients not included) or (2) due to any reason within the first 90 days following cohort entry (e.g., treatment discontinuation, occurrence of non-confirmed hepatic event, disenrollment from the health plan, or end of the study) were characterized on the aggregate, by matched cohort (Appendices V-A, V-B, and V-C). Comparison of these patients to the overall duloxetine and matched comparator cohorts suggests that patients who dropped out during study follow-up had similar baseline characteristics as the overall matched cohorts.

6. Discussion

We identified a cohort of patients with depression who received duloxetine over an approximately 6-year period between August 2004 and September 2010. We created 3 cohorts of patients with similar characteristics (initiators of venlafaxine, initiators of SSRIs, and patients with depression who remained pharmacologically untreated), each matched to duloxetine initiators on the propensity score to facilitate comparisons of the incidence of clinically significant hepatic injury. In our study, 0 confirmed cases of hepatic-related death or hepatic failure were identified in the overall study population. We found that duloxetine initiators had a higher incidence rate of other clinically significant hepatic injuries compared to initiators of venlafaxine, though confidence intervals overlapped.

Potential hepatic injuries, such as elevated hepatic enzyme levels have been reported in pre-marketing clinical trials(1) and in the post-marketing period(17), but these reports have typically involved patients with pre-existing liver disease or risk factors for liver disease, such as heavy alcohol use. The IRs in our study are comparable or slightly lower than those observed in the earlier safety study of duloxetine conducted by OptumInsight (18), possibly due in part to the restriction of the study population in the current study to patients without evidence of pre-existing hepatic conditions in the baseline period, and are lower (albeit within the confidence limits) compared with IR observed in a previous study of drug-associated liver injury based on electronic medical record data that similarly restricted the study population to patients without evidence of pre-existing liver disease or other comorbidity to minimize capture of non-drug-related liver injury.(20). The earlier assessment conducted by OptumInsight using the Optum Research Database found higher incidence rates of hepatic injury of lesser severity among duloxetine users relative to propensity score-matched venlafaxine users, but not relative to SSRIs.(18) Our study –

which was restricted to patients without baseline hepatic disorders as identified using the health care claims – provides additional information suggestive of a potential increased incidence of hepatic events of lesser severity among duloxetine initiators relative to propensity score-matched venlafaxine initiators.

The outcomes of interest for this study were defined as clinically significant hepatic events in the absence of explicit identification of an alternative etiology. The advantage of this approach is that it can strengthen the associations by removing cases attributable to extraneous causes. As described by Rothman and Ray(21), however, exclusion of cases on the basis of "known" causes of disease can be problematic. A study drug may confer a higher risk for an adverse event through interactions with other known causes. In addition, exclusion of cases without a corresponding exclusion of the associated person-time at risk may dilute the incidence rates observed in the exposed and the comparator cohorts to unknown and potentially differing extents. If more cases were excluded from the duloxetine cohort relative to the other cohorts on the basis of known alternate causes, this may have led to an underestimate of the relative incidence rates. To assess the potential impact of these case exclusions, we conducted an additional as-matched analysis in which all clinically significant hepatic events (with or without identified alternate causes) were included, as a comparison to the pre-specified primary analysis. We found that duloxetine initiators had an IR suggestive of elevated risk for clinically significant hepatic injury combined, albeit with confidence limits including 1.0, when compared with initiators of venlafaxine (IRR: 3.2; exact 95% CI: 0.9, 13.7) (Appendix VI-A); smaller non-significant elevations were observed comparing duloxetine initiators to initiators of SSRIs (IRR: 1.3; exact 95% CI: 0.5, 3.3), and similar IRs were observed among duloxetine initiators and the untreated cohort (IRR: 1.0; exact 95% CI: 0.4, 2.9). These results suggest that the exclusion of hepatic cases with alternate etiology without corresponding exclusions of associated person-time at risk had little substantive effect on the primary study analyses.

For this additional analysis, we also conducted a separate array sensitivity analysis to quantify the impact of potential residual confounding (Appendix IV-B). As described in the Methods, the magnitude of residual confounding due to unmeasured confounders was assessed using data on medical record-confirmed baseline characteristics, including prevalence of the confounder (P_C) and the association between these factors and exposure status (OR_{EC}), from among the randomly sampled duloxetine initiators and comparators. The degree of potential confounding is a joint function of the prevalence of exposure (P_E), the prevalence of confounder (P_C), the relative risk for disease associated with the confounder (RR_{CD}), and the exposure-confounder odds ratio (OR_{EC}).(22) Applying baseline prevalence estimates of smoking derived from the duloxetine and venlafaxine baseline validation samples (21.5% vs. 16.5%, respectively), we found that fully-adjusted RRs remained 2.3 or greater for all combinations of $RR_{CD}<10$ and $P_{C1}<27\%$ (given $P_{C0}=16.5\%$), suggesting that the observed higher IR of other clinically significant hepatic events among duloxetine initiators cannot be fully accounted for by potential confounders on par to the conditions simulated using estimates of smoking prevalence.

This study has several limitations and considerations.

As described in the study protocol, as a preparatory step to conducting the safety study, OptumInsight performed an assessment of the impact of using baseline periods of varying lengths (6 months, 9 months, or 12 months) on sample size and the capture of important study exclusion and confounder information. In this assessment, lengthening of the baseline period from 6 months to 12 months was associated with an approximately 23%

reduction in size of the duloxetine population. Use of a shorter baseline period, however, may have also led to underascertainment of baseline hepatic exclusions, though the amount of relative underascertainment appeared to be consistent across the study cohorts. Following review of the Baseline Assessment Report (dated 03 August 2011), it was determined by Eli Lilly that removal of sources of heterogeneity through restriction of the study population (i.e., to assess the risks associated with duloxetine use among a population without pre-existing hepatic conditions) and enhanced capture of important confounder information through the use of the 12-month baseline period should be prioritized with the understanding that a smaller sample size would confer more limited power to detect differences in effect. In addition, power calculations conducted at the outset of the study assumed a person-time accrual ranging from 17,000 to 35,000 person-years and a 25% reduction in incidence estimates of hepatic injury to account for the exclusion of patients with baseline liver disease in the protocol for an anticipated risk of all clinically significant hepatic events of 7.6 per 10,000 person-years and an anticipated risk of hepatic failure of 0.75 per 10,000 person years. Our findings indicate that the length of time initiators remained on duloxetine (and as such the person-time at risk for a study outcome) and the incidence of hepatic injury (restricted to confirmed events without alternate etiology upon medical record review) in this population was lower than projected.

As an observational study, patients who received duloxetine may differ from those who received a comparator drug or those who did not receive any pharmacological treatment for depression. If these differences are associated with hepatic injury, then the comparison of the duloxetine initiators to comparators may be biased. Duloxetine initiators and their comparators were not matched directly on specific baseline characteristics. Instead, this study used propensity score techniques to match a comparator group to the exposed cohort and address potential confounding through numerous covariates that are integrated into this single variable; comparison of the duloxetine initiators to the comparator cohorts suggested the cohorts were well-balanced for the claims-based covariates included in the propensity score model.

While balanced on claims-based covariates, information obtained from the medical records in the baseline validation sample suggests that duloxetine initiators may have differed from the comparator cohorts on certain characteristics that may not be adequately captured using the health care claims (e.g., smoking, pain-related syndromes, alcohol use/abuse). Medical record documentation of important potential confounders may itself be incomplete or differentially captured (e.g., alcohol use or abuse). Approximately one-third of charts sought for the validation of baseline characteristics were not available, and if the patients for whom medical records were obtained are not representative of the random sample for these characteristics, these factors may result in prevalence estimates of baseline characteristics that may have inaccurately informed our assessments of the extent of potential residual confounding. Finally, the label of duloxetine includes hepatotoxicity in the “Warnings and Precautions” section and warns against prescribing this drug to patients with substantial alcohol use or evidence of chronic liver disease. If heightened awareness of the risk for hepatotoxicity led clinicians to conduct more comprehensive assessments when deciding to prescribe duloxetine or as a part of monitoring therapy, the resulting surveillance bias may have led to differential rates of diagnosis of hepatic injury. While the extent and impact of alternate explanations can be evaluated through sensitivity analyses, such assessments may have limited meaning due to the small number of events in our study.

The strengths of this study include the use of propensity score methods to rigorously account for potential confounding and further mitigation of potential confounding from the presence of pre-existing hepatic disease through restriction of the study population to patients without baseline hepatic disorders (on the basis of the health care claims). In addition, this study focused on clinically significant potentially drug-induced liver injury events, validated by medical record review, occurring while exposed to a drug of interest or up to 15 days after last drug availability to evaluate the risk of idiosyncratic drug-induced liver injury at the typical time of its occurrence.

7. Conclusion

Using data from the Optum Research Database, this propensity score-matched retrospective cohort study quantified the absolute and relative risk of clinically significant hepatic events associated with duloxetine initiation compared to initiation of venlafaxine or SSRI, and patients with depression who were pharmacologically untreated. The statistical power of this study to evaluate relative risks was limited due to the rarity of these outcomes. We observed no cases of hepatic-related death or liver failure in the duloxetine or the 3 comparator cohorts, and the study is inconclusive regarding their association with duloxetine use. This study does offer insights into the association between duloxetine use and the incidence of other clinically significant hepatic events among a cohort of patients without evidence of pre-existing hepatic conditions. Our study identified a statistically non-significant elevated risk for other clinically significant hepatic outcomes in the duloxetine initiators compared with the propensity score-matched venlafaxine cohort and a lower statistically non-significant increase compared with the SSRI cohort in the protocol-specified and post-hoc analyses. These differences are not statistically significant and remain consistent with chance, and therefore an elevated risk cannot be ruled in or out. Similar rates of clinically significant hepatic outcomes were observed when comparing the duloxetine and untreated comparator cohorts. Overall, the number of confirmed clinically significant hepatic events was small, resulting in wide confidence limits.

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8. Tables

Table 1a. Accounting for patient selection and exclusions

	Duloxetine		Venlafaxine		SSRI		Pharmacologically Untreated	
	N removed	N eligible remaining	N removed	N eligible remaining	N removed	N eligible remaining	N removed	N eligible remaining
Member of commercial health insurance plan with approval to request medical charts, with medical coverage and pharmacy benefits, and presence of qualifying event* during the accrual period		156,682		231,793		1,314,147		1,577,784
Baseline exclusions								
Less than 18 years at index date	1,396	155,286	2,482	229,311	33,476	1,280,671	60,552	1,517,232
Less than 12 months prior continuous enrollment	79,819	75,467	136,147	93,164	780,943	499,728	791,027	726,205
Prior dispensing of study drug or drug class in the baseline	0	75,467	23,753	69,411	134,294	365,434	334,496	391,709
Had no depression diagnosis in the baseline	27,596	47,871	24,844	44,567	153,173	212,261	0	391,709
Had hepatic injury/chronic hepatic condition in the baseline	10,592	37,279	9,173	35,394	39,354	172,907	76,815	314,894
Region affected by Hurricane Katrina	489	36,790	509	34,885	2,020	170,887	3,556	311,338
Cohort assignment based on earliest qualifying index date (pre-propensity score matching)	30,844		29,243		166,236		311,338	

*Initiation of a study drug, or for untreated patients, a claim for depression associated with a physician visit

Table 1b. Distribution of select baseline characteristics across the study cohorts derived from the Optum Research Database, 01 August 2004 -- 30 September 2010, before propensity score matching

Baseline Characteristic	Duloxetine (N=30,844)		Venlafaxine (N=29,243)		SSRIs (N=166,236)		Untreated (N=311,338)	
Age group (years) (N %)								
18-25	2,202	7.1	3,130	10.7	23,841	14.3	41,182	13.2
26-30	2,126	6.9	2,937	10.0	18,809	11.3	33,868	10.9
31-35	3,242	10.5	3,665	12.5	21,445	12.9	40,323	13.0
36-40	4,280	13.9	4,152	14.2	23,101	13.9	43,079	13.8
41-50	9,544	30.9	8,244	28.2	41,800	25.1	80,826	26.0
51-60	7,192	23.3	5,459	18.7	27,168	16.3	51,577	16.6
61-70	2,001	6.5	1,459	5.0	8,577	5.2	17,333	5.6
≥71	257	0.8	197	0.7	1,495	0.9	3,150	1.0
Gender (N %)								
Female	22,486	72.9	20,703	70.8	106,200	63.9	179,348	57.6
Male	8,358	27.1	8,540	29.2	60,036	36.1	131,990	42.4
Geographic region of health plan (N %)								
Northeast	1,752	5.7	2,120	7.3	12,489	7.5	32,598	10.5
Midwest	7,845	25.4	8,619	29.5	47,681	28.7	79,962	25.7
South/Southeast	18,197	59.0	15,295	52.3	86,934	52.3	159,346	51.2
West	3,050	9.9	3,209	11.0	19,132	11.5	39,432	12.7
Calendar year of cohort entry (N %)								
2004	1,658	5.4	3,016	10.3	11,659	7.0	23,507	7.6
2005	4,841	15.7	5,743	19.6	25,568	15.4	47,576	15.3
2006	6,036	19.6	5,786	19.8	28,243	17.0	47,896	15.4
2007	6,250	20.3	5,460	18.7	27,409	16.5	47,545	15.3
2008	5,374	17.4	4,422	15.1	27,602	16.6	48,955	15.7
2009	4,158	13.5	2,812	9.6	26,913	16.2	51,974	16.7
2010	2,527	8.2	2,004	6.9	18,842	11.3	43,885	14.1

Table 1b. Continued

Baseline Characteristic	Duloxetine (N=30,844)		Venlafaxine (N=29,243)		SSRIs (N=166,236)		Untreated (N=311,338)	
Neuropsychological comorbidities (N %)								
Depressive disorder, not elsewhere classified	14,464	46.9	13,896	47.5	63,918	38.5	54,747	17.6
Episodic mood disorders (with depressive component)	11,321	36.7	8,320	28.5	32,605	19.6	35,277	11.3
Episodic mood disorders (without depressive component)	2,307	7.5	1,769	6.1	7,529	4.5	11,628	3.7
Adjustment reaction	4,544	14.7	4,179	14.3	25,343	15.3	95,900	30.8
Anxiety, dissociative and somatoform disorders	15,809	51.3	16,381	56.0	97,041	58.4	161,210	51.8
Psychotic disorders	12,829	41.6	9,621	32.9	39,630	23.8	46,592	15.0
ADHD	1,533	5.0	1,126	3.9	5,362	3.2	9,115	2.9
Alcohol abuse and addiction (diagnosis)	1,016	3.3	966	3.3	4,542	2.7	5,690	1.8
Alcohol abuse and addiction (treatment)	559	1.8	389	1.3	1,374	0.8	1,131	0.4
Cocaine abuse and addiction	177	0.6	152	0.5	739	0.4	880	0.3
Heroin abuse and addiction	477	1.6	224	0.8	962	0.6	957	0.3
Other substance abuse and addiction	886	2.9	665	2.3	3,041	1.8	3,448	1.1
Smoking (tobacco use disorder - diagnosis)	1,919	6.2	1,766	6.0	9,405	5.7	12,894	4.1
Smoking (tobacco use disorder - treatment)	154	0.5	104	0.4	510	0.3	597	0.2
Overdoses	50	0.2	27	0.1	143	0.1	138	0.0
Suicide attempts	204	0.7	180	0.6	593	0.4	496	0.2
Seizure	304	1.0	220	0.8	1,023	0.6	1,539	0.5
Chronic pain	640	2.1	217	0.7	890	0.5	1,164	0.4
Stress urinary incontinence	333	1.1	250	0.9	927	0.6	1,341	0.4
Fibromyalgia	4,676	15.2	2,037	7.0	8,204	4.9	12,352	4.0
Diabetic neuropathy	383	1.2	162	0.6	750	0.5	1,137	0.4
Back pain	5,707	18.5	3,388	11.6	16,271	9.8	25,865	8.3

Table 1b. Continued

Baseline Characteristic	Duloxetine (N=30,844)		Venlafaxine (N=29,243)		SSRIs (N=166,236)		Untreated (N=311,338)	
Hepatic risks (N %)								
Hypercholesterolemia / dyslipidemia (diagnosis)	8,052	26.1	6,584	22.5	33,305	20.0	59,494	19.1
Hypercholesterolemia / dyslipidemia (treatment)	4,396	14.3	3,325	11.4	14,319	8.6	21,543	6.9
Hyperglycemia	468	1.5	392	1.3	2,241	1.4	3,561	1.1
Albuminuria	121	0.4	91	0.3	604	0.4	1,047	0.3
Diabetes mellitus (diagnosis)	2,514	8.2	1,750	6.0	9,205	5.5	16,178	5.2
Diabetes mellitus (treatment)	2,282	7.4	1,569	5.4	8,188	4.9	13,026	4.2
CMV infection	3	0.0	3	0.0	8	0.0	15	0.0
EBV infection	65	0.2	55	0.2	365	0.2	562	0.2
Obesity (diagnosis)	1,859	6.0	1,516	5.2	7,286	4.4	13,312	4.3
Obesity (treatment)	8	0.0	5	0.0	20	0.0	35	0.0
Liver ultrasound scans								
0	29,464	95.5	28,135	96.2	160,551	96.6	303,032	97.3
1	1,309	4.2	1,061	3.6	5,429	3.3	7,962	2.6
2+	71	0.2	47	0.2	256	0.2	344	0.1
Bilirubin test	1,537	5.0	1,330	4.6	6,294	3.8	11,632	3.7
ALT/AST/ALP test	1,362	4.4	1,048	3.6	5,416	3.3	8,335	2.7
NSAID use (excluding diclofenac)	9,668	31.3	7,197	24.6	35,145	21.1	50,065	16.1
NSAID use (diclofenac only)	1,381	4.5	834	2.9	4,197	2.5	5,461	1.8
Isoniazid	6	0.0	11	0.0	64	0.0	77	0.0
Phenytoin	86	0.3	72	0.3	376	0.2	520	0.2
Valproic acid	757	2.5	530	1.8	1,800	1.1	2,563	0.8
Nitrofurantoin	1,290	4.2	1,060	3.6	5,381	3.2	7,856	2.5
Propylthiouracil	13	0.0	18	0.1	66	0.0	143	0.1
Rifampin	69	0.2	35	0.1	194	0.1	285	0.1
Fluconazole	2,718	8.8	2,172	7.4	10,242	6.2	15,335	4.9
Chlorpromazine	38	0.1	25	0.1	79	0.1	63	0.0

Table 1b. Continued

Baseline Characteristic	Duloxetine (N=30,844)		Venlafaxine (N=29,243)		SSRIs (N=166,236)		Untreated (N=311,338)	
Hepatic risks (N %)								
Interferon beta	107	0.4	61	0.2	237	0.1	286	0.1
Amiodarone	21	0.1	29	0.1	122	0.1	173	0.1
Statins	5,105	16.6	3,719	12.7	18,444	11.1	28,333	9.1
Naloxone	272	0.9	150	0.5	597	0.4	678	0.2
Naltrexone	105	0.3	89	0.3	218	0.1	131	0.0
Disulfiram	69	0.2	63	0.2	208	0.1	161	0.1
Acamprosate	160	0.5	126	0.4	439	0.3	204	0.1
Use of medications (N %)								
Duloxetine (excluding index drug)	0	0.0	1,061	3.6	2,643	1.6	0	0.0
Venlafaxine (excluding index drug)	3,621	11.7	0	0.0	6,484	3.9	0	0.0
SSRI (excluding index drug)	12,241	39.7	10,351	35.4	0	0.0	0	0.0
Other antidepressants	12,957	42.0	9,692	33.1	51,119	30.8	0	0.0
Bupropion	5,891	19.1	4,064	13.9	12,106	7.3	0	0.0
Anticonvulsants	10,437	33.8	6,238	21.3	23,122	13.9	23,142	7.4
Anxiolytics or sedative hypnotics	16,410	53.2	12,993	44.4	66,587	40.1	77,832	25.0
Antihistamines	7,109	23.1	5,764	19.7	25,458	15.3	34,238	11.0
Antipsychotics	3,114	10.1	1,986	6.8	6,086	3.7	5,727	1.8
Narcotic analgesics	16,165	52.4	11,907	40.7	58,249	35.0	83,622	26.9
History of (N %)								
Hypertension	8,182	26.5	6,333	21.7	35,811	21.5	61,920	19.9
Stroke	529	1.7	339	1.2	2,013	1.2	2,631	0.9
MI	155	0.5	130	0.4	840	0.5	1,150	0.4
Angina	287	0.9	233	0.8	1,382	0.8	2,076	0.7
Unstable angina/acute coronary syndromes	215	0.7	140	0.5	1,025	0.6	1,427	0.5

Table 1b. Continued

Baseline Characteristic	Duloxetine (N=30,844)		Venlafaxine (N=29,243)		SSRIs (N=166,236)		Untreated (N=311,338)	
Specified health services (N % unless otherwise noted)								
Number of unique ICD-9 codes								
0-4	2,346	7.6	3,053	10.4	23,588	14.2	65,266	21.0
5-8	5,140	16.7	6,507	22.3	42,347	25.5	85,585	27.5
9-12	6,175	20.0	6,657	22.8	37,862	22.8	68,049	21.9
13-16	5,436	17.6	4,964	17.0	26,307	15.8	43,078	13.8
17+	11,747	38.1	8,062	27.6	36,132	21.7	49,360	15.9
Number of different drugs dispensed								
0-3	2,657	8.6	4,730	16.2	42,356	25.5	159,107	51.1
4-7	7,615	24.7	9,577	32.8	62,302	37.5	93,124	29.9
8+	20,572	66.7	14,936	51.1	61,578	37.0	59,107	19.0
Use of intensive care and critical care services	413	1.3	304	1.0	1,689	1.0	1,933	0.6
Hospitalization	4,648	15.1	3,617	12.4	18,125	10.9	19,640	6.3
Psychiatrist/psychologist specialty at index visit	3,907	12.7	2,614	8.9	11,043	6.6	63,449	20.4
Number of visits to a psychiatrist/psychologist (mean std)	2.9	6.9	2.1	5.7	1.3	4.2	1.3	4.6
Number of visits to other physicians (mean std)	11.8	11.7	9.5	9.6	7.9	8.5	7.2	7.5
Number of different psychiatric drugs dispensed (mean std)	2.3	1.2	2.0	1.1	1.3	0.6	0.0	0.2
Number of emergency room visits (mean std)	2.1	5.3	1.5	4.3	1.2	3.7	1.1	3.6
Number of psychiatric-related hospitalizations (mean std)	0.0	0.2	0.0	0.1	0.0	0.1	0.0	0.1
Number of other laboratory tests (mean std)	3.4	3.7	2.9	3.3	2.7	3.2	2.3	2.8
Total costs (mean std)	10,230.3	18,417.7	6,825.9	16,700.1	5,500.7	13,470.1	4,034.6	9,865.6
Patient pharmacy costs (mean std)	795.9	714.5	523.6	549.2	352.3	431.3	240.6	361.0

Table 1b. Continued

Baseline Characteristic	Duloxetine (N=30,844)		Venlafaxine (N=29,243)		SSRIs (N=166,236)		Untreated (N=311,338)	
Specified health services (N % unless otherwise noted)								
Non-patient pharmacy costs (mean std)	1,992.5	3,678.9	1,137.4	2,136.1	711.4	2,095.9	490.7	1,548.6
Facility costs (mean std)	4,525.0	14,274.0	3,086.4	13,982.0	2,701.8	10,973.9	1,838.0	7,984.8
Number of months of prior continuous enrollment (mean std)	37.0	26.5	35.3	25.0	35.7	25.4	36.7	25.5

SSRI: selective serotonin reuptake inhibitor; ADHD: attention deficit hyperactivity disorder; CMV: cytomegalovirus; EBV: Epstein-Barr virus; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; NSAID: nonsteroidal anti-inflammatory drug; MI: myocardial infarction; ICD-9: International Classification of Diseases, 9th Edition; std: standard deviation

Table 2a. Distribution of dosage among treated study cohorts derived from the Optum Research Database, 01 August 2004 -- 30 September 2010, before and after propensity score matching

Before Propensity Score Matching	All Duloxetine Initiators (N=30,844)		All Venlafaxine Initiators (N=29,243)		All SSRI Initiators (N=166,236)	
	N	%	N	%	N	%
Above Modal Dose	1,705	5.5	11,045	37.8	29,927	18.0
Modal Dose	19,349	62.7	14,431	49.4	113,256	68.1
Below Modal Dose	9,790	31.7	3,767	12.9	23,053	13.9
After Propensity Score Matching	**Duloxetine Initiators, Matched to Any Comparator (N=29,509)**		**Venlafaxine Initiators, Matched to Duloxetine (N=21,000)**		**SSRI Initiators, Matched to Duloxetine (N=28,479)**	
	N	%	N	%	N	%
Above Modal Dose	1,598	5.4	8,156	38.8	6,056	21.3
Modal Dose	18,479	62.6	10,060	47.9	18,789	66.0
Below Modal Dose	9,432	32.0	2,784	13.3	3,634	12.8

IQR: interquartile range

The modal dose for duloxetine, based on distribution of average daily doses among duloxetine initiators prior to propensity score matching, was 60 (median [IQR]: 60 [30]). The modal dose for venlafaxine, based on distribution of average daily doses among venlafaxine initiators prior to propensity score matching, was 75 (median [IQR]: 75 [75]). The modal dose for SSRIs was calculated separately for each SSRI drug. Initiators were classified as above, at, or below the modal dose for their cohort-qualifying SSRI drug. Initiators prescribed more than 1 SSRI on the index date were classified as above modal dose.

Table 2b. Distribution of duloxetine dosage among duloxetine initiators derived from the Optum Research Database, 01 August 2004 -- 30 September 2010, after propensity score matching and stratified by matched cohort

After Propensity Score Matching	Duloxetine Initiators, Matched to Venlafaxine (N=21,000)		Duloxetine Initiators, Matched to SSRI (N=28,479)		Duloxetine Initiators, Matched to Untreated (N=22,714)	
	N	%	N	%	N	%
Above Modal Dose	1,046	5.0	1,517	5.3	1,102	4.9
Modal Dose	13,161	62.7	17,824	62.6	14,200	62.5
Below Modal Dose	6,793	32.4	9,138	32.1	7,412	32.6

IQR: interquartile range

The modal dose for duloxetine, based on distribution of average daily doses among duloxetine initiators prior to propensity score matching, was 60 (median [IQR]: 60 [30]).

Table 3a. Distribution of selected baseline characteristics for the venlafaxine and duloxetine cohorts derived from the Optum Research Database, 01 August 2004 -- 30 September 2010, after propensity score matching

Baseline Characteristic	Matched Initiators				Standardized Difference	Unmatched Duloxetine Initiators	
	Duloxetine (N=21,000)		Venlafaxine (N=21,000)			(N=9,844)	
Age group (years) (N %)*							
18-25	1,855	8.8	1,807	8.6	0.01	347	3.5
26-30	1,748	8.3	1,758	8.4	0.00	378	3.8
31-35	2,473	11.8	2,487	11.8	0.00	769	7.8
36-40	3,067	14.6	2,979	14.2	0.01	1,213	12.3
41-50	6,152	29.3	6,218	29.6	0.01	3,392	34.5
51-60	4,371	20.8	4,419	21.0	0.01	2,821	28.7
61-70	1,176	5.6	1,175	5.6	0.00	825	8.4
≥71	158	0.8	157	0.7	0.00	99	1.0
Gender (N %)*							
Female	15,074	71.8	15,092	71.9	0.00	7,412	75.3
Male	5,926	28.2	5,908	28.1	0.00	2,432	24.7
Geographic region of health plan (N %)*							
Northeast	1,344	6.4	1,343	6.4	0.00	408	4.1
Midwest	5,734	27.3	5,695	27.1	0.00	2,111	21.4
South/Southeast	11,760	56.0	11,806	56.2	0.00	6,437	65.4
West	2,162	10.3	2,156	10.3	0.00	888	9.0
Calendar year of cohort entry (N %)							
2004	1,191	5.7	1,118	5.3	0.02	467	4.7
2005	3,374	16.1	3,391	16.1	0.00	1,467	14.9
2006	4,102	19.5	4,146	19.7	0.01	1,934	19.6
2007	4,315	20.5	4,334	20.6	0.00	1,935	19.7
2008	3,687	17.6	3,663	17.4	0.00	1,687	17.1
2009	2,583	12.3	2,592	12.3	0.00	1,575	16.0
2010	1,748	8.3	1,756	8.4	0.00	779	7.9

Table 3a. Continued

Baseline Characteristic	Matched Initiators				Standardized Difference	Unmatched Duloxetine Initiators	
	Duloxetine (N=21,000)		Venlafaxine (N=21,000)			(N=9,844)	
Neuropsychological comorbidities (N %)							
Depressive disorder, not elsewhere classified*	10,000	47.6	9,957	47.4	0.00	4,464	45.3
Episodic mood disorders (with depressive component)*	6,743	32.1	6,726	32.0	0.00	4,578	46.5
Episodic mood disorders (without depressive component)*	1,436	6.8	1,416	6.7	0.00	871	8.8
Adjustment reaction*	3,086	14.7	3,057	14.6	0.00	1,458	14.8
Anxiety, dissociative and somatoform disorders*	11,252	53.6	11,172	53.2	0.01	4,557	46.3
Psychotic disorders	7,746	36.9	7,685	36.6	0.01	5,083	51.6
ADHD	959	4.6	883	4.2	0.02	574	5.8
Alcohol abuse and addiction (diagnosis)	684	3.3	683	3.3	0.00	332	3.4
Alcohol abuse and addiction (treatment)	280	1.3	320	1.5	0.02	279	2.8
Cocaine abuse and addiction	115	0.5	101	0.5	0.01	62	0.6
Heroin abuse and addiction	231	1.1	199	0.9	0.02	246	2.5
Other substance abuse and addiction	511	2.4	497	2.4	0.00	375	3.8
Smoking (tobacco use disorder - diagnosis)	1,231	5.9	1,316	6.3	0.02	688	7.0
Smoking (tobacco use disorder - treatment)	95	0.5	91	0.4	0.00	59	0.6
Overdoses	23	0.1	17	0.1	0.01	27	0.3
Suicide attempts	133	0.6	128	0.6	0.00	71	0.7
Seizure	169	0.8	172	0.8	0.00	135	1.4
Chronic pain	235	1.1	211	1.0	0.01	405	4.1
Stress urinary incontinence	207	1.0	196	0.9	0.01	126	1.3
Fibromyalgia*	1,936	9.2	1,858	8.8	0.01	2,740	27.8
Diabetes neuropathy	183	0.9	154	0.7	0.02	200	2.0
Back pain	2,974	14.2	2,863	13.6	0.02	2,733	27.8
Hepatic risks (N %)							
Hypercholesterolemia / dyslipidemia (diagnosis)	5,040	24.0	5,067	24.1	0.00	3,012	30.6
Hypercholesterolemia / dyslipidemia (treatment)	2,580	12.3	2,576	12.3	0.00	1,816	18.4
Hyperglycemia	300	1.4	319	1.5	0.01	168	1.7
Albuminuria	66	0.3	66	0.3	0.00	55	0.6

Table 3a. Continued

Baseline Characteristic	Matched Initiators				Standardized Difference	Unmatched Duloxetine Initiators	
	Duloxetine (N=21,000)		Venlafaxine (N=21,000)			(N=9,844)	
Hepatic risks (N %)							
Diabetes mellitus (diagnosis)	1,447	6.9	1,446	6.9	0.00	1,067	10.8
Diabetes mellitus (treatment)	1,317	6.3	1,302	6.2	0.00	965	9.8
CMV infection	2	0.0	3	0.0	0.00	1	0.0
EBV infection	40	0.2	42	0.2	0.00	25	0.3
Obesity (diagnosis)	1,159	5.5	1,184	5.6	0.01	700	7.1
Obesity (treatment)	5	0.0	4	0.0	0.00	3	0.0
Liver ultrasound scans*							
0	20,189	96.1	20,165	96.0	0.01	9,275	94.2
1	778	3.7	800	3.8	0.01	531	5.4
2+	33	0.2	35	0.2	0.00	38	0.4
Bilirubin test*	971	4.6	972	4.6	0.00	566	5.7
ALT/AST/ALP test*	788	3.8	790	3.8	0.00	574	5.8
NSAID use (excluding diclofenac)	5,643	26.9	5,730	27.3	0.01	4,025	40.9
NSAID use (diclofenac only)	736	3.5	710	3.4	0.01	645	6.6
Isoniazid	3	0.0	7	0.0	0.01	3	0.0
Phenytoin	45	0.2	52	0.2	0.01	41	0.4
Valproic acid	408	1.9	439	2.1	0.01	349	3.5
Nitrofurantoin	796	3.8	773	3.7	0.01	494	5.0
Propylthiouracil	10	0.0	10	0.0	0.00	3	0.0
Rifampin	39	0.2	33	0.2	0.01	30	0.3
Fluconazole*	1,684	8.0	1,701	8.1	0.00	1,034	10.5
Chlorpromazine	17	0.1	20	0.1	0.00	21	0.2
Interferon beta	66	0.3	49	0.2	0.02	41	0.4
Amiodarone	12	0.1	17	0.1	0.01	9	0.1
Statins	3,008	14.3	3,002	14.3	0.00	2,097	21.3
Naloxone	117	0.6	138	0.7	0.01	155	1.6
Naltrexone	58	0.3	74	0.4	0.01	47	0.5
Disulfiram	37	0.2	37	0.2	0.00	32	0.3
Acamprosate	92	0.4	104	0.5	0.01	68	0.7

Table 3a. Continued

Baseline Characteristic	Matched Initiators				Standardized Difference	Unmatched Duloxetine Initiators	
	Duloxetine (N=21,000)		Venlafaxine (N=21,000)			(N=9,844)	
Use of medications (N %)							
Duloxetine (excluding index drug)	0	0.0	1,007	4.8	0.32	0	0.0
Venlafaxine (excluding index drug)	1,922	9.2	0	0.0	0.45	1,699	17.3
SSRI (excluding index drug)	7,963	37.9	8,024	38.2	0.01	4,278	43.5
Other antidepressants	7,860	37.4	7,808	37.2	0.01	5,097	51.8
Bupropion	3,524	16.8	3,422	16.3	0.01	2,367	24.0
Anticonvulsants*	5,403	25.7	5,406	25.7	0.00	5,034	51.1
Anxiolytics or sedative hypnotics	10,192	48.5	10,072	48.0	0.01	6,218	63.2
Antihistamines	4,364	20.8	4,315	20.5	0.01	2,745	27.9
Antipsychotics	1,689	8.0	1,710	8.1	0.00	1,425	14.5
Narcotic analgesics	9,533	45.4	9,452	45.0	0.01	6,632	67.4
History of (N %)							
Hypertension	4,938	23.5	4,976	23.7	0.00	3,244	33.0
Stroke	288	1.4	282	1.3	0.00	241	2.4
MI	102	0.5	96	0.5	0.00	53	0.5
Angina	171	0.8	177	0.8	0.00	116	1.2
Unstable angina/acute coronary syndromes	125	0.6	101	0.5	0.02	90	0.9
Specified health services (N % unless otherwise noted)							
Number of unique ICD-9 codes*							
0-4	1,924	9.2	1,948	9.3	0.00	422	4.3
5-8	4,228	20.1	4,208	20.0	0.00	912	9.3
9-12	4,603	21.9	4,657	22.2	0.01	1,572	16.0
13-16	3,706	17.6	3,704	17.6	0.00	1,730	17.6
17+	6,539	31.1	6,483	30.9	0.01	5,208	52.9
Number of different drugs dispensed*							
0-3	2,525	12.0	2,410	11.5	0.02	132	1.3
4-7	6,365	30.3	6,427	30.6	0.01	1,250	12.7
8+	12,110	57.7	12,163	57.9	0.01	8,462	86.0

Table 3a. Continued

Baseline Characteristic	Matched Initiators				Standardized Difference	Unmatched Duloxetine Initiators	
	Duloxetine (N=21,000)		Venlafaxine (N=21,000)			(N=9,844)	
Specified health services (N % unless otherwise noted)							
Use of intensive care and critical care services*	241	1.1	221	1.1	0.01	172	1.7
Hospitalization*	2,763	13.2	2,679	12.8	0.01	1,885	19.1
Psychiatrist/psychologist specialty at index visit*	2,235	10.6	2,221	10.6	0.00	1,672	17.0
Number of visits to a psychiatrist/psychologist (mean std)*	2.4	6.1	2.4	6.2	0.01	4.0	8.2
Number of visits to other physicians (mean std)*	10.3	10.3	10.1	10.1	0.02	15.1	13.8
Number of different psychiatric drugs dispensed	2.1	1.1	2.1	1.2	0.01	2.6	1.3
Number of emergency room visits (mean std)*	1.7	4.8	1.7	4.6	0.00	2.9	6.3
Number of psychiatric-related hospitalizations (mean std)*	0.0	0.1	0.0	0.1	0.00	0.0	0.2
Number of other laboratory tests (mean std)	3.1	3.4	3.1	3.3	0.00	4.1	4.3
Total costs (mean std)*	7,944.9	14,910.5	7,685.7	14,071.0	0.02	15,105.6	23,530.8
Patient pharmacy costs (mean std)*	620.7	560.3	607.8	598.5	0.02	1,169.6	851.3
Non-patient pharmacy costs (mean std)*	1,403.4	2,410.7	1,353.0	2,357.0	0.02	3,249.2	5,262.3
Facility costs (mean std)*	3,579.3	11,802.2	3,417.9	10,735.4	0.01	6,542.4	18,311.1
Number of months of prior continuous enrollment (mean std)*	35.8	25.4	35.7	25.6	0.00	39.7	28.5
Other diagnoses, procedures, or dispensings (N %)							
Menopausal and postmenopausal disorders (ICD-9 627)*	1,878	8.9	1,881	9.0	0.00	935	9.5

SSRI: selective serotonin reuptake inhibitor; ADHD: attention deficit hyperactivity disorder; CMV: cytomegalovirus; EBV: Epstein-Barr virus; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; NSAID: nonsteroidal anti-inflammatory drug; MI: myocardial infarction; ICD-9: International Classification of Diseases, 9th Edition; std: standard deviation

* Variables that were retained in the final propensity score models across all calendar blocks for the duloxetine-venlafaxine comparison.

