

PASS Information

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Table of Contents

Section	Page
Table of Contents	3
1. Abstract	9
2. List of abbreviations.....	11
3. Investigators.....	12
4. Other responsible parties	13
5. Milestones.....	14
6. Rationale and background	15
6.1. Treatment of Depression during Pregnancy	15
6.2. Safety of Antidepressants in Pregnant Women	15
6.2.1 Major Congenital Malformations	16
6.2.2 Low Birth Weight, Preterm Delivery and Small for Gestational Age.....	16
6.2.3 Other fetal outcomes	16
6.2.4 Preeclampsia	16
6.2.5 Postpartum Haemorrhage	16
6.3. Duloxetine	17
7. Research question and objectives	18
8. Amendments and updates.....	19
9. Research methods	20
9.1. Study design.....	20
9.2. Setting.....	21
9.3. Subjects.....	21
9.4. Variables.....	23
9.4.1 Exposure.....	23
9.4.2 Contrasts of interest	23
9.4.3 Outcomes	26
9.4.4 Covariates	28
9.5. Data sources.....	32
9.6. Bias.....	32
9.7. Study size.....	33
9.8. Data Management	34
9.9. Statistical methods	34
9.9.1 Main summary measures.....	34

9.9.2	Main statistical methods.....	34
9.9.3	Missing values	35
9.9.4	Sensitivity analyses	35
9.9.5	Validation Study	37
9.9.6	Claims Profile Review	37
9.9.7	Exploratory analyses	37
9.9.8	Amendments to the statistical analysis plan.....	41
9.10	Quality Control	42
10	Results	43
10.1	Participants	43
10.1.1	Study population for the major congenital malformations outcome (cohort I).....	43
10.1.2	Study population for preterm and small for gestational age outcome (cohort II)	43
10.1.3	Study population for the preeclampsia outcome (cohort III)	43
10.1.4	Study population for the postpartum haemorrhage outcome (cohort IV)	43
10.2	Descriptive data	44
10.2.1	Cohort I: Major congenital malformations.....	44
10.2.2	Cohorts II-IV: Preterm/SGA, preeclampsia, postpartum haemorrhage	46
10.3	Outcome data	47
10.3.1	Major congenital malformations.....	47
10.3.2	Preterm and small for gestational age	47
10.3.3	Preeclampsia	48
10.3.4	Postpartum haemorrhage	48
10.4	Main results	48
10.4.1	Major congenital malformations.....	48
10.4.2	Preterm and small for gestational age	54
10.4.3	Preeclampsia	60
10.4.4	Postpartum haemorrhage	62
10.5	Exploratory Analyses: Non-live birth outcomes	66
10.6	Other Analyses.....	69
10.7	Adverse events/adverse reactions	70
11.	Discussion.....	71
11.1	Key results	71
11.2	Limitations.....	72
11.3	Interpretation.....	74
11.4	Generalisability	77

12	Other information.....	78
13	Conclusion.....	79
14	References	80
Annex 1.	List of standalone documents	585
Annex 2.	Additional information.....	586
<u>Appendix 1:</u>	External adjustment of the observed crude and adjusted relative risk (RR_{ED}) using the NHANES data (1999- 2014) to estimate the prevalence of confounders (obesity, smoking and alcohol use) in a similar population.	586
<u>Appendix 2:</u>	Rule out residual confounding	586
<u>Appendix 3:</u>	Impact of restriction to livebirths	587
<u>Appendix 4:</u>	Chart based outcome validation study	587

List of Tables

Table 1	Summary of study design including Medicaid eligibility requirements for mothers and offspring, duloxetine exposure windows, outcome assessment windows, and covariate assessment windows.	20
Table 2	Definition of exposure and reference groups for the contrasts of interest	25
Table 3	ICD-9 codes for major congenital malformations	27
Table 4	ICD-9 and CPT codes for preterm delivery	28
Table 5	Covariates included in each of the analyses and the associated covariate assessment window	29
Table 6	ICD-9 codes used to define covariates, as well as specific generics used to define medication classes used as covariates.	30
Table 7	Power to detect associations based on the number exposed and relative risks	33
Table 8	Pre-specified Sensitivity Analyses	35
Table 9	Codes for live and non-live pregnancy outcomes	39
Table 10	Procedures to identify live and non-live pregnancy outcomes and corresponding gestational age	40
Table 11	Definition of genital malformations	41
Table 12	Cohort selection	44
Table 13	Prevalence of obesity, smoking, and alcohol use by exposure group according to NHANES 1999-2014.....	586

List of figures

Figure 1	Standardized differences for baseline characteristics between duloxetine exposed and unexposed pregnancies before adjustment in Cohort I	45
Figure 2	Standardized differences for baseline characteristics between duloxetine exposed and SSRI exposed (red dots), venlafaxine exposed (green dots) and duloxetine discontinuers (orange dots) during pregnancy before adjustment in Cohort I.....	45
Figure 3	Standardized differences for baseline characteristics between duloxetine exposed and all comparison groups after adjustment in Cohort I. Dot color code as in Figure 1 and 2.	46
Figure 4	Risk of congenital malformations associated with first trimester exposure to duloxetine: fully adjusted analyses	49
Figure 5	Risk of cardiac malformations associated with first trimester exposure to duloxetine: sensitivity analyses.....	52
Figure 6	Risk of cardiac malformations associated with first trimester exposure to duloxetine: sensitivity analyses to address outcome misclassification	53
Figure 7	Risk of preterm birth and small for gestational age associated with early and late pregnancy exposure to duloxetine: fully adjusted analyses	56
Figure 8	Risk of small for gestational age associated with <u>early</u> pregnancy exposure to duloxetine: sensitivity analyses.....	57
Figure 9	Risk of small for gestational age associated with <u>early</u> pregnancy exposure to duloxetine: sensitivity analyses to address outcome misclassification	58
Figure 10	Risk of small for gestational age associated with <u>late</u> pregnancy exposure to duloxetine: sensitivity analyses.....	59
Figure 11	Risk of small for gestational age associated with <u>late</u> pregnancy exposure to duloxetine: sensitivity analyses to address outcome misclassification	60
Figure 12	Risk of preeclampsia associated with early and late pregnancy exposure to duloxetine: fully adjusted analyses	62
Figure 13	Risk of postpartum haemorrhage associated with exposure to duloxetine during the final 30 days of pregnancy: fully adjusted analyses	64
Figure 14	Risk of postpartum haemorrhage associated with exposure to duloxetine during the final 30 days of pregnancy: sensitivity analyses	65
Figure 15	Risk of postpartum haemorrhage associated with exposure to duloxetine during the final 30 days of pregnancy: sensitivity analyses to address outcome misclassification.....	66
Figure 16	Risk of stillbirth associated with exposure to duloxetine during pregnancy	68

Figure 17	Risk of spontaneous abortion associated with exposure to duloxetine during pregnancy.....	69

1. Abstract

Title: Observational Studies to Assess Maternal and Fetal Outcomes Following Exposure to Duloxetine.

Keywords: Duloxetine, safety, pregnancy, cohort, Medicaid Analytic eXtract

Rationale and background: There are no published large controlled studies examining the safety of duloxetine in pregnancy. Given the limitations of spontaneous adverse reports and the small sample size of the duloxetine registry, there is currently limited information regarding the safety of duloxetine in pregnancy.

Research question and objectives: To determine whether exposure to duloxetine during pregnancy is associated with an increased risk of adverse maternal and fetal outcomes, including major congenital malformations, cardiac malformations, preterm birth, small for gestational age, preeclampsia, and postpartum haemorrhage. The risk of spontaneous abortion and stillbirth was also explored.

Study design: Retrospective cohort study

Setting: Nationwide cohort of publicly insured pregnant women 18 to 55 years of age.

Subjects and study size, including dropouts: 8,410,882 pregnant women from 46 US states and Washington, DC with completed pregnancies between July 2004 and December 2013, linked to a liveborn infant. After implementing the Medicaid eligibility criteria, as well as cohort-specific exclusion criteria, the cohort sizes were 1.3 – 1.5 million for the congenital malformation, preterm/small for gestational age, and preeclampsia cohorts, and 4.1 million for the postpartum haemorrhage cohort. The number of duloxetine-exposed women varied by cohort and exposure contrast and was around 2,500 for first trimester exposure, around 3,000 for early pregnancy exposure (defined as LMP to LMP+140 days), and 900-950 for exposure late in pregnancy (defined as LMP+141 to LMP+245 days; 30 days before delivery). The comparator groups assessed included pregnancies among those (1) unexposed to duloxetine, (2) exposed to SSRIs, (3) exposed to venlafaxine, and (4) who discontinue duloxetine.

Variables and data sources: The Medicaid Analytic eXtract (MAX) 2004-2013 was used as the data source. Exposure to duloxetine is defined based on filling a prescription during the etiologically relevant exposure time window. Covariates that could potentially confound the association between duloxetine exposure and the outcomes of interest include medical indications for duloxetine, maternal demographic characteristics, comorbid medical conditions, obstetric characteristics/conditions, maternal medications, and measures of healthcare utilization. Imbalances in these variables was accounted for by restricting the cohort to women with a recorded indication for duloxetine, and by fine stratification on the propensity score, estimated in a logistic regression model with inclusion of all listed variables without further selection.

Results: Although there were differences in baseline characteristics between duloxetine-exposed women and the reference groups, after adjustment for measured potential confounding variables all baseline characteristics were well balanced for all exposure contrasts. The base risk per 1,000 unexposed women was 36.6 (95% CI, 36.3 – 36.9) for congenital malformations overall; 13.7 (13.5 – 13.9) for cardiovascular malformations; 107.8 (107.3 – 108.3) for preterm birth; 20.4 (20.1 – 20.6) for small for gestational age; 33.6 (33.3 – 33.9) for preeclampsia; and 23.3 (23.1 – 23.4) for postpartum haemorrhage.

In fully adjusted analyses, the $RR_{vs. \text{unexposed}}$ for congenital malformations overall was 1.11 (95% CI, 0.93 – 1.33). For cardiovascular malformations, the $RR_{vs. \text{unexposed}}$ was 1.29 (0.99 – 1.68) and the $RR_{vs. \text{SSRI-exposed}}$ was 1.27 (0.93 – 1.74). Results for other malformation types were consistent with a null finding. For preterm birth, the $RR_{vs. \text{unexposed}}$,

early was 1.01 (0.92 – 1.10) and the $RR_{vs. \text{ unexposed; late }}$ was 1.19 (1.04 – 1.37). For SGA, the $RR_{vs. \text{ unexposed, early }}$ was 1.14 (0.92 – 1.41) and the $RR_{vs. \text{ unexposed; late }}$ was 1.20 (0.83 – 1.72). For preeclampsia, the $RR_{vs. \text{ unexposed, early }}$ was 1.12 (0.96 – 1.31) and the $RR_{vs. \text{ unexposed; late }}$ was 1.04 (0.80 – 1.35). For postpartum haemorrhage, the $RR_{vs. \text{ unexposed }}$ was 1.53 (1.08 – 2.18, the $RR_{vs. \text{ SSRI-exposed }}$ was 1.48 (1.03 – 2.12), and the $RR_{vs. \text{ venlafaxine-exposed }}$ was 1.04 (0.69 – 1.56).

Discussion: Evidence from this large cohort study suggests duloxetine is unlikely to be a major teratogen. Interpretation of the evidence from primary analyses coupled with a broad range of sensitivity analyses, leads us to conclude that there is no increase in the risk of congenital malformations overall, preterm birth, or preeclampsia associated with duloxetine exposure during pregnancy. Evidence suggests an increased risk of postpartum haemorrhage, which was present also for venlafaxine (another SNRI). A potential small increase in the risk of congenital cardiac malformations was identified, but the magnitude of the association was less than a 1.3, with upper bounds of the 95%CI below 2-fold increase in risk. Similarly, a potential small increase in the risk of small for gestational age was identified. It should be noted, however, that this association was not consistently observed in all sensitivity analyses. These potential small increases in risk of relatively uncommon outcomes have to be weighed against the benefits of treating depression during pregnancy for both the mother's and the infant's health; a trade off that is likely to be different for each individual patient.

Marketing Authorisation Holder(s): Eli Lilly and Company

Names and affiliations of principal investigators: PPD

[Redacted]

2. List of abbreviations

Term	Definition
AD	Antidepressant
AE	Adverse event
AR	Adverse reaction
BMI	Body mass index
CI	Confidence interval
hdPS	High-dimensional propensity score
IRB	Institutional Review Board
LMP	Last menstrual period
MAOIs	Monoamine oxidase inhibitors
MAX	Medicaid Analytic eXtract
NHANES	National Health and Nutrition Examination Survey
NSAIDs	non-steroidal anti-inflammatory drugs
OTC	Over the counter
PPV	Positive predictive value
PPH	Postpartum haemorrhage
PPHN	Persistent pulmonary hypertension in the newborn
PS	Propensity score
SAE	Serious adverse event
SAR	Serious adverse reaction
SGA	Small for gestational age
SNRI	Serotonin-norepinephrine reuptake inhibitors
SSRI	Selective serotonin reuptake inhibitors
TCA	Tricyclic antidepressant

3. Investigators



4. Other responsible parties

Eli Lilly:

PPD

PPD

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5. Milestones

Milestone	Planned date	Actual date	Comments
Start of data collection	01 November 2016	01 November 2016	
End of data collection	30 April 2018	30 April 2018	
<Registration in the EU PAS register> [EU PASS Only]	01 November 2016	01 November 2016	
Draft final report of study results	30 June 2018	13 July 2018	
Final report of study results	31 October 2018		

6. Rationale and background

6.1. Treatment of Depression during Pregnancy

Studies suggest that up to 15% of all pregnant women display some signs of depression,^{1,2} about 10% develop major depression,³ and around 3 to 13% are treated with medications.⁴⁻⁶ Use of antidepressants (AD)s in pregnant women has grown steadily over time.⁴⁻⁹ Selective serotonin reuptake inhibitors (SSRI)s are the most commonly used ADs worldwide,^{7,10} followed by serotonin-norepinephrine reuptake inhibitors (SNRI)s.¹¹

Some women need to take ADs throughout pregnancy to control their symptoms.¹² Studies have suggested that ADs control mood effectively and reduce the risks of serious consequences associated with untreated depression for both the mother and her offspring.¹³⁻¹⁵ A mood disorder in the mother may cause significant morbidity for both the mother and her child.^{14,16-18} Yet, large numbers of pregnant women with depression might go untreated,¹⁹⁻²¹ and around 60% of the women who use ADs before pregnancy stop taking them in the first trimester.^{11,22}

In addition, depression and anxiety have been associated with an increased risk for obstetric complications, puerperal pathologies and impaired fetal and postnatal development including gestational hypertension and subsequent preeclampsia, bleeding, prematurity, and small for gestational age.^{21,23-42} However, since most studies did not assess the potential independent effect of medications,^{26,40} it remains unclear whether such associations are due to biologic or behavioral factors intrinsic to women with mood disorders, to medications used to treat the disorder, or a combination of both. Furthermore, women suffering from depression are more likely to smoke or use alcohol or other substances, which may confound the association between depression and pregnancy outcomes.^{41,42}

Duloxetine is frequently used in the treatment of pain conditions. Although pain itself is not considered a cause of teratogenicity or other adverse obstetric events, the underlying reasons for the pain, behavioral factors associated with the pain condition, and concomitant use of certain analgesic medications may be risk factors for adverse pregnancy outcomes. For instance, first trimester exposure to opioids has been associated with the risk of oral clefts, neural tube and cardiac defects,⁴³⁻⁴⁵ and chronic opioid use in pregnancy has also been associated with Cesarean delivery, postpartum haemorrhage due to uterine atony, fetal growth restriction, and other adverse neonatal outcomes.⁴⁶ Therefore, specific pain indications and concomitant analgesics should be considered as potential risk factors when evaluating the safety of duloxetine during pregnancy.

6.2. Safety of Antidepressants in Pregnant Women

In recent years there has been increasing concern about the safety of AD use during pregnancy. The risks of several maternal complications, including preeclampsia, bleeding and the requirement for a Cesarean section have been reported to be increased among women taking ADs during pregnancy.⁴⁷ In some studies, first trimester exposure to certain SSRIs has been associated with some specific birth defects,⁴⁸⁻⁵² while SSRI use late in pregnancy has been associated with pulmonary hypertension of the newborn (PPHN),⁵³⁻⁵⁴ prematurity,⁵⁵⁻⁵⁷ low birth weight,^{56,57} small size for gestational age,⁵⁸ and various neonatal complications.^{55,56,59,60} However, other studies have not found these associations. Again, since most studies did not assess the potential independent effects of medications and depression severity, it has been unclear to what extent such associations are due to biologic or behavioral factors intrinsic to women with mood disorders (such as smoking, substance abuse, or poor diet), to medications used to treat the disorder, or a combination of both. Data regarding the safety of SNRIs during pregnancy is sparse, particularly for SNRIs other than venlafaxine.

6.2.1 Major Congenital Malformations

One of the most concerning adverse effects of medications during pregnancy is teratogenicity.⁶¹ A large number of studies (and an even larger number of reviews) have been published on the association between SSRIs and birth defects. One review concluded that some cardiac defects occur 2-3.5 times more frequently among infants of women treated with paroxetine or fluoxetine early in pregnancy.⁶²⁻⁶³ However, other studies have found no association after accounting for depression severity.⁶⁴⁻⁶⁶ Some of the more recent evidence on this topic has clearly demonstrated the impact of confounding by the underlying indication using a variety of different methodological approaches: restriction of the cohort to women with a depression diagnosis,⁶⁴ sibling controlled analyses,⁶⁵ and comparison between pregnancies with exposure to SSRIs during the first trimester versus pregnancies with SSRI treatment discontinuation.⁶⁷ Evidence for non-SSRI antidepressants is scarce. In general, studies have found no association between SNRIs and major malformations; but they were based on small exposed cohorts.^{68,69} In the context of multiple comparisons and without adjusting for the indication, the National Birth Defects Prevention Study found an association between venlafaxine and anencephaly, atrial septal defects, coarctation of the aorta, cleft palate, and gastroschisis.⁷⁰ First-trimester in utero exposure to venlafaxine was not associated with an increased risk of major congenital malformations in cohort studies, though some were small and uncontrolled.^{64,65,69,71,72} The amount of data for duloxetine is more limited but does not suggest meaningfully increased risk.

6.2.2 Low Birth Weight, Preterm Delivery and Small for Gestational Age

Maternal use of SSRIs during pregnancy has been associated with prematurity,^{55-57,59} low birth weight,^{56,57} and SGA.^{56,73} However, evidence is conflicting.⁷⁴ Some studies have also reported an increased risk of prematurity and SGA in patients treated with non-SSRI antidepressants,^{56,59} raising concerns about the potential adverse effects of depression itself. Psychological conditions such as stress, anxiety and depression may elevate the risk of these outcomes through increased activity of the hypothalamo-pituitary-adrenal axis and release of corticotropin-releasing hormone or other vasoactive hormones and neuroendocrine transmitters.^{29,75,76} Whether these risks extend to SNRIs is unclear.

6.2.3 Other fetal outcomes

Duloxetine during pregnancy has been associated with an increase in the risk of spontaneous abortion and stillbirths.^{77,78} It is however uncertain whether the increased risk is due to duloxetine use, the depression, factors related to depression, or combinations of the above.

6.2.4 Preeclampsia

Along with various vascular disorders, psychological conditions such as stress,⁷⁹ anxiety and depression^{26,40} have been associated with preeclampsia. Depression and anxiety may increase the risk of hypertension through the altered release of vasoactive hormones or other neuroendocrine transmitters.^{25,75} Alternatively, ADs could potentially increase the risk of preeclampsia through their vascular effects.^{80,81} SNRIs can cause elevations of diastolic blood pressure, probably due to their noradrenergic effects.⁸²

6.2.5 Postpartum Haemorrhage

Serotonin is crucial for platelet aggregation and blood clotting.⁸³ Bleeding is more common in users of serotonergic ADs.^{84,85,86,87} Because women giving birth are actively bleeding postpartum, they are particularly susceptible to

drugs that may further increase their risk for bleeding. The potential effect of SNRIs on PPH was largely unknown prior to this study.

6.3. Duloxetine

Duloxetine (Cymbalta) is a selective serotonin and norepinephrine reuptake inhibitor (SNRI) approved in the United States in 2004. It is currently indicated for the treatment of depression, anxiety, diabetic peripheral neuropathic pain, fibromyalgia, and chronic musculoskeletal pain. These conditions are common among women of childbearing age.⁸⁸ Information from post-marketing surveillance systems suggests a similar pattern of adverse pregnancy outcomes in women using duloxetine during pregnancy compared to the general population.⁷⁸ Two cases reported in the literature described infants with neonatal withdrawal symptoms.^{89,90} Another two exposed cases reported had no signs of toxicity.^{91,92} One uncontrolled pregnancy registry including 168 livebirths prenatally exposed to duloxetine reported 3 major malformations (1.8%), which was considered within the expected baseline range in that population.⁹³ One study based on the Swedish Birth Registry identified 286 live-born infants exposed to duloxetine in the first trimester, seven were born with malformations (relative risk of 0.8 versus unexposed).⁷¹

A recent review concluded that the evidence for duloxetine is limited but does not suggest a clinically important increased risk of major congenital malformations.⁹⁴ However, there are no published large controlled studies examining the safety of duloxetine in pregnancy. Given the limitations of spontaneous adverse reports and the small sample size of the registry, additional information is needed to support conclusions about the safety of duloxetine. Moreover, there is no well-controlled study on the risk of other adverse outcomes such as preeclampsia, PPH, preterm birth, low birth weight, or SGA.

7. Research question and objectives

The objective of this study was to evaluate the safety of duloxetine in pregnant women. Therefore, we quantified the risk of fetal and maternal outcomes in relation to duloxetine in a population-based cohort of pregnant women with clinically diagnosed depression, anxiety, or specific pain indications (i.e., one or more indications for duloxetine). We compared the risk of pre-specified major adverse maternal and fetal outcomes between pregnant women exposed to duloxetine during specific gestational periods and a cohort of women with similar underlying disease, but not treated with duloxetine.

The study objectives were:

- To assess the safety of duloxetine for the *developing fetus*. Specifically:
 - To assess the relative risk of major congenital malformations overall and specific malformations previously hypothesized to be associated with certain antidepressants (i.e., cardiovascular defects) in relation to 1st trimester exposure to duloxetine.
 - To assess the relative risk of preterm birth and small for gestational age in relation to early and late pregnancy exposure to duloxetine.
 - To explore the relative risk of spontaneous abortion and stillbirth in relation to exposure to duloxetine during pregnancy. These analyses were considered exploratory given the difficulties of ascertaining pregnancy losses without systematic repeated pregnancy tests, as well as challenges associated with estimating the gestational length of pregnancies not ending with livebirths.
- To assess the safety of duloxetine for the *pregnant woman*. Specifically:
 - To assess the relative risk of preeclampsia in relation to early and late pregnancy exposure to duloxetine.
 - To assess the relative risk of postpartum haemorrhage in relation to exposure to duloxetine in the last month of pregnancy.

8. Amendments and updates

Not applicable

9. Research methods

9.1. Study design

We conducted a cohort study nested in the nationwide Medicaid Analytic eXtract (MAX) for the period 2004-2013. Maternal use of duloxetine and other medications was determined based on pharmacy dispensing records. Exposure was defined based on a dispensed prescription for duloxetine during etiologically relevant windows.

Outcomes were defined based on the presence of inpatient and/or outpatient diagnoses and procedures recorded in healthcare utilization data. The primary study outcomes were: overall and organ-specific malformations, preterm delivery, SGA, preeclampsia, and postpartum haemorrhage. In order to ensure complete capture of exposure, outcomes, and covariates recorded in the claims, we imposed requirements for Medicaid eligibility that were applied to both the mother and the offspring. The last menstrual period (LMP) was defined using a validated algorithm based on delivery date and diagnostic codes indicative of pre-term delivery in the maternal and infant records.⁹⁵ The eligibility requirements varied based on the outcome being considered and are delineated below ([Table 1](#)). Four different reference groups were defined: (i) women not exposed to duloxetine during the etiologically relevant time window; (ii) women exposed to selective serotonin reuptake inhibitors, (iii) women exposed to venlafaxine, and (iv) women exposed to duloxetine before, but not during pregnancy. The main effect measure was the relative risk of the outcome associated with duloxetine exposure during the etiologically relevant window.

The etiologically relevant window for the study of congenital malformations is exposure during the first trimester (the time period during which organogenesis occurs). For postpartum haemorrhage, the hypothesized mechanism by which duloxetine and similar drugs might increase the risk is by depleting platelet serotonin.^{96,97} Consequently, the etiologically relevant window for this outcome is exposure in the month prior to delivery. For the outcomes of preterm delivery, SGA and preeclampsia, two pregnancy exposure periods are potentially etiologically relevant. These three outcomes have been associated with abnormalities in placental development, as well as maternal and fetal factors that develop in late pregnancy. If the medication confers risk of these outcomes by impairing placentation⁹⁸, then the etiologically relevant period for exposure may be during the first 20 weeks of gestation (i.e., LMP to day 140 of pregnancy). If the risk for these outcomes occurs as a consequence of late pregnancy exposure, then a later exposure window is more relevant (day 141 of pregnancy to day 245—the time point at which the outcomes can begin to occur).

Table 1 Summary of study design including Medicaid eligibility requirements for mothers and offspring, duloxetine exposure windows, outcome assessment windows, and covariate assessment windows.

	Medicaid eligibility requirement-mother	Medicaid eligibility requirement-offspring	Duloxetine exposure window	Outcome assessment window	Covariate assessment window
Congenital malformations	90 days prior to the LMP to 30 days after delivery	3 months after delivery (unless died)	Dispensed in 1st trimester	Delivery to 3 months post delivery	90 days prior to the LMP to the end of the 1st trimester
Postpartum haemorrhage	4 months prior to delivery to 1 month post-delivery	None	Dispensed 1 month prior to delivery to delivery	Delivery admission	4 months prior to delivery to 1 day prior to delivery

	Medicaid eligibility requirement- mother	Medicaid eligibility requirement- offspring	Duloxetine exposure window	Outcome assessment window	Covariate assessment window
EARLY EXPOSURE					
Preterm	90 days prior to the LMP to 30 days after delivery	1 month after delivery (unless died)	Dispensed LMP to LMP+140	Delivery to 1 month post delivery	90 days prior to the LMP to LMP+140
Small for gestational age	90 days prior to the LMP to 30 days after delivery	1 month after delivery (unless died)	Dispensed LMP to LMP+140	Delivery to 1 month post delivery	90 days prior to the LMP to LMP+140
Preeclampsia	90 days prior to the LMP to 30 days after delivery	None	Dispensed LMP to LMP+140	Delivery admission	90 days prior to the LMP to LMP+140
LATE EXPOSURE					
Preterm	90 days prior to the LMP to 30 days after delivery	1 month after delivery (unless died)	Dispensed LMP+141 to LMP+244	Delivery to 1 month post delivery	90 days prior to the LMP to LMP+244
Small for gestational age	90 days prior to the LMP to 30 days after delivery	1 month after delivery (unless died)	Dispensed LMP+141 to LMP+244	Delivery to 1 month post delivery	90 days prior to the LMP to LMP+244
Preeclampsia	90 days prior to the LMP to 30 days after delivery	None	Dispensed LMP+141 to LMP+244	Delivery admission	90 days prior to the LMP to LMP+244

9.2. Setting

Completed pregnancies in Medicaid insured women 18 to 55 years of age were linked to liveborn infants for the period 2004-2013. The year 2013 is the latest year for which data from the Medicaid Analytic eXtract (MAX) were available at the time of the study conduct. The linkage was conducted using a previously developed algorithm based on state, Medicaid case number (which identifies family units), date of delivery, and birth hospital.⁹⁹ Strict eligibility criteria were applied to ensure complete claim information for the mother and infant (See Section 9.3 for details).

9.3. Subjects

The inclusion and exclusion criteria vary slightly depending on the outcome studied, and are detailed below.

I. Major congenital malformations.

a. Inclusion criteria:

- i. Base cohort includes pregnancies drawn from the MAX database with linked offspring from 2004 to 2013
- ii. Maternal eligibility for Medicaid from 3 months prior to the LMP until 1 month post delivery
- iii. Offspring eligibility from months 1 to 3 after the delivery, unless the infant died prior to the end of the 3 months, in which case a shorter eligibility period until death was

permitted

- b. Exclusion criteria:
 - i. Pregnancies in which the mother has restricted benefits, private insurance, or ineligible managed care plan from 3 months prior to the LMP until 1 month post delivery
 - ii. Pregnancies for which at least one baby has restricted benefits, private insurance, or ineligible managed care plan during months 1 to 3 after the delivery month
 - iii. Pregnancies with a chromosomal abnormality based on at least one inpatient or outpatient ICD-9 code for 758.xx or 759.81-759.83 within the first 90 days of the date of birth in the infant and/or maternal claims
 - iv. Pregnancies complicated by outpatient exposure to definite teratogens including warfarin, antineoplastic agents, isotretinoin, misoprostol, lithium and thalidomide from LMP through LMP plus 90 days (i.e., days of exposure overlap with 1st trimester)
 - v. Pregnancies in which duloxetine was dispensed in the 3 months prior to the LMP but not during the first trimester (to insure that there is not misclassification of the non-exposed), except for the analyses using these duloxetine discontinuers as the reference group.

II. Postpartum haemorrhage

- a. This cohort was similar to that used to study major congenital malformations, with the exception of the exclusions for chromosomal abnormalities and 1st trimester teratogenic medication exposures (which are not necessary when considering this outcome). The eligibility period for the mother was different, given that the exposure window is during the final month of pregnancy. Finally, for this maternal outcome, no eligibility criteria were imposed on the offspring.
- b. Inclusion criteria:
 - i. Base cohort includes pregnancies drawn from the MAX database with linked offspring
 - ii. Maternal eligibility for Medicaid from 4 months prior to delivery until 1 month post delivery
- c. Exclusion criteria:
 - i. Pregnancies in which the mother has restricted benefits, private insurance, or ineligible managed care plan from 4 months prior to delivery until 1 month post delivery
 - ii. Duloxetine was dispensed in the 4 months prior to the delivery but not during the final month of pregnancy.

III. Preterm delivery, SGA, and preeclampsia

- a. This cohort was similar to that used to study major congenital malformations, with the exception of the exclusions for chromosomal abnormalities and 1st trimester teratogenic medication exposures (which are not necessary when considering these outcomes) and the required eligibility period for infants.
- b. Inclusion criteria:
 - i. Base cohort included pregnancies drawn from the MAX database with linked offspring
 - ii. Maternal eligibility for Medicaid from 3 months prior to the LMP until 1 month post delivery
 - iii. For the outcomes of preterm delivery and SGA we required offspring eligibility for at

least month 1 after the delivery, unless the infant died prior to the end of the 1st month, in which case a shorter eligibility period was permitted. Note, that infant eligibility was not required to study the outcome of preeclampsia.

c. Exclusion criteria:

- i. Exclude pregnancies in which the mother has restricted benefits, private insurance, or ineligible managed care plan from 3 months prior to the LMP until 1 month post delivery
- ii. Exclude pregnancies for which at least one baby has restricted benefits, private insurance, or ineligible managed care plan during month 1 after the delivery for the outcomes of preterm delivery and SGA.
- iii. We excluded pregnancies in which duloxetine was dispensed in the 3 months prior to the LMP but not during pregnancy itself.

9.4. Variables

9.4.1 Exposure

Maternal exposure to duloxetine was derived from pharmacy dispensing records, with exposure status on any given day based on the dispensing date and, for some analyses, number of days supply. Automated pharmacy dispensing information is usually seen as a more valid source of drug exposure compared to self-reported information¹⁰⁰ or prescribing records in outpatient medical records.¹⁰¹

9.4.2 Contrasts of interest

Comparisons to unexposed women address questions about the safety of duloxetine versus no pharmacological treatment (unexposed reference group). Comparisons to women exposed to SSRIs address questions about the comparative safety of duloxetine versus the commonly used antidepressant medication class (SSRI reference group). Comparisons to women exposed to venlafaxine address questions about the comparative safety of duloxetine versus another SNRI (venlafaxine reference group). Women who have been treated with duloxetine but discontinued because of their pregnancy might be more comparable to women who continue during pregnancy than women who were never treated with duloxetine. We therefore also compared the risk of malformations between women who were treated with duloxetine during the three months before the start of pregnancy and continued treatment during the first trimester, and women who discontinued treatment before the first trimester (discontinuers reference group). To reduce the likelihood of misclassifying as unexposed women who still had medication from their last fill available to consume early in pregnancy, we set the gap between the last prescription fill and the start of pregnancy for the discontinuers at 8 weeks. While possibly superior for confounding control, the disadvantage of this approach is that this analysis has limited power because of the size of the exposed and reference group.

I. Unexposed reference group

- a. **Major congenital malformations:** Exposure was defined by one or more dispensed prescriptions for duloxetine from the LMP to day 90 of pregnancy. The reference group consisted of pregnancies without exposure to duloxetine from 90 days prior to the LMP to day 90 of pregnancy.

- b. **Postpartum haemorrhage:** Exposure was defined by one or more dispensed prescriptions for duloxetine during the final 30 days of pregnancy. The reference group consisted of pregnancies without exposure to duloxetine from 90 days prior to the LMP to delivery.
- c. **Preeclampsia, SGA, and Preterm delivery**
 - i. **Associated with early pregnancy exposure:** Exposure was defined by one or more dispensed prescriptions for duloxetine from the LMP to day 140 of pregnancy. The reference group consisted of pregnancies without exposure to duloxetine from 90 days prior to the LMP to day 140 of pregnancy.
 - ii. **Associated with late pregnancy exposure:** Exposure was defined by one or more dispensed prescriptions for duloxetine from day 141 of pregnancy to day 245 of pregnancy. The reference group consisted of pregnancies without exposure to duloxetine from 90 days prior to the LMP to day 245 of pregnancy.

No exclusions were implemented based on the use of other antidepressants.

II. SSRI reference group

- a. **Major congenital malformations:** Exposure was defined by one or more dispensed prescriptions for duloxetine from the LMP to day 90 of pregnancy. The reference group was defined by one or more dispensed prescriptions for a SSRI from the LMP to day 90 of pregnancy. Those exposed to both duloxetine and a SSRI during the exposure window were excluded.
- b. **Postpartum haemorrhage:** Exposure was defined by one or more dispensed prescriptions for duloxetine during the final 30 days of pregnancy. The reference group was defined by one or more dispensed prescriptions for a SSRI during the final 30 days of pregnancy. Those exposed to both duloxetine and a SSRI during the exposure window were excluded.
- c. **Preeclampsia, SGA, and Preterm delivery**
 - i. **Associated with early pregnancy exposure:** Exposure was defined by one or more dispensed prescriptions for duloxetine from the LMP to day 140 of pregnancy. The reference group was defined by one or more dispensed prescriptions for a SSRI from the LMP to day 140 of pregnancy. Those exposed to both duloxetine and a SSRI during the exposure window were excluded.
 - ii. **Associated with late pregnancy exposure:** Exposure was defined by one or more dispensed prescriptions for duloxetine from day 141 of pregnancy to day 245 of pregnancy. The reference group was defined by one or more dispensed prescriptions for a SSRI from day 141 of pregnancy to day 245 of pregnancy. Those exposed to both duloxetine and a SSRI during the exposure window were excluded.

We excluded women with dispensings for both duloxetine and SSRI during the exposure window or baseline period from the cohort. No exclusions were implemented based on the use of antidepressants other than duloxetine or SSRIs.

III. Venlafaxine reference group

- a. **Major congenital malformations:** Exposure was defined by one or more dispensed prescriptions for duloxetine from the LMP to day 90 of pregnancy. The reference group was defined by one or more

- dispensed prescriptions for venlafaxine from the LMP to day 90 of pregnancy. Those exposed to both duloxetine and venlafaxine during the exposure window were excluded.
- b. **Postpartum haemorrhage:** Exposure was defined by one or more dispensed prescriptions for duloxetine during the final 30 days of pregnancy. The reference group was defined by one or more dispensed prescriptions for venlafaxine during the final 30 days of pregnancy. Those exposed to both duloxetine and venlafaxine during the exposure window were excluded.
 - c. **Preeclampsia, SGA, and Preterm delivery**
 - i. **Associated with early pregnancy exposure:** Exposure was defined by one or more dispensed prescriptions for duloxetine from the LMP to day 140 of pregnancy. The reference group was defined by one or more dispensed prescriptions for venlafaxine from the LMP to day 140 of pregnancy. Those exposed to both duloxetine and venlafaxine during the exposure window were excluded.
 - ii. **Associated with late pregnancy exposure:** Exposure was defined by one or more dispensed prescriptions for duloxetine from day 141 of pregnancy to day 245 of pregnancy. The reference group was defined by one or more dispensed prescriptions for venlafaxine from day 141 of pregnancy to day 245 of pregnancy. Those exposed to both duloxetine and venlafaxine during the exposure window were excluded.

We excluded women with dispensings for both duloxetine and venlafaxine during the exposure window or baseline period from the cohort. No exclusions were implemented based on the use of antidepressants other than duloxetine or venlafaxine.

IV. Discontinuers reference group

- a. **Major congenital malformations:** Exposure was defined by one or more dispensed prescriptions for duloxetine from the LMP to day 90 of pregnancy. The reference group was defined by women with a dispensed prescription for duloxetine between 6 months and 60 days before the LMP, but not during the first trimester.
- b. **Postpartum haemorrhage:** not applicable
- c. **Preeclampsia, SGA, and Preterm delivery:** not applicable

No exclusions were implemented based on the use of other antidepressants.

Table 2 Definition of exposure and reference groups for the contrasts of interest

Cohort	Outcome	Exposure group	Reference group	Definition
Cohort 1a	Congenital malformations	≥1 duloxetine dispensing LMP to LMP+90	Unexposed	no duloxetine dispensing between LMP-90 to LMP+90
			SSRI*	≥1 SSRI dispensing LMP to LMP+90
			Venlafaxine**	≥1 venlafaxine dispensing LMP to LMP+90
Cohort 1b	Congenital malformations	≥1 duloxetine dispensing LMP to LMP+90	Duloxetine discontinuers	≥1 duloxetine dispensing between 6 months and 60 days before the LMP, but not during the first trimester
EARLY EXPOSURE				
Cohort 2a	Preterm, Small for	≥1 duloxetine dispensing	Unexposed	no duloxetine dispensing between LMP-

Cohort	Outcome	Exposure group	Reference group	Definition
	gestational age	LMP to LMP+140		90 to LMP+140
			SSRI*	≥1 SSRI Dispensing LMP to LMP+140
			Venlafaxine**	≥1 venlafaxine dispensing LMP to LMP+140
Cohort 3a	Preeclampsia	≥1 duloxetine dispensing LMP to LMP+140	Unexposed	no duloxetine dispensing between LMP-90 to LMP+140
			SSRI*	≥1 SSRI Dispensing LMP to LMP+140
			Venlafaxine**	≥1 venlafaxine dispensing LMP to LMP+140
LATE EXPOSURE				
Cohort 2b	Preterm, Small for gestational age	≥1 duloxetine dispensing LMP+141 to LMP+245	Unexposed	no duloxetine dispensing between LMP-90 to LMP+245
			SSRI*	≥1 SSRI dispensing LMP+141 to LMP+245
			Venlafaxine**	≥1 venlafaxine dispensing LMP+141 to LMP+245
Cohort 3b	Preeclampsia	≥1 duloxetine dispensing LMP+141 to LMP+245	Unexposed	no duloxetine dispensing between LMP-90 to LMP+245
			SSRI*	≥1 SSRI Dispensing LMP+141 to LMP+245
			Venlafaxine**	≥1 venlafaxine dispensing LMP+141 to LMP+245
Cohort 4	Postpartum haemorrhage	≥1 duloxetine dispensing delivery-30 to delivery	Unexposed	no duloxetine dispensing between LMP-90 to delivery
			SSRI*	≥1 SSRI dispensing delivery-30 to delivery
			Venlafaxine**	≥1 venlafaxine dispensing delivery-30 to delivery

* Exclude women with dispensing for both duloxetine and SSRI during exposure window or baseline period from the cohort. There are no exclusions based on use of antidepressants other than duloxetine and SSRIs.

** Exclude women with dispensing for both duloxetine and venlafaxine during exposure window or baseline period from the cohort. There are no exclusions based on use of antidepressants other than duloxetine and venlafaxine.

9.4.3 Outcomes

I. Major congenital malformations

- a. We first defined the presence of one of 13 organ-specific malformations based on the following criteria, using the ICD-9 and CPT codes shown in [Table 3](#) below. Inpatient and outpatient claims from both the infant and maternal record were used as claims pertaining to the care of the infant are sometimes applied to the maternal claims in the first few months of life.
 - i. If there was >1 date with a ICD-9 code indicating a malformation documented in the infant records between delivery and delivery+90 and/or in the maternal records between delivery and delivery+30 or,
 - ii. If there was one date with a code for the malformation (as specified above) and a specific surgery code for the correction of a malformation documented in the infant records between delivery and delivery+90 and/or in the maternal records between delivery and delivery+30, or
 - iii. If there was one date with a code (as specified above) for the malformation group and infant death in the first 30 days.

- b. If there was a code for this malformation group in the maternal records between 90 days prior to the LMP and LMP+105 (see first flag above) and there were no codes in the infant record between delivery and delivery+90 (i.e., the outcome was defined based on maternal codes between delivery and delivery+30), then the assumption was made that the malformation was maternal and we considered the infant as being unaffected.
- c. If an infant had one or more of the 13 organ specific malformations, then we considered them as having a major malformation overall.
- d. Analyses were conducted examining the association between first trimester duloxetine exposure with malformations overall and with the 13 organ specific malformations.

Table 3 ICD-9 codes for major congenital malformations

Malformation Group	ICD-9 Code
1. Central Nervous System	740.xx-742.xx
2. Eye Anomalies	743.xx (exclude if only 743.6x and 743.8x)
3. Ear Anomalies	744.xx (exclude if only 744.1x, 744.21, 744.29, and 744.4x-744.9x)
4. Cardiovascular Anomalies	745.xx-747.xx (exclude if only 745.5 AND preterm, 746.02 AND preterm, 746.4x, 746.6x, 746.99, 747.0x and preterm, 747.3 and preterm, 747.5x)
5. Other vascular (non-cardiac)	747.6x-747.9x (exclude if only 747.83)
6. Respiratory malformations	748.xx (do not count if only 748.1x)
7. Oral cleft	749.xx
8. Gastrointestinal	750.xx-751.xx (do not count if only 750.0x, 750.1x, 750.50, 751.0x)
9. Genital (male and female)	752.xx-753.xx (do not count if only 752.42, 752.52) (in addition, do not count 752.5x if preterm)
10. Urinary	753.xx (do not include if only 753.7x)
11. Musculoskeletal (no limbs, includes omphalocele ad gastroschisis)	754.xx and 756.xx (do not count if only 754.3x, 754.81, 754.82, 756.2x)
12. Limb defects	755.xx (exclude if only 755.65)
13. Other	757.xx; 759.xx (excl if only 757.2-757.6, 759.81-759.83)

- II. **Postpartum haemorrhage:** Defined by the presence of ≥ 1 ICD-9 diagnostic codes 666.xx in the maternal inpatient hospitalization claims during the delivery hospitalization
- III. **Preeclampsia:** Defined by the presence of ≥ 1 ICD-9 diagnostic codes 642.4x, 642.5x, 642.6x, 642.7x in the maternal inpatient claims during the delivery hospitalization
- IV. **Small for gestational age:** Defined by the presence of ≥ 1 ICD-9 diagnostic codes in maternal or infant claims from delivery to delivery + 30 including 656.5x, 764.0x, 764.1x, 764.9x
- V. **Preterm delivery:** Defined by the presence of any inpatient or outpatient codes for preterm (listed in [Table 4](#) below) in the mother or infant record between delivery and delivery + 30 days

Table 4 ICD-9 and CPT codes for preterm delivery

ICD-9	Description
644.2x	early onset of delivery
776.6x	anemia of prematurity
362.20	retinopathy of prematurity, unspecified
362.22	retinopathy of prematurity, stage 0
362.23	retinopathy of prematurity, stage 1
362.24	retinopathy of prematurity, stage 2
362.25	retinopathy of prematurity, stage 3
362.26	retinopathy of prematurity, stage 4
362.27	retinopathy of prematurity, stage 5
765.xx, excluding 765.09, 765.19, 765.20, 765.29	disorders relating to short gestation and low birth-weight
CPT	
49491	repair, initial inguinal hernia, preterm infant (younger than 37 weeks gestation at birth), performed from birth up to 50 weeks postconception
49492	repair, initial inguinal hernia, preterm infant (younger than 37 weeks gestation at birth), performed from birth up to 50 weeks postconception
67229	treatment of extensive or progressive retinopathy, 1 or more sessions; preterm infant (less than 37 weeks gestation at birth), performed from
00836	anesthesia for hernia repairs in the lower abdomen not otherwise specified, infants younger than 37 weeks gestational age at birth

- VI. **Validation studies:** Using MAX claims (from the years 2000 to 2007) linked to medical records, coding algorithms were previously validated for preeclampsia and cardiac defects.¹⁰² The positive predictive value (PPV) (95% CI) for preeclampsia based on codes recorded during an inpatient hospitalization was 94.5 (95% CI 84.0, 98.3). The PPV for cardiac malformations based on a diagnostic code recorded on more than one date was 77.6 (95% CI 65.7, 86.2). All other outcomes considered were validated as part of the present study (Appendix 3: Chart based outcome validation study).

9.4.4 Covariates

We considered six groups of covariates that could potentially confound the association between duloxetine exposure and the outcomes of interest: medical indications for duloxetine (i.e., depression, anxiety, specific pain conditions), maternal demographic characteristics, comorbid medical conditions, obstetric characteristics/conditions, maternal medications, and measures of healthcare utilization. The included covariates were selected because they are potential risk factors for the outcomes or potential proxies for such risk factors.

We also assessed the use of medications during the baseline period, which may be markers for the presence or the severity of comorbid illness. For the analysis of congenital malformations, we also assessed the use of suspected teratogenic medications. The covariates included in each of the analyses, their covariate assessment window, and the codes or generic names used to define each of the covariates are summarized in [Table 5](#) and [Table 6](#).

Table 5 Covariates included in each of the analyses and the associated covariate assessment window

Covariate assessment window			
Congenital malformations	PPH	Preterm, SGA, preeclampsia	
		Early exposure	Late exposure
<u>Maternal demographics characteristics</u>			
Age, Race/ethnicity, Geographic region			
n/a	n/a	n/a	n/a
<u>Chronic comorbid conditions</u>			
Chronic hypertension, Diabetes, Renal Disease, Obesity or overweight, Obstetric comorbidity score (divided into quartiles)			
3 months pre-LMP to 90 days after LMP	4 months prior to delivery to 1 day prior to delivery	3 months pre-LMP to 140 days after the LMP	3 months pre-LMP to 245 days after the LMP
<u>Infections</u>			
Toxoplasmosis, Rubella, Cytomegalovirus, Herpes, Syphilis, Varicella, Parvovirus B19, Zika virus, Lymphocytic choriomeningitis virus (LCMV), Influenza, chlamydia, human papilloma virus, gonorrhea, HIV, trichomoniasis			
3 months pre-LMP to 90 days after LMP	n/a	3 months pre-LMP to 140 days after the LMP	3 months pre-LMP to 245 days after the LMP
<u>Indications for duloxetine</u>			
Depression, Anxiety, Neuropathic Pain, Fibromyalgia, Non-neuropathic Pain			
3 months pre-LMP to 90 days after LMP	4 months prior to delivery to 1 day prior to delivery	3 months pre-LMP to 140 days after the LMP	3 months pre-LMP to 245 days after the LMP
<u>Other psychiatric conditions</u>			
Sleep disorder, Bipolar disorder, Psychosis, Schizophrenia, Personality disorder, Adjustment disorder			
3 months pre-LMP to 90 days after LMP	4 months prior to delivery to 1 day prior to delivery	3 months pre-LMP to 140 days after the LMP	3 months pre-LMP to 245 days after the LMP
<u>Tobacco use, alcohol abuse or dependence, drug abuse or dependence</u>			
3 months pre-LMP to 90 days after LMP	4 months prior to delivery to 1 day prior to delivery	3 months pre-LMP to 140 days after the LMP	3 months pre-LMP to 245 days after the LMP
<u>Markers of healthcare utilization</u>			
Number of non-duloxetine generics, Number of outpatient medical visits, Number of hospital admissions, Number of distinct 3 digit ICD 9 codes, Number of emergency department, Psychiatric hospitalization, Visits with a psychiatrist			
3 months pre-LMP to LMP	4 months prior to delivery to 1 month prior to delivery	3 months pre-LMP to LMP	3 months pre-LMP to 140 days after the LMP
<u>Other medication exposures (markers of comorbidity)</u>			
Benzodiazepines, Other hypnotics, Barbiturates, Anxiolytics, Anticonvulsants, Antipsychotics, Antidepressants (other than duloxetine), Stimulants, Antidiabetic oral medications, Insulin, Antihypertensive, Opioid analgesics, Triptans, NSAIDs			
3 months pre-LMP to 90 days after LMP	4 months prior to delivery to 1 day prior to delivery	3 months pre-LMP to 140 days after the LMP	3 months pre-LMP to 245 days after the LMP
<u>Obstetrical conditions</u>			
Multifetal gestation			
LMP to delivery	LMP to delivery	LMP to delivery	LMP to delivery
<u>Potentially teratogenic medication exposures</u>			
ACEI, Danazol, Progestins, Methimazole, Propylthiouracil, Corticosteroids, Fluconazole			

Covariate assessment window			
Congenital malformations	PPH	Preterm, SGA, preeclampsia	
		Early exposure	Late exposure
Days supply overlapping T1	n/a	n/a	n/a

Table 6 ICD-9 codes used to define covariates, as well as specific generics used to define medication classes used as covariates.