Table 3b. Distribution of selected baseline characteristics for the SSRI and duloxetine cohorts derived from the Optum Research Database, 01 August 2004 -- 30 September 2010, after propensity score matching

Baseline Characteristic	Matched Initiators				Standardized Difference	Unmatched Duloxetine Initiators	
	Duloxetine (N=28,479)		SSRIs (N=28,479)			(N=2,365)	
Age group (years) (N %)*							
18-25	2,154	7.6	2,057	7.2	0.01	48	2.0
26-30	2,070	7.3	1,992	7.0	0.01	56	2.4
31-35	3,101	10.9	3,128	11.0	0.00	141	6.0
36-40	4,034	14.2	4,008	14.1	0.00	246	10.4
41-50	8,667	30.4	8,733	30.7	0.01	877	37.1
51-60	6,390	22.4	6,436	22.6	0.00	802	33.9
61-70	1,817	6.4	1,871	6.6	0.01	184	7.8
≥71	246	0.9	254	0.9	0.00	11	0.5
Gender (N %)*							
Female	20,570	72.2	20,405	71.6	0.01	1,916	81.0
Male	7,909	27.8	8,074	28.4	0.01	449	19.0
Geographic region of health plan (N %)*							
Northeast	1,666	5.8	1,524	5.4	0.02	86	3.6
Midwest	7,268	25.5	7,198	25.3	0.01	577	24.4
South/Southeast	16,724	58.7	16,937	59.5	0.02	1,473	62.3
West	2,821	9.9	2,820	9.9	0.00	229	9.7
Calendar year of cohort entry (N %)							
2004	1,438	5.0	1,327	4.7	0.02	220	9.3
2005	4,246	14.9	4,281	15.0	0.00	595	25.2
2006	5,425	19.0	5,445	19.1	0.00	611	25.8
2007	5,750	20.2	5,747	20.2	0.00	500	21.1
2008	5,117	18.0	5,165	18.1	0.00	257	10.9
2009	4,042	14.2	4,037	14.2	0.00	116	4.9
2010	2,461	8.6	2,477	8.7	0.00	66	2.8

Table 3b. Continued

Baseline Characteristic	Matched Initiators				Standardized Difference	Unmatched Duloxetine Initiators (N=2,365)	
	Duloxetine (N=28,479)		SSRIs (N=28,479)				
Neuropsychological comorbidities (N %)							
Depressive disorder, not elsewhere classified*	13,256	46.5	13,545	47.6	0.02	1,208	51.1
Episodic mood disorders (with depressive component)*	9,774	34.3	9,732	34.2	0.00	1,547	65.4
Episodic mood disorders (without depressive component)*	2,029	7.1	2,033	7.1	0.00	278	11.8
Adjustment reaction*	4,173	14.7	4,084	14.3	0.01	371	15.7
Anxiety, dissociative and somatoform disorders*	14,746	51.8	14,654	51.5	0.01	1,063	44.9
Psychotic disorders	11,187	39.3	11,029	38.7	0.01	1,642	69.4
ADHD	1,377	4.8	1,431	5.0	0.01	156	6.6
Alcohol abuse and addiction (diagnosis)	928	3.3	899	3.2	0.01	88	3.7
Alcohol abuse and addiction (treatment)	469	1.6	450	1.6	0.01	90	3.8
Cocaine abuse and addiction	163	0.6	149	0.5	0.01	14	0.6
Heroin abuse and addiction	387	1.4	340	1.2	0.01	90	3.8
Other substance abuse and addiction	763	2.7	747	2.6	0.00	123	5.2
Smoking (tobacco use disorder - diagnosis)	1,740	6.1	1,797	6.3	0.01	179	7.6
Smoking (tobacco use disorder - treatment)	139	0.5	128	0.4	0.01	15	0.6
Overdoses	37	0.1	29	0.1	0.01	13	0.5
Suicide attempts	179	0.6	154	0.5	0.01	25	1.1
Seizure	264	0.9	287	1.0	0.01	40	1.7

Table 3b. Continued

Baseline Characteristic	Matched Initiators				Standardized Difference	Unmatched Duloxetine Initiators (N=2,365)	
	Duloxetine (N=28,479)		SSRIs (N=28,479)				
Neuropsychological comorbidities (N %)							
Chronic pain	538	1.9	477	1.7	0.02	102	4.3
Stress urinary incontinence	300	1.1	267	0.9	0.01	33	1.4
Fibromyalgia*	3,760	13.2	3,625	12.7	0.01	916	38.7
Diabetes neuropathy	320	1.1	308	1.1	0.00	63	2.7
Back pain	4,916	17.3	4,921	17.3	0.00	791	33.4
Hepatic risks (N %)							
Hypercholesterolemia / dyslipidemia (diagnosis)	7,237	25.4	7,381	25.9	0.01	815	34.5
Hypercholesterolemia / dyslipidemia (treatment)	3,787	13.3	3,944	13.8	0.02	609	25.8
Hyperglycemia	429	1.5	471	1.7	0.01	39	1.6
Albuminuria	105	0.4	115	0.4	0.01	16	0.7
Diabetes mellitus (diagnosis)	2,241	7.9	2,322	8.2	0.01	273	11.5
Diabetes mellitus (treatment)	2,026	7.1	2,092	7.3	0.01	256	10.8
CMV infection	3	0.0	2	0.0	0.00	0	0.0
EBV infection	57	0.2	61	0.2	0.00	8	0.3
Obesity (diagnosis)	1,662	5.8	1,685	5.9	0.00	197	8.3
Obesity (treatment)	7	0.0	5	0.0	0.00	1	0.0
Liver ultrasound scans*							
0	27,269	95.8	27,274	95.8	0.00	2,195	92.8
1	1,151	4.0	1,144	4.0	0.00	158	6.7
2+	59	0.2	61	0.2	0.00	12	0.5

Table 3b. Continued

Baseline Characteristic	Matched Initiators				Standardized Difference	Unmatched Duloxetine Initiators (N=2,365)	
	Duloxetine (N=28,479)		SSRIs (N=28,479)				
Hepatic risks (N %)							
Bilirubin test*	1,364	4.8	1,350	4.7	0.00	173	7.3
ALT/AST/ALP test*	1,205	4.2	1,208	4.2	0.00	157	6.6
NSAID use (excluding diclofenac)	8,573	30.1	8,591	30.2	0.00	1,095	46.3
NSAID use (diclofenac only)	1,206	4.2	1,203	4.2	0.00	175	7.4
Isoniazid	6	0.0	10	0.0	0.01	0	0.0
Phenytoin	80	0.3	87	0.3	0.00	6	0.3
Valproic acid	653	2.3	673	2.4	0.00	104	4.4
Nitrofurantoin	1,146	4.0	1,121	3.9	0.00	144	6.1
Propylthiouracil	13	0.0	9	0.0	0.01	0	0.0
Rifampin	60	0.2	56	0.2	0.00	9	0.4
Fluconazole*	2,428	8.5	2,417	8.5	0.00	290	12.3
Chlorpromazine	25	0.1	36	0.1	0.01	13	0.5
Interferon beta	88	0.3	88	0.3	0.00	19	0.8
Amiodarone	19	0.1	25	0.1	0.01	2	0.1
Statins	4,518	15.9	4,666	16.4	0.01	587	24.8
Naloxone	223	0.8	216	0.8	0.00	49	2.1
Naltrexone	83	0.3	85	0.3	0.00	22	0.9
Disulfiram	61	0.2	67	0.2	0.00	8	0.3
Acamprosate	142	0.5	123	0.4	0.01	18	0.8
Use of medications (N %)							
Duloxetine (excluding index drug)	0	0.0	1,454	5.1	0.33	0	0.0
Venlafaxine (excluding index drug)*	3,017	10.6	3,064	10.8	0.01	604	25.5
SSRI (excluding index drug)	11,013	38.7	0	0.0	1.12	1,228	51.9

Table 3b. Continued

Baseline Characteristic	Matched Initiators				Standardized Difference	Unmatched Duloxetine Initiators (N=2,365)	
	Duloxetine (N=28,479)		SSRIs (N=28,479)				
Use of medications (N %)							
Other antidepressants	11,385	40.0	11,163	39.2	0.02	1,572	66.5
Bupropion*	5,000	17.6	5,158	18.1	0.01	891	37.7
Anticonvulsants*	8,817	31.0	8,745	30.7	0.01	1,620	68.5
Anxiolytics or sedative hypnotics	14,698	51.6	14,701	51.6	0.00	1,712	72.4
Antihistamines	6,230	21.9	6,183	21.7	0.00	879	37.2
Antipsychotics	2,549	9.0	2,510	8.8	0.00	565	23.9
Narcotic analgesics	14,366	50.4	14,339	50.3	0.00	1,799	76.1
History of (N %)							
Hypertension	7,384	25.9	7,669	26.9	0.02	798	33.7
Stroke	469	1.6	467	1.6	0.00	60	2.5
MI	139	0.5	149	0.5	0.00	16	0.7
Angina	260	0.9	272	1.0	0.00	27	1.1
Unstable angina/acute coronary syndromes	192	0.7	184	0.6	0.00	23	1.0
Specified health services (N % unless otherwise noted)							
Number of unique ICD-9 codes*							
0-4	2,291	8.0	2,169	7.6	0.02	55	2.3
5-8	5,002	17.6	5,006	17.6	0.00	138	5.8
9-12	5,893	20.7	6,039	21.2	0.01	282	11.9
13-16	5,059	17.8	5,086	17.9	0.00	377	15.9
17+	10,234	35.9	10,179	35.7	0.00	1,513	64.0
Number of different drugs dispensed*							
0-3	2,656	9.3	2,253	7.9	0.05	1	0.0
4-7	7,553	26.5	7,654	26.9	0.01	62	2.6
8+	18,270	64.2	18,572	65.2	0.02	2,302	97.3

Table 3b. Continued

Baseline Characteristic	Matched Initiators				Standardized Difference	Unmatched Duloxetine Initiators (N=2,365)	
	Duloxetine (N=28,479)		SSRIs (N=28,479)				
Specified health services (N % unless otherwise noted)							
Use of intensive care and critical care services*	364	1.3	365	1.3	0.00	49	2.1
Hospitalization*	4,052	14.2	3,909	13.7	0.01	596	25.2
Psychiatrist/psychologist specialty at index visit*	3,359	11.8	3,372	11.8	0.00	548	23.2
Number of visits to a psychiatrist/psychologist (mean std)*	2.6	6.3	2.5	6.2	0.01	6.8	11.3
Number of visits to other physicians (mean std)*	11.2	10.9	11.1	11.6	0.01	19.2	17.6
Number of different psychiatric drugs dispensed (mean std)**	2.2	1.2	1.7	1.0	0.47	3.3	1.4
Number of emergency room visits (mean std)*	2.0	5.1	1.9	4.9	0.01	3.8	7.3
Number of psychiatric-related hospitalizations (mean std)*	0.0	0.1	0.0	0.1	0.01	0.0	0.2
Number of other laboratory tests (mean std)*	3.3	3.6	3.3	3.4	0.01	4.7	5.0
Total costs (mean std)*	9,354.0	16,773.2	9,113.6	18,729.4	0.01	20,782.8	30,262.7
Patient pharmacy costs (mean std)*	711.9	615.1	693.4	667.5	0.03	1,806.6	998.0
Non-patient pharmacy costs (mean std)*	1,723.5	3,353.3	1,639.0	2,973.7	0.03	5,231.8	5,454.5
Facility costs (mean std)*	4,219.8	13,064.4	4,154.5	15,320.8	0.00	8,199.6	24,239.5
Number of months of prior continuous enrollment (mean std)*	36.8	26.4	36.7	26.7	0.00	39.9	28.0

Table 3b. Continued

Baseline Characteristic	Matched Initiators				Standardized Difference	Unmatched Duloxetine Initiators (N=2,365)	
	Duloxetine (N=28,479)		SSRIs (N=28,479)				
Other diagnoses, procedures, or dispensings (N %)							
General symptoms (ICD-9 780)*	14,358	50.4	14,399	50.6	0.00	1,500	63.4
Ind psych insight m eval 30 mn (CPT 90805)*	3,081	10.8	3,059	10.7	0.00	708	29.9
Ind psych insight m eval 50 mn (CPT 90807)*	1,535	5.4	1,546	5.4	0.00	288	12.2
Medication management (CPT 90862)*	4,646	16.3	4,706	16.5	0.01	961	40.6
Calcium channel blocking agents*	1,590	5.6	1,635	5.7	0.01	182	7.7
Contraceptives, oral*	3,395	11.9	3,305	11.6	0.01	195	8.2
Beta-adrenergic blocking agents*	2,925	10.3	2,978	10.5	0.01	351	14.8

SSRI: selective serotonin reuptake inhibitor; ADHD: attention deficit hyperactivity disorder; CMV: cytomegalovirus; EBV: Epstein-Barr virus; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; NSAID: nonsteroidal anti-inflammatory drug; MI: myocardial infarction; ICD-9: International Classification of Diseases, 9th Edition; std: standard deviation.

* Variables that were retained in the final propensity score models across all calendar blocks for the duloxetine-SSRI comparison.

** The variable, number of different psychiatric drugs, includes enumeration of the number of antidepressant therapies used. Given the general placement of SSRIs versus duloxetine in the management pathway for depression, this variable was excluded from the stepwise regression in favor of allowing individual psychiatric drugs or drug classes to enter the duloxetine-SSRI propensity score model separately.

Table 3c. Distribution of selected baseline characteristics for the pharmacologically untreated depression and duloxetine cohorts derived from the Optum Research Database, 01 August 2004 -- 30 September 2010, after propensity score matching

Baseline Characteristic	Matched initiators				Standardized Difference	Unmatched	
	Duloxetine (N=22,714)		Untreated (N=22,714)			Duloxetine (N=8,130)	
Age group (years) (N %)*							
18-25	1,829	8.1	1,812	8.0	0.00	373	4.6
26-30	1,746	7.7	1,764	7.8	0.00	380	4.7
31-35	2,493	11.0	2,501	11.0	0.00	749	9.2
36-40	3,160	13.9	3,108	13.7	0.01	1,120	13.8
41-50	6,725	29.6	6,703	29.5	0.00	2,819	34.7
51-60	5,041	22.2	5,030	22.1	0.00	2,151	26.5
61-70	1,506	6.6	1,582	7.0	0.01	495	6.1
≥71	214	0.9	214	0.9	0.00	43	0.5
Gender (N %)*							
Female	15,974	70.3	16,020	70.5	0.00	6,512	80.1
Male	6,740	29.7	6,694	29.5	0.00	1,618	19.9
Geographic region of health plan (N %)*							
Northeast	1,338	5.9	1,298	5.7	0.01	414	5.1
Midwest	5,738	25.3	5,734	25.2	0.00	2,107	25.9
South/Southeast	13,374	58.9	13,407	59.0	0.00	4,823	59.3
West	2,264	10.0	2,275	10.0	0.00	786	9.7
Calendar year of cohort entry (N %)							
2004	1,142	5.0	1,049	4.6	0.02	516	6.3
2005	3,341	14.7	3,381	14.9	0.00	1,500	18.5
2006	4,165	18.3	4,205	18.5	0.00	1,871	23.0
2007	4,454	19.6	4,525	19.9	0.01	1,796	22.1
2008	4,153	18.3	4,109	18.1	0.01	1,221	15.0
2009	3,319	14.6	3,310	14.6	0.00	839	10.3
2010	2,140	9.4	2,135	9.4	0.00	387	4.8

Table 3c. Continued

Baseline Characteristic	Matched initiators				Standardized Difference	Unmatched	
	Duloxetine (N=22,714)		Untreated (N=22,714)			Duloxetine (N=8,130)	
Neuropsychological comorbidities (N %)							
Depressive disorder, not elsewhere classified*	9,662	42.5	9,808	43.2	0.01	4,802	59.1
Episodic mood disorders (with depressive	6,227	27.4	6,146	27.1	0.01	5,094	62.7
Episodic mood disorders (without depressive component)*	1,435	6.3	1,519	6.7	0.01	872	10.7
Adjustment reaction*	3,361	14.8	3,197	14.1	0.02	1,183	14.6
Anxiety, dissociative and somatoform disorders*	11,598	51.1	11,646	51.3	0.00	4,211	51.8
Psychotic disorders*	7,345	32.3	7,349	32.4	0.00	5,484	67.5
ADHD	1,003	4.4	1,022	4.5	0.00	530	6.5
Alcohol abuse and addiction (diagnosis)	600	2.6	544	2.4	0.02	416	5.1
Alcohol abuse and addiction (treatment)	292	1.3	270	1.2	0.01	267	3.3
Cocaine abuse and addiction	101	0.4	102	0.4	0.00	76	0.9
Heroin abuse and addiction	226	1.0	195	0.9	0.01	251	3.1
Other substance abuse and addiction	469	2.1	454	2.0	0.00	417	5.1
Smoking (tobacco use disorder - diagnosis)	1,325	5.8	1,365	6.0	0.01	594	7.3
Smoking (tobacco use disorder - treatment)	107	0.5	102	0.4	0.00	47	0.6
Overdoses	20	0.1	20	0.1	0.00	30	0.4
Suicide attempts	90	0.4	96	0.4	0.00	114	1.4
Seizure	191	0.8	198	0.9	0.00	113	1.4
Chronic pain	373	1.6	325	1.4	0.02	267	3.3
Stress urinary incontinence	222	1.0	201	0.9	0.01	111	1.4
Fibromyalgia*	2,610	11.5	2,620	11.5	0.00	2,066	25.4
Diabetic neuropathy*	260	1.1	261	1.1	0.00	123	1.5
Back pain	3,658	16.1	3,764	16.6	0.01	2,049	25.2

Table 3c. Continued

Baseline Characteristic	Matched initiators				Standardized Difference	Unmatched	
	Duloxetine (N=22,714)		Untreated (N=22,714)			Duloxetine (N=8,130)	
Hepatic risks (N %)							
Hypercholesterolemia / dyslipidemia (diagnosis)	5,877	25.9	5,948	26.2	0.01	2,175	26.8
Hypercholesterolemia / dyslipidemia (treatment)	2,937	12.9	3,035	13.4	0.01	1,459	17.9
Hyperglycemia	357	1.6	359	1.6	0.00	111	1.4
Albuminuria	86	0.4	102	0.4	0.01	35	0.4
Diabetes mellitus (diagnosis)	1,884	8.3	1,933	8.5	0.01	630	7.7
Diabetes mellitus (treatment)	1,699	7.5	1,734	7.6	0.01	583	7.2
CMV infection	2	0.0	0	0.0	0.01	1	0.0
EBV infection	44	0.2	50	0.2	0.01	21	0.3
Obesity (diagnosis)	1,348	5.9	1,389	6.1	0.01	511	6.3
Obesity (treatment)	6	0.0	6	0.0	0.00	2	0.0
Liver ultrasound scans*							
0	21,780	95.9	21,749	95.8	0.01	7,684	94.5
1	886	3.9	915	4.0	0.01	423	5.2
2+	48	0.2	50	0.2	0.00	23	0.3
Bilirubin test*	1,042	4.6	1,031	4.5	0.00	495	6.1
ALT/AST/ALP test*	924	4.1	952	4.2	0.01	438	5.4
NSAID use (excluding diclofenac)	6,534	28.8	6,776	29.8	0.02	3,134	38.5
NSAID use (diclofenac only)	900	4.0	920	4.1	0.00	481	5.9
Isoniazid	2	0.0	9	0.0	0.02	4	0.0
Phenytoin	54	0.2	82	0.4	0.02	32	0.4
Valproic acid*	451	2.0	471	2.1	0.01	306	3.8
Nitrofurantoin	875	3.9	962	4.2	0.02	415	5.1
Propylthiouracil	9	0.0	15	0.1	0.01	4	0.0
Rifampin	45	0.2	41	0.2	0.00	24	0.3
Fluconazole*	1,872	8.2	1,974	8.7	0.02	846	10.4

Table 3c. Continued

Baseline Characteristic	Matched initiators				Standardized Difference	Unmatched	
	Duloxetine (N=22,714)		Untreated (N=22,714)			Duloxetine (N=8,130)	
Hepatic risks (N %)							
Chlorpromazine	18	0.1	18	0.1	0.00	20	0.2
Interferon beta	62	0.3	58	0.3	0.00	45	0.6
Amiodarone	15	0.1	19	0.1	0.01	6	0.1
Statins	3,584	15.8	3,609	15.9	0.00	1,521	18.7
Naloxone	153	0.7	148	0.7	0.00	119	1.5
Naltrexone	44	0.2	41	0.2	0.00	61	0.8
Disulfiram	35	0.2	35	0.2	0.00	34	0.4
Acamprosate	79	0.3	62	0.3	0.01	81	1.0
Use of medications (N %)							
Duloxetine (excluding index drug)	0	0.0	0	0.0	.	0	0.0
Venlafaxine (excluding index drug)	2,200	9.7	0	0.0	0.46	1,421	17.5
SSRI (excluding index drug)	8,037	35.4	0	0.0	1.05	4,204	51.7
Other antidepressants	8,073	35.5	0	0.0	1.05	4,884	60.1
Bupropion	3,571	15.7	0	0.0	0.61	2,320	28.5
Anticonvulsants*	5,799	25.5	5,774	25.4	0.00	4,638	57.0
Anxiolytics or sedative hypnotics	10,673	47.0	10,724	47.2	0.00	5,737	70.6
Antihistamines	4,699	20.7	4,920	21.7	0.02	2,410	29.6
Antipsychotics	1,455	6.4	1,773	7.8	0.05	1,659	20.4
Narcotic analgesics	10,923	48.1	11,090	48.8	0.01	5,242	64.5
History of (N %)							
Hypertension*	6,023	26.5	6,010	26.5	0.00	2,159	26.6
Stroke	365	1.6	318	1.4	0.02	164	2.0
MI	120	0.5	111	0.5	0.01	35	0.4
Angina	214	0.9	217	1.0	0.00	73	0.9
Unstable angina/acute coronary syndromes	160	0.7	149	0.7	0.01	55	0.7

Table 3c. Continued

Baseline Characteristic	Matched initiators				Standardized Difference	Unmatched	
	Duloxetine (N=22,714)		Untreated (N=22,714)			Duloxetine (N=8,130)	
Specified health services (N % unless otherwise noted)							
Number of unique ICD-9 codes*							
0-4	2,019	8.9	1,894	8.3	0.02	327	4.0
5-8	4,270	18.8	4,145	18.2	0.01	870	10.7
9-12	4,874	21.5	4,866	21.4	0.00	1,301	16.0
13-16	4,071	17.9	4,092	18.0	0.00	1,365	16.8
17+	7,480	32.9	7,717	34.0	0.02	4,267	52.5
Number of different drugs dispensed*							
0-3	2,640	11.6	2,482	10.9	0.02	17	0.2
4-7	6,890	30.3	6,873	30.3	0.00	725	8.9
8+	13,184	58.0	13,359	58.8	0.02	7,388	90.9
Use of intensive care and critical care services*	259	1.1	245	1.1	0.01	154	1.9
Hospitalization*	2,810	12.4	2,776	12.2	0.00	1,838	22.6
Psychiatrist/psychologist specialty at index visit*	2,876	12.7	2,936	12.9	0.01	1,031	12.7
Number of visits to a psychiatrist/psychologist (mean std)*	1.9	4.7	1.8	7.1	0.01	5.9	10.2
Number of visits to other physicians (mean std)*	10.5	10.3	10.5	9.5	0.00	15.6	14.4
Number of different psychiatric drugs dispensed (mean std)**	2.0	1.1	0.1	0.4	2.44	2.9	1.3
Number of emergency room visits (mean std)*	1.7	4.6	1.7	4.6	0.01	3.3	6.9
Number of psychiatric-related hospitalizations	0.0	0.1	0.0	0.1	0.01	0.0	0.2
Number of other laboratory tests (mean std)*	3.2	3.6	3.2	3.4	0.01	4.0	4.1
Total healthcare utilization costs (mean std)*	8,295.0	15,748.1	8,201.4	15,713.5	0.01	15,637.3	23,545.4
Patient pharmacy costs (mean std)*	621.7	543.8	620.5	656.9	0.00	1,282.5	888.4
Non-patient pharmacy costs (mean std)*	1,459.2	2,539.7	1,446.8	2,965.6	0.00	3,482.5	5,505.7

Table 3c. Continued

Baseline Characteristic	Matched initiators				Standardized Difference	Unmatched	
	Duloxetine (N=22,714)		Untreated (N=22,714)			Duloxetine (N=8,130)	
Specified health services (N % unless otherwise noted)							
Facility costs (mean std)*	3,765.5	12,488.9	3,691.3	12,632.2	0.01	6,646.7	18,197.3
Number of months of prior continuous enrollment (mean std)*	36.7	26.4	36.9	26.0	0.01	37.8	26.9
Corticosteroids (dispensings)*	4,764	21.0	4,807	21.2	0.00	2,097	25.8
General symptoms (ICD-9 780)*	10,894	48.0	11,153	49.1	0.02	4,964	61.1
Ind psych insight m eval 30 mn (CPT 90805)*	1,787	7.9	1,756	7.7	0.01	2,002	24.6
Ind psych insight inoff 50 mn (CPT 90806)*	4,566	20.1	4,406	19.4	0.02	2,518	31.0
Other diagnoses, procedures, or dispensings (N %)							
Ind psych insight m eval 50 mn (CPT 90807)*	912	4.0	914	4.0	0.00	911	11.2
Medication management (CPT 90862)*	2,711	11.9	2,674	11.8	0.01	2,896	35.6
Office/outpatient visit (CPT 99213)*	18,797	82.8	18,944	83.4	0.02	7,137	87.8
Emergency dept visit (CPT 99285)*	2,219	9.8	2,256	9.9	0.01	1,182	14.5
Sedative-hypnotics, non-barbiturate*	4,670	20.6	4,664	20.5	0.00	3,373	41.5
Anti-mania drugs*	307	1.4	349	1.5	0.02	198	2.4
Platelet aggregation inhibitors*	405	1.8	389	1.7	0.01	134	1.6
Topical anti-inflammatory steroidal*	1,860	8.2	1,879	8.3	0.00	675	8.3
Penicillins*	5,747	25.3	5,843	25.7	0.01	2,179	26.8
Macrolides*	6,166	27.1	6,173	27.2	0.00	2,315	28.5
Quinolones*	4,828	21.3	4,889	21.5	0.01	2,140	26.3
Antivirals, general*	1,887	8.3	1,875	8.3	0.00	739	9.1

SSRI: selective serotonin reuptake inhibitor; ADHD: attention deficit hyperactivity disorder; CMV: cytomegalovirus; EBV: Epstein-Barr virus; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; NSAID: nonsteroidal anti-inflammatory drug; MI: myocardial infarction; ICD-9: International Classification of Diseases, 9th Edition; std: standard deviation

* Variables that were retained in the final propensity score models across all calendar blocks for the duloxetine-pharmacologically untreated depression comparison.

** The variable, number of different psychiatric drugs, includes enumeration of the number of antidepressant therapies used. Given the restrictions on prior antidepressant use applied during creation of the pharmacologically untreated cohort, this variable was excluded from the stepwise regression in favor of allowing individual psychiatric drugs or drug classes to enter the duloxetine-untreated propensity score model separately.

Table 4. Medical record-validation of baseline comparability (including exclusions) of cohorts among randomly selected patients from the matched duloxetine cohort

	Baseline Validation Sample: Duloxetine Initiators With Abstracted Medical Records							
	Overall, Matched to At Least One Comparator		Matched to Venlafaxine		Matched to SSRI		Matched to Untreated	
Baseline Characteristic	N=213		N=158		N=203		N=150	
Average propensity score (mean std)	NA	NA	0.52	0.15	0.30	0.21	0.29	0.24
Demographic and lifestyle factors (N %)								
Obesity	44	20.7	33	20.9	43	21.2	32	21.3
Alcohol use or abuse	13	6.1	8	5.1	13	6.4	10	6.7
Cigarette Smoking / Tobacco Use: Current	44	20.7	34	21.5	42	20.7	27	18.0
Cigarette Smoking / Tobacco Use: Past	10	4.7	8	5.1	10	4.9	5	3.3
Neuropsychological comorbidities (N % unless otherwise noted)								
Psychotic disorders	9	4.2	4	2.5	9	4.5	5	3.4
Attention deficit / hyperactivity disorder	10	4.7	5	3.2	10	4.9	6	4.0
IV drug use	0	0.0	0	0.0	0	0.0	0	0.0
Cocaine abuse and addiction	1	0.5	1	0.6	1	0.5	1	0.7
Heroin abuse and addiction	1	0.5	1	0.6	1	0.5	1	0.7
Polysubstance abuse and addiction	4	1.9	4	2.6	4	2.0	3	2.0
History of overdoses	0	0.0	0	0.0	0	0.0	0	0.0
History of seizure	2	0.9	1	0.6	2	1.0	2	1.3
Suicide attempt related to hospitalization	0	0.0	0	0.0	0	0.0	0	0.0

Table 4. Continued

Baseline Characteristic	Baseline Validation Sample: Duloxetine Initiators With Abstracted Medical Records							
	Overall, Matched to At Least One Comparator		Matched to Venlafaxine		Matched to SSRI		Matched to Untreated	
	N=213		N=158		N=203		N=150	
Neuropsychological comorbidities (N % unless otherwise noted)								
Number of suicide attempts (mean std)	0.2	0.5	0.2	0.6	0.2	0.5	0.2	0.6
Anxiety disorders	79	37.1	55	35.5	77	38.7	54	36.7
Chronic pain	34	16.0	19	12.1	33	16.5	21	14.0
Stress urinary incontinence	1	0.5	1	0.6	1	0.5	1	0.7
Fibromyalgia	17	8.0	10	6.3	15	7.4	11	7.3
Diabetes neuropathy	4	1.9	3	1.9	4	2.0	2	1.3
Low back pain	23	10.8	10	6.4	21	10.5	14	9.4
Hepatic comorbidities (N %)								
Hepatic insufficiency / failure	0	0.0	0	0.0	0	0.0	0	0.0
Positive markers for hepatitis B surface antigen or E antigen	0	0.0	0	0.0	0	0.0	0	0.0
Positive markers for hepatitis C infection	0	0.0	0	0.0	0	0.0	0	0.0
Abnormal liver enzymes	8	3.8	6	3.8	7	3.5	7	4.7
Abnormal bilirubin	0	0.0	0	0.0	0	0.0	0	0.0
Non-alcoholic hepatitis	0	0.0	0	0.0	0	0.0	0	0.0
Chronic liver disease	3	1.4	2	1.3	3	1.5	2	1.3
Primary or metastatic neoplasia of the liver and hepatic ducts	0	0.0	0	0.0	0	0.0	0	0.0

SSRI: selective serotonin reuptake inhibitors; std: standard deviation; IV: intravenous

Table 5a. Medical record identification of baseline cohort characteristics: participants in the overall duloxetine and comparator validation samples with abstracted medical records

Baseline Characteristic	Duloxetine, Matched to At Least One Comparator		Venlafaxine		SSRI		Untreated	
Overall matched cohort	**N=29,509**		**N=21,000**		**N=28,479**		**N=22,714**	
Mean propensity score (std)	NA	NA	0.51	0.15	0.29	0.20	0.30	0.24
Baseline validation sample: participants with abstracted charts	**N=213**		**N=212**		**N=223**		**N=212**	
Mean propensity score (std)	NA	NA	0.51	0.15	0.29	0.20	0.30	0.24
Demographic and lifestyle factors (N %)								
Obesity	44	20.7	38	17.9	42	18.8	38	17.9
Alcohol use or abuse	13	6.1	18	8.5	7	3.1	8	3.8
Cigarette Smoking / Tobacco Use: Current	44	20.7	35	16.5	25	11.2	41	19.3
Cigarette Smoking / Tobacco Use: Past	10	4.7	13	6.1	20	9.0	18	8.5
Neuropsychological comorbidities (N % unless otherwise noted)								
Psychotic disorders	9	4.2	9	4.3	9	4.1	12	5.7
Attention deficit / hyperactivity disorder	10	4.7	10	4.7	6	2.7	8	3.8
IV drug use	0	0.0	0	0.0	0	0.0	2	0.9
Cocaine abuse and addiction	1	0.5	1	0.5	1	0.5	2	1.0
Heroin abuse and addiction	1	0.5	0	0.0	0	0.0	2	0.9
Polysubstance abuse and addiction	4	1.9	3	1.4	3	1.4	4	1.9
History of overdoses	0	0.0	1	0.5	0	0.0	2	0.9
History of seizure	2	0.9	0	0.0	0	0.0	2	1.0
Suicide attempt related to hospitalization	0	0.0	2	1.0	0	0.0	1	0.5
Number of suicide attempts (mean std)	0.2	0.5	0.4	0.6	0.1	0.2	0.4	1.2
Anxiety disorders	79	37.1	99	48.3	80	36.9	76	36.5
Chronic pain	34	16.0	24	11.3	39	17.5	29	13.8
Stress urinary incontinence	1	0.5	0	0.0	4	1.8	2	0.9

Table 5a. Continued

Baseline validation sample: participants with abstracted charts	N=213		N=212		N=223		N=212	
Neuropsychological comorbidities (N % unless otherwise noted)								
Fibromyalgia	17	8.0	3	1.4	6	2.7	5	2.4
Diabetes neuropathy	4	1.9	1	0.5	0	0.0	1	0.5
Low back pain	23	10.8	14	6.6	30	13.5	28	13.3
Hepatic comorbidities								
Hepatic insufficiency / failure	0	0.0	0	0.0	0	0.0	0	0.0
Positive markers for hepatitis B surface	0	0.0	1	0.5	0	0.0	0	0.0
Positive markers for hepatitis C infection	0	0.0	0	0.0	0	0.0	0	0.0
Abnormal liver enzymes	8	3.8	10	4.7	8	3.6	6	2.8
Abnormal bilirubin	0	0.0	3	1.4	2	0.9	0	0.0
Non-alcoholic hepatitis	0	0.0	0	0.0	0	0.0	0	0.0
Chronic liver disease	3	1.4	1	0.5	2	0.9	2	1.0
Primary or metastatic neoplasia of the liver and hepatic ducts	0	0.0	0	0.0	0	0.0	0	0.0

SSRI: selective serotonin reuptake inhibitor; std: standard deviation; IV: intravenous

Table 5b. Medical record identification of baseline cohort characteristics: matched duloxetine-venlafaxine cohorts

Baseline Characteristic	Duloxetine		Venlafaxine		P-value*
Overall matched cohort	**N=21,000**		**N=21,000**		
Mean propensity score (std)	0.51	0.15	0.51	0.15	NS
Baseline validation sample: participants with abstracted charts	**N=158**		**N=212**		**P-value***
Mean propensity score (std)	0.52	0.15	0.51	0.15	NS
Demographic and lifestyle factors (N %)					
Obesity	33	20.9	38	17.9	NS
Alcohol use or abuse	8	5.1	18	8.5	NS
Cigarette Smoking / Tobacco Use: Current	34	21.5	35	16.5	NS
Cigarette Smoking / Tobacco Use: Past	8	5.1	13	6.1	NS
Neuropsychological comorbidities (N % unless otherwise noted)					
Psychotic disorders	4	2.5	9	4.3	NS
Attention deficit / hyperactivity disorder	5	3.2	10	4.7	NS
IV drug use	0	0.0	0	0.0	–
Cocaine abuse and addiction	1	0.6	1	0.5	NS
Heroin abuse and addiction	1	0.6	0	0.0	NS
Polysubstance abuse and addiction	4	2.6	3	1.4	NS
History of overdoses	0	0.0	1	0.5	NS
History of seizure	1	0.6	0	0.0	NS
Suicide attempt related to hospitalization	0	0.0	2	1.0	NS
Number of suicide attempts (mean std)	0.2	0.6	0.4	0.6	NS
Anxiety disorders	55	35.5	99	48.3	0.02
Chronic pain	19	12.1	24	11.3	NS
Stress urinary incontinence	1	0.6	0	0.0	NS

Table 5b. Continued

Baseline validation sample: participants with abstracted charts	N=158		N=212		P-value*
Neuropsychological comorbidities (N % unless otherwise noted)					
Fibromyalgia	10	6.3	3	1.4	0.01
Diabetes neuropathy	3	1.9	1	0.5	NS
Low back pain	10	6.4	14	6.6	NS
Hepatic comorbidities (N %)					
Hepatic insufficiency / failure	0	0.0	0	0.0	–
Positive markers for hepatitis B surface antigen or E	0	0.0	1	0.5	NS
Positive markers for hepatitis C infection	0	0.0	0	0.0	–
Abnormal liver enzymes	6	3.8	10	4.7	NS
Abnormal bilirubin	0	0.0	3	1.4	NS
Non-alcoholic hepatitis	0	0.0	0	0.0	–
Chronic liver disease	2	1.3	1	0.5	NS
Primary or metastatic neoplasia of the liver and hepatic ducts	0	0.0	0	0.0	–

SSRI: selective serotonin reuptake inhibitors; std: standard deviation; IV: intravenous; NS: not statistically significant ($p \geq 0.05$)

* P value from Chi-square test (or Fisher's exact test) for categorical variables and from T-test for continuous variables.

Table 5c. Medical record identification of baseline cohort characteristics: matched duloxetine-SSRI cohorts

Baseline Characteristic	Duloxetine		SSRI		P-value*
Overall propensity score-matched cohort	**N=28,479**		**N=28,479**		
Mean propensity score (std)	0.29	0.20	0.29	0.20	NS
Baseline validation sample: participants with abstracted charts	**N=203**		**N=223**		**P-value***
Mean propensity score (std)	0.30	0.21	0.29	0.20	NS
Demographic and lifestyle factors (N %)					
Obesity	43	21.2	42	18.8	NS
Alcohol use or abuse	13	6.4	7	3.1	NS
Cigarette Smoking / Tobacco Use: Current	42	20.7	25	11.2	0.01
Cigarette Smoking / Tobacco Use: Past	10	4.9	20	9.0	NS
Neuropsychological comorbidities (N % unless otherwise noted)					
Psychotic disorders	9	4.5	9	4.1	NS
Attention deficit / hyperactivity disorder	10	4.9	6	2.7	NS
IV drug use	0	0.0	0	0.0	–
Cocaine abuse and addiction	1	0.5	1	0.5	NS
Heroin abuse and addiction	1	0.5	0	0.0	NS
Polysubstance abuse and addiction	4	2.0	3	1.4	NS
History of overdoses	0	0.0	0	0.0	–
History of seizure	2	1.0	0	0.0	NS
Suicide attempt related to hospitalization	0	0.0	0	0.0	–
Number of suicide attempts (mean std)	0.2	0.5	0.1	0.2	NS
Anxiety disorders	77	38.7	80	36.9	NS
Chronic pain	33	16.5	39	17.5	NS
Stress urinary incontinence	1	0.5	4	1.8	NS

Table 5c. Continued

Baseline validation sample: participants with abstracted charts	N=203		N=223		P-value*
Neuropsychological comorbidities (N % unless otherwise noted)					
Fibromyalgia	15	7.4	6	2.7	0.03
Diabetes neuropathy	4	2.0	0	0.0	0.04
Low back pain	21	10.5	30	13.5	NS
Hepatic comorbidities (N %)					
Hepatic insufficiency / failure	0	0.0	0	0.0	–
Positive markers for hepatitis B surface antigen or E antigen	0	0.0	0	0.0	–
Positive markers for hepatitis C infection	0	0.0	0	0.0	–
Abnormal liver enzymes	7	3.5	8	3.6	NS
Abnormal bilirubin	0	0.0	2	0.9	NS
Non-alcoholic hepatitis	0	0.0	0	0.0	–
Chronic liver disease	3	1.5	2	0.9	NS
Primary or metastatic neoplasia of the liver and hepatic ducts	0	0.0	0	0.0	–

SSRI: selective serotonin reuptake inhibitors; std: standard deviation; IV: intravenous; NS: not statistically significant ($p \geq 0.05$)

* P value from Chi-square test (or Fisher's exact test) for categorical variables and from T-test for continuous variables.

Table 5d. Medical record identification of baseline cohort characteristics: matched duloxetine-pharmacologically untreated cohorts

Baseline Characteristic	Duloxetine		Untreated		P-value*
Overall propensity score-matched cohort	**N=22,714**		**N=22,714**		
Mean propensity score (std)	0.30	0.24	0.30	0.24	NS
Baseline validation sample: participants with abstracted charts	**N=150**		**N=212**		**P-value***
Mean propensity score (std)	0.29	0.24	0.30	0.24	NS
Demographic and lifestyle factors (N %)					
Obesity	32	21.3	38	17.9	NS
Alcohol use or abuse	10	6.7	8	3.8	NS
Cigarette Smoking / Tobacco Use: Current	27	18.0	41	19.3	NS
Cigarette Smoking / Tobacco Use: Past	5	3.3	18	8.5	0.05
Neuropsychological comorbidities (N % unless otherwise noted)					
Psychotic disorders	5	3.4	12	5.7	NS
Attention deficit / hyperactivity disorder	6	4.0	8	3.8	NS
IV drug use	0	0.0	2	0.9	NS
Cocaine abuse and addiction	1	0.7	2	1.0	NS
Heroin abuse and addiction	1	0.7	2	0.9	NS
Polysubstance abuse and addiction	3	2.0	4	1.9	NS
History of overdoses	0	0.0	2	0.9	NS
History of seizure	2	1.3	2	1.0	NS
Suicide attempt related to hospitalization	0	0.0	1	0.5	NS
Number of suicide attempts (mean std)	0.2	0.6	0.4	1.2	NS
Anxiety disorders	54	36.7	76	36.5	NS
Chronic pain	21	14.0	29	13.8	NS
Stress urinary incontinence	1	0.7	2	0.9	NS

Table 5d. Continued

Baseline validation sample: participants with abstracted charts	N=150		N=212		P-value*
Neuropsychological comorbidities (N % unless otherwise noted)					
Fibromyalgia	11	7.3	5	2.4	0.02
Diabetes neuropathy	2	1.3	1	0.5	NS
Low back pain	14	9.4	28	13.3	NS
Hepatic comorbidities (N %)					
Hepatic insufficiency / failure	0	0.0	0	0.0	–
Positive markers for hepatitis B surface antigen or E antigen	0	0.0	0	0.0	–
Positive markers for hepatitis C infection	0	0.0	0	0.0	–
Abnormal liver enzymes	7	4.7	6	2.8	NS
Abnormal bilirubin	0	0.0	0	0.0	–
Non-alcoholic hepatitis	0	0.0	0	0.0	–
Chronic liver disease	2	1.3	2	1.0	NS
Primary or metastatic neoplasia of the liver and hepatic ducts	0	0.0	0	0.0	–

SSRI: selective serotonin reuptake inhibitors; std: standard deviation; IV: intravenous; NS: not statistically significant ($p \geq 0.05$)

* P value from Chi-square test (or Fisher's exact test) for categorical variables and from T-test for continuous variables.

Table 6a. Validation of hepatic events identified through claims data by review of medical records

Claims-Identified Hepatic Event	Number Identified in Claims Data*	Number Reviewed	All cases adjudicated (prior to restriction to current therapy plus 15- or 30-day window)							
			Not an Event	Confirmed event, with or without documented alternate etiology**				Confirmed event, without documented alternate etiology			
				DT	LF	OH	EE	DT	LF	OH	EE
Potential hepatic-related death (episode-level)	9	6	5	0	0	1	0	0	0	0	0
Potential hepatic failure (episode-level)	32	25	15	0	0	10	0	0	0	1	0
Potential other clinically significant hepatic injury, excluding claims-identified hepatic-related death and hepatic failure episodes (episode-level)	928	685	642	0	0	36	7	0	0	11	6
Total potential hepatic injuries (episode-level)	969	716	662	0	0	47	7	0	0	12	6
Potential other clinically significant hepatic injury (individual-level)***	962	712	666	0	0	46	7	0	0	12	6
Potential non-serious hepatic enzyme elevation (individual-level)****	962	712	705	0	0	46	7	0	0	12	6

DT: hepatic-related death; LF: hepatic (liver) failure; OH: other clinically significant hepatic injury; EE: non-serious hepatic enzyme elevation; NA: not applicable

* A total of 969 potential events were identified for 962 individuals.

** Alternate etiologies documented upon medical record review included: cholelithiasis with or without pancreatitis; liver injury following motor vehicle accident; acetominophen toxicity; alcohol-related injury; Epstein Barr virus; hepatitis C virus; fatty liver disease; hypotension; sepsis; other medications; pancreatic cancer; and lymphoma.

*** Confirmed cases of other clinically significant hepatic injury could be adjudicated from any potential event identified in the initial claims screen (i.e., from any diagnosis or procedure code used to identify potential hepatic-related death, hepatic failure, or other clinically significant hepatic injury). For individuals with more than one claims-identified hepatic event, the first claims-identified event was retained for the analysis. Among the 962 individuals who had at least one claims-identified hepatic event, 46 unique cases of other clinically significant hepatic injury were confirmed, of which 12 were confirmed cases without documented alternate etiology. In the case of one individual who had a claims-identified hepatic-related death and a claims-identified other clinically significant hepatic injury event, review of the medical records indicated that the two claims-identified events represented a single episode of other clinically significant hepatic injury.

**** Confirmed cases of non-serious hepatic enzyme elevation could be adjudicated from any potential event identified in the initial claims screen (i.e., any diagnosis or procedure codes used to identify potential occurrences of hepatic-related death, hepatic failure, or other clinically significant hepatic injury). For individuals with more than one claims-identified hepatic event, the first claims-identified event was retained for the analysis of other clinically significant hepatic injury.

Table 6b. Diagnostic characteristics of non-confirmed potential cases

Claims-identified event	Total number of non-confirmed potential events*	Reason for non-confirmation						
		Chart not available for review	Confirmed as "not a hepatic event"	Confirmed event attributed to alternate etiology	Confirmed as another hepatic outcome			
					DT	LF	OH	EE
Potential hepatic-related death (episode-level) (n=9)	9	3	5	1	NA	0	0	0
Potential hepatic failure (episode-level) (n=32)	32	7	15	9	0	NA	1	0
Potential other clinically significant hepatic injury, excluding claims-identified hepatic-related death and hepatic failure (episode-level) (n=928)	917	243	642	26	0	0	NA	6
Total potential hepatic injuries (episode-level) (n=969)	951	253	662	36	0	0	12	6
Potential other clinically significant hepatic injury (individual-level) (n=962) **	950	250	659	35	0	0	NA	6
Potential non-serious hepatic enzyme elevation (individual-level) (n=962) ***	956	250	659	35	0	0	12	NA

DT: hepatic-related death; LF: hepatic (liver) failure; OH: other clinically significant hepatic injury; EE: non-serious hepatic enzyme elevation; NA: Not applicable

* Number of non-confirmed potential events prior to additional restrictions to current therapy plus 15- or 30-day exposure window.

** Confirmed cases of other clinically significant hepatic injury could be adjudicated from any potential event identified in the initial claims screen (i.e., from any diagnosis or procedure code used to identify potential hepatic-related death, hepatic failure, or other clinically significant hepatic injury). For individuals with more than one claims-identified hepatic event, the first claims-identified event was retained for the analysis. Among the 962 individuals who had at least one claims-identified hepatic event, 46 unique cases of other clinically significant hepatic injury were confirmed, of which 12 were confirmed cases without documented alternate etiology. In the case of one individual who had a claims-identified hepatic-related death and a claims-identified other clinically significant hepatic injury event, review of the medical records indicated that the two claims-identified events represented a single episode of other clinically significant hepatic injury.

*** Confirmed cases of non-serious hepatic enzyme elevation could be adjudicated from any potential event identified in the initial claims screen (i.e., any diagnosis or procedure codes used to identify potential occurrences of hepatic-related death, hepatic failure, or other clinically significant hepatic injury). For individuals with more than one claims-identified hepatic event, the first claims-identified event was retained for the analysis of other clinically significant hepatic injury.

Table 7a. Incidence rate (IR), as-matched rate ratio (RR), and 95% confidence interval (CI) of hepatic events in the matched duloxetine and comparator cohorts, all follow-up through 15 days following treatment discontinuation

Outcome of Interest	Cohort	Person-Years	Number of Cases	IR	95% CI Lower	95% CI Upper	Unadjusted RR	95% CI Lower	95% CI Upper
Hepatic-related death	Duloxetine	7,633.5	0	0.0	0.0	0.4	NA	NA	NA
	Venlafaxine	8,838.7	0	0.0	0.0	0.3			
	Duloxetine	10,411.9	0	0.0	0.0	0.3	NA	NA	NA
	SSRI	9,835.6	0	0.0	0.0	0.3			
	Duloxetine	8,116.7	0	0.0	0.0	0.4	NA	NA	NA
	Untreated	5,966.1	0	0.0	0.0	0.5			
Hepatic failure	Duloxetine	7,631.7	0	0.0	0.0	0.4	NA	NA	NA
	Venlafaxine	8,836.6	0	0.0	0.0	0.3			
	Duloxetine	10,410.6	0	0.0	0.0	0.3	NA	NA	NA
	SSRI	9,833.9	0	0.0	0.0	0.3			
	Duloxetine	8,116.2	0	0.0	0.0	0.4	NA	NA	NA
	Untreated	5,965.8	0	0.0	0.0	0.5			
Other clinically significant hepatic injury	Duloxetine	7,548.5	5	0.7	0.2	1.5	HR: NA	NA	NA
	Venlafaxine	8,745.2	0	0.0	0.0	0.3	IRR: undef.	1.1	inf.
	Duloxetine	10,300.9	4	0.4	0.1	1.0	HR: NA	NA	NA
	SSRI	9,753.2	0	0.0	0.0	0.3	IRR: undef.	0.6	inf.
	Duloxetine	8,035.8	4	0.5	0.1	1.3	HR: 1.2	0.3	5.3
	Untreated	5,931.9	3	0.5	0.1	1.5	IRR: 1.0	0.2	6.7

Table 7a. Continued

Outcome of Interest	Cohort	Person-Years	Number of Cases	IR	95% CI Lower	95% CI Upper	Unadjusted RR		95% CI Lower	95% CI Upper
Hepatic-related death and liver failure combined	Duloxetine	7,631.7	0	0.0	0.0	0.4		NA	NA	NA
	Venlafaxine	8,836.6	0	0.0	0.0	0.3				
	Duloxetine	10,410.6	0	0.0	0.0	0.3		NA	NA	NA
	SSRI	9,833.8	0	0.0	0.0	0.3				
	Duloxetine	8,116.2	0	0.0	0.0	0.4		NA	NA	NA
	Untreated	5,965.6	0	0.0	0.0	0.5				
All clinically significant hepatic categories combined	Duloxetine	7,548.5	5	0.7	0.2	1.5	HR:	NA	NA	NA
	Venlafaxine	8,745.2	0	0.0	0.0	0.3	IRR:	undef.	1.1	inf.
	Duloxetine	10,300.9	4	0.4	0.1	1.0	HR:	NA	NA	NA
	SSRI	9,753.2	0	0.0	0.0	0.3	IRR:	undef.	0.6	inf.
	Duloxetine	8,035.8	4	0.5	0.1	1.3	HR:	1.2	0.3	5.3
	Untreated	5,931.9	3	0.5	0.1	1.5	IRR:	1.0	0.2	6.7
Non-serious hepatic enzyme elevation	Duloxetine	7,548.5	1	0.1	0.0	0.7	HR:	NA	NA	NA
	Venlafaxine	8,745.2	0	0.0	0.0	0.3	IRR:	undef.	0.0	inf.
	Duloxetine	10,300.9	1	0.1	0.0	0.5	HR:	0.5	0.0	5.3
	SSRI	9,753.0	2	0.2	0.0	0.7	IRR:	0.5	0.0	9.1
	Duloxetine	8,035.8	1	0.1	0.0	0.7	HR:	NA	NA	NA
	Untreated	5,932.0	0	0.0	0.0	0.5	IRR:	undef.	0.0	inf.

IR: incidence rate, representing number of events per 1,000 person-years; CI: confidence interval; RR: rate ratio; NA: not available; HR: hazard ratio; IRR: incidence rate ratio; undef.=undefined; inf.=infinity

Table 7b. Incidence rate (IR), as-matched rate ratio (RR), and 95% confidence interval (CI) of hepatic events in the matched duloxetine and comparator cohorts, follow-up censored at 90 days following cohort entry

Outcome of Interest	Cohort	Person-Years	Number of Cases	IR	95% CI Lower	95% CI Upper	Unadjusted RR	95% CI Lower	95% CI Upper
Hepatic-related death	Duloxetine	3,792.1	0	0.0	0.0	0.8	NA	NA	NA
	Venlafaxine	3,901.7	0	0.0	0.0	0.8			
	Duloxetine	5,167.7	0	0.0	0.0	0.6	NA	NA	NA
	SSRI	5,121.7	0	0.0	0.0	0.6			
	Duloxetine	4,097.6	0	0.0	0.0	0.7	NA	NA	NA
	Untreated	3,715.3	0	0.0	0.0	0.8			
Hepatic failure	Duloxetine	3,792.0	0	0.0	0.0	0.8	NA	NA	NA
	Venlafaxine	3,901.6	0	0.0	0.0	0.8			
	Duloxetine	5,167.4	0	0.0	0.0	0.6	NA	NA	NA
	SSRI	5,121.3	0	0.0	0.0	0.6			
	Duloxetine	4,097.4	0	0.0	0.0	0.7	NA	NA	NA
	Untreated	3,714.8	0	0.0	0.0	0.8			
Other clinically significant hepatic injury	Duloxetine	3,779.5	3	0.8	0.2	2.3	HR: NA	NA	NA
	Venlafaxine	3,890.6	0	0.0	0.0	0.8	IRR: undef.	0.4	inf.
	Duloxetine	5,150.9	2	0.4	0.0	1.4	HR: NA	NA	NA
	SSRI	5,108.2	0	0.0	0.0	0.6	IRR: undef.	0.2	inf.
	Duloxetine	4,084.0	3	0.7	0.2	2.1	HR: 0.9	0.2	4.6
	Untreated	3,703.4	3	0.8	0.2	2.4	IRR: 0.9	0.1	6.8

Table 7b. Continued

Outcome of Interest	Cohort	Person-Years	Number of Cases	IR	95% CI Lower	95% CI Upper	Unadjusted RR		95% CI Lower	95% CI Upper
Hepatic-related death and liver failure combined	Duloxetine	3,792.0	0	0.0	0.0	0.8		NA	NA	NA
	Venlafaxine	3,901.6	0	0.0	0.0	0.8				
	Duloxetine	5,167.4	0	0.0	0.0	0.6		NA	NA	NA
	SSRI	5,121.3	0	0.0	0.0	0.6				
	Duloxetine	4,097.4	0	0.0	0.0	0.7		NA	NA	NA
	Untreated	3,714.8	0	0.0	0.0	0.8				
All clinically significant hepatic categories combined	Duloxetine	3,779.5	3	0.8	0.2	2.3	HR:	NA	NA	NA
	Venlafaxine	3,890.6	0	0.0	0.0	0.8	IRR:	undef.	0.4	inf.
	Duloxetine	5,150.9	2	0.4	0.0	1.4	HR:	NA	NA	NA
	SSRI	5,108.2	0	0.0	0.0	0.6	IRR:	undef.	0.2	inf.
	Duloxetine	4,084.0	3	0.7	0.2	2.1	HR:	0.9	0.2	4.6
	Untreated	3,703.4	3	0.8	0.2	2.4	IRR:	0.9	0.1	6.8
Non-serious hepatic enzyme elevation	Duloxetine	3,779.5	0	0.0	0.0	0.8		NA	NA	NA
	Venlafaxine	3,890.6	0	0.0	0.0	0.8				
	Duloxetine	5,150.9	0	0.0	0.0	0.6	HR:	NA	NA	NA
	SSRI	5,108.0	2	0.4	0.0	1.4	IRR:	0.0	0.0	5.3
	Duloxetine	4,084.0	0	0.0	0.0	0.7		NA	NA	NA
	Untreated	3,703.4	0	0.0	0.0	0.8				

IR: incidence rate, representing number of events per 1,000 person-years; CI: confidence interval; RR: rate ratio; NA: not available; HR: hazard ratio; IRR: incidence rate ratio; undef.=undefined; inf.=infinity

Table 8. Sensitivity analysis for all clinically significant events combined and for each outcome category: follow-up through 30 days following treatment discontinuation

Outcome of Interest	Cohort	Person-Years	Number of Cases	IR	95% CI Lower	95% CI Upper	Unadjusted RR		95% CI Lower	95% CI Upper
Hepatic-related death	Duloxetine	8,321.8	0	0.0	0.0	0.4		NA	NA	NA
	Venlafaxine	9,500.3	0	0.0	0.0	0.3				
	Duloxetine	11,345.2	0	0.0	0.0	0.3		NA	NA	NA
	SSRI	10,784.5	0	0.0	0.0	0.3				
	Duloxetine	8,862.7	0	0.0	0.0	0.3		NA	NA	NA
	Untreated	6,540.5	0	0.0	0.0	0.5				
Hepatic failure	Duloxetine	8,319.8	0	0.0	0.0	0.4		NA	NA	NA
	Venlafaxine	9,498.0	0	0.0	0.0	0.3				
	Duloxetine	11,343.6	0	0.0	0.0	0.3		NA	NA	NA
	SSRI	10,782.6	0	0.0	0.0	0.3				
	Duloxetine	8,862.0	0	0.0	0.0	0.3		NA	NA	NA
	Untreated	6,540.0	0	0.0	0.0	0.5				
Other clinically significant hepatic injury	Duloxetine	8,230.3	5	0.6	0.2	1.4	HR:	NA	NA	NA
	Venlafaxine	9,400.2	0	0.0	0.0	0.3	IRR:	undef.	1.0	inf.
	Duloxetine	11,225.0	4	0.4	0.1	0.9	HR:	NA	NA	NA
	SSRI	10,694.6	0	0.0	0.0	0.3	IRR:	undef.	0.6	inf.
	Duloxetine	8,775.0	4	0.5	0.1	1.2	HR:	1.2	0.3	5.3
	Untreated	6,502.4	3	0.5	0.1	1.3	IRR:	1.0	0.2	6.7

Table 8. Continued

Outcome of Interest	Cohort	Person-Years	Number of Cases	IR	95% CI Lower	95% CI Upper	Unadjusted RR		95% CI Lower	95% CI Upper
Hepatic-related death and liver failure combined	Duloxetine	8,319.8	0	0.0	0.0	0.4		NA	NA	NA
	Venlafaxine	9,497.9	0	0.0	0.0	0.3				
	Duloxetine	11,343.6	0	0.0	0.0	0.3		NA	NA	NA
	SSRI	10,782.6	0	0.0	0.0	0.3				
	Duloxetine	8,862.0	0	0.0	0.0	0.3		NA	NA	NA
	Untreated	6,539.8	0	0.0	0.0	0.5				
All clinically significant hepatic categories combined	Duloxetine	8,230.3	5	0.6	0.2	1.4	HR:	NA	NA	NA
	Venlafaxine	9,400.2	0	0.0	0.0	0.3	IRR:	undef.	1.0	inf.
	Duloxetine	11,225.0	4	0.4	0.1	0.9	HR:	NA	NA	NA
	SSRI	10,694.6	0	0.0	0.0	0.3	IRR:	undef.	0.6	inf.
	Duloxetine	8,775.0	4	0.5	0.1	1.2	HR:	1.2	0.3	5.3
	Untreated	6,502.4	3	0.5	0.1	1.3	IRR:	1.0	0.2	6.7
Non-serious hepatic enzyme elevation	Duloxetine	8,230.3	1	0.1	0.0	0.7	HR:	1.1	0.1	17.6
	Venlafaxine	9,400.2	1	0.1	0.0	0.6	IRR:	1.1	0.0	89.7
	Duloxetine	11,225.0	1	0.1	0.0	0.5	HR:	0.5	0.0	5.3
	SSRI	10,694.5	2	0.2	0.0	0.7	IRR:	0.5	0.0	9.2
	Duloxetine	8,775.0	1	0.1	0.0	0.6	HR:	NA	NA	NA
	Untreated	6,502.5	0	0.0	0.0	0.5	IRR:	undef.	0.0	inf.

IR: incidence rate, representing number of events per 1,000 person-years; CI: confidence interval; RR: rate ratio; NA: not available; HR: hazard ratio; IRR: incidence rate ratio; undef.=undefined; inf.=infinity

Table 9. Cases of clinically significant hepatic injury among the treated cohorts (current therapy plus 15 days): comorbidities and medications before the confirmed case date

Characteristic	Cases (n=5)	
	N	%
Age Group (years) (N %)		
18-25	0	0.0
26-30	1	20.0
31-35	1	20.0
36-40	1	20.0
41-50	1	20.0
51-60	1	20.0
61-70	0	0.0
≥71	0	0.0
Gender (N %)		
Female	3	60.0
Male	2	40.0
Geographic region of health plan (N %)		
Northeast	0	0.0
Midwest	1	20.0
South/Southeast	4	80.0
West	0	0.0
Calendar year of cohort entry (N %)		
2004	0	0.0
2005	0	0.0
2006	1	20.0
2007	0	0.0
2008	2	40.0
2009	1	20.0
2010	1	20.0
Condition within 45 days of event date, on the basis of health care claims		
Use of duloxetine on event date	5	100.0
Use of venlafaxine on event date	0	0.0

Table 9. Continued

Characteristic	Cases (n=5)	
	N	%
Condition within 45 days of event date, on the basis of health care claims		
Use of SSRI on event date	0	0.0
Use of duloxetine within 45 days of event date	5	100.0
Use of venlafaxine within 45 days of event date	0	0.0
Use of SSRI within 45 days of event date	1	20.0
Sepsis/septic shock	0	0.0
Heart failure (with and without myocardial Infarction)	0	0.0
Cardiogenic shock, acute myocardial infarction	0	0.0
Acute viral infection (hepatitis A, B, C, D, E; EBV, CMV, HSV)	1	20.0
Autoimmune hepatitis	0	0.0
Alcoholic hepatitis	0	0.0
Non-alcohol liver-related diagnoses	0	0.0
Alcoholic liver disease	0	0.0
Cholecystitis, choledocholithiasis	0	0.0
Acetaminophen toxicity	0	0.0
Hepatic vein obstruction (Budd-Chiari syndrome), portal vein obstruction	0	0.0
Primary neoplasia of the liver or metastatic disease in liver from primary tumors elsewhere	0	0.0
Hepatorenal syndrome	0	0.0
Chronic liver disease, cirrhosis, or fibrosis	1	20.0
Metabolic liver injury (hemochromatosis, Wilson Disease, alpha-1 antitrypsin deficiency)	0	0.0
Sclerosing colangitis	0	0.0
Thrombocytopenia	0	0.0
Use of valproic acid	0	0.0
Use of diclofenac	0	0.0
Use of nefazodone	0	0.0
Use of statins/ lipid lowering drugs	0	0.0
Use of isoniazid	0	0.0
Use of phenytoin	0	0.0
Use of nitrofurantoin	0	0.0

Table 9. Continued

Characteristic	Cases (n=5)	
	N	%
Condition within 45 days of event date, on the basis of health care claims		
Use of prophylthiouracil	0	0.0
Use of rifampin	0	0.0
Use of fluconazole	0	0.0
Use of chlorpromazine	1	20.0
Use of interferon beta	0	0.0
Use of amiodarone	0	0.0
Use of either naloxone, naltrexone, disulfiram, acamprosate	0	0.0
Chart-based characteristics (during 12 months prior to the confirmed case date)		
BMI		
Obese/Overweight	0	0.0
Normal weight	1	20.0
Missing	4	80.0
Alcohol abuse/addiction	0	0.0
Smoking		
Current smoker	1	20.0
Past smoker	1	20.0
Never smoker	3	60.0
Missing	0	0.0
Cocaine abuse and addiction	0	0.0
Heroin abuse and addiction	0	0.0
Polysubstance abuse and addiction	0	0.0

EBV: Epstein Barr virus; CMV: cytomegalovirus; HSV: herpes simplex virus; BMI: body mass index

Table 10. Distribution of claims-identified characteristics during 12 month baseline period among cases of hepatic events from the matched duloxetine cohort and comparator cohorts

Baseline Characteristic	Hepatic related death (n=0)		Hepatic failure (n=0)		Other clinically significant hepatic injury (n=8)		Non-serious hepatic enyzme elevations (n=3)	
Age Group (years) (N %)								
18-25	NA	NA	NA	NA	0	0.0	0	0.0
26-30	NA	NA	NA	NA	1	12.5	0	0.0
31-35	NA	NA	NA	NA	2	25.0	0	0.0
36-40	NA	NA	NA	NA	1	12.5	0	0.0
41-50	NA	NA	NA	NA	1	12.5	2	66.7
51-60	NA	NA	NA	NA	2	25.0	1	33.3
61-70	NA	NA	NA	NA	1	12.5	0	0.0
≥71	NA	NA	NA	NA	0	0.0	0	0.0
Gender (N %)								
Female	NA	NA	NA	NA	5	62.5	3	100.0
Male	NA	NA	NA	NA	3	37.5	0	0.0
Geographic region of health plan (N %)								
Northeast	NA	NA	NA	NA	0	0.0	3	100.0
Midwest	NA	NA	NA	NA	1	12.5	0	0.0
South/Southeast	NA	NA	NA	NA	6	75.0	0	0.0
West	NA	NA	NA	NA	1	12.5	0	0.0
Calendar year of cohort entry (N %)								
2004	NA	NA	NA	NA	0	0.0	0	0.0
2005	NA	NA	NA	NA	0	0.0	1	33.3
2006	NA	NA	NA	NA	1	12.5	0	0.0
2007	NA	NA	NA	NA	0	0.0	0	0.0
2008	NA	NA	NA	NA	3	37.5	1	33.3
2009	NA	NA	NA	NA	3	37.5	1	33.3
2010	NA	NA	NA	NA	1	12.5	0	0.0