Covariate	ICD 9 codes
Chronic comorbid conditions	
Chronic hypertension	401.x-405.x, 642.0x-642.2x, 642.7x, 642.9x
Diabetes	250.x, 648.0x, 648.8x
Renal Disease	582.xx, 583.xx, 585.xx, 586.xx, 587.xx, 642.1x 250.4x, 250.40, 250.41, 250.42, 250.43, 403.xx, 404.xx, 572.4x, 580.xx, 584.xx, 580.0x, 580.4x, 580.89, 580.9x, 582.4x, 642.1x, 791.2x, 791.3x 274.10, 440.1x, 442.1x, 453.3x, 581.xx, 593.xx, 753.0x, 753.3x, 866.00, 866.01, 866.1x
Obesity or overweight	278.00, 278.01, 278.03, 649.1x, V85.3x, V85.4x, 278.02
Obstetric comorbidity score	See Bateman et al. ¹⁰³ ; validated in Metcalfe et al. ¹⁰⁴
Infections	Toxoplasmosis (130.xx), Rubella (056.xx), Cytomegalovirus (078.5x, 484.1x), Herpes (054.xx), Syphilis (090.xx-097.xx), Varicella (052.xx), Parvovirus B19 (079.83), Zika virus and other mosquito borne viral illnesses (066.3x), Lymphocytic choriomeningitis virus (049.0x), Influenza (487.xx-488.xx), chlamydia (078.88, 079.98, 483.1, 099.41, 099.5), human papilloma virus (079.4x), gonorrhea (098.xx, 647.1x, V02.7), HIV (042.xx, V08), trichomoniasis (131.xx)
Indications for duloxetine	
Depression	293.83, 296.2x, 296.3x, 298.0x, 300.4x, 309.0x, 309.1x, 309.28, 311.xx
Anxiety	293.84, 300.0x, 300.2x, 300.3x, 309.24, 308.0x, 309.81, 313.0x, 300.02
Neuropathic Pain	053.1x, 337.1x, 337.2x, 250.6x, 357.2, 350.1x, 350.2x, 352.1x, 353.xx, 354.xx, 355.xx, 357.xx, 729.2x, 721.1x, 721.41, 721.42, 721.91, 722.7x, 723.4x, 724.3x, 724.4 x
Fibromyalgia	729.1x
Non-neuropathic Pain	715.xx, 720.0x, 720.1x, 720.2x, 721.3x, 722.10, 722.32, 722.5x, 722.83, 722.93, 724.00, 724.02, 724.2x, 724.5x, 724.6x, 724.70, 724.71, 724.79, 720.81, 720.89, 720.9x, 721.0x, 721.2x, 721.5x, 721.6x, 721.7x, 721.8x, 721.90, 722.11, 722.30, 722.31, 722.39, 722.4x, 722.6x, 722.80, 722.81, 722.82, 722.90, 722.91, 722.92, 723.xx (except 723.4x), 724.01, 724.1x, 724.8x, 724.9x, 710.xx-714.xx, 716.xx-719.xx, 725.xx-729.xx (excluding 729.1x-2x)]
Other psychiatric conditions	
Sleep disorder	307.4x, 347.xx, 780.5x, 327.0x, 327.2x
Bipolar disorder	296.0x, 296.1x, 296.4x, 296.5x, 296.6x, 296.7x, 296.8x, 296.99
Psychosis	290.8x, 290.9x, 297.xx, 298.xx, 299.xx, 780.1x
Schizophrenia	295.xx
Personality disorder	301.xx
Adjustment disorder	309.21-309.23, 309.29, 309.3x, 309.4x, 309.82, 309.83, 309.89, 309.9x
Tobacco use	305.1x, 649.0x, V15.82
Alcohol abuse or dependence	291.xx, 303.xx, 305.0x, 357.5x, 425.5x, E860.0, V11.3, 571.0x - 571.3x
Drug abuse or dependence	304.xx, 305.2x-305.9x (exclude 305.8x, antidepressant type abuse), 648.3-648.4
Other medication exposures	Generics included

Covariate	ICD 9 codes
Benzodiazepines	Alprazolam, Chlordiazepoxide, Clobazam, Clonazepam, Clorazepate, Diazepam, Lorazepam, Midazolam, Oxazepam, Estazolam, Flurazepam, Quazepam, Temazepam, Triazolam
Other hypnotics	Zolpidem, Zaleplon, Eszopiclone, Chloral hydrate, Diphenhydramine, Ethchlorvynol, Glutethimide, Hydroxyzine (hydrochloride/pamoate), Methaqualone, Ramelteon
Barbiturates	Amobarbital sodium/amobarbital, Butobarbital sodium/butobarbital, Pentobarbital sodium/pentobarbital, Butalbital, Secobarbital
Anxiolytics	Buspirone, meprobamate
Anticonvulsants	Carbamazepine, eslicarbazepine, ethoin, ethosuximide, ezogabine, felbamate, fosphenytoin, gabapentin, lacosamide, lamotrigine, levetiracetam, mephenytoin, mephobarbital, methsuximide, oxcarbazepine, perampanel, phenobarbital, phenytoin, pregabalin, primidone, rufinamide, tiagabine, topiramate, valproate (divalproex, valproic acid, valproate sodium), vigabatrin, zonisamide
Antipsychotics	Aripiprazole, Asenapine, Clozapine, Iloperidone, Lurasidone, Olanzapine, Olanzapine/fluoxetine, Paliperidone, Quetiapine, Risperidone, Ziprasidone, Chlorpromazine, chlorprothixene, fluphenazine, haloperidol, loxapine, mesoridazine, molindone, perphenazine, perphenazine/amitriptyline, pimozide, promazine, propiomazine, thioridazine, thiothixene, trifluoperazine, triflupromazine
SSRIs	Citalopram, Escitalopram, Fluoxetine, Fluvoxamine, Paroxetine, Sertraline,
SNRIs (other than duloxetine)	Venlafaxine, Desvenlafaxine, Levomilnacipran
Other	Amitriptyline, Amoxapine, Clomipramine, Desipramine, Doxepin, Imipramine, Maprotiline, Nortriptyline, Protriptyline, Trimipramine, Isocarboxazid, Phenelzine, Tranylcypromine, Bupropion, Mirtazapine, Nefazodone, Trazodone, Vilazodone, Vortioxetine
Stimulants	Amphetamine, amphetamine/dextroamphetamine, dextroamphetamine, methamphetamine, lisdexamfetamine, methylphenidate, dexamethylphenidate, pemoline, atomoxetine, guanfacine, clonidine
Antidiabetic oral medications	Acarbose, Acetohexamide, Chlorpropamide, Glimepiride, Glipizide, Glyburide, Metformin, Miglitol, Nateglinide, Pioglitazone, Repaglinide, Rosiglitazone, Tolazamide, Tolbutamide, Troglitazone
Insulin	Insulin
Antihypertensives	ATC codes: C02 Antihypertensives C03 Diuretics C07 Beta blocking agents C08 Calcium channel blockers C09 Agents acting on the renin-angiotensin system
Opioid analgesics	Buprenorphine, butorphanol, codeine, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine, methadone, morphine, oxycodone, oxymorphone, pentazocine, propoxyphene, tapentadol, tramadol (Including combination drugs that contain the compounds above.)
Triptans	Sumatriptan, rizatriptan, naratriptan, zolmitriptan, eletriptan, almotriptan, frovatriptan
NSAIDs	Aspirin, Celecoxib, Diclofenac, Diflunisal, Etodolac, Fenoprofen, Flurbiprofen, Ibuprofen, Indomethacin, Ketoprofen, Ketorolac, Mefenamic Acid, Meloxicam, Nabumetone, Naproxen, Oxaprozin, Piroxicam, Sulindac, Tolmetin
<u>Obstetrical conditions</u>	
Multifetal gestation	V27.2, V27.3, V27.4, V27.5, V27.6, V31, V32, V33, V34, V35, V36, V37, 651, 651.0x, 651.1x, 651.2x, 651.4x, 651.5x, 651.6x, 651.7x, 651.8x, 651.9x, 652.6x, 660.5x, 662.3x, 761.5x
<u>Potentially teratogenic medication exposures</u>	
Danazol	
Progestins	drospirenone/estradiol, estradiol/norethindrone, hydroxyprogesterone, leuprolide, medroxyprogesterone, medroxyprogesterone, norethindrone, progesterone

Covariate	ICD 9 codes
Methimazole	
Propylthiouracil	
Corticosteroids	betamethasone, budesonide, ciclesonide, cortisone, dexamethasone, dexamethasone, flunisolide, fluticasone, hydrocortisone, methylprednisolone, mometasone, prednisolone, prednisone, triamcinolone
Fluconazole	

A greater disparity in baseline characteristics before adjustment indicates a higher likelihood for confounding factors to play a role in the association. Balance in characteristics after adjustment indicates a lower risk of confounding by both measured and unmeasured characteristics. However, unmeasured confounders may still bias the estimate, particularly if not correlated with the measured characteristics.

To address the potential for residual confounding by factors not accounted for by measured covariates, we used comparator groups (in addition to a non-exposed comparator) in the analyses that are more likely to be exchangeable with the duloxetine user group, including women exposed to venlafaxine, SSRIs, and women who discontinue duloxetine prior to pregnancy.

9.5. Data sources

The data source that was employed for the study is the Medicaid Analytic eXtract (MAX). Medicaid covers approximately half of all births in the U.S. Data was drawn from MAX claims from 2004 to 2013. There is a several years delay in CMS releasing complete, nationwide Medicaid claims. For details regarding the creation of the MAX pregnancy cohort, please see the manuscript by Palmsten et al⁹⁹. This cohort has been used extensively for studies of the safety of medications in pregnancy. The strengths of this data source for studying the safety of duloxetine include the following: (1) The MAX is a large, population-based cohort; (2) It allows for objective assessment of drug exposure. Drug exposure is defined by filled prescriptions during etiologically relevant periods, and is not subject to recall bias; (3) It contains detailed information of potential confounders. The claims data in MAX contain rich information regarding conditions that can potentially confound the association between drug exposures and pregnancy outcomes. These can be measured and adjusted for in the analyses in a robust manner. Further, the data allow very careful attention to the issue of confounding by indication.

We required that women be eligible for Medicaid during the baseline, exposure window, and follow up period. We further required that the offspring be eligible for Medicaid during the relevant follow up period. The eligibility requirements vary according to the analysis being conducted and are outlined in [Table 1](#). For all analyses, to ensure complete ascertainment of claims, the cohort was restricted to women without restricted benefits, private insurance, or certain capitated managed care programs that underreport claims to MAX.

9.6. Bias

To guard against exposure misclassification (i.e., false positives), we favored specificity over sensitivity in our exposure definition. Other exposure definitions were evaluated in sensitivity analyses. We used validated outcome definitions with a high PPV. The outcome definitions were highly specific, since this results in unbiased estimates of the relative risk as long as the sensitivity is non-differential with respect to exposure status. In addition to using high-dimensional propensity score techniques to account for proxies of unmeasured variables, we conducted formal

sensitivity analyses to quantify the potential impact of residual confounding by variables that are poorly recorded or not documented in claims data (e.g., lifestyle factors) using external information. We performed sensitivity analyses to assess the potential impact of missing non-livebirths on the risk estimate for duloxetine and malformation (i.e., potential selection bias).

9.7. Study size

In developing the study protocol, we projected about 1500 patients exposed to duloxetine during the first trimester based on preliminary analyses of women eligible from 3 months prior to the LMP to delivery included in the linked cohort. The frequency of exposure decreases during pregnancy such that we projected approximately 300 to 500 exposed during the “late pregnancy” exposure window. We estimated the power to detect significant differences ($\alpha=0.05$, 2-sided) at various numbers of exposed women and levels of relative risk for outcomes assuming a prevalence in the unexposed of 10% (e.g., preterm delivery, SGA), 3% (e.g., preeclampsia, postpartum haemorrhage), 1% (e.g., cardiac malformations), and 0.1% (e.g., rare malformations). We assumed a ratio of 5 for the number of unexposed to exposed women.

Table 7 Power to detect associations based on the number exposed and relative risks

Exposed	RR					RR				
	1.25	1.5	2	3	5	1.25	1.5	2	3	5
RISK IN UNEXPOSED: 10%						RISK IN UNEXPOSED: 3%				
150	0.16	0.44	0.90	1.00	1.00	0.08	0.18	0.46	0.87	1.00
300	0.27	0.70	0.99	1.00	1.00	0.12	0.29	0.70	0.99	1.00
450	0.36	0.85	1.00	1.00	1.00	0.15	0.39	0.84	1.00	1.00
600	0.45	0.93	1.00	1.00	1.00	0.18	0.48	0.92	1.00	1.00
750	0.53	0.97	1.00	1.00	1.00	0.20	0.55	0.96	1.00	1.00
900	0.60	0.99	1.00	1.00	1.00	0.23	0.62	0.98	1.00	1.00
1,050	0.67	0.99	1.00	1.00	1.00	0.26	0.68	0.99	1.00	1.00
1,200	0.72	1.00	1.00	1.00	1.00	0.29	0.74	1.00	1.00	1.00
1,350	0.77	1.00	1.00	1.00	1.00	0.32	0.78	1.00	1.00	1.00
1,500	0.81	1.00	1.00	1.00	1.00	0.34	0.82	1.00	1.00	1.00
RISK IN UNEXPOSED: 1%						RISK IN UNEXPOSED: 0.1%				
150	0.06	0.10	0.22	0.50	0.87	0.04	0.06	0.09	0.15	0.26
300	0.07	0.14	0.34	0.73	0.99	0.04	0.06	0.11	0.20	0.38
450	0.08	0.18	0.45	0.86	1.00	0.05	0.07	0.13	0.24	0.48
600	0.09	0.22	0.54	0.93	1.00	0.05	0.08	0.14	0.29	0.57
750	0.11	0.25	0.62	0.97	1.00	0.05	0.08	0.16	0.32	0.64
900	0.12	0.29	0.69	0.99	1.00	0.05	0.09	0.17	0.36	0.71
1,050	0.13	0.32	0.74	0.99	1.00	0.05	0.09	0.18	0.40	0.76
1,200	0.14	0.35	0.79	1.00	1.00	0.06	0.10	0.20	0.43	0.80
1,350	0.15	0.38	0.83	1.00	1.00	0.06	0.10	0.21	0.46	0.84
1,500	0.15	0.41	0.86	1.00	1.00	0.06	0.10	0.22	0.49	0.87

9.8. Data Management

The research team operates a secure, state-of-the-art computing environment hosted at Partners Healthcare's data center. The server environment is Linux-based and offers SAS 9.4, Stata 10, and R. We maintain over 100 terabytes of redundant storage for maximal data integrity and high-speed data access. This storage is mounted to the Linux environment that we exclusively utilize, and allows us to develop and utilize cutting-edge analytics and enables extremely fast SAS-based cohort creation and analysis.

The Partners data center is a secure facility that houses both our computing environment as well as clinical systems and electronic medical records for several large hospitals in Eastern Massachusetts. Entry into the server room requires passing through staffed building security, a successful fingerprint scan, and then passing through staffed server room security; all visits are logged and all visitors must be accompanied by staff at all times. The Division's machines are connected to the Partners networking backbone with 10 gigabit-per-second fiber links. Network security is overseen by Partners Healthcare Information Security, who apply the same standards used for the hospital's electronic medical records systems to the research team's data. All data are transmitted to programmers' workstations in an encrypted state. Backups are created using 256-bit AES encryption, the current Department of Defense standard for data security, and are stored in a secure facility. The redundancy, extensive data power, and security of our computer facility confirms our capacity to collect and manage data and ensures confidentiality for all project participants.

All analyses were conducted in SAS 9.4. Most variables are dichotomous (present/absent).

9.9. Statistical methods

9.9.1 Main summary measures

The baseline characteristics of the study cohorts stratified by exposure group are described using numbers and proportions for categorical variables and mean, standard deviation, median and interquartile range for continuous variables. Balance of the baseline covariates is assessed using standardized mean differences.

$$SD = \frac{\bar{X}_{exp} - \bar{X}_{ref}}{\sqrt{\frac{s_{exp}^2 + s_{ref}^2}{2}}}$$

With s^2 representing the sample variance in the duloxetine exposed and the reference group. An absolute standardized mean difference > 0.1 was considered evidence of imbalance of that characteristic between the exposure groups.

For each outcome, the number of events, as well as the absolute and relative risk with their 95% CI are reported

9.9.2 Main statistical methods

The same analytic approach was followed for each of the maternal and fetal outcomes, unless otherwise noted.

The reference groups consisted of: (i) women not exposed to duloxetine during the etiologically relevant exposure window; (ii) women exposed to selective serotonin reuptake inhibitors, (iii) women exposed to venlafaxine, and (iv) women exposed to duloxetine before, but not during pregnancy.

We compared the distributions of socio-demographic, clinical and healthcare utilization characteristics during the relevant baseline period for the duloxetine exposed and reference group. Balance was assessed using the standardized mean difference. An absolute standardized difference greater than 0.1 was considered an indicator for substantial imbalances between the two exposure groups.¹⁰⁵ Absolute risks for the outcome and unadjusted relative risks with their 95% confidence interval (CI) were calculated.

Results are presented for four levels of adjustment: (i) unadjusted, (ii) restricted to women with recorded depression, anxiety, specific pain conditions to control for the potential effect of the underlying illness or factors associated with it, using PS stratification to account for imbalances in the specific indication, (iii) restricted to women with a recorded diagnosis of the indications, using PS stratification to further control for imbalances in the specific indication, proxies of severity of the underlying indication and other potential confounders¹⁰⁶, and (iv) restricted to women with a recorded diagnosis of the indications, using high-dimensional propensity score (hdPS) stratification to further reduce residual confounding by controlling for proxies of unmeasured confounders.¹⁰⁷

PS were derived from the predicted probability of treatment estimated in a logistic regression model, which contained all covariates without additional variable selection. We trimmed the cohort by excluding observations from the non-overlapping regions of the PS distributions. Such trimming of the tails of the PS distribution is recommended to reduce the potential for unmeasured confounding. We then created 50 equally sized PS-strata based on the distribution among the duloxetine treated women.^{108,109} In the outcome models, the untreated observations were weighted using the distribution of the treated among PS-strata. Adjusted relative risks were estimated using generalized linear models (SAS PROC GENMOD with a weight statement and loglink function). Balance of baseline characteristics in this weighted population was assessed using the absolute standardized difference.

The hdPS algorithm evaluates thousands of diagnoses, procedures, and pharmacy claim codes to identify and prioritize those covariates that serve as proxies for unmeasured confounders. These empirically identified confounders (n=200) were combined with the investigator-identified covariates described above to further improve confounding adjustment and thus validity.¹⁰⁷

9.9.3 *Missing values*

In defining baseline covariates and inclusion and exclusion criteria, we assumed that a condition was truly absent if it was not recorded.

9.9.4 *Sensitivity analyses*

Sensitivity analyses were conducted to test the robustness of the findings. The pre-specified sensitivity analyses for each outcome are summarized in [Table 8](#). The overall findings were interpreted in light of the results of these pre-specified sensitivity analyses.

Table 8 Pre-specified Sensitivity Analyses

Outcome	Sensitivity Analyses
All outcomes	1. Re-define exposure as having filled ≥ 2 prescriptions for duloxetine during the etiologically relevant time window 2. Redefine exposure as days supply that overlaps with the etiologically relevant time window 3. Restrict population to women with a recorded diagnosis of fibromyalgia 4. Probabilistic bias analysis: Correct relative risks for outcome misclassification using sensitivities and specificities consistent with the PPV estimated in the

	internal validation study 5. Assess impact of excluding outcomes designated as “probably occurred” or “likely did not occur” based on review of claims profiles 6. Restrict cohort to the first pregnancy occurring within the study period 7. External adjustment of the relative risk*
Neonatal outcomes	
Congenital malformations⁶⁴	8. Re-define outcome based on infant claims only 9. Restrict outcome to inpatient diagnoses only 10. Extend infant follow-up to 1 year 11. Examine the potential impact of differences in the proportion of terminations among women treated with duloxetine versus those untreated within levels of covariates used in the adjustment.**
Preterm delivery	N/A
Small for gestational age	N/A
Maternal outcomes	
Pre-eclampsia⁹⁹	N/A
Post partum haemorrhage⁹⁷	12. Days supply of duloxetine overlapping the date of delivery 13. Classify women with duloxetine dispensed <14 days before delivery, regardless of days of supply on the delivery date, as having current exposure.

*** External adjustment of the relative risk**

There are covariates (e.g. smoking, obesity) that may be important confounders and that are not well documented in the source data but for which we can obtain supplementary information. In addition to adjusting for measured confounders by PS stratification, and for proxies of unmeasured factors by hdPS stratification, we explored the impact of potential residual confounding by unmeasured lifestyle factors with additional information on covariates from external data using binary algebraic solutions, and/or bias analyses. We used publicly-available files from the National Health and Nutrition Examination Survey (NHANES) for 1999-2014, restricted the sample to women of childbearing age, stratified them based on insurance (Medicaid vs. private), and assessed the association between use of duloxetine and potential confounders (e.g., BMI, alcohol, and smoking). Information from the literature was used to inform estimates of the strength of the association between these factors and the outcome.

Similarly, the potential impact of residual confounding by factors not measured in external sources, was quantified using bias analyses. This was done by defining the strength (confounder-outcome relative risk) of a hypothetical residual confounder which, if present, would explain the observed effect across a range of confounder prevalence measures in the exposed and unexposed.¹¹⁰ The results from this analysis can be used to judge whether it is clinically plausible that such a confounder exists.

**** Potential impact of selection bias due to restriction to live births**

We evaluated the potential impact of selection bias due to the restriction of our cohort to live births for the main fetal outcomes, using methods proposed by Greenland and Khoury.^{111,112} These methods have been previously described in detail by our group⁶⁴. Briefly, we modeled a range of non-livebirth frequencies for malformed infants in the unexposed and exposed and then calculated “corrected” relative risk estimates based on these inputs and the adjusted relative risk estimate from the main analysis. As such, we conducted a formal quantification of the potential impact of the selection bias.

Multiple comparisons

For these pre-specified analyses, no adjustments were made for multiple comparisons, but all results (“negative” or “non-significant” and “positive” or “significant”) were reported.¹¹³⁻¹¹⁵

9.9.5 Validation Study

For outcomes where no validation study was already available (major congenital malformations other than cardiac, post partum haemorrhage, preterm delivery, SGA), medical record validation was conducted.

We linked pregnancies in MAX with the outcome of interest defined based on diagnostic or procedure claims with medical records for patients who were treated at hospitals that are part of Partners Healthcare (which includes Brigham and Women’s Hospital and Massachusetts General Hospital). Fifty medical records from pregnancies defined with these codes were then retrieved for each outcome. Two physicians who were blinded to the drug exposure status reviewed the charts based on established clinical criteria and classified the outcome as present or absent. The PPV (and 95% CI) of the claims-based algorithm was calculated.¹⁰² Where necessary, the algorithms were refined based on the findings from the validation study. The PPV defined based on these algorithms was used to inform a probabilistic bias analysis which generated corrected relative risk estimates.

9.9.6 Claims Profile Review

In a sensitivity analysis, we matched exposed to non-exposed women (from the primary analysis for each outcome) in a 1:1 ratio for outcomes with a prevalence of $\geq 3\%$ in the unexposed, and in a 1:5 ratio for outcomes with a prevalence of $< 3\%$ using a nearest neighbor algorithm. De-identified claims profiles of mothers or infants with the outcome of interest as defined using the algorithms were generated for all cases in the matched cohort. Expert clinicians reviewed the profiles, blinded to the exposure status, and “adjudicated” each case as (1) the outcome likely occurred, (2) the outcome probably occurred, or (3) the outcome likely did not occur. Since we strive for high specificity of the outcome definition, the effect of excluding (2) and/or (3) on the relative risk estimates was assessed. Two clinicians reviewed each profile. Disagreements in the initial determination was resolved through discussion.

9.9.7 Exploratory analyses

Exploratory analyses were conducted to assess the risk of non-live births. These analyses are considered exploratory because non-live births have not previously been studied using the MAX data and no validated algorithms are currently available for the identification of the outcome or the estimation of gestational age at the time of the pregnancy loss.

All women in the MAX cohort were identified for the years 2004 through 2013, regardless of the duration of their Medicaid eligibility. We first identified the subset of women within this cohort that were previously successfully linked to live births using their Medicaid Case ID, and assigned the date of delivery. We subsequently identified 6 different pregnancy outcomes using the list of pre-specified codes from [Table 9](#): live birth, stillbirth, unclassified delivery, spontaneous abortion, termination, and unclassified end of pregnancy.

Unclassified deliveries were pregnancies with evidence of a delivery but uncertain outcome regarding live birth or stillbirth. Unclassified end of pregnancy were outcomes not otherwise classified, i.e., there was evidence of a

pregnancy but how it ended was unclear. For live births, unclassified delivery and unclassified end of pregnancy codes, only inpatient codes were considered. For spontaneous abortion, we required at least 2 outpatient codes within a 7-day window, or one or more inpatient codes. For stillbirth and termination, both inpatient and outpatient codes were accepted (Table 10).

For linked livebirths LMP was assigned following a validated algorithm that incorporates prematurity indicators. For inpatient deliveries (i.e., unlinked live birth, unclassified delivery, unclassified end of pregnancy), the LMP was assigned at 270 days before the diagnosis or procedure code. For stillbirths, the LMP was assigned 196 days before the diagnosis or procedure code, which corresponds to a pregnancy duration of 28 weeks. For spontaneous abortions and terminations, the LMP was assigned at 63 days before the diagnosis or procedure code, which corresponds to a pregnancy duration of 9 weeks (Table 10).

We subsequently imposed the following hierarchy to address the occurrence of multiple different outcomes recorded in claims for a small proportion of pregnancies among those not linked to a livebirth (Table 10).

- Stillbirth codes were given priority
- Inpatient deliveries (i.e., livebirth, unclassified delivery, unclassified end of pregnancy):
 - If a stillbirth code occurred during the inpatient delivery, then the stillbirth was given priority
 - If patients had more than one inpatient admission (either stillbirth or livebirth) separated by 140 days or less, only the first admission was included.
 - The date of delivery was assigned using the date of the first recorded CPT or ICD-9 procedure code indicating delivery. If no such code was available, the date of delivery was assigned as the date of the start of the inpatient admission.
- Terminations:
 - If there was an inpatient delivery or stillbirth within the time window from LMP to LMP+270 (i.e., LMP is referring to the estimated LMP for termination), then the termination code was ignored (most likely referred to a past pregnancy).
- Spontaneous abortion:
 - If there was an inpatient delivery or stillbirth within the time frame from LMP to LMP+270 (i.e., LMP is referring to the estimated LMP for spontaneous abortion), then the spontaneous abortion code was ignored (most likely referred to a past pregnancy).
 - If there was a termination within the window of spontaneous abortion $\pm$ 8 weeks, then the spontaneous abortion code was ignored assuming it referred to the termination.

We subsequently imposed the following minimum Medicaid enrollment prior to end of pregnancy eligibility criteria (Table 10):

- 52 weeks for inpatient deliveries and linked live births (40 weeks pregnancy + 12 weeks baseline)
- 40 weeks for stillbirths (28 weeks pregnancy + 12 weeks baseline)
- 21 weeks for spontaneous abortions and terminations (9 weeks pregnancy + 12 weeks baseline)

Table 9 Codes for live and non-live pregnancy outcomes

Pregnancy Outcome	Code	Description
1. Live birth	ICD-9 Dx: V27.0, V27.2, V27.5	Single/Twins/Other multiple birth, all liveborn
2. Unclassified delivery	CPT4: 1960	Anesthesia for vaginal delivery only
	CPT4: 1961	Anesthesia for cesarean delivery only
	CPT4: 1962	Anesthesia for urgent hysterectomy following delivery
	CPT4: 1963	Anesthesia for cesarean hysterectomy w/o any labor analgesia/anesthesia care
	CPT4: 1967	Neuraxial labor analgesia/anesthesia, planned vaginal delivery
	CPT4: 1968	Anesthesia for cesarean delivery following neuraxial labor analgesia/anesthesia
	CPT4: 1969	Anesthesia for cesarean hysterectomy following neuraxial labor analgesia/anesthesia
	CPT4: 59409	Vaginal delivery only (w/wo episiotomy &/or forceps)
	CPT4: 59410	Vaginal delivery only (w/wo episiotomy &/or forceps); w/postpartum care
	CPT4: 59514	Cesarean delivery only
	CPT4: 59515	Cesarean delivery only; w/postpartum care
	CPT4: 59612	Vaginal delivery only, after previous cesarean delivery (with or without episiotomy and/or forceps)
	CPT4: 59614	Vaginal delivery only, previous cesarean delivery w/postpartum care
	CPT4: 59620	Cesarean delivery after failed vaginal delivery, previous cesarean delivery
	CPT4: 59622	Cesarean delivery after failed vaginal delivery, previous cesarean delivery; w/postpartum care
	ICD-9 Proc: 74.xx (exclude 74.3)	Cesarean section and removal of fetus
3. Unclassified end of pregnancy code	ICD-9 Proc: 72.x	Forceps, vacuum, & breech
4. Stillbirth	CPT4: 88016	Autopsy of stillborn infant
	ICD-9 Dx: 656.4x	Intrauterine Death
	ICD-9 Dx: V27.1	Single stillborn
5. Spontaneous abortion	ICD-9 Dx: 632.xx	Missed abortion
	ICD-9 Dx: 634.xx	Spontaneous Abortion
6. Termination	CPT4: 59840	Induced abortion by dilation and uterine scraping
	CPT4: 59841	Induced abortion by dilation and removal of contents
	CPT4: 59850	Induced abortion by amniotic fluid injections
	CPT4: 59851	Induced abortion by amniotic fluid injections
	CPT4: 59852	Induced abortion by amniotic fluid injections
	CPT4: 59855	Induced abortion by vaginal suppositories
	CPT4: 59856	Induced abortion by vaginal suppositories
	CPT4: 59857	Induced abortion by vaginal suppositories
	ICD-9 Proc: 69.01	Dilation and curettage for termination of pregnancy
	ICD-9 Proc: 69.51	Aspiration curettage of uterus for termination
	ICD-9 Proc: 74.91	Hysterectomy to terminate pregnancy
	ICD-9 Proc: 75.0x	Intra-amniotic injection for abortion

Table 10 Procedures to identify live and non-live pregnancy outcomes and corresponding gestational age

Outcome	Type of codes considered	Estimation of LMP	Hierarchy	Medicaid eligibility
1. Live birth	Inpatient codes	270 days before	• If stillbirth code during inpatient delivery, consider stillbirth • If >1 inpatient admission (either stillbirth or livebirth) separated by 140 days or less, consider only first admission • Assign date of delivery using the first recorded diagnosis or procedure code. If no such code, assign as start of inpatient admission	52 weeks (40 weeks pregnancy + 12 weeks baseline)
2. Unclassified delivery	Inpatient codes	270 days before		
3. Unclassified end of pregnancy	Inpatient codes	270 days before		
4. Stillbirth	Inpatient or outpatient codes	196 days before (i.e., 28 weeks)	Priority	40 weeks (28 weeks pregnancy + 12 weeks baseline)
5. Spontaneous abortion	≥ 2 outpatient codes within a 7-day window, or ≥ 1 inpatient code	63 days before (i.e., 9 weeks)	• If inpatient delivery or stillbirth within the time frame from LMP to LMP+270 (i.e., estimated LMP for spontaneous abortion), then ignore spontaneous abortion. • If termination within the window of spontaneous abortion ± 8 weeks, then ignore spontaneous abortion.	21 weeks (9 weeks pregnancy + 12 weeks baseline)
6. Termination	Inpatient or outpatient codes	63 days before	If inpatient delivery or stillbirth within the time window from LMP to LMP+270 (i.e., estimated LMP for termination), then ignore termination.	21 weeks (9 weeks pregnancy + 12 weeks baseline)

Stillbirths

For analyses involving the stillbirth outcome, we included both linked and non-linked livebirths, but removed spontaneous abortions and terminations since only pregnancies that survive 20 weeks are at risk of stillbirth. We restricted the cohort to women with a recorded diagnosis for any of the indications for duloxetine during the 3 months before the LMP.

The following exposure groups were defined:

- Unexposed: women who did not fill a prescription for duloxetine from 3 months before the LMP through 196 days after LMP
- Exposed 1: women who filled a prescription for duloxetine between LMP and LMP + 30 days
- Exposed 2: women who filled a prescription for duloxetine during (LMP + 30 to LMP + 120 days)
- Exposed 3: women who filled a prescription for duloxetine during (LMP + 120 to LMP + 196 days)
- Exposed 4: women who filled a prescription for duloxetine between LMP and LMP + 196 days.

Both absolute risks and crude and adjusted relative risks were estimated. Adjustment for potential confounding variables was conducted the same way as for the live birth outcomes, with the exception that covariates were measured during the 3 months before the LMP.

Spontaneous abortion

For analyses involving the spontaneous abortion outcome, we included both linked and non-linked livebirths, stillbirths and spontaneous abortions, but removed terminations. We restricted the cohort to women with a recorded diagnosis for any of the indications for duloxetine during the 3 months before the LMP.

The following exposure groups were defined:

- Unexposed: women who did not fill a prescription for duloxetine from 3 months before the LMP through 63 days after LMP
- Exposed 1: women who filled a prescription for duloxetine between LMP and LMP + 30 days
- Exposed 2: women who filled a prescription for duloxetine during (LMP + 30 to LMP + 63 days)
- Exposed 3: women who filled a prescription for duloxetine between LMP and LMP + 63 days.

Both absolute risks and crude and adjusted relative risks were estimated. Covariates for adjustment were measured during the 3 months before the LMP.

Post-hoc analyses

In post-hoc analyses, we compared the risk of non-live birth in duloxetine exposed women to the risk in women exposed to SSRIs. We also evaluated the known associations between diabetes and stillbirth, and between diabetes and spontaneous abortion, as a positive control analysis to help with the assessment of the potential role of outcome misclassification.

9.9.8 Amendments to the statistical analysis plan

In a few instances, we had to deviate from the pre-specified statistical analysis plan. These instances are explained below:

- **Outcome definition:** A correction was made to the definition of genital malformations, because urinary malformations had erroneously been included in the original definition

Table 11 Definition of genital malformations

Original definition:
752.xx-753.xx (do not count if only 752.42, 752.52) (in addition, do not count 752.5x if preterm)
Revised definition:
752.xx (do not count if only 752.42, 752.52) (in addition, do not count 752.5x if preterm)
752.6x (do not count if only 752.62-752.69)
752.5x if NOT preterm (do not count if only 752.52)

- **Probabilistic bias analysis:** Instead of adjusting for the continuous PS as originally planned, we applied the probabilistic bias analyses to a 1:1 PS matched cohort for computational efficiency reasons. The run time with adjustment for the continuous PS was multiple days. This would not be expected to impact on the conclusions derived from this analysis.

- **Re-estimating the relative risk after excluding certain outcomes based on the claims profile review:**
In contrast to what was stated in the protocol, we were not able to estimate the unadjusted RR since the claims profile review was done in matched cohorts. Only adjusted RR are therefore presented.
- **External adjustment of the RR:** Although we stratified women based on type of insurance in the descriptive tables from NHANES, we used percentages from the overall sample – rather than the Medicaid insured sub-sample – to inform the sensitivity analyses due to small numbers.

9.10 Quality Control

All aspects of data analysis were conducted according to standard procedures of the Division of Pharmacoepidemiology, Brigham and Women's hospital and those mentioned in the corresponding contract. Programming for this project was conducted by a primary analyst and validated by a separate analyst (validation analyst). For all data processing and analysis steps, the validation analyst reviewed the program along with input and output data sets, and for select steps of the project employed double programming techniques to reduce the potential for programming errors.

10 Results

10.1 Participants

We identified 8,410,882 pregnant women age 18 to 55 years from 46 US states and Washington, DC with completed pregnancies between Jul 2004 and Dec 2013. Within this cohort we applied maternal and infant eligibility criteria necessary for each outcome, which resulted in the four cohorts described below. [Table 12](#) shows the restrictions imposed in creating each of the four cohorts. The number of exposed and unexposed women varies within these cohorts based on the different definitions of exposure and reference groups for the contrasts of interests (described in [Table 1](#)). The number of duloxetine exposed women changes among comparisons because for the SSRI and venlafaxine comparisons, duloxetine users who also used SSRI and venlafaxine were excluded.

10.1.1 Study population for the major congenital malformations outcome (cohort I)

Cohort I was designed to evaluate major congenital malformations and included 1,287,359 pregnancies ([Table 12](#)). Among those, 2,532 women were identified as duloxetine-exposed and 1,284,827 as non-exposed to duloxetine during the etiologically relevant exposure window. 1,966 duloxetine-exposed women were identified for comparison with 52,018 SSRI-exposed women; 2,467 duloxetine-exposed women were identified for comparison with 6,369 venlafaxine-exposed women; and 2,532 duloxetine-exposed women were identified for comparison with 2,456 women exposed to duloxetine before, but not during pregnancy.

10.1.2 Study population for preterm and small for gestational age outcome (cohort II)

Cohort II was designed to evaluate the risk of preterm birth and small for gestational age and included 1,367,199 pregnancies ([Table 12](#)). Among those, 2,903 pregnant women with duloxetine dispensing between LMP to LMP+140 ("early exposure") were compared with a reference group of 1,364,247 unexposed women; and 880 women with duloxetine dispensing between LMP+141 to LMP+244 ("late exposure") were compared with 1,364,101 unexposed women. 1,989 duloxetine "early exposed" women were selected for comparison with 67,222 SSRI-exposed women, and 2,779 duloxetine "early exposed" women were selected for comparison with 7,258 venlafaxine exposed women. For "late exposure", 621 women in the duloxetine group were compared with 46,098 in the SSRI group, and 828 women in duloxetine group were compared with 2,770 in the venlafaxine group.

10.1.3 Study population for the preeclampsia outcome (cohort III)

Cohort III was designed to evaluate the risk of preeclampsia and included 1,450,755 pregnancies ([Table 12](#)). Among those, 3,059 women with duloxetine dispensing between LMP to LMP+140 ("early exposure") were compared with 1,447,644 unexposed; and 933 women with duloxetine dispensing between LMP+141 to LMP+244 ("late exposure") were compared with 1,447,493 unexposed. 2,104 duloxetine "early exposed" women were selected for comparison with 70,926 SSRI exposed women, and 2,927 duloxetine "early exposed" women were selected for comparison with 7,642 venlafaxine exposed women. For "late exposure", 662 women in the duloxetine group were compared with 48,672 in the SSRI group; and 879 women in the duloxetine group were compared with 2,943 in the venlafaxine group.

10.1.4 Study population for the postpartum haemorrhage outcome (cohort IV)

Cohort IV was designed to evaluate the risk of postpartum haemorrhage and included 4,135,000 pregnancies ([Table 12](#)). Among those, 955 women were identified as duloxetine-exposed and 4,128,460 as non-exposed to

duloxetine during the etiologically relevant exposure window. 869 duloxetine-exposed women were compared with 65,303 SSRI- exposed women, and 948 duloxetine-exposed women were compared to 3,573 venlafaxine-exposed women.

Table 12 Cohort selection

	Cohort I Malformations	Cohort II Preterm/SGA	Cohort III Preeclampsia	Cohort IV Postpartum Haemorrhage
Step	Counts			
Pregnancies 2004-2013	9,079,307			
Restrict to age ≥ 18 years	8,410,882			
Implement maternal eligibility criteria	1,452,823	1,452,823	1,452,823	4,135,740
Implement infant eligibility criteria	1,294,742	1,369,189	-	-
Exclude pregnancies with chromosomal abnormality	1,292,075	-	-	-
Exclude pregnancies with exposure to definite teratogen	1,289,296	-	-	-
Exclude pregnancies with duloxetine exposure before but not during etiologically relevant window	1,287,359	1,367,199	1,450,755	4,135,000
Exposed to duloxetine	2,532 (T1)	2,903 (early) 880 (late)	3,059 (early) 933 (late)	955 (month before delivery)

10.2 Descriptive data

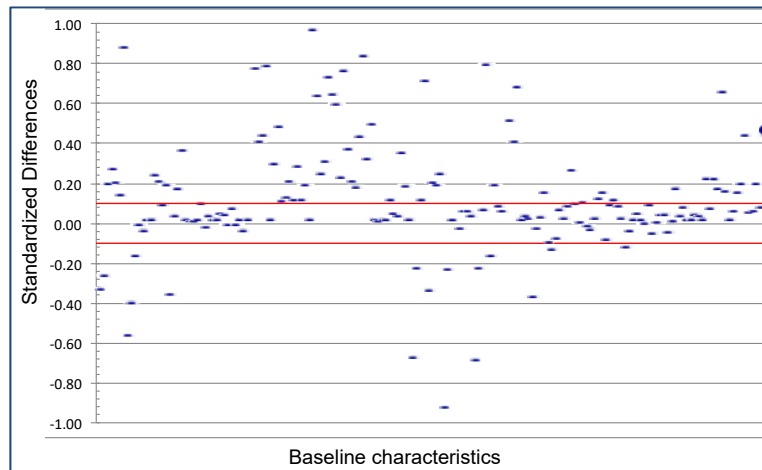
10.2.1 Cohort I: Major congenital malformations

Baseline characteristics before adjustment

Duloxetine versus unexposed:

Women taking duloxetine during the first trimester were slightly older (mean [SD] age, 27.7 [5.53] years) compared to unexposed women (24.9 [5.4] years) and they were more likely to be white. They had a higher burden of chronic comorbid conditions, including hypertension, diabetes, and overweight or obesity, and a higher mean maternal obstetric comorbidity index (1.58 for duloxetine exposed versus 0.92 for unexposed women). Women taking duloxetine more often had recorded diagnoses for duloxetine indications (depression, anxiety, fibromyalgia, neuropathic, and non-neuropathic pain) and other psychiatric conditions (sleep disorder, bipolar disorder, schizophrenia, and personality disorder). They were more likely to smoke and to have a recorded diagnosis of drug abuse or dependence. They also had a higher number of distinct diagnoses recorded. They more frequently used other medications including benzodiazepines, other hypnotics, barbiturates, anxiolytics, anticonvulsants, antipsychotics, other antidepressants, stimulants, antidiabetics, antihypertensives, NSAIDs, triptans, and opioids. They had a higher use of some potentially teratogenic medications, specifically corticosteroids and fluconazole. Duloxetine exposed women tended to use more healthcare than unexposed women, with a higher number of outpatient and psychiatric visits, as well as a higher number of emergency department visits and psychiatric hospitalizations. In summary, 41 out of 66 distinct covariates were imbalanced judged by an absolute standardized difference >0.1 (Figure 1, Table 15.1.1).

Figure 1 Standardized differences for baseline characteristics between duloxetine exposed and unexposed pregnancies before adjustment in Cohort I

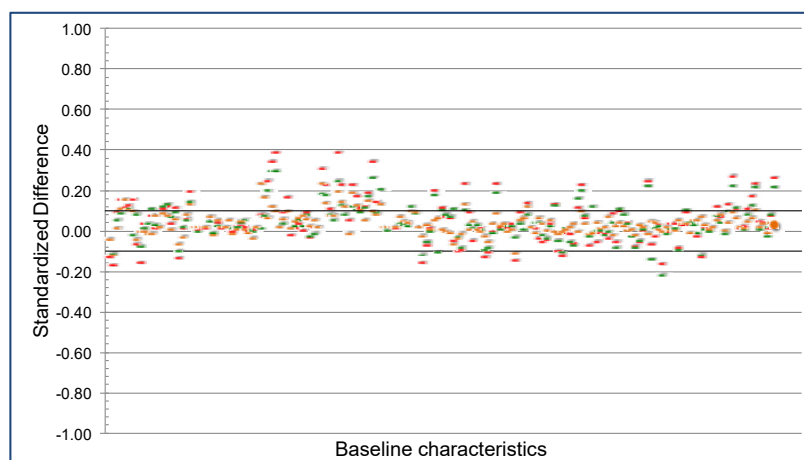


Note: There are more than 66 data point displayed in this figure because all levels of categorical variables are displayed

Duloxetine versus SSRI, venlafaxine, duloxetine discontinuers:

As expected, the baseline characteristics were better balanced when comparing duloxetine users with users of other antidepressants (SSRIs, venlafaxine) or with women who used duloxetine before but not during the first trimester. Only 21 out of 66 covariates were imbalanced, defined as a $SD > 0.1$, versus SSRI exposed women, 16 covariates were imbalanced versus venlafaxine exposed women, and 13 covariates were imbalanced versus duloxetine discontinuers. Duloxetine exposed women were slightly older than women exposed to SSRIs (26.2 [5.4] years), venlafaxine (26.8 [5.3] years) and duloxetine discontinuers (26.7 [5.3] years). Other imbalances centered mostly on the specific pain indications for duloxetine (e.g., fibromyalgia, neuropathic and non-neuropathic pain), other medication exposures, and some markers of healthcare use intensity (Figure 2, Table 15.1.2 through Table 15.1.4).

Figure 2 Standardized differences for baseline characteristics between duloxetine exposed and SSRI exposed (red dots), venlafaxine exposed (green dots) and duloxetine discontinuers (orange dots) during pregnancy before adjustment in Cohort I



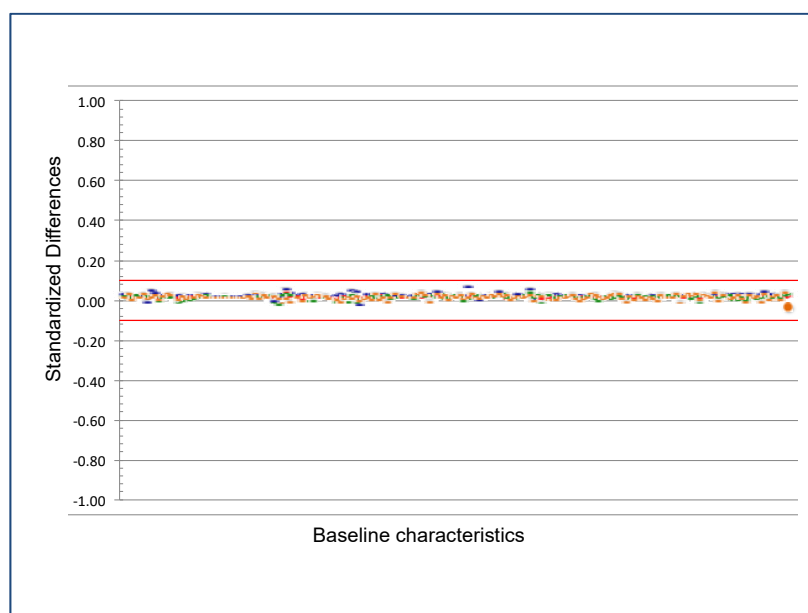
Note: There are more than 66 data point displayed in this figure because all levels of categorical variables are displayed

Baseline characteristics after adjustment

Restricting the cohort to women with a recorded diagnosis for at least one of the duloxetine indications and accounting for the specific indication through fine stratification on the PS (which includes the treatment indications) greatly reduced the imbalances for all contrasts. Accounting for all potential confounding variables through fine stratification on the PS (which includes all covariates) resulted in cohorts that were balanced in terms of all measured covariates, using the criterion of an absolute value of the standardized difference >0.1 . The only two exceptions were slight residual imbalances in the number of distinct generics filled other than duloxetine which were slightly higher among the SSRI (6.1 versus 5.6 among unexposed) and the venlafaxine (6.4 versus 5.8 among unexposed) group (Figure 3).