Table 10. Continued

Baseline Characteristic	Hepatic related death (n=0)		Hepatic failure (n=0)		Other clinically significant hepatic injury (n=8)		Non-serious hepatic enyzme elevations (n=3)	
Neuropsychological comorbidities (N %)								
Depressive disorder, not elsewhere classified	NA	NA	NA	NA	6	75.0	3	100.0
Episodic mood disorders (including depressive component)	NA	NA	NA	NA	3	37.5	1	33.3
Episodic mood disorders (without depressive component)	NA	NA	NA	NA	0	0.0	0	0.0
Adjustment reaction	NA	NA	NA	NA	2	25.0	1	33.3
Anxiety, dissociative and somatoform disorders	NA	NA	NA	NA	5	62.5	2	66.7
Psychotic disorders	NA	NA	NA	NA	3	37.5	1	33.3
ADHD	NA	NA	NA	NA	0	0.0	0	0.0
Alcohol abuse and addiction (diagnosis)	NA	NA	NA	NA	1	12.5	1	33.3
Alcohol abuse and addiction (treatment)	NA	NA	NA	NA	0	0.0	1	33.3
Cocaine abuse and addiction	NA	NA	NA	NA	0	0.0	1	33.3
Heroin abuse and addiction	NA	NA	NA	NA	1	12.5	0	0.0
Other substance abuse and addiction	NA	NA	NA	NA	1	12.5	1	33.3
Smoking (tobacco use disorder - diagnosis)	NA	NA	NA	NA	2	25.0	1	33.3
Smoking (tobacco use disorder - treatment)	NA	NA	NA	NA	1	12.5	0	0.0
Overdoses	NA	NA	NA	NA	0	0.0	0	0.0
Suicide attempts	NA	NA	NA	NA	0	0.0	0	0.0
Seizure	NA	NA	NA	NA	0	0.0	0	0.0

Table 10. Continued

Baseline Characteristic	Hepatic related death (n=0)		Hepatic failure (n=0)		Other clinically significant hepatic injury (n=8)		Non-serious hepatic enyzme elevations (n=3)	
Neuropsychological comorbidities (N %)								
Chronic pain	NA	NA	NA	NA	0	0.0	0	0.0
Stress urinary incontinence	NA	NA	NA	NA	0	0.0	0	0.0
Fibromyalgia	NA	NA	NA	NA	0	0.0	0	0.0
Diabetes neuropathy	NA	NA	NA	NA	0	0.0	0	0.0
Low back pain	NA	NA	NA	NA	2	25.0	1	33.3
Hepatic risks (N %)								
Hypercholesterolemia / dyslipidemia (diagnosis)	NA	NA	NA	NA	2	25.0	1	33.3
Hypercholesterolemia / dyslipidemia (treatment)	NA	NA	NA	NA	1	12.5	0	0.0
Hyperglycemia	NA	NA	NA	NA	0	0.0	0	0.0
Albuminuria	NA	NA	NA	NA	0	0.0	0	0.0
Diabetes mellitus (diagnosis)	NA	NA	NA	NA	0	0.0	0	0.0
Diabetes mellitus (treatment)	NA	NA	NA	NA	0	0.0	0	0.0
CMV infection	NA	NA	NA	NA	0	0.0	0	0.0
EBV infection	NA	NA	NA	NA	0	0.0	0	0.0
Obesity (diagnosis)	NA	NA	NA	NA	0	0.0	0	0.0
Obesity (treatment)	NA	NA	NA	NA	0	0.0	0	0.0
Liver ultrasound scans								
0	NA	NA	NA	NA	8	100.0	2	66.7
1	NA	NA	NA	NA	0	0.0	1	33.3
2+	NA	NA	NA	NA	0	0.0	0	0.0
Prior bilirubin test	NA	NA	NA	NA	0	0.0	0	0.0

Table 10. Continued

Baseline Characteristic	Hepatic related death (n=0)		Hepatic failure (n=0)		Other clinically significant hepatic injury (n=8)		Non-serious hepatic enyzme elevations (n=3)	
Hepatic risks (N %)								
Prior ALT/ASP/ALP test	NA	NA	NA	NA	1	12.5	0	0.0
NSAID use (excluding diclofenac)	NA	NA	NA	NA	1	12.5	1	33.3
NSAID use (diclofenac only)	NA	NA	NA	NA	0	0.0	0	0.0
Isoniazid	NA	NA	NA	NA	0	0.0	0	0.0
Phentoin	NA	NA	NA	NA	0	0.0	0	0.0
Valproic acid	NA	NA	NA	NA	0	0.0	0	0.0
Nitrofurantoin	NA	NA	NA	NA	0	0.0	0	0.0
Propylthiouracil	NA	NA	NA	NA	0	0.0	0	0.0
Rifampin	NA	NA	NA	NA	0	0.0	0	0.0
Fluconazole	NA	NA	NA	NA	0	0.0	0	0.0
Chlorpromazine	NA	NA	NA	NA	0	0.0	0	0.0
Interferon beta	NA	NA	NA	NA	1	12.5	0	0.0
Amiodarone	NA	NA	NA	NA	0	0.0	0	0.0
Statins	NA	NA	NA	NA	3	37.5	0	0.0
Naloxone	NA	NA	NA	NA	0	0.0	0	0.0
Naltrexone	NA	NA	NA	NA	0	0.0	0	0.0
Disulfiram	NA	NA	NA	NA	0	0.0	1	33.3
Acamprosate	NA	NA	NA	NA	0	0.0	0	0.0
Use of Medications (N %)								
Duloxetine (not including index drug)	NA	NA	NA	NA	0	0.0	0	0.0
Venlafaxine (not including index drug)	NA	NA	NA	NA	1	12.5	1	33.3
SSRI (not including index drug)	NA	NA	NA	NA	1	12.5	0	0.0
Other antidepressants	NA	NA	NA	NA	3	37.5	2	66.7

Table 10. Continued

Baseline Characteristic	Hepatic related death (n=0)		Hepatic failure (n=0)		Other clinically significant hepatic injury (n=8)		Non-serious hepatic enyzme elevations (n=3)	
Use of Medications (N %)								
Bupropion	NA	NA	NA	NA	2	25.0	0	0.0
Anticonvulsants	NA	NA	NA	NA	3	37.5	1	33.3
Anxiolytics or sedative hypnotics	NA	NA	NA	NA	3	37.5	2	66.7
Antihistamines	NA	NA	NA	NA	1	12.5	1	33.3
Antipsychotics	NA	NA	NA	NA	2	25.0	0	0.0
Narcotic analgesics	NA	NA	NA	NA	2	25.0	2	66.7
History of (N %)								
Hypertension	NA	NA	NA	NA	2	25.0	2	66.7
Stroke	NA	NA	NA	NA	0	0.0	0	0.0
MI	NA	NA	NA	NA	0	0.0	0	0.0
Angina	NA	NA	NA	NA	0	0.0	0	0.0
Unstable angina/acute coronary syndromes	NA	NA	NA	NA	0	0.0	0	0.0
Use of specified health services (N % unless otherwise noted)								
Number of unique ICD-9 codes								
0-4	NA	NA	NA	NA	0	0.0	0	0.0
5-8	NA	NA	NA	NA	1	12.5	1	33.3
9-12	NA	NA	NA	NA	2	25.0	0	0.0
13-16	NA	NA	NA	NA	2	25.0	1	33.3
17+	NA	NA	NA	NA	3	37.5	1	33.3

Table 10. Continued

Baseline Characteristic	Hepatic related death (n=0)		Hepatic failure (n=0)		Other clinically significant hepatic injury (n=8)		Non-serious hepatic enyzme elevations (n=3)	
Use of specified health services (N % unless otherwise noted)								
Number of different drugs dispensed								
0-3	NA	NA	NA	NA	0	0.0	0	0.0
4-7	NA	NA	NA	NA	3	37.5	1	33.3
8+	NA	NA	NA	NA	5	62.5	2	66.7
Use of intensive care and critical care	NA	NA	NA	NA	0	0.0	0	0.0
Prior hospitalization	NA	NA	NA	NA	2	25.0	1	33.3
Provider specialty at index visit	NA	NA	NA	NA	0	0.0	0	0.0
Number of visits to a psychiatrist/psychologist (mean std*)	NA	NA	NA	NA	0.9	1.8	2.3	4.0
Number of visits to other physicians (mean std)	NA	NA	NA	NA	16.1	12.3	12.0	5.6
Number of different psychiatric drugs dispensed (mean std)	NA	NA	NA	NA	1.9	2.1	2.7	1.2
Number of emergency room visits (mean std)	NA	NA	NA	NA	1.8	2.0	2.3	4.0
Number of psychiatric-related hospitalizations (mean std)	NA	NA	NA	NA	0	0.0	0	0.0
Number of other laboratory tests (mean std)	NA	NA	NA	NA	2.5	2.0	0.67	1.2
Total healthcare utilization costs (mean std)	NA	NA	NA	NA	12,093.2	12,748.9	8,140.1	5,874.6
Patient pharmacy costs (mean std)	NA	NA	NA	NA	723.9	430.4	540.0	77.0
Non-patient pharmacy costs (mean std)	NA	NA	NA	NA	5,940.0	12,278.1	518.9	370.8

Table 10. Continued

Baseline Characteristic	Hepatic related death (n=0)		Hepatic failure (n=0)		Other clinically significant hepatic injury (n=8)		Non-serious hepatic enyzme elevations (n=3)	
Use of specified health services (N % unless otherwise noted)								
Total healthcare costs (mean std)	NA	NA	NA	NA	3426.7	3179.7	4862.3	4313.9
Number of months of prior continuous enrollment (mean std)	NA	NA	NA	NA	26.1	15.5	91.2	75.9
Baseline average daily dose of received antidepressant								
Above modal	NA	NA	NA	NA	1	12.5	0	0.0
Modal	NA	NA	NA	NA	2	25.0	3	100.0
Below modal	NA	NA	NA	NA	2	25.0	0	0.0
Untreated cohort	NA	NA	NA	NA	3	37.5	0	0.0
Exposure and follow-up								
Days from index date to onset of the hepatic event (mean std)	NA	NA	NA	NA	67.1	80.2	110.3	95.8
Current duloxetine user (based on current therapy plus 15 days extension)	NA	NA	NA	NA	5	62.5	1	33.3
Switchers to duloxetine during follow-up	NA	NA	NA	NA	0	0.0	0	
Days of duloxetine current user status (mean std)	NA	NA	NA	NA	82.4	99.8	221	--

SSRI: selective serotonin reuptake inhibitor; ADHD: attention deficit hyperactivity disorder; CMV: cytomegalovirus; EBV: Epstein-Barr virus; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; NSAID: nonsteroidal anti-inflammatory drug; MI: myocardial infarction; ICD-9: International Classification of Diseases, 9th Edition; std: standard deviation

Table 11a. Time to onset of hepatic events according to select claims-based characteristics during 12-month baseline period within the PS-matched duloxetine and venlafaxine cohorts

	Hepatic-related death				Hepatic failure				Other clinically significant hepatic injury				Non-serious hepatic enzyme elevation			
	Duloxetine (n=0)		Venlafaxine (n=0)		Duloxetine (n=0)		Venlafaxine (n=0)		Duloxetine (n=5)		Venlafaxine (n=0)		Duloxetine (n=1)		Venlafaxine (n=0)	
Baseline Characteristic	Median number of days	IQR	Median number of days	IQR	Median number of days	IQR	Median number of days	IQR	Median number of days	IQR	Median number of days	IQR	Median number of days	IQR	Median number of days	IQR
Age group (years)																
18-25	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
26-30	-	-	-	-	-	-	-	-	29	NA	-	-	-	-	-	-
31-35	-	-	-	-	-	-	-	-	6	NA	-	-	-	-	-	-
36-40	-	-	-	-	-	-	-	-	232	NA	-	-	-	-	-	-
41-50	-	-	-	-	-	-	-	-	5	NA	-	-	-	-	-	-
51-60	-	-	-	-	-	-	-	-	135	NA	-	-	220	NA	-	-
61-70	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
≥71	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Gender																
Female	-	-	-	-	-	-	-	-	29	226	-	-	220	NA	-	-
Male	-	-	-	-	-	-	-	-	70	130	-	-	-	-	-	-

IQR: interquartile range; NA: not available

Table 11b. Time to onset of hepatic events according to select claims-based characteristics during 12-month baseline period within the PS-matched duloxetine and SSRI cohorts

	Hepatic-related death				Hepatic failure				Other clinically significant hepatic injury				Non-serious hepatic enzyme elevation			
	Duloxetine (n=0)		SSRI (n=0)		Duloxetine (n=0)		SSRI (n=0)		Duloxetine (n=4)		SSRI (n=0)		Duloxetine (n=1)		SSRI (n=2)	
Baseline Characteristic	Median number of days	IQR	Median number of days	IQR	Median number of days	IQR	Median number of days	IQR	Median number of days	IQR	Median number of days	IQR	Median number of days	IQR	Median number of days	IQR
Age group (years)																
18-25	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
26-30	-	-	-	-	-	-	-	-	29	NA	-	-	-	-	-	-
31-35	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
36-40	-	-	-	-	-	-	-	-	232	NA	-	-	-	-	-	-
41-50	-	-	-	-	-	-	-	-	5	NA	-	-	-	-	55.5	25
51-60	-	-	-	-	-	-	-	-	135	NA	-	-	220	NA	-	-
61-70	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
≥71	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Gender																
Female	-	-	-	-	-	-	-	-	130.5	203	-	-	220	NA	55.5	25
Male	-	-	-	-	-	-	-	-	70	130	-	-	-	-	-	-

IQR: interquartile range; NA: not available

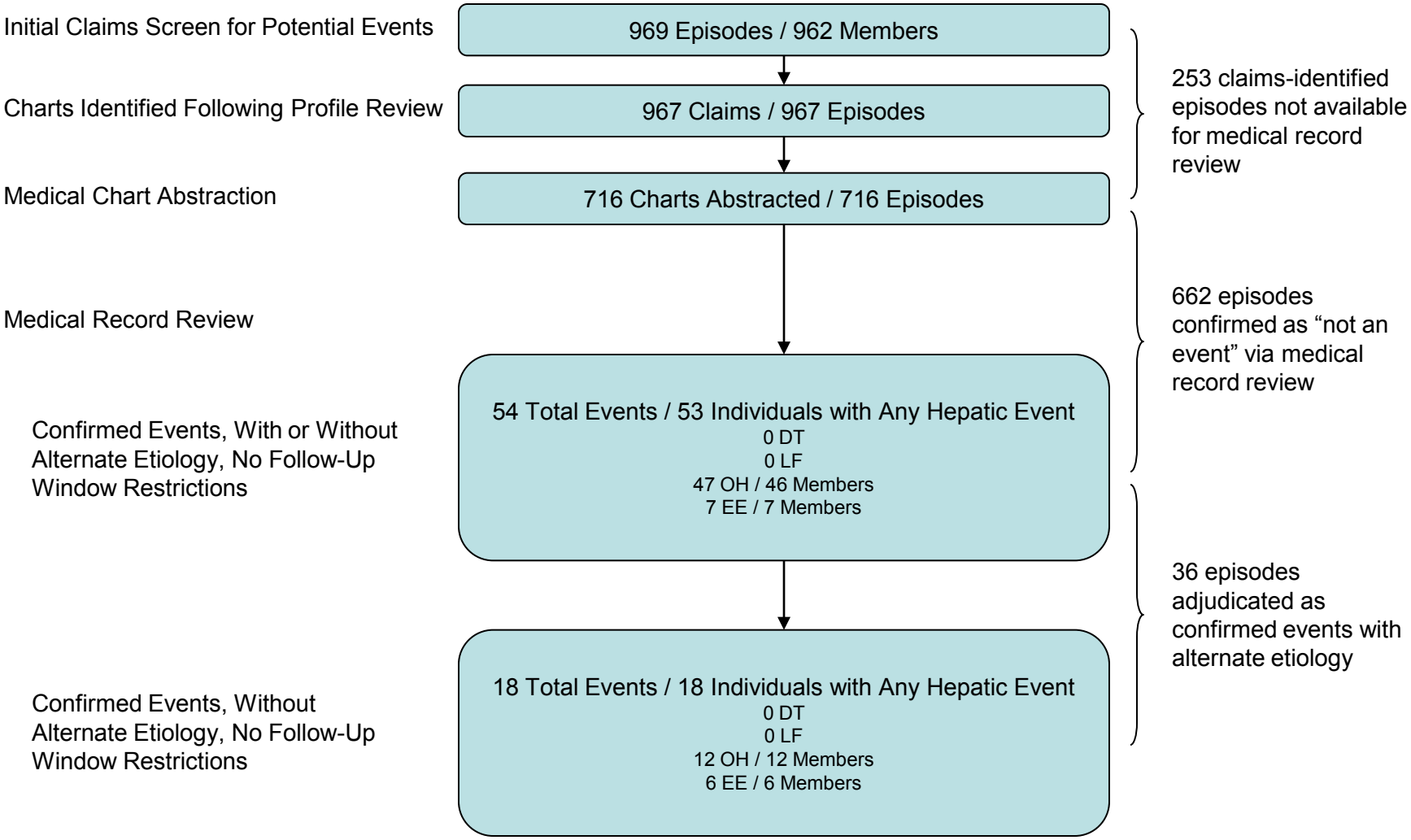
Table 11c. Time to onset of hepatic events according to select claims-based characteristics during 12-month baseline period within the PS-matched duloxetine and untreated cohorts

	Hepatic-related death				Hepatic failure				Other clinically significant hepatic injury				Non-serious hepatic enzyme elevation			
	Duloxetine (n=0)		Untreated (n=0)		Duloxetine (n=0)		Untreated (n=0)		Duloxetine (n=4)		Untreated (n=3)		Duloxetine (n=1)		Untreated (n=0)	
Baseline Characteristic	Median number of days	IQR	Median number of days	IQR	Median number of days	IQR	Median number of days	IQR	Median number of days	IQR	Median number of days	IQR	Median number of days	IQR	Median number of days	IQR
Age group (years)																
18-25	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
26-30	-	-	-	-	-	-	-	-	29	NA	-	-	-	-	-	-
31-35	-	-	-	-	-	-	-	-	6	NA	45	NA	-	-	-	-
36-40	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
41-50	-	-	-	-	-	-	-	-	5	NA	-	-	-	-	-	-
51-60	-	-	-	-	-	-	-	-	135	NA	7	NA	220	NA	-	-
61-70	-	-	-	-	-	-	-	-	-	-	78	NA	-	-	-	-
≥71	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Gender																
Female	-	-	-	-	-	-	-	-	17.5	23	26	38	220	NA	-	-
Male	-	-	-	-	-	-	-	-	70	130	78	NA	-	-	-	-

IQR: interquartile range; NA: not available

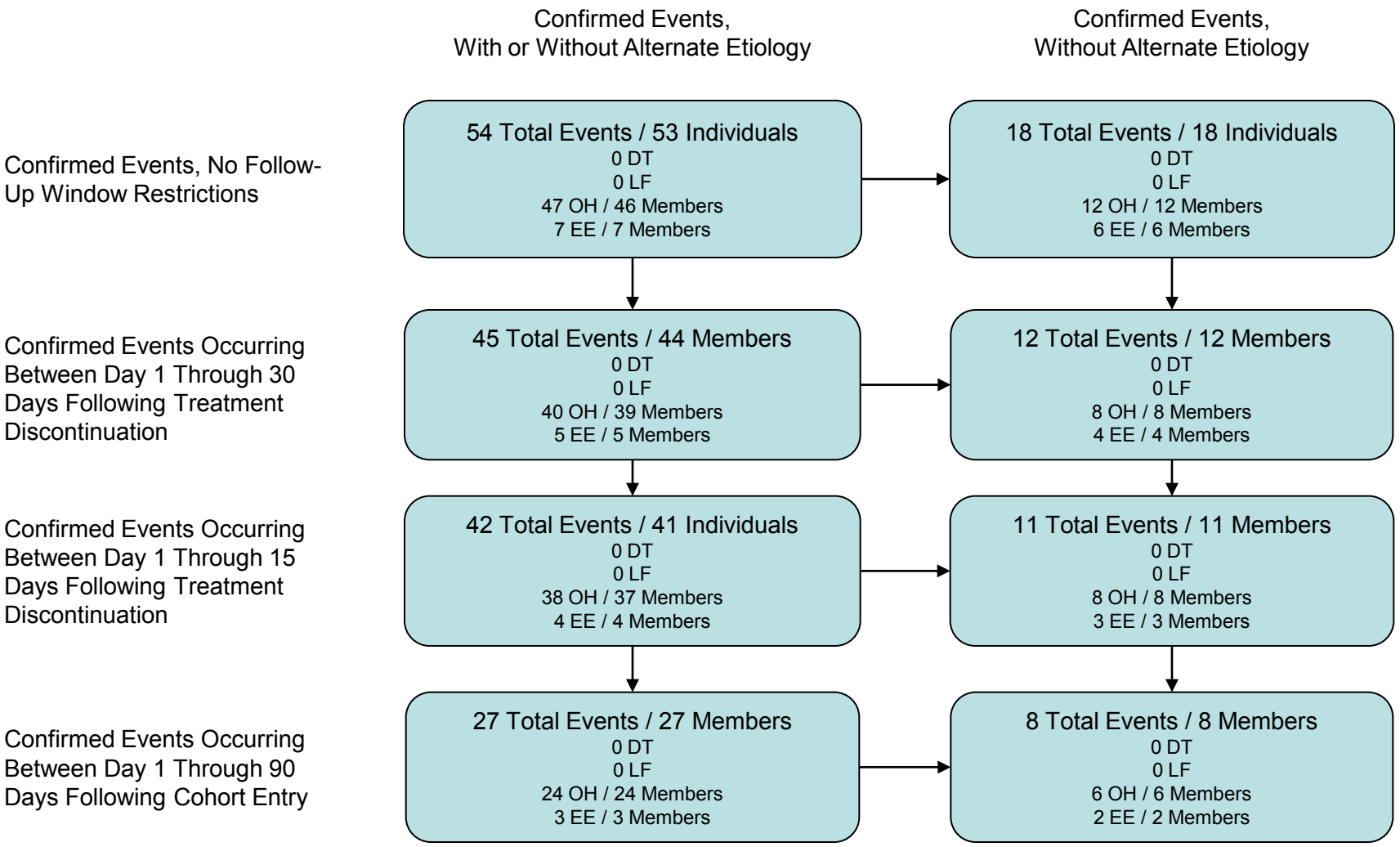
9. Figures

Figure 1. Flowchart of Results from Medical Chart Abstraction and Adjudication



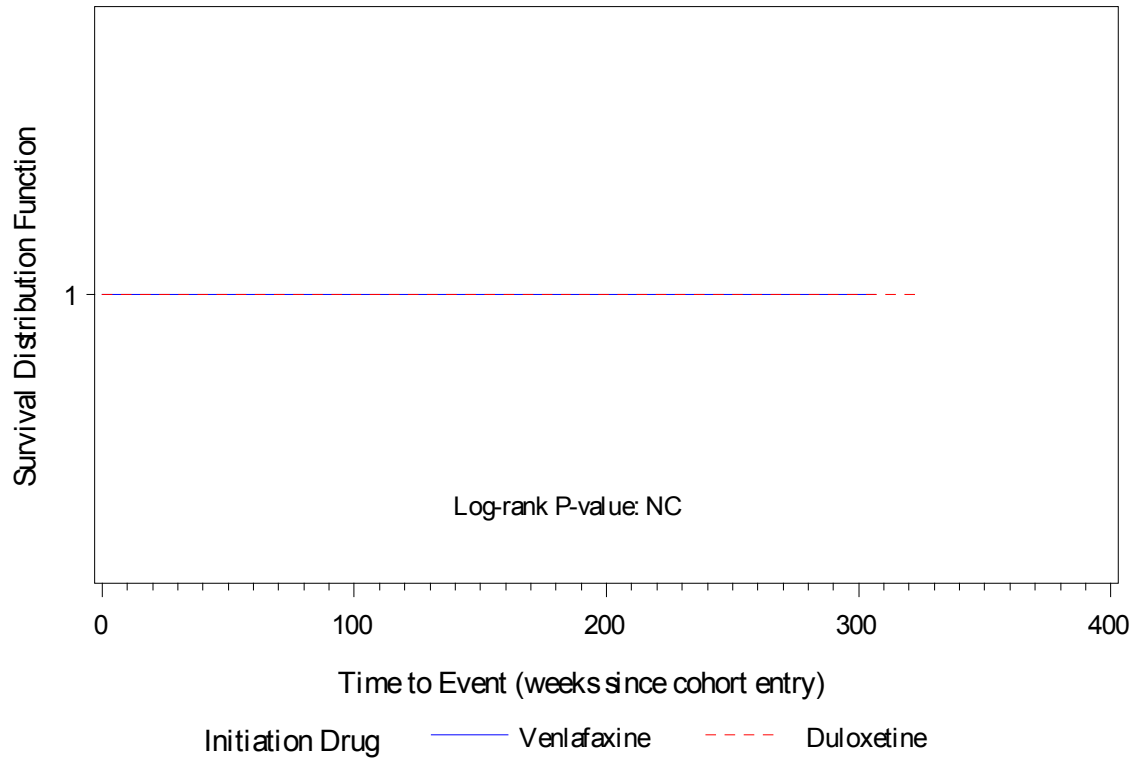
DT: hepatic-related death; LF: liver failure; OH: other clinically significant hepatic injury; EE: non-serious hepatic enzyme elevation

Figure 2. Flowchart of Follow-up Window Restrictions: Impact on the Number of Confirmed Hepatic Events



DT: hepatic-related death; LF: liver failure; OH: other clinically significant hepatic injury; EE: non-serious hepatic enzyme elevation

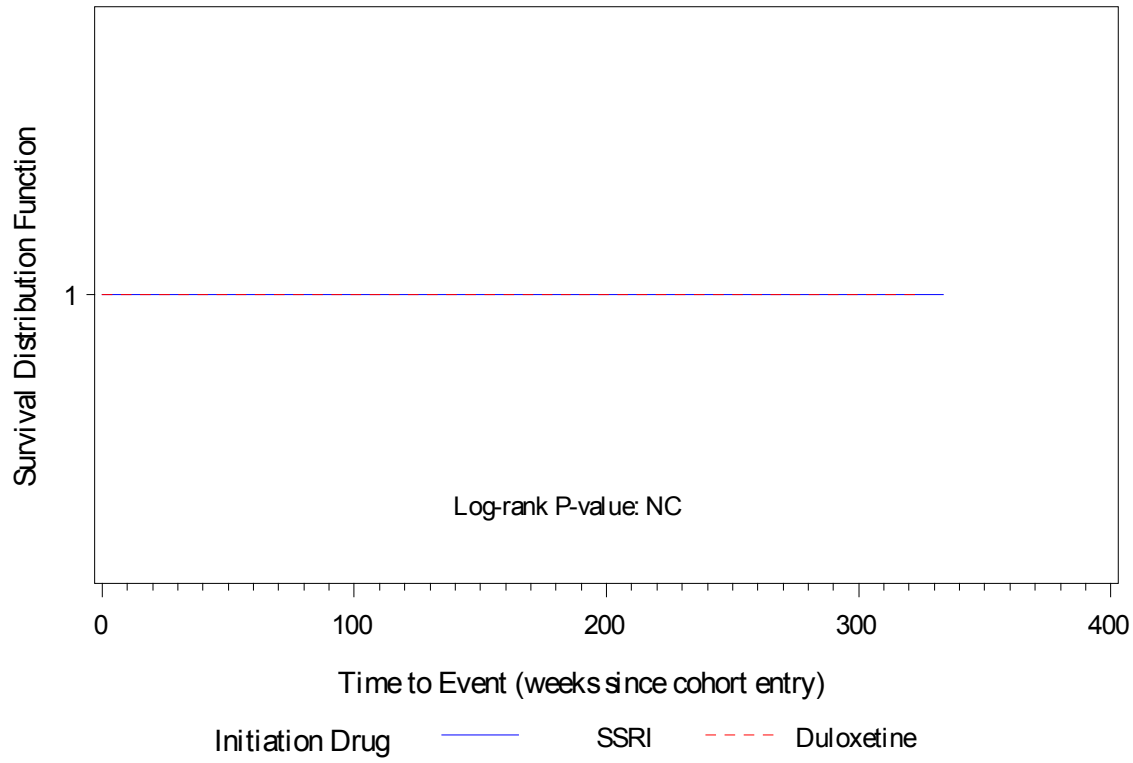
Figure 3a-1. Current Therapy Plus 15-Day Exposure Window: Time to Occurrence of Hepatic-Related Death, Duloxetine Initiators vs. Venlafaxine Initiators



Number of Patients Remaining at Risk

Cohort	Time Since Cohort Entry (Weeks)																
	0	2	4	6	8	10	12	14	16	18	20	22	24	26	52	78	104
Duloxetine	21000	20614	20049	19286	11502	10963	9030	8263	7070	6308	5712	5156	4760	4321	1545	704	306
Venlafaxine	21000	20614	20078	19332	12324	11709	10025	9247	8074	7339	6674	6088	5624	5159	2067	1013	539

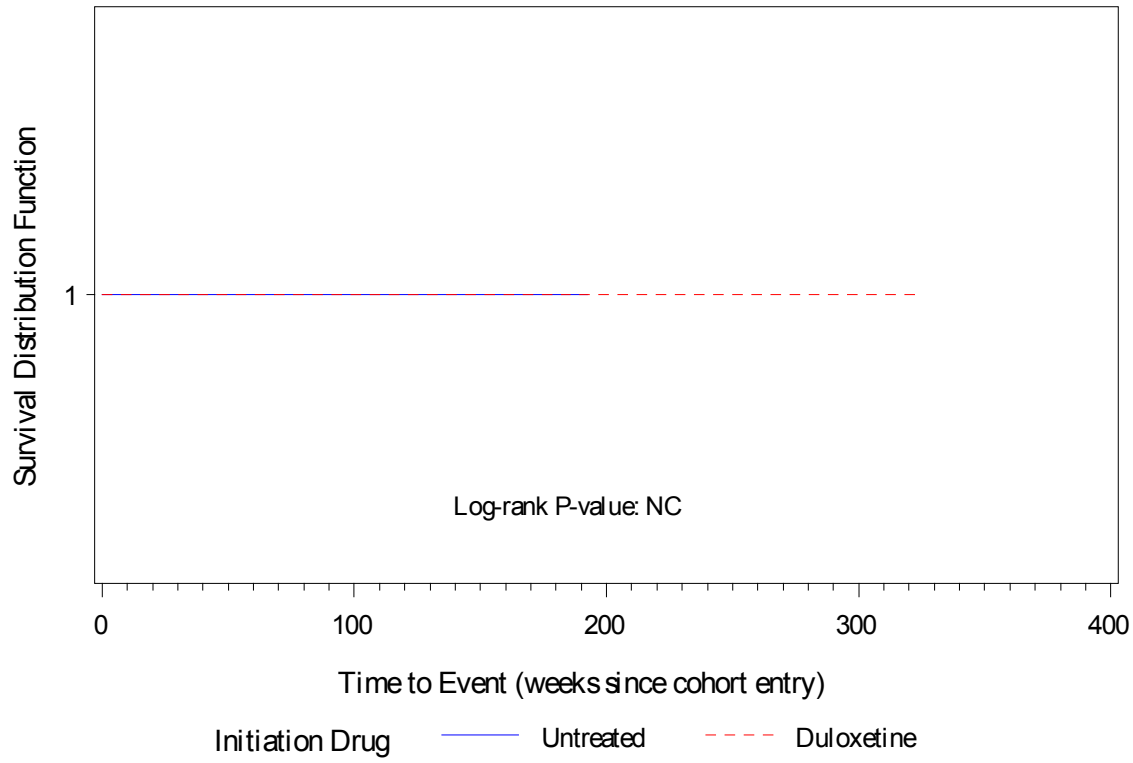
Figure 3b-1. Current Therapy Plus 15-Day Exposure Window: Time to Occurrence of Hepatic-Related Death, Duloxetine Initiators vs. SSRI Initiators



Number of Patients Remaining at Risk

Cohort	Time Since Cohort Entry (Weeks)																
	0	2	4	6	8	10	12	14	16	18	20	22	24	26	52	78	104
Duloxetine	28479	27959	27227	26199	15794	15031	12412	11372	9704	8682	7817	7053	6489	5903	2099	960	434
SSRI	28479	27983	27330	26448	15338	14516	11973	10906	9218	8199	7387	6697	6080	5496	1831	769	342

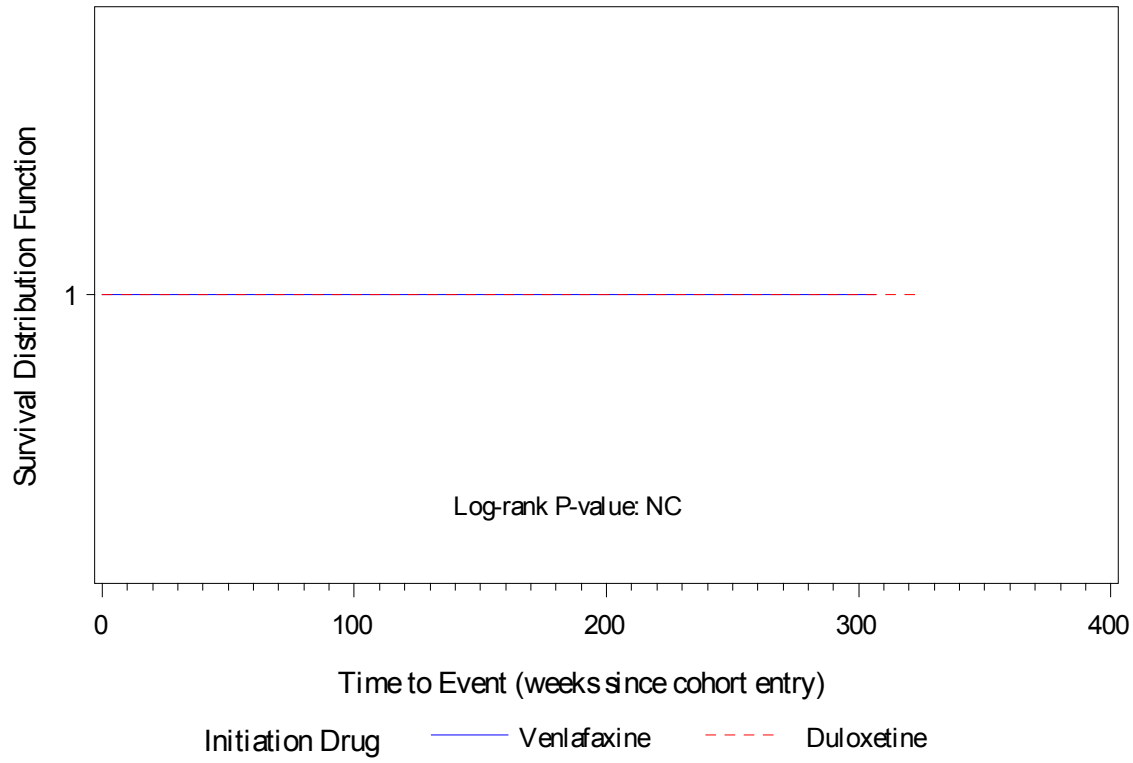
Figure 3c-1. Current Therapy Plus 15-Day Exposure Window: Time to Occurrence of Hepatic-Related Death, Duloxetine Initiators vs. Pharmacologically Untreated Cohort



Number of Patients Remaining at Risk

Cohort	Time Since Cohort Entry (Weeks)																
	0	2	4	6	8	10	12	14	16	18	20	22	24	26	52	78	104
Duloxetine	22714	22303	21711	20915	12370	11811	9701	8874	7560	6738	6089	5478	5028	4572	1611	717	318
Untreated	22714	21441	20102	18690	10673	9898	7865	6962	5747	4979	4353	3772	3344	2944	725	227	62

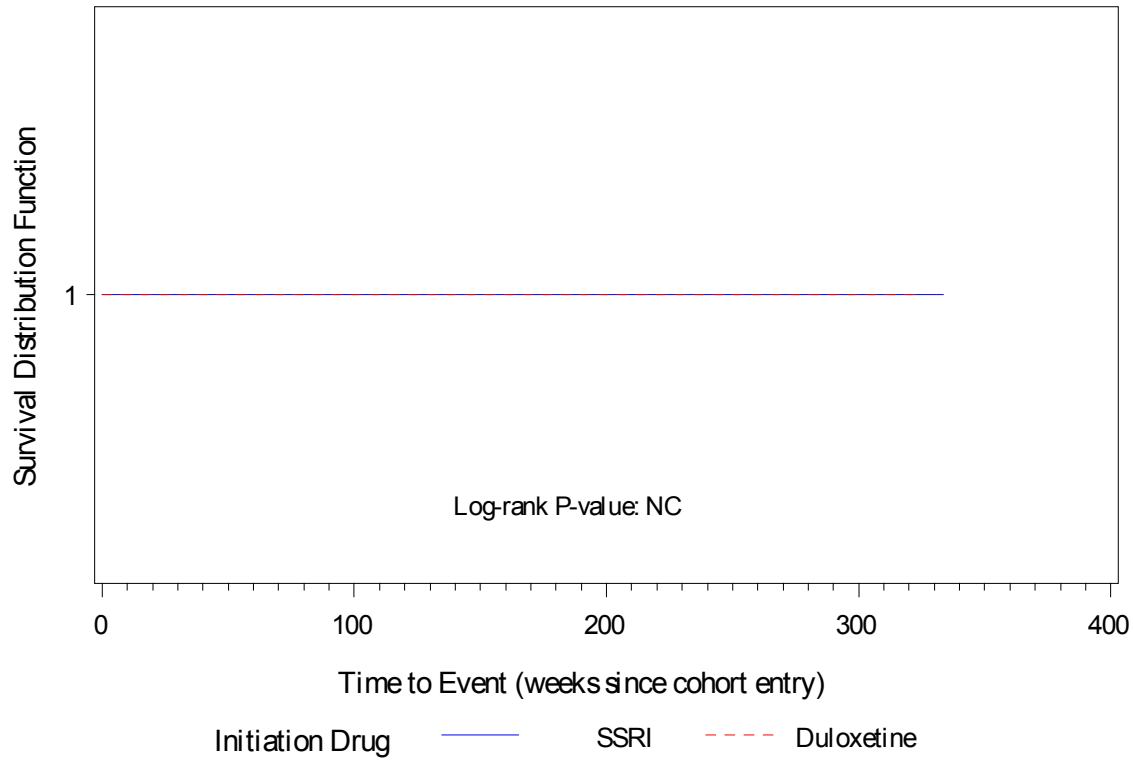
Figure 3a-2. Current Therapy Plus 15-Day Exposure Window: Time to Occurrence of Hepatic failure, Duloxetine Initiators vs. Venlafaxine Initiators



Number of Patients Remaining at Risk

Cohort	Time Since Cohort Entry (Weeks)																
	0	2	4	6	8	10	12	14	16	18	20	22	24	26	52	78	104
Duloxetine	21000	20614	20049	19286	11501	10961	9028	8261	7068	6306	5710	5154	4758	4319	1544	703	306
Venlafaxine	21000	20614	20079	19332	12323	11708	10024	9246	8071	7336	6671	6085	5621	5154	2067	1013	539

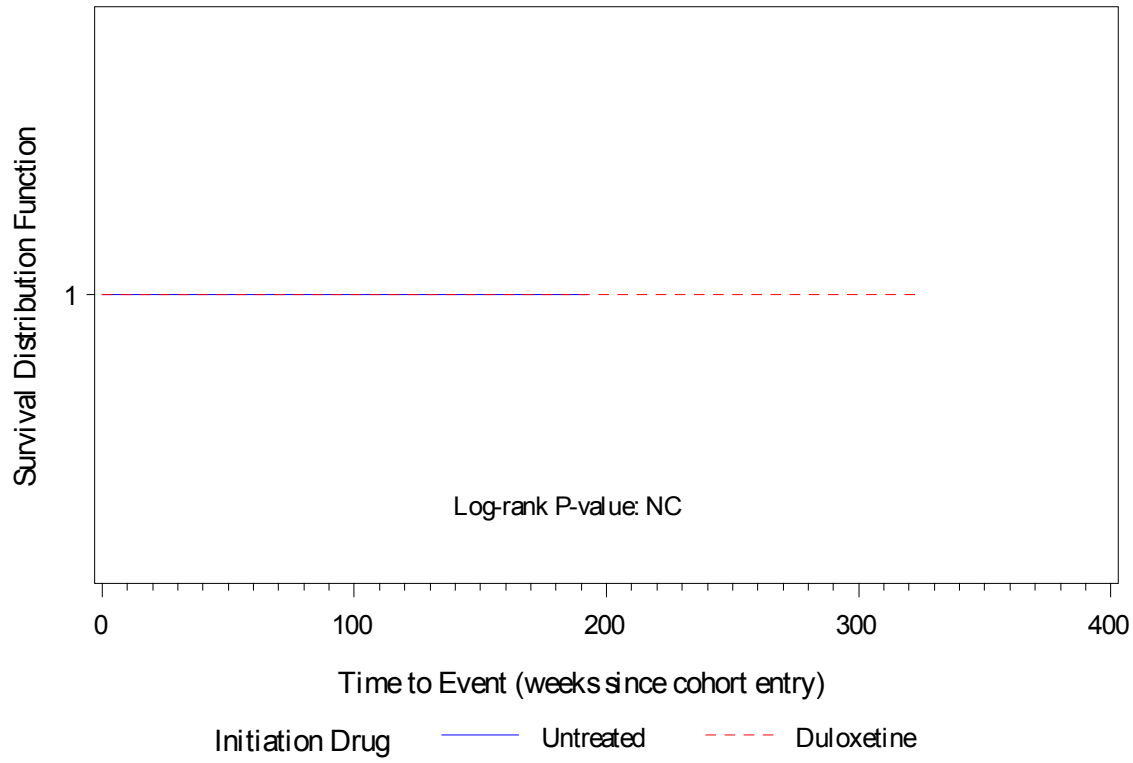
Figure 3b-2. Current Therapy Plus 15-Day Exposure Window: Time to Occurrence of Hepatic failure, Duloxetine Initiators vs. SSRI Initiators



Number of Patients Remaining at Risk

Cohort	Time Since Cohort Entry (Weeks)																
	0	2	4	6	8	10	12	14	16	18	20	22	24	26	52	78	104
Duloxetine	28479	27958	27225	26197	15793	15029	12410	11370	9702	8680	7815	7051	6487	5901	2098	960	434
SSRI	28479	27983	27331	26446	15336	14513	11969	10903	9216	8197	7385	6695	6077	5493	1831	769	342

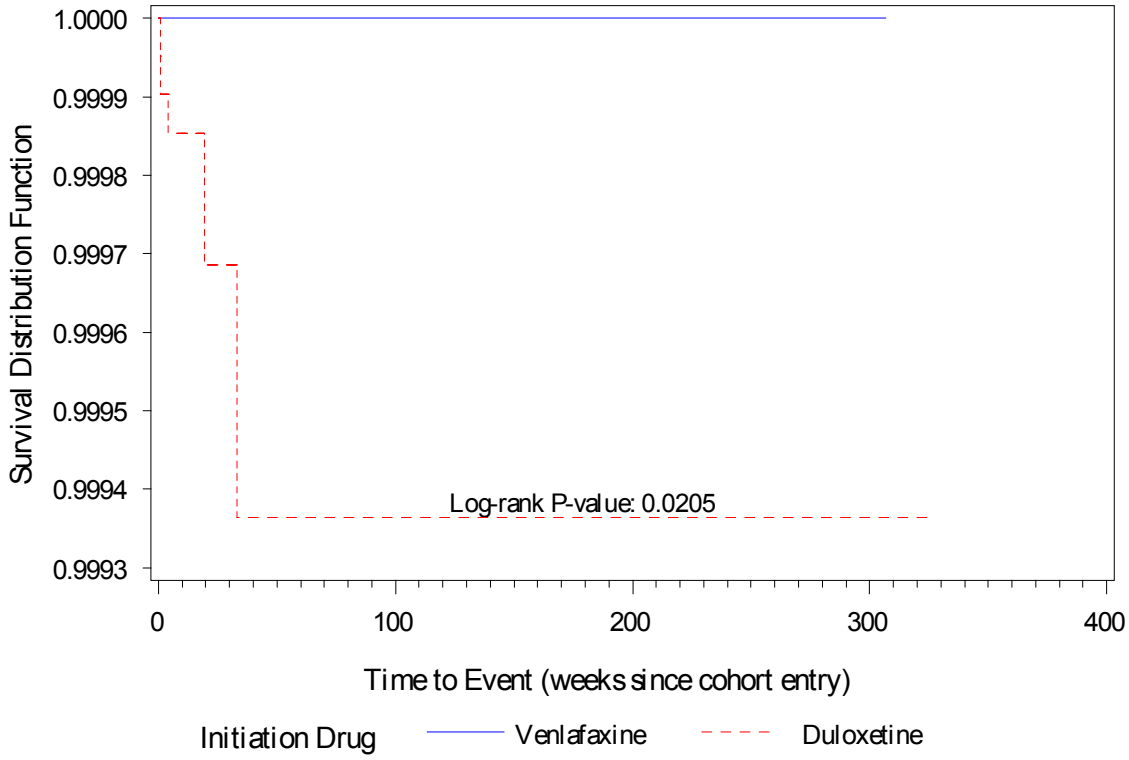
Figure 3c-2. Current Therapy Plus 15-Day Exposure Window: Time to Occurrence of Hepatic failure, Duloxetine Initiators vs. Pharmacologically Untreated Cohort



Number of Patients Remaining at Risk

Cohort	Time Since Cohort Entry (Weeks)																
	0	2	4	6	8	10	12	14	16	18	20	22	24	26	52	78	104
Duloxetine	22714	22302	21709	20913	12370	11811	9701	8874	7560	6738	6089	5478	5028	4572	1610	717	318
Untreated	22714	21440	20100	18687	10671	9896	7863	6960	5746	4978	4353	3773	3345	2945	725	227	62

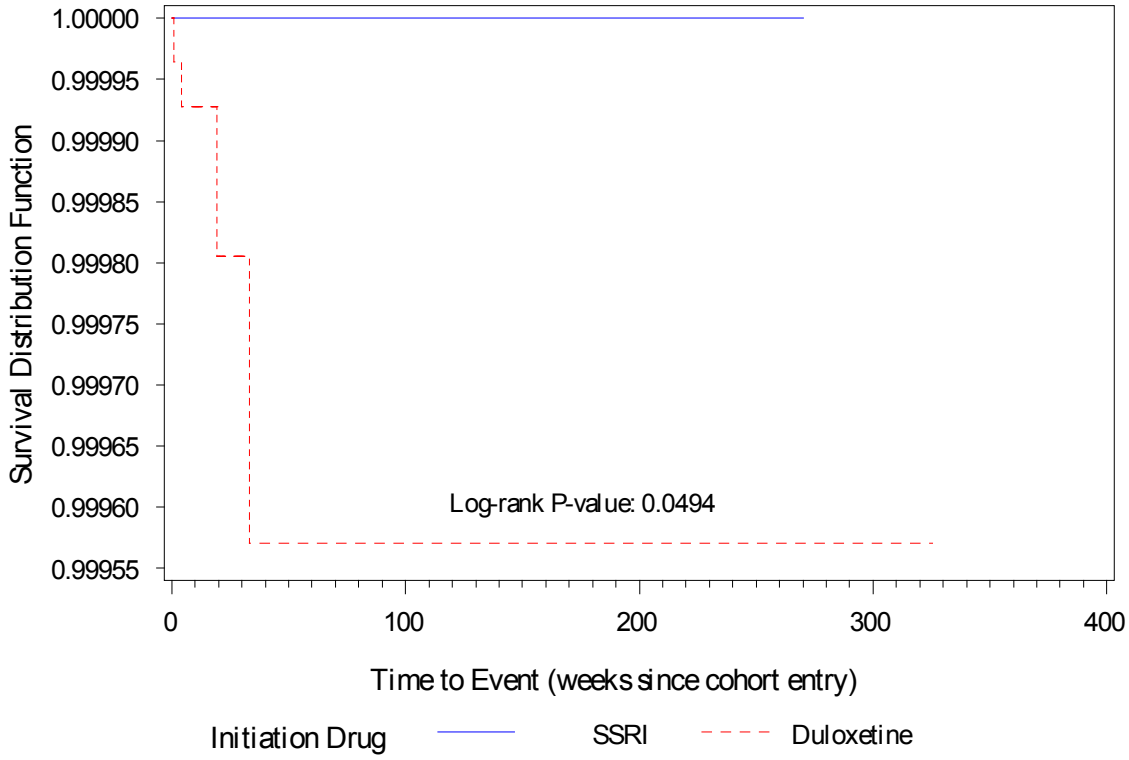
Figure 3a-3. Current Therapy Plus 15-Day Exposure Window: Time to Occurrence of Other Clinically Significant Hepatic Injury, Duloxetine Initiators vs. Venlafaxine Initiators



Number of Patients Remaining at Risk

Cohort	Time Since Cohort Entry (Weeks)																
	0	2	4	6	8	10	12	14	16	18	20	22	24	26	52	78	104
Duloxetine	21000	20584	19987	19203	11449	10905	8977	8210	7014	6253	5658	5106	4709	4272	1504	679	295
Venlafaxine	21000	20587	20036	19269	12273	11650	9969	9191	8016	7284	6621	6033	5567	5099	2027	988	524

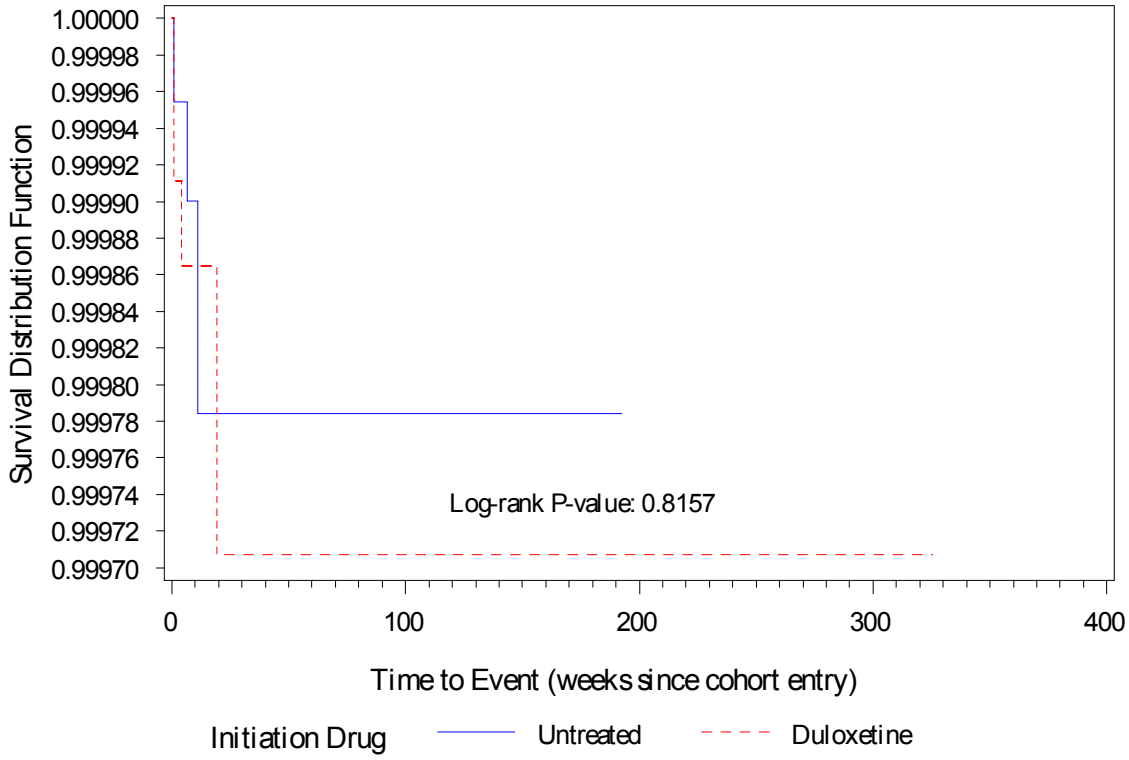
Figure 3b-3. Current Therapy Plus 15-Day Exposure Window: Time to Occurrence of Other Clinically Significant Hepatic Injury, Duloxetine Initiators vs. SSRI Initiators



Number of Patients Remaining at Risk

Cohort	Time Since Cohort Entry (Weeks)																
	0	2	4	6	8	10	12	14	16	18	20	22	24	26	52	78	104
Duloxetine	28479	27917	27145	26085	15726	14954	12344	11303	9635	8617	7752	6988	6419	5834	2048	928	418
SSRI	28479	27957	27277	26371	15279	14443	11900	10837	9154	8140	7330	6637	6019	5439	1805	744	328

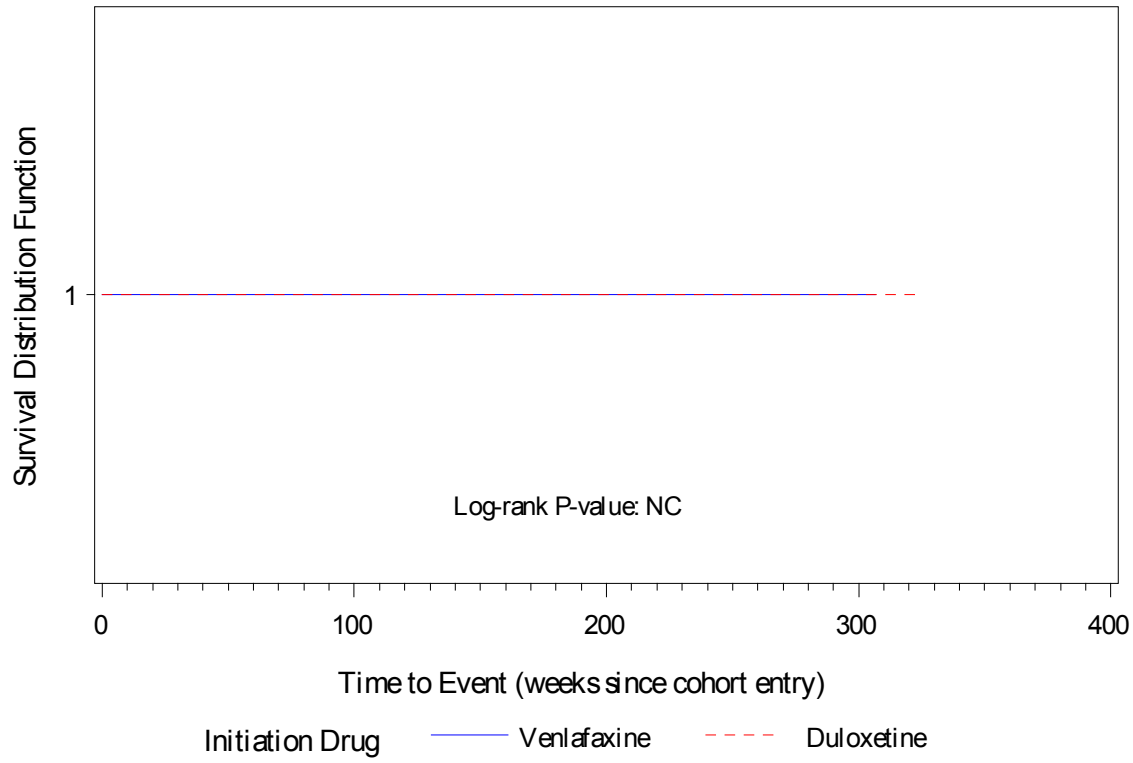
Figure 3c-3. Current Therapy Plus 15-Day Exposure Window: Time to Occurrence of Other Clinically Significant Hepatic Injury, Duloxetine Initiators vs. Pharmacologically Untreated Cohort



Number of Patients Remaining at Risk

Cohort	Time Since Cohort Entry (Weeks)																
	0	2	4	6	8	10	12	14	16	18	20	22	24	26	52	78	104
Duloxetine	22714	22266	21641	20819	12316	11753	9649	8821	7506	6683	6033	5425	4972	4519	1575	696	308
Untreated	22714	21408	20045	18620	10624	9844	7815	6910	5699	4932	4313	3735	3314	2916	713	225	62

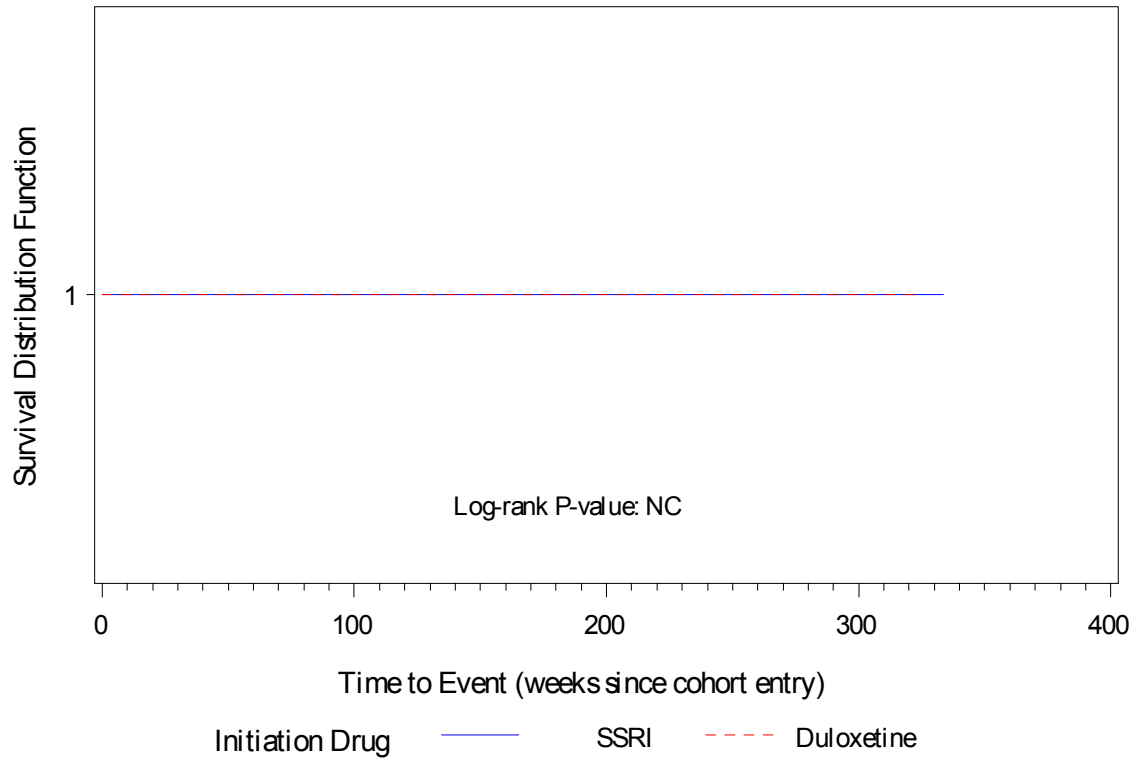
Figure 3a-4. Current Therapy Plus 15-Day Exposure Window: Time to Occurrence of Hepatic-Related Death or Hepatic failure, Duloxetine Initiators vs. Venlafaxine Initiators



Number of Patients Remaining at Risk

Cohort	Time Since Cohort Entry (Weeks)																
	0	2	4	6	8	10	12	14	16	18	20	22	24	26	52	78	104
Duloxetine	21000	20614	20049	19286	11501	10961	9028	8261	7068	6306	5710	5154	4758	4319	1544	703	306
Venlafaxine	21000	20614	20078	19331	12323	11708	10024	9246	8071	7336	6671	6085	5621	5154	2067	1013	539

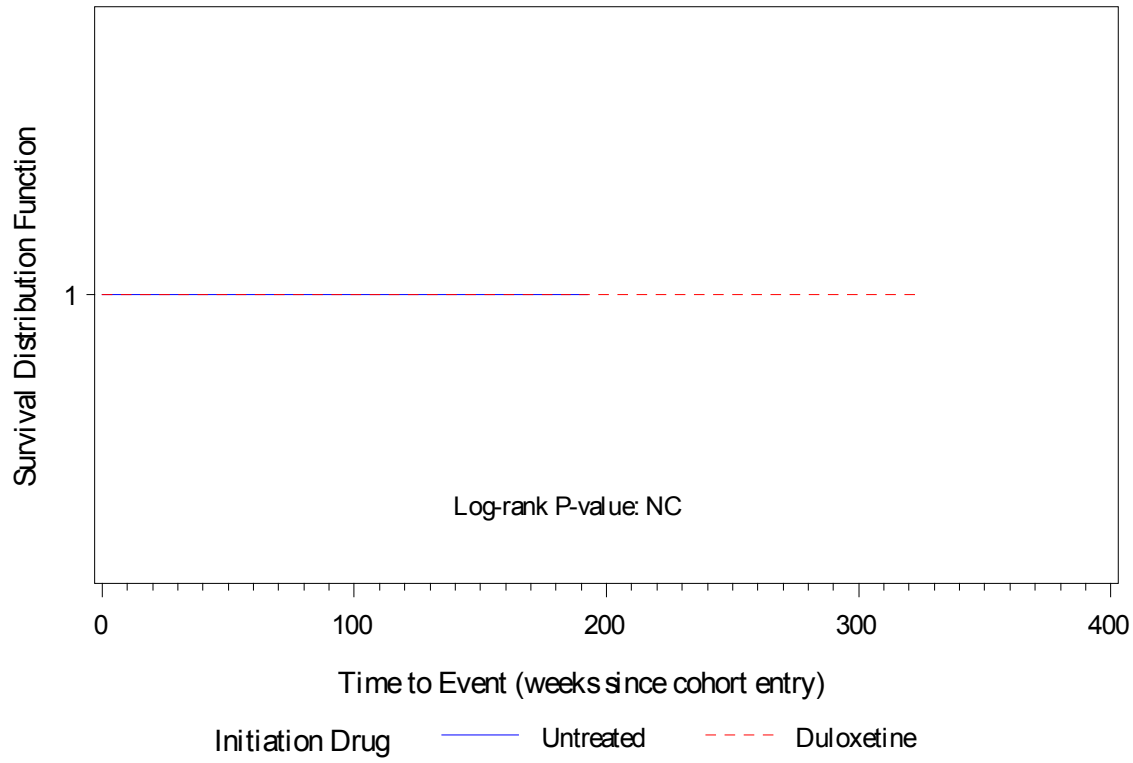
Figure 3b-4. Current Therapy Plus 15-Day Exposure Window: Time to Occurrence of Hepatic-Related Death or Hepatic failure, Duloxetine Initiators vs. SSRI Initiators



Number of Patients Remaining at Risk

Cohort	Time Since Cohort Entry (Weeks)																
	0	2	4	6	8	10	12	14	16	18	20	22	24	26	52	78	104
Duloxetine	28479	27958	27225	26197	15793	15029	12410	11370	9702	8680	7815	7051	6487	5901	2098	960	434
SSRI	28479	27983	27330	26446	15336	14513	11969	10903	9216	8197	7385	6695	6077	5493	1831	769	342

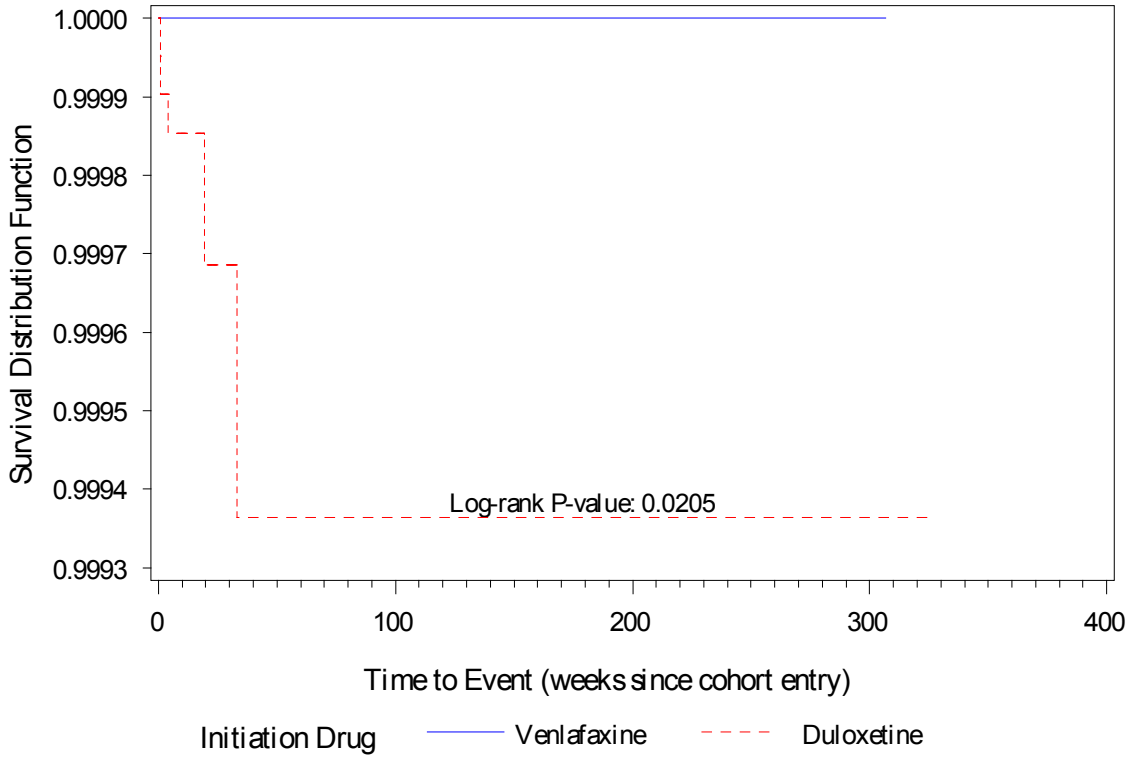
Figure 3c-4. Current Therapy Plus 15-Day Exposure Window: Time to Occurrence of Hepatic-Related Death or Hepatic failure, Duloxetine Initiators vs. Pharmacologically Untreated Cohort



Number of Patients Remaining at Risk

Cohort	Time Since Cohort Entry (Weeks)																
	0	2	4	6	8	10	12	14	16	18	20	22	24	26	52	78	104
Duloxetine	22714	22302	21709	20913	12370	11811	9701	8874	7560	6738	6089	5478	5028	4572	1610	717	318
Untreated	22714	21440	20100	18687	10671	9896	7863	6960	5746	4978	4353	3772	3344	2944	725	227	62

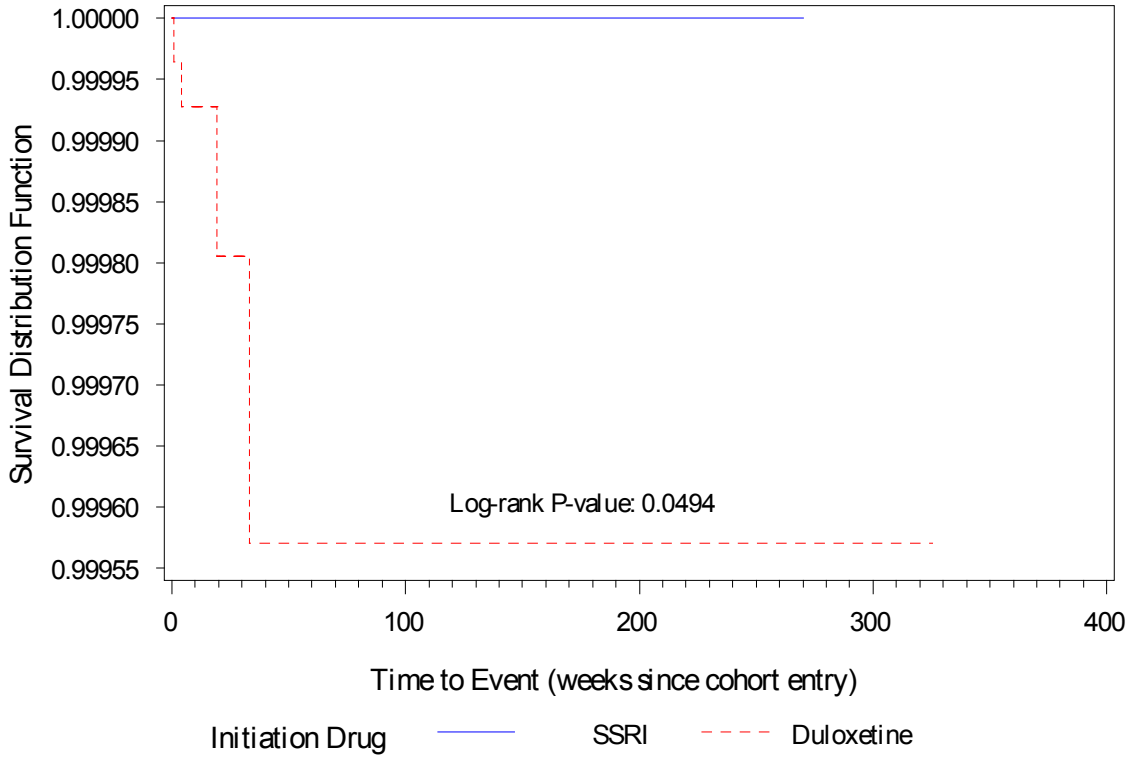
Figure 3a-5. Current Therapy Plus 15-Day Exposure Window: Time to Occurrence of Any Clinically Significant Hepatic Injury (All Categories Combined), Duloxetine Initiators vs. Venlafaxine Initiators