Please refer to Table 15.1.5 through Table 15.1.12 for the complete list of baseline characteristics after adjustment for all 4 exposure contrasts.

Figure 3 Standardized differences for baseline characteristics between duloxetine exposed and all comparison groups after adjustment in Cohort I. Dot color code as in Figure 1 and 2.



10.2.2 Cohorts II-IV: Preterm/SGA, preeclampsia, postpartum haemorrhage

The same general trends with respect to baseline characteristics are seen for the other cohorts, and are therefore not described in detail here. Across all analyses, after adjustment for all measured potential confounding variables through fine stratification on the PS, all characteristics are well balanced for all contrasts, as assessed based on an absolute standardized difference <0.1 .

Please refer to Table 15.2.1 through 15.2.18 for the complete list of baseline characteristics before and after adjustment for cohort II (Preterm/SGA), Table 15.3.1 through Table 15.3.18 for cohort III (Preeclampsia), and Table 15.4.1 through Table 15.4.9 for cohort IV (Postpartum haemorrhage).

10.3 Outcome data

10.3.1 Major congenital malformations

The risk of congenital malformations was 50.6 per 1,000 (95% CI, 42.3 – 59.8) in duloxetine users (128 events among 2,532 exposed women). For the reference groups, the risk was 36.6 per 1,000 (95% CI, 36.3 – 36.9) in non-users (47,001 events among 1,284,827 unexposed women); 42.1 per 1,000 (95% CI, 40.4 – 43.9) in SSRI users (2,192 events among 52,018 SSRI exposed women); 42.4 per 1,000 (95% CI, 37.6 – 47.6) in venlafaxine users (270 events among 6,369 venlafaxine exposed women); and 46.4 per 1,000 (95% CI, 38.4 – 55.5) in duloxetine discontinuers (114 events among 2,456 duloxetine discontinuers).

Cardiovascular malformations were the most common type of malformation, with a prevalence of 23.3 (95% CI, 17.8 – 30.0) per 1,000 among duloxetine users *versus* 13.7 (95% CI, 13.5 – 13.9) among unexposed women, 15.6 (95% CI, 14.5 – 16.7) per 1,000 among SSRI users, 15.1 (95% CI, 12.2 – 18.4) per 1,000 among venlafaxine users, and 17.5 (95% CI, 12.7 – 23.5) per 1,000 among duloxetine discontinuers. The prevalences of other types of malformations are provided in [Table 15.1.13](#).

It should be noted that the absolute risk for duloxetine exposed women for this and other outcomes differs slightly for the different contrasts because of different exclusions based on the definition of the reference group.

10.3.2 Preterm and small for gestational age

Preterm birth – early exposure: The risk of preterm birth was 143.6 per 1,000 (95% CI, 131.1 – 156.9) in women exposed to duloxetine early in pregnancy (417 events among 2,903 exposed women). For the reference groups, the risk was 107.8 per 1,000 (95% CI, 107.3 – 108.3) in non-users (147,034 events among 1,364,247 unexposed women); 134.1 per 1,000 (95% CI, 131.5 – 136.7) in SSRI exposed women (9,013 events among 67,222 SSRI exposed women); and 138.9 per 1,000 (95% CI, 131.0 – 147.1) in venlafaxine exposed women (1,008 events among 7,258 venlafaxine exposed women). ([Table 15.2.19](#))

Preterm birth – late exposure: The risk of preterm birth was 203.4 per 1,000 (95% CI, 177.3 – 231.5) in women exposed to duloxetine late in pregnancy (179 events among 880 exposed women). For the reference groups, the risk was 107.8 per 1,000 (95% CI, 107.2 – 108.3) in non-users (147,007 events among 1,364,101 unexposed women); 166.7 per 1,000 (95% CI, 163.3 – 170.1) in SSRI exposed women (7,685 events among 46,098 SSRI exposed women); and 201.8 per 1,000 (95% CI, 187.0 – 217.2) in venlafaxine exposed women (559 events among 2,770 venlafaxine exposed women). ([Table 15.2.20](#))

Small for gestational age (SGA) – early exposure: The risk of SGA was 29.6 per 1,000 (95% CI, 23.8 – 36.5) in women exposed to duloxetine early in pregnancy (86 events among 2,903 exposed women). For the reference groups, the risk was 20.4 per 1,000 (95% CI, 20.1 – 20.6) in non-users (27,767 events among 1,364,247 unexposed women); 25.2 per 1,000 (95% CI, 24.1 – 26.5) in SSRI exposed women (1,697 events among 67,222 SSRI exposed women); and 22.9 per 1,000 (95% CI, 19.6 – 26.6) in venlafaxine exposed women (166 events among 7,258 venlafaxine exposed women). ([Table 15.2.19](#))

SGA – late exposure: The risk of SGA was 33.0 per 1,000 (95% CI, 22.2 – 47.0) in women exposed to duloxetine late in pregnancy (29 events among 880 exposed women). For the reference groups, the risk was 20.4 per 1,000 (95% CI, 20.1 – 20.6) in non-users (27,762 events among 1,364,101 unexposed women); 25.8 per 1,000 (95% CI,

24.4 – 27.3) in SSRI exposed women (1,189 events among 46,098 SSRI exposed women); and 22.0 per 1,000 (95% CI, 16.9 – 28.2) in venlafaxine exposed women (61 events among 2,770 venlafaxine exposed women). ([Table 15.2.20](#))

10.3.3 Preeclampsia

Early exposure: The risk of preeclampsia was 55.9 per 1,000 (95% CI, 48.0 – 64.6) in women exposed to duloxetine early in pregnancy (171 events among 3,059 exposed women). For the reference groups, the risk was 33.6 per 1,000 (95% CI, 33.3 – 33.9) in non-users (48,599 events among 1,447,644 unexposed women); 35.8 per 1,000 (95% CI, 34.5 – 37.2) in SSRI exposed women (2,540 events among 70,926 SSRI exposed women); and 46.7 per 1,000 (95% CI, 42.1 – 51.7) in venlafaxine exposed women (357 events among 7,642 venlafaxine exposed women). ([Table 15.3.19](#))

Late exposure: The risk of preeclampsia was 62.2 per 1,000 (95% CI, 47.5 – 79.6) in women exposed to duloxetine late in pregnancy (58 events among 933 exposed women). For the reference groups, the risk was 33.6 per 1,000 (95% CI, 33.3 – 33.9) in non-users (48,593 events among 1,447,493 unexposed women); 37.7 per 1,000 (95% CI, 36.0 – 39.4) in SSRI exposed women (1,835 events among 48,672 SSRI exposed women); and 62.9 per 1,000 (95% CI, 54.4 – 72.2) in venlafaxine exposed women (185 events among 2,943 venlafaxine exposed women). ([Table 15.3.20](#))

10.3.4 Postpartum haemorrhage

The risk of postpartum haemorrhage was 35.6 per 1,000 (95% CI, 24.8 – 49.4) in women exposed to duloxetine (34 events among 955 exposed women). For the reference groups, the risk was 23.3 per 1,000 (95% CI, 23.1 – 23.4) in non-users (95,988 events among 4,128,460 unexposed women); 28.8 per 1,000 (95% CI, 27.5 – 30.1) in SSRI exposed women (1,879 events among 65,303 SSRI exposed women); and 37.8 per 1,000 (95% CI, 31.8 – 44.6) in venlafaxine exposed women (135 events among 3,573 venlafaxine exposed women). ([Table 15.4.10](#))

10.4 Main results

10.4.1 Major congenital malformations

Malformations overall

Compared to unexposed women, the risk of major congenital malformations overall was increased in unadjusted analyses with a relative risk (RR) of 1.38 (95% CI, 1.17 – 1.64). The RR attenuated with increasing levels of adjustment: 1.23 (1.03 – 1.47) after restricting to and adjusting for treatment indication; 1.11 (0.93 – 1.33) after adjustment for all possible confounding variables (i.e., full adjustment); and 1.08 (0.91 – 1.30) with hdPS adjustment. ([Table 15.1.14](#))

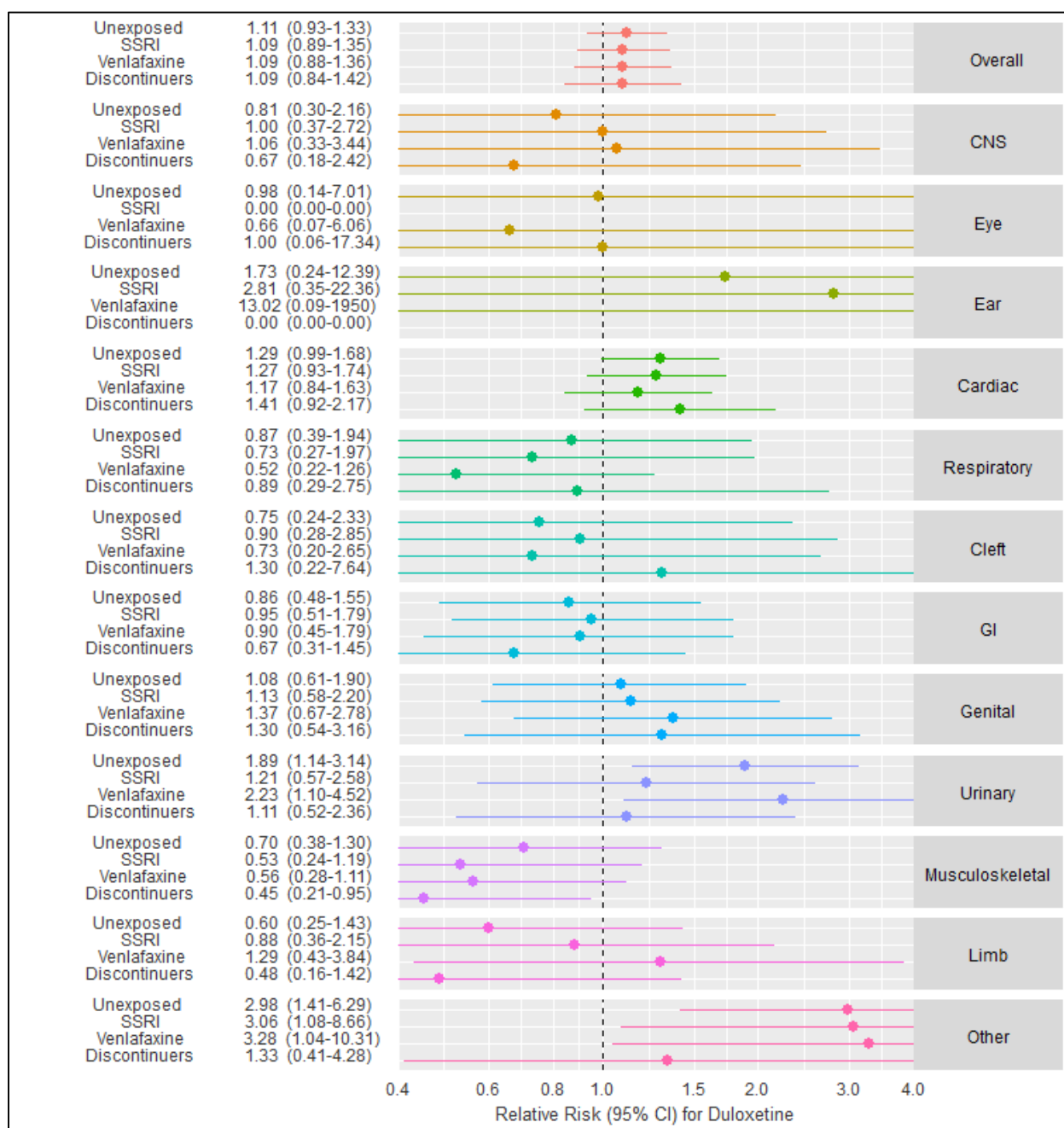
A similar attenuation of the RR was observed for some of the other reference groups: from an unadjusted RR of 1.20 (0.98 – 1.45) to a fully adjusted RR of 1.09 (0.89 – 1.35) versus SSRIs; and from an unadjusted RR of 1.21 (0.99 – 1.49) to a fully adjusted RR of 1.09 (0.88 – 1.36) versus venlafaxine. Adjustment did not affect the RR versus

duloxetine discontinuers, with an unadjusted RR of 1.09 (0.85 – 1.39) and a fully adjusted RR of 1.09 (0.84 – 1.42). (Table 15.1.15 through Table 15.1.17; Figure 4)

Results from sensitivity analyses were consistent with those from the main analyses given the width of the CIs in these analyses (Table 15.1.18 through Table 15.1.26; Figure 16.1.2; Figure 16.1.3; Figure 16.1.6; Figure 16.1.8; Figure 16.1.10).

These findings are consistent with no increased risk of major congenital malformations overall.

Figure 4 Risk of congenital malformations associated with first trimester exposure to duloxetine: fully adjusted analyses



Cardiovascular malformations

Compared to unexposed women, the risk of cardiovascular malformations was increased in unadjusted analyses with a RR of 1.70 (95% CI, 1.32 – 2.19). The RR attenuated with increasing levels of adjustment: 1.53 (1.17 – 2.00) after restricting to and adjusting for treatment indication; 1.29 (0.99 – 1.68) after full adjustment; and 1.26 (0.96 – 1.65) with hdPS adjustment. ([Table 15.1.14](#))

When compared to SSRI exposed women, the RR was 1.50 (1.12 – 2.02) in unadjusted analyses and 1.27 (0.93 – 1.74) in fully adjusted analyses. When compared to venlafaxine exposed women, the RR was 1.56 (1.13 – 2.15) in unadjusted analyses and 1.17 (0.84 – 1.63) in fully adjusted analyses. When compared to duloxetine discontinuers, the RR was 1.33 (0.90 – 1.96) in unadjusted analyses and 1.41 (0.92 – 2.17) in fully adjusted analyses. ([Table 15.1.15](#) through [Table 15.1.17](#))

A range of sensitivity analyses were conducted to assess the robustness of this finding. Accounting for the width of the CIs, these analyses yielded very similar estimates to those from the primary analysis. These analyses included (SA#1) re-defining exposure based on two dispensings during the first trimester, (SA#2) re-defining exposure based on days supply overlapping the first trimester, (SA#3) restricting to women with a diagnosis of fibromyalgia, (SA#4) generating corrected RRs for outcome misclassification using sensitivities and specificities consistent with the PPV estimated in chart based validation, (SA#5) re-estimating RR based on blinded profile reviews, (SA#6) restricting to the first pregnancy for each woman in the cohort, (SA#8) redefining the outcome based on infant claims only, (SA#9) redefining the outcome based on inpatient claims only, and (SA#10) requiring 1 year of follow-up for all infants.

When exposure was re-defined based on two dispensings of duloxetine during the first trimester (which is performed to reduce the potential for exposure misclassification due to incomplete adherence), the risk estimates strengthened compared with those in the primary analysis when the referent groups were unexposed, SSRI exposed, or duloxetine discontinuers. The fully adjusted estimates from this analysis were as follows: compared to the unexposed (RR 1.71, 95% CI 1.21-2.41), SSRI (RR 1.69, 95% CI 1.11-2.56), venlafaxine (RR 1.38, 95% CI 0.90-2.11), and discontinuers (RR 2.10, 95% CI 1.14-3.85). Other sensitivity analyses in which exposure or outcome were re-defined, as well as the analysis restricted to the first pregnancy for each woman in the cohort, yielded similar results to those from the main analysis, accounting for the width of the CI. Likewise, when outcomes were readjudicated based on claims profile reviews, the point estimates for cardiac malformation shifted just slightly towards the null compared to the 1:1 PS matched results (the RR including only those outcomes adjudicated as “likely occurred” was 1.16 (0.84 to 1.60) and for those adjudicated as “likely or probably occurred” was 1.19 (0.87 to 1.63). When the analysis was restricted to women with a diagnosis of fibromyalgia, the estimates were not informative given the very wide CIs. ([Table 15.1.18](#) through [Table 15.1.26](#); [Figure 5](#); [Figure 6](#))

External adjustment of RR estimates was performed based on the observed prevalence of unmeasured confounders (obesity, smoking and alcohol use) in women of reproductive age using duloxetine, SSRIs, or venlafaxine who were included in the NHANES survey (Appendix 1). Across a range of plausible confounder-outcome associations, the risk estimates from the primary analysis did not shift substantially. ([Figure 16.1.7](#))

Likewise, using the “rule out” approach described in Appendix 2, we found that for an unmeasured confounder to fully explain the observed increase in cardiovascular malformations associated with duloxetine, it would have to be a very strong risk factor for the outcome and be much more prevalent in the exposed, suggesting that this is an unlikely explanation for the observed association. ([Figure 16.1.9](#))

When we assessed the potential impact of restricting the analysis to only livebirths (Appendix 3), even under the most extreme scenarios considered (e.g., 50% probability of livebirth for foetuses with cardiovascular malformations in the reference group; 20% higher probability of livebirth among foetuses with cardiovascular malformations in the exposed group) the corrected risk estimate remained above the null. (Figure 16.1.11)

Overall, we observed a null association between duloxetine and major congenital malformations. However, findings are consistent with a small increased risk of cardiovascular malformations associated with duloxetine use early in pregnancy. Although the observed data is still compatible with the null for cardiac malformations, particularly in the primary analysis, the conclusion is based on the modest but consistently elevated point estimate across analyses. On the other hand, the upper bound of the 95%CI for cardiac malformation remained below 2-fold, thus ruling out a substantial increase in the risk.

Figure 5 Risk of cardiac malformations associated with first trimester exposure to duloxetine: sensitivity analyses

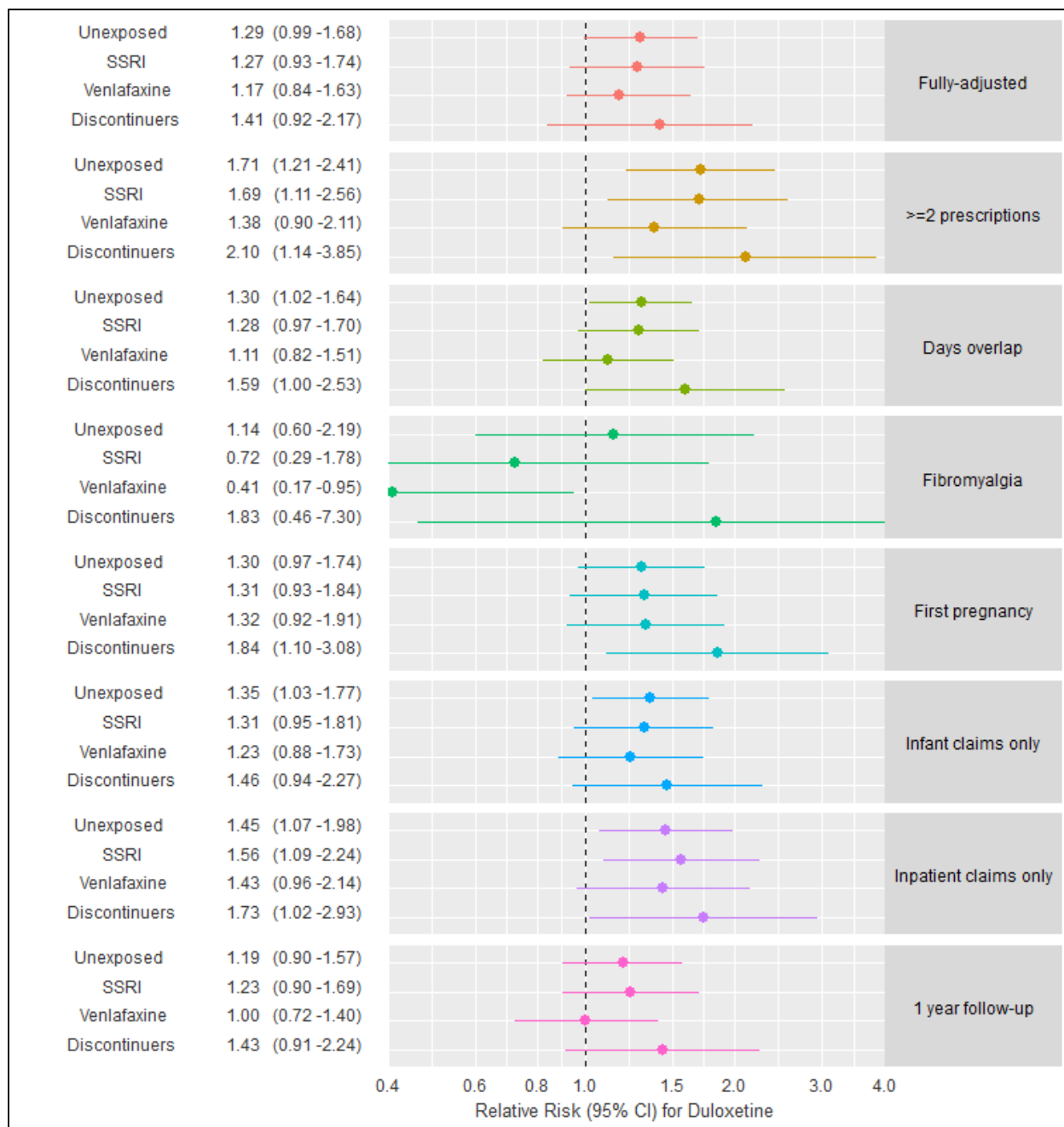
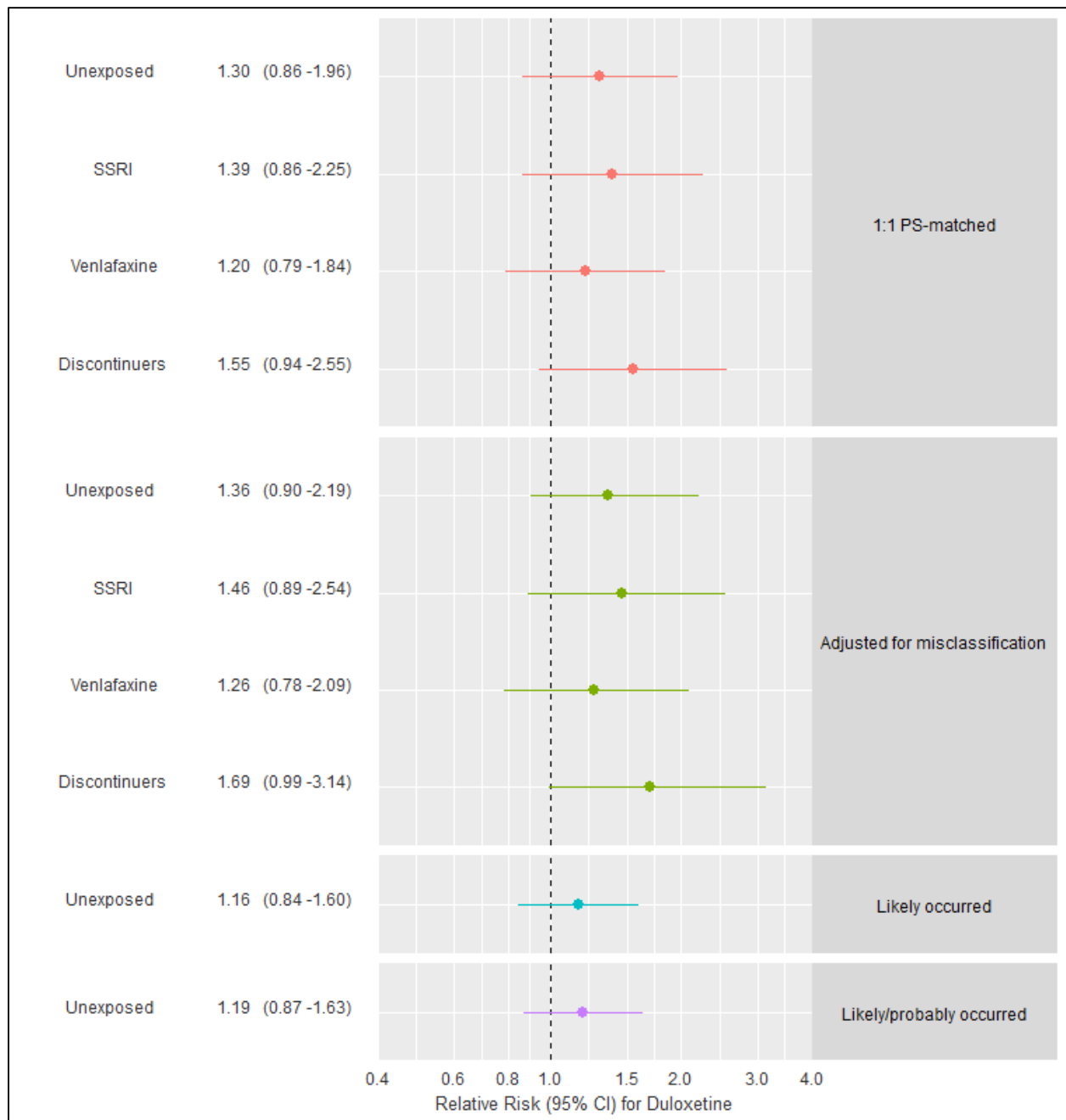


Figure 6 Risk of cardiac malformations associated with first trimester exposure to duloxetine: sensitivity analyses to address outcome misclassification



Note: Results from the probabilistic bias analysis based on the outcome validation study and the profile review should be compared against matched analyses.

Other types of malformations

While results were consistent with a null finding for most malformation types, two subtypes warrant further discussion: urinary malformations and other malformations (i.e., a heterogeneous group of malformations other than

the main categories). For urinary malformations, the fully adjusted RR was 1.89 (1.14 – 3.14) versus unexposed women, 1.21 (0.57 – 2.58) versus SSRI exposed women, 2.23 (1.10 – 4.52) versus venlafaxine exposed women, and 1.11 (0.52 – 2.36) versus duloxetine discontinuers. For other malformations, the fully adjusted RR was 2.98 (1.41 – 6.29) versus unexposed women, 3.06 (1.08 – 8.66) versus SSRI exposed women, 3.28 (1.04 – 10.31) versus venlafaxine exposed women, and 1.33 (0.41 – 4.28) versus duloxetine discontinuers. For both malformation types, the number of exposed events is small: 15 or less for urinary malformations and <11 for other malformations. Inspection of the distribution of specific ICD-9 diagnostic codes among exposed and unexposed cases did not identify a clear specific malformation subtype with increased risk. These findings may be due to random error (i.e., chance), rather than a true causal association. (Figure 4; Table 15.1.14 through Table 15.1.17) However, it is notable that in the study by Einarson, 2 of the 165 pregnancies exposed to duloxetine had urinary malformations⁹³ and in the Quebec Pregnancy Cohort venlafaxine exposure was associated with a relative risk of 1.43 (95% CI, 0.75 to 2.73) for urinary malformations.⁷² Thus, future studies should further explore the association between duloxetine exposure and urinary malformations.

10.4.2 Preterm and small for gestational age

Preterm birth – early exposure: Compared to unexposed women, the risk of preterm birth for women with exposure to duloxetine early in pregnancy was increased in unadjusted analyses with a RR of 1.33 (95% CI, 1.22 – 1.46). The RR attenuated with increasing levels of adjustment: 1.11 (1.01 – 1.22) after restricting to and adjusting for treatment indication; 1.01 (0.92 – 1.10) after full adjustment; and 0.99 (0.90 – 1.09) with hdPS adjustment. Compared to SSRI exposed women, the fully adjusted RR was 0.95 (0.84 – 1.06). Compared to venlafaxine exposed women, the fully adjusted RR was 0.94 (0.84 – 1.06).

Preterm birth – late exposure: A similar pattern was seen for late exposure although the associations tended to be stronger. Compared to unexposed women, the risk of preterm birth was 1.89 (1.66 – 2.15) in unadjusted analyses, 1.44 (1.25 – 1.66) after restricting to and adjusting for treatment indication; 1.19 (1.04 – 1.37) after full adjustment; and 1.13 (0.98 – 1.31) with hdPS adjustment. Compared to SSRI exposed women, the fully adjusted RR was 1.02 (0.87 – 1.21). Compared to venlafaxine exposed women, the fully adjusted RR was 0.88 (0.75 – 1.04).

These results are consistent with no increased risk of preterm birth for either early or late pregnancy exposure. (Table 15.2.21 through Table 15.2.23, Figure 7).

Sensitivity analyses were generally consistent with the primary analyses and support this finding. (Table 15.2.24 through 15.2.29; Figures 16.2.2; Figure 16.2.3; Figure 16.2.6; Figure 16.2.7; Figure 16.2.10; Figure 16.2.11).

SGA – early exposure: Compared to unexposed women, the risk of SGA for women with exposure to duloxetine early in pregnancy was increased in unadjusted analyses with a RR of 1.46 (95% CI, 1.18 – 1.79). The RR attenuated with increasing levels of adjustment: 1.26 (1.01 – 1.56) after restricting to and adjusting for treatment indication; 1.14 (0.92 – 1.41) after full adjustment; and 1.10 (0.89 – 1.37) with hdPS adjustment. Compared to SSRI exposed women, the fully adjusted RR was 1.26 (0.97 – 1.64). Compared to venlafaxine exposed women, the fully adjusted RR was 1.18 (0.90 – 1.56). (Table 15.2.21 through 15.2.23; Figure 7)

SGA – late exposure: A similar pattern was seen for late exposure. Compared to unexposed women, the risk of SGA was 1.62 (1.13 – 2.32) in unadjusted analyses, 1.40 (0.97 – 2.01) after restricting to and adjusting for treatment indication; 1.20 (0.83 – 1.72) after full adjustment; and 1.12 (0.78 – 1.61) with hdPS adjustment. Compared to SSRI

exposed women, the fully adjusted RR was 1.17 (0.73 – 1.88). Compared to venlafaxine exposed women, the fully adjusted RR was 1.32 (0.83 – 2.09). (Table 15.2.21 through 15.2.23; Figure 7)

Across the sensitivity analyses conducted for both early and late exposure, including redefining exposure based on two dispensings during the exposure window and based on days' supply overlapping the exposure window, and restricting to the first pregnancy for women in the cohort, point estimates suggested a small increase but with CIs that generally intersect the null. Estimates when restricting to women with a diagnosis of fibromyalgia were again uninformative in the setting of very wide CIs. Note, for both early and late exposure the risk estimates for SGA in the 1:1 PS matched analysis with an unexposed referent were close to the null, but with relatively wide CIs. The results from the probabilistic bias analysis accounting for misclassification and the estimates for the claims based adjudication need to be considered in comparison to the 1:1 PS matched analysis upon which they are based. Indeed, the point estimates from these sensitivity analyses do not shift substantially from the base 1:1 PS matched estimate, but remain close to the null. (Table 15.2.24 through 15.2.29; Figure 8; Figure 9; Figure 10; Figure 11)

External adjustment for differences in the prevalence of obesity, smoking, and alcohol use in the exposure and reference groups did not substantially shift the risk estimates from the main analysis across a wide range of modelled confounder-outcomes associations. (Figure 16.2.10)

The “rule-out” analysis also suggested that for an unmeasured confounder to explain the observed association it would have to have a strong association with the outcome, be common, and be very imbalanced between the exposed and reference groups (within levels of measured covariates). (Figure 16.2.11)

These results, in aggregate, suggest a potentially small increased risk of SGA for early and late pregnancy exposure, although it should be noted that the data are also consistent with no-association (confidence intervals include the null) in the primary analyses, and the increased risk was not seen consistently across all sensitivity analyses (i.e., no increased risk was observed in the 1:1 PS matched analysis, with and without correction for possible outcome misclassification).

Figure 7 Risk of preterm birth and small for gestational age associated with early and late pregnancy exposure to duloxetine: fully adjusted analyses

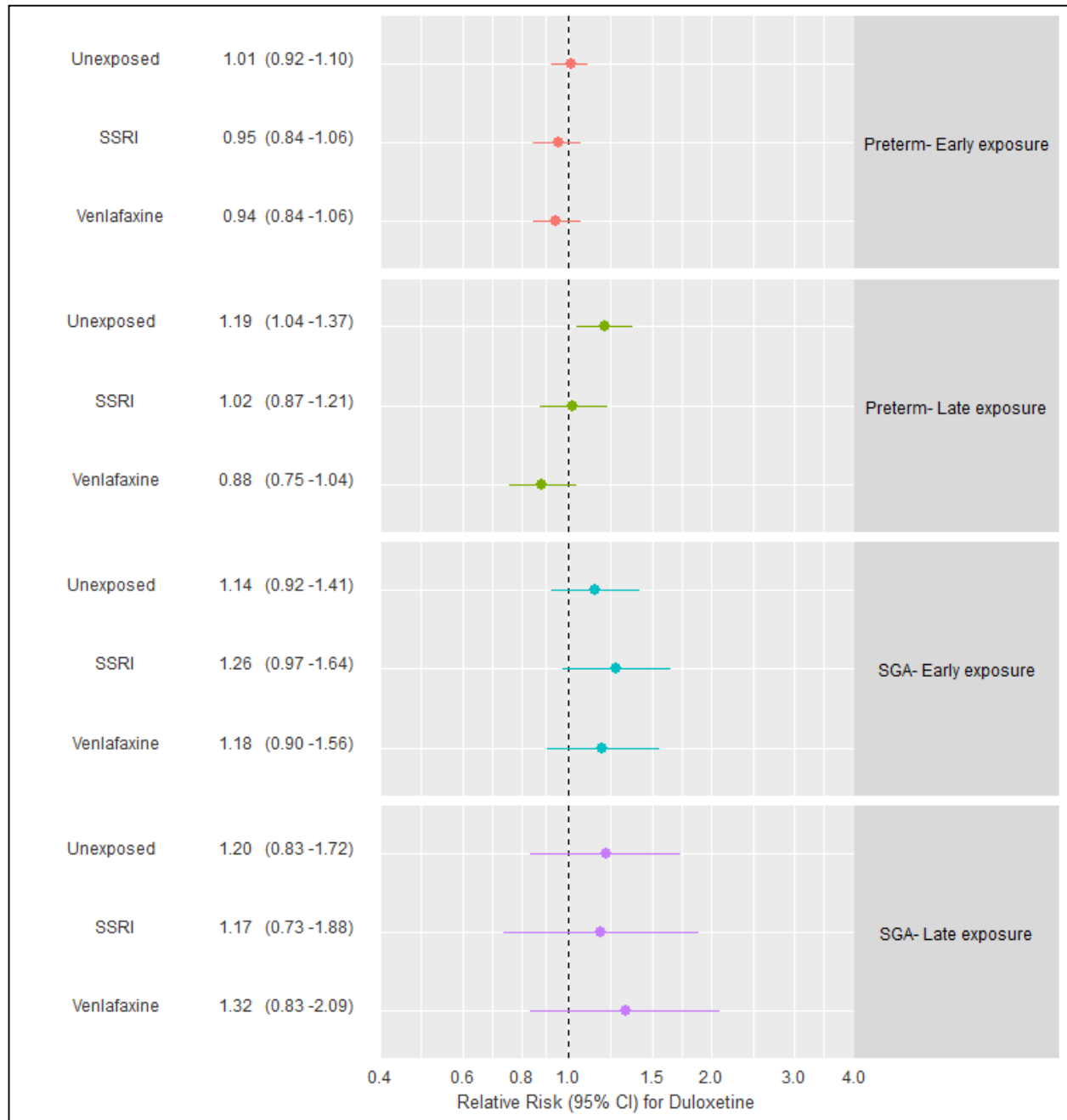


Figure 8 Risk of small for gestational age associated with early pregnancy exposure to duloxetine: sensitivity analyses

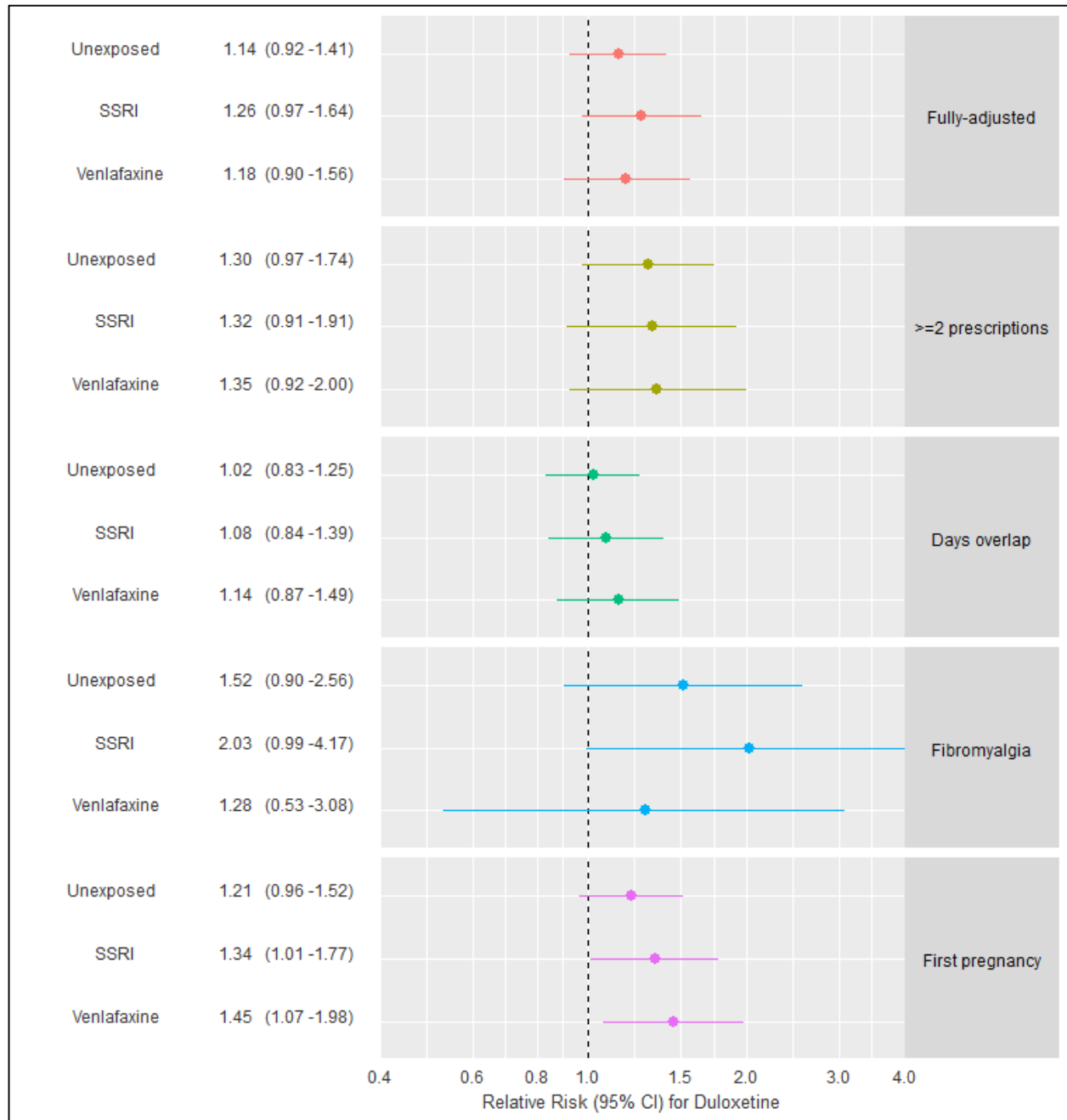
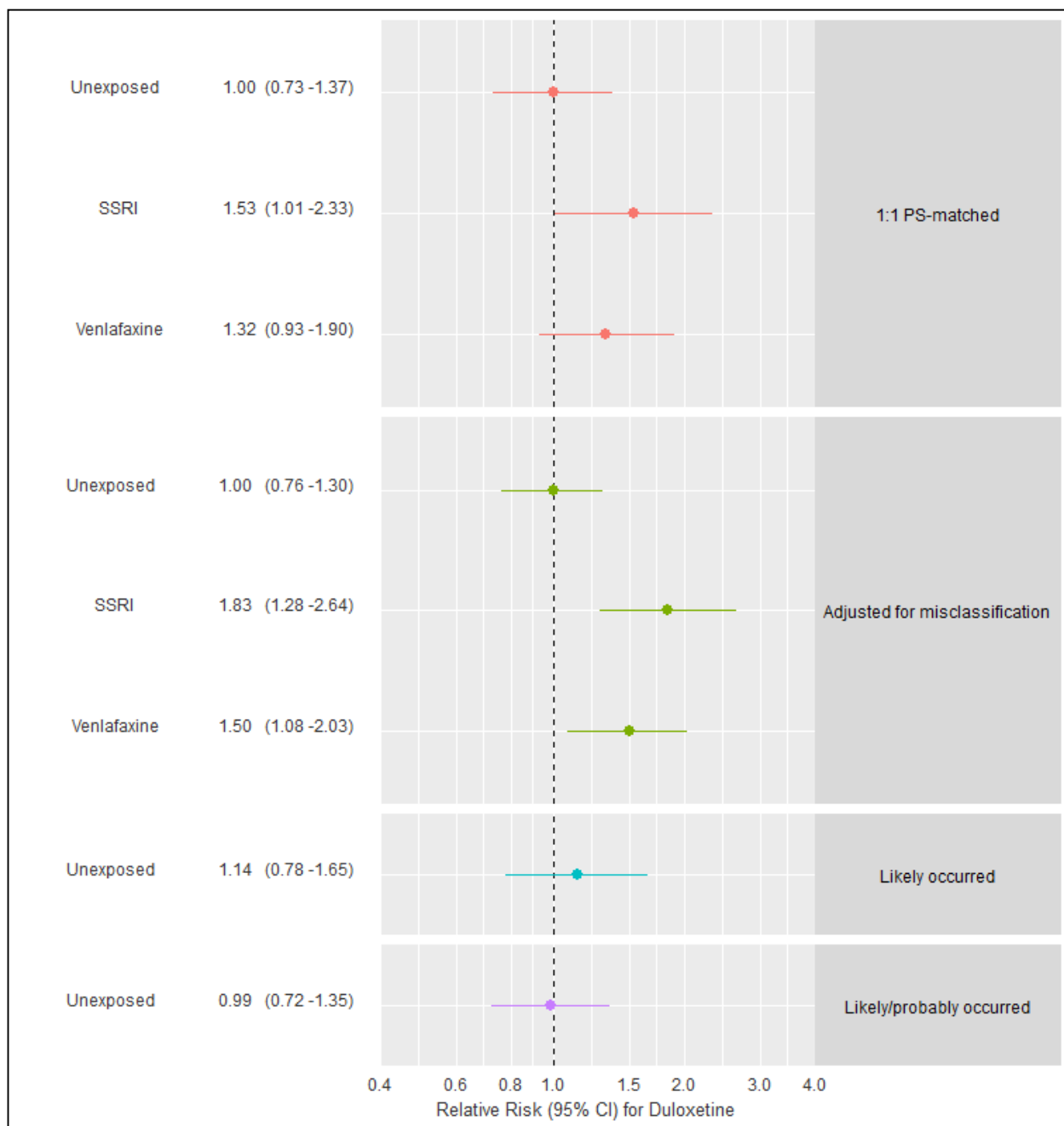


Figure 9 Risk of small for gestational age associated with early pregnancy exposure to duloxetine: sensitivity analyses to address outcome misclassification



Note: Results from the probabilistic bias analysis based on the outcome validation study and the profile review should be compared against matched analyses.

Figure 10 Risk of small for gestational age associated with late pregnancy exposure to duloxetine: sensitivity analyses

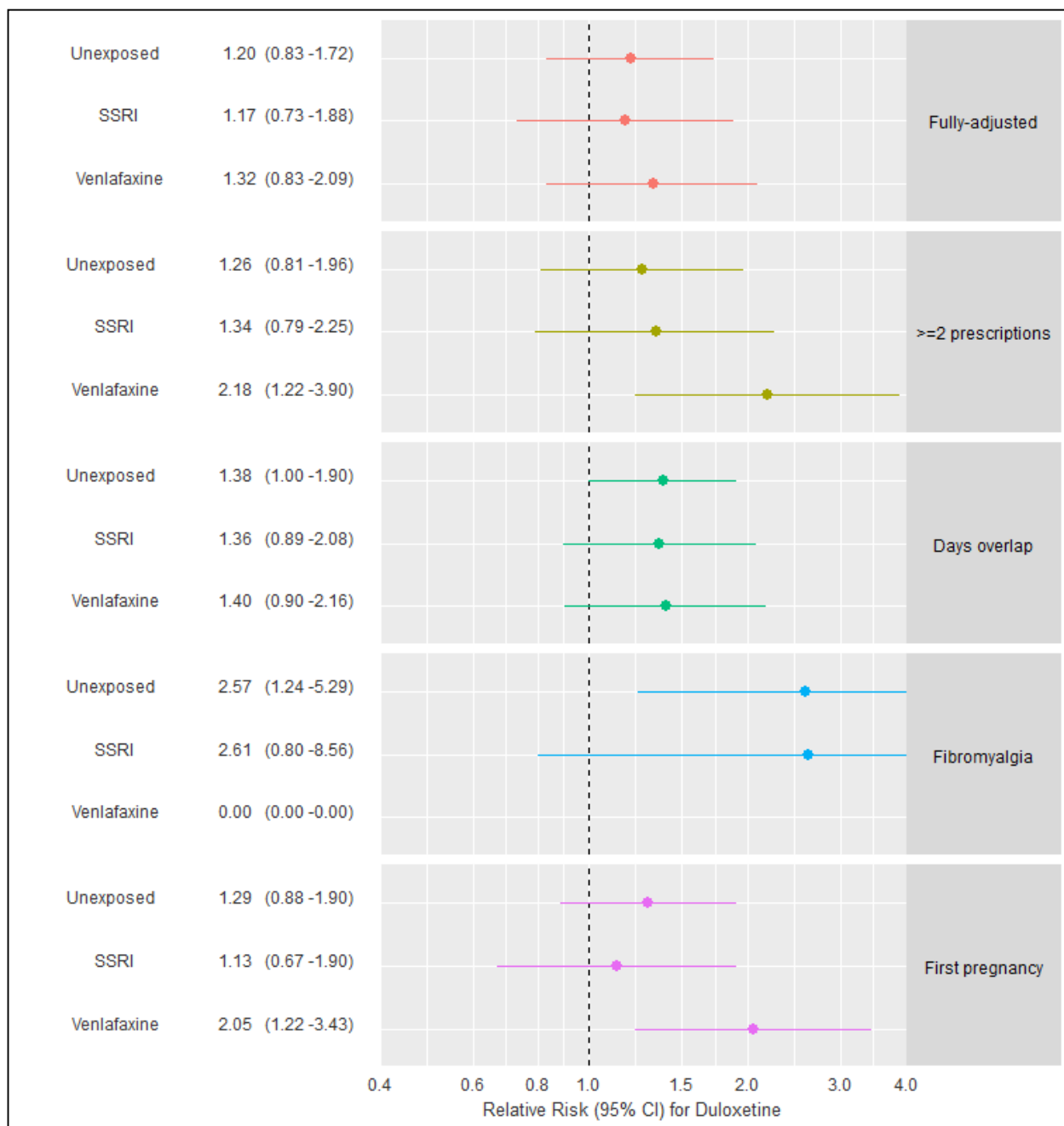
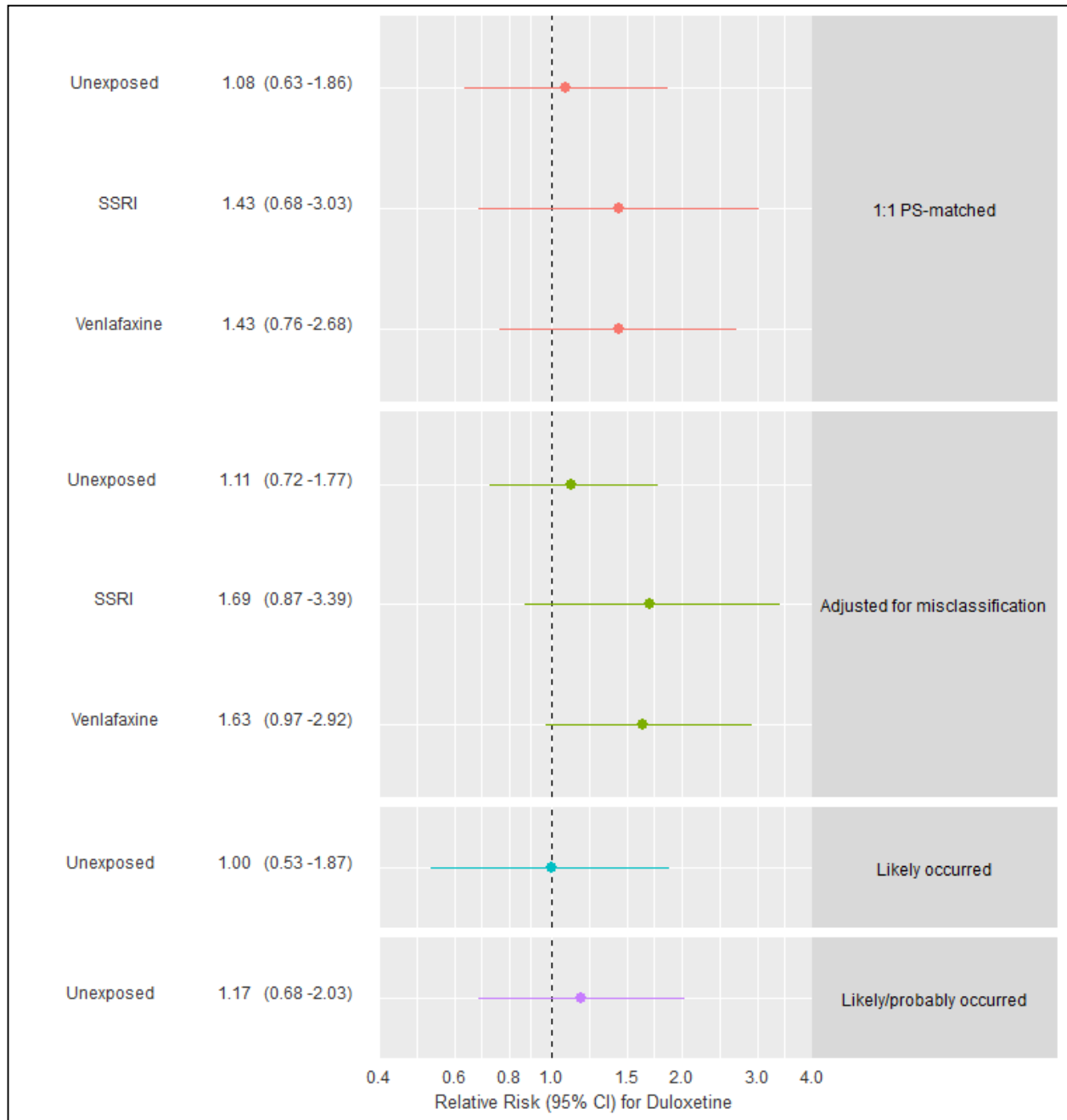


Figure 11 Risk of small for gestational age associated with late pregnancy exposure to duloxetine: sensitivity analyses to address outcome misclassification



Note: Results from the probabilistic bias analysis based on the outcome validation study and the profile review should be compared against matched analyses.

10.4.3 Preeclampsia

Early exposure: Compared to unexposed women, the risk of preeclampsia for women with exposure to duloxetine early in pregnancy was increased in unadjusted analyses with a RR of 1.67 (95% CI, 1.44 – 1.93). The RR attenuated with increasing levels of adjustment: 1.46 (1.25 – 1.70) after restricting to and adjusting for treatment

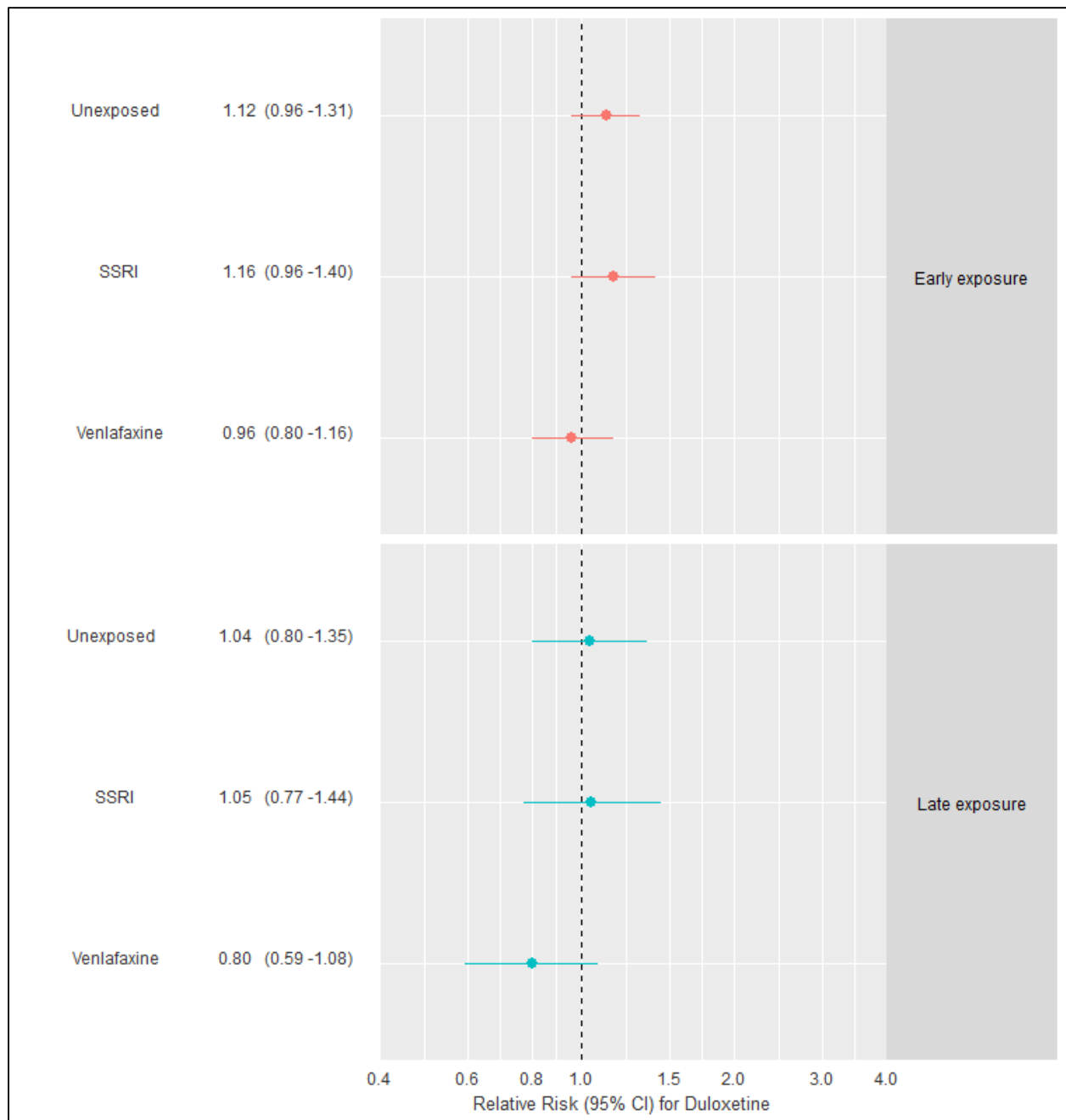
indication; 1.12 (0.96 – 1.31) after full adjustment; and 1.12 (0.96 – 1.31) with hdPS adjustment. Compared to SSRI exposed women, the fully adjusted RR was 1.16 (0.96 – 1.40). Compared to venlafaxine exposed women, the fully adjusted RR was 0.96 (0.80 – 1.16).

Late exposure: A similar pattern was seen for late exposure. Compared to unexposed women, the risk of preeclampsia was 1.85 (1.44 – 2.38) in unadjusted analyses, 1.64 (1.26 – 2.13) after restricting to and adjusting for treatment indication; 1.04 (0.80 – 1.35) after full adjustment; and 1.02 (0.78 – 1.33) with hdPS adjustment. Compared to SSRI exposed women, the fully adjusted RR was 1.05 (0.77 – 1.44). Compared to venlafaxine exposed women, the fully adjusted RR was 0.80 (0.59 – 1.08).

These results are consistent with no increased risk of preeclampsia for either early or late pregnancy exposure. (Table 15.3.21 through Table 15.3.23; Figure 12)

Sensitivity analyses were generally constant with these findings, although when exposure was redefined based on 2 dispensings during the early exposure window, duloxetine exposure was associated with a small increase in the risk for preeclampsia compared to that in unexposed or SSRI exposed women (but not venlafaxine exposed women). (Table 15.3.24 through Table 15.3.29; Figure 16.3.2 through Figure 16.3.7)

Figure 12 Risk of preeclampsia associated with early and late pregnancy exposure to duloxetine: fully adjusted analyses



10.4.4 Postpartum haemorrhage

When compared to unexposed women, the risk of post partum haemorrhage was increased in unadjusted analyses with a RR of 1.53 (1.10 – 2.13). The strength of the association did not change much with increasing levels of adjustment: 1.55 (1.09 – 2.20) after restricting to and adjusting for treatment indication; 1.53 (1.08 – 2.18) after full adjustment; and 1.48 (1.04 – 2.10) with hdPS adjustment. (Table 15.4.11; Figure 13).

An increased risk of postpartum haemorrhage was also observed compared to SSRI exposed women: 1.32 (0.94 – 1.85) in unadjusted analyses, 1.42 (0.99 – 2.03) after restricting to and adjusting for treatment indication; 1.48 (1.03 – 2.12) after full adjustment; and 1.31 (0.91 – 1.87) with hdPS adjustment. (Table 15.4.12; Figure 13)

In contrast, no increased risk of postpartum haemorrhage was observed compared to venlafaxine exposed women: 0.95 (0.66 – 1.37) in unadjusted analyses, 1.11 (0.74 – 1.66) after restricting to and adjusting for treatment indication; 1.04 (0.69 – 1.56) after full adjustment; and 0.98 (0.65 – 1.47) with hdPS adjustment. (Table 15.4.13; Figure 13)

Sensitivity analyses including redefining exposure based on days supply overlapping the exposure window (SA#2), dispensed medication <14 days prior to delivery (SA#12), days supply overlapping delivery (SA#13), and restricting to the first pregnancy for women in the cohort (SA#6), all had results consistent with those of the main analyses (increased risk when the referent was unexposed women or SSRI exposed women). (Table 15.4.15; Table 15.4.19 through Table 15.4.21; Figure 14)

The sensitivity analysis in which exposure was based on 2 dispensings (SA#1) and that in which the cohort was restricted to women with fibromyalgia (SA#3) were uninformative in the setting of very wide CIs. (Table 15.4.14; Table 15.4.16; Figure 14)

The results from the probabilistic bias analysis accounting for misclassification and the estimates for the claims based adjudication need to be considered in comparison to the 1:1 PS matched analysis upon which they are based. The point estimates from these sensitivity analyses do not shift substantially from the base 1:1 PS matched estimate. (Table 15.4.17; Table 15.4.18; Figure 15)

As with the other examples evaluated in this study, external adjustment for alcohol use, smoking, and obesity did not substantially alter the estimates from the main analysis. (Figure 16.4.4)

Likewise, the “rule out” analysis suggests that for the findings to be explained by an unmeasured confounder, it would have to be highly prevalent, imbalanced between the exposed and relevant referent group (unexposed or SSRI exposed) within levels of the covariates adjusted for in the main analyses, and have a very strong association with the outcome. (Figure 16.4.5)

These results, taken together, suggest an increased risk of postpartum haemorrhage, which appears to be an SNRI class effect.

Figure 13 Risk of postpartum haemorrhage associated with exposure to duloxetine during the final 30 days of pregnancy: fully adjusted analyses

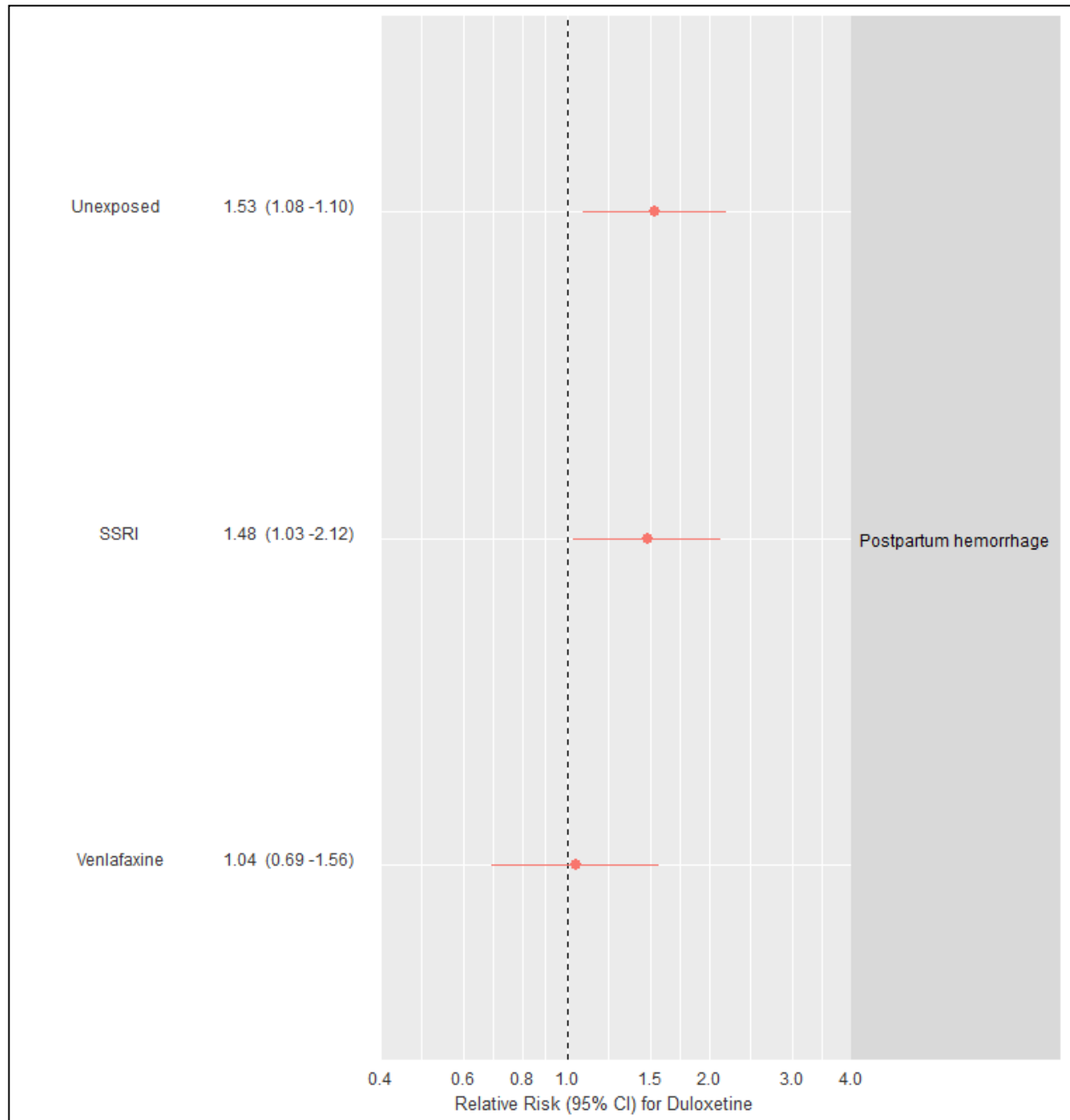


Figure 14 Risk of postpartum haemorrhage associated with exposure to duloxetine during the final 30 days of pregnancy: sensitivity analyses

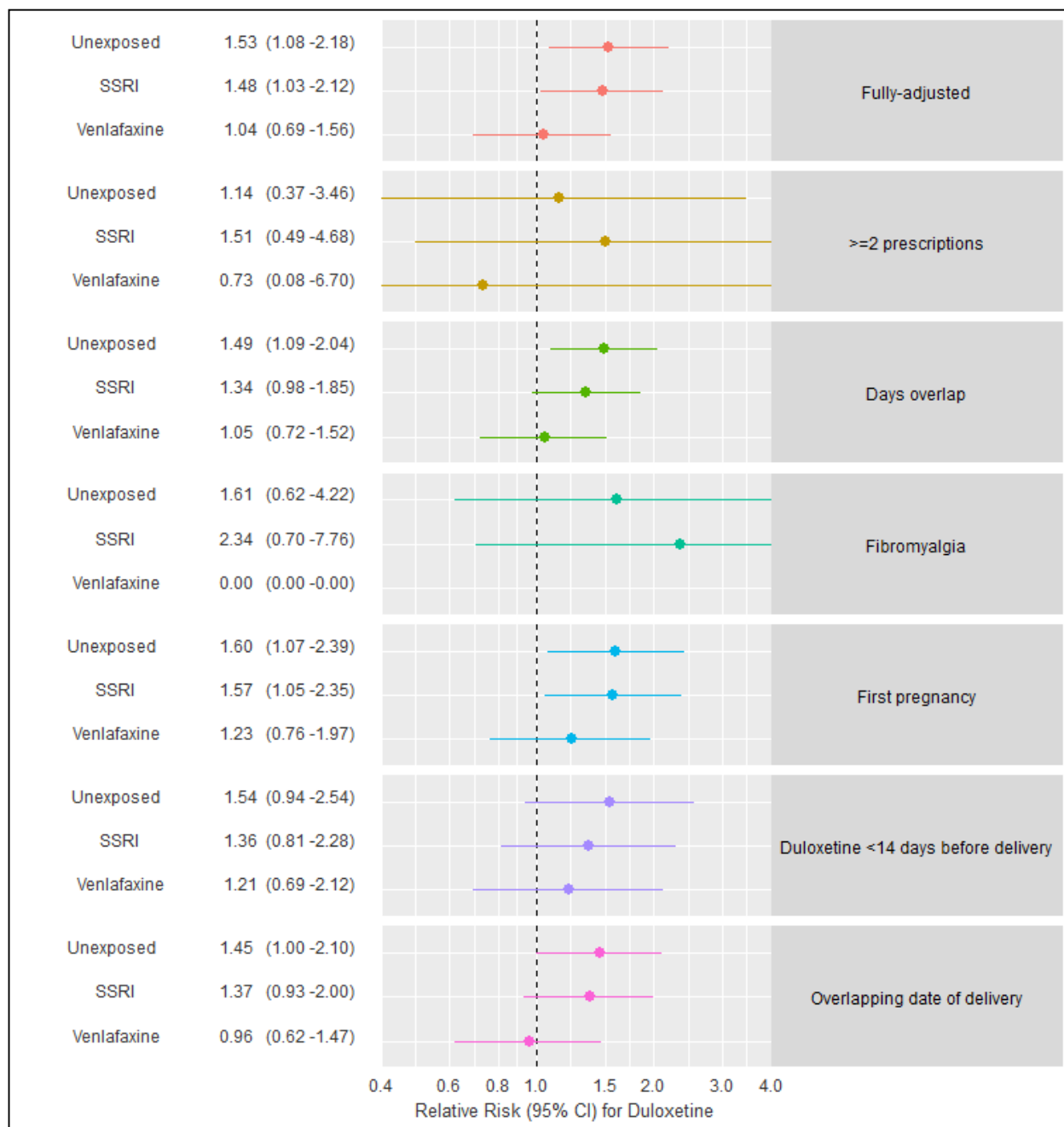
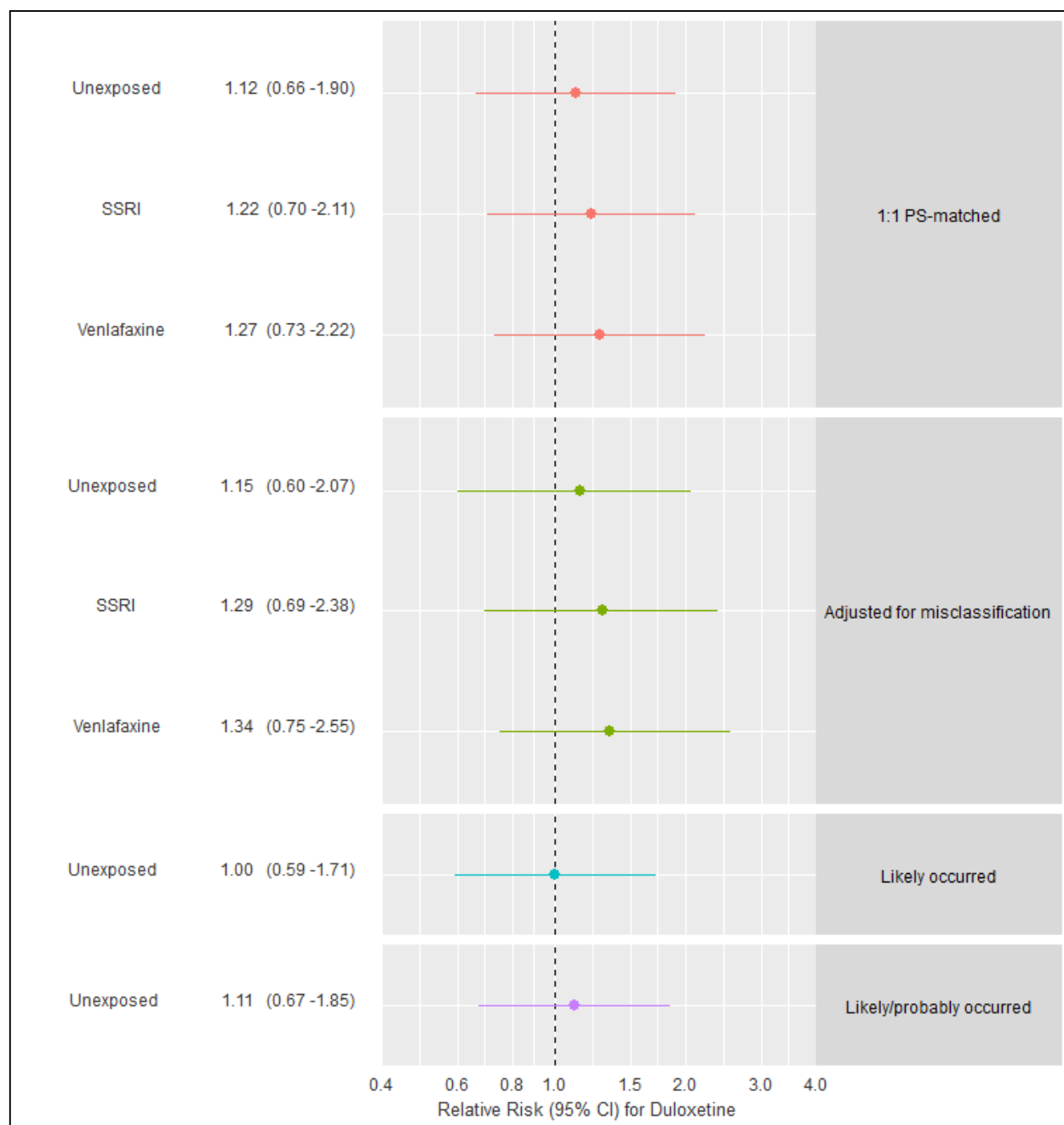


Figure 15 Risk of postpartum haemorrhage associated with exposure to duloxetine during the final 30 days of pregnancy: sensitivity analyses to address outcome misclassification



Note: Results from the probabilistic bias analysis based on the outcome validation study and the profile review should be compared against matched analyses.

10.5 Exploratory Analyses: Non-live birth outcomes

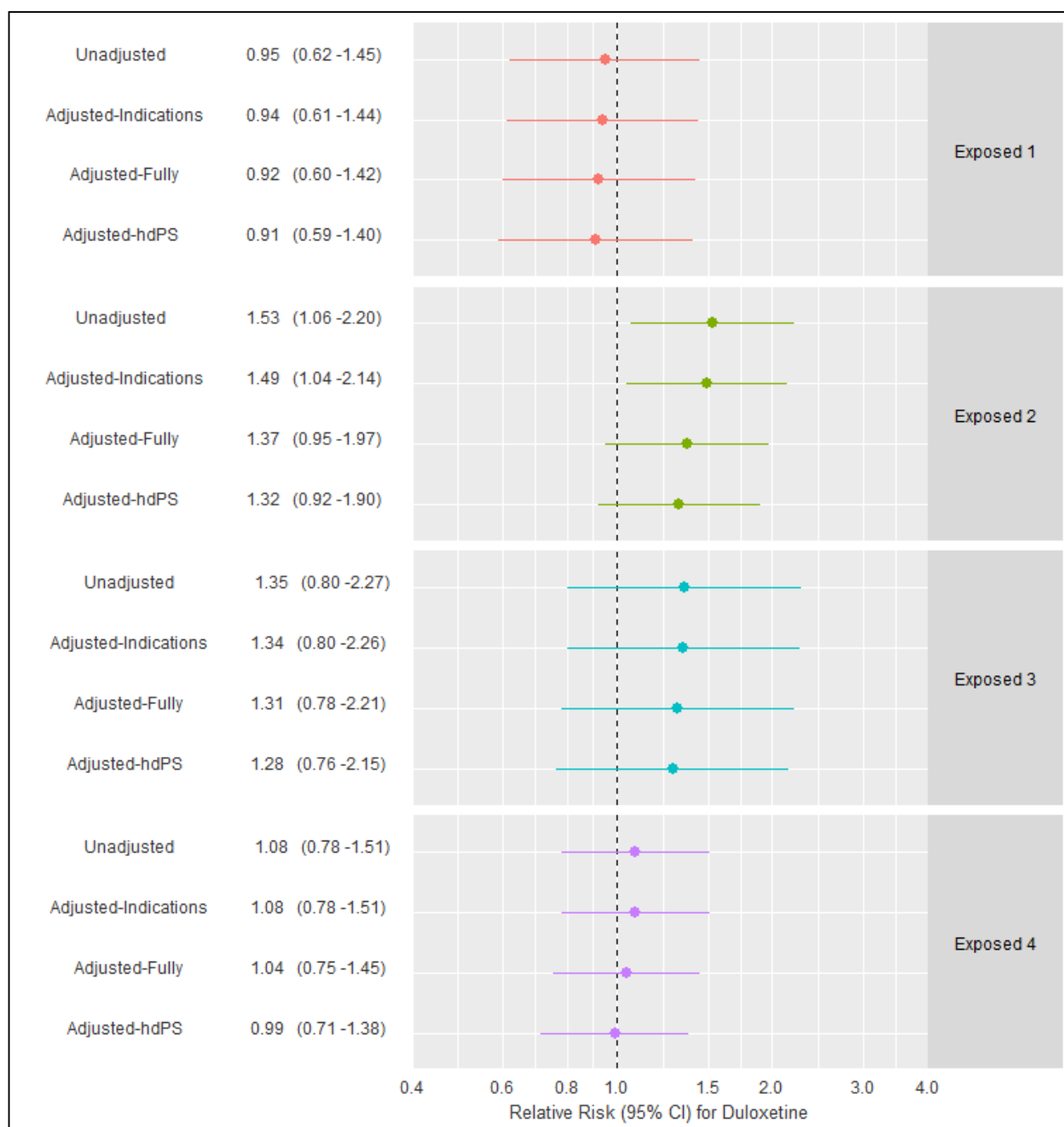
We identified a total of 220,405 (9.4%) spontaneous abortions and 17,588 (0.8%) stillbirths in the cohort overall. In the cohort restricted to women with a recorded diagnosis for any of the duloxetine indications, the numbers were 43,928 (11.5%) and 2,911 (0.8%) respectively. ([Table 15.5.1](#))

There was no evidence of a meaningfully increased risk of stillbirth following exposure to duloxetine at any time before the loss. The PS adjusted estimate for exposure at any point between LMP and LMP + 196 days was 1.04 (95% CI, 0.75 – 1.45); and the hdPS adjusted estimate was 0.99 (95% CI, 0.71 – 1.38). Results were less precise for the shorter exposure windows; the point estimates for the later windows were somewhat elevated: PS adjusted RR = 1.37, 0.95 – 1.97 for an exposure window from LMP + 30 to LMP + 120 days, and PS adjusted RR = 1.31, 0.78 – 2.21 for an exposure window from LMP + 120 to LMP + 196 days. ([Table 15.5.2](#); [Figure 16](#))

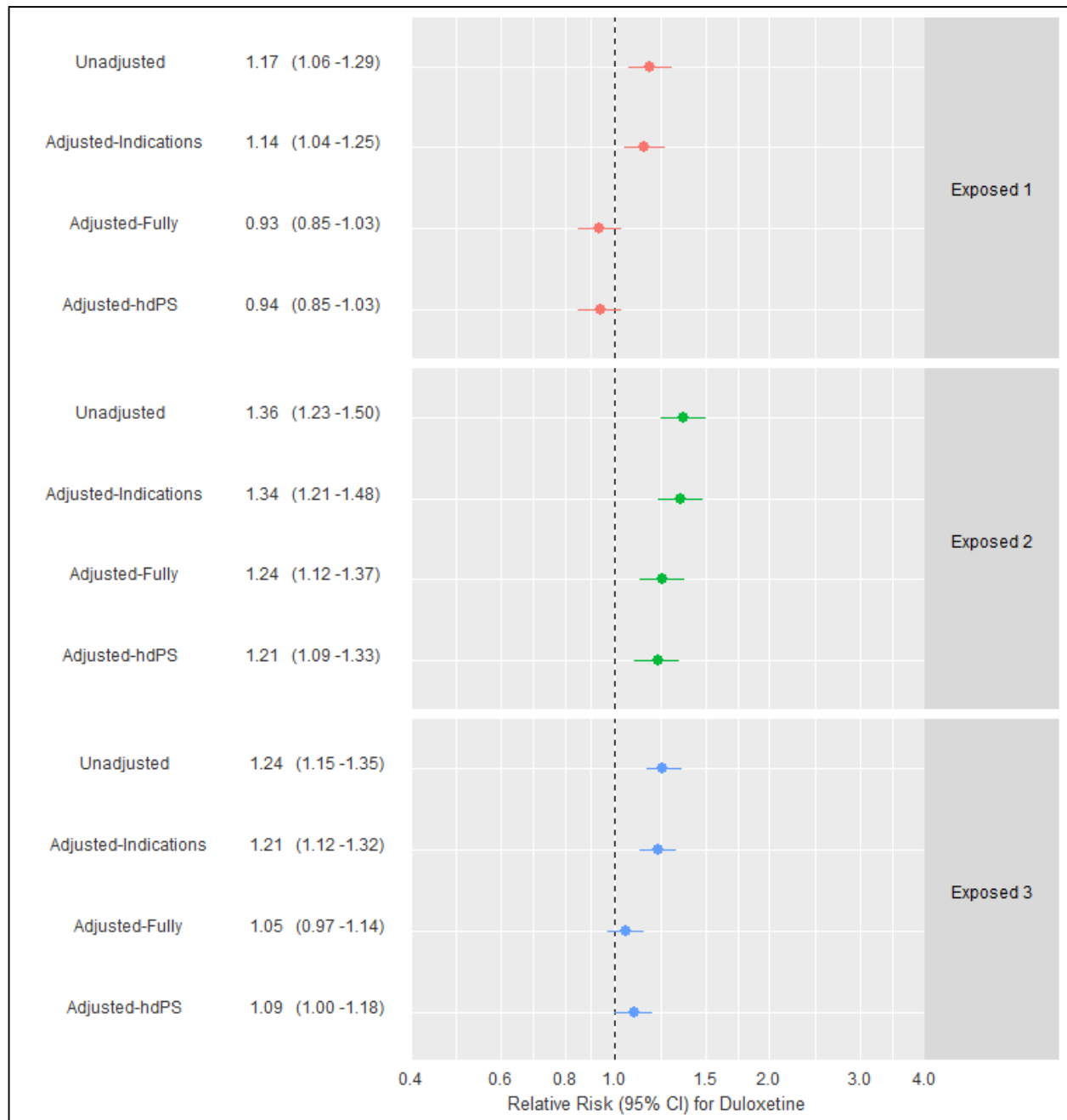
For spontaneous abortion the PS adjusted estimate was 1.14 (1.06 – 1.23) and the hdPS adjusted estimate was 1.16 (1.08 – 1.25) for exposure at any point between LMP and LMP + 63 days. There was evidence of a modest increase for exposure shortly before the pregnancy loss with a PS adjusted relative risk of 1.33 (1.21 – 1.46) for an exposure window from LMP + 30 and LMP + 63 days. ([Table 15.5.3](#); [Figure 17](#))

These results remained largely the same when we compared duloxetine to SSRI antidepressants in a post-hoc analysis, although the estimates for spontaneous abortion were slightly attenuated (PS adjusted RR = 1.05, 0.97 – 1.14; and hdPS adjusted RR = 1.09, 1.00 – 1.18). ([Table 15.5.4](#); [Table 15.5.5](#))

The positive control analysis where we examined the risk of stillbirth and spontaneous abortion for women with diabetes, suggest that the overall findings for duloxetine were unlikely to be due to misclassification of the outcome as we were able to replicate the known association between diabetes and stillbirth (RR = 2.78, 2.43 – 3.18) and between diabetes and spontaneous abortion (RR = 1.64, 1.58 – 1.70).

Figure 16 Risk of stillbirth associated with exposure to duloxetine during pregnancy

Note: Exposed 1 = LMP to LMP + 30 days; Exposed 2 = LMP + 30 days to LMP + 120 days; Exposed 3 = LMP + 120 days to LMP + 196 days; Exposed 4 = LMP to LMP + 196 days

Figure 17 Risk of spontaneous abortion associated with exposure to duloxetine during pregnancy

Note: Exposed 1 = LMP to LMP + 30 days; Exposed 2 = LMP + 30 days to LMP + 63 days; Exposed 3 = LMP to LMP + 63 days

10.6 Other Analyses

Not applicable.

10.7 Adverse events/adverse reactions

Not applicable.

11. Discussion

11.1 Key results

The objective of this study was to provide estimates of the risk associated with the use of duloxetine by pregnant women. Specifically, we investigated whether exposure to duloxetine during pregnancy is associated with an increased risk of adverse fetal and maternal outcomes including major congenital malformations, cardiac malformations, preterm birth, small for gestational age, pregnancy losses (stillbirth and spontaneous abortion), preeclampsia, and postpartum haemorrhage. To compare the risk of these outcomes between duloxetine exposed and a comparable reference group we first restricted the cohort to pregnant women with clinically diagnosed depression, anxiety, or specific pain indications (i.e., one or more indications for duloxetine) and balanced other characteristics through propensity scores.

- Before restriction, we identified 8,410,882 pregnant women age 18-55 years from 46 US states and Washington, DC with completed pregnancies between Jul 2004 and Dec 2013. The number of duloxetine-exposed women varied by cohort and by exposure contrast and ranged between 880 and 3059 women.
- When comparing duloxetine-exposed women to a reference group of unexposed women, many differences existed in terms of baseline characteristics. Balance was much improved when selecting women exposed to another antidepressant (i.e., SSRI, venlafaxine) or women discontinuing duloxetine prior to the start of pregnancy as the reference group instead. After adjustment for potential confounding variables, all baseline characteristics were well balanced for all exposure contrasts. This observation is consistent with recent evidence on antidepressants safety in pregnancy, which has clearly demonstrated the impact of confounding by the underlying indication.
- The base risk among unexposed women was 36.6 per 1,000 (95% CI, 36.3 – 36.9) for congenital malformations overall; 13.7 per 1,000 (95% CI, 13.5 – 13.9) for cardiovascular malformations; 107.8 per 1,000 (95% CI, 107.3 – 108.3) for preterm birth; 20.4 per 1,000 (95% CI, 20.1 – 20.6) for small for gestational age; 33.6 per 1,000 (95% CI, 33.3 – 33.9) for preeclampsia; and 23.3 per 1,000 (95% CI, 23.1 – 23.4) for postpartum haemorrhage. The risk of these pregnancy outcomes was generally higher than in the general unexposed population. However, the differences were largely explained by measured characteristics as indicated by the shift of the relative risk estimates towards the null upon adjustment.
- There was no evidence of an increase in the risk of congenital malformations overall, with a fully adjusted RR of 1.11 (95% CI, 0.93 – 1.33) versus unexposed women. Results were similar in the active comparator analyses. Sensitivity analyses were consistent with those from the main analyses accounting for the width of the CIs.
- The fully adjusted RR for cardiovascular malformations was 1.29 (95% CI, 0.99 – 1.68) versus unexposed women. Results were similar in the active comparator analyses. Sensitivity analyses yielded very similar estimates to those from the primary analyses. Overall, these findings are consistent with a potentially small increased risk of cardiovascular malformations, while ruling out substantial effects. The conclusion is based on the consistently elevated point estimate across analyses, which suggests that the most likely scenario would be a RR around 1.3; with upper bounds consistently under 2-fold in primary analyses.

- Results for most other malformation types were consistent with a null finding, with the possible exception of ‘urinary malformations’ and ‘other malformations’. However, since (i) the number of exposed events was small for both these malformation types and (ii) we were not able to identify specific patterns or subtype events with increased risk, these are suspected to be chance findings.
- The fully adjusted RR for preterm birth compared with unexposed women was 1.01 (95% CI, 0.92 – 1.10) for early pregnancy exposure, and 1.19 (95% CI, 1.04 – 1.37) for late pregnancy exposure. While the estimate associated with late pregnancy exposure from the primary analysis was elevated, the RR attenuated in the hdPS adjusted analysis and was not elevated in the active comparator and discontinuer analyses. Furthermore, this small increase in risk was not consistently observed across the sensitivity analyses conducted. Thus, the results are consistent with no meaningful increased risk of preterm birth for either early or late pregnancy exposure.
- The fully adjusted RR for SGA compared with unexposed women was 1.14 (95% CI, 0.92 – 1.41) for early pregnancy exposure, and 1.20 (95% CI, 0.83 – 1.72) for late pregnancy exposure. These associations strengthened in some of the active comparator analyses, suggesting a possible small increase in risk. It should be noted, however, that the association was not consistently seen across all the sensitivity analyses conducted.
- The fully adjusted RR for preeclampsia compared with unexposed women was 1.12 (95% CI, 0.96 – 1.31) for early pregnancy exposure, and 1.04 (95% CI, 0.80 – 1.35) for late pregnancy exposure. Sensitivity analyses were generally consistent with these findings of no increased risk of preeclampsia.
- The fully adjusted RR for postpartum haemorrhage compared with unexposed women was 1.53 (95% CI, 1.08 – 2.18). An increased risk was also observed compared to SSRI-exposed women, but not compared to venlafaxine-exposed women (RR=1.04; 95% CI, 0.69 – 1.56). These results, which were consistent in sensitivity analyses, suggest an increased risk of postpartum haemorrhage, which may be an SNRI class effect.
- Based on the internal validation study, the PPV was 84% (95% CI: 72%, 92%) for SGA; 86% (95% CI: 74%, 94%) for preeclampsia; 88% (95% CI: 77%, 95%) for non-cardiac congenital malformation; between 74% (95% CI: 61%, 85%) and 88% (77%, 95%) for PPH, and between 78% (95% CI: 65%, 88%) and 88% (95% CI: 77%, 95%) for preterm delivery depending on the validation criteria used. Given the high PPVs for these and the previously validated outcomes, the probabilistic bias analyses generated relative risk estimates corrected for potential outcome misclassification that were very similar to the primary analyses.
- In exploratory analyses focusing on non-live birth outcomes, a total of 220,405 (9.4%) spontaneous abortions and 17,588 (0.8%) stillbirths were identified. There was no evidence of a meaningfully increased risk of stillbirth following exposure to duloxetine at any time before the loss (RR=1.04, 95% CI 0.75 – 1.45), but exposure after the first gestational month was associated with a 31-37% increase in risk. There was evidence of a modest increase in the risk of spontaneous abortion for exposure shortly before the pregnancy loss (RR=1.33, 95% CI 1.21 – 1.46). The RR for exposure at any time before the loss was 1.14 (95% CI, 1.06 – 1.23).

11.2 Limitations

Use of the Medicaid Analytic eXtract offers many strengths for pharmacoepidemiologic research, including its very large population-based cohort, reliable assessment of drug exposure, access to medical records, and availability of information on a wide range of potential confounders. The study limitations are those characteristics of studies

using large healthcare utilization databases or nationwide registries and center around the potential for misclassification and selection bias.

- Selection bias. The main study cohorts only included information on pregnancies that result in liveborn infants. This is potentially problematic for studies of the teratogenic potential of medications as there is no information about stillbirths, spontaneous or therapeutic abortions related to the presence of malformations. If non-livebirth of offspring with malformations occurs with greater frequency among women with exposure to duloxetine compared to the non-exposed or active comparator groups (within levels of covariates used for adjustment in the analysis), then the analysis which includes only pregnancies resulting in livebirth would underestimate the relative risk of malformations associated with exposure to duloxetine. We therefore performed sensitivity analyses to assess the potential impact of missing non-livebirth on the risk estimate for duloxetine and malformations. It should be noted that pregnancy registries typically enroll women late in the first trimester, thus missing a large proportion of abortions, and rarely have anatomic-pathologic information on the product of abortion, thus being unable to include potential malformations in these pregnancy losses.
- Exposure misclassification. To guard against exposure misclassification (i.e., false positives), we favored specificity over sensitivity in our exposure definition, requiring women to have filled a duloxetine prescription during the etiologically relevant window (as opposed to having a medication supply available that overlapped with the exposure window). In sensitivity analyses, we required women to have filled ≥ 2 prescriptions (i.e., stricter definition) under the assumption that filling multiple prescriptions increases the likelihood that the medication is being taken as prescribed, and we explored the associations for women with a medications supply that overlaps with the exposure window (i.e., looser definition). There is no risk of recall bias given the data source used, and no risk of false negatives given that duloxetine is not available over-the-counter. Rather, given the prospective recording of prescriptions with respect to outcomes, any potential misclassification is expected to be non-differential and would bias towards the null (though the sensitivity analyses suggest no meaningful impact).
- Outcome misclassification. We used highly specific outcome definitions, since this will result in unbiased estimates of the relative risk as long as the sensitivity is non-differential. We used validated outcome definitions with high PPV. For the exploratory analyses involving non-live birth outcomes, we replicated some known associations in our dataset. Regardless of these measures taken, some potential for outcome misclassification remains.
- Confounder misclassification. Information on lifestyle factors contained in administrative data is incomplete (e.g., smoking, obesity, alcohol and drug abuse/dependence) or absent (e.g., BMI, genetic factors), which may confound the observed associations to the extent that these factors are not accounted for through adjustment for factors correlated with them (e.g., depression diagnosis). We conducted formal sensitivity analyses using external information (i.e., NHANES) to quantify the potential impact of such residual confounding by lifestyle factors.
- Medications or vitamins purchased over-the-counter and illicit drug use are not recorded in the source data. However, prescription vitamin use as well as OTC drugs received with a prescription (e.g., acetaminophen) are recorded, as are codes for drug misuse and abuse. Since duloxetine is only available through prescription and since OTC medications are not expected to be strong confounders, missing information on OTC medications is expected to have very limited impact on the study.
- We did not have information on breastfeeding.

Despite the large size of the data source, since these maternal and neonatal outcomes (except prematurity) tend to be rare, we had limited statistical power to detect small increases in risk.

11.3 Interpretation

Findings from this study using a large national cohort of publicly insured pregnant women in the US with careful control for confounding and extensive sensitivity analyses to explore the impact of exposure and outcome misclassification and residual confounding, suggest duloxetine is not a major teratogen. We found a potential small increase in the risk of congenital cardiac malformations following in-utero exposure to duloxetine during the first trimester, but no strong signal of increased risk for other malformation types, although some confidence intervals are wide. There was no evidence of an increased risk of preterm birth or preeclampsia, but a potential small increase in the risk of SGA was observed, although associations were imprecisely estimated and they were not replicated in all sensitivity analyses. We found a potential increase in the risk of postpartum haemorrhage, which could be an SNRI class effect.

Data on the association between prenatal SSRI exposure and major malformations has accumulated for over a decade.⁶³ Although it is widely accepted that early pregnancy use of SSRIs does not result in an increased risk of congenital malformations overall, the risk of cardiovascular malformations has been the most consistently reported and is still under debate.^{62,64} Animal studies have suggested that neurotransmitters such as serotonin are important for cell signaling for a variety of tissues during embryogenesis, including heart development. SSRIs may disrupt cell communication and disturb cardiac development.¹¹⁶

In contrast, data on the teratogenicity of SNRIs is scarce. Of the limited information from animal models, at least two studies reported that venlafaxine use during pregnancy had adverse effects on rat fetuses and induced cardiac anomalies.^{117,118} It has been proposed that, since norepinephrine influences neural crest cell formation and differentiation during embryogenesis,¹¹⁹ SNRIs might interfere with these embryologic signaling pathways and could affect cardiac development. In humans, until 2012 venlafaxine accounted for a large proportion of SNRI use, thus initial pregnancy safety studies referring to SNRIs reflected mainly venlafaxine effects.¹²⁰

In a multicenter, retrospective (women enrolled after neonatal screening), uncontrolled study (no internal comparison group, and thus no control for indication, no attempt to control for depression severity), **Einarson et al.** followed 154 pregnancies exposed to venlafaxine during the first trimester of pregnancy.^{121,68} Of these, two newborns presented major malformations (hypospadias and neural tube defect with club foot). Overall, the prevalence of malformations was not above the baseline expected in the population. With a similar design, **Einarson et al** followed 206 women who took duloxetine during early pregnancy.⁹³ These women were compared with 208 women who had inquired about the use of other antidepressants during pregnancy and 208 women who had inquired about the use of substances not considered to be teratogenic. Out of 165 live births prenatally exposed to duloxetine, 3 (1.8%) had major malformations (clubfoot, hydronephrosis, kidney agenesis). The prevalence of malformations overall was similar for the other groups. The sample size was insufficient for these studies to consider specific malformations.

Oberlander et al. used administrative health care data from British Columbia to look at SNRIs prescriptions during the first trimester including venlafaxine individually and as a group, and found no increased risk for birth defects overall when compared to women unexposed to SNRIs or SSRIs (combined).⁶⁹ The risk of cardiac malformations was 0.65% (0.40–1.03) in the SNRI/SSRI monotherapy group and 0.48% (0.44–0.52) in the unexposed group (i.e.,

RR of 1.35), which reportedly strengthened with adjustment and increased with concomitant benzodiazepine use. Based on only 250 exposed, venlafaxine was not associated with an increased risk.

Hoog et al reported 233 prospectively recorded cases of duloxetine exposure during pregnancy identified from the Eli Lilly Safety System database and the FDA Adverse events reporting system. The frequency of major congenital malformations (3%) was like that expected in the general population; while the risk of spontaneous abortions (18%) was larger.⁷⁸ **Kjaersgaard** et al. found in data from Danish population-based registries an association between both venlafaxine and duloxetine and spontaneous abortion (RR 1.80; 95% CI: 1.19–2.72 and RR 3.12; 95% CI: 1.55–6.31, respectively) in women diagnosed with depression.⁷⁷

Polen et al analyzed data from the National Birth Defects Prevention Study and, in the context of multiple comparisons, found an association between venlafaxine and anencephaly, atrial septal defects, coarctation of the aorta, cleft palate, and gastroschisis; with ORs ranging from 1.5 to 6.3 (anencephaly (adjusted OR 6.3; 95% CI: 1.5–20.2), atrial septal defect secundum (OR 3.1; 95% CI: 1.3–7.4), coarctation of aorta (OR 4.1; 95% CI: 1.3–11.5), cleft palate (OR 3.3; 95% CI: 1.1–8.8) and gastroschisis (OR 5.7; 95% CI: 1.8–15.9)).⁷⁰ This case-control study was based on 77 exposed cases and did not control for indication. Interestingly, no differences were observed between venlafaxine-exposed and unexposed mothers in terms of potential risk factors such as smoking or alcohol consumption during early pregnancy. The same group reported an association between venlafaxine and hypospadias (OR 2.4; 95% CI 1.0 - 6.0) as a separate publication.¹²²

In a previous study using data from the Medicaid Analytic eXtract focused on studying the safety of SSRIs, we reported a RR for cardiac malformations of 1.51 among 6,904 women exposed to SNRIs in the first trimester (95% CI, 1.20 to 1.90). The RR moved to 1.20 (0.91 to 1.57) after adjustment. During the study period (2000–2007) most of the SNRI use was from venlafaxine.⁶⁴

In a population-based prospective cohort study using nationwide registries from Denmark, Finland, Iceland, Norway, and Sweden by **Furu** et al; the association between venlafaxine in the first trimester of pregnancy (N=2,763) and the risk of cardiac malformations was evaluated in comparison with infants not exposed to any antidepressant in utero.⁶⁵ The covariate adjusted OR of malformations overall in venlafaxine exposed infants was 1.06 (95%CI: 0.86–1.32); the OR for any cardiac defects was 1.14 (95% CI: 0.82 to 1.57). **Kallen** had previously reported on 732 pregnancies exposed to SNRIs (501 on venlafaxine, none on duloxetine) from the Swedish registries, concluding there was no increased risk for major malformations associated with SNRI (OR 0.85; 95% CI, 0.58–1.24). The corresponding OR for infants born of women who used SSRIs was 0.89 (95% CI, 0.79–1.07). A total of 10 infants exposed to SNRIs had cardiac defects (OR 1.2; 95% CI, 0.6–2.2). These analyses did not adjust for depression.¹²³ Kallen repeated the publication with 1,351 early pregnancy SNRI exposures (859 venlafaxine and 39 duloxetine) and found 20 cardiac malformations (RR 1.33; 95%CI 0.84–2.09).¹²⁴ Kallen later reported on 1,577 pregnancies, with 26 cardiac defects and a RR of 1.28 (0.87–1.89).⁷¹ In this study the authors identified 286 live-born infants exposed to duloxetine in the first trimester, seven were born with malformations (RR of 0.8 vs unexposed); 2 of them had cardiac defects.

In a Canadian longitudinal prospective cohort study (Quebec Pregnancy Cohort) of pregnant women with depression comparing venlafaxine users exposed in the first trimester (n=738) to antidepressant unexposed controls (n=14,847) the adjusted prevalence odds ratio of malformations overall was 1.10 (0.87 to 1.38).⁷² The study size was relatively small to evaluate specific malformations and consequently the RRs were unstable. For example, they were 0.80 (0.47 to 1.38) for cardiac, 1.43 (0.75 to 2.73) for urinary, and 2.17 (1.07 to 4.38) for respiratory malformations. Overall, this study supports no increased risk of cardiac malformations associated with venlafaxine, with a 1.38

upper bound of the CI. The RRs moved little upon adjustment within the depression-restricted cohort, suggesting little role of residual confounding. However, the Quebec Pregnancy Cohort has an unusually large proportion of major malformations (>12%), which raises concerns about misclassification of major malformations or inclusion of minor malformations.

Taken together, evidence does not point at a teratogenic effect of venlafaxine. The prior evidence for duloxetine was too limited to reach any definitive conclusion but did not suggest a clinically meaningful increased risk of major congenital malformations overall.⁹⁴ There was insufficient evidence to draw any conclusions about the risk of cardiac malformations.

Some studies had reported an increased risk of prematurity and SGA in patients treated with non-SSRI antidepressants,^{56,59} raising concerns about the potential adverse effects of depression itself. For our analyses of duloxetine, measured confounders account for the small elevation in the risk of prematurity, but did not seem to completely account for the modest association observed with SGA, although results were not consistent across all sensitivity analyses. Since only a small proportion of infants born SGA also had a diagnosis of a congenital malformation (6 out of 86 with early duloxetine exposure and 1 out of 29 with late duloxetine exposure), the association does not appear to be explained by a larger proportion of malformed newborns in the exposed group.

No study had previously evaluated the association between duloxetine and preeclampsia. Its inclusion in this study was justified by a theoretical possibility given ADs' vascular effects.^{80,81} Specifically, SNRIs can cause elevations of diastolic blood pressure.⁸²

The potential effect of duloxetine on postpartum haemorrhage had not previously been evaluated. Postpartum haemorrhage was evaluated because of the known role of serotonin in platelet aggregation and blood clotting.⁸³ Bleeding is more common in users of serotonergic AD.^{84,85,86,87} We hypothesized that women might be susceptible during delivery and post-partum to drugs that increase their risk for bleeding. Given that this is the first study to suggest the increased risk, this finding will need to be replicated before reaching any conclusion.

Exploratory analyses suggested a potential modest increase in risk of stillbirth associated with exposure during months 2 to 4 of pregnancy, which may be an important period in placental development, but other exposure windows did not appear to be associated with an increase in risk. Similarly, some analyses pointed to a potential modest increase in the risk of spontaneous abortion. The strength of this association (~30% increase in risk) is much smaller than what has been suggested in an earlier study (i.e., 3-fold increase in risk).

Duloxetine during pregnancy had previously been associated with an increase in the risk of spontaneous abortion. It was, however, uncertain whether the increased risk was due to duloxetine use, the depression, factors related to depression, or combinations of the above.^{77,78} Our findings suggest that a modest association may remain after accounting for confounders. However, these exploratory analyses rest on many assumptions which have not been validated and must therefore be interpreted with great caution. The results require replication in other studies to confirm or refute whether the potential signal is real.

The findings from this study should be placed in the context of other benefits and potential adverse effects of duloxetine relative to alternative treatment strategies.

11.4 Generalisability

Medicaid covers the medical expenses for close to 50% of births in the United States, making publicly-insured pregnant women an important population to study. Moreover, the Medicaid population consists of a young, racially diverse vulnerable population that is traditionally understudied. The findings from this study should be generalizable as long as these factors do not affect the biologic relations studied.¹²⁵ Prior work has suggested that there is no evidence of effect measure modification by age or race.⁶⁴

12 Other information

Not applicable.

13 Conclusion

Evidence from this large cohort study suggests duloxetine is unlikely to be a major teratogen. Interpretation of the evidence from primary analyses coupled with a broad range of sensitivity analyses, leads us to conclude that there is no evidence of an increase in the risk of congenital malformations overall, preterm birth, or preeclampsia. Potential small increases in the risk of congenital cardiac malformations, postpartum haemorrhage and small for gestational age were identified, but the magnitude of the associations was less than a 1.5 to 2-fold increase in risk. These potential small increases in risk of relatively uncommon outcomes have to be weighed against the benefits of treating depression during pregnancy for both the mother's and the infant's health; a trade off that is likely to be different for each individual patient.

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15. Tables

List of Tables

	Page
15.1. 1. Malformations- Baseline characteristics of duloxetine exposed vs. unexposed women: unadjusted	92
15.1. 2. Malformations- Baseline characteristics of duloxetine exposed vs. SSRI exposed women: unadjusted	99
15.1. 3. Malformations- Baseline characteristics of duloxetine exposed vs. venlafaxine exposed women: unadjusted	105
15.1. 4. Malformations- Baseline characteristics of duloxetine exposed women vs. duloxetine discontinuers: unadjusted	111
15.1. 5. Malformations- Baseline characteristics of duloxetine exposed vs. unexposed women: adjusted for treatment indications	118
15.1. 6. Malformations- Baseline characteristics of duloxetine exposed vs. SSRI exposed women: adjusted for treatment indications	124
15.1. 7. Malformations- Baseline characteristics of duloxetine exposed vs. venlafaxine exposed women: adjusted for treatment indications	130
15.1. 8. Malformations- Baseline characteristics of duloxetine exposed vs. duloxetine discontinuers: adjusted for treatment indications	136
15.1. 9. Malformations- Baseline characteristics of duloxetine exposed vs. unexposed women: fully adjusted	143
15.1. 10. Malformations- Baseline characteristics of duloxetine exposed vs. SSRI exposed women: fully adjusted	149
15.1. 11. Malformations- Baseline characteristics of duloxetine exposed vs. venlafaxine exposed women: fully adjusted	155
15.1. 12. Malformations- Baseline characteristics of duloxetine exposed women vs. duloxetine discontinuers: fully adjusted	161
15.1. 13. Malformations- Absolute risks	168
15.1. 14. Malformations- Relative risks for duloxetine exposed vs. unexposed women	170
15.1. 15. Malformations- Relative risks for duloxetine exposed vs. SSRI exposed women	172
15.1. 16. Malformations- Relative risks for duloxetine exposed vs. venlafaxine exposed women	174
15.1. 17. Malformations- Relative risk for duloxetine exposed women vs. duloxetine discontinuers	176
15.1. 18. Malformations- Sensitivity Analyses #1: Re-define exposure as having filled ≥ 2 prescriptions	178
15.1. 19. Malformations- Sensitivity Analyses #2: Re-define exposure as days supply overlap	182

15.1. 20.	Malformations- Sensitivity Analyses #3: Restrict cohort to women with a recorded diagnosis of fibromyalgia	188
15.1. 21.	Malformations- Sensitivity Analyses #4: Correct relative risks for outcome misclassification	194
15.1. 22.	Malformations- Sensitivity Analyses #5: Redefine outcome based on claims profile review	195
15.1. 23.	Malformations- Sensitivity Analyses #6: Restrict cohort to the first pregnancy occurring within the study period	196
15.1. 24.	Malformations- Sensitivity Analyses #8: Redefine outcome based on infant claims only	200
15.1. 25.	Malformations- Sensitivity Analyses #9: Restrict outcome to inpatient diagnoses only	204
15.1. 26.	Malformations- Sensitivity Analyses #10: Extend infant follow-up to 1 year	208
15.2. 1.	Preterm/SGA- Baseline characteristics of duloxetine exposed vs. unexposed women- early exposure: unadjusted	212
15.2. 2.	Preterm/SGA- Baseline characteristics of duloxetine exposed vs. SSRI exposed women- early exposure: unadjusted	218
15.2. 3.	Preterm/SGA- Baseline characteristics of duloxetine exposed vs. venlafaxine exposed women- early exposure: unadjusted	224
15.2. 4.	Preterm/SGA- Baseline characteristics of duloxetine exposed vs. unexposed women - early exposure: adjusted for treatment indications	230
15.2. 5.	Preterm/SGA- Baseline characteristics of duloxetine exposed vs. SSRI exposed women - early exposure: adjusted for treatment indications	236
15.2. 6.	Preterm/SGA- Baseline characteristics of duloxetine exposed vs. venlafaxine exposed women - early exposure: adjusted for treatment indications	242
15.2. 7.	Preterm/SGA- Baseline characteristics of duloxetine exposed vs. unexposed women - early exposure: fully adjusted	248
15.2. 8.	Preterm/SGA- Baseline characteristics of duloxetine exposed vs. SSRI exposed women - early exposure: fully adjusted	254
15.2. 9.	Preterm/SGA- Baseline characteristics of duloxetine exposed vs. venlafaxine exposed women - early exposure: fully adjusted	260
15.2. 10.	Preterm/SGA- Baseline characteristics of duloxetine exposed vs. unexposed women - late exposure: unadjusted	266

15.2. 11.	Preterm/SGA- Baseline characteristics of duloxetine exposed vs. SSRI exposed women - late exposure: unadjusted	272
15.2. 12.	Preterm/SGA- Baseline characteristics of duloxetine exposed vs. venlafaxine exposed women - late exposure: unadjusted	278
15.2. 13.	Preterm/SGA- Baseline characteristics of duloxetine exposed vs. unexposed women - late exposure: adjusted for treatment indications	284
15.2. 14.	Preterm/SGA- Baseline characteristics of duloxetine exposed vs. SSRI exposed women - late exposure: adjusted for treatment indications	290
15.2. 15.	Preterm/SGA- Baseline characteristics of duloxetine exposed vs. venlafaxine exposed women - late exposure: adjusted for treatment indications	296
15.2. 16.	Preterm/SGA- Baseline characteristics of duloxetine exposed vs. unexposed women - late exposure: fully adjusted	302
15.2. 17.	Preterm/SGA- Baseline characteristics of duloxetine exposed vs. SSRI exposed women - late exposure: fully adjusted	308
15.2. 18.	Preterm/SGA- Baseline characteristics of duloxetine exposed vs. venlafaxine exposed women - late exposure: fully adjusted	314
15.2. 19.	Preterm/SGA- Absolute risks for early exposure	320
15.2. 20.	Preterm/SGA- Absolute risks for late exposure	321
15.2. 21.	Preterm/SGA- Relative risks for duloxetine exposed vs. unexposed women	322
15.2. 22.	Preterm/SGA- Relative risks for duloxetine exposed vs. SSRI exposed women	324
15.2. 23.	Preterm/SGA- Relative risks for duloxetine exposed vs. venlafaxine exposed women	326
15.2. 24.	Preterm/SGA- Sensitivity Analyses #1: Re-define exposure as having filled ≥ 2 prescriptions	328
15.2. 25.	Preterm/SGA- Sensitivity Analyses #2: Re-define exposure as days supply overlap	331
15.2. 26.	Preterm/SGA- Sensitivity Analyses #3: Restrict cohort to women with a recorded diagnosis of fibromyalgia	334
15.2. 27.	Preterm/SGA- Sensitivity Analyses #4: Correct relative risks for outcome misclassification	337
15.2. 28.	Preterm/SGA- Sensitivity Analyses #5: Redefine outcome based on claims profile review	339
15.2. 29.	Preterm/SGA- Sensitivity Analyses #6: Restrict cohort to the first pregnancy occurring within the study period	340

15.3. 1.	Preeclampsia- Baseline characteristics of duloxetine exposed vs. unexposed women- early exposure: unadjusted	342
15.3. 2.	Preeclampsia- Baseline characteristics of duloxetine exposed vs. SSRI exposed women- early exposure: unadjusted	348
15.3. 3.	Preeclampsia- Baseline characteristics of duloxetine exposed vs. venlafaxine exposed women- early exposure: unadjusted	354
15.3. 4.	Preeclampsia- Baseline characteristics of duloxetine exposed vs. unexposed women - early exposure: adjusted for treatment indications	360
15.3. 5.	Preeclampsia- Baseline characteristics of duloxetine exposed vs. SSRI exposed women - early exposure: adjusted for treatment indications	366
15.3. 6.	Preeclampsia- Baseline characteristics of duloxetine exposed vs. venlafaxine exposed women - early exposure: adjusted for treatment indications	372
15.3. 7.	Preeclampsia- Baseline characteristics of duloxetine exposed vs. unexposed women - early exposure: fully adjusted	378
15.3. 8.	Preeclampsia- Baseline characteristics of duloxetine exposed vs. SSRI exposed women - early exposure: fully adjusted	384
15.3. 9.	Preeclampsia- Baseline characteristics of duloxetine exposed vs. venlafaxine exposed women - early exposure: fully adjusted	390
15.3. 10.	Preeclampsia- Baseline characteristics of duloxetine exposed vs. unexposed women - late exposure: unadjusted	396
15.3. 11.	Preeclampsia- Baseline characteristics of duloxetine exposed vs. SSRI exposed women - late exposure: unadjusted	402
15.3. 12.	Preeclampsia- Baseline characteristics of duloxetine exposed vs. venlafaxine exposed women - late exposure: unadjusted	408
15.3. 13.	Preeclampsia- Baseline characteristics of duloxetine exposed vs. unexposed women - late exposure: adjusted for treatment indications	414
15.3. 14.	Preeclampsia- Baseline characteristics of duloxetine exposed vs. SSRI exposed women - late exposure: adjusted for treatment indications	420
15.3. 15.	Preeclampsia- Baseline characteristics of duloxetine exposed vs. venlafaxine exposed women - late exposure: adjusted for treatment indications	426

15.3. 16.	Preeclampsia- Baseline characteristics of duloxetine exposed vs. unexposed women - late exposure: fully adjusted	432
15.3. 17.	Preeclampsia- Baseline characteristics of duloxetine exposed vs. SSRI exposed women - late exposure: fully adjusted	438
15.3. 18.	Preeclampsia- Baseline characteristics of duloxetine exposed vs. venlafaxine exposed women - late exposure: fully adjusted	444
15.3. 19.	Preeclampsia- Absolute risks for early exposure	450
15.3. 20.	Preeclampsia- Absolute risks for late exposure	451
15.3. 21.	Preeclampsia- Relative risks for duloxetine exposed vs. unexposed women	452
15.3. 22.	Preeclampsia- Relative risks for duloxetine exposed vs. SSRI exposed women	453
15.3. 23.	Preeclampsia- Relative risks for duloxetine exposed vs. venlafaxine exposed women	454
15.3. 24.	Preeclampsia- Sensitivity Analyses #1: Re-define exposure as having filled ≥ 2 prescriptions	455
15.3. 25.	Preeclampsia- Sensitivity Analyses #2: Re-define exposure as days supply overlap	458
15.3. 26.	Preeclampsia- Sensitivity Analyses #3: Restrict cohort to women with a recorded diagnosis of fibromyalgia	461
15.3. 27.	Preeclampsia- Sensitivity Analyses #4: Correct relative risks for outcome misclassification	464
15.3. 28.	Preeclampsia- Sensitivity Analyses #5: Redefine outcome based on claims profile review	465
15.3. 29.	Preeclampsia- Sensitivity Analyses #6: Restrict cohort to the first pregnancy occurring within the study period	466
15.4. 1.	Postpartum Haemorrhage- Baseline characteristics of duloxetine exposed vs. unexposed women: unadjusted	468
15.4. 2.	Postpartum Haemorrhage- Baseline characteristics of duloxetine exposed vs. SSRI exposed women: unadjusted	474
15.4. 3.	Postpartum Haemorrhage- Baseline characteristics of duloxetine exposed vs. venlafaxine exposed women: unadjusted	480
15.4. 4.	Postpartum Haemorrhage- Baseline characteristics of duloxetine exposed vs. unexposed women: adjusted for treatment indications	486
15.4. 5.	Postpartum Haemorrhage- Baseline characteristics of duloxetine exposed vs. SSRI exposed women: adjusted for treatment indications	492
15.4. 6.	Postpartum Haemorrhage- Baseline characteristics of duloxetine exposed vs. venlafaxine exposed women: adjusted for treatment indications	498

15.4. 7.	Postpartum Haemorrhage- Baseline characteristics of duloxetine exposed vs. unexposed women: fully adjusted	504
15.4. 8.	Postpartum Haemorrhage- Baseline characteristics of duloxetine exposed vs. SSRI exposed women: fully adjusted	510
15.4. 9.	Postpartum Haemorrhage- Baseline characteristics of duloxetine exposed vs. venlafaxine exposed women: fully adjusted	516
15.4. 10.	Postpartum Haemorrhage- Absolute risks	522
15.4. 11.	Postpartum Haemorrhage- Relative risks for duloxetine exposed vs. unexposed women	523
15.4. 12.	Postpartum Haemorrhage- Relative risks for duloxetine exposed vs. SSRI exposed women	524
15.4. 13.	Postpartum Haemorrhage- Relative risks for duloxetine exposed vs. venlafaxine exposed women	525
15.4. 14.	Postpartum Haemorrhage- Sensitivity Analyses #1: Re-define exposure as having filled ≥ 2 prescriptions	526
15.4. 15.	Postpartum Haemorrhage- Sensitivity Analyses #2: Re-define exposure as days supply overlap	527
15.4. 16.	Postpartum Haemorrhage- Sensitivity Analyses #3: Restrict cohort to women with a recorded diagnosis of fibromyalgia	528
15.4. 17.	Postpartum Haemorrhage- Sensitivity Analyses #4: Correct relative risks for outcome misclassification	529
15.4. 18.	Postpartum Haemorrhage- Sensitivity Analyses #5: Redefine outcome based on claims profile review	530
15.4. 19.	Postpartum Haemorrhage- Sensitivity Analyses #6: Restrict cohort to the first pregnancy occurring within the study period	531
15.4. 20.	Postpartum Haemorrhage- Sensitivity Analyses #12: Consider as exposed women with duloxetine dispensing <14 days before delivery	532
15.4. 21.	Postpartum Haemorrhage- Sensitivity Analyses #13: Consider as exposed women with days supply overlapping delivery date	533
15.5. 1.	Cohort of live and non-live births	534
15.5. 2.	Risk of stillbirth associated with duloxetine exposure during pregnancy, as compared to unexposed women	535
15.5. 3.	Risk of spontaneous abortion associated with duloxetine exposure during pregnancy, as compared to unexposed women	536
15.5. 4.	Risk of stillbirth associated with duloxetine exposure during pregnancy, as compared to SSRI exposure	537
15.5. 5.	Risk of spontaneous abortion associated with duloxetine exposure during pregnancy, as compared to SSRI exposure	538

15.1. 1. Malformations- Baseline characteristics of duloxetine exposed vs. unexposed women: unadjusted

	Duloxetine N/Mean	Duloxetine %/SD	Unexposed N/Mean	Unexposed %/SD	Standardized Difference
Total	2,532	100.00	1,284,827	100.00	
Demographics					
Age, mean (SD)	27.75	5.53	24.94	5.36	0.52
Age categorical, N (%)					
<=19	125	4.94	198,878	15.48	-0.35
20-24	645	25.47	498,092	38.77	-0.29
25-29	872	34.44	339,922	26.46	0.17
30-34	560	22.12	164,280	12.79	0.25
35-39	258	10.19	68,371	5.32	0.18
>=40	72	2.84	15,284	1.19	0.12
Race, N (%)					
White	2,003	79.11	518,455	40.35	0.86
Black or African American	219	8.65	400,432	31.17	-0.59
Hispanic or Latino	70	2.76	181,970	14.16	-0.42
Asian or Other Pacific Islander	32	1.26	56,128	4.37	-0.19
American Indian	33	1.3	21,136	1.65	-0.03
Other	117	4.62	75,858	5.9	-0.06
Unknown	58	2.29	30,848	2.4	-0.01
Chronic comorbid conditions, N (%)					
Hypertension	191	7.54	34,556	2.69	0.22
Diabetes	152	6	30,063	2.34	0.18
Renal Disease	23	0.91	4,695	0.37	0.07
Obesity Overweight	152	6	33,501	2.61	0.17
Comorbidity Index Q1	882	34.83	684,901	53.31	-0.38
Comorbidity Index Q2	639	25.24	315,016	24.52	0.02
Comorbidity Index Q3	427	16.86	149,957	11.67	0.15
Comorbidity Index Q4	584	23.06	134,953	10.5	0.34
Infections, N (%)					
Toxoplasmosis	0	0	168	0.01	-0.02
Rubella	0	0	146	0.01	-0.02

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Cytomegalovirus	0	0	46	0	-0.01
Herpes	41	1.62	10,470	0.81	0.07
Syphilis	0	0	1,112	0.09	-0.04
Varicella	<11	0.04	236	0.02	0.01
Parvovirus B19	0	0	31	0	-0.01
Zika virus other mosquito	0	0	0	0	0.00
Lymphocytic choriomeningitis	<11	0.04	12	0	0.03
Influenza	21	0.83	8,263	0.64	0.02
Chlamydia	11	0.43	8,447	0.66	-0.03
Human papilloma virus	25	0.99	6,735	0.52	0.05
Gonorrhea	13	0.51	9,783	0.76	-0.03
HIV	<11	0.28	3,911	0.3	-0.01
Trichomoniasis	18	0.71	16,337	1.27	-0.06
Indications for duloxetine, N (%)					
Depression	1,235	48.78	77,678	6.05	1.09
Anxiety	778	30.73	52,167	4.06	0.75
Neuropathic Pain	267	10.55	20,024	1.56	0.38
Fibromyalgia	264	10.43	11,829	0.92	0.42
Non neuropathic Pain	1,234	48.74	198,581	15.46	0.76
Other psychiatric conditions, N (%)					
Sleep disorder	144	5.69	10,560	0.82	0.28
Bipolar disorder	330	13.03	17,340	1.35	0.46
Psychosis	20	0.79	2,570	0.2	0.08
Schizophrenia	25	0.99	2,096	0.16	0.11
Personality disorder	56	2.21	2,613	0.2	0.18
Adjustment disorder	29	1.15	4,620	0.36	0.09
Tobacco use, N (%)	279	11.02	52,341	4.07	0.27
Alcohol abuse or dependence, N (%)	31	1.22	4,744	0.37	0.10
Drug abuse or dependence, N (%)	84	3.32	11,587	0.9	0.17
Other medication exposures, N (%)					
Benzodiazepines	979	38.67	46,726	3.64	0.95
Other hypnotics	608	24.01	48,070	3.74	0.61

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Barbiturates	124	4.9	14,042	1.09	0.22
Anxiolytics	129	5.09	5,852	0.46	0.29
Anticonvulsants	642	25.36	29,354	2.28	0.71
Antipsychotics	505	19.94	18,630	1.45	0.63
SSRIs	705	27.84	88,971	6.92	0.57
SNRIs	103	4.07	10,809	0.84	0.21
Other Antidep	720	28.44	40,109	3.12	0.74
Stimulants	198	7.82	10,738	0.84	0.35
Antidiabetic	100	3.95	13,468	1.05	0.19
Insulin	80	3.16	12,212	0.95	0.16
Antihyperten	373	14.73	41,000	3.19	0.41
Opioid analgesics	1,554	61.37	310,792	24.19	0.81
Triptans	178	7.03	15,504	1.21	0.30
NSAIDs	958	37.84	221,631	17.25	0.47
Obstetric conditions, N (%)					
Multifetal gestation Flag	87	3.44	47,282	3.68	-0.01
Potentially teratogenic medication exposures, N (%)					
Danazol	0	0	21	0	-0.01
Synthetic progestins	88	3.48	25,715	2	0.09
Methimazole	<11	0.12	678	0.05	0.02
Propylthiouracil	<11	0.16	1,466	0.11	0.01
Corticosteroids	453	17.89	92,250	7.18	0.33
Fluconazole	133	5.25	28,109	2.19	0.16
Markers of healthcare utilization					
Number of distinct 3 digit ICD 9 codes=0	123	4.86	381,993	29.73	-0.70
Number of distinct 3 digit ICD 9 codes: tertile 1 for number >0	489	19.31	382,768	29.79	-0.25
Number of distinct 3 digit ICD 9 codes: tertile 2 for number >0	552	21.8	232,714	18.11	0.09
Number of distinct 3 digit ICD 9 codes: tertile 3 for number >0	1,368	54.03	287,352	22.37	0.69
Number of ED visits=0	1,570	62.01	1,003,539	78.11	-0.36
Number of ED visits=1	547	21.6	187,476	14.59	0.18
Number of ED visits=2	223	8.81	59,512	4.63	0.17
Number of ED visits>2	192	7.58	34,300	2.67	0.22

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Number of non-duloxetine generics dispensed=0	173	6.83	566,240	44.07	-0.95
Number of non-duloxetine generics dispensed: tertile 1 for number >0	188	7.42	198,005	15.41	-0.25
Number of non-duloxetine generics dispensed: tertile 2 for number >0	542	21.41	279,520	21.76	-0.01
Number of non-duloxetine generics dispensed: tertile 3 for number >0	1,629	64.34	241,062	18.76	1.04
Number of hospital admissions=0	2,413	95.3	1,237,019	96.28	-0.05
Number of hospital admissions=1	102	4.03	42,630	3.32	0.04
Number of hospital admissions=2	15	0.59	4,616	0.36	0.03
Number of hospital admissions>2	<11	0.08	562	0.04	0.01
Number of outpatient visits=0	230	9.08	476,767	37.11	-0.71
Number of outpatient visits: tertile 1 for number >0	284	11.22	258,343	20.11	-0.25
Number of outpatient visits: tertile 2 for number >0	631	24.92	294,125	22.89	0.05
Number of outpatient visits: tertile 3 for number >0	1,387	54.78	255,592	19.89	0.77
Number of psychiatric hospitalizations Q1	2,456	97	1,277,549	99.43	-0.18
Number of psychiatric hospitalizations Q2	66	2.61	6,613	0.51	0.17
Number of psychiatric hospitalizations Q3	<11	0.32	568	0.04	0.06
Number of psychiatric hospitalizations Q4	<11	0.08	97	0.01	0.03
Number of psychiatrist visits=0	1,097	43.33	1,160,052	90.29	-1.15
Number of psychiatrist visits=1	534	21.09	63,878	4.97	0.49
Number of psychiatrist visits=2	274	10.82	21,689	1.69	0.38
Number of psychiatrist visits>2	627	24.76	39,208	3.05	0.66
Geographic region					
Arkansas	PPD		974	0.08	0.01
Alabama	PPD		5,482	0.43	0.00
California	173	6.83	254,774	19.83	-0.39
Colorado	PPD		5,013	0.39	-0.04
District of Columbia	PPD		350	0.03	0.01
Delaware	66	2.61	11,507	0.9	0.13
Florida	PPD		20,584	1.6	-0.12
Georgia	PPD		29,229	2.27	-0.16

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Hawaii	PPD		8,498	0.66	-0.10
Iowa	26	1.03	7,908	0.62	0.05
Idaho	PPD		1,299	0.1	0.01
Illinois	299	11.81	126,753	9.87	0.06
Indiana	241	9.52	45,592	3.55	0.24
Kansas	41	1.62	10,185	0.79	0.08
Kentucky	41	1.62	24,201	1.88	-0.02
Louisiana	87	3.44	27,391	2.13	0.08
Massachusetts	PPD		4,403	0.34	-0.04
Maryland	31	1.22	24,512	1.91	-0.06
Maine	PPD		3,199	0.25	0.01
Minnesota	146	5.77	46,740	3.64	0.10
Missouri	139	5.49	37,185	2.89	0.13
Mississippi	14	0.55	20,819	1.62	-0.10
North Carolina	56	2.21	16,711	1.3	0.07
North Dakota	25	0.99	3,297	0.26	0.09
Nebraska	24	0.95	5,159	0.4	0.07
New Hampshire	PPD		3,239	0.25	0.00
New Jersey	0	0	13,206	1.03	-0.14
New Mexico	20	0.79	19,068	1.48	-0.07
Nevada	PPD		1,046	0.08	0.00
New York	458	18.09	219,227	17.06	0.03
Ohio	33	1.3	17,972	1.4	-0.01
Oklahoma	27	1.07	17,179	1.34	-0.02
Oregon	42	1.66	11,123	0.87	0.07
Pennsylvania	17	0.67	18,482	1.44	-0.08
Rhode Island	PPD		1,857	0.14	-0.02
South Carolina			1,648	0.13	0.02
South Dakota	14	0.55	5,521	0.43	0.02
Tennessee	159	6.28	104,215	8.11	-0.07
Texas	PPD		4,386	0.34	-0.01
Utah	60	2.37	7,004	0.55	0.15

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Virginia	60	2.37	27,290	2.12	0.02
Vermont	27	1.07	7,246	0.56	0.06
Washington	PPD		730	0.06	-0.01
Wisconsin	117	4.62	60,354	4.7	0.00
West Virginia	PPD		1,248	0.1	0.02
Wyoming			1,021	0.08	0.01
Opioids					
buprenorphine	68	2.69	3,408	0.27	0.20
butorphanol	<11	0.16	133	0.01	0.05
codeine	338	13.35	94,860	7.38	0.20
fentanyl	32	1.26	809	0.06	0.15
hydrocodone	1,056	41.71	186,748	14.53	0.63
hydromorphone	31	1.22	1,400	0.11	0.14
Levorphanol	0	0	<11	0	0.00
meperidine	<11	0.2	925	0.07	0.03
methadone	26	1.03	1,000	0.08	0.13
morphine	44	1.74	1,081	0.08	0.17
oxycodone	398	15.72	46,261	3.6	0.42
oxymorphone	<11	0.08	117	0.01	0.03
pentazocine	<11	0.12	305	0.02	0.04
propoxyphene	144	5.69	28,894	2.25	0.18
tapentadol	<11	0.2	78	0.01	0.06
tramadol	417	16.47	38,456	2.99	0.47
Healthcare Utilization, mean (SD)					
Comorbidity Index	1.58	1.85	0.917	1.4	0.40
Morphine equivalents	19773.7	489395.76	753.835	67877.08	0.05
Number of diagnoses	5.95	4.65	2.799	3.33	0.78
Number of ED visits	0.72	1.3	0.345	0.89	0.33
Number of non-duloxetine generics dispensed	5.63	4.19	1.807	2.48	1.11
Number of hospitalizations	0.05	0.27	0.042	0.23	0.05
Number of outpatient visits	5.58	6.43	2.114	3.43	0.67
Number of psychiatric hospitalizations	0.04	0.22	0.006	0.09	0.17

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Number of psychiatrist visits	2.28	4.94	0.326	2.14	0.51

15.1. 2. Malformations- Baseline characteristics of duloxetine exposed vs. SSRI exposed women: unadjusted

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Total	1,966	100.00	52,018	100.00	
Demographics					
Age, mean (SD)	27.7	5.51	26.21	5.4	0.27
Age categorical, N (%)					
<=19	103	5.24	4,736	9.1	-0.15
20-24	499	25.38	17,675	33.98	-0.19
25-29	679	34.54	16,298	31.33	0.07
30-34	435	22.13	8,793	16.9	0.13
35-39	192	9.77	3,762	7.23	0.09
>=40	58	2.95	754	1.45	0.10
Race, N (%)					
White	1,547	78.69	38,077	73.2	0.13
Black/African American	179	9.1	6,131	11.79	-0.09
Hispanic/Latino	54	2.75	3,386	6.51	-0.18
Asian or Other Pacific	24	1.22	556	1.07	0.01
American Indian	28	1.42	806	1.55	-0.01
Other	92	4.68	1,884	3.62	0.05
Unknown	42	2.14	1,178	2.26	-0.01
Chronic comorbid conditions, N (%)					
Hypertension	146	7.43	2,792	5.37	0.08
Diabetes	125	6.36	2,163	4.16	0.10
Renal Disease	15	0.76	326	0.63	0.02
Obesity Overweight	124	6.31	2,209	4.25	0.09
Comorbidity Index Q1	693	35.25	22,400	43.06	-0.16
Comorbidity Index Q2	498	25.33	13,332	25.63	-0.01
Comorbidity Index Q3	329	16.73	7,991	15.36	0.04
Comorbidity Index Q4	446	22.69	8,295	15.95	0.17
Infections, N (%)					
Toxoplasmosis	0	0	<11	0.02	-0.02
Rubella	0	0	<11	0.01	-0.01
Cytomegalovirus	0	0	0	0	-0.01

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Herpes	32	1.63	680	1.31	0.03
Syphilis	<11	0	40	0.08	-0.04
Varicella	<11	0.05	<11	0.02	0.02
Parvovirus B19	0	0	0	0	-0.01
Zika virus other mosquito	0	0	0	0	.
Lymphocytic choriomeningitis	<11	0.05	0	0	0.03
Influenza	15	0.76	517	0.99	-0.02
Chlamydia	<11	0.51	248	0.48	0.00
Human papilloma virus	15	0.76	393	0.76	0.00
Gonorrhea	<11	0.51	264	0.51	0.00
HIV	<11	0.25	206	0.4	-0.02
Trichomoniasis	16	0.81	496	0.95	-0.01
Indications for duloxetine, N (%)					
Depression	904	45.98	22,382	43.03	0.06
Anxiety	562	28.59	13,740	26.41	0.05
Neuropathic Pain	202	10.27	2,310	4.44	0.22
Fibromyalgia	203	10.33	1,325	2.55	0.32
Non neuropathic Pain	966	49.14	16,406	31.54	0.36
Other psychiatric conditions, N (%)					
Sleep disorder	112	5.7	2,180	4.19	0.07
Bipolar disorder	245	12.46	4,224	8.12	0.14
Psychosis	13	0.66	538	1.03	-0.04
Schizophrenia	18	0.92	528	1.02	-0.01
Personality disorder	30	1.53	712	1.37	0.01
Adjustment disorder	19	0.97	602	1.16	-0.02
Tobacco use, N (%)	213	10.83	4,565	8.78	0.07
Alcohol abuse or dependence, N (%)	18	0.92	787	1.51	-0.05
Drug abuse or dependence, N (%)	59	3	1,601	3.08	0.00
Other medication exposures, N (%)					
Benzodiazepines	733	37.28	12,568	24.16	0.29
Other hypnotics	441	22.43	7,593	14.6	0.20
Barbiturates	95	4.83	1,626	3.13	0.09

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Anxiolytics	88	4.48	1,804	3.47	0.05
Anticonvulsants	496	25.23	5,950	11.44	0.36
Antipsychotics	373	18.97	6,081	11.69	0.20
SSRIs	139	7.07	52,018	100	-5.13
SNRIs	73	3.71	1,651	3.17	0.03
Other Antidep	532	27.06	9,636	18.52	0.20
Stimulants	161	8.19	2,376	4.57	0.15
Antidiabetic	80	4.07	1,276	2.45	0.09
Insulin	68	3.46	982	1.89	0.10
Antihyperten	276	14.04	4,560	8.77	0.17
Opioid analgesics	1,210	61.55	23,787	45.73	0.32
Triptans	132	6.71	2,083	4	0.12
NSAIDs	731	37.18	14,918	28.68	0.18
Obstetric conditions, N (%)					
Multifetal gestation Flag	71	3.61	2,079	4	-0.02
Potentially teratogenic medication exposures, N (%)					
Danazol	0	0	<11	0.01	-0.01
Synthetic progestins	67	3.41	1,659	3.19	0.01
Methimazole	<11	0.1	38	0.07	0.01
Propylthiouracil	<11	0.15	68	0.13	0.01
Corticosteroids	343	17.45	7,202	13.85	0.10
Fluconazole	109	5.54	2,084	4.01	0.07
Markers of healthcare utilization					
Number of distinct 3 digit ICD 9 codes=0	104	5.29	5,237	10.07	-0.18
Number of distinct 3 digit ICD 9 codes: tertile 1 for number >0	380	19.33	11,939	22.95	-0.09
Number of distinct 3 digit ICD 9 codes: tertile 2 for number >0	428	21.77	11,486	22.08	-0.01
Number of distinct 3 digit ICD 9 codes: tertile 3 for number >0	1,054	53.61	23,356	44.9	0.17
Number of ED visits=0	1,200	61.04	34,899	67.09	-0.13
Number of ED visits=1	449	22.84	9,949	19.13	0.09
Number of ED visits=2	175	8.9	3,964	7.62	0.05
Number of ED visits>2	142	7.22	3,206	6.16	0.04
Number of non-duloxetine generics dispensed=0	150	7.63	4,945	9.51	-0.07

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Number of non-duloxetine generics dispensed: tertile 1 for number >0	151	7.68	5,827	11.2	-0.12
Number of non-duloxetine generics dispensed: tertile 2 for number >0	431	21.92	13,952	26.82	-0.11
Number of non-duloxetine generics dispensed: tertile 3 for number >0	1,234	62.77	27,294	52.47	0.21
Number of hospital admissions=0	1,888	96.03	49,167	94.52	0.07
Number of hospital admissions=1	67	3.41	2,516	4.84	-0.07
Number of hospital admissions=2	<11	0.46	272	0.52	-0.01
Number of hospital admissions>2	<11	0.1	63	0.12	-0.01
Number of outpatient visits=0	190	9.66	7,656	14.72	-0.15
Number of outpatient visits: tertile 1 for number >0	223	11.34	8,069	15.51	-0.12
Number of outpatient visits: tertile 2 for number >0	498	25.33	13,728	26.39	-0.02
Number of outpatient visits: tertile 3 for number >0	1,055	53.66	22,565	43.38	0.21
Number of psychiatric hospitalizations Q1	1,919	97.61	50,847	97.75	-0.01
Number of psychiatric hospitalizations Q2	41	2.09	1,019	1.96	0.01
Number of psychiatric hospitalizations Q3	<11	0.2	121	0.23	-0.01
Number of psychiatric hospitalizations Q4	<11	0.1	31	0.06	0.01
Number of psychiatrist visits=0	891	45.32	28,009	53.84	-0.17
Number of psychiatrist visits=1	433	22.02	9,969	19.16	0.07
Number of psychiatrist visits=2	205	10.43	4,802	9.23	0.04
Number of psychiatrist visits>2	437	22.23	9,238	17.76	0.11
Geographic region					
Arkansas	PPD		36	0.07	-0.01
Alabama			340	0.65	-0.06
California	141	7.17	4,838	9.3	-0.08
Colorado	PPD		263	0.51	-0.06
District of Columbia			PPD		0.01
Delaware	50	2.54			0.11
Florida	PPD		721	1.39	-0.12
Georgia			1,029	1.98	-0.15
Hawaii			77	0.15	-0.03

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Iowa	17	0.86	635	1.22	-0.04
Idaho	0	0	157	0.3	-0.08
Illinois	220	11.19	4,417	8.49	0.09
Indiana	200	10.17	2,529	4.86	0.20
Kansas	28	1.42	518	1	0.04
Kentucky	29	1.48	1,441	2.77	-0.09
Louisiana	62	3.15	875	1.68	0.10
Massachusetts	PPD		308	0.59	-0.07
Maryland	23	1.17	794	1.53	-0.03
Maine	PPD		287	0.55	-0.04
Minnesota	101	5.14	3,369	6.48	-0.06
Missouri	106	5.39	2,082	4	0.07
Mississippi	PPD		648	1.25	-0.07
North Carolina	44	2.24	640	1.23	0.08
North Dakota	19	0.97	255	0.49	0.06
Nebraska	15	0.76	323	0.62	0.02
New Hampshire	PPD		326	0.63	-0.05
New Jersey	0	0	254	0.49	-0.10
New Mexico	15	0.76	808	1.55	-0.07
Nevada	PPD		87	0.17	-0.02
New York	379	19.28	5,852	11.25	0.22
Ohio	28	1.42	1,360	2.61	-0.08
Oklahoma	17	0.86	701	1.35	-0.05
Oregon	34	1.73	840	1.61	0.01
Pennsylvania	PPD		1,600	3.08	-0.18
Rhode Island	PPD		107	0.21	-0.03
South Carolina	PPD		102	0.2	0.01
South Dakota	PPD		268	0.52	0.01
Tennessee	139	7.07	5,204	10	-0.11
Texas	PPD		141	0.27	0.01
Utah	45	2.29	697	1.34	0.07
Virginia	48	2.44	1,213	2.33	0.01

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Vermont	22	1.12	768	1.48	-0.03
Washington	PPD		62	0.12	-0.05
Wisconsin	88	4.48	4,271	8.21	-0.15
West Virginia	PPD		120	0.23	-0.01
Wyoming			65	0.12	-0.01
Opioids					
buprenorphine	54	2.75	702	1.35	0.10
butorphanol	<11	0.2	20	0.04	0.05
codeine	243	12.36	6,793	13.06	-0.02
fentanyl	23	1.17	139	0.27	0.11
hydrocodone	814	41.4	15,398	29.6	0.25
hydromorphone	21	1.07	173	0.33	0.09
Levorphanol	0	0	<11	0	-0.01
meperidine	<11	0.2	103	0.2	0.00
methadone	23	1.17	202	0.39	0.09
morphine	38	1.93	194	0.37	0.15
oxycodone	302	15.36	4,498	8.65	0.21
oxymorphone	<11	0.1	19	0.04	0.02
pentazocine	<11	0.15	46	0.09	0.02
propoxyphene	109	5.54	3,006	5.78	-0.01
tapentadol	<11	0.2	13	0.02	0.05
tramadol	319	16.23	4,308	8.28	0.24
Healthcare Utilization, mean (SD)					
Comorbidity Index	1.56	1.83	1.23	1.61	0.19
Morphine equivalents	24772.14	555308.29	3417.44	162034.31	0.05
Number of diagnoses	5.85	4.56	5	4.36	0.19
Number of ED visits	0.72	1.31	0.62	1.43	0.07
Number of non-duloxetine generics dispensed	5.4	4.07	4.47	3.65	0.24
Number of hospitalizations	0.05	0.25	0.06	0.28	-0.06
Number of outpatient visits	5.35	6.03	4.33	5.49	0.18
Number of psychiatric hospitalizations	0.03	0.2	0.03	0.2	0.01
Number of psychiatrist visits	2.06	4.75	1.7	4.5	0.08

15.1. 3. Malformations- Baseline characteristics of duloxetine exposed vs. venlafaxine exposed women: unadjusted

	Duloxetine N/Mean	Duloxetine %/SD	Venlafaxine N/Mean	Venlafaxine %/SD	Standardized Difference
Total	2,467	100.00	6,369	100.00	
Demographics					
Age, mean (SD)	27.74	5.53	26.75	5.3	0.18
Age categorical, N (%)					
<=19	123	4.99	409	6.42	-0.06
20-24	631	25.58	2,023	31.76	-0.14
25-29	847	34.33	2,099	32.96	0.03
30-34	544	22.05	1,245	19.55	0.06
35-39	253	10.26	495	7.77	0.09
>=40	69	2.8	98	1.54	0.09
Race, N (%)					
White	1,950	79.04	5,140	80.7	-0.04
Black/African American	215	8.72	456	7.16	0.06
Hispanic/Latino	67	2.72	286	4.49	-0.10
Asian or Other Pacific	28	1.13	78	1.22	-0.01
American Indian	33	1.34	77	1.21	0.01
Other	117	4.74	194	3.05	0.09
Unknown	57	2.31	138	2.17	0.01
Chronic comorbid conditions, N (%)					
Hypertension	188	7.62	335	5.26	0.10
Diabetes	150	6.08	235	3.69	0.11
Renal Disease	22	0.89	33	0.52	0.04
Obesity Overweight	148	6	280	4.4	0.07
Comorbidity Index Q1	856	34.7	2,580	40.51	-0.12
Comorbidity Index Q2	623	25.25	1,617	25.39	0.00
Comorbidity Index Q3	423	17.15	1,019	16	0.03
Comorbidity Index Q4	565	22.9	1,153	18.1	0.12
Infections, N (%)					
Toxoplasmosis	0	0	<11	0.03	-0.03
Rubella	0	0	0	0	
Cytomegalovirus	0	0	0	0	

	Duloxetine N/Mean	Duloxetine %/SD	Venlafaxine N/Mean	Venlafaxine %/SD	Standardized Difference
Herpes	39	1.58	81	1.27	0.03
Syphilis	<11	0	<11	0.05	-0.03
Varicella	<11	0.04	<11	0.03	0.00
Parvovirus B19	0	0	0	0	
Zika virus other mosquito	0	0	0	0	
Lymphocytic choriomeningitis	0	0.04	<11	0	0.03
Influenza	20	0.81	58	0.91	-0.01
Chlamydia	11	0.45	30	0.47	0.00
Human papilloma virus	23	0.93	47	0.74	0.02
Gonorrhea	13	0.53	21	0.33	0.03
HIV	<11	0.28	24	0.38	-0.02
Trichomoniasis	18	0.73	61	0.96	-0.02
Indications for duloxetine, N (%)					
Depression	1,201	48.68	3,130	49.14	-0.01
Anxiety	750	30.4	1,785	28.03	0.05
Neuropathic Pain	253	10.26	352	5.53	0.18
Fibromyalgia	254	10.3	217	3.41	0.28
Non neuropathic Pain	1,200	48.64	2,250	35.33	0.27
Other psychiatric conditions, N (%)					
Sleep disorder	140	5.67	344	5.4	0.01
Bipolar disorder	317	12.85	663	10.41	0.08
Psychosis	20	0.81	58	0.91	-0.01
Schizophrenia	23	0.93	57	0.89	0.00
Personality disorder	53	2.15	112	1.76	0.03
Adjustment disorder	27	1.09	69	1.08	0.00
Tobacco use, N (%)	273	11.07	588	9.23	0.06
Alcohol abuse or dependence, N (%)	31	1.26	117	1.84	-0.05
Drug abuse or dependence, N (%)	81	3.28	255	4	-0.04
Other medication exposures, N (%)					
Benzodiazepines	946	38.35	1,966	30.87	0.16
Other hypnotics	584	23.67	1,115	17.51	0.15
Barbiturates	118	4.78	228	3.58	0.06

	Duloxetine N/Mean	Duloxetine %/SD	Venlafaxine N/Mean	Venlafaxine %/SD	Standardized Difference
Anxiolytics	124	5.03	280	4.4	0.03
Anticonvulsants	622	25.21	1,031	16.19	0.22
Antipsychotics	487	19.74	1,007	15.81	0.10
SSRIs	677	27.44	1,587	24.92	0.06
SNRIs	38	1.54	6,369	100	-11.30
Other Antidep	695	28.17	1,520	23.87	0.10
Stimulants	192	7.78	370	5.81	0.08
Antidiabetic	98	3.97	172	2.7	0.07
Insulin	80	3.24	113	1.77	0.09
Antihyperten	362	14.67	630	9.89	0.15
Opioid analgesics	1,513	61.33	3,138	49.27	0.24
Triptans	174	7.05	341	5.35	0.07
NSAIDs	936	37.94	1,880	29.52	0.18
Obstetric conditions, N (%)					
Multifetal gestation Flag	86	3.49	244	3.83	-0.02
Potentially teratogenic medication exposures, N (%)					
Danazol	<11	0	<11	0	
Synthetic progestins	85	3.45	206	3.23	0.01
Methimazole	<11	0.12	<11	0.09	0.01
Propylthiouracil	<11	0.16	<11	0.16	0.00
Corticosteroids	439	17.79	909	14.27	0.10
Fluconazole	130	5.27	253	3.97	0.06
Markers of healthcare utilization					
Number of distinct 3 digit ICD 9 codes=0	121	4.9	534	8.38	-0.14
Number of distinct 3 digit ICD 9 codes: tertile 1 for number >0	478	19.38	1,432	22.48	-0.08
Number of distinct 3 digit ICD 9 codes: tertile 2 for number >0	541	21.93	1,457	22.88	-0.02
Number of distinct 3 digit ICD 9 codes: tertile 3 for number >0	1,327	53.79	2,946	46.26	0.15
Number of ED visits=0	1,535	62.22	4,344	68.21	-0.13
Number of ED visits=1	530	21.48	1,163	18.26	0.08
Number of ED visits=2	217	8.8	461	7.24	0.06
Number of ED visits>2	185	7.5	401	6.3	0.05
Number of non-duloxetine generics dispensed=0	172	6.97	318	4.99	0.08

	Duloxetine N/Mean	Duloxetine %/SD	Venlafaxine N/Mean	Venlafaxine %/SD	Standardized Difference
Number of non-duloxetine generics dispensed: tertile 1 for number >0	186	7.54	576	9.04	-0.05
Number of non-duloxetine generics dispensed: tertile 2 for number >0	528	21.4	1,639	25.73	-0.10
Number of non-duloxetine generics dispensed: tertile 3 for number >0	1,581	64.09	3,836	60.23	0.08
Number of hospital admissions=0	2,355	95.46	6,070	95.31	0.01
Number of hospital admissions=1	96	3.89	260	4.08	-0.01
Number of hospital admissions=2	14	0.57	31	0.49	0.01
Number of hospital admissions>2	<11	0.08	<11	0.13	-0.01
Number of outpatient visits=0	228	9.24	810	12.72	-0.11
Number of outpatient visits: tertile 1 for number >0	275	11.15	923	14.49	-0.10
Number of outpatient visits: tertile 2 for number >0	618	25.05	1,684	26.44	-0.03
Number of outpatient visits: tertile 3 for number >0	1,346	54.56	2,952	46.35	0.16
Number of psychiatric hospitalizations Q1	2,396	97.12	6,202	97.38	-0.02
Number of psychiatric hospitalizations Q2	61	2.47	143	2.25	0.02
Number of psychiatric hospitalizations Q3	<11	0.32	19	0.3	0.00
Number of psychiatric hospitalizations Q4	<11	0.08	<11	0.08	0.00
Number of psychiatrist visits=0	1,076	43.62	2,946	46.26	-0.05
Number of psychiatrist visits=1	528	21.4	1,326	20.82	0.01
Number of psychiatrist visits=2	268	10.86	715	11.23	-0.01
Number of psychiatrist visits>2	595	24.12	1,382	21.7	0.06
Geographic region					
Arkansas	PPD		PPD		0.02
Alabama			19	0.3	0.02
California	168	6.81	505	7.93	-0.04
Colorado	PPD		32	0.5	-0.06
District of Columbia			PPD		0.00
Delaware	65	2.63	79	1.24	0.10
Florida	PPD		63	0.99	-0.07
Georgia			118	1.85	-0.13
Hawaii			PPD		-0.01

	Duloxetine N/Mean	Duloxetine %/SD	Venlafaxine N/Mean	Venlafaxine %/SD	Standardized Difference
Iowa	25	1.01	124	1.95	-0.08
Idaho	PPD		38	0.6	-0.09
Illinois	293	11.88	501	7.87	0.13
Indiana	239	9.69	328	5.15	0.17
Kansas	40	1.62	66	1.04	0.05
Kentucky	39	1.58	142	2.23	-0.05
Louisiana	85	3.45	120	1.88	0.10
Massachusetts	PPD		16	0.25	-0.02
Maryland	31	1.26	94	1.48	-0.02
Maine	PPD		36	0.57	-0.04
Minnesota	140	5.67	403	6.33	-0.03
Missouri	135	5.47	321	5.04	0.02
Mississippi	14	0.57	104	1.63	-0.10
North Carolina	56	2.27	74	1.16	0.09
North Dakota	25	1.01	33	0.52	0.06
Nebraska	23	0.93	51	0.8	0.01
New Hampshire	PPD		38	0.6	-0.05
New Jersey			33	0.52	-0.10
New Mexico	18	0.73	93	1.46	-0.07
Nevada	PPD		PPD		-0.01
New York	449	18.2	719	11.29	0.20
Ohio	32	1.3	248	3.89	-0.16
Oklahoma	27	1.09	77	1.21	-0.01
Oregon	42	1.7	106	1.66	0.00
Pennsylvania	17	0.69	289	4.54	-0.24
Rhode Island	PPD		14	0.22	-0.04
South Carolina			16	0.25	-0.01
South Dakota	14	0.57	40	0.63	-0.01
Tennessee	149	6.04	579	9.09	-0.12
Texas	PPD		PPD		0.02
Utah	59	2.39	84	1.32	0.08
Virginia	57	2.31	127	1.99	0.02

	Duloxetine N/Mean	Duloxetine %/SD	Venlafaxine N/Mean	Venlafaxine %/SD	Standardized Difference
Vermont	27	1.09	64	1	0.01
Washington	PPD		PPD		-0.03
Wisconsin	113	4.58	507	7.96	-0.14
West Virginia	PPD		14	0.22	-0.01
Wyoming	PPD		14	0.22	-0.02
Opioids					
buprenorphine	64	2.59	114	1.79	0.05
butorphanol	<11	0.16	<11	0.09	0.02
codeine	326	13.21	916	14.38	-0.03
fentanyl	31	1.26	35	0.55	0.07
hydrocodone	1,029	41.71	2,050	32.19	0.20
hydromorphone	29	1.18	23	0.36	0.09
levorphanol	<11	0	<11	0	
meperidine	<11	0.2	17	0.27	-0.01
methadone	25	1.01	31	0.49	0.06
morphine	44	1.78	41	0.64	0.10
oxycodone	384	15.57	595	9.34	0.19
oxymorphone	<11	0.08	<11	0.13	-0.01
pentazocine	<11	0.12	<11	0.13	0.00
propoxyphene	136	5.51	421	6.61	-0.05
tapentadol	<11	0.2	<11	0.02	0.06
tramadol	405	16.42	631	9.91	0.19
Healthcare Utilization, mean (SD)					
Comorbidity Index	1.57	1.83	1.32	1.64	0.14
Morphine equivalents	20232.43	495794.92	2551.52	86147.49	0.05
Number of diagnoses	5.91	4.6	5.14	4.34	0.17
Number of ED visits	0.71	1.29	0.62	1.36	0.07
Number of non-duloxetine generics dispensed	5.58	4.15	5.18	3.9	0.10
Number of hospitalizations	0.05	0.26	0.05	0.27	-0.01
Number of outpatient visits	5.52	6.27	4.66	5.84	0.14
Number of psychiatric hospitalizations	0.03	0.22	0.03	0.21	0.01
Number of psychiatrist visits	2.23	4.77	2.03	4.76	0.04

15.1. 4. Malformations- Baseline characteristics of duloxetine exposed women vs. duloxetine discontinuers: unadjusted

	Duloxetine	Duloxetine	Duloxetine discontinuers	Duloxetine discontinuers	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Total	2,532	100.00	2,456	100.00	
Demographics					
Age, mean (SD)	27.75	5.53	26.67	5.25	0.12
Age categorical, N (%)					
<=19	125	4.94	159	6.47	-0.07
20-24	645	25.47	783	31.88	-0.14
25-29	872	34.44	855	34.81	-0.01
30-34	560	22.12	456	18.57	0.09
35-39	258	10.19	163	6.64	0.13
>=40	72	2.84	40	1.63	0.08
Race, N (%)					
White	2,003	79.11	1,866	75.98	0.08
Black/African American	219	8.65	260	10.59	-0.07
Hispanic/Latino	70	2.76	78	3.18	-0.02
Asian or Other Pacific	32	1.26	39	1.59	-0.03
American Indian	33	1.3	42	1.71	-0.03
Other	117	4.62	132	5.37	-0.03
Unknown	58	2.29	39	1.59	0.05
Chronic comorbid conditions, N (%)					
Hypertension	191	7.54	145	5.9	0.07
Diabetes	152	6	117	4.76	0.05
Renal Disease	23	0.91	25	1.02	-0.01
Obesity Overweight	152	6	128	5.21	0.03
Comorbidity Index Q1	882	34.83	960	39.09	-0.09
Comorbidity Index Q2	639	25.24	674	27.44	-0.05
Comorbidity Index Q3	427	16.86	364	14.82	0.06
Comorbidity Index Q4	584	23.06	458	18.65	0.11
Infections, N (%)					
Toxoplasmosis	0	0	0	0	
Rubella	0	0	0	0	

	Duloxetine	Duloxetine	Duloxetine	Duloxetine	
	N/Mean	%/SD	discontinuers N/Mean	discontinuers %/SD	Standardized Difference
Cytomegalovirus	0	0	0	0	
Herpes	41	1.62	27	1.1	0.04
Syphilis	<11	0	<11	0.08	-0.04
Varicella	<11	0.04	<11	0	0.03
Parvovirus B19	0	0	0	0	
Zika virus other mosquito	0	0	0	0	
Lymphocytic choriomeningitis	<11	0.04	0	0	0.03
Influenza	21	0.83	29	1.18	-0.04
Chlamydia	11	0.43	13	0.53	-0.01
Human papilloma virus	25	0.99	18	0.73	0.03
Gonorrhea	13	0.51	15	0.61	-0.01
HIV	<11	0.28	11	0.45	-0.03
Trichomoniasis	18	0.71	32	1.3	-0.06
Indications for duloxetine, N (%)					
Depression	1,235	48.78	943	38.4	0.21
Anxiety	778	30.73	601	24.47	0.14
Neuropathic Pain	267	10.55	228	9.28	0.04
Fibromyalgia	264	10.43	187	7.61	0.10
Non neuropathic Pain	1,234	48.74	1,104	44.95	0.08
Other psychiatric conditions, N (%)					
Sleep disorder	144	5.69	121	4.93	0.03
Bipolar disorder	330	13.03	260	10.59	0.08
Psychosis	20	0.79	21	0.86	-0.01
Schizophrenia	25	0.99	19	0.77	0.02
Personality disorder	56	2.21	41	1.67	0.04
Adjustment disorder	29	1.15	16	0.65	0.05
Tobacco use, N (%)	279	11.02	243	9.89	0.04
Alcohol abuse or dependence, N (%)	31	1.22	29	1.18	0.00
Drug abuse or dependence, N (%)	84	3.32	69	2.81	0.03
Other medication exposures, N (%)					
Benzodiazepines	979	38.67	709	28.87	0.21

	Duloxetine	Duloxetine	Duloxetine	Duloxetine	
	N/Mean	%/SD	discontinuers N/Mean	discontinuers %/SD	Standardized Difference
Other hypnotics	608	24.01	472	19.22	0.12
Barbiturates	124	4.9	93	3.79	0.05
Anxiolytics	129	5.09	99	4.03	0.05
Anticonvulsants	642	25.36	451	18.36	0.17
Antipsychotics	505	19.94	376	15.31	0.12
SSRIs	705	27.84	579	23.57	0.10
SNRIs	103	4.07	118	4.8	-0.04
Other Antidep	720	28.44	527	21.46	0.16
Stimulants	198	7.82	129	5.25	0.10
Antidiabetic	100	3.95	63	2.57	0.08
Insulin	80	3.16	66	2.69	0.03
Antihyperten	373	14.73	259	10.55	0.13
Opioid analgesics	1,554	61.37	1,419	57.78	0.07
Triptans	178	7.03	139	5.66	0.06
NSAIDs	958	37.84	805	32.78	0.11
Obstetric conditions, N (%)					
Multifetal gestation Flag	87	3.44	86	3.5	0.00
Potentially teratogenic medication exposures, N (%)					
Danazol	<11	0	<11	0	
Synthetic progestins	88	3.48	66	2.69	0.05
Methimazole	<11	0.12	<11	0.04	0.03
Propylthiouracil	<11	0.16	<11	0.08	0.02
Corticosteroids	453	17.89	373	15.19	0.07
Fluconazole	133	5.25	94	3.83	0.07
Markers of healthcare utilization					
Number of distinct 3 digit ICD 9 codes=0	123	4.86	146	5.94	-0.05
Number of distinct 3 digit ICD 9 codes: tertile 1 for number >0	489	19.31	468	19.06	0.01
Number of distinct 3 digit ICD 9 codes: tertile 2 for number >0	552	21.8	550	22.39	-0.01
Number of distinct 3 digit ICD 9 codes: tertile 3 for number >0	1,368	54.03	1,292	52.61	0.03
Number of ED visits=0	1,570	62.01	1,472	59.93	0.04
Number of ED visits=1	547	21.6	546	22.23	-0.02

	Duloxetine	Duloxetine	Duloxetine	Duloxetine	
	N/Mean	%/SD	discontinuers N/Mean	discontinuers %/SD	Standardized Difference
Number of ED visits=2	223	8.81	233	9.49	-0.02
Number of ED visits>2	192	7.58	205	8.35	-0.03
Number of non-duloxetine generics dispensed=0	173	6.83	226	9.2	-0.09
Number of non-duloxetine generics dispensed: tertile 1 for number >0	188	7.42	220	8.96	-0.06
Number of non-duloxetine generics dispensed: tertile 2 for number >0	542	21.41	561	22.84	-0.03
Number of non-duloxetine generics dispensed: tertile 3 for number >0	1,629	64.34	1,449	59	0.11
Number of hospital admissions=0	2,413	95.3	2,348	95.6	-0.01
Number of hospital admissions=1	102	4.03	87	3.54	0.03
Number of hospital admissions=2	15	0.59	17	0.69	-0.01
Number of hospital admissions>2	<11	0.08	<11	0.16	-0.02
Number of outpatient visits=0	230	9.08	259	10.55	-0.05
Number of outpatient visits: tertile 1 for number >0	284	11.22	337	13.72	-0.08
Number of outpatient visits: tertile 2 for number >0	631	24.92	596	24.27	0.02
Number of outpatient visits: tertile 3 for number >0	1,387	54.78	1,264	51.47	0.07
Number of psychiatric hospitalizations Q1	2,456	97	2,382	96.99	0.00
Number of psychiatric hospitalizations Q2	66	2.61	59	2.4	0.01
Number of psychiatric hospitalizations Q3	<11	0.32	12	0.49	-0.03
Number of psychiatric hospitalizations Q4	<11	0.08	<11	0.12	-0.01
Number of psychiatrist visits=0	1,097	43.33	1,224	49.84	-0.13
Number of psychiatrist visits=1	534	21.09	487	19.83	0.03
Number of psychiatrist visits=2	274	10.82	236	9.61	0.04
Number of psychiatrist visits>2	627	24.76	509	20.72	0.10
Geographic region					
Arkansas	PPD		PPD		-0.03
Alabama					0.04
California	173	6.83	158	6.43	0.02
Colorado	PPD		PPD		-0.02
District of Columbia					0.03

	Duloxetine	Duloxetine	Duloxetine	Duloxetine	
	N/Mean	%/SD	discontinuers	discontinuers	Standardized
			N/Mean	%/SD	Difference
Delaware	66	2.61	74	3.01	-0.02
Florida	PPD		17	0.69	-0.03
Georgia			16	0.65	-0.02
Hawaii			PPD		-0.01
Iowa	26	1.03	26	1.06	0.00
Idaho	PPD		PPD		0.01
Illinois	299	11.81	310	12.62	-0.02
Indiana	241	9.52	184	7.49	0.07
Kansas	41	1.62	35	1.43	0.02
Kentucky	41	1.62	52	2.12	-0.04
Louisiana	87	3.44	99	4.03	-0.03
Massachusetts	PPD		PPD		0.02
Maryland	31	1.22	32	1.3	-0.01
Maine	PPD		PPD		0.00
Minnesota	146	5.77	116	4.72	0.05
Missouri	139	5.49	160	6.51	-0.04
Mississippi	14	0.55	13	0.53	0.00
North Carolina	56	2.21	47	1.91	0.02
North Dakota	25	0.99	23	0.94	0.01
Nebraska	24	0.95	28	1.14	-0.02
New Hampshire	PPD		PPD		-0.02
New Jersey					-0.04
New Mexico	20	0.79	18	0.73	0.01
Nevada	PPD		PPD		0.00
New York	458	18.09	481	19.58	-0.04
Ohio	33	1.3	26	1.06	0.02
Oklahoma	27	1.07	21	0.86	0.02
Oregon	42	1.66	46	1.87	-0.02
Pennsylvania	17	0.67	22	0.9	-0.03
Rhode Island	PPD		PPD		0.00
South Carolina					-0.02

	Duloxetine	Duloxetine	Duloxetine	Duloxetine	
	N/Mean	%/SD	discontinuers	discontinuers	Standardized
			N/Mean	%/SD	Difference
South Dakota	14	0.55	17	0.69	-0.02
Tennessee	159	6.28	136	5.54	0.03
Texas	PPD		PPD		0.01
Utah	60	2.37	54	2.2	0.01
Virginia	60	2.37	70	2.85	-0.03
Vermont	27	1.07	19	0.77	0.03
Washington	PPD		0	0	0.03
Wisconsin	117	4.62	91	3.71	0.05
West Virginia	PPD		PPD		0.01
Wyoming					-0.01
Opioids					
buprenorphine	68	2.69	54	2.2	0.03
butorphanol	<11	0.16	0	0	0.06
codeine	338	13.35	343	13.97	-0.02
fentanyl	32	1.26	26	1.06	0.02
hydrocodone	1,056	41.71	938	38.19	0.07
hydromorphone	31	1.22	20	0.81	0.04
Levorphanol	0	0	0	0	
meperidine	<11	0.2	<11	0.24	-0.01
methadone	26	1.03	19	0.77	0.03
morphine	44	1.74	31	1.26	0.04
oxycodone	398	15.72	316	12.87	0.08
oxymorphone	<11	0.08	<11	0.08	0.00
pentazocine	<11	0.12	<11	0.08	0.01
propoxyphene	144	5.69	156	6.35	-0.03
tapentadol	<11	0.2	<11	0.12	0.02
tramadol	417	16.47	379	15.43	0.03
Healthcare Utilization, mean (SD)					
Comorbidity Index	1.58	1.85	1.36	1.7	0.12
Morphine equivalents	19773.7	489395.76	5061.95	60497.3	0.04
Number of diagnoses	5.95	4.65	5.8	4.59	0.03

	Duloxetine	Duloxetine	Duloxetine discontinuers	Duloxetine discontinuers	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Number of ED visits	0.72	1.3	0.81	1.64	-0.06
Number of non-duloxetine generics dispensed	5.63	4.19	5.11	4.11	0.12
Number of hospitalizations	0.05	0.27	0.05	0.28	0.00
Number of outpatient visits	5.58	6.43	5.2	6.2	0.06
Number of psychiatric hospitalizations	0.04	0.22	0.04	0.24	-0.01
Number of psychiatrist visits	2.28	4.94	1.95	4.62	0.07

15.1. 5. Malformations- Baseline characteristics of duloxetine exposed vs. unexposed women: adjusted for treatment indications

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Total	2,224	100.00	420,806	100.00	
Demographics					
Age, mean (SD)	27.81	5.55	25.56	5.37	0.41
Age categorical, N (%)					
<=19	104	4.68	50,583	12.02	-0.27
20-24	566	25.45	153,724	36.53	-0.24
25-29	766	34.44	123,411	29.33	0.11
30-34	490	22.03	62,340	14.81	0.19
35-39	232	10.43	25,157	5.98	0.16
>=40	66	2.97	5,591	1.33	0.11
Race, N (%)					
White	1,762	79.23	252,955	60.11	0.43
Black or African American	193	8.68	86,777	20.62	-0.34
Hispanic or Latino	61	2.74	35,141	8.35	-0.25
Asian or Other Pacific Islander	30	1.35	8,377	1.99	-0.05
American Indian	29	1.3	8,904	2.12	-0.06
Other	101	4.54	19,285	4.58	0.00
Unknown	48	2.16	9,366	2.23	0.00
Chronic comorbid conditions, N (%)					
Hypertension	173	7.78	21,774	5.17	0.11
Diabetes	135	6.07	16,772	3.99	0.10
Renal Disease	22	0.99	3,332	0.79	0.02
Obesity Overweight	142	6.38	21,580	5.13	0.05
Comorbidity Index Q1	760	34.17	185,743	44.14	-0.21
Comorbidity Index Q2	557	25.04	107,783	25.61	-0.01
Comorbidity Index Q3	377	16.95	62,568	14.87	0.06
Comorbidity Index Q4	530	23.83	64,712	15.38	0.21
Infections, N (%)					
Toxoplasmosis	0	0	96	0.02	-0.02
Rubella	0	0	31	0.01	-0.01
Cytomegalovirus	0	0	17	0	-0.01

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Herpes	35	1.57	5,794	1.38	0.02
Syphilis	0	0	387	0.09	-0.04
Varicella	0	0	97	0.02	-0.02
Parvovirus B19	0	0	13	0	-0.01
Zika virus other mosquito	0	0	0	0	
Lymphocytic choriomeningitis	<11	0.04	0	0	0.03
Influenza	19	0.85	4,511	1.07	-0.02
Chlamydia	<11	0.45	2,799	0.67	-0.03
Human papilloma virus	22	0.99	3,135	0.74	0.03
Gonorrhea	<11	0.45	3,069	0.73	-0.04
HIV	<11	0.27	1,574	0.37	-0.02
Trichomoniasis	16	0.72	5,528	1.31	-0.06
Indications for duloxetine, N (%)					
Depression	1,235	55.53	233,764	55.55	0.00
Anxiety	778	34.98	165,619	39.36	-0.09
Neuropathic Pain	267	12.01	54,610	12.98	-0.03
Fibromyalgia	264	11.87	44,917	10.67	0.04
Non neuropathic Pain	1,234	55.49	233,039	55.38	0.00
Other psychiatric conditions, N (%)					
Sleep disorder	136	6.12	16,358	3.89	0.10
Bipolar disorder	294	13.22	26,836	6.38	0.23
Psychosis	19	0.85	4,510	1.07	-0.02
Schizophrenia	23	1.03	3,005	0.71	0.03
Personality disorder	55	2.47	6,076	1.44	0.07
Adjustment disorder	26	1.17	5,344	1.27	-0.01
Tobacco use, N (%)	266	11.96	43,161	10.26	0.05
Alcohol abuse or dependence, N (%)	28	1.26	5,685	1.35	-0.01
Drug abuse or dependence, N (%)	80	3.6	12,277	2.92	0.04
Other medication exposures, N (%)					
Benzodiazepines	912	41.01	88,357	21	0.44
Other hypnotics	564	25.36	51,907	12.34	0.34
Barbiturates	111	4.99	12,165	2.89	0.11

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Anxiolytics	119	5.35	12,771	3.03	0.12
Anticonvulsants	591	26.57	43,109	10.24	0.43
Antipsychotics	463	20.82	33,952	8.07	0.37
SSRIs	645	29	151,272	35.95	-0.15
SNRIs	92	4.14	21,945	5.22	-0.05
Other Antidep	668	30.04	67,730	16.1	0.34
Stimulants	172	7.73	14,746	3.5	0.18
Antidiabetic	86	3.87	7,669	1.82	0.12
Insulin	69	3.1	6,876	1.63	0.10
Antihyperten	329	14.79	29,803	7.08	0.25
Opioid analgesics	1,426	64.12	205,291	48.79	0.31
Triptans	165	7.42	14,619	3.47	0.17
NSAIDs	894	40.2	139,596	33.17	0.15
Obstetric conditions, N (%)					
Multifetal gestation Flag	77	3.46	16,670	3.96	-0.03
Potentially teratogenic medication exposures, N (%)					
Danazol	<11	0	13	0	-0.01
Synthetic progestins	80	3.6	11,423	2.71	0.05
Methimazole	<11	0.13	291	0.07	0.02
Propylthiouracil	<11	0.18	668	0.16	0.01
Corticosteroids	402	18.08	52,804	12.55	0.15
Fluconazole	115	5.17	15,011	3.57	0.08
Markers of healthcare utilization					
Number of distinct 3 digit ICD 9 codes=0	69	3.1	25,683	6.1	-0.14
Number of distinct 3 digit ICD 9 codes: tertile 1 for number >0	386	17.36	73,866	17.55	-0.01
Number of distinct 3 digit ICD 9 codes: tertile 2 for number >0	483	21.72	89,258	21.21	0.01
Number of distinct 3 digit ICD 9 codes: tertile 3 for number >0	1,286	57.82	232,000	55.13	0.05
Number of ED visits=0	1,326	59.62	246,297	58.53	0.02
Number of ED visits=1	497	22.35	94,017	22.34	0.00
Number of ED visits=2	214	9.62	40,892	9.72	0.00
Number of ED visits>2	187	8.41	39,599	9.41	-0.04
Number of non-duloxetine generics dispensed=0	132	5.94	69,365	16.48	-0.34

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Number of non-duloxetine generics dispensed: tertile 1 for number >0	152	6.83	47,388	11.26	-0.15
Number of non-duloxetine generics dispensed: tertile 2 for number >0	455	20.46	103,585	24.62	-0.10
Number of non-duloxetine generics dispensed: tertile 3 for number >0	1,485	66.77	200,467	47.64	0.39
Number of hospital admissions=0	2,113	95.01	393,832	93.59	0.06
Number of hospital admissions=1	94	4.23	23,204	5.51	-0.06
Number of hospital admissions=2	15	0.67	3,093	0.73	-0.01
Number of hospital admissions>2	<11	0.09	677	0.16	-0.02
Number of outpatient visits=0	150	6.74	44,726	10.63	-0.14
Number of outpatient visits: tertile 1 for number >0	219	9.85	54,915	13.05	-0.10
Number of outpatient visits: tertile 2 for number >0	557	25.04	104,838	24.91	0.00
Number of outpatient visits: tertile 3 for number >0	1,298	58.36	216,327	51.41	0.14
Number of psychiatric hospitalizations Q1	2,150	96.67	407,027	96.73	0.00
Number of psychiatric hospitalizations Q2	64	2.88	12,013	2.85	0.00
Number of psychiatric hospitalizations Q3	<11	0.36	1,454	0.35	0.00
Number of psychiatric hospitalizations Q4	<11	0.09	312	0.07	0.01
Number of psychiatrist visits=0	841	37.81	180,549	42.91	-0.10
Number of psychiatrist visits=1	520	23.38	99,668	23.69	-0.01
Number of psychiatrist visits=2	265	11.92	48,551	11.54	0.01
Number of psychiatrist visits>2	598	26.89	92,038	21.87	0.12
Geographic region					
Arkansas	PPD		425	0.1	0.01
Alabama	PPD		2,355	0.56	-0.02
California	146	6.56	48,988	11.64	-0.18
Colorado	PPD		1,288	0.31	-0.05
District of Columbia	PPD		130	0.03	0.01
Delaware	53	2.38	3,507	0.83	0.12
Florida	PPD		4,489	1.07	-0.08
Georgia	PPD		7,601	1.81	-0.13
Hawaii	PPD		1,946	0.46	-0.07

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Iowa	24	1.08	3,245	0.77	0.03
Idaho	PPD		726	0.17	-0.01
Illinois	258	11.6	31,871	7.57	0.14
Indiana	217	9.76	23,130	5.5	0.16
Kansas	36	1.62	3,590	0.85	0.07
Kentucky	35	1.57	12,691	3.02	-0.10
Louisiana	77	3.46	7,430	1.77	0.11
Massachusetts	PPD		1,459	0.35	-0.03
Maryland	27	1.21	8,958	2.13	-0.07
Maine	PPD		2,315	0.55	-0.04
Minnesota	141	6.34	27,214	6.47	-0.01
Missouri	119	5.35	12,295	2.92	0.12
Mississippi	PPD		7,257	1.72	-0.12
North Carolina	50	2.25	7,090	1.68	0.04
North Dakota	24	1.08	2,142	0.51	0.06
Nebraska	21	0.94	2,422	0.58	0.04
New Hampshire	PPD		2,653	0.63	-0.05
New Jersey	0	0	2,637	0.63	-0.11
New Mexico	20	0.9	7,340	1.74	-0.07
Nevada	PPD		572	0.14	-0.01
New York	386	17.36	51,406	12.22	0.15
Ohio	29	1.3	9,692	2.3	-0.08
Oklahoma	26	1.17	5,771	1.37	-0.02
Oregon	40	1.8	6,479	1.54	0.02
Pennsylvania	16	0.72	9,050	2.15	-0.12
Rhode Island	PPD		1,022	0.24	-0.04
South Carolina			764	0.18	0.01
South Dakota	13	0.58	2,552	0.61	0.00
Tennessee	142	6.38	43,001	10.22	-0.14
Texas	PPD		1,052	0.25	-0.01
Utah	48	2.16	2,959	0.7	0.12
Virginia	56	2.52	10,928	2.6	-0.01

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Vermont	26	1.17	5,057	1.2	0.00
Washington	PPD		227	0.05	0.00
Wisconsin	106	4.77	31,706	7.53	-0.12
West Virginia	PPD		862	0.2	-0.02
Wyoming			512	0.12	0.00
Opioids					
buprenorphine	57	2.56	3,773	0.9	0.13
butorphanol	<11	0.18	203	0.05	0.04
codeine	308	13.85	56,695	13.47	0.01
fentanyl	27	1.21	1,600	0.38	0.09
hydrocodone	977	43.93	136,618	32.47	0.24
hydromorphone	29	1.3	1,935	0.46	0.09
Levorphanol	0	0	<11	0	0.00
meperidine	<11	0.22	919	0.22	0.00
methadone	25	1.12	1,946	0.46	0.07
morphine	39	1.75	2,280	0.54	0.11
oxycodone	373	16.77	42,660	10.14	0.20
oxymorphone	<11	0.09	360	0.09	0.00
pentazocine	<11	0.13	393	0.09	0.01
propoxyphene	135	6.07	24,323	5.78	0.01
tapentadol	<11	0.22	231	0.05	0.05
tramadol	395	17.76	42,091	10	0.23
Healthcare Utilization, mean (SD)					
Comorbidity Index	1.62	1.88	1.21	1.62	0.23
Morphine equivalents	21626.78	521245.43	3191.88	122561.71	0.05
Number of diagnoses	6.33	4.7	6.07	4.79	0.06
Number of ED visits	0.77	1.32	0.85	1.63	-0.05
Number of non-duloxetine generics dispensed	5.88	4.25	4.1	3.74	0.44
Number of hospitalizations	0.06	0.28	0.08	0.32	-0.06
Number of outpatient visits	5.97	6.62	5.09	5.8	0.14
Number of psychiatric hospitalizations	0.04	0.23	0.04	0.23	0.00
Number of psychiatrist visits	2.49	5.1	2	4.41	0.10

15.1. 6. Malformations- Baseline characteristics of duloxetine exposed vs. SSRI exposed women: adjusted for treatment indications

	Duloxetine N/Mean	Duloxetine %/SD	SSRI N/Mean	SSRI %/SD	Standardized Difference
Total	1,705	100.00	40,671	100.00	
Demographics					
Age, mean (SD)	27.77	5.54	26.43	5.42	0.24
Age categorical, N (%)					
<=19	84	4.93	3,416	8.4	-0.14
20-24	431	25.28	13,347	32.82	-0.17
25-29	592	34.72	12,968	31.88	0.06
30-34	374	21.94	7,181	17.66	0.11
35-39	171	10.03	3,145	7.73	0.08
>=40	53	3.11	614	1.51	0.11
Race, N (%)					
White	1346	78.94	30,125	74.07	0.12
Black/African American	156	9.15	4,563	11.22	-0.07
Hispanic/Latino	46	2.7	2,459	6.05	-0.16
Asian or Other Pacific	22	1.29	474	1.17	0.01
American Indian	25	1.47	682	1.68	-0.02
Other	77	4.52	1,432	3.52	0.05
Unknown	33	1.94	936	2.3	-0.03
Chronic comorbid conditions, N (%)					
Hypertension	133	7.8	2,521	6.2	0.06
Diabetes	110	6.45	1,888	4.64	0.08
Renal Disease	15	0.88	335	0.82	0.01
Obesity Overweight	115	6.74	2,100	5.16	0.07
Comorbidity Index Q1	591	34.66	16,389	40.3	-0.12
Comorbidity Index Q2	424	24.87	10,383	25.53	-0.02
Comorbidity Index Q3	285	16.72	6,603	16.24	0.01
Comorbidity Index Q4	405	23.75	7,296	17.94	0.14
Infections, N (%)					
Toxoplasmosis	0	0	<11	0.01	-0.02
Rubella	0	0	<11	0	-0.01
Cytomegalovirus	0	0	<11	0.01	-0.01

	Duloxetine N/Mean	Duloxetine %/SD	SSRI N/Mean	SSRI %/SD	Standardized Difference
Herpes	27	1.58	581	1.43	0.01
Syphilis	0	0	36	0.09	-0.04
Varicella	0	0	14	0.03	-0.03
Parvovirus B19	0	0	<11	0	-0.01
Zika virus other mosquito	0	0	<11	0	
Lymphocytic choriomeningitis	<11	0.06	<11	0	0.03
Influenza	13	0.76	469	1.15	-0.04
Chlamydia	<11	0.53	211	0.52	0.00
Human papilloma virus	12	0.7	314	0.77	-0.01
Gonorrhea	<11	0.41	228	0.56	-0.02
HIV	<11	0.23	158	0.39	-0.03
Trichomoniasis	14	0.82	381	0.94	-0.01
Indications for duloxetine, N (%)					
Depression	904	53.02	21,587	53.08	0.00
Anxiety	562	32.96	13,211	32.48	0.01
Neuropathic Pain	202	11.85	5,701	14.02	-0.06
Fibromyalgia	203	11.91	4,866	11.96	0.00
Non neuropathic Pain	966	56.66	23,592	58.01	-0.03
Other psychiatric conditions, N (%)					
Sleep disorder	107	6.28	2,137	5.25	0.04
Bipolar disorder	216	12.67	3,697	9.09	0.12
Psychosis	12	0.7	469	1.15	-0.05
Schizophrenia	16	0.94	414	1.02	-0.01
Personality disorder	29	1.7	687	1.69	0.00
Adjustment disorder	17	1	527	1.29	-0.03
Tobacco use, N (%)	201	11.79	4,435	10.91	0.03
Alcohol abuse or dependence, N (%)	15	0.88	659	1.62	-0.07
Drug abuse or dependence, N (%)	56	3.28	1,429	3.51	-0.01
Other medication exposures, N (%)					
Benzodiazepines	677	39.71	11,857	29.15	0.22
Other hypnotics	404	23.7	6,990	17.19	0.16
Barbiturates	83	4.87	1,593	3.92	0.05

	Duloxetine N/Mean	Duloxetine %/SD	SSRI N/Mean	SSRI %/SD	Standardized Difference
Anxiolytics	79	4.63	1,691	4.16	0.02
Anticonvulsants	452	26.51	6,217	15.28	0.28
Antipsychotics	337	19.77	5,317	13.07	0.18
SSRIs	126	7.39	40,671	100	-5.01
SNRIs	62	3.64	1,466	3.6	0.00
Other Antidep	494	28.97	9,062	22.28	0.15
Stimulants	139	8.15	2,088	5.13	0.12
Antidiabetic	66	3.87	1,097	2.7	0.07
Insulin	57	3.34	837	2.06	0.08
Antihyperten	239	14.02	4,011	9.86	0.13
Opioid analgesics	1,101	64.57	23,064	56.71	0.16
Triptans	122	7.16	1,960	4.82	0.10
NSAIDs	676	39.65	15,210	37.4	0.05
Obstetric conditions, N (%)					
Multifetal gestation Flag	63	3.7	1,666	4.1	-0.02
Potentially teratogenic medication exposures, N (%)					
Danazol	<11	0	<11	0	-0.01
Synthetic progestins	60	3.52	1,338	3.29	0.01
Methimazole	<11	0.12	28	0.07	0.02
Propylthiouracil	<11	0.18	74	0.18	0.00
Corticosteroids	302	17.71	6,574	16.16	0.04
Fluconazole	94	5.51	1,833	4.51	0.05
Markers of healthcare utilization					
Number of distinct 3 digit ICD 9 codes=0	56	3.28	2,181	5.36	-0.10
Number of distinct 3 digit ICD 9 codes: tertile 1 for number >0	294	17.24	6,826	16.78	0.01
Number of distinct 3 digit ICD 9 codes: tertile 2 for number >0	372	21.82	8,523	20.96	0.02
Number of distinct 3 digit ICD 9 codes: tertile 3 for number >0	983	57.65	23,141	56.9	0.02
Number of ED visits=0	994	58.3	24,283	59.71	-0.03
Number of ED visits=1	407	23.87	8,775	21.58	0.05
Number of ED visits=2	167	9.79	3,852	9.47	0.01
Number of ED visits>2	137	8.04	3,760	9.25	-0.04
Number of non-duloxetine generics dispensed=0	116	6.8	2,891	7.11	-0.01

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Number of non-duloxetine generics dispensed: tertile 1 for number >0	121	7.1	3,422	8.41	-0.05
Number of non-duloxetine generics dispensed: tertile 2 for number >0	354	20.76	9,312	22.9	-0.05
Number of non-duloxetine generics dispensed: tertile 3 for number >0	1,114	65.34	25,046	61.58	0.08
Number of hospital admissions=0	1,633	95.78	38,216	93.96	0.08
Number of hospital admissions=1	61	3.58	2,129	5.24	-0.08
Number of hospital admissions=2	<11	0.53	265	0.65	-0.02
Number of hospital admissions>2	<11	0.12	62	0.15	-0.01
Number of outpatient visits=0	121	7.1	3,599	8.85	-0.06
Number of outpatient visits: tertile 1 for number >0	168	9.85	4,974	12.23	-0.08
Number of outpatient visits: tertile 2 for number >0	435	25.51	10,111	24.86	0.02
Number of outpatient visits: tertile 3 for number >0	981	57.54	21,987	54.06	0.07
Number of psychiatric hospitalizations Q1	1,660	97.36	39,487	97.09	0.02
Number of psychiatric hospitalizations Q2	39	2.29	1,036	2.55	-0.02
Number of psychiatric hospitalizations Q3	<11	0.23	120	0.3	-0.01
Number of psychiatric hospitalizations Q4	<11	0.12	27	0.07	0.02
Number of psychiatrist visits=0	674	39.53	18,456	45.38	-0.12
Number of psychiatrist visits=1	420	24.63	9,012	22.16	0.06
Number of psychiatrist visits=2	196	11.5	4,487	11.03	0.01
Number of psychiatrist visits>2	415	24.34	8,716	21.43	0.07
Geographic region					
Arkansas	PPD		36	0.09	-0.01
Alabama			281	0.69	-0.06
California	116	6.8	3,456	8.5	-0.06
Colorado	PPD		PPD		-0.07
District of Columbia					0.02
Delaware	40	2.35	424	1.04	0.10
Florida	PPD		519	1.28	-0.11
Georgia			787	1.94	-0.14
Hawaii			51	0.13	-0.02

	Duloxetine N/Mean	Duloxetine %/SD	SSRI N/Mean	SSRI %/SD	Standardized Difference
Iowa	15	0.88	481	1.18	-0.03
Idaho	0	0	118	0.29	-0.08
Illinois	183	10.73	3,194	7.85	0.10
Indiana	180	10.56	2,202	5.41	0.19
Kansas	23	1.35	353	0.87	0.05
Kentucky	25	1.47	1,252	3.08	-0.11
Louisiana	54	3.17	679	1.67	0.10
Massachusetts	PPD		212	0.52	-0.06
Maryland	19	1.11	680	1.67	-0.05
Maine	PPD		220	0.54	-0.04
Minnesota	98	5.75	2,752	6.77	-0.04
Missouri	91	5.34	1,466	3.61	0.08
Mississippi	PPD		519	1.28	-0.09
North Carolina	40	2.35	536	1.32	0.08
North Dakota	18	1.06	213	0.52	0.06
Nebraska	13	0.76	254	0.63	0.02
New Hampshire	PPD		283	0.7	-0.05
New Jersey	0	0	165	0.41	-0.09
New Mexico	15	0.88	663	1.63	-0.07
Nevada	PPD		80	0.2	-0.02
New York	313	18.36	4,190	10.3	0.23
Ohio	24	1.41	1,070	2.63	-0.09
Oklahoma	17	1	488	1.2	-0.02
Oregon	32	1.88	666	1.64	0.02
Pennsylvania	PPD		1,252	3.08	-0.18
Rhode Island			89	0.22	-0.02
South Carolina			90	0.22	0.01
South Dakota			229	0.56	0.01
Tennessee	123	7.21	4,446	10.93	-0.13
Texas	PPD		92	0.23	0.00
Utah	37	2.17	488	1.2	0.08
Virginia	45	2.64	993	2.44	0.01

	Duloxetine N/Mean	Duloxetine %/SD	SSRI N/Mean	SSRI %/SD	Standardized Difference
Vermont	21	1.23	583	1.43	-0.02
Washington	0	0	45	0.11	-0.05
Wisconsin	80	4.69	3,740	9.2	-0.18
West Virginia	PPD		100	0.25	-0.02
Wyoming			52	0.13	0.00
Opioids					
buprenorphine	44	2.58	539	1.33	0.09
butorphanol	<11	0.23	29	0.07	0.04
codeine	216	12.67	6,277	15.43	-0.08
fentanyl	21	1.23	222	0.55	0.07
hydrocodone	749	43.93	15,839	38.94	0.10
hydromorphone	19	1.11	219	0.54	0.06
Levorphanol	0	0	<11	0	-0.01
meperidine	<11	0.23	100	0.25	0.00
methadone	22	1.29	320	0.79	0.05
morphine	34	1.99	349	0.86	0.10
oxycodone	283	16.6	5,166	12.7	0.11
oxymorphone	<11	0.12	29	0.07	0.02
pentazocine	<11	0.18	57	0.14	0.01
propoxyphene	102	5.98	3,104	7.63	-0.07
tapentadol	<11	0.23	25	0.06	0.05
tramadol	300	17.6	5,152	12.67	0.14
Healthcare Utilization, mean (SD)					
Comorbidity Index	1.6	1.87	1.33	1.67	0.15
Morphine equivalents	27429.55	595178.24	3571.45	113830.53	0.06
Number of diagnoses	6.26	4.61	6.24	4.86	0.00
Number of ED visits	0.78	1.32	0.84	1.72	-0.04
Number of non-duloxetine generics dispensed	5.64	4.13	5.31	4.04	0.08
Number of hospitalizations	0.05	0.26	0.07	0.3	-0.07
Number of outpatient visits	5.75	6.22	5.39	5.97	0.06
Number of psychiatric hospitalizations	0.03	0.21	0.03	0.22	-0.01
Number of psychiatrist visits	2.28	4.95	1.96	4.56	0.07

15.1. 7. Malformations- Baseline characteristics of duloxetine exposed vs. venlafaxine exposed women: adjusted for treatment indications

	Duloxetine N/Mean	Duloxetine %/SD	Venlafaxine N/Mean	Venlafaxine %/SD	Standardized Difference
Total	2,166	100.00	5,235	100.00	
Demographics					
Age, mean (SD)	27.78	5.55	26.95	5.3	0.15
Age categorical, N (%)					
<=19	103	4.76	301	5.75	-0.04
20-24	555	25.62	1,621	30.97	-0.12
25-29	744	34.35	1,739	33.22	0.02
30-34	474	21.88	1,061	20.27	0.04
35-39	227	10.48	425	8.12	0.08
>=40	63	2.91	88	1.67	0.08
Race, N (%)					
White	1715	79.18	4,244	81.06	-0.05
Black/African American	189	8.73	370	7.06	0.06
Hispanic/Latino	59	2.72	216	4.13	-0.08
Asian or Other Pacific	26	1.2	69	1.33	-0.01
American Indian	29	1.34	69	1.31	0.00
Other	101	4.66	160	3.05	0.08
Unknown	47	2.17	107	2.05	0.01
Chronic comorbid conditions, N (%)					
Hypertension	170	7.85	328	6.27	0.06
Diabetes	133	6.14	220	4.2	0.09
Renal Disease	21	0.97	26	0.5	0.06
Obesity Overweight	138	6.37	276	5.27	0.05
Comorbidity Index Q1	739	34.12	2,050	39.16	-0.10
Comorbidity Index Q2	543	25.07	1,310	25.02	0.00
Comorbidity Index Q3	373	17.22	861	16.44	0.02
Comorbidity Index Q4	511	23.59	1,015	19.38	0.10
Infections, N (%)					
Toxoplasmosis	0	0	<11	0.04	-0.03
Rubella	0	0	0	0	
Cytomegalovirus	0	0	0	0	

	Duloxetine N/Mean	Duloxetine %/SD	Venlafaxine N/Mean	Venlafaxine %/SD	Standardized Difference
Herpes	33	1.52	76	1.45	0.01
Syphilis	<11	0	<11	0.05	-0.03
Varicella	<11	0	<11	0.01	-0.02
Parvovirus B19	0	0	0	0	
Zika virus other mosquito	0	0	0	0	
Lymphocytic choriomeningitis	<11	0.05	<11	0	0.03
Influenza	18	0.83	51	0.98	-0.02
Chlamydia	<11	0.46	26	0.5	-0.01
Human papilloma virus	20	0.92	33	0.64	0.03
Gonorrhea	<11	0.46	20	0.38	0.01
HIV	<11	0.28	23	0.44	-0.03
Trichomoniasis	16	0.74	59	1.12	-0.04
Indications for duloxetine, N (%)					
Depression	1,201	55.45	2,972	56.78	-0.03
Anxiety	750	34.63	1,923	36.74	-0.04
Neuropathic Pain	253	11.68	694	13.26	-0.05
Fibromyalgia	254	11.73	628	12	-0.01
Non neuropathic Pain	1,200	55.4	2,908	55.55	0.00
Other psychiatric conditions, N (%)					
Sleep disorder	132	6.09	332	6.35	-0.01
Bipolar disorder	282	13.02	586	11.19	0.06
Psychosis	19	0.88	62	1.19	-0.03
Schizophrenia	21	0.97	49	0.94	0.00
Personality disorder	52	2.4	106	2.03	0.03
Adjustment disorder	24	1.11	58	1.1	0.00
Tobacco use, N (%)	260	12	534	10.21	0.06
Alcohol abuse or dependence, N (%)	28	1.29	101	1.92	-0.05
Drug abuse or dependence, N (%)	77	3.55	214	4.09	-0.03
Other medication exposures, N (%)					
Benzodiazepines	881	40.67	1,887	36.04	0.10
Other hypnotics	541	24.98	1,059	20.24	0.11
Barbiturates	105	4.85	228	4.35	0.02

	Duloxetine N/Mean	Duloxetine %/SD	Venlafaxine N/Mean	Venlafaxine %/SD	Standardized Difference
Anxiolytics	115	5.31	258	4.93	0.02
Anticonvulsants	571	26.36	1,056	20.18	0.15
Antipsychotics	448	20.68	906	17.31	0.09
SSRIs	619	28.58	1,398	26.71	0.04
SNRIs	34	1.57	5,235	100	-11.20
Other Antidep	643	29.69	1,410	26.93	0.06
Stimulants	166	7.66	321	6.13	0.06
Antidiabetic	84	3.88	148	2.82	0.06
Insulin	69	3.19	108	2.06	0.07
Antihyperten	318	14.68	562	10.73	0.12
Opioid analgesics	1,387	64.04	3,030	57.88	0.13
Triptans	161	7.43	341	6.51	0.04
NSAIDs	872	40.26	1,909	36.46	0.08
Obstetric conditions, N (%)					
Multifetal gestation Flag	76	3.51	220	4.19	-0.04
Potentially teratogenic medication exposures, N (%)					
Danazol	0	0	0	0	
Synthetic progestins	79	3.65	178	3.41	0.01
Methimazole	<11	0.14	<11	0.08	0.02
Propylthiouracil	<11	0.18	<11	0.17	0.00
Corticosteroids	388	17.91	862	16.46	0.04
Fluconazole	113	5.22	217	4.15	0.05
Markers of healthcare utilization					
Number of distinct 3 digit ICD 9 codes=0	68	3.14	266	5.08	-0.10
Number of distinct 3 digit ICD 9 codes: tertile 1 for number >0	377	17.41	915	17.47	0.00
Number of distinct 3 digit ICD 9 codes: tertile 2 for number >0	473	21.84	1,126	21.52	0.01
Number of distinct 3 digit ICD 9 codes: tertile 3 for number >0	1,248	57.62	2,928	55.92	0.03
Number of ED visits=0	1,297	59.88	3,292	62.89	-0.06
Number of ED visits=1	481	22.21	1,010	19.29	0.07
Number of ED visits=2	208	9.6	479	9.14	0.02
Number of ED visits>2	180	8.31	454	8.68	-0.01
Number of non-duloxetine generics dispensed=0	131	6.05	221	4.23	0.08

	Duloxetine N/Mean	Duloxetine %/SD	Venlafaxine N/Mean	Venlafaxine %/SD	Standardized Difference
Number of non-duloxetine generics dispensed: tertile 1 for number >0	151	6.97	354	6.76	0.01
Number of non-duloxetine generics dispensed: tertile 2 for number >0	444	20.5	1,149	21.95	-0.04
Number of non-duloxetine generics dispensed: tertile 3 for number >0	1,440	66.48	3,511	67.07	-0.01
Number of hospital admissions=0	2,061	95.15	4,944	94.43	0.03
Number of hospital admissions=1	89	4.11	251	4.79	-0.03
Number of hospital admissions=2	14	0.65	33	0.64	0.00
Number of hospital admissions>2	<11	0.09	<11	0.14	-0.01
Number of outpatient visits=0	149	6.88	444	8.49	-0.06
Number of outpatient visits: tertile 1 for number >0	212	9.79	609	11.64	-0.06
Number of outpatient visits: tertile 2 for number >0	546	25.21	1,287	24.58	0.01
Number of outpatient visits: tertile 3 for number >0	1,259	58.13	2,894	55.29	0.06
Number of psychiatric hospitalizations Q1	2,097	96.81	5,063	96.72	0.01
Number of psychiatric hospitalizations Q2	59	2.72	147	2.8	0.00
Number of psychiatric hospitalizations Q3	<11	0.37	20	0.38	0.00
Number of psychiatric hospitalizations Q4	<11	0.09	<11	0.1	0.00
Number of psychiatrist visits=0	826	38.13	2,102	40.16	-0.04
Number of psychiatrist visits=1	514	23.73	1,157	22.1	0.04
Number of psychiatrist visits=2	259	11.96	646	12.34	-0.01
Number of psychiatrist visits>2	567	26.18	1,330	25.41	0.02
Geographic region					
Arkansas	PPD		PPD		0.03
Alabama			21	0.4	0.00
California	141	6.51	388	7.42	-0.04
Colorado	PPD		22	0.43	-0.07
District of Columbia			PPD		0.00
Delaware	52	2.4	62	1.19	0.09
Florida	PPD		50	0.95	-0.07
Georgia			91	1.73	-0.12
Hawaii			PPD		0.00

	Duloxetine N/Mean	Duloxetine %/SD	Venlafaxine N/Mean	Venlafaxine %/SD	Standardized Difference
Iowa	23	1.06	96	1.83	-0.06
Idaho	PPD		31	0.59	-0.09
Illinois	252	11.63	385	7.35	0.15
Indiana	216	9.97	297	5.68	0.16
Kansas	36	1.66	51	0.97	0.06
Kentucky	34	1.57	124	2.36	-0.06
Louisiana	75	3.46	101	1.94	0.09
Massachusetts	PPD		PPD		0.01
Maryland	27	1.25	88	1.68	-0.04
Maine	PPD		28	0.53	-0.04
Minnesota	135	6.23	368	7.02	-0.03
Missouri	115	5.31	257	4.91	0.02
Mississippi	PPD		77	1.47	-0.10
North Carolina	50	2.31	59	1.13	0.09
North Dakota	24	1.11	31	0.6	0.06
Nebraska	20	0.92	38	0.73	0.02
New Hampshire	PPD		30	0.58	-0.04
New Jersey	0	0	26	0.5	-0.10
New Mexico	18	0.83	80	1.53	-0.06
Nevada	PPD		PPD		-0.01
New York	377	17.41	556	10.63	0.20
Ohio	28	1.29	221	4.21	-0.18
Oklahoma	26	1.2	58	1.12	0.01
Oregon	40	1.85	88	1.68	0.01
Pennsylvania	16	0.74	211	4.03	-0.22
Rhode Island	PPD		PPD		-0.03
South Carolina			13	0.26	-0.01
South Dakota	13	0.6	36	0.68	-0.01
Tennessee	135	6.23	494	9.44	-0.12
Texas	PPD		PPD		0.02
Utah	47	2.17	64	1.21	0.07
Virginia	53	2.45	109	2.09	0.02

	Duloxetine N/Mean	Duloxetine %/SD	Venlafaxine N/Mean	Venlafaxine %/SD	Standardized Difference
Vermont	26	1.2	49	0.93	0.03
Washington	PPD		PPD		-0.02
Wisconsin	102	4.71	465	8.88	-0.17
West Virginia	PPD		PPD		-0.01
Wyoming					-0.01
Opioids					
buprenorphine	53	2.45	82	1.56	0.06
butorphanol	<11	0.18	<11	0.17	0.00
codeine	296	13.67	875	16.71	-0.08
fentanyl	26	1.2	54	1.04	0.02
hydrocodone	952	43.95	2,048	39.13	0.10
hydromorphone	27	1.25	27	0.52	0.08
Levorphanol	0	0	<11	0	
meperidine	<11	0.23	22	0.43	-0.03
methadone	24	1.11	52	1	0.01
morphine	39	1.8	66	1.26	0.04
oxycodone	359	16.57	674	12.87	0.10
oxymorphone	<11	0.09	12	0.23	-0.03
pentazocine	<11	0.14	<11	0.18	-0.01
propoxyphene	127	5.86	419	8	-0.08
tapentadol	<11	0.23	<11	0.02	0.06
tramadol	383	17.68	733	14	0.10
Healthcare Utilization, mean (SD)					
Comorbidity Index	1.61	1.87	1.39	1.68	0.12
Morphine equivalents	22135.27	528168.26	3271.34	87006.52	0.05
Number of diagnoses	6.29	4.65	6.2	4.85	0.02
Number of ED visits	0.76	1.31	0.78	1.57	-0.01
Number of non-duloxetine generics dispensed	5.82	4.21	5.99	4.4	-0.04
Number of hospitalizations	0.06	0.27	0.07	0.29	-0.03
Number of outpatient visits	5.89	6.45	5.53	5.9	0.06
Number of psychiatric hospitalizations	0.04	0.23	0.04	0.23	0.00
Number of psychiatrist visits	2.43	4.91	2.26	4.69	0.04

15.1. 8. Malformations- Baseline characteristics of duloxetine exposed vs. duloxetine discontinuers: adjusted for treatment indications

	Duloxetine	Duloxetine	Duloxetine	Duloxetine	
	N/Mean	%/SD	discontinuers N/Mean	discontinuers %/SD	Standardized Difference
Total	2,224	100.00	1,992	100.00	
Demographics					
Age, mean (SD)	27.81	5.55	26.92	5.28	0.16
Age categorical, N (%)					
<=19	104	4.68	115	5.78	-0.05
20-24	566	25.45	625	31.4	-0.13
25-29	766	34.44	684	34.32	0.00
30-34	490	22.03	388	19.5	0.06
35-39	232	10.43	146	7.34	0.11
>=40	66	2.97	33	1.66	0.09
Race, N (%)					
White	1762	79.23	1,515	76.07	0.08
Black/African American	193	8.68	196	9.86	-0.04
Hispanic/Latino	61	2.74	62	3.12	-0.02
Asian or Other Pacific	30	1.35	37	1.85	-0.04
American Indian	29	1.3	40	2.02	-0.06
Other	101	4.54	112	5.61	-0.05
Unknown	48	2.16	30	1.48	0.05
Chronic comorbid conditions, N (%)					
Hypertension	173	7.78	139	6.95	0.03
Diabetes	135	6.07	111	5.55	0.02
Renal Disease	22	0.99	25	1.23	-0.02
Obesity Overweight	142	6.38	113	5.66	0.03
Comorbidity Index Q1	760	34.17	752	37.73	-0.07
Comorbidity Index Q2	557	25.04	541	27.14	-0.05
Comorbidity Index Q3	377	16.95	282	14.17	0.08
Comorbidity Index Q4	530	23.83	417	20.95	0.07
Infections, N (%)					
Toxoplasmosis	0	0	0	0	
Rubella	0	0	0	0	

	Duloxetine	Duloxetine	Duloxetine	Duloxetine	
	N/Mean	%/SD	discontinuers N/Mean	discontinuers %/SD	Standardized Difference
Cytomegalovirus	0	0	0	0	
Herpes	35	1.57	25	1.25	0.03
Syphilis	<11	0	<11	0.09	-0.04
Varicella	0	0	0	0	
Parvovirus B19	0	0	0	0	
Zika virus other mosquito	0	0	0	0	
Lymphocytic choriomeningitis	<11	0.04	0	0	0.03
Influenza	19	0.85	25	1.28	-0.04
Chlamydia	<11	0.45	<11	0.52	-0.01
Human papilloma virus	22	0.99	14	0.69	0.03
Gonorrhea	<11	0.45	<11	0.54	-0.01
HIV	<11	0.27	<11	0.37	-0.02
Trichomoniasis	16	0.72	25	1.24	-0.05
Indications for duloxetine, N (%)					
Depression	1,235	55.53	1,109	55.65	0.00
Anxiety	778	34.98	699	35.08	0.00
Neuropathic Pain	267	12.01	271	13.63	-0.05
Fibromyalgia	264	11.87	264	13.28	-0.04
Non neuropathic Pain	1,234	55.49	1,151	57.76	-0.05
Other psychiatric conditions, N (%)					
Sleep disorder	136	6.12	123	6.19	0.00
Bipolar disorder	294	13.22	240	12.03	0.04
Psychosis	19	0.85	21	1.05	-0.02
Schizophrenia	23	1.03	17	0.84	0.02
Personality disorder	55	2.47	40	2.02	0.03
Adjustment disorder	26	1.17	17	0.83	0.03
Tobacco use, N (%)	266	11.96	216	10.82	0.04
Alcohol abuse or dependence, N (%)	28	1.26	28	1.4	-0.01
Drug abuse or dependence, N (%)	80	3.6	66	3.33	0.01
Other medication exposures, N (%)					
Benzodiazepines	912	41.01	703	35.27	0.12

	Duloxetine	Duloxetine	Duloxetine	Duloxetine	
	N/Mean	%/SD	discontinuers N/Mean	discontinuers %/SD	Standardized Difference
Other hypnotics	564	25.36	449	22.56	0.07
Barbiturates	111	4.99	97	4.85	0.01
Anxiolytics	119	5.35	101	5.07	0.01
Anticonvulsants	591	26.57	443	22.26	0.10
Antipsychotics	463	20.82	353	17.74	0.08
SSRIs	645	29	560	28.12	0.02
SNRIs	92	4.14	120	6.05	-0.09
Other Antidep	668	30.04	517	25.96	0.09
Stimulants	172	7.73	117	5.87	0.07
Antidiabetic	86	3.87	55	2.74	0.06
Insulin	69	3.1	63	3.15	0.00
Antihyperten	329	14.79	238	11.92	0.08
Opioid analgesics	1,426	64.12	1,265	63.53	0.01
Triptans	165	7.42	137	6.89	0.02
NSAIDs	894	40.2	742	37.24	0.06
Obstetric conditions, N (%)					
Multifetal gestation Flag	77	3.46	70	3.51	0.00
Potentially teratogenic medication exposures, N (%)					
Danazol	0	0	0	0	
Synthetic progestins	80	3.6	50	2.51	0.06
Methimazole	<11	0.13	<11	0.07	0.02
Propylthiouracil	<11	0.18	<11	0.07	0.03
Corticosteroids	402	18.08	323	16.22	0.05
Fluconazole	115	5.17	87	4.38	0.04
Markers of healthcare utilization					
Number of distinct 3 digit ICD 9 codes=0	69	3.1	49	2.46	0.04
Number of distinct 3 digit ICD 9 codes: tertile 1 for number >0	386	17.36	275	13.83	0.10
Number of distinct 3 digit ICD 9 codes: tertile 2 for number >0	483	21.72	413	20.74	0.02
Number of distinct 3 digit ICD 9 codes: tertile 3 for number >0	1,286	57.82	1,254	62.97	-0.11
Number of ED visits=0	1,326	59.62	1,098	55.11	0.09
Number of ED visits=1	497	22.35	463	23.25	-0.02

	Duloxetine	Duloxetine	Duloxetine	Duloxetine	
	N/Mean	%/SD	discontinuers N/Mean	discontinuers %/SD	Standardized Difference
Number of ED visits=2	214	9.62	225	11.29	-0.05
Number of ED visits>2	187	8.41	206	10.35	-0.07
Number of non-duloxetine generics dispensed=0	132	5.94	118	5.95	0.00
Number of non-duloxetine generics dispensed: tertile 1 for number >0	152	6.83	138	6.95	0.00
Number of non-duloxetine generics dispensed: tertile 2 for number >0	455	20.46	415	20.83	-0.01
Number of non-duloxetine generics dispensed: tertile 3 for number >0	1,485	66.77	1,320	66.28	0.01
Number of hospital admissions=0	2,113	95.01	1,884	94.56	0.02
Number of hospital admissions=1	94	4.23	86	4.31	0.00
Number of hospital admissions=2	15	0.67	18	0.91	-0.03
Number of hospital admissions>2	<11	0.09	<11	0.22	-0.03
Number of outpatient visits=0	150	6.74	113	5.7	0.04
Number of outpatient visits: tertile 1 for number >0	219	9.85	210	10.52	-0.02
Number of outpatient visits: tertile 2 for number >0	557	25.04	439	22.05	0.07
Number of outpatient visits: tertile 3 for number >0	1,298	58.36	1,230	61.73	-0.07
Number of psychiatric hospitalizations Q1	2,150	96.67	1,913	96.03	0.03
Number of psychiatric hospitalizations Q2	64	2.88	61	3.06	-0.01
Number of psychiatric hospitalizations Q3	<11	0.36	15	0.75	-0.05
Number of psychiatric hospitalizations Q4	<11	0.09	<11	0.16	-0.02
Number of psychiatrist visits=0	841	37.81	706	35.46	0.05
Number of psychiatrist visits=1	520	23.38	482	24.2	-0.02
Number of psychiatrist visits=2	265	11.92	250	12.57	-0.02
Number of psychiatrist visits>2	598	26.89	553	27.78	-0.02
Geographic region					
Arkansas	PPD		PPD		-0.04
Alabama					0.03
California	146	6.56	125	6.26	0.01
Colorado	PPD		PPD		-0.01
District of Columbia			0	0	0.03

	Duloxetine	Duloxetine	Duloxetine	Duloxetine	
	N/Mean	%/SD	discontinuers	discontinuers	Standardized
			N/Mean	%/SD	Difference
Delaware	53	2.38	63	3.15	-0.05
Florida	PPD		PPD		-0.03
Georgia					0.00
Hawaii					-0.01
Iowa	24	1.08	21	1.08	0.00
Idaho	PPD		PPD		0.03
Illinois	258	11.6	224	11.25	0.01
Indiana	217	9.76	157	7.87	0.07
Kansas	36	1.62	28	1.39	0.02
Kentucky	35	1.57	47	2.36	-0.06
Louisiana	77	3.46	63	3.16	0.02
Massachusetts	PPD		PPD		0.04
Maryland	27	1.21	24	1.18	0.00
Maine	PPD		PPD		0.01
Minnesota	141	6.34	115	5.8	0.02
Missouri	119	5.35	126	6.33	-0.04
Mississippi	PPD		PPD		-0.02
North Carolina	50	2.25	44	2.19	0.00
North Dakota	24	1.08	25	1.26	-0.02
Nebraska	21	0.94	26	1.32	-0.04
New Hampshire	PPD		PPD		-0.03
New Jersey	0	0			-0.04
New Mexico	20	0.9	14	0.72	0.02
Nevada	PPD		PPD		0.01
New York	386	17.36	375	18.82	-0.04
Ohio	29	1.3	27	1.35	0.00
Oklahoma	26	1.17	18	0.88	0.03
Oregon	40	1.8	49	2.46	-0.05
Pennsylvania	16	0.72	17	0.85	-0.01
Rhode Island	PPD		PPD		0.01
South Carolina					-0.02

	Duloxetine	Duloxetine	Duloxetine	Duloxetine	
	N/Mean	%/SD	discontinuers	discontinuers	Standardized
			N/Mean	%/SD	Difference
South Dakota	13	0.58	14	0.69	-0.01
Tennessee	142	6.38	113	5.66	0.03
Texas	PPD		PPD		0.01
Utah	48	2.16	40	2.03	0.01
Virginia	56	2.52	53	2.64	-0.01
Vermont	26	1.17	15	0.76	0.04
Washington	PPD		0	0	0.03
Wisconsin	106	4.77	84	4.19	0.03
West Virginia	PPD		PPD		0.01
Wyoming					-0.02
Opioids					
buprenorphine	57	2.56	43	2.14	0.03
butorphanol	<11	0.18	0	0	0.06
codeine	308	13.85	308	15.47	-0.05
fentanyl	27	1.21	31	1.54	-0.03
hydrocodone	977	43.93	846	42.45	0.03
hydromorphone	29	1.3	20	0.99	0.03
Levorphanol	0	0	0	0	
meperidine	<11	0.22	<11	0.28	-0.01
methadone	25	1.12	17	0.86	0.03
morphine	39	1.75	28	1.42	0.03
oxycodone	373	16.77	311	15.63	0.03
oxymorphone	<11	0.09	<11	0.11	-0.01
pentazocine	<11	0.13	<11	0.12	0.00
propoxyphene	135	6.07	145	7.26	-0.05
tapentadol	<11	0.22	<11	0.19	0.01
tramadol	395	17.76	374	18.78	-0.03
Healthcare Utilization, mean (SD)					
Comorbidity Index	1.62	1.88	1.46	1.83	0.08
Morphine equivalents	21626.78	521245.43	6217.5	71561.19	0.04
Number of diagnoses	6.33	4.7	6.84	4.82	-0.11

	Duloxetine	Duloxetine	Duloxetine discontinuers	Duloxetine discontinuers	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Number of ED visits	0.77	1.32	0.97	1.86	-0.12
Number of non-duloxetine generics dispensed	5.88	4.25	5.84	4.34	0.01
Number of hospitalizations	0.06	0.28	0.07	0.31	-0.03
Number of outpatient visits	5.97	6.62	6.3	6.85	-0.05
Number of psychiatric hospitalizations	0.04	0.23	0.05	0.28	-0.05
Number of psychiatrist visits	2.49	5.1	2.55	5.06	-0.01

15.1. 9. Malformations- Baseline characteristics of duloxetine exposed vs. unexposed women: fully adjusted

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Total	2,223	100.00	392,928	100.00	
Demographics					
Age, mean (SD)	27.81	5.55	27.76	5.56	0.01
Age categorical, N (%)					
<=19	104	4.68	17,224	4.38	0.01
20-24	565	25.42	100,162	25.49	0.00
25-29	766	34.46	136,727	34.8	-0.01
30-34	490	22.04	86,737	22.07	0.00
35-39	232	10.44	40,585	10.33	0.00
>=40	66	2.97	11,494	2.93	0.00
Race, N (%)					
White	1,761	79.22	315,827	80.38	-0.03
Black or African American	193	8.68	30,859	7.85	0.03
Hispanic or Latino	61	2.74	9,549	2.43	0.02
Asian or Other Pacific Islander	30	1.35	5,155	1.31	0.00
American Indian	29	1.3	5,056	1.29	0.00
Other	101	4.54	18,013	4.58	0.00
Unknown	48	2.16	8,469	2.16	0.00
Chronic comorbid conditions, N (%)					
Hypertension	173	7.78	30,313	7.71	0.00
Diabetes	135	6.07	23,922	6.09	0.00
Renal Disease	22	0.99	3,970	1.01	0.00
Obesity Overweight	142	6.39	24,906	6.34	0.00
Comorbidity Index Q1	759	34.14	133,573	33.99	0.00
Comorbidity Index Q2	557	25.06	99,443	25.31	-0.01
Comorbidity Index Q3	377	16.96	67,495	17.18	-0.01
Comorbidity Index Q4	530	23.84	92,416	23.52	0.01
Infections, N (%)					
Toxoplasmosis	0	0	0	0	
Rubella	0	0	0	0	
Cytomegalovirus	0	0	0	0	

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Herpes	35	1.57	6,382	1.62	0.00
Syphilis	0	0	0	0	
Varicella	0	0	0	0	
Parvovirus B19	0	0	0	0	
Zika virus other mosquito	0	0	0	0	
Lymphocytic choriomeningitis	0	0	19	0	-0.01
Influenza	19	0.85	3,297	0.84	0.00
Chlamydia	<11	0.45	1,841	0.47	0.00
Human papilloma virus	22	0.99	3,857	0.98	0.00
Gonorrhea	<11	0.45	1,725	0.44	0.00
HIV	<11	0.27	1,030	0.26	0.00
Trichomoniasis	16	0.72	2,702	0.69	0.00
Indications for duloxetine, N (%)					
Depression	1,234	55.51	223,353	56.84	-0.03
Anxiety	777	34.95	138,909	35.35	-0.01
Neuropathic Pain	267	12.01	46,252	11.77	0.01
Fibromyalgia	263	11.83	42,201	10.74	0.03
Non neuropathic Pain	1,233	55.47	213,645	54.37	0.02
Other psychiatric conditions, N (%)					
Sleep disorder	136	6.12	23,672	6.02	0.00
Bipolar disorder	294	13.23	50,799	12.93	0.01
Psychosis	19	0.85	3,359	0.85	0.00
Schizophrenia	23	1.03	4,041	1.03	0.00
Personality disorder	55	2.47	9,490	2.42	0.00
Adjustment disorder	25	1.12	4,382	1.12	0.00
Tobacco use, N (%)	266	11.97	47,559	12.1	0.00
Alcohol abuse or dependence, N (%)	28	1.26	5,054	1.29	0.00
Drug abuse or dependence, N (%)	80	3.6	14,339	3.65	0.00
Other medication exposures, N (%)					
Benzodiazepines	911	40.98	160,239	40.78	0.00
Other hypnotics	563	25.33	97,232	24.75	0.01
Barbiturates	111	4.99	19,572	4.98	0.00

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Anxiolytics	118	5.31	20,392	5.19	0.01
Anticonvulsants	590	26.54	99,450	25.31	0.03
Antipsychotics	463	20.83	77,907	19.83	0.02
SSRIs	645	29.01	121,358	30.89	-0.04
SNRIs	92	4.14	17,233	4.39	-0.01
Other Antidep	667	30	116,681	29.7	0.01
Stimulants	172	7.74	29,167	7.42	0.01
Antidiabetic	86	3.87	15,036	3.83	0.00
Insulin	69	3.1	12,322	3.14	0.00
Antihyperten	329	14.8	56,095	14.28	0.01
Opioid analgesics	1,425	64.1	252,815	64.34	0.00
Triptans	165	7.42	28,900	7.36	0.00
NSAIDs	894	40.22	157,677	40.13	0.00
Obstetric conditions, N (%)					
Multifetal gestation Flag	77	3.46	13,572	3.45	0.00
Potentially teratogenic medication exposures, N (%)					
Danazol	0	0	0	0	
Synthetic progestins	80	3.6	14,054	3.58	0.00
Methimazole	<11	0.13	570	0.15	0.00
Propylthiouracil	<11	0.18	742	0.19	0.00
Corticosteroids	402	18.08	70,912	18.05	0.00
Fluconazole	115	5.17	19,664	5	0.01
Markers of healthcare utilization					
Number of distinct 3 digit ICD 9 codes=0	69	3.1	10,373	2.64	0.03
Number of distinct 3 digit ICD 9 codes: tertile 1 for number >0	386	17.36	67,632	17.21	0.00
Number of distinct 3 digit ICD 9 codes: tertile 2 for number >0	483	21.73	86,846	22.1	-0.01
Number of distinct 3 digit ICD 9 codes: tertile 3 for number >0	1,285	57.8	228,076	58.05	0.00
Number of ED visits=0	1,326	59.65	235,802	60.01	-0.01
Number of ED visits=1	496	22.31	86,949	22.13	0.00
Number of ED visits=2	214	9.63	37,435	9.53	0.00
Number of ED visits>2	187	8.41	32,743	8.33	0.00
Number of non-duloxetine generics dispensed=0	132	5.94	19,025	4.84	0.05

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Number of non-duloxetine generics dispensed: tertile 1 for number >0	152	6.84	25,486	6.49	0.01
Number of non-duloxetine generics dispensed: tertile 2 for number >0	455	20.47	82,608	21.02	-0.01
Number of non-duloxetine generics dispensed: tertile 3 for number >0	1,484	66.76	265,809	67.65	-0.02
Number of hospital admissions=0	2,112	95.01	373,779	95.13	-0.01
Number of hospital admissions=1	94	4.23	16,229	4.13	0.00
Number of hospital admissions=2	15	0.67	2,606	0.66	0.00
Number of hospital admissions>2	<11	0.09	315	0.08	0.00
Number of outpatient visits=0	150	6.75	24,088	6.13	0.03
Number of outpatient visits: tertile 1 for number >0	219	9.85	37,386	9.51	0.01
Number of outpatient visits: tertile 2 for number >0	557	25.06	100,242	25.51	-0.01
Number of outpatient visits: tertile 3 for number >0	1,297	58.34	231,211	58.84	-0.01
Number of psychiatric hospitalizations Q1	2,149	96.67	380,333	96.79	-0.01
Number of psychiatric hospitalizations Q2	64	2.88	10,850	2.76	0.01
Number of psychiatric hospitalizations Q3	<11	0.36	1,443	0.37	0.00
Number of psychiatric hospitalizations Q4	<11	0.09	301	0.08	0.00
Number of psychiatrist visits=0	841	37.83	141,701	36.06	0.04
Number of psychiatrist visits=1	520	23.39	96,269	24.5	-0.03
Number of psychiatrist visits=2	265	11.92	48,552	12.36	-0.01
Number of psychiatrist visits>2	597	26.86	106,406	27.08	-0.01
Geographic region					
Arkansas	PPD		588	0.15	0.00
Alabama			1,792	0.46	0.00
California	146	6.57	24,834	6.32	0.01
Colorado	PPD		310	0.08	0.00
District of Columbia			168	0.04	0.00
Delaware	53	2.38	9,357	2.38	0.00
Florida	PPD		1,504	0.38	0.00
Georgia			1,682	0.43	0.00
Hawaii			313	0.08	0.00

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Iowa	24	1.08	4,353	1.11	0.00
Idaho	PPD		555	0.14	0.00
Illinois	257	11.56	45,161	11.49	0.00
Indiana	217	9.76	38,248	9.73	0.00
Kansas	36	1.62	6,539	1.66	0.00
Kentucky	35	1.57	6,264	1.59	0.00
Louisiana	77	3.46	13,706	3.49	0.00
Massachusetts	PPD		704	0.18	0.00
Maryland	27	1.21	4,676	1.19	0.00
Maine	PPD		1,051	0.27	0.00
Minnesota	141	6.34	25,257	6.43	0.00
Missouri	119	5.35	21,365	5.44	0.00
Mississippi	PPD		1,675	0.43	0.00
North Carolina	50	2.25	8,734	2.22	0.00
North Dakota	24	1.08	4,105	1.04	0.00
Nebraska	21	0.94	3,717	0.95	0.00
New Hampshire	PPD		1,272	0.32	0.00
New Jersey	0	0	0	0	
New Mexico	20	0.9	3,454	0.88	0.00
Nevada	PPD		392	0.1	0.00
New York	386	17.36	68,874	17.53	0.00
Ohio	29	1.3	5,290	1.35	0.00
Oklahoma	26	1.17	4,670	1.19	0.00
Oregon	40	1.8	7,183	1.83	0.00
Pennsylvania	16	0.72	2,702	0.69	0.00
Rhode Island	PPD		341	0.09	0.00
South Carolina			917	0.23	0.00
South Dakota	13	0.58	2,193	0.56	0.00
Tennessee	142	6.39	25,265	6.43	0.00
Texas	PPD		893	0.23	0.00
Utah	48	2.16	8,410	2.14	0.00
Virginia	56	2.52	9,872	2.51	0.00

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Vermont	26	1.17	4,712	1.2	0.00
Washington	PPD		185	0.05	0.00
Wisconsin	106	4.77	18,519	4.71	0.00
West Virginia	PPD		560	0.14	0.00
Wyoming			563	0.14	0.00
Opioids					
buprenorphine	57	2.56	9,345	2.38	0.01
butorphanol	<11	0.18	601	0.15	0.01
codeine	308	13.86	55,124	14.03	-0.01
fentanyl	27	1.21	4,223	1.07	0.01
hydrocodone	977	43.95	174,263	44.35	-0.01
hydromorphone	29	1.3	4,679	1.19	0.01
Levorphanol	0	0	0	0	
meperidine	<11	0.22	923	0.23	0.00
methadone	25	1.12	4,094	1.04	0.01
morphine	39	1.75	5,687	1.45	0.02
oxycodone	373	16.78	64,465	16.41	0.01
oxymorphone	<11	0.09	389	0.1	0.00
pentazocine	<11	0.13	559	0.14	0.00
propoxyphene	135	6.07	24,611	6.26	-0.01
tapentadol	<11	0.22	672	0.17	0.01
tramadol	394	17.72	68,552	17.45	0.01
Healthcare Utilization, mean (SD)					
Comorbidity Index	1.62	1.88	1.61	1.85	0.01
Morphine equivalents	21635.09	521362.51	18277.93	373452.64	0.01
Number of diagnoses	6.33	4.7	6.43	4.77	-0.02
Number of ED visits	0.77	1.32	0.81	1.66	-0.03
Number of non-duloxetine generics dispensed	5.88	4.25	5.93	4.31	-0.01
Number of hospitalizations	0.06	0.28	0.06	0.28	0.01
Number of outpatient visits	5.96	6.62	5.94	6.38	0.00
Number of psychiatric hospitalizations	0.04	0.23	0.04	0.23	0.01
Number of psychiatrist visits	2.48	5.09	2.46	5.05	0.00

15.1. 10. Malformations- Baseline characteristics of duloxetine exposed vs. SSRI exposed women: fully adjusted

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Total	1,703	100.00	39,395	100.00	
Demographics					
Age, mean (SD)	27.77	5.53	27.77	5.58	0.00
Age categorical, N (%)					
<=19	84	4.93	1,909	4.85	0.00
20-24	430	25.25	9,952	25.26	0.00
25-29	592	34.76	13,675	34.71	0.00
30-34	374	21.96	8,688	22.05	0.00
35-39	171	10.04	3,964	10.06	0.00
>=40	52	3.05	1,206	3.06	0.00
Race, N (%)					
White	1,344	78.92	31,110	78.97	0.00
Black/African American	156	9.16	3,588	9.11	0.00
Hispanic/Latino	46	2.7	1,041	2.64	0.00
Asian or Other Pacific	22	1.29	514	1.3	0.00
American Indian	25	1.47	574	1.46	0.00
Other	77	4.52	1,791	4.55	0.00
Unknown	33	1.94	779	1.98	0.00
Chronic comorbid conditions, N (%)					
Hypertension	133	7.81	3,117	7.91	0.00
Diabetes	110	6.46	2,600	6.6	-0.01
Renal Disease	15	0.88	343	0.87	0.00
Obesity Overweight	115	6.75	2,667	6.77	0.00
Comorbidity Index Q1	590	34.64	13,629	34.6	0.00
Comorbidity Index Q2	424	24.9	9,752	24.75	0.00
Comorbidity Index Q3	285	16.74	6,653	16.89	0.00
Comorbidity Index Q4	404	23.72	9,360	23.76	0.00
Infections, N (%)					
Toxoplasmosis	0	0	0	0	
Rubella	0	0	0	0	
Cytomegalovirus	0	0	0	0	

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Herpes	27	1.59	637	1.62	0.00
Syphilis	0	0	0	0	
Varicella	0	0	0	0	
Parvovirus B19	0	0	0	0	
Zika virus other mosquito	0	0	0	0	
Lymphocytic choriomeningitis	0	0	0	0	
Influenza	13	0.76	284	0.72	0.00
Chlamydia	<11	0.53	219	0.55	0.00
Human papilloma virus	12	0.7	277	0.7	0.00
Gonorrhea	<11	0.41	163	0.41	0.00
HIV	<11	0.23	90	0.23	0.00
Trichomoniasis	14	0.82	312	0.79	0.00
Indications for duloxetine, N (%)					
Depression	902	52.97	20,951	53.18	0.00
Anxiety	561	32.94	13,130	33.33	-0.01
Neuropathic Pain	201	11.8	4,557	11.57	0.01
Fibromyalgia	201	11.8	4,309	10.94	0.03
Non neuropathic Pain	964	56.61	22,278	56.55	0.00
Other psychiatric conditions, N (%)					
Sleep disorder	107	6.28	2,460	6.24	0.00
Bipolar disorder	216	12.68	5,074	12.88	-0.01
Psychosis	12	0.7	278	0.71	0.00
Schizophrenia	16	0.94	377	0.96	0.00
Personality disorder	29	1.7	689	1.75	0.00
Adjustment disorder	16	0.94	353	0.9	0.00
Tobacco use, N (%)	200	11.74	4,674	11.86	0.00
Alcohol abuse or dependence, N (%)	15	0.88	341	0.87	0.00
Drug abuse or dependence, N (%)	56	3.29	1,299	3.3	0.00
Other medication exposures, N (%)					
Benzodiazepines	675	39.64	15,763	40.01	-0.01
Other hypnotics	402	23.61	9,366	23.77	0.00
Barbiturates	83	4.87	1,901	4.83	0.00

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Anxiolytics	78	4.58	1,836	4.66	0.00
Anticonvulsants	451	26.48	10,297	26.14	0.01
Antipsychotics	337	19.79	7,897	20.05	-0.01
SSRIs	125	7.34	39,395	100	-5.02
SNRIs	62	3.64	1,459	3.7	0.00
Other Antidep	492	28.89	11,355	28.82	0.00
Stimulants	139	8.16	3,164	8.03	0.00
Antidiabetic	66	3.88	1,534	3.89	0.00
Insulin	57	3.35	1,333	3.38	0.00
Antihyperten	239	14.03	5,449	13.83	0.01
Opioid analgesics	1,099	64.53	25,463	64.64	0.00
Triptans	122	7.16	2,821	7.16	0.00
NSAIDs	675	39.64	15,711	39.88	-0.01
Obstetric conditions, N (%)					
Multifetal gestation Flag	63	3.7	1,463	3.71	0.00
Potentially teratogenic medication exposures, N (%)					
Danazol	<11	0	<11	0	
Synthetic progestins	60	3.52	1,387	3.52	0.00
Methimazole	<11	0.12	48	0.12	0.00
Propylthiouracil	<11	0.18	70	0.18	0.00
Corticosteroids	302	17.73	6,953	17.65	0.00
Fluconazole	94	5.52	2,144	5.44	0.00
Markers of healthcare utilization					
Number of distinct 3 digit ICD 9 codes=0	56	3.29	1,252	3.18	0.01
Number of distinct 3 digit ICD 9 codes: tertile 1 for number >0	294	17.26	6,728	17.08	0.00
Number of distinct 3 digit ICD 9 codes: tertile 2 for number >0	372	21.84	8,723	22.14	-0.01
Number of distinct 3 digit ICD 9 codes: tertile 3 for number >0	981	57.6	22,692	57.6	0.00
Number of ED visits=0	993	58.31	22,897	58.12	0.00
Number of ED visits=1	406	23.84	9,425	23.92	0.00
Number of ED visits=2	167	9.81	3,880	9.85	0.00
Number of ED visits>2	137	8.04	3,194	8.11	0.00
Number of non-duloxetine generics dispensed=0	116	6.81	2,704	6.86	0.00

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Number of non-duloxetine generics dispensed: tertile 1 for number >0	121	7.11	2,749	6.98	0.01
Number of non-duloxetine generics dispensed: tertile 2 for number >0	354	20.79	8,186	20.78	0.00
Number of non-duloxetine generics dispensed: tertile 3 for number >0	1,112	65.3	25,756	65.38	0.00
Number of hospital admissions=0	1,631	95.77	37,732	95.78	0.00
Number of hospital admissions=1	61	3.58	1,409	3.58	0.00
Number of hospital admissions=2	<11	0.53	213	0.54	0.00
Number of hospital admissions>2	<11	0.12	42	0.11	0.00
Number of outpatient visits=0	121	7.11	2,729	6.93	0.01
Number of outpatient visits: tertile 1 for number >0	168	9.86	3,814	9.68	0.01
Number of outpatient visits: tertile 2 for number >0	435	25.54	10,156	25.78	-0.01
Number of outpatient visits: tertile 3 for number >0	979	57.49	22,696	57.61	0.00
Number of psychiatric hospitalizations Q1	1,658	97.36	38,368	97.39	0.00
Number of psychiatric hospitalizations Q2	39	2.29	887	2.25	0.00
Number of psychiatric hospitalizations Q3	<11	0.23	97	0.25	0.00
Number of psychiatric hospitalizations Q4	<11	0.12	44	0.11	0.00
Number of psychiatrist visits=0	674	39.58	15,471	39.27	0.01
Number of psychiatrist visits=1	419	24.6	9,717	24.67	0.00
Number of psychiatrist visits=2	196	11.51	4,516	11.46	0.00
Number of psychiatrist visits>2	414	24.31	9,691	24.6	-0.01
Geographic region					
Arkansas	PPD		23	0.06	0.00
Alabama			115	0.29	0.00
California	116	6.81	2,644	6.71	0.00
Colorado	PPD		20	0.05	0.00
District of Columbia			21	0.05	0.00
Delaware	40	2.35	918	2.33	0.00
Florida	PPD		112	0.28	0.00
Georgia			158	0.4	0.00
Hawaii			22	0.05	0.00

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Iowa	15	0.88	335	0.85	0.00
Idaho	PPD		PPD		
Illinois	182	10.69	4,191	10.64	0.00
Indiana	179	10.51	4,174	10.59	0.00
Kansas	23	1.35	545	1.38	0.00
Kentucky	25	1.47	559	1.42	0.00
Louisiana	54	3.17	1,296	3.29	-0.01
Massachusetts	PPD		71	0.18	0.00
Maryland	19	1.12	442	1.12	0.00
Maine	PPD		109	0.28	0.00
Minnesota	98	5.75	2,238	5.68	0.00
Missouri	91	5.34	2,152	5.46	-0.01
Mississippi	PPD		185	0.47	0.00
North Carolina	40	2.35	931	2.36	0.00
North Dakota	18	1.06	403	1.02	0.00
Nebraska	13	0.76	307	0.78	0.00
New Hampshire	PPD		141	0.36	0.00
New Jersey	0	0	0	0	
New Mexico	15	0.88	335	0.85	0.00
Nevada	PPD		50	0.13	0.00
New York	313	18.38	7,302	18.54	0.00
Ohio	24	1.41	554	1.41	0.00
Oklahoma	17	1	391	0.99	0.00
Oregon	32	1.88	745	1.89	0.00
Pennsylvania	PPD		247	0.63	0.00
Rhode Island	PPD		44	0.11	0.00
South Carolina	PPD		123	0.31	0.00
South Dakota	PPD		233	0.59	0.01
Tennessee	123	7.22	2,824	7.17	0.00
Texas	PPD		93	0.24	0.00
Utah	37	2.17	879	2.23	0.00
Virginia	45	2.64	1,035	2.63	0.00

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Vermont	21	1.23	485	1.23	0.00
Washington	PPD		PPD		
Wisconsin	80	4.7	1,828	4.64	0.00
West Virginia	PPD		70	0.18	0.00
Wyoming			46	0.12	0.00
Opioids					
buprenorphine	44	2.58	976	2.48	0.01
butorphanol	<11	0.23	85	0.22	0.00
codeine	216	12.68	4,985	12.65	0.00
fentanyl	21	1.23	457	1.16	0.01
hydrocodone	748	43.92	17,501	44.42	-0.01
hydromorphone	19	1.12	411	1.04	0.01
Levorphanol	0	0	0	0	
meperidine	<11	0.23	97	0.25	0.00
methadone	22	1.29	496	1.26	0.00
morphine	34	2	690	1.75	0.02
oxycodone	283	16.62	6,506	16.52	0.00
oxymorphone	<11	0.12	53	0.13	0.00
pentazocine	<11	0.18	73	0.18	0.00
propoxyphene	102	5.99	2,409	6.12	-0.01
tapentadol	<11	0.18	72	0.18	0.00
tramadol	298	17.5	6,867	17.43	0.00
Healthcare Utilization, mean (SD)					
Comorbidity Index	1.6	1.87	1.6	1.84	0.00
Morphine equivalents	27456.17	595527.12	17331.44	358985.02	0.02
Number of diagnoses	6.26	4.61	6.28	4.65	0.00
Number of ED visits	0.78	1.32	0.82	1.68	-0.03
Number of non-duloxetine generics dispensed	5.64	4.13	6.08	4.57	-0.10
Number of hospitalizations	0.05	0.26	0.05	0.26	0.00
Number of outpatient visits	5.74	6.22	5.72	6.17	0.00
Number of psychiatric hospitalizations	0.03	0.21	0.03	0.23	0.00
Number of psychiatrist visits	2.27	4.95	2.23	4.78	0.01

15.1. 11. Malformations- Baseline characteristics of duloxetine exposed vs. venlafaxine exposed women: fully adjusted

	Duloxetine N/Mean	Duloxetine %/SD	Venlafaxine N/Mean	Venlafaxine %/SD	Standardized Difference
Total	2,160	100.00	5,085	100.00	
Demographics					
Age, mean (SD)	27.78	5.54	27.76	5.55	0.00
Age categorical, N (%)					
<=19	103	4.77	240	4.71	0.00
20-24	553	25.6	1,316	25.88	-0.01
25-29	742	34.35	1,750	34.42	0.00
30-34	474	21.94	1,099	21.62	0.01
35-39	227	10.51	534	10.51	0.00
>=40	61	2.82	146	2.86	0.00
Race, N (%)					
White	1,710	79.17	4,014	78.94	0.01
Black/African American	189	8.75	442	8.68	0.00
Hispanic/Latino	59	2.73	136	2.68	0.00
Asian or Other Pacific	26	1.2	71	1.4	-0.02
American Indian	29	1.34	70	1.38	0.00
Other	100	4.63	239	4.7	0.00
Unknown	47	2.18	113	2.22	0.00
Chronic comorbid conditions, N (%)					
Hypertension	169	7.82	440	8.65	-0.03
Diabetes	131	6.06	332	6.54	-0.02
Renal Disease	21	0.97	51	1	0.00
Obesity Overweight	138	6.39	345	6.78	-0.02
Comorbidity Index Q1	737	34.12	1,754	34.5	-0.01
Comorbidity Index Q2	543	25.14	1,271	25	0.00
Comorbidity Index Q3	372	17.22	877	17.26	0.00
Comorbidity Index Q4	508	23.52	1,182	23.24	0.01
Infections, N (%)					
Toxoplasmosis	0	0	0	0	
Rubella	0	0	0	0	
Cytomegalovirus	0	0	0	0	

	Duloxetine N/Mean	Duloxetine %/SD	Venlafaxine N/Mean	Venlafaxine %/SD	Standardized Difference
Herpes	33	1.53	75	1.47	0.00
Syphilis	0	0	0	0	
Varicella	0	0	0	0	
Parvovirus B19	0	0	0	0	
Zika virus other mosquito	0	0	0	0	
Lymphocytic choriomeningitis	0	0	0	0	
Influenza	18	0.83	41	0.8	0.00
Chlamydia	<11	0.46	26	0.51	-0.01
Human papilloma virus	20	0.93	46	0.9	0.00
Gonorrhea	<11	0.46	23	0.44	0.00
HIV	<11	0.28	15	0.3	0.00
Trichomoniasis	16	0.74	35	0.69	0.01
Indications for duloxetine, N (%)					
Depression	1,198	55.46	2,904	57.11	-0.03
Anxiety	749	34.68	1,868	36.73	-0.04
Neuropathic Pain	249	11.53	576	11.33	0.01
Fibromyalgia	250	11.57	559	11	0.02
Non neuropathic Pain	1,196	55.37	2,800	55.06	0.01
Other psychiatric conditions, N (%)					
Sleep disorder	132	6.11	313	6.16	0.00
Bipolar disorder	282	13.06	697	13.72	-0.02
Psychosis	19	0.88	55	1.08	-0.02
Schizophrenia	21	0.97	59	1.16	-0.02
Personality disorder	52	2.41	136	2.67	-0.02
Adjustment disorder	23	1.06	52	1.03	0.00
Tobacco use, N (%)	258	11.94	603	11.86	0.00
Alcohol abuse or dependence, N (%)	28	1.3	69	1.35	0.00
Drug abuse or dependence, N (%)	77	3.56	189	3.72	-0.01
Other medication exposures, N (%)					
Benzodiazepines	877	40.6	2,130	41.88	-0.03
Other hypnotics	538	24.91	1,331	26.18	-0.03
Barbiturates	103	4.77	246	4.84	0.00

	Duloxetine N/Mean	Duloxetine %/SD	Venlafaxine N/Mean	Venlafaxine %/SD	Standardized Difference
Anxiolytics	113	5.23	293	5.76	-0.02
Anticonvulsants	568	26.3	1,316	25.88	0.01
Antipsychotics	448	20.74	1,122	22.06	-0.03
SSRIs	615	28.47	1,483	29.16	-0.02
SNRIs	34	1.57	5,085	100	-11.18
Other Antidep	641	29.68	1,521	29.92	-0.01
Stimulants	166	7.69	390	7.67	0.00
Antidiabetic	84	3.89	204	4.02	-0.01
Insulin	68	3.15	166	3.27	-0.01
Antihyperten	317	14.68	742	14.59	0.00
Opioid analgesics	1,381	63.94	3,231	63.54	0.01
Triptans	160	7.41	391	7.69	-0.01
NSAIDs	868	40.19	2,053	40.37	0.00
Obstetric conditions, N (%)					
Multifetal gestation Flag	76	3.52	178	3.51	0.00
Potentially teratogenic medication exposures, N (%)					
Danazol	0	0	0	0	
Synthetic progestins	79	3.66	193	3.8	-0.01
Methimazole	<11	0.14	<11	0.13	0.00
Propylthiouracil	<11	0.19	<11	0.17	0.00
Corticosteroids	386	17.87	903	17.75	0.00
Fluconazole	112	5.19	253	4.98	0.01
Markers of healthcare utilization					
Number of distinct 3 digit ICD 9 codes=0	68	3.15	163	3.2	0.00
Number of distinct 3 digit ICD 9 codes: tertile 1 for number >0	376	17.41	854	16.79	0.02
Number of distinct 3 digit ICD 9 codes: tertile 2 for number >0	472	21.85	1,128	22.18	-0.01
Number of distinct 3 digit ICD 9 codes: tertile 3 for number >0	1,244	57.59	2,940	57.83	0.00
Number of ED visits=0	1,294	59.91	3,047	59.91	0.00
Number of ED visits=1	479	22.18	1,105	21.73	0.01
Number of ED visits=2	207	9.58	484	9.52	0.00
Number of ED visits>2	180	8.33	449	8.83	-0.02
Number of non-duloxetine generics dispensed=0	130	6.02	313	6.16	-0.01

	Duloxetine	Duloxetine	Venlafaxine	Venlafaxine	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Number of non-duloxetine generics dispensed: tertile 1 for number >0	150	6.94	355	6.97	0.00
Number of non-duloxetine generics dispensed: tertile 2 for number >0	444	20.56	1,023	20.12	0.01
Number of non-duloxetine generics dispensed: tertile 3 for number >0	1,436	66.48	3,394	66.75	-0.01
Number of hospital admissions=0	2,056	95.19	4,841	95.2	0.00
Number of hospital admissions=1	88	4.07	206	4.06	0.00
Number of hospital admissions=2	14	0.65	34	0.67	0.00
Number of hospital admissions>2	<11	0.09	<11	0.07	0.01
Number of outpatient visits=0	148	6.85	338	6.65	0.01
Number of outpatient visits: tertile 1 for number >0	212	9.81	478	9.4	0.01
Number of outpatient visits: tertile 2 for number >0	546	25.28	1,286	25.3	0.00
Number of outpatient visits: tertile 3 for number >0	1,254	58.06	2,982	58.65	-0.01
Number of psychiatric hospitalizations Q1	2,092	96.85	4,930	96.95	-0.01
Number of psychiatric hospitalizations Q2	58	2.69	133	2.62	0.00
Number of psychiatric hospitalizations Q3	<11	0.37	18	0.36	0.00
Number of psychiatric hospitalizations Q4	<11	0.09	<11	0.07	0.01
Number of psychiatrist visits=0	822	38.06	1,880	36.97	0.02
Number of psychiatrist visits=1	513	23.75	1,207	23.75	0.00
Number of psychiatrist visits=2	259	11.99	600	11.8	0.01
Number of psychiatrist visits>2	566	26.2	1,398	27.49	-0.03
Geographic region					
Arkansas	PPD		PPD		0.01
Alabama			27	0.53	-0.02
California	141	6.53	333	6.55	0.00
Colorado	PPD		PPD		0.00
District of Columbia					0.00
Delaware	52	2.41	115	2.26	0.01
Florida	PPD		16	0.32	0.01
Georgia			24	0.48	0.00
Hawaii			PPD		0.00

	Duloxetine N/Mean	Duloxetine %/SD	Venlafaxine N/Mean	Venlafaxine %/SD	Standardized Difference
Iowa	23	1.06	54	1.06	0.00
Idaho	PPD		PPD		0.01
Illinois	251	11.62	580	11.41	0.01
Indiana	214	9.91	517	10.17	-0.01
Kansas	36	1.67	96	1.89	-0.02
Kentucky	34	1.57	81	1.59	0.00
Louisiana	75	3.47	175	3.43	0.00
Massachusetts	PPD		PPD		-0.01
Maryland	27	1.25	66	1.29	0.00
Maine	PPD		14	0.27	0.00
Minnesota	135	6.25	324	6.38	-0.01
Missouri	115	5.32	278	5.47	-0.01
Mississippi	PPD		23	0.46	0.00
North Carolina	50	2.31	116	2.29	0.00
North Dakota	24	1.11	53	1.05	0.01
Nebraska	20	0.93	47	0.93	0.00
New Hampshire	PPD		16	0.32	0.00
New Jersey	0	0	0	0	
New Mexico	18	0.83	42	0.83	0.00
Nevada	PPD		PPD		0.00
New York	375	17.36	875	17.2	0.00
Ohio	28	1.3	67	1.32	0.00
Oklahoma	26	1.2	57	1.13	0.01
Oregon	40	1.85	91	1.79	0.00
Pennsylvania	16	0.74	33	0.65	0.01
Rhode Island	PPD		PPD		0.00
South Carolina					0.01
South Dakota	13	0.6	26	0.51	0.01
Tennessee	135	6.25	326	6.4	-0.01
Texas	PPD		PPD		0.00
Utah	47	2.18	133	2.61	-0.03
Virginia	52	2.41	118	2.33	0.01

	Duloxetine N/Mean	Duloxetine %/SD	Venlafaxine N/Mean	Venlafaxine %/SD	Standardized Difference
Vermont	26	1.2	61	1.2	0.00
Washington	PPD		PPD		0.00
Wisconsin	102	4.72	221	4.34	0.02
West Virginia	PPD		PPD		0.00
Wyoming	PPD		PPD		0.00
Opioids					
buprenorphine	52	2.41	118	2.31	0.01
butorphanol	<11	0.19	12	0.24	-0.01
codeine	296	13.7	722	14.2	-0.01
fentanyl	26	1.2	61	1.2	0.00
hydrocodone	950	43.98	2,274	44.72	-0.01
hydromorphone	25	1.16	59	1.17	0.00
Levorphanol	0	0	0	0	
meperidine	<11	0.23	13	0.26	-0.01
methadone	24	1.11	57	1.13	0.00
morphine	39	1.81	80	1.58	0.02
oxycodone	357	16.53	836	16.44	0.00
oxymorphone	<11	0.09	<11	0.12	-0.01
pentazocine	<11	0.14	<11	0.13	0.00
propoxyphene	127	5.88	307	6.05	-0.01
tapentadol	<11	0.14	<11	0.12	0.01
tramadol	380	17.59	872	17.15	0.01
Healthcare Utilization, mean (SD)					
Comorbidity Index	1.61	1.86	1.57	1.77	0.02
Morphine equivalents	12168.33	251960.54	7875.27	185277.7	0.02
Number of diagnoses	6.28	4.65	6.36	4.79	-0.02
Number of ED visits	0.76	1.31	0.83	1.61	-0.05
Number of non-duloxetine generics dispensed	5.82	4.21	6.43	4.86	-0.13
Number of hospitalizations	0.06	0.27	0.06	0.27	0.00
Number of outpatient visits	5.88	6.45	5.82	5.92	0.01
Number of psychiatric hospitalizations	0.04	0.23	0.04	0.22	0.01
Number of psychiatrist visits	2.43	4.91	2.43	4.76	0.00

15.1. 12. Malformations- Baseline characteristics of duloxetine exposed women vs. duloxetine discontinuers: fully adjusted

	Duloxetine	Duloxetine	Duloxetine discontinuers	Duloxetine discontinuers	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Total	2,215	100.00	1,978	100.00	
Demographics					
Age, mean (SD)	27.81	5.55	27.93	5.56	-0.02
Age categorical, N (%)					
<=19	104	4.7	95	4.78	0.00
20-24	563	25.42	490	24.75	0.02
25-29	762	34.4	692	34.96	-0.01
30-34	490	22.12	441	22.32	0.00
35-39	230	10.38	207	10.44	0.00
>=40	66	2.98	54	2.74	0.01
Race, N (%)					
White	1,755	79.23	1,572	79.49	-0.01
Black/African American	192	8.67	173	8.74	0.00
Hispanic/Latino	61	2.75	53	2.66	0.01
Asian or Other Pacific	30	1.35	30	1.52	-0.01
American Indian	28	1.26	25	1.24	0.00
Other	101	4.56	85	4.3	0.01
Unknown	48	2.17	41	2.06	0.01
Chronic comorbid conditions, N (%)					
Hypertension	173	7.81	161	8.15	-0.01
Diabetes	135	6.09	119	6	0.00
Renal Disease	22	0.99	21	1.07	-0.01
Obesity Overweight	142	6.41	129	6.51	0.00
Comorbidity Index Q1	756	34.13	677	34.24	0.00
Comorbidity Index Q2	553	24.97	489	24.71	0.01
Comorbidity Index Q3	377	17.02	336	17	0.00
Comorbidity Index Q4	529	23.88	476	24.05	0.00
Infections, N (%)					
Toxoplasmosis	0	0	0	0	
Rubella	0	0	0	0	

	Duloxetine	Duloxetine	Duloxetine	Duloxetine	
	N/Mean	%/SD	discontinuers	discontinuers	Standardized
			N/Mean	%/SD	Difference
Cytomegalovirus	0	0	0	0	
Herpes	35	1.58	31	1.59	0.00
Syphilis	0	0	0	0	
Varicella	0	0	0	0	
Parvovirus B19	0	0	0	0	
Zika virus other mosquito	0	0	0	0	
Lymphocytic choriomeningitis	0	0	0	0	
Influenza	19	0.86	16	0.82	0.00
Chlamydia	<11	0.45	<11	0.49	-0.01
Human papilloma virus	22	0.99	16	0.83	0.02
Gonorrhea	<11	0.45	<11	0.5	-0.01
HIV	<11	0.27	<11	0.23	0.01
Trichomoniasis	16	0.72	14	0.73	0.00
Indications for duloxetine, N (%)					
Depression	1,232	55.62	1,100	55.6	0.00
Anxiety	774	34.94	701	35.46	-0.01
Neuropathic Pain	267	12.05	257	12.97	-0.03
Fibromyalgia	262	11.83	240	12.13	-0.01
Non neuropathic Pain	1,227	55.4	1,117	56.49	-0.02
Other psychiatric conditions, N (%)					
Sleep disorder	134	6.05	122	6.15	0.00
Bipolar disorder	293	13.23	274	13.84	-0.02
Psychosis	19	0.86	16	0.79	0.01
Schizophrenia	23	1.04	21	1.05	0.00
Personality disorder	55	2.48	49	2.47	0.00
Adjustment disorder	25	1.13	20	1.03	0.01
Tobacco use, N (%)	264	11.92	232	11.74	0.01
Alcohol abuse or dependence, N (%)	28	1.26	24	1.23	0.00
Drug abuse or dependence, N (%)	79	3.57	74	3.73	-0.01
Other medication exposures, N (%)					
Benzodiazepines	909	41.04	824	41.67	-0.01

	Duloxetine	Duloxetine	Duloxetine	Duloxetine	
	N/Mean	%/SD	discontinuers N/Mean	discontinuers %/SD	Standardized Difference
Other hypnotics	559	25.24	518	26.21	-0.02
Barbiturates	110	4.97	102	5.17	-0.01
Anxiolytics	118	5.33	107	5.4	0.00
Anticonvulsants	586	26.46	532	26.89	-0.01
Antipsychotics	462	20.86	409	20.66	0.00
SSRIs	643	29.03	591	29.87	-0.02
SNRIs	92	4.15	86	4.36	-0.01
Other Antidep	664	29.98	593	29.99	0.00
Stimulants	171	7.72	159	8.02	-0.01
Antidiabetic	86	3.88	71	3.57	0.02
Insulin	69	3.12	67	3.39	-0.02
Antihyperten	327	14.76	293	14.79	0.00
Opioid analgesics	1,418	64.02	1,292	65.32	-0.03
Triptans	164	7.4	147	7.41	0.00
NSAIDs	889	40.14	783	39.57	0.01
Obstetric conditions, N (%)					
Multifetal gestation Flag	77	3.48	67	3.4	0.00
Potentially teratogenic medication exposures, N (%)					
Danazol	0	0	0	0	.
Synthetic progestins	80	3.61	73	3.67	0.00
Methimazole	<11	0.14	<11	0.09	0.01
Propylthiouracil	<11	0.18	<11	0.09	0.02
Corticosteroids	401	18.1	353	17.83	0.01
Fluconazole	115	5.19	114	5.74	-0.02
Markers of healthcare utilization					
Number of distinct 3 digit ICD 9 codes=0	69	3.12	56	2.85	0.02
Number of distinct 3 digit ICD 9 codes: tertile 1 for number >0	384	17.34	344	17.39	0.00
Number of distinct 3 digit ICD 9 codes: tertile 2 for number >0	481	21.72	421	21.3	0.01
Number of distinct 3 digit ICD 9 codes: tertile 3 for number >0	1,281	57.83	1,156	58.46	-0.01
Number of ED visits=0	1,321	59.64	1,176	59.44	0.00
Number of ED visits=1	495	22.35	446	22.56	-0.01

	Duloxetine	Duloxetine	Duloxetine	Duloxetine	
	N/Mean	%/SD	discontinuers N/Mean	discontinuers %/SD	Standardized Difference
Number of ED visits=2	213	9.62	187	9.43	0.01
Number of ED visits>2	186	8.4	170	8.57	-0.01
Number of non-duloxetine generics dispensed=0	132	5.96	119	6.03	0.00
Number of non-duloxetine generics dispensed: tertile 1 for number >0	151	6.82	127	6.44	0.02
Number of non-duloxetine generics dispensed: tertile 2 for number >0	455	20.54	406	20.55	0.00
Number of non-duloxetine generics dispensed: tertile 3 for number >0	1,477	66.68	1,325	66.98	-0.01
Number of hospital admissions=0	2,104	94.99	1,879	94.97	0.00
Number of hospital admissions=1	94	4.24	86	4.33	0.00
Number of hospital admissions=2	15	0.68	12	0.63	0.01
Number of hospital admissions>2	<11	0.09	<11	0.07	0.01
Number of outpatient visits=0	149	6.73	127	6.41	0.01
Number of outpatient visits: tertile 1 for number >0	217	9.8	194	9.79	0.00
Number of outpatient visits: tertile 2 for number >0	557	25.15	490	24.8	0.01
Number of outpatient visits: tertile 3 for number >0	1,292	58.33	1,167	59.01	-0.01
Number of psychiatric hospitalizations Q1	2,141	96.66	1,913	96.72	0.00
Number of psychiatric hospitalizations Q2	64	2.89	56	2.84	0.00
Number of psychiatric hospitalizations Q3	<11	0.36	<11	0.37	0.00
Number of psychiatric hospitalizations Q4	<11	0.09	<11	0.07	0.01
Number of psychiatrist visits=0	837	37.79	737	37.26	0.01
Number of psychiatrist visits=1	520	23.48	480	24.26	-0.02
Number of psychiatrist visits=2	263	11.87	235	11.86	0.00
Number of psychiatrist visits>2	595	26.86	527	26.62	0.01
Geographic region					
Arkansas	PPD		PPD		-0.01
Alabama					-0.02
California	146	6.59	139	7	-0.02
Colorado	PPD		PPD		0.00
District of Columbia					

	Duloxetine	Duloxetine	Duloxetine	Duloxetine	
	N/Mean	%/SD	discontinuers	discontinuers	Standardized
			N/Mean	%/SD	Difference
Delaware	53	2.39	47	2.38	0.00
Florida	PPD		PPD		0.01
Georgia	PPD		PPD		-0.01
Hawaii	PPD		PPD		-0.02
Iowa	24	1.08	23	1.16	-0.01
Idaho	PPD		PPD		0.00
Illinois	257	11.6	219	11.08	0.02
Indiana	216	9.75	187	9.47	0.01
Kansas	36	1.63	33	1.65	0.00
Kentucky	35	1.58	34	1.72	-0.01
Louisiana	77	3.48	70	3.56	0.00
Massachusetts	PPD		PPD		0.01
Maryland	27	1.22	20	1.02	0.02
Maine	PPD		PPD		0.01
Minnesota	141	6.37	130	6.56	-0.01
Missouri	119	5.37	118	5.96	-0.03
Mississippi	PPD		PPD		0.00
North Carolina	50	2.26	48	2.42	-0.01
North Dakota	24	1.08	21	1.06	0.00
Nebraska	21	0.95	19	0.97	0.00
New Hampshire	PPD		PPD		-0.01
New Jersey	0	0	0	0	
New Mexico	20	0.9	20	1	-0.01
Nevada	PPD		PPD		-0.02
New York	384	17.34	335	16.96	0.01
Ohio	29	1.31	26	1.34	0.00
Oklahoma	26	1.17	24	1.22	0.00
Oregon	40	1.81	37	1.85	0.00
Pennsylvania	16	0.72	PPD		0.01
Rhode Island	PPD		PPD		-0.03
South Carolina	PPD		PPD		0.00

	Duloxetine	Duloxetine	Duloxetine	Duloxetine	
	N/Mean	%/SD	discontinuers	discontinuers	Standardized
			N/Mean	%/SD	Difference
South Dakota	13	0.59	PPD		0.01
Tennessee	142	6.41	123	6.22	0.01
Texas	PPD		PPD		0.01
Utah	45	2.03	45	2.27	-0.02
Virginia	56	2.53	47	2.36	0.01
Vermont	26	1.17	22	1.12	0.00
Washington	0	0	0	0	
Wisconsin	106	4.79	85	4.28	0.02
West Virginia	PPD		PPD		-0.02
Wyoming					0.01
Opioids					
buprenorphine	55	2.48	51	2.59	-0.01
Butorphanol	0	0	0	0	
codeine	307	13.86	269	13.59	0.01
fentanyl	26	1.17	24	1.24	-0.01
hydrocodone	974	43.97	892	45.1	-0.02
hydromorphone	29	1.31	24	1.19	0.01
Levorphanol	0	0	0	0	
meperidine	<11	0.23	<11	0.22	0.00
methadone	25	1.13	28	1.42	-0.03
morphine	39	1.76	31	1.59	0.01
oxycodone	371	16.75	343	17.36	-0.02
oxymorphone	<11	0.09	<11	0.09	0.00
pentazocine	<11	0.14	<11	0.1	0.01
propoxyphene	134	6.05	127	6.42	-0.02
tapentadol	<11	0.23	<11	0.12	0.02
tramadol	392	17.7	371	18.76	-0.03
Healthcare Utilization, mean (SD)					
Comorbidity Index	1.62	1.89	1.62	1.89	0.00
Morphine equivalents	7127.54	103333.53	7473.86	75448.41	0.00
Number of diagnoses	6.33	4.7	6.54	4.87	-0.04

	Duloxetine	Duloxetine	Duloxetine discontinuers	Duloxetine discontinuers	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Number of ED visits	0.77	1.32	0.83	1.66	-0.04
Number of non-duloxetine generics dispensed	5.87	4.25	6.1	4.53	-0.05
Number of hospitalizations	0.06	0.28	0.06	0.27	0.00
Number of outpatient visits	5.97	6.63	6.1	6.59	-0.02
Number of psychiatric hospitalizations	0.04	0.23	0.04	0.22	0.00
Number of psychiatrist visits	2.49	5.1	2.52	5.09	-0.01

15.1. 13. Malformations- Absolute risks

	Exposed					Reference							
Outcome	Events	N	Risk (/1,000)	95% CI		Events	N	Risk (/1,000)	95% CI		RR	95% CI	
				lower	upper				lower	upper		lower	upper
Duloxetine versus Unexposed													
Any Congenital Malformation	128	2,532	50.6	42.3	59.8	47,001	1,284,827	36.6	36.3	36.9	1.38	1.17	1.64
Central Nervous System	<11	2,532	1.6	0.4	4.0	2,339	1,284,827	1.8	1.7	1.9	0.87	0.33	2.31
Eye Anomalies	<11	2,532	0.4	0.0	2.2	491	1,284,827	0.4	0.3	0.4	1.03	0.15	7.35
Ear Anomalies	<11	2,532	0.4	0.0	2.2	276	1,284,827	0.2	0.2	0.2	1.84	0.26	13.09
Cardiovascular Anomalies	59	2,532	23.3	17.8	30.0	17,605	1,284,827	13.7	13.5	13.9	1.70	1.32	2.19
Other vascular	0	2,532				269	1,284,827	0.2	0.2	0.2			
Respiratory malformations	<11	2,532	2.4	0.9	5.2	2,887	1,284,827	2.2	2.2	2.3	1.05	0.47	2.35
Oral cleft	<11	2,532	1.6	0.4	4.0	1,501	1,284,827	1.2	1.1	1.2	1.35	0.51	3.60
Gastrointestinal	12	2,532	4.7	2.5	8.3	5,696	1,284,827	4.4	4.3	4.5	1.07	0.61	1.88
Genital	14	2,532	5.5	3.0	9.3	5,037	1,284,827	3.9	3.8	4.0	1.41	0.84	2.38
Urinary	15	2,532	5.9	3.3	9.8	3,607	1,284,827	2.8	2.7	2.9	2.11	1.27	3.50
Musculoskeletal	12	2,532	4.7	2.5	8.3	5,983	1,284,827	4.7	4.5	4.8	1.02	0.58	1.79
Limb defects	<11	2,532	2.0	0.6	4.6	5,446	1,284,827	4.2	4.1	4.4	0.47	0.19	1.12
Other	<11	2,532	3.2	1.4	6.2	1,406	1,284,827	1.1	1.0	1.2	2.89	1.44	5.78
Duloxetine versus SSRI													
Any Congenital Malformation	99	1,966	50.4	41.1	61.0	2,192	52,018	42.1	40.4	43.9	1.20	0.98	1.45
Central Nervous System	<11	1,966	2.0	0.6	5.2	116	52,018	2.2	1.8	2.7	0.91	0.34	2.47
Eye Anomalies	0	1,966				24	52,018	0.5	0.3	0.7			
Ear Anomalies	<11	1,966	0.5	0.0	2.8	13	52,018	0.2	0.1	0.4	2.04	0.27	15.55
Cardiovascular Anomalies	46	1,966	23.4	17.2	31.1	810	52,018	15.6	14.5	16.7	1.50	1.12	2.02
Other vascular	0	1,966				16	52,018	0.3	0.2	0.5			
Respiratory malformations	<11	1,966	2.0	0.6	5.2	158	52,018	3.0	2.6	3.5	0.67	0.25	1.81
Oral cleft	<11	1,966	2.0	0.6	5.2	80	52,018	1.5	1.2	1.9	1.32	0.49	3.61
Gastrointestinal	11	1,966	5.6	2.8	10.0	291	52,018	5.6	5.0	6.3	1.00	0.55	1.82
Genital	11	1,966	5.6	2.8	10.0	246	52,018	4.7	4.2	5.4	1.18	0.65	2.16
Urinary	<11	1,966	3.6	1.4	7.3	172	52,018	3.3	2.8	3.8	1.08	0.51	2.29
Musculoskeletal	<11	1,966	4.1	1.8	8.0	313	52,018	6.0	5.4	6.7	0.68	0.34	1.36
Limb defects	<11	1,966	2.5	0.8	5.9	173	52,018	3.3	2.8	3.9	0.76	0.31	1.86
Other	<11	1,966	2.5	0.8	5.9	59	52,018	1.1	0.9	1.5	2.24	0.90	5.58

	Exposed					Reference							
Outcome	Events	N	Risk (/1,000)	95% CI		Events	N	Risk (/1,000)	95% CI		RR	95% CI	
				lower	upper				lower	upper		lower	upper
Duloxetine versus Venlafaxine													
Any Congenital Malformation	127	2,467	51.5	43.1	60.9	270	6,369	42.4	37.6	47.6	1.21	0.99	1.49
Central Nervous System	<11	2,467	1.6	0.4	4.1	16	6,369	2.5	1.4	4.1	0.65	0.22	1.93
Eye Anomalies	<11	2,467	0.4	0.0	2.3	<11	6,369	0.8	0.3	1.8	0.52	0.06	4.42
Ear Anomalies	<11	2,467	0.4	0.0	2.3	<11	6,369	0.2	0	0.9	2.58	0.16	41.26
Cardiovascular Anomalies	58	2,467	23.5	17.9	30.3	96	6,369	15.1	12.2	18.4	1.56	1.13	2.15
Other vascular	0	2,467				<11	6,369	0.2	0	0.9			
Respiratory malformations	<11	2,467	2.4	0.9	5.3	24	6,369	3.8	2.4	5.6	0.65	0.26	1.58
Oral cleft	<11	2,467	1.6	0.4	4.1	<11	6,369	1.4	4.9	4.9	1.15	0.35	3.72
Gastrointestinal	12	2,467	4.9	2.5	8.5	33	6,369	5.2	3.6	7.3	0.94	0.49	1.81
Genital	14	2,467	5.7	3.1	9.5	30	6,369	4.7	3.2	6.7	1.20	0.64	2.27
Urinary	15	2,467	6.1	3.4	10.0	16	6,369	2.5	1.4	4.1	2.42	1.20	4.89
Musculoskeletal	12	2,467	4.9	2.5	8.5	50	6,369	7.9	5.8	10.3	0.62	0.33	1.16
Limb defects	<11	2,467	2.0	0.7	4.7	19	6,369	3	1.8	4.7	0.68	0.25	1.82
Other	<11	2,467	3.2	1.4	6.4	<11	6,369	1.3	0.5	2.5	2.58	0.97	6.87
Duloxetine versus Duloxetine Discontinuers													
Any Congenital Malformation	128	2,532	50.6	42.3	59.8	114	2,456	46.4	38.4	55.5	1.09	0.85	1.39
Central Nervous System	<11	2,532	1.6	0.4	4.0	<11	2,456	2.9	1.1	5.9	0.55	0.16	1.89
Eye Anomalies	<11	2,532	0.4	0.0	2.2	<11	2,456	0.8	0.1	2.9	0.49	0.04	5.35
Ear Anomalies	0	2,532	0.4	0.0	2.2	<11	2,456						
Cardiovascular Anomalies	59	2,532	23.3	17.8	30.0	43	2,456	17.5	12.7	23.5	1.33	0.90	1.96
Other vascular	<11	2,532				<11	2,456	0.4	0.0	2.3			
Respiratory malformations	<11	2,532	2.4	0.9	5.2	<11	2,456	2.4	0.9	5.3	0.97	0.31	3.00
Oral cleft	<11	2,532	1.6	0.4	4.0	<11	2,456	1.2	0.3	3.6	1.29	0.29	5.77
Gastrointestinal	12	2,532	4.7	2.5	8.3	17	2,456	6.9	4.0	11.1	0.68	0.33	1.43
Genital	14	2,532	5.5	3.0	9.3	12	2,456	4.9	2.5	8.5	1.13	0.52	2.44
Urinary	15	2,532	5.9	3.3	9.8	<11	2,456	4.1	2.0	7.5	1.46	0.65	3.23
Musculoskeletal	12	2,532	4.7	2.5	8.3	21	2,456	8.6	5.3	13.0	0.55	0.27	1.12
Limb defects	<11	2,532	2.0	0.6	4.6	<11	2,456	2.9	1.1	5.9	0.69	0.22	2.18
Other	<11	2,532	3.2	1.4	6.2	<11	2,456	1.2	0.3	3.6	2.59	0.69	9.74

15.1. 14. Malformations- Relative risks for duloxetine exposed vs. unexposed women

	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Unadjusted Analyses							
Any Congenital Malformation	128	2,532	47,001	1,284,827	1.38	1.17	1.64
Central Nervous System	<11	2,532	2,339	1,284,827	0.87	0.33	2.31
Eye Anomalies	<11	2,532	491	1,284,827	1.03	0.15	7.35
Ear Anomalies	<11	2,532	276	1,284,827	1.84	0.26	13.09
Cardiovascular Anomalies	59	2,532	17,605	1,284,827	1.70	1.32	2.19
Other vascular	0	2,532	269	1,284,827			
Respiratory malformations	<11	2,532	2,887	1,284,827	1.05	0.47	2.35
Oral cleft	<11	2,532	1,501	1,284,827	1.35	0.51	3.60
Gastrointestinal	12	2,532	5,696	1,284,827	1.07	0.61	1.88
Genital	14	2,532	5,037	1,284,827	1.41	0.84	2.38
Urinary	15	2,532	3,607	1,284,827	2.11	1.27	3.50
Musculoskeletal	12	2,532	5,983	1,284,827	1.02	0.58	1.79
Limb defects	<11	2,532	5,446	1,284,827	0.47	0.19	1.12
Other	<11	2,532	1,406	1,284,827	2.89	1.44	5.78
Adjusted: Restricted + PS1 (indications)							
Any Congenital Malformation	116	2,224	17,032	420,806	1.23	1.03	1.47
Central Nervous System	<11	2,224	830	420,806	0.87	0.33	2.33
Eye Anomalies	<11	2,224	182	420,806	1.01	0.14	7.20
Ear Anomalies	<11	2,224	100	420,806	1.70	0.24	12.14
Cardiovascular Anomalies	53	2,224	6,331	420,806	1.53	1.17	2.00
Other vascular	0	2,224	92	420,806			
Respiratory malformations	<11	2,224	1,178	420,806	0.85	0.38	1.88
Oral cleft	<11	2,224	557	420,806	0.93	0.30	2.90
Gastrointestinal	11	2,224	2,104	420,806	0.93	0.52	1.68
Genital	12	2,224	1,816	420,806	1.14	0.65	2.01
Urinary	15	2,224	1,294	420,806	2.13	1.28	3.53
Musculoskeletal	<11	2,224	2,263	420,806	0.77	0.42	1.43
Limb defects	<11	2,224	1,804	420,806	0.54	0.22	1.29
Other	<11	2,224	483	420,806	2.83	1.34	5.96
Adjusted: Restricted + PS2 (All covariates)							
Any Congenital Malformation	116	2,223	16,067	392,928	1.11	0.93	1.33

Outcome	Exposed		Reference		RR	95% CI lower	95% CI upper
	Events	N	Events	N			
Central Nervous System	<11	2,223	780	392,928	0.81	0.30	2.16
Eye Anomalies	<11	2,223	174	392,928	0.98	0.14	7.01
Ear Anomalies	<11	2,223	95	392,928	1.73	0.24	12.39
Cardiovascular Anomalies	53	2,223	5,967	392,928	1.29	0.99	1.68
Other vascular	0	2,223	84	392,928			
Respiratory malformations	<11	2,223	1,116	392,928	0.87	0.39	1.94
Oral cleft	<11	2,223	531	392,928	0.75	0.24	2.33
Gastrointestinal	11	2,223	1,997	392,928	0.86	0.48	1.55
Genital	12	2,223	1,711	392,928	1.08	0.61	1.90
Urinary	15	2,223	1,227	392,928	1.89	1.14	3.14
Musculoskeletal	<11	2,223	2,156	392,928	0.70	0.38	1.30
Limb defects	<11	2,223	1,656	392,928	0.60	0.25	1.43
Other	<11	2,223	452	392,928	2.98	1.41	6.29
Adjusted: Restricted + hdPS							
Any Congenital Malformation	114	2,218	15,926	390,080	1.08	0.91	1.30
Central Nervous System	<11	2,218	766	390,080	0.76	0.28	2.03
Eye Anomalies	<11	2,218	169	390,080	1.29	0.18	9.20
Ear Anomalies	<11	2,218	95	390,080	1.73	0.24	12.42
Cardiovascular Anomalies	52	2,218	5,926	390,080	1.26	0.96	1.65
Other vascular	0	2,218	82	390,080			
Respiratory malformations	<11	2,218	1,110	390,080	0.84	0.38	1.88
Oral cleft	<11	2,218	527	390,080	0.76	0.25	2.37
Gastrointestinal	11	2,218	1,994	390,080	0.84	0.46	1.51
Genital	11	2,218	1,691	390,080	0.96	0.53	1.74
Urinary	14	2,218	1,209	390,080	1.80	1.06	3.04
Musculoskeletal	<11	2,218	2,143	390,080	0.72	0.39	1.35
Limb defects	<11	2,218	1,636	390,080	0.55	0.23	1.32
Other	<11	2,218	450	390,080	3.04	1.44	6.42

15.1. 15. Malformations- Relative risks for duloxetine exposed vs. SSRI exposed women

	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Unadjusted Analyses							
Any Congenital Malformation	99	1,966	2,192	52,018	1.20	0.98	1.45
Central Nervous System	<11	1,966	116	52,018	0.91	0.34	2.47
Eye Anomalies	0	1,966	24	52,018			
Ear Anomalies	<11	1,966	13	52,018	2.04	0.27	15.55
Cardiovascular Anomalies	46	1,966	810	52,018	1.50	1.12	2.02
Other vascular	0	1,966	16	52,018			
Respiratory malformations	<11	1,966	158	52,018	0.67	0.25	1.81
Oral cleft	<11	1,966	80	52,018	1.32	0.49	3.61
Gastrointestinal	11	1,966	291	52,018	1.00	0.55	1.82
Genital	11	1,966	246	52,018	1.18	0.65	2.16
Urinary	<11	1,966	172	52,018	1.08	0.51	2.29
Musculoskeletal	<11	1,966	313	52,018	0.68	0.34	1.36
Limb defects	<11	1,966	173	52,018	0.76	0.31	1.86
Other	<11	1,966	59	52,018	2.24	0.90	5.58
Adjusted: Restricted + PS1 (indications)							
Any Congenital Malformation	87	1,705	1,718	40,671	1.17	0.95	1.44
Central Nervous System	<11	1,705	89	40,671	0.99	0.36	2.69
Eye Anomalies	0	1,705	17	40,671			
Ear Anomalies	<11	1,705	12	40,671	2.47	0.32	19.36
Cardiovascular Anomalies	40	1,705	634	40,671	1.44	1.05	1.97
Other vascular	0	1,705	12	40,671			
Respiratory malformations	<11	1,705	139	40,671	0.66	0.24	1.77
Oral cleft	<11	1,705	58	40,671	1.06	0.33	3.37
Gastrointestinal	<11	1,705	231	40,671	0.94	0.50	1.77
Genital	<11	1,705	184	40,671	1.20	0.62	2.35
Urinary	<11	1,705	131	40,671	1.27	0.60	2.72
Musculoskeletal	<11	1,705	252	40,671	0.57	0.25	1.28
Limb defects	<11	1,705	132	40,671	1.00	0.41	2.43
Other	<11	1,705	46	40,671	2.26	0.81	6.30
Adjusted: Restricted + PS2 (All covariates)							
Any Congenital Malformation	87	1,703	1,670	39,395	1.09	0.89	1.35

Outcome	Exposed		Reference		RR	95% CI lower	95% CI upper
	Events	N	Events	N			
Central Nervous System	<11	1,703	84	39,395	1.00	0.37	2.72
Eye Anomalies	0	1,703	17	39,395			
Ear Anomalies	<11	1,703	12	39,395	2.81	0.35	22.36
Cardiovascular Anomalies	40	1,703	620	39,395	1.27	0.93	1.74
Other vascular	0	1,703	11	39,395			
Respiratory malformations	<11	1,703	135	39,395	0.73	0.27	1.97
Oral cleft	<11	1,703	58	39,395	0.90	0.28	2.85
Gastrointestinal	<11	1,703	224	39,395	0.95	0.51	1.79
Genital	<11	1,703	174	39,395	1.13	0.58	2.20
Urinary	<11	1,703	129	39,395	1.21	0.57	2.58
Musculoskeletal	<11	1,703	246	39,395	0.53	0.24	1.19
Limb defects	<11	1,703	128	39,395	0.88	0.36	2.15
Other	<11	1,703	46	39,395	3.06	1.08	8.66
Adjusted: Restricted + hdPS							
Any Congenital Malformation	87	1,697	1,718	40,670	1.10	0.89	1.36
Central Nervous System	<11	1,697	89	40,670	0.95	0.35	2.58
Eye Anomalies	0	1,697	17	40,670			
Ear Anomalies	<11	1,697	12	40,670	3.17	0.39	25.52
Cardiovascular Anomalies	40	1,697	634	40,670	1.35	0.99	1.85
Other vascular	0	1,697	12	40,670			
Respiratory malformations	<11	1,697	139	40,670	0.79	0.29	2.14
Oral cleft	<11	1,697	58	40,670	0.94	0.30	2.97
Gastrointestinal	<11	1,697	231	40,670	0.93	0.49	1.74
Genital	<11	1,697	184	40,670	1.06	0.54	2.06
Urinary	<11	1,697	131	40,670	1.15	0.54	2.45
Musculoskeletal	<11	1,697	252	40,670	0.53	0.23	1.18
Limb defects	<11	1,697	132	40,670	0.83	0.34	2.03
Other	<11	1,697	46	40,670	2.92	1.03	8.23

15.1. 16. Malformations- Relative risks for duloxetine exposed vs. venlafaxine exposed women

	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Unadjusted Analyses							
Any Congenital Malformation	127	2,467	270	6,369	1.21	0.99	1.49
Central Nervous System	<11	2,467	16	6,369	0.65	0.22	1.93
Eye Anomalies	<11	2,467	<11	6,369	0.52	0.06	4.42
Ear Anomalies	<11	2,467	<11	6,369	2.58	0.16	41.26
Cardiovascular Anomalies	58	2,467	96	6,369	1.56	1.13	2.15
Other vascular	0	2,467	<11	6,369			
Respiratory malformations	<11	2,467	24	6,369	0.65	0.26	1.58
Oral cleft	<11	2,467	<11	6,369	1.15	0.35	3.72
Gastrointestinal	12	2,467	33	6,369	0.94	0.49	1.81
Genital	14	2,467	30	6,369	1.20	0.64	2.27
Urinary	15	2,467	16	6,369	2.42	1.20	4.89
Musculoskeletal	12	2,467	50	6,369	0.62	0.33	1.16
Limb defects	<11	2,467	19	6,369	0.68	0.25	1.82
Other	<11	2,467	<11	6,369	2.58	0.97	6.87
Adjusted: Restricted + PS1 (indications)							
Any Congenital Malformation	116	2,166	235	5,235	1.14	0.92	1.42
Central Nervous System	<11	2,166	12	5,235	1.03	0.32	3.32
Eye Anomalies	<11	2,166	<11	5,235	0.59	0.07	5.25
Ear Anomalies	<11	2,166	<11	5,235	3.56	0.16	77.77
Cardiovascular Anomalies	53	2,166	84	5,235	1.32	0.95	1.84
Other vascular	0	2,166	<11	5,235			
Respiratory malformations	<11	2,166	23	5,235	0.57	0.24	1.39
Oral cleft	<11	2,166	<11	5,235	0.73	0.20	2.65
Gastrointestinal	11	2,166	31	5,235	0.89	0.45	1.77
Genital	12	2,166	25	5,235	1.18	0.59	2.35
Urinary	15	2,166	13	5,235	2.87	1.36	6.07
Musculoskeletal	<11	2,166	43	5,235	0.59	0.29	1.17
Limb defects	<11	2,166	15	5,235	0.94	0.34	2.64
Other	<11	2,166	<11	5,235	1.62	0.62	4.21
Adjusted: Restricted + PS2 (All covariates)							
Any Congenital Malformation	114	2,160	228	5,085	1.09	0.88	1.36

Outcome	Exposed		Reference		RR	95% CI lower	95% CI upper
	Events	N	Events	N			
Central Nervous System	<11	2,160	12	5,085	1.06	0.33	3.44
Eye Anomalies	<11	2,160	<11	5,085	0.66	0.07	6.06
Ear Anomalies	<11	2,160	<11	5,085	13.02	0.09	1950.26
Cardiovascular Anomalies	51	2,160	81	5,085	1.17	0.84	1.63
Other vascular	0	2,160	<11	5,085			
Respiratory malformations	<11	2,160	22	5,085	0.52	0.22	1.26
Oral cleft	<11	2,160	<11	5,085	0.73	0.20	2.65
Gastrointestinal	11	2,160	31	5,085	0.90	0.45	1.79
Genital	12	2,160	25	5,085	1.37	0.67	2.78
Urinary	15	2,160	12	5,085	2.23	1.10	4.52
Musculoskeletal	<11	2,160	40	5,085	0.56	0.28	1.11
Limb defects	<11	2,160	15	5,085	1.29	0.43	3.84
Other	<11	2,160	<11	5,085	3.28	1.04	10.31
Adjusted: Restricted + hdPS							
Any Congenital Malformation	113	2,143	229	5,037	0.98	0.79	1.21
Central Nervous System	<11	2,143	12	5,037	1.04	0.32	3.38
Eye Anomalies	<11	2,143	<11	5,037	0.63	0.07	5.68
Ear Anomalies	<11	2,143	<11	5,037	7.95	0.13	481.54
Cardiovascular Anomalies	50	2,143	82	5,037	1.01	0.73	1.40
Other vascular	0	2,143	<11	5,037			
Respiratory malformations	<11	2,143	22	5,037	0.38	0.16	0.89
Oral cleft	<11	2,143	<11	5,037	0.54	0.15	1.88
Gastrointestinal	11	2,143	31	5,037	1.05	0.51	2.12
Genital	12	2,143	24	5,037	1.06	0.54	2.09
Urinary	15	2,143	13	5,037	2.65	1.27	5.53
Musculoskeletal	<11	2,143	40	5,037	0.70	0.34	1.41
Limb defects	<11	2,143	14	5,037	0.96	0.34	2.70
Other	<11	2,143	<11	5,037	3.40	1.07	10.84

15.1. 17. Malformations- Relative risk for duloxetine exposed women vs. duloxetine discontinuers

	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Unadjusted Analyses							
Any Congenital Malformation	128	2,532	114	2,456	1.09	0.85	1.39
Central Nervous System	<11	2,532	<11	2,456	0.55	0.16	1.89
Eye Anomalies	<11	2,532	<11	2,456	0.49	0.04	5.35
Ear Anomalies	0	2,532	<11	2,456			
Cardiovascular Anomalies	59	2,532	43	2,456	1.33	0.90	1.96
Other vascular	0	2,532	<11	2,456			
Respiratory malformations	<11	2,532	<11	2,456	0.97	0.31	3.00
Oral cleft	<11	2,532	<11	2,456	1.29	0.29	5.77
Gastrointestinal	12	2,532	17	2,456	0.68	0.33	1.43
Genital	14	2,532	12	2,456	1.13	0.52	2.44
Urinary	15	2,532	<11	2,456	1.46	0.65	3.23
Musculoskeletal	12	2,532	21	2,456	0.55	0.27	1.12
Limb defects	<11	2,532	<11	2,456	0.69	0.22	2.18
Other	<11	2,532	<11	2,456	2.59	0.69	9.74
Adjusted: Restricted + PS1 (indications)							
Any Congenital Malformation	116	2,224	88	1,992	1.04	0.80	1.34
Central Nervous System	<11	2,224	<11	1,992	1.10	0.25	4.73
Eye Anomalies	<11	2,224	<11	1,992	0.62	0.05	8.00
Ear Anomalies	0	2,224	<11	1,992			
Cardiovascular Anomalies	53	2,224	30	1,992	1.42	0.92	2.17
Other vascular	0	2,224	<11	1,992			
Respiratory malformations	<11	2,224	<11	1,992	0.91	0.29	2.84
Oral cleft	<11	2,224	<11	1,992	1.49	0.24	9.41
Gastrointestinal	11	2,224	16	1,992	0.47	0.23	0.98
Genital	12	2,224	<11	1,992	1.20	0.51	2.85
Urinary	15	2,224	<11	1,992	1.03	0.49	2.16
Musculoskeletal	<11	2,224	19	1,992	0.48	0.22	1.04
Limb defects	<11	2,224	<11	1,992	0.86	0.25	2.91
Other	<11	2,224	<11	1,992	1.68	0.48	5.88
Adjusted: Restricted + PS2 (All covariates)							
Any Congenital Malformation	116	2,215	88	1,978	1.09	0.84	1.42

Outcome	Exposed		Reference		RR	95% CI lower	95% CI upper
	Events	N	Events	N			
Central Nervous System	<11	2,215	<11	1,978	0.67	0.18	2.42
Eye Anomalies	<11	2,215	<11	1,978	1.00	0.06	17.34
Ear Anomalies	0	2,215	<11	1,978			
Cardiovascular Anomalies	53	2,215	30	1,978	1.41	0.92	2.17
Other vascular	0	2,215	<11	1,978			
Respiratory malformations	<11	2,215	<11	1,978	0.89	0.29	2.75
Oral cleft	<11	2,215	<11	1,978	1.30	0.22	7.64
Gastrointestinal	11	2,215	16	1,978	0.67	0.31	1.45
Genital	12	2,215	<11	1,978	1.30	0.54	3.16
Urinary	15	2,215	<11	1,978	1.11	0.52	2.36
Musculoskeletal	<11	2,215	19	1,978	0.45	0.21	0.95
Limb defects	<11	2,215	<11	1,978	0.48	0.16	1.42
Other	<11	2,215	<11	1,978	1.33	0.41	4.28
Adjusted: Restricted + hdPS							
Any Congenital Malformation	112	2,110	85	1,943	1.11	0.85	1.46
Central Nervous System	<11	2,110	<11	1,943	1.06	0.20	5.56
Eye Anomalies	<11	2,110	<11	1,943	0.60	0.05	7.35
Ear Anomalies	0	2,110	<11	1,943			
Cardiovascular Anomalies	51	2,110	27	1,943	1.67	1.06	2.63
Other vascular	0	2,110	<11	1,943			
Respiratory malformations	<11	2,110	<11	1,943	1.09	0.33	3.54
Oral cleft	<11	2,110	<11	1,943	1.74	0.25	11.95
Gastrointestinal	11	2,110	16	1,943	0.64	0.30	1.38
Genital	11	2,110	<11	1,943	0.63	0.29	1.34
Urinary	15	2,110	<11	1,943	1.75	0.74	4.12
Musculoskeletal	<11	2,110	19	1,943	0.69	0.31	1.57
Limb defects	<11	2,110	<11	1,943	0.67	0.21	2.13
Other	<11	2,110	<11	1,943	0.95	0.33	2.71

	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Any Congenital Malformation	62	1,019	145	2,995	1.26	0.94	1.68
Central Nervous System	<11	1,019	<11	2,995	0.98	0.20	4.85
Eye Anomalies	0	1,019	<11	2,995			
Ear Anomalies	0	1,019	<11	2,995			
Cardiovascular Anomalies	32	1,019	62	2,995	1.52	1.00	2.31
Other vascular	0	1,019	0	2,995			
Respiratory malformations	<11	1,019	11	2,995	0.80	0.22	2.87
Oral cleft	<11	1,019	<11	2,995	0.49	0.06	4.06
Gastrointestinal	<11	1,019	14	2,995	0.84	0.28	2.55
Genital	<11	1,019	17	2,995	1.04	0.41	2.62
Urinary	<11	1,019	<11	2,995	2.52	0.85	7.48
Musculoskeletal	<11	1,019	23	2,995	0.89	0.39	2.08
Limb defects	<11	1,019	<11	2,995	0.37	0.05	2.93
Other	<11	1,019	<11	2,995	2.94	0.74	11.73
Duloxetine versus Duloxetine Discontinuers							
Any Congenital Malformation	62	1,047	57	1,144	1.19	0.84	1.69
Central Nervous System	<11	1,047	<11	1,144	0.73	0.12	4.35
Eye Anomalies	0	1,047	<11	1,144			
Ear Anomalies	0	1,047	0	1,144			
Cardiovascular Anomalies	32	1,047	19	1,144	1.84	1.05	3.23
Other vascular	0	1,047	0	1,144			
Respiratory malformations	<11	1,047	<11	1,144	3.28	0.34	31.46
Oral cleft	<11	1,047	<11	1,144	0.55	0.05	6.02
Gastrointestinal	<11	1,047	<11	1,144	0.62	0.18	2.13
Genital	<11	1,047	<11	1,144	0.82	0.29	2.35
Urinary	<11	1,047	<11	1,144	0.94	0.32	2.78
Musculoskeletal	<11	1,047	12	1,144	0.64	0.25	1.61
Limb defects	<11	1,047	<11	1,144	0.18	0.02	1.51
Other	<11	1,047	<11	1,144	1.46	0.33	6.49
Fully Adjusted Analyses							
	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Duloxetine versus Unexposed							
Any Congenital Malformation	59	925	15,041	363,271	1.35	1.06	1.73

Outcome	Exposed		Reference		RR	95% CI lower	95% CI upper
	Events	N	Events	N			
Central Nervous System	<11	925	720	363,271	1.01	0.25	4.06
Eye Anomalies	0	925	166	363,271			
Ear Anomalies	0	925	90	363,271			
Cardiovascular Anomalies	31	925	5,628	363,271	1.71	1.21	2.41
Other vascular	0	925	81	363,271			
Respiratory malformations	<11	925	1,048	363,271	1.13	0.37	3.51
Oral cleft	<11	925	502	363,271	0.68	0.10	4.81
Gastrointestinal	<11	925	1,874	363,271	0.78	0.29	2.08
Genital	<11	925	1,607	363,271	1.09	0.45	2.61
Urinary	<11	925	1,163	363,271	1.92	0.86	4.27
Musculoskeletal	<11	925	2,030	363,271	1.22	0.58	2.56
Limb defects	<11	925	1,505	363,271	0.28	0.04	1.97
Other	<11	925	431	363,271	3.44	1.11	10.70
Duloxetine versus SSRI							
Any Congenital Malformation	44	732	674	15,925	1.31	0.98	1.76
Central Nervous System	<11	732	44	15,925	1.10	0.27	4.56
Eye Anomalies	0	732	<11	15,925			
Ear Anomalies	0	732	<11	15,925			
Cardiovascular Anomalies	23	732	264	15,925	1.69	1.11	2.56
Other vascular	0	732	<11	15,925			
Respiratory malformations	<11	732	50	15,925	1.64	0.51	5.29
Oral cleft	<11	732	24	15,925	0.90	0.12	6.61
Gastrointestinal	<11	732	76	15,925	0.80	0.30	2.17
Genital	<11	732	71	15,925	0.83	0.26	2.64
Urinary	<11	732	59	15,925	1.20	0.44	3.26
Musculoskeletal	<11	732	93	15,925	0.69	0.22	2.16
Limb defects	<11	732	51	15,925	0.55	0.08	3.98
Other	<11	732	21	15,925	1.87	0.24	14.37
Duloxetine versus Venlafaxine							
Any Congenital Malformation	59	897	124	2,395	1.18	0.88	1.59
Central Nervous System	<11	897	<11	2,395	1.06	0.21	5.45
Eye Anomalies	0	897	<11	2,395			
Ear Anomalies	0	897	<11	2,395			

Outcome	Exposed		Reference				
	Events	N	Events	N	RR	95% CI lower	95% CI upper
Cardiovascular Anomalies	31	897	54	2,395	1.38	0.90	2.11
Other vascular	0	897	0	2,395			
Respiratory malformations	<11	897	<11	2,395	0.45	0.13	1.53
Oral cleft	<11	897	<11	2,395	0.42	0.05	3.45
Gastrointestinal	<11	897	14	2,395	1.59	0.46	5.48
Genital	<11	897	13	2,395	0.82	0.30	2.23
Urinary	<11	897	<11	2,395	3.46	1.03	11.60
Musculoskeletal	<11	897	21	2,395	1.16	0.48	2.81
Limb defects	<11	897	<11	2,395	0.34	0.04	2.72
Other	<11	897	<11	2,395	3.39	0.62	18.62
Duloxetine versus Duloxetine Discontinuers							
Any Congenital Malformation	59	916	47	939	1.23	0.85	1.77
Central Nervous System	<11	916	<11	939	0.65	0.11	3.77
Eye Anomalies	0	916	<11	939			
Ear Anomalies	0	916	0	939			
Cardiovascular Anomalies	31	916	15	939	2.10	1.14	3.85
Other vascular	0	916	0	939			
Respiratory malformations