Number of Patients Remaining at Risk

Cohort	Time Since Cohort Entry (Weeks)																
	0	2	4	6	8	10	12	14	16	18	20	22	24	26	52	78	104
Duloxetine	21000	20584	19987	19203	11449	10905	8977	8210	7014	6253	5658	5106	4709	4272	1504	679	295
Venlafaxine	21000	20587	20036	19269	12273	11650	9969	9191	8016	7284	6621	6033	5567	5099	2027	988	524

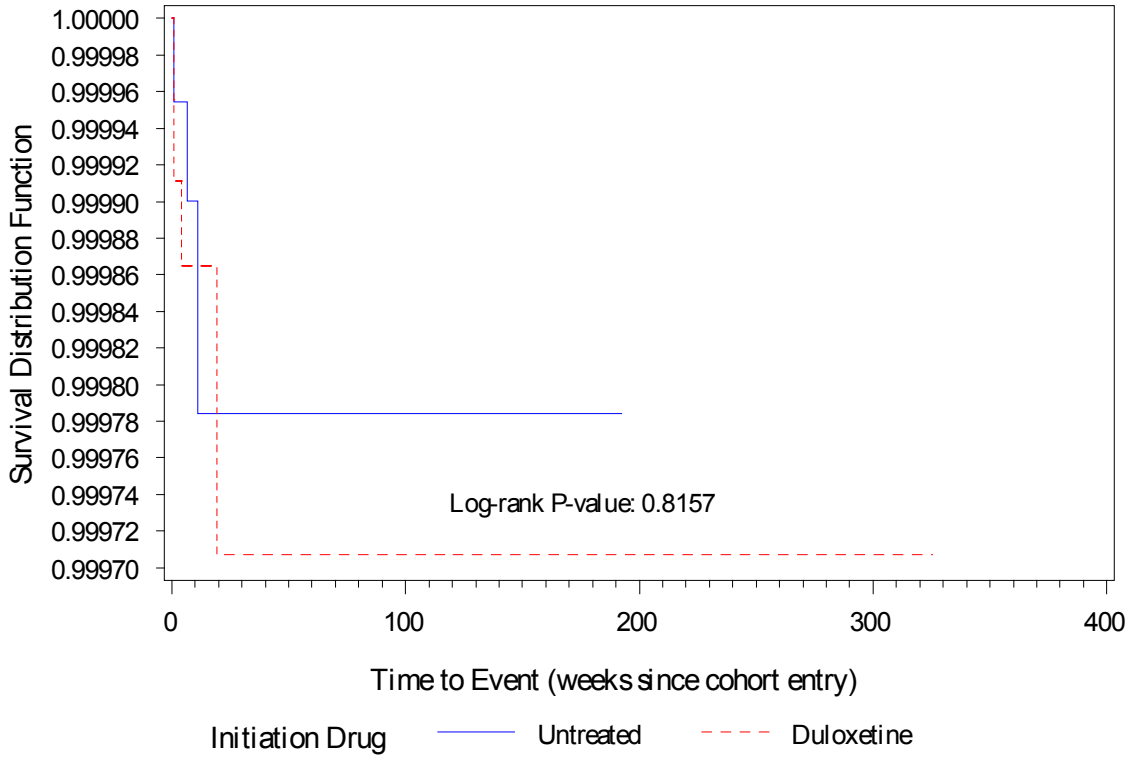
Figure 3b-5. Current Therapy Plus 15-Day Exposure Window: Time to Occurrence of Any Clinically Significant Hepatic Injury (All Categories Combined), Duloxetine Initiators vs. SSRI Initiators



Number of Patients Remaining at Risk

Cohort	Time Since Cohort Entry (Weeks)																
	0	2	4	6	8	10	12	14	16	18	20	22	24	26	52	78	104
Duloxetine	28479	27917	27145	26085	15726	14954	12344	11303	9635	8617	7752	6988	6419	5834	2048	928	418
SSRI	28479	27957	27277	26371	15279	14443	11900	10837	9154	8140	7330	6637	6019	5439	1805	744	328

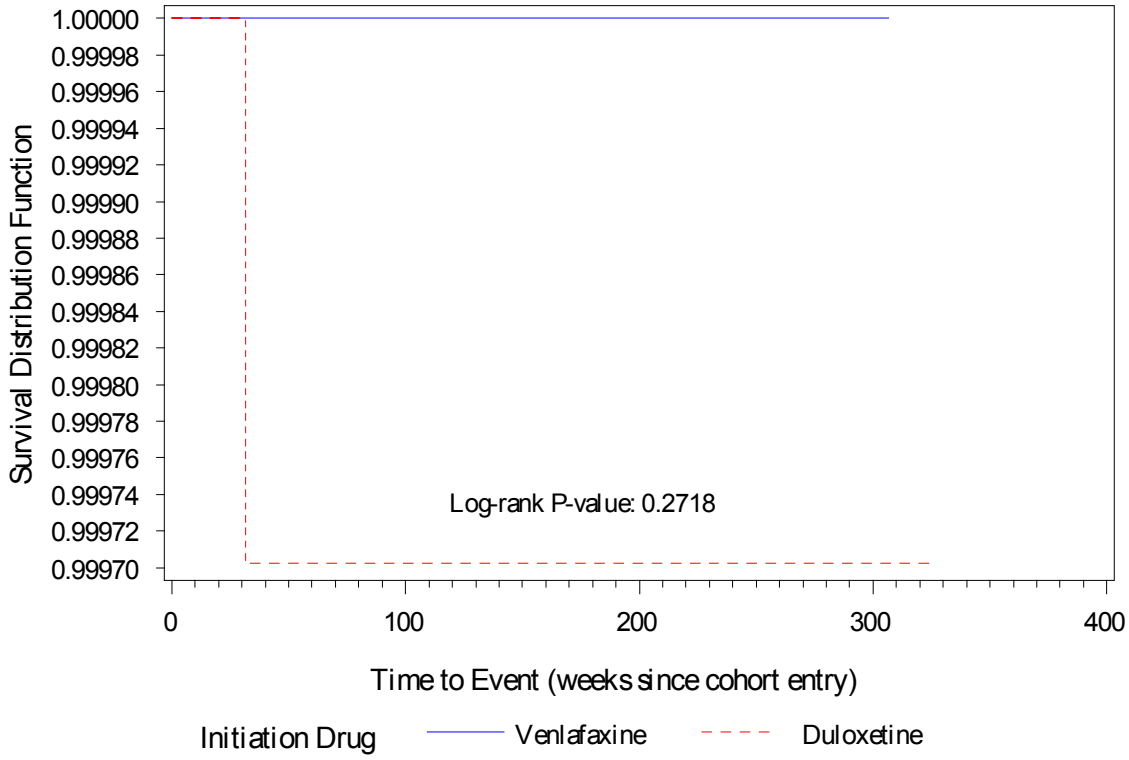
Figure 3c-5. Current Therapy Plus 15-Day Exposure Window: Time to Occurrence of Any Clinically Significant Hepatic Injury (All Categories Combined), Duloxetine Initiators vs. Pharmacologically Untreated Cohort



Number of Patients Remaining at Risk

Cohort	Time Since Cohort Entry (Weeks)																
	0	2	4	6	8	10	12	14	16	18	20	22	24	26	52	78	104
Duloxetine	22714	22266	21641	20819	12316	11753	9649	8821	7506	6683	6033	5425	4972	4519	1575	696	308
Untreated	22714	21408	20045	18620	10624	9844	7815	6910	5699	4932	4313	3735	3314	2916	713	225	62

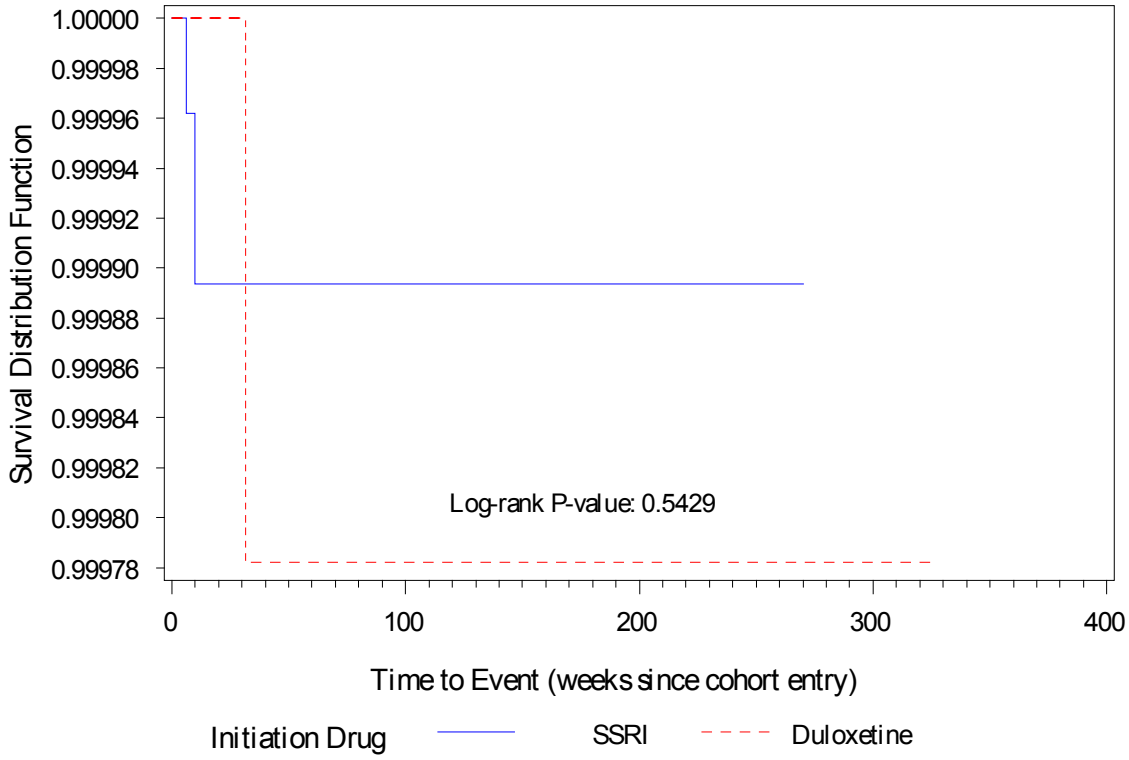
Figure 3a-6. Current Therapy Plus 15-Day Exposure Window: Time to Occurrence of Non-Serious Hepatic Enzyme Elevation, Duloxetine Initiators vs. Venlafaxine Initiators



Number of Patients Remaining at Risk

Cohort	Time Since Cohort Entry (Weeks)																
	0	2	4	6	8	10	12	14	16	18	20	22	24	26	52	78	104
Duloxetine	21000	20584	19987	19203	11449	10905	8977	8210	7014	6253	5658	5106	4709	4272	1504	679	295
Venlafaxine	21000	20587	20036	19269	12273	11650	9969	9191	8016	7284	6621	6033	5567	5099	2027	988	524

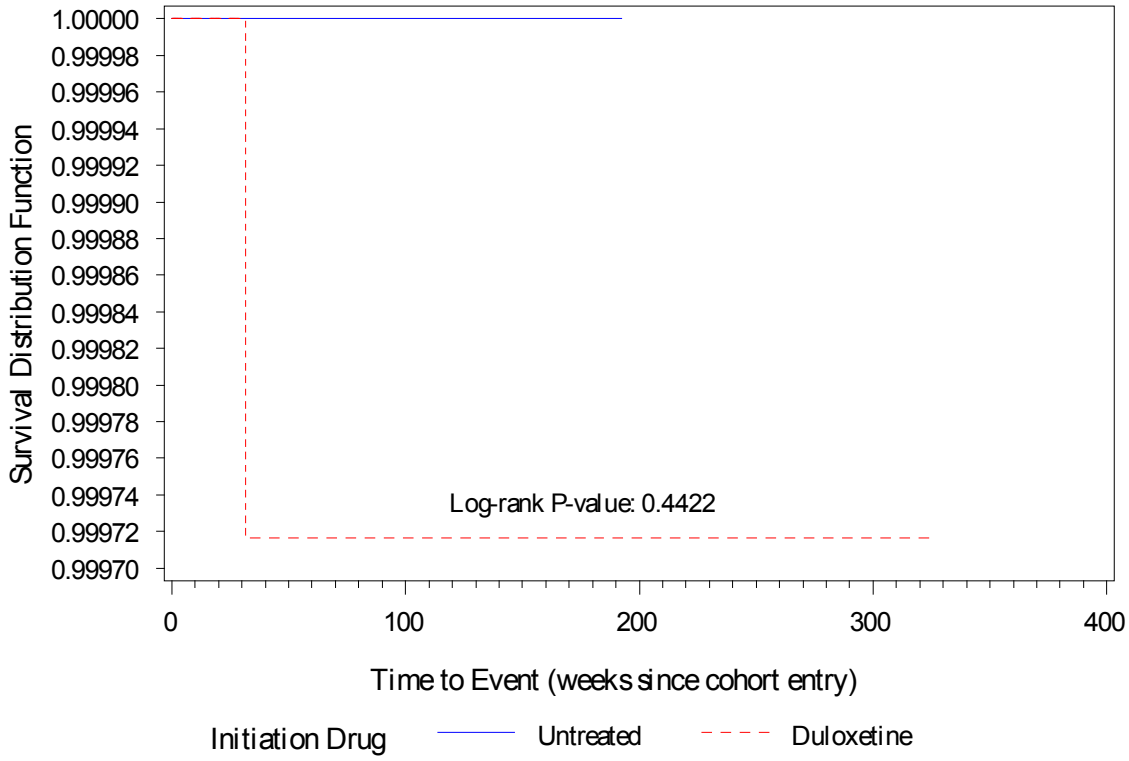
Figure 3b-6. Current Therapy Plus 15-Day Exposure Window: Time to Occurrence of Non-Serious Hepatic Enzyme Elevation, Duloxetine Initiators vs. SSRI Initiators



Number of Patients Remaining at Risk

Cohort	Time Since Cohort Entry (Weeks)																
	0	2	4	6	8	10	12	14	16	18	20	22	24	26	52	78	104
Duloxetine	28479	27917	27145	26085	15726	14954	12344	11303	9635	8617	7752	6988	6419	5834	2048	928	418
SSRI	28479	27956	27276	26370	15277	14443	11900	10838	9155	8140	7330	6637	6019	5439	1805	744	328

Figure 3c-6. Current Therapy Plus 15-Day Exposure Window: Time to Occurrence of Non-Serious Hepatic Enzyme Elevation, Duloxetine Initiators vs. Pharmacologically Untreated Cohort



Number of Patients Remaining at Risk

Cohort	Time Since Cohort Entry (Weeks)																
	0	2	4	6	8	10	12	14	16	18	20	22	24	26	52	78	104
Duloxetine	22714	22266	21641	20819	12316	11753	9649	8821	7506	6683	6033	5425	4972	4519	1575	696	308
Untreated	22714	21409	20045	18620	10624	9844	7815	6910	5699	4932	4313	3735	3314	2916	713	225	62

10. Appendices

Appendix I. Claims Codes Used to Apply Study Eligibility Criteria

I-A. Codes to Identify Dispensings of Cohort-Defining Drugs

Study Drug Cohort Codes	HICL	Description
Duloxetine	026521	DULOXETINE HCL
	026522	DULOXETINE HCL
Venlafaxine	008847	VENLAFAXINE HCL
	021508	VENLAFAXINE HCL
Selective Serotonin Reuptake Inhibitors	001655	FLUOXETINE HCL
	006324	SERTRALINE HCL
	006338	FLUVOXAMINE MALEATE
	007344	PAROXETINE HCL
	010321	CITALOPRAM HYDROBROMIDE
	021461	CITALOPRAM HYDROBROMIDE
	021463	FLUVOXAMINE MALEATE
	021464	FLUOXETINE HCL
	021465	PAROXETINE HCL
	021466	SERTRALINE HCL
	024022	ESCITALOPRAM OXALATE
	024023	ESCITALOPRAM OXALATE
	025796	PAROXETINE MESYLATE
	025797	PAROXETINE MESYLATE
	025800	OLANZAPINE/FLUOXETINE HCL
	025801	OLANZAPINE/FLUOXETINE HCL
	033191	FLUOXETINE
	034689	FLUOXETINE HCL/DIET. SUPP NO.8
	034690	FLUOXETINE HCL/DIET. SUPP NO.8
	034691	FLUOXETINE HCL/DIET.SUPP NO.17
	034692	FLUOXETINE HCL/DIET.SUPP NO.17

I-B. ICD-9 Codes for Depression

ICD-9 Code	Description
311.xx	Depressive disorder, not elsewhere classified
296.xx	Episodic mood disorders
309.xx	Adjustment reaction
300.xx	Anxiety, dissociative and somatoform disorders

I-C. Claims Codes to Identify Baseline Exclusions

Condition	Code Type	Code(s)
Heart failure	ICD-9	428.x, 402.x1, 404.x1, 404.x3, 398.91, 518.4x
Thrombocytopenia	ICD-9	287.3x, 287.4x, 287.5x
Positive markers for hepatitis infections*	ICD-9	V02.60, V02.61, V02.62, V02.69, 070.x
HIV infection	ICD-9	795.71, 042.x, 079.53, V08
Abnormal aminotransferases (ALT or AST >=2x ULN)*	ICD-9	790.4
Total bilirubin > 1.5x ULN*	ICD-9	277.4
Abnormal transferrin saturation (>50%)*	ICD-9	275.0x
Jaundice/icterus	ICD-9	782.4
Acute or sub-acute necrosis of liver	ICD-9	570
Veno-occlusive liver disease (not including Budd Chiari syndrome)	ICD-9	573.8
Liver infarction	ICD-9	573.4
Hepatic coma	ICD-9	070.0, 070.2x, 070.4x, 070.6, 070.71, 572.2
Hepatorenal syndrome	ICD-9	572.4
Chronic liver disease, cirrhosis, and fibrosis (combined)	ICD-9	571.0, 571.1, 571.2, 571.3, 571.4x, 571.5, 571.6, 571.8, 571.9, 572.0, 572.1, 572.2, 572.3, 572.4, 572.8, 573.0, 006.3, 070.x (except 070.0 and 070.1)
Chronic hepatitis (includes autoimmune, chronic persistent, unspecified chronic, other chronic)	ICD-9	571.4x, 070.22, 070.23, 070.32, 070.33, 070.44, 070.54
Chronic active hepatitis	ICD-9	571.49
Acute hepatitis	ICD-9	070.20, 070.21, 070.30, 070.31, 070.41, 070.51, 571.1
Alcoholic hepatitis	ICD-9	571.1, 571.2
Autoimmune hepatitis	ICD-9	571.42

Condition	Code Type	Code(s)
Viral hepatitis	ICD-9	070.x
Unspecified or cryptogenic hepatitis	ICD-9	573.1, 573.2, 573.3, 571.40
Nonalcoholic hepatitis	ICD-9	571.4x, 070.x, 573.1, 573.2, 573.3
Biliary tract obstruction, stricture, stones	ICD-9	574.x, 575.x, 576.x, 751.6x
Primary or metastatic neoplasia of the liver and hepatic ducts	ICD-9	155.x, 156.x, 197.7, 211.5, 230.8, 235.3, V10.07
Primary or metastatic tumors elsewhere	ICD-9	140.x - 208.x, 209.x, 210.x -229.x, 230.x - 234.x, 235.x - 238.x, V10.x
Hepatic encephalopathy	ICD-9	572.2x
Liver transplant	ICD-9	V42.7, 50.5x
		OR
	CPT	47133 - 47147
Ascites	ICD-9	789.5x
Hepatectomy	CPT	47120, 47122, 47125, 47130
		OR
	ICD-9	50.2x
Other liver operations	CPT	47765
		OR
	ICD-9	50.x (except 50.5x and 50.2x)
Hereditary hemochromatosis	ICD-9	275.01
Disorders of copper metabolism (Wilson's disease)	ICD-9	275.1
Alpha-1 antitripsin deficiency	ICD-9	273.4
Celiac disease	ICD-9	579.0
Sclerosing cholangitis	ICD-9	576.1
Primary biliary cirrhosis	ICD-9	571.6
Liver helminth, fluke, parasite	ICD-9	121.0, 121.1, 121.3, 128.8

Condition	Code Type	Code(s)
Budd-Chiari Syndrome	ICD-9	453.0
Abdominal trauma	ICD-9	863.x-868.x, 879.2x-879.5x, 902.x

* To implement baseline hepatic exclusion criteria on the basis of health care claims, the exclusion criteria for positive markers of hepatitis infection, abnormal aminotransferases, elevated total bilirubin, abnormal transferrin saturation, and elevated alkaline phosphatase were operationalized into available ICD-9 codes, as appropriate, to serve as proxies for the lab-based exclusions.

Appendix II. Claims Codes Used to Identify Potential Clinically Significant Hepatic Events

Appendix II-A. Claims Codes to Identify Potential Clinically Significant Hepatic Events Using the Health Care Claims

Claims-Identified Event	Code Type	Code(s)
1.Claims-identified death (in conjunction with any hepatic claims code listed below)		
	ICD-9	798.xx
	OR	
	Patient discharge status	20,21, 22, 23, 24, 25, 26, 27,28, 29, 40, 41, 42
2. Claims-identified potential hepatic failure		
Hepatic failure	ICD-9	570
Hepatic encephalopathy/coma	ICD-9	070.0, 070.2x, 070.4x, 070.6, 070.71, 572.2
Liver transplant	ICD-9	V42.7, 50.5, 50.51, 50.59
	OR	
	CPT	47135, 47136
3. Claims-identified potential other clinically significant hepatic injury		
Toxic liver disease	ICD-9	571.0, 571.2
Toxic hepatitis	ICD-9	573.3, 571.1
Acute hepatitis	ICD-9	571.1, 070.20, 070.30, 070.31, 070.41, 070.51
Jaundice	ICD-9	782.4, 277.4
Ascites	ICD-9	789.5, 789.51, 789.59
Liver injury	ICD-9	864.xx
Other/unspecified disorders of the liver	ICD-9	573.8, 573.9
Hepatomegaly	ICD-9	789.1
Abnormal liver scan	ICD-9	794.8
Liver biopsy	CPT/HCPCS	47000, 47001, 47100
	OR	
	ICD-9	50.1x
Liver imaging	CPT/HCPCS	78205, 78206
Hepatorenal syndrome	ICD-9	572.4
Other sequelae of chronic liver disease	ICD-9	572.8
Hypoprothombinemia	ICD-9	286.7
Abnormal coagulation, nonspecific	ICD-9	790.92
Abnormal hepatic enzyme levels - outpatient (CPT and ICD-9 0-7 days after CPT)		
AST	CPT and ICD-9	(84450, 80050, 80053, or 80076) and (790.4 or 790.5)
ALT	CPT and ICD-9	(84460, 80050, 80053, or 80076) and (790.4 or 790.5)
Bilirubin	CPT and ICD-9	(82247, 82248, 80050, 80053, or 80076) and 277.4
Abnormal hepatic enzyme levels - inpatient		
AST and ALT	ICD-9	790.4, 790.5
Bilirubin	ICD-9	277.4

Appendix II-B. ICD-10 Diagnosis Codes for Identification of Hepatic-Related Deaths in the National Death Index Data

ICD-10	Description
B15	Acute hepatitis A
B16	Acute hepatitis B
B17	Other acute viral hepatitis
B18	Chronic viral hepatitis
B19	Unspecified viral hepatitis
K70	Alcoholic liver disease
K71	Toxic liver disease
K72	Hepatic failure, not elsewhere classified
K73	Chronic hepatitis, not elsewhere classified
K74	Fibrosis and cirrhosis of liver
K75	Other inflammatory liver diseases
K76	Other diseases of the liver
K77	Liver disorders in diseases classified elsewhere
B94.2	Sequelae of viral hepatitis
R17	Unspecified jaundice
R18	Ascites

Appendix III. Suggested Approach for Managing Hepatic Outcome Validation of Billing Codes for Hepatic Events versus Medical Records Data in Observational Studies

The original adjudication algorithm is provided below. In addition to the criteria described in the original algorithm, 2 additional rules were identified during the adjudication consensus process:

- A liver injury was considered to be due to an alternative etiology if there was a plausible explanation other than drug-induced injury included in the medical history. If there was no clear alternative explanation, we assumed the cause was the drug (possible drug-induced).
- Adjudicators identified the first date for which the chart met criteria for the highest level of liver injury. If the dates of diagnosis selected by the 2 reviewers differed by less than or equal to 5 days, the earlier date was set as the case date.

(Approach validated by external hepatic expert: Dr. William Lee)

General Recommendations:

- Since there are occasional inconsistencies and often lack of specificity in the use of certain hepatic terms in clinical practice (e.g. hepatic failure, acute liver failure, fulminant hepatitis, severe liver injury) the appearance of such a term in the chart should not be considered conclusive evidence for its acceptance, if there is compelling evidence to the contrary (see examples below).
- The absence of a hepatic term in the chart should not be considered conclusive evidence for its absence, if there is compelling evidence to the contrary (see examples below).
- It is strongly recommended that all inconsistencies involving severe liver injury with or without liver failure be adjudicated by a hepatologist.

Findings *suggestive of liver failure* in the absence of corresponding condition-specific codes

In patients with claims codes or diagnoses suggestive of liver injury, *any* of the following should be considered as evidence of liver failure:

- PT-INR ≥ 1.5 in the presence of abnormal liver tests (ALT or AST ≥ 3x ULN) and in the absence of other causes for prolonged PT (e.g. warfarin therapy, congestive heart failure)
- PT ≥ 16 seconds in the presence of abnormal liver tests (ALT or AST ≥ 3x ULN) and in the absence of other causes for prolonged PT (e.g. warfarin therapy, congestive heart failure)
- Blood level of factor V ≤ 50%

Findings *contradicting liver failure* in patients with codes/diagnoses suggestive of liver failure

In patients with claims codes or diagnoses suggestive of ***liver failure***, ***any one*** of the following should be considered as contradicting evidence for a diagnosis of liver failure:

- PT < 16 seconds in the absence of a recent history of fresh frozen plasma transfusion.
- PT-INR ≤ 1.5 in the absence of a recent history of fresh frozen plasma transfusion.
- Total bilirubin ≤ 3 mg/dL

Findings *contradicting acute liver failure or fulminant liver failure* in patients *with* actual liver failure codes/diagnoses

In patients with claim code/diagnoses of ***acute liver failure*** or ***fulminant liver failure, any one*** of the following findings (in pre or post drug exposure) should be considered as evidence of *pre-existing chronic liver disease,* and should therefore be regarded as contradicting evidence for a diagnosis of ***acute liver failure*** or ***fulminant liver failure***:

- History of nodular liver/cirrhosis on an imaging study
- Esophageal varices on upper endoscopy
- Gastric varices on upper endoscopy
- Any historical evidence of preexisting chronic liver disease (e.g. history of ascites, hepatocellular carcinoma, alcoholic hepatitis, chronic hepatitis B/C, autoimmune hepatitis, primary biliary cirrhosis, etc.)

Findings suggestive of severe liver injury

Any of the following lab tests should be considered as suggestive of severe liver injury:

- ALT or AST ≥ 10x ULN
- ALT or AST ≥ 3x ULN **AND** Total bilirubin ≥ 2x ULN and alk phosph < 2x ULN

Findings contradicting severe liver injury

Any of the following combinations of lab results point against severe liver injury despite appearance of suggestive terms in the chart:

- ALT and AST < 3x ULN **AND** Total bilirubin < 2x ULN
- ALT and AST within normal limits **AND** Total bilirubin < 4x ULN

Appendix IV. Case Detail Listing - All Confirmed Hepatic Injury Events Without Alternate Etiology (n=12)

	Cases During On-Therapy Plus 15-Day Exposure Window											Cases During Days 16-30 Following Discontinuation of Study Drug
Characteristic	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Age at cohort entry	54	39	32	29	57	47	49	50	61	56	31	41
Gender	F	F	F	F	M	M	F	F	M	F	F	M
Region	NORTHEAST	SOUTH	SOUTH	SOUTH	MIDWEST	SOUTH	NORTHEAST	NORTHEAST	SOUTH	SOUTH	WEST	SOUTH
Cohort membership	dulox	dulox	dulox	dulox	dulox	dulox	ssri	ssri	untx	untx	untx	venlaf
Cohort entry year	2005	2008	2006	2008	2010	2009	2008	2009	2008	2009	2009	2007
Medical-record confirmed or NDI search-identified hepatic outcome	EE	OH	OH	OH	OH	OH	EE	EE	OH	OH	OH	EE
based on medical records	2005	2009	2006	2008	2010	2009	2009	2009	2008	2009	2009	2008
Claims-Based Baseline Characteristics (1 year prior to cohort entry)												
Depressive disorder, not elsewhere classified	YES	YES	YES	YES	YES	YES	YES	YES	NO	NO	YES	NO
Episodic mood disorders, including bipolar disorder	NO	NO	YES	NO	YES	YES	NO	YES	NO	NO	NO	NO
Adjustment reaction	NO	YES	NO	NO	NO	NO	YES	NO	YES	NO	NO	NO
and somatoform disorders	NO	YES	NO	NO	YES	NO	YES	YES	YES	YES	YES	YES
Psychotic disorders	NO	NO	YES	NO	YES	YES	NO	YES	NO	NO	NO	NO
ADHD	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
Alcohol abuse and addiction or use of naloxone, naltrexone, disulfiram, acamprosate	NO	NO	NO	NO	YES	NO	NO	YES	NO	NO	NO	NO
Cocaine abuse and addiction	NO	NO	NO	NO	NO	NO	NO	YES	NO	NO	NO	NO
Heroin abuse and addiction	NO	NO	YES	NO	NO	NO	NO	NO	NO	NO	NO	NO
Other substance abuse and addiction	NO	NO	YES	NO	NO	NO	NO	YES	NO	NO	NO	NO
Smoking (tobacco use disorder)	NO	NO	YES	NO	YES	NO	NO	YES	NO	NO	NO	NO
Overdoses	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
Suicide attempt	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
Seizure	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO

Appendix IV. Continued

	Cases During On-Therapy Plus 15-Day Exposure Window											Cases During Days 16-30 Following Discontinuation of Study Drug
Characteristic	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Chronic pain	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
Stress urinary incontinence	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
Fibromyalgia	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
Diabetic neuropathy	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
Back pain	NO	NO	YES	NO	NO	NO	NO	YES	NO	YES	NO	YES
Hypercholesterolemia/ dyslipidemia	YES	NO	NO	NO	NO	NO	NO	NO	YES	YES	NO	NO
Diabetes mellitus	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
Obesity	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
Use of any antidepressants	YES	YES	YES	NO	YES	NO	YES	YES	NO	NO	NO	NO
Use of duloxetine	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
Use of venlafaxine	NO	NO	YES	NO	NO	NO	YES	NO	NO	NO	NO	NO
Use of SSRI	NO	YES	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
Use of bupropion	NO	YES	NO	NO	YES	NO	NO	NO	NO	NO	NO	NO
Use of anticonvulsants	YES	NO	YES	NO	YES	NO	NO	NO	YES	NO	NO	NO
Use of antipsychotics	NO	NO	YES	NO	YES	NO	NO	NO	NO	NO	NO	NO
Use of narcotic analgesics	YES	NO	YES	NO	NO	NO	NO	YES	NO	NO	YES	NO
Use of anxiolytics or sedative hynotics	YES	NO	NO	NO	NO	YES	NO	YES	YES	NO	YES	NO
Use of antihistamines	YES	NO	YES	NO	NO	NO	NO	NO	NO	NO	NO	YES
Use of prescription NSAIDs (excluding diclofenac)	NO	NO	YES	NO	NO	NO	NO	YES	NO	NO	NO	YES
Use of prescription NSAIDs (diclofenac only)	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
Number of visits to a psychiatrist/ psychologist	0	0	2	0	5	0	0	7	0	0	0	0
Number of visits to other physicians	17	16	45	8	18	7	6	13	10	11	14	5
Number of different drugs dispensed	15	17	26	9	6	6	5	14	10	10	5	5
Number of unique ICD-9 codes	15	12	29	10	14	5	5	18	20	15	24	6

Appendix IV. Continued

	Cases During On-Therapy Plus 15-Day Exposure Window											Cases During Days 16-30 Following Discontinuation of Study Drug
Characteristic	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Number of different psychiatric drugs dispensed	2	5	4	1	4	1	2	4	0	0	0	1
Number of emergency room visits	0	1	5	0	1	3	0	7	0	4	0	0
Prior hospitalization	NO	NO	YES	NO	YES	NO	NO	YES	NO	NO	NO	NO
and critical care services	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
Number of laboratory tests	2	2	1	3	7	1	0	2	3	4	1	0
Total health care costs	$12,065.68	$8,900.62	$18,866.21	$40,646.76	$10,665.90	$1,719.22	$1,386.33	$10,968.38	$3,630.02	$8,864.95	$3,451.91	$643.67
Received above modal dose of anti-depressant	NO	NO	NO	NO	YES	NO	NO	NO	NO	NO	NO	NO
Received modal dose of anti-depressant	YES	NO	YES	YES	NO	NO	YES	YES	NO	NO	NO	YES
Received below modal dose of anti-depressant	NO	YES	NO	NO	NO	YES	NO	NO	NO	NO	NO	NO
As of confirmed case date												
Current study drug use												
Duloxetine	YES	YES	YES	YES	YES	YES	NO	NO	NO	NO	NO	NO
Venlafaxine	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	YES
SSRI	NO	NO	NO	NO	NO	NO	YES	YES	NO	NO	NO	NO
Duration as a current study drug user in days												
Duloxetine	221	233	7	30	136	6	.	.	.	.	.	.
Venlafaxine	.	.	.	.	.	.	.	.	.	.	.	56
SSRI	.	.	.	.	.	.	44	69	.	.	.	.
Days from cohort entry to onset of confirmed event	220	232	6	29	135	5	43	68	78	7	45	55
hepatic outcome (ICD-9 literal)	790.5, 794.8	794.8	573.3, 790.4	573.3, 782.4, 790.4	790.4	573.3	794.8	794.8	570.0	794.8	794.8	790.4
Year of diagnosis based on claims	2005	2009	2006	2008	2010	2009	2009	2009	2008	2009	2009	2008

Appendix IV. Continued

	Cases During On-Therapy Plus 15-Day Exposure Window											Cases During Days 16-30 Following Discontinuation of Study Drug
Characteristic	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
hepatic events indicated from NDI search	.	.	.	.	.	.	.	.	.	.	.	.
Underlying cause of death indicated by death certificate as hepatic event	.	.	.	.	.	.	.	.	.	.	.	.
Medical-record confirmed or NDI search-identified hepatic outcome	EE	OH	OH	OH	OH	OH	EE	EE	OH	OH	OH	EE
based on medical records	2005	2009	2006	2008	2010	2009	2009	2009	2008	2009	2009	2008
Within 45 days prior to confirmed outcome, documented diagnoses or drug exposures:												
Sepsis/septic shock	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
Heart failure (with and without MI)	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
Cardiogenic shock, acute MI	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
Acute viral infection (hepatitis A, B, C, D, E; EBV, CMV, HSV)	NO	YES	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
Autoimmune hepatitis	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
Alcoholic hepatitis	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
Any non-alcohol liver-related ICD-9 code (571.1, 571.4, 571.5, 571.6, 571.9)	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
Alcoholic liver, fatty liver, or cirrhosis alcoholic condition	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO

Appendix IV. Continued

	Cases During On-Therapy Plus 15-Day Exposure Window											Cases During Days 16-30 Following Discontinuation of Study Drug
Characteristic	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Cholecystitis, choledocholithiasis	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	YES	NO
Acetaminophen toxicity	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
(Budd-Chiari syndrome), portal vein obstruction	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
Primary neoplasia of the liver, or metastatic disease in liver from primary tumors elsewhere	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
Hepatorenal syndrome	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
Chronic liver disease, cirrhosis, fibrosis	NO	YES	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
Metabolic liver injury (hemochromatosis, Wilson Disease, alpha-1 antitrypsin deficiency)	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
Sclerosing colangitis	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
Thrombocytopenia	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
Use of duloxetine	YES	YES	YES	YES	YES	YES	NO	NO	NO	NO	NO	NO
Use of venlafaxine	NO	NO	NO	NO	NO	NO	YES	NO	NO	NO	NO	YES
Use of SSRI	NO	NO	YES	NO	NO	NO	YES	YES	NO	NO	NO	NO
Use of valproic acid	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
Use of diclofenac	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
Use of nefazodone	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
Use of statins/ lipid lowering drugs	NO	NO	NO	NO	NO	NO	NO	NO	YES	YES	NO	NO
Use of isoniazid	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
Use of phenytoin	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
Use of nitrofurantoin	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
Use of propyluracil	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
Use of rifampin	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
Use of fluconazole	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
Use of chlorpromazine	NO	NO	NO	NO	YES	NO	NO	NO	NO	NO	NO	NO
Use of iInterferon beta	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO

Appendix IV. Continued

	Cases During On-Therapy Plus 15-Day Exposure Window											Cases During Days 16-30 Following Discontinuation of Study Drug
Characteristic	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Use of amiodarone	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
Use of either naloxone, naltrexone, disulfiram, acamprosate (proxies for alcoholism)	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO

SSRI: selective serotonin re-uptake inhibitor; dulox: duloxetine; untx: pharmacologically untreated; venlaf: venlafaxine; ADHD: attention deficit hyperactivity disorder; NSAID: nonsteroidal anti-inflammatory drug; ICD-9: International Classification of Diseases, 9th Edition; NDI: National Death Index; EE: non-serious asymptomatic hepatic enzyme elevation; OH: other clinically significant hepatic injury; EBV: Epstein Barr virus; CMV: cytomegalovirus; HSV: herpes simplex virus
. = missing or not applicable

Appendix V-A: Baseline characteristics comparison: members within the duloxetine-venlafaxine propensity score-matched cohorts who dropped out during follow-up, by cohort

	Overall cohort				Censored due to treatment discontinuation or censored at non-confirmed claims-identified event date during the follow-up period (15-day discontinuation window)				Censored due to treatment discontinuation, administrative censoring, or censoring on non-confirmed claims-identified event date within the 1st 90 days following cohort			
Characteristic	Duloxetine (N=21,000)		Venlafaxine (N=21,000)		Duloxetine (N=17,008)		Venlafaxine (N=16,356)		Duloxetine (N=12,521)		Venlafaxine (N=11,538)	
Age group (years) (N %)												
18-25	1,855	8.8	1,807	8.6	1,557	9.2	1,484	9.1	1,283	10.3	1,134	9.8
26-30	1,748	8.3	1,758	8.4	1,380	8.1	1,374	8.4	1,146	9.2	1,070	9.3
31-35	2,473	11.8	2,487	11.8	2,014	11.8	1,958	12.0	1,595	12.7	1,496	13.0
36-40	3,067	14.6	2,979	14.2	2,484	14.6	2,309	14.1	1,876	15.0	1,668	14.5
41-50	6,152	29.3	6,218	29.6	4,997	29.4	4,840	29.6	3,533	28.2	3,295	28.6
51-60	4,371	20.8	4,419	21.0	3,524	20.7	3,376	20.6	2,410	19.3	2,268	19.7
61-70	1,176	5.6	1,175	5.6	934	5.5	890	5.4	602	4.8	530	4.6
≥71	158	0.8	157	0.8	118	0.7	125	0.8	76	0.6	77	0.7
Gender (N %)												
Female	15,074	71.8	15,092	71.9	12,218	71.8	11,739	71.8	9,006	71.9	8,212	71.2
Male	5,926	28.2	5,908	28.1	4,790	28.2	4,617	28.2	3,515	28.1	3,326	28.8
Geographic region of health plan (N %)												
Northeast	1,344	6.4	1,343	6.4	1,057	6.2	989	6.1	825	6.6	749	6.5
Midwest	5,734	27.3	5,695	27.1	4,588	27.0	4,425	27.1	3,306	26.4	3,014	26.1
South/Southeast	11,760	56.0	11,806	56.2	9,673	56.9	9,297	56.8	7,147	57.1	6,614	57.3
West	2,162	10.3	2,156	10.3	1,690	9.9	1,645	10.1	1,243	9.9	1,161	10.1
Calendar year of cohort entry (N %)												
2004	1,191	5.7	1,118	5.3	950	5.6	891	5.5	713	5.7	586	5.1
2005	3,374	16.1	3,391	16.2	2,817	16.6	2,681	16.4	2,004	16.0	1,823	15.8
2006	4,102	19.5	4,146	19.7	3,363	19.8	3,257	19.9	2,389	19.1	2,249	19.5
2007	4,315	20.6	4,334	20.6	3,586	21.1	3,418	20.9	2,615	20.9	2,322	20.1
2008	3,687	17.6	3,663	17.4	3,017	17.7	2,916	17.8	2,164	17.3	2,028	17.6
2009	2,583	12.3	2,592	12.3	2,031	11.9	2,013	12.3	1,594	12.7	1,505	13.0
2010	1,748	8.3	1,756	8.4	1,244	7.3	1,180	7.2	1,042	8.3	1,025	8.9

Appendix V-A Continued

	Overall cohort				Censored due to treatment discontinuation or censored at non-confirmed claims-identified event date during the follow-up period (15-day discontinuation window)				Censored due to treatment discontinuation, administrative censoring, or censoring on non-confirmed claims-identified event date within the 1st 90 days following cohort			
Characteristic	Duloxetine (N=21,000)		Venlafaxine (N=21,000)		Duloxetine (N=17,008)		Venlafaxine (N=16,356)		Duloxetine (N=12,521)		Venlafaxine (N=11,538)	
Neuropsychological comorbidities (N %)												
Depressive disorder, not elsewhere classified	10,000	47.6	9,957	47.4	8,021	47.2	7,691	47.0	5,925	47.3	5,355	46.4
Episodic mood disorders (with depressive component)	6,743	32.1	6,726	32.0	5,461	32.1	5,194	31.8	3,919	31.3	3,677	31.9
Episodic mood disorders (without depressive component)	1,436	6.8	1,416	6.7	1,169	6.9	1,106	6.8	873	7.0	795	6.9
Adjustment reaction	3,086	14.7	3,057	14.6	2,492	14.7	2,376	14.5	1,842	14.7	1,708	14.8
Anxiety, dissociative and somatoform disorders	11,252	53.6	11,172	53.2	9,095	53.5	8,677	53.1	6,813	54.4	6,276	54.4
Psychotic disorders	7,746	36.9	7,685	36.6	6,276	36.9	5,950	36.4	4,519	36.1	4,225	36.6
ADHD	959	4.6	883	4.2	802	4.7	696	4.3	609	4.9	502	4.4
Alcohol abuse and addiction (diagnosis)	684	3.3	683	3.3	557	3.3	535	3.3	433	3.5	418	3.6
Alcohol abuse and addiction (treatment)	280	1.3	320	1.5	232	1.4	246	1.5	189	1.5	196	1.7
Cocaine abuse and addiction	115	0.6	101	0.5	99	0.6	78	0.5	81	0.7	74	0.6
Heroin abuse and addiction	231	1.1	199	1.0	195	1.2	162	1.0	163	1.3	136	1.2
Other substance abuse and addiction	511	2.4	497	2.4	418	2.5	400	2.5	337	2.7	327	2.8
Smoking (tobacco use disorder - diagnosis)	1,231	5.9	1,316	6.3	996	5.9	1,039	6.4	814	6.5	794	6.9
Smoking (tobacco use disorder - treatment)	95	0.5	91	0.4	75	0.4	78	0.5	57	0.5	55	0.5
Overdoses	23	0.1	17	0.1	20	0.1	15	0.1	16	0.1	10	0.1
Suicide attempts	133	0.6	128	0.6	104	0.6	93	0.6	85	0.7	78	0.7
Seizure	169	0.8	172	0.8	131	0.8	133	0.8	105	0.8	91	0.8
Chronic pain	235	1.1	211	1.0	184	1.1	155	1.0	154	1.2	124	1.1
Stress urinary incontinence	207	1.0	196	0.9	167	1.0	154	0.9	127	1.0	104	0.9

Appendix V-A Continued

	Overall cohort				Censored due to treatment discontinuation or censored at non-confirmed claims-identified event date during the follow-up period (15-day discontinuation window)				Censored due to treatment discontinuation, administrative censoring, or censoring on non-confirmed claims-identified event date within the 1st 90 days following cohort			
Characteristic	**Duloxetine (N=21,000)**		**Venlafaxine (N=21,000)**		**Duloxetine (N=17,008)**		**Venlafaxine (N=16,356)**		**Duloxetine (N=12,521)**		**Venlafaxine (N=11,538)**	
Neuropsychological comorbidities (N %)												
Fibromyalgia	1,936	9.2	1,858	8.9	1,559	9.2	1,460	8.9	1,177	9.4	1,052	9.1
Diabetic neuropathy	183	0.9	154	0.7	155	0.9	112	0.7	116	0.9	78	0.7
Back pain	2,974	14.2	2,863	13.6	2,441	14.4	2,261	13.8	1,870	14.9	1,662	14.4
Hepatic risks (N %)												
Hypercholesterolemia / dyslipidemia (diagnosis)	5,040	24.0	5,067	24.1	3,997	23.5	3,899	23.8	2,816	22.5	2,567	22.3
Hypercholesterolemia / dyslipidemia (treatment)	2,580	12.3	2,576	12.3	2,034	12.0	1,989	12.2	1,393	11.1	1,213	10.5
Hyperglycemia	300	1.4	319	1.5	233	1.4	246	1.5	171	1.4	176	1.5
Albuminuria	66	0.3	66	0.3	56	0.3	48	0.3	43	0.3	36	0.3
Diabetes mellitus (diagnosis)	1,447	6.9	1,446	6.9	1,196	7.0	1,087	6.7	877	7.0	756	6.6
Diabetes mellitus (treatment)	1,317	6.3	1,302	6.2	1,088	6.4	973	6.0	779	6.2	662	5.7
CMV infection	2	0.0	3	0.0	2	0.0	3	0.0	0	0.0	1	0.0
EBV infection	40	0.2	42	0.2	32	0.2	32	0.2	25	0.2	21	0.2
Obesity (diagnosis)	1,159	5.5	1,184	5.6	929	5.5	908	5.6	708	5.7	645	5.6
Obesity (treatment)	5	0.0	4	0.0	5	0.0	3	0.0	3	0.0	2	0.0
Liver ultrasound scans												
0	20,189	96.1	20,165	96.0	16,344	96.1	15,690	95.9	12,014	96.0	11,051	95.8
1	778	3.7	800	3.8	636	3.7	633	3.9	483	3.9	462	4.0
2+	33	0.2	35	0.2	28	0.2	33	0.2	24	0.2	25	0.2
Bilirubin test	971	4.6	972	4.6	783	4.6	751	4.6	599	4.8	510	4.4
ALT/AST/ALP test	788	3.8	790	3.8	623	3.7	592	3.6	444	3.6	388	3.4
NSAID use (excluding diclofenac)	5,643	26.9	5,730	27.3	4,585	27.0	4,524	27.7	3,504	28.0	3,238	28.1
NSAID use (diclofenac only)	736	3.5	710	3.4	578	3.4	578	3.5	451	3.6	391	3.4
Isoniazid	3	0.0	7	0.0	1	0.0	7	0.0	0	0.0	4	0.0
Phenytoin	45	0.2	52	0.3	43	0.3	45	0.3	25	0.2	32	0.3
Valproic acid	408	1.9	439	2.1	328	1.9	339	2.1	253	2.0	241	2.1
Nitrofurantoin	796	3.8	773	3.7	636	3.7	603	3.7	470	3.8	435	3.8
Propylthiouracil	10	0.1	10	0.1	9	0.1	9	0.1	5	0.0	4	0.0
Rifampin	39	0.2	33	0.2	35	0.2	27	0.2	24	0.2	17	0.2
Fluconazole	1,684	8.0	1,701	8.1	1,367	8.0	1,340	8.2	1,037	8.3	945	8.2
Chlorpromazine	17	0.1	20	0.1	12	0.1	18	0.1	11	0.1	14	0.1
Interferon beta	66	0.3	49	0.2	59	0.4	35	0.2	35	0.3	23	0.2

Appendix V-A Continued

	Overall cohort				Censored due to treatment discontinuation or censored at non-confirmed claims-identified event date during the follow-up period (15-day discontinuation window)				Censored due to treatment discontinuation, administrative censoring, or censoring on non-confirmed claims-identified event date within the 1st 90 days following cohort			
Characteristic	Duloxetine (N=21,000)		Venlafaxine (N=21,000)		Duloxetine (N=17,008)		Venlafaxine (N=16,356)		Duloxetine (N=12,521)		Venlafaxine (N=11,538)	
Hepatic risks (N %)												
Amiodarone	12	0.1	17	0.1	8	0.1	12	0.1	6	0.1	9	0.1
Statins	3,008	14.3	3,002	14.3	2,339	13.8	2,260	13.8	1,601	12.8	1,449	12.6
Naloxone	117	0.6	138	0.7	98	0.6	110	0.7	85	0.7	92	0.8
Naltrexone	58	0.3	74	0.4	48	0.3	56	0.3	45	0.4	43	0.4
Disulfiram	37	0.2	37	0.2	31	0.2	31	0.2	23	0.2	17	0.2
Acamprosate	92	0.4	104	0.5	76	0.5	78	0.5	55	0.4	61	0.5
Use of medications (N %)												
Duloxetine (excluding index drug)	0	0.0	1,007	4.8	0	0.0	765	4.7	0	0.0	520	4.5
Venlafaxine (excluding index drug)	1,922	9.2	0	0.0	1,538	9.0	0	0.0	1,041	8.3	0	0.0
SSRI (excluding index drug)	7,963	37.9	8,024	38.2	6,258	36.8	6,040	36.9	4,463	35.6	4,056	35.2
Other antidepressants	7,860	37.4	7,808	37.2	6,292	37.0	6,050	37.0	4,517	36.1	4,139	35.9
Bupropion	3,524	16.8	3,422	16.3	2,808	16.5	2,661	16.3	1,941	15.5	1,745	15.1
Anticonvulsants	5,403	25.7	5,406	25.7	4,366	25.7	4,175	25.5	3,254	26.0	2,995	26.0
Anxiolytics or sedative hypnotics	10,192	48.5	10,072	48.0	8,255	48.5	7,836	47.9	6,162	49.2	5,668	49.1
Antihistamines	4,364	20.8	4,315	20.6	3,538	20.8	3,372	20.6	2,632	21.0	2,387	20.7
Antipsychotics	1,689	8.0	1,710	8.1	1,345	7.9	1,307	8.0	1,007	8.0	950	8.2
Narcotic analgesics	9,533	45.4	9,452	45.0	7,750	45.6	7,414	45.3	5,928	47.3	5,378	46.6
History of (N %)												
Hypertension	4,938	23.5	4,976	23.7	3,985	23.4	3,808	23.3	2,834	22.6	2,570	22.3
Stroke	288	1.4	282	1.3	232	1.4	225	1.4	172	1.4	151	1.3
MI	102	0.5	96	0.5	82	0.5	72	0.4	59	0.5	44	0.4
Angina	171	0.8	177	0.8	145	0.9	137	0.8	106	0.9	86	0.8
Unstable angina/acute coronary syndromes	125	0.6	101	0.5	106	0.6	76	0.5	79	0.6	46	0.4
Specified health services (N % unless otherwise noted)												
Number of unique ICD-9 codes												
0-4	1,924	9.2	1,948	9.3	1,579	9.3	1,501	9.2	1,148	9.2	1,114	9.7
5-8	4,228	20.1	4,208	20.0	3,366	19.8	3,314	20.3	2,480	19.8	2,298	19.9
9-12	4,603	21.9	4,657	22.2	3,739	22.0	3,552	21.7	2,700	21.6	2,481	21.5
13-16	3,706	17.7	3,704	17.6	3,010	17.7	2,912	17.8	2,186	17.5	2,021	17.5
17+	6,539	31.1	6,483	30.9	5,314	31.2	5,077	31.0	4,007	32.0	3,624	31.4

Appendix V-A Continued

	Overall cohort				Censored due to treatment discontinuation or censored at non-confirmed claims-identified event date during the follow-up period (15-day discontinuation window)				Censored due to treatment discontinuation, administrative censoring, or censoring on non-confirmed claims-identified event date within the 1st 90 days following cohort			
Characteristic	**Duloxetine (N=21,000)**		**Venlafaxine (N=21,000)**		**Duloxetine (N=17,008)**		**Venlafaxine (N=16,356)**		**Duloxetine (N=12,521)**		**Venlafaxine (N=11,538)**	
Specified health services (N % unless otherwise noted)												
Number of different drugs dispensed												
0-3	2,525	12.0	2,410	11.5	2,057	12.1	1,887	11.5	1,522	12.2	1,380	12.0
4-7	6,365	30.3	6,427	30.6	5,187	30.5	5,015	30.7	3,756	30.0	3,522	30.5
8+	12,110	57.7	12,163	57.9	9,764	57.4	9,454	57.8	7,243	57.9	6,636	57.5
Use of intensive care and critical care services	241	1.2	221	1.1	191	1.1	171	1.1	146	1.2	115	1.0
Hospitalization	2,763	13.2	2,679	12.8	2,195	12.9	2,066	12.6	1,717	13.7	1,545	13.4
Psychiatrist/psychologist specialty at index visit	2,235	10.6	2,221	10.6	1,832	10.8	1,739	10.6	1,299	10.4	1,166	10.1
Number of visits to a psychiatrist/psychologist (mean std)	2	6.1	2	6.2	2	6.1	2	6.1	2	6.0	2	6.0
Number of visits to other physicians (mean std)	10	10.3	10	10.1	10	10.3	10	10.1	10	10.5	10	9.9
Number of different psychiatric drugs dispensed (mean std)	2	1.1	2	1.2	2	1.1	2	1.2	2	1.1	2	1.2
Number of emergency room visits (mean std)	2	4.8	2	4.6	2	4.8	2	4.6	2	4.5	2	4.6
Number of psychiatric-related hospitalizations (mean std)	0	0.1	0	0.1	0	0.1	0	0.1	0	0.1	0	0.2
Number of other laboratory tests (mean std)	3	3.4	3	3.3	3	3.4	3	3.3	3	3.4	3	3.4
Total costs (mean std)	7,945	14,910.5	7,686	14,071.0	7,852	14,857.9	7,606	13,977.9	7,880	15,352.5	7,545	13,430.8
Patient pharmacy costs (mean std)	621	560.3	608	598.5	608	552.4	593	593.1	576	527.1	554	569.7

Appendix V-A Continued

	Overall cohort				Censored due to treatment discontinuation or censored at non-confirmed claims-identified event date during the follow-up period (15-day discontinuation window)				Censored due to treatment discontinuation, administrative censoring, or censoring on non-confirmed claims-identified event date within the 1st 90 days following cohort			
Characteristic	**Duloxetine (N=21,000)**		**Venlafaxine (N=21,000)**		**Duloxetine (N=17,008)**		**Venlafaxine (N=16,356)**		**Duloxetine (N=12,521)**		**Venlafaxine (N=11,538)**	
Specified health services (N % unless otherwise noted)												
Non-patient pharmacy costs (mean std)	1,403	2,410.7	1,353	2,357.1	1,374	2,426.3	1,322	2,345.1	1,265	2,297.6	1,234	2,332.6
Facility costs (mean std)	3,579	11,802.2	3,418	10,735.4	3,543	11,803.4	3,376	10,562.2	3,710	12,278.1	3,435	9,803.0
Number of months of prior continuous enrollment (mean std)	36	25.5	36	25.6	36	25.5	36	25.8	35	24.8	35	25.2
Chart-confirmed events (15-day treatment discontinuation window)												
Hepatic-related death	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Liver failure	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Other clinically significant hepatic injury	5	0.0	0	0.0	4	0.0	0	0.0	3	0.0	0	0.0
Non-serious hepatic enzyme elevation	1	0.0	0	0.0	1	0.0	0	0.0	0	0.0	0	0.0

SSRI: selective serotonin reuptake inhibitor; ADHD: attention deficit hyperactivity disorder; CMV: cytomegalovirus; EBV: Epstein-Barr virus; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; NSAID: nonsteroidal anti-inflammatory drug; MI: myocardial infarction; ICD-9: International Classification of Diseases, 9th Edition; std: standard deviation

Appendix V-B: Baseline characteristics comparison: members within the duloxetine-SSRI propensity score-matched cohorts who dropped out during follow-up, by cohort

	Overall cohort				Censored due to treatment discontinuation or censored at non-confirmed claims-identified event date during the follow-up period (15-day				Censored due to treatment discontinuation, administrative censoring, or censoring on non-confirmed claims-identified event date			
Characteristic	Duloxetine (N=28,479)		SSRI (N=28,479)		Duloxetine (N=23,052)		SSRI (N=23,394)		Duloxetine (N=16,787)		SSRI (N=17,242)	
Age group (years) (N %)												
18-25	2,154	7.6	2,057	7.2	1,806	7.8	1,778	7.6	1,475	8.8	1,425	8.3
26-30	2,070	7.3	1,992	7.0	1,647	7.1	1,606	6.9	1,350	8.0	1,323	7.7
31-35	3,101	10.9	3,128	11.0	2,526	11.0	2,548	10.9	2,001	11.9	2,005	11.6
36-40	4,034	14.2	4,008	14.1	3,256	14.1	3,335	14.3	2,464	14.7	2,508	14.6
41-50	8,667	30.4	8,733	30.7	7,048	30.6	7,198	30.8	4,978	29.7	5,193	30.1
51-60	6,390	22.4	6,436	22.6	5,149	22.3	5,270	22.5	3,481	20.7	3,649	21.2
61-70	1,817	6.4	1,871	6.6	1,436	6.2	1,459	6.2	919	5.5	1,014	5.9
≥71	246	0.9	254	0.9	184	0.8	200	0.9	119	0.7	125	0.7
Gender (N %)												
Female	20,570	72.2	20,405	71.7	16,660	72.3	16,826	71.9	12,090	72.0	12,346	71.6
Male	7,909	27.8	8,074	28.4	6,392	27.7	6,568	28.1	4,697	28.0	4,896	28.4
Geographic region of health plan (N %)												
Northeast	1,666	5.9	1,524	5.4	1,315	5.7	1,199	5.1	1,007	6.0	879	5.1
Midwest	7,268	25.5	7,198	25.3	5,818	25.2	5,841	25.0	4,167	24.8	4,183	24.3
South/Southeast	16,724	58.7	16,937	59.5	13,707	59.5	14,116	60.3	9,995	59.5	10,525	61.0
West	2,821	9.9	2,820	9.9	2,212	9.6	2,238	9.6	1,618	9.6	1,655	9.6
Calendar year of cohort entry (N %)												
2004	1,438	5.1	1,327	4.7	1,150	5.0	1,124	4.8	858	5.1	803	4.7
2005	4,246	14.9	4,281	15.0	3,542	15.4	3,609	15.4	2,507	14.9	2,638	15.3
2006	5,425	19.1	5,445	19.1	4,446	19.3	4,528	19.4	3,118	18.6	3,277	19.0
2007	5,750	20.2	5,747	20.2	4,752	20.6	4,780	20.4	3,422	20.4	3,511	20.4
2008	5,117	18.0	5,165	18.1	4,224	18.3	4,292	18.4	2,964	17.7	3,100	18.0
2009	4,042	14.2	4,037	14.2	3,210	13.9	3,261	13.9	2,472	14.7	2,438	14.1
2010	2,461	8.6	2,477	8.7	1,728	7.5	1,800	7.7	1,446	8.6	1,475	8.6

Appendix V-B Continued

	Overall cohort				Censored due to treatment discontinuation or censored at non-confirmed claims-identified event date during the follow-up period (15-day				Censored due to treatment discontinuation, administrative censoring, or censoring on non-confirmed claims-identified event date			
Characteristic	Duloxetine (N=28,479)		SSRI (N=28,479)		Duloxetine (N=23,052)		SSRI (N=23,394)		Duloxetine (N=16,787)		SSRI (N=17,242)	
Neuropsychological comorbidities (N %)												
Depressive disorder, not elsewhere classified	13,256	46.6	13,545	47.6	10,642	46.2	11,071	47.3	7,785	46.4	8,252	47.9
Episodic mood disorders (with depressive component)	9,774	34.3	9,732	34.2	7,900	34.3	8,006	34.2	5,663	33.7	5,847	33.9
Episodic mood disorders (without depressive component)	2,029	7.1	2,033	7.1	1,645	7.1	1,640	7.0	1,211	7.2	1,238	7.2
Adjustment reaction	4,173	14.7	4,084	14.3	3,382	14.7	3,331	14.2	2,491	14.8	2,496	14.5
Anxiety, dissociative and somatoform disorders	14,746	51.8	14,654	51.5	11,921	51.7	12,024	51.4	8,819	52.5	8,944	51.9
Psychotic disorders	11,187	39.3	11,029	38.7	9,035	39.2	9,064	38.7	6,508	38.8	6,640	38.5
ADHD	1,377	4.8	1,431	5.0	1,146	5.0	1,200	5.1	864	5.2	895	5.2
Alcohol abuse and addiction (diagnosis)	928	3.3	899	3.2	766	3.3	749	3.2	582	3.5	581	3.4
Alcohol abuse and addiction (treatment)	469	1.7	450	1.6	394	1.7	370	1.6	304	1.8	284	1.7
Cocaine abuse and addiction	163	0.6	149	0.5	138	0.6	122	0.5	118	0.7	115	0.7
Heroin abuse and addiction	387	1.4	340	1.2	324	1.4	273	1.2	262	1.6	231	1.3
Other substance abuse and addiction	763	2.7	747	2.6	633	2.8	608	2.6	505	3.0	509	3.0
Smoking (tobacco use disorder - diagnosis)	1,740	6.1	1,797	6.3	1,433	6.2	1,482	6.3	1,128	6.7	1,154	6.7
Smoking (tobacco use disorder - treatment)	139	0.5	128	0.5	113	0.5	113	0.5	81	0.5	71	0.4
Overdoses	37	0.1	29	0.1	31	0.1	23	0.1	21	0.1	17	0.1
Suicide attempts	179	0.6	154	0.5	142	0.6	122	0.5	117	0.7	93	0.5
Seizure	264	0.9	287	1.0	209	0.9	235	1.0	155	0.9	167	1.0
Chronic pain	538	1.9	477	1.7	431	1.9	381	1.6	345	2.1	307	1.8
Stress urinary incontinence	300	1.1	267	0.9	244	1.1	218	0.9	176	1.1	152	0.9

Appendix V-B Continued

	Overall cohort				Censored due to treatment discontinuation or censored at non-confirmed claims-identified event date during the follow-up period (15-day				Censored due to treatment discontinuation, administrative censoring, or censoring on non-confirmed claims-identified event date			
Characteristic	Duloxetine (N=28,479)		SSRI (N=28,479)		Duloxetine (N=23,052)		SSRI (N=23,394)		Duloxetine (N=16,787)		SSRI (N=17,242)	
Neuropsychological comorbidities (N %)												
Fibromyalgia	3,760	13.2	3,625	12.7	3,018	13.1	2,998	12.8	2,261	13.5	2,296	13.3
Diabetic neuropathy	320	1.1	308	1.1	266	1.2	249	1.1	205	1.2	177	1.0
Back pain	4,916	17.3	4,921	17.3	4,033	17.5	4,053	17.3	3,076	18.3	3,097	18.0
Hepatic risks (N %)												
Hypercholesterolemia / dyslipidemia (diagnosis)	7,237	25.4	7,381	25.9	5,736	24.9	5,990	25.6	4,003	23.9	4,184	24.3
Hypercholesterolemia / dyslipidemia (treatment)	3,787	13.3	3,944	13.9	2,998	13.0	3,220	13.8	2,015	12.0	2,101	12.2
Hyperglycemia	429	1.5	471	1.7	334	1.5	383	1.6	243	1.5	268	1.6
Albuminuria	105	0.4	115	0.4	88	0.4	90	0.4	69	0.4	70	0.4
Diabetes mellitus (diagnosis)	2,241	7.9	2,322	8.2	1,846	8.0	1,864	8.0	1,324	7.9	1,306	7.6
Diabetes mellitus (treatment)	2,026	7.1	2,092	7.4	1,669	7.2	1,689	7.2	1,185	7.1	1,165	6.8
CMV infection	3	0.0	2	0.0	3	0.0	2	0.0	0	0.0	2	0.0
EBV infection	57	0.2	61	0.2	46	0.2	48	0.2	37	0.2	37	0.2
Obesity (diagnosis)	1,662	5.8	1,685	5.9	1,341	5.8	1,384	5.9	1,003	6.0	1,063	6.2
Obesity (treatment)	7	0.0	5	0.0	5	0.0	5	0.0	3	0.0	4	0.0
Liver ultrasound scans												
0	27,269	95.8	27,274	95.8	22,056	95.7	22,388	95.7	16,039	95.5	16,440	95.4
1	1,151	4.0	1,144	4.0	948	4.1	953	4.1	700	4.2	763	4.4
2+	59	0.2	61	0.2	48	0.2	53	0.2	48	0.3	39	0.2
Bilirubin test	1,364	4.8	1,350	4.7	1,098	4.8	1,134	4.9	824	4.9	784	4.6
ALT/AST/ALP test	1,205	4.2	1,208	4.2	971	4.2	972	4.2	681	4.1	688	4.0
NSAID use (excluding diclofenac)	8,573	30.1	8,591	30.2	6,952	30.2	7,100	30.4	5,195	31.0	5,287	30.7
NSAID use (diclofenac only)	1,206	4.2	1,203	4.2	973	4.2	1,004	4.3	728	4.3	753	4.4
Isoniazid	6	0.0	10	0.0	4	0.0	7	0.0	2	0.0	6	0.0
Phenytoin	80	0.3	87	0.3	68	0.3	66	0.3	39	0.2	52	0.3
Valproic acid	653	2.3	673	2.4	529	2.3	555	2.4	378	2.3	401	2.3
Nitrofurantoin	1,146	4.0	1,121	3.9	913	4.0	921	3.9	685	4.1	694	4.0
Propylthiouracil	13	0.1	9	0.0	12	0.1	8	0.0	8	0.1	4	0.0

Appendix V-B Continued

	Overall cohort				Censored due to treatment discontinuation or censored at non-confirmed claims-identified event date during the follow-up period (15-day				Censored due to treatment discontinuation, administrative censoring, or censoring on non-confirmed claims-identified event date			
Characteristic	Duloxetine (N=28,479)		SSRI (N=28,479)		Duloxetine (N=23,052)		SSRI (N=23,394)		Duloxetine (N=16,787)		SSRI (N=17,242)	
Hepatic risks (N %)												
Rifampin	60	0.2	56	0.2	54	0.2	48	0.2	37	0.2	36	0.2
Fluconazole	2,428	8.5	2,417	8.5	1,975	8.6	1,991	8.5	1,485	8.9	1,524	8.8
Chlorpromazine	25	0.1	36	0.1	20	0.1	30	0.1	16	0.1	26	0.2
Interferon beta	88	0.3	88	0.3	78	0.3	68	0.3	52	0.3	43	0.3
Amiodarone	19	0.1	25	0.1	13	0.1	19	0.1	12	0.1	13	0.1
Statins	4,518	15.9	4,666	16.4	3,523	15.3	3,728	15.9	2,368	14.1	2,525	14.6
Naloxone	223	0.8	216	0.8	190	0.8	177	0.8	151	0.9	144	0.8
Naltrexone	83	0.3	85	0.3	64	0.3	67	0.3	59	0.4	57	0.3
Disulfiram	61	0.2	67	0.2	52	0.2	56	0.2	36	0.2	34	0.2
Acamprosate	142	0.5	123	0.4	124	0.5	107	0.5	90	0.5	72	0.4
Use of medications (N %)												
Duloxetine (excluding index drug)	0	0.0	1,454	5.1	0	0.0	1,122	4.8	0	0.0	787	4.6
Venlafaxine (excluding index drug)	3,017	10.6	3,064	10.8	2,396	10.4	2,359	10.1	1,586	9.5	1,611	9.3
SSRI (excluding index drug)	11,013	38.7	0	0.0	8,681	37.7	0	0.0	6,114	36.4	0	0.0
Other antidepressants	11,385	40.0	11,163	39.2	9,153	39.7	9,103	38.9	6,501	38.7	6,545	38.0
Bupropion	5,000	17.6	5,158	18.1	4,003	17.4	4,199	18.0	2,741	16.3	2,990	17.3
Anticonvulsants	8,817	31.0	8,745	30.7	7,121	30.9	7,120	30.4	5,233	31.2	5,347	31.0
Anxiolytics or sedative hypnotics	14,698	51.6	14,701	51.6	11,914	51.7	12,020	51.4	8,764	52.2	9,023	52.3
Antihistamines	6,230	21.9	6,183	21.7	5,066	22.0	5,097	21.8	3,721	22.2	3,788	22.0
Antipsychotics	2,549	9.0	2,510	8.8	2,024	8.8	1,998	8.5	1,504	9.0	1,509	8.8
Narcotic analgesics	14,366	50.4	14,339	50.4	11,680	50.7	11,807	50.5	8,755	52.2	8,926	51.8
History of (N %)												
Hypertension	7,384	25.9	7,669	26.9	5,975	25.9	6,153	26.3	4,185	24.9	4,356	25.3
Stroke	469	1.7	467	1.6	378	1.6	369	1.6	282	1.7	262	1.5
MI	139	0.5	149	0.5	114	0.5	114	0.5	82	0.5	84	0.5
Angina	260	0.9	272	1.0	214	0.9	218	0.9	162	1.0	166	1.0
Unstable angina/acute coronary syndromes	192	0.7	184	0.7	160	0.7	138	0.6	121	0.7	102	0.6

Appendix V-B Continued

	Overall cohort				Censored due to treatment discontinuation or censored at non-confirmed claims-identified event date during the follow-up period (15-day				Censored due to treatment discontinuation, administrative censoring, or censoring on non-confirmed claims-identified event date			
Characteristic	Duloxetine (N=28,479)		SSRI (N=28,479)		Duloxetine (N=23,052)		SSRI (N=23,394)		Duloxetine (N=16,787)		SSRI (N=17,242)	
Specified health services (N % unless otherwise noted)												
Number of unique ICD-9 codes												
0-4	2,291	8.0	2,169	7.6	1,875	8.1	1,809	7.7	1,351	8.1	1,347	7.8
5-8	5,002	17.6	5,006	17.6	3,991	17.3	4,092	17.5	2,895	17.3	3,037	17.6
9-12	5,893	20.7	6,039	21.2	4,781	20.7	4,959	21.2	3,390	20.2	3,554	20.6
13-16	5,059	17.8	5,086	17.9	4,084	17.7	4,192	17.9	2,970	17.7	3,095	18.0
17+	10,234	35.9	10,179	35.7	8,321	36.1	8,342	35.7	6,181	36.8	6,209	36.0
Number of different drugs dispensed												
0-3	2,656	9.3	2,253	7.9	2,163	9.4	1,905	8.1	1,598	9.5	1,403	8.1
4-7	7,553	26.5	7,654	26.9	6,166	26.8	6,299	26.9	4,415	26.3	4,695	27.2
8+	18,270	64.2	18,572	65.2	14,723	63.9	15,190	64.9	10,774	64.2	11,144	64.6
Use of intensive care and critical care services	364	1.3	365	1.3	290	1.3	286	1.2	227	1.4	211	1.2
Hospitalization	4,052	14.2	3,909	13.7	3,264	14.2	3,161	13.5	2,486	14.8	2,469	14.3
Psychiatrist/psychologist specialty at index visit	3,359	11.8	3,372	11.8	2,752	11.9	2,794	11.9	1,934	11.5	1,980	11.5
Number of visits to a psychiatrist/psychologist (mean std)	3	6.3	3	6.2	3	6.3	3	6.2	3	6.1	2	6.2
Number of visits to other physicians (mean std)	11	10.9	11	11.6	11	10.9	11	11.6	11	11.2	11	11.7
Number of different psychiatric drugs dispensed (mean std)	2	1.2	2	1.0	2	1.2	2	1.0	2	1.2	2	1.0
Number of emergency room visits (mean std)	2	5.1	2	4.9	2	5.1	2	4.9	2	4.9	2	4.8
Number of psychiatric-related hospitalizations (mean std)	0	0.2	0	0.1	0	0.2	0	0.1	0	0.2	0	0.2
Number of other laboratory tests (mean std)	3	3.6	3	3.4	3	3.6	3	3.4	3	3.6	3	3.5

Appendix V-B Continued

	Overall cohort				Censored due to treatment discontinuation or censored at non-confirmed claims-identified event date during the follow-up period (15-day				Censored due to treatment discontinuation, administrative censoring, or censoring on non-confirmed claims-identified event date			
Characteristic	Duloxetine (N=28,479)		SSRI (N=28,479)		Duloxetine (N=23,052)		SSRI (N=23,394)		Duloxetine (N=16,787)		SSRI (N=17,242)	
Specified health services (N % unless otherwise noted)												
Total costs (mean std)	9,354	16,773.2	9,114	18,729.4	9,341	16,854.3	8,901	17,647.3	9,315	17,252.1	9,013	17,727.4
Patient pharmacy costs (mean std)	712	615.1	693	667.5	699	609.2	675	653.8	658	573.0	638	630.6
Non-patient pharmacy costs (mean std)	1,724	3,353.3	1,639	2,973.7	1,695	3,456.2	1,572	2,817.4	1,565	3,142.3	1,492	2,918.7
Facility costs (mean std)	4,220	13,064.4	4,155	15,320.8	4,239	13,088.9	4,048	14,192.9	4,409	13,745.0	4,261	14,215.2
Number of months of prior continuous enrollment (mean std)	37	26.4	37	26.7	37	26.4	37	26.9	36	25.9	36	26.0
Chart-confirmed events (15-day discontinuation window)												
Hepatic-related death	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Liver failure	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Other clinically significant hepatic injury	4	0.0	0	0.0	3	0.0	0	0.0	2	0.0	0	0.0
Non-serious hepatic enzyme elevation	1	0.0	2	0.0	1	0.0	2	0.0	0	0.0	1	0.0

SSRI: selective serotonin reuptake inhibitor; ADHD: attention deficit hyperactivity disorder; CMV: cytomegalovirus; EBV: Epstein-Barr virus; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; NSAID: nonsteroidal anti-inflammatory drug; MI: myocardial infarction; ICD-9: International Classification of Diseases, 9th Edition; std: standard deviation

Appendix V-C: Baseline characteristics comparison: members within the duloxetine-untreated propensity score-matched cohorts who dropped out during follow-up, by cohort

	Overall cohort				Censored due to treatment discontinuation or censored at non-confirmed claims-identified event date during the follow-up period (15-day				Censored due to treatment discontinuation, administrative censoring, or censoring on non-confirmed claims-identified event date			
Baseline Characteristic	Duloxetine (N=22,714)		Untreated (N=22,714)		Duloxetine (N=18,427)		Untreated (N=17,884)		Duloxetine (N=13,607)		Untreated (N=15,433)	
Age group (years) (N %)												
18-25	1,829	8.1	1,812	8.0	1,536	8.3	1,400	7.8	1,277	9.4	1,261	8.2
26-30	1,746	7.7	1,764	7.8	1,388	7.5	1,315	7.4	1,145	8.4	1,231	8.0
31-35	2,493	11.0	2,501	11.0	2,038	11.1	1,921	10.7	1,605	11.8	1,713	11.1
36-40	3,160	13.9	3,108	13.7	2,564	13.9	2,414	13.5	1,948	14.3	2,139	13.9
41-50	6,725	29.6	6,703	29.5	5,474	29.7	5,273	29.5	3,951	29.0	4,544	29.4
51-60	5,041	22.2	5,030	22.1	4,065	22.1	4,104	23.0	2,808	20.6	3,341	21.7
61-70	1,506	6.6	1,582	7.0	1,199	6.5	1,280	7.2	770	5.7	1,066	6.9
≥71	214	0.9	214	0.9	163	0.9	177	1.0	103	0.8	138	0.9
Gender (N %)												
Female	15,974	70.3	16,020	70.5	12,966	70.4	12,577	70.3	9,556	70.2	10,852	70.3
Male	6,740	29.7	6,694	29.5	5,461	29.6	5,307	29.7	4,051	29.8	4,581	29.7
Geographic region of health plan (N %)												
Northeast	1,338	5.9	1,298	5.7	1,048	5.7	990	5.5	818	6.0	901	5.8
Midwest	5,738	25.3	5,734	25.2	4,617	25.1	4,492	25.1	3,318	24.4	3,935	25.5
South/Southeast	13,374	58.9	13,407	59.0	10,986	59.6	10,648	59.5	8,146	59.9	9,066	58.7
West	2,264	10.0	2,275	10.0	1,776	9.6	1,754	9.8	1,325	9.7	1,531	9.9
Calendar year of cohort entry (N %)												
2004	1,142	5.0	1,049	4.6	909	4.9	746	4.2	699	5.1	733	4.8
2005	3,341	14.7	3,381	14.9	2,816	15.3	2,603	14.6	1,998	14.7	2,349	15.2
2006	4,165	18.3	4,205	18.5	3,439	18.7	3,351	18.7	2,439	17.9	2,851	18.5
2007	4,454	19.6	4,525	19.9	3,688	20.0	3,544	19.8	2,702	19.9	3,025	19.6
2008	4,153	18.3	4,109	18.1	3,425	18.6	3,308	18.5	2,434	17.9	2,785	18.1
2009	3,319	14.6	3,310	14.6	2,634	14.3	2,649	14.8	2,066	15.2	2,282	14.8
2010	2,140	9.4	2,135	9.4	1,516	8.2	1,683	9.4	1,269	9.3	1,408	9.1

Appendix V-C Continued

	Overall cohort				Censored due to treatment discontinuation or censored at non-confirmed claims-identified event date during the follow-up period (15-day				Censored due to treatment discontinuation, administrative censoring, or censoring on non-confirmed claims-identified event date			
Baseline Characteristic	Duloxetine (N=22,714)		Untreated (N=22,714)		Duloxetine (N=18,427)		Untreated (N=17,884)		Duloxetine (N=13,607)		Untreated (N=15,433)	
Neuropsychological comorbidities (N %)												
Depressive disorder, not elsewhere classified	9,662	42.5	9,808	43.2	7,757	42.1	7,606	42.5	5,792	42.6	6,724	43.6
Episodic mood disorders (with depressive component)	6,227	27.4	6,146	27.1	5,048	27.4	4,732	26.5	3,701	27.2	4,149	26.9
Episodic mood disorders (without depressive component)	1,435	6.3	1,519	6.7	1,155	6.3	1,133	6.3	877	6.5	1,020	6.6
Adjustment reaction	3,361	14.8	3,197	14.1	2,734	14.8	2,528	14.1	2,032	14.9	2,182	14.1
Anxiety, dissociative and somatoform disorders	11,598	51.1	11,646	51.3	9,427	51.2	9,119	51.0	7,027	51.6	7,903	51.2
Psychotic disorders	7,345	32.3	7,349	32.4	5,951	32.3	5,641	31.5	4,374	32.2	4,960	32.1
ADHD	1,003	4.4	1,022	4.5	836	4.5	763	4.3	640	4.7	703	4.6
Alcohol abuse and addiction (diagnosis)	600	2.6	544	2.4	494	2.7	400	2.2	375	2.8	377	2.4
Alcohol abuse and addiction (treatment)	292	1.3	270	1.2	244	1.3	205	1.2	192	1.4	190	1.2
Cocaine abuse and addiction	101	0.4	102	0.5	82	0.4	70	0.4	73	0.5	72	0.5
Heroin abuse and addiction	226	1.0	195	0.9	190	1.0	138	0.8	163	1.2	133	0.9
Other substance abuse and addiction	469	2.1	454	2.0	381	2.1	317	1.8	325	2.4	322	2.1
Smoking (tobacco use disorder - diagnosis)	1,325	5.8	1,365	6.0	1,087	5.9	1,032	5.8	867	6.4	925	6.0
Smoking (tobacco use disorder - treatment)	107	0.5	102	0.5	83	0.5	86	0.5	63	0.5	69	0.5
Overdoses	20	0.1	20	0.1	15	0.1	12	0.1	10	0.1	14	0.1
Suicide attempts	90	0.4	96	0.4	73	0.4	72	0.4	64	0.5	64	0.4
Seizure	191	0.8	198	0.9	149	0.8	152	0.9	119	0.9	134	0.9
Chronic pain	373	1.6	325	1.4	308	1.7	247	1.4	249	1.8	218	1.4
Stress urinary incontinence	222	1.0	201	0.9	181	1.0	166	0.9	137	1.0	142	0.9

Appendix V-C Continued

	Overall cohort				Censored due to treatment discontinuation or censored at non-confirmed claims-identified event date during the follow-up period (15-day				Censored due to treatment discontinuation, administrative censoring, or censoring on non-confirmed claims-identified event date			
Baseline Characteristic	Duloxetine (N=22,714)		Untreated (N=22,714)		Duloxetine (N=18,427)		Untreated (N=17,884)		Duloxetine (N=13,607)		Untreated (N=15,433)	
Neuropsychological comorbidities (N %)												
Fibromyalgia	2,610	11.5	2,620	11.5	2,113	11.5	2,040	11.4	1,596	11.7	1,751	11.4
Diabetic neuropathy	260	1.1	261	1.2	219	1.2	216	1.2	171	1.3	166	1.1
Back pain	3,658	16.1	3,764	16.6	3,009	16.3	2,883	16.1	2,316	17.0	2,561	16.6
Hepatic risks (N %)												
Hypercholesterolemia / dyslipidemia (diagnosis)	5,877	25.9	5,948	26.2	4,685	25.4	4,764	26.6	3,325	24.4	4,036	26.2
Hypercholesterolemia / dyslipidemia (treatment)	2,937	12.9	3,035	13.4	2,341	12.7	2,444	13.7	1,615	11.9	2,043	13.2
Hyperglycemia	357	1.6	359	1.6	286	1.6	293	1.6	205	1.5	252	1.6
Albuminuria	86	0.4	102	0.5	71	0.4	87	0.5	59	0.4	69	0.5
Diabetes mellitus (diagnosis)	1,884	8.3	1,933	8.5	1,559	8.5	1,558	8.7	1,119	8.2	1,295	8.4
Diabetes mellitus (treatment)	1,699	7.5	1,734	7.6	1,398	7.6	1,417	7.9	996	7.3	1,152	7.5
CMV infection	2	0.0	0	0.0	2	0.0	0	0.0	0	0.0	0	0.0
EBV infection	44	0.2	50	0.2	36	0.2	41	0.2	29	0.2	34	0.2
Obesity (diagnosis)	1,348	5.9	1,389	6.1	1,086	5.9	1,099	6.2	828	6.1	939	6.1
Obesity (treatment)	6	0.0	6	0.0	5	0.0	3	0.0	3	0.0	3	0.0
Liver ultrasound scans												
0	21,780	95.9	21,749	95.8	17,653	95.8	17,150	95.9	13,032	95.8	14,779	95.8
1	886	3.9	915	4.0	735	4.0	695	3.9	538	4.0	620	4.0
2+	48	0.2	50	0.2	39	0.2	39	0.2	37	0.3	34	0.2
Bilirubin test	1,042	4.6	1,031	4.5	838	4.6	804	4.5	638	4.7	668	4.3
ALT/AST/ALP test	924	4.1	952	4.2	756	4.1	751	4.2	533	3.9	619	4.0
NSAID use (excluding diclofenac)	6,534	28.8	6,776	29.8	5,290	28.7	5,325	29.8	4,031	29.6	4,610	29.9
NSAID use (diclofenac only)	900	4.0	920	4.1	722	3.9	725	4.1	564	4.1	626	4.1
Isoniazid	2	0.0	9	0.0	0	0.0	5	0.0	0	0.0	7	0.1
Phenytoin	54	0.2	82	0.4	46	0.3	57	0.3	27	0.2	60	0.4
Valproic acid	451	2.0	471	2.1	364	2.0	369	2.1	271	2.0	326	2.1
Nitrofurantoin	875	3.9	962	4.2	692	3.8	713	4.0	527	3.9	637	4.1
Propylthiouracil	9	0.0	15	0.1	9	0.1	13	0.1	5	0.0	11	0.1

Appendix V-C Continued

	Overall cohort				Censored due to treatment discontinuation or censored at non-confirmed claims-identified event date during the follow-up period (15-day				Censored due to treatment discontinuation, administrative censoring, or censoring on non-confirmed claims-identified event date			
Baseline Characteristic	Duloxetine (N=22,714)		Untreated (N=22,714)		Duloxetine (N=18,427)		Untreated (N=17,884)		Duloxetine (N=13,607)		Untreated (N=15,433)	
Hepatic risks (N %)												
Rifampin	45	0.2	41	0.2	39	0.2	33	0.2	28	0.2	29	0.2
Fluconazole	1,872	8.2	1,974	8.7	1,516	8.2	1,549	8.7	1,182	8.7	1,355	8.8
Chlorpromazine	18	0.1	18	0.1	15	0.1	13	0.1	12	0.1	11	0.1
Interferon beta	62	0.3	58	0.3	53	0.3	47	0.3	39	0.3	39	0.3
Amiodarone	15	0.1	19	0.1	12	0.1	16	0.1	10	0.1	12	0.1
Statins	3,584	15.8	3,609	15.9	2,822	15.3	2,886	16.1	1,945	14.3	2,440	15.8
Naloxone	153	0.7	148	0.7	129	0.7	111	0.6	104	0.8	102	0.7
Naltrexone	44	0.2	41	0.2	36	0.2	30	0.2	33	0.2	29	0.2
Disulfiram	35	0.2	35	0.2	30	0.2	27	0.2	23	0.2	26	0.2
Acamprosate	79	0.4	62	0.3	65	0.4	49	0.3	48	0.4	42	0.3
Use of medications (N %)												
Duloxetine (excluding index drug)	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Venlafaxine (excluding index drug)	2,200	9.7	0	0.0	1,728	9.4	0	0.0	1,153	8.5	0	0.0
SSRI (excluding index drug)	8,037	35.4	0	0.0	6,377	34.6	0	0.0	4,553	33.5	0	0.0
Other antidepressants	8,073	35.5	0	0.0	6,506	35.3	0	0.0	4,672	34.3	0	0.0
Bupropion	3,571	15.7	0	0.0	2,873	15.6	0	0.0	1,979	14.5	0	0.0
Anticonvulsants	5,799	25.5	5,774	25.4	4,704	25.5	4,396	24.6	3,534	26.0	3,881	25.2
Anxiolytics or sedative hypnotics	10,673	47.0	10,724	47.2	8,678	47.1	8,354	46.7	6,515	47.9	7,251	47.0
Antihistamines	4,699	20.7	4,920	21.7	3,834	20.8	3,887	21.7	2,861	21.0	3,342	21.7
Antipsychotics	1,455	6.4	1,773	7.8	1,157	6.3	1,335	7.5	899	6.6	1,176	7.6
Narcotic analgesics	10,923	48.1	11,090	48.8	8,896	48.3	8,571	47.9	6,806	50.0	7,547	48.9
History of (N %)												
Hypertension	6,023	26.5	6,010	26.5	4,882	26.5	4,778	26.7	3,478	25.6	4,061	26.3
Stroke	365	1.6	318	1.4	296	1.6	245	1.4	230	1.7	217	1.4
MI	120	0.5	111	0.5	96	0.5	85	0.5	71	0.5	82	0.5
Angina	214	0.9	217	1.0	178	1.0	174	1.0	136	1.0	150	1.0
Unstable angina/acute coronary syndromes	160	0.7	149	0.7	133	0.7	128	0.7	101	0.7	98	0.6

Appendix V-C Continued

	Overall cohort				Censored due to treatment discontinuation or censored at non-confirmed claims-identified event date during the follow-up period (15-day				Censored due to treatment discontinuation, administrative censoring, or censoring on non-confirmed claims-identified event date			
Baseline Characteristic	Duloxetine (N=22,714)		Untreated (N=22,714)		Duloxetine (N=18,427)		Untreated (N=17,884)		Duloxetine (N=13,607)		Untreated (N=15,433)	
Specified health services (N % unless otherwise noted)												
Number of unique ICD-9 codes												
0-4	2,019	8.9	1,894	8.3	1,652	9.0	1,517	8.5	1,203	8.8	1,277	8.3
5-8	4,270	18.8	4,145	18.3	3,412	18.5	3,221	18.0	2,504	18.4	2,821	18.3
9-12	4,874	21.5	4,866	21.4	3,964	21.5	3,920	21.9	2,864	21.1	3,313	21.5
13-16	4,071	17.9	4,092	18.0	3,308	18.0	3,231	18.1	2,427	17.8	2,761	17.9
17+	7,480	32.9	7,717	34.0	6,091	33.1	5,995	33.5	4,609	33.9	5,261	34.1
Number of different drugs dispensed												
0-3	2,640	11.6	2,482	10.9	2,152	11.7	1,968	11.0	1,591	11.7	1,689	10.9
4-7	6,890	30.3	6,873	30.3	5,641	30.6	5,456	30.5	4,059	29.8	4,736	30.7
8+	13,184	58.0	13,359	58.8	10,634	57.7	10,460	58.5	7,957	58.5	9,008	58.4
Use of intensive care and critical care services	259	1.1	245	1.1	209	1.1	190	1.1	173	1.3	173	1.1
Hospitalization	2,810	12.4	2,776	12.2	2,272	12.3	2,073	11.6	1,768	13.0	1,913	12.4
Psychiatrist/psychologist specialty at index visit	2,876	12.7	2,936	12.9	2,370	12.9	2,274	12.7	1,677	12.3	1,988	12.9
Number of visits to a psychiatrist/psychologist (mean std)	2	4.8	2	7.1	2	4.7	2	6.9	2	4.8	2	6.8
Number of visits to other physicians (mean std)	10	10.3	10	9.5	11	10.4	10	9.4	11	10.5	11	9.5
Number of different psychiatric drugs dispensed (mean std)	2	1.1	0	0.4	2	1.1	0	0.4	2	1.1	0	0.4
Number of emergency room visits (mean std)	2	4.6	2	4.6	2	4.6	2	4.6	2	4.4	2	4.6
Number of psychiatric-related hospitalizations (mean std)	0	0.1	0	0.1	0	0.1	0	0.1	0	0.1	0	0.1
Number of other laboratory tests (mean std)	3	3.6	3	3.4	3	3.6	3	3.4	3	3.5	3	3.4

Appendix V-C Continued

	Overall cohort				Censored due to treatment				Censored due to treatment			
Baseline Characteristic	**Duloxetine (N=22,714)**		**Untreated (N=22,714)**		**Duloxetine (N=18,427)**		**Untreated (N=17,884)**		**Duloxetine (N=13,607)**		**Untreated (N=15,433)**	
Specified health services (N % unless otherwise noted)												
Total costs (mean std)	8,295	15,748.1	8,201	15,713.5	8,275	15,977.6	8,129	16,099.0	8,289	16,126.8	8,321	16,716.1
Patient pharmacy costs (mean std)	622	543.8	620	656.9	609	532.0	626	664.9	581	514.9	610	647.9
Non-patient pharmacy costs (mean std)	1,459	2,539.7	1,447	2,965.6	1,426	2,536.6	1,454	2,943.2	1,358	2,627.4	1,409	2,845.5
Facility costs (mean std)	3,766	12,488.9	3,691	12,632.2	3,790	12,705.9	3,622	12,934.3	3,908	12,909.6	3,843	13,688.7
Number of months of prior continuous enrollment (mean std)	37	26.4	37	26.0	37	26.5	38	26.5	36	26.0	37	25.8
Chart-confirmed events (15-day treatment discontinuation window)												
Hepatic-related death	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Liver failure	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Other clinically significant hepatic injury	4	0.0	3	0.0	3	0.0	3	0.0	3	0.0	2	0.0
Non-serious hepatic enzyme elevation	1	0.0	0	0.0	1	0.0	0	0.0	0	0.0	0	0.0

SSRI: selective serotonin reuptake inhibitor; ADHD: attention deficit hyperactivity disorder; CMV: cytomegalovirus; EBV: Epstein-Barr virus; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; NSAID: nonsteroidal anti-inflammatory drug; MI: myocardial infarction; ICD-9: International Classification of Diseases, 9th Edition; std: standard deviation

Appendix VI-A. Sensitivity Analysis: Incidence rate (IR), as-matched rate ratio (RR), and 95% confidence interval (CI) of hepatic events with or without alternate etiology in the matched duloxetine and comparator cohorts, follow-up through 15 days following treatment discontinuation

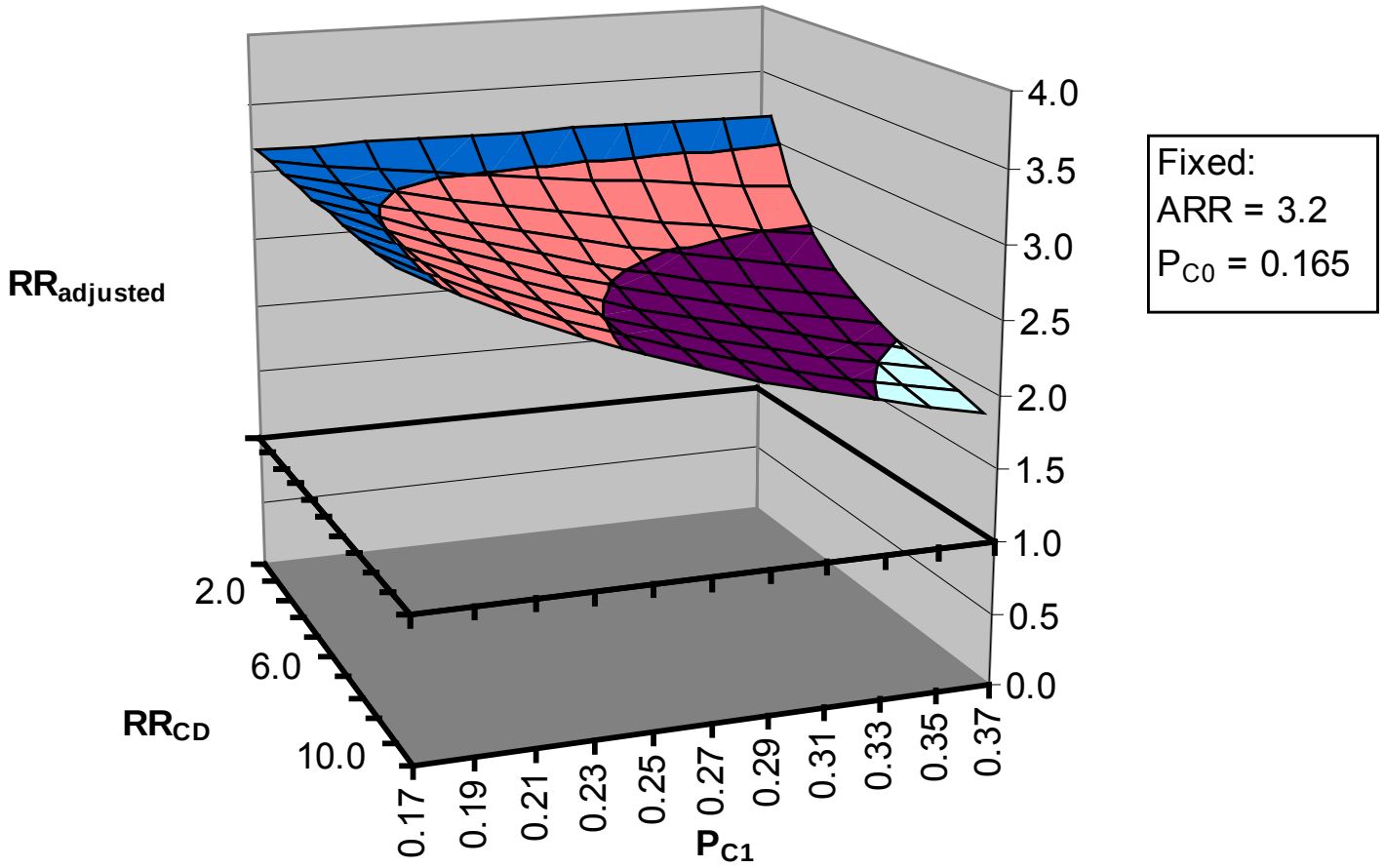
Outcome of Interest	Cohort	Person-Years	Number of Cases	IR	95% CI Lower	95% CI Upper	Unadjusted RR	95% CI Lower	95% CI Upper
Hepatic-related death	Duloxetine	7,633.5	0	0.0	0.0	0.4	NA	NA	NA
	Venlafaxine	8,838.7	0	0.0	0.0	0.3			
	Duloxetine	10,411.9	0	0.0	0.0	0.3	NA	NA	NA
	SSRI	9,835.6	0	0.0	0.0	0.3			
	Duloxetine	8,116.7	0	0.0	0.0	0.4	NA	NA	NA
	Untreated	5,966.1	0	0.0	0.0	0.5			
Hepatic failure	Duloxetine	7,631.7	0	0.0	0.0	0.4	NA	NA	NA
	Venlafaxine	8,836.6	0	0.0	0.0	0.3			
	Duloxetine	10,410.6	0	0.0	0.0	0.3	NA	NA	NA
	SSRI	9,833.9	0	0.0	0.0	0.3			
	Duloxetine	8,116.2	0	0.0	0.0	0.4	NA	NA	NA
	Untreated	5,965.8	0	0.0	0.0	0.5			
Other clinically significant hepatic injury	Duloxetine	7,548.5	11	1.5	0.7	2.6	HR: 3.0	1.0	9.5
	Venlafaxine	8,745.2	4	0.5	0.1	1.2	IRR: 3.2	0.9	13.7
	Duloxetine	10,300.9	14	1.4	0.7	2.3	HR: 1.4	0.6	3.1
	SSRI	9,753.2	10	1.0	0.5	1.9	IRR: 1.3	0.5	3.3
	Duloxetine	8,035.8	11	1.4	0.7	2.4	HR: 1.2	0.5	2.9
	Untreated	5,931.9	8	1.3	0.6	2.7	IRR: 1.0	0.4	2.9

Appendix VI-A. Continued

Outcome of Interest	Cohort	Person-Years	Number of Cases	IR	95% CI Lower	95% CI Upper	Unadjusted RR		95% CI Lower	95% CI Upper
Hepatic-related death and liver failure combined	Duloxetine	7,631.7	0	0.0	0.0	0.4		NA	NA	NA
	Venlafaxine	8,836.6	0	0.0	0.0	0.3				
	Duloxetine	10,410.6	0	0.0	0.0	0.3		NA	NA	NA
	SSRI	9,833.8	0	0.0	0.0	0.3				
	Duloxetine	8,116.2	0	0.0	0.0	0.4		NA	NA	NA
	Untreated	5,965.6	0	0.0	0.0	0.5				
All clinically significant hepatic categories	Duloxetine	7,548.5	11	1.5	0.7	2.6	HR:	3.0	1.0	9.5
	Venlafaxine	8,745.2	4	0.5	0.1	1.2	IRR:	3.2	0.9	13.7
	Duloxetine	10,300.9	14	1.4	0.7	2.3	HR:	1.4	0.6	3.1
	SSRI	9,753.2	10	1.0	0.5	1.9	IRR:	1.3	0.5	3.3
	Duloxetine	8,035.8	11	1.4	0.7	2.4	HR:	1.2	0.5	2.9
	Untreated	5,931.9	8	1.3	0.6	2.7	IRR:	1.0	0.4	2.9
Non-serious hepatic enzyme elevation	Duloxetine	7,548.5	1	0.1	0.0	0.7	HR:	NA	NA	NA
	Venlafaxine	8,745.2	0	0.0	0.0	0.3	IRR:	undef.	0.0	inf.
	Duloxetine	10,300.9	1	0.1	0.0	0.5	HR:	0.5	0.0	5.3
	SSRI	9,753.0	2	0.2	0.0	0.7	IRR:	0.5	0.0	9.1
	Duloxetine	8,035.8	1	0.1	0.0	0.7	HR:	0.7	0.0	12.2
	Untreated	5,932.0	1	0.2	0.0	0.9	IRR:	0.7	0.0	57.9

IR: incidence rate, representing number of events per 1,000 person-years; CI: confidence interval; RR: rate ratio; NA: not available; HR: hazard ratio; IRR: incidence rate ratio; undef.=undefined; inf.=infinity

VI-B. Sensitivity Analysis – Array Approach to Assess Residual Confounding: Estimation of Fully-Adjusted RR Between Duloxetine Initiation and All Clinically Significant Hepatic Categories Combined



Appendix VII. Addendum: Discussion of Post-hoc Review of the Etiology of Selected Cases

The purpose of this addendum is to qualitatively document the *post hoc* identification of a discrepancy between the adjudicated status of alternate etiology for Case #2 in Appendix IV and the actual presence of an alternate etiology. We also describe the implications of this misclassification on the study results.

Protocol Requirement

Protocol defined inclusion/exclusion criteria:

Initially-eligible patients with a claim for hepatic conditions occurring during the baseline period (and patients with longer standing chronic hepatic illness if documented in baseline claims) were excluded from all study analyses. The reason for exclusion of patients with pre-existing liver disease was to reduce potential confounding of the drug exposure-outcome association given that the aim of this study was to focus on drug induced liver injury.

Protocol specified adjudication process:

As specified in the study protocol, which was written by Optum and approved by Eli Lilly, an independent adjudication panel of 2 hepatologists reviewed each potential case. The adjudicators adjudicated whether a hepatic injury occurred and made an assessment of whether an alternate etiology was present. This adjudication process was developed to reduce the risk of misclassification of outcomes that might arise as a result of review by a single adjudicator. The adjudicators were also blinded to study drug exposure, such that should misclassification of outcome occur, the misclassification would be expected to be non-differential with respect to study exposure. This process was not a guarantee that both reviewers would correctly and similarly classify an outcome event. The protocol also included the provision that should the 2 adjudicators disagree in their classification, they would discuss the case.

Identification of the Discrepant Case

Case #2 was initially confirmed after review of the medical record by independent adjudicators as a hepatic injury event *without* alternate etiology. However, after Optum issued the study report, it was noted that the claims data displayed in Appendix IV suggested that Case #2 had alternate etiologies of acute viral infection and chronic liver disease, cirrhosis, or fibrosis within 45 days prior to the date of the confirmed outcome.

	Cases During On-Therapy Plus 15-Day Exposure Window											Cases During Days 16-30 Following Discontinuation of Study Drug
Characteristic	1	2	3	4	5	6	7	8	9	10	11	12
Acute viral infection (hepatitis A, B, C, D, E; EBV, CMV, HSV)	NO	YES	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
Chronic liver disease, cirrhosis, fibrosis	NO	YES	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO

After discussions between investigators at Eli Lilly and Optum, we requested an additional review of the medical record of Case #2 by the independent adjudicators to further investigate this discrepancy. This additional review occurred several months following the initial, main

review and results from the review were to be provided as a communication separate from the main body of the study report.

In the additional review of the medical record of Case #2, which was undertaken outside of the protocol and after delivery of the final report, the reviewers adjudicated this case as a confirmed hepatic injury event *with* alternate etiology, contrary to their initial assessment. This subsequent finding suggests that there is some variability in case determination by the same reviewer over time, at least for this case.

Impact of the Discrepant Case

In the discussion between Optum and Eli Lilly that ensued, we evaluated the implications of the misclassification of Case #2 on the interpretation of the study results and identified the following related points that contextualize this case of misclassification:

- The additional medical record review was not applied systematically to all potential cases and, therefore, not all cases had the same opportunity to receive an alternate designation.
- There could be no guarantee that the second review would be more accurate than the initial review. Indeed, a small risk of misclassification is inherent when humans are involved in the adjudication process. This misclassification is, in expectation, non-differential with respect to exposure because of the blinding of the reviewed medical records.
- The extremely low statistical power of the study meant that despite any modifications to case classification or analyses, the study data would remain inconclusive.

Based on these considerations we did not believe it was necessary to conduct a formal re-review of the medical records of all of the cases. Similarly, we declined to estimate the impact of misclassification of alternate etiology status on the various estimates of effect, because any error due to misclassification would have been small in comparison to the large uncertainty present from sparse data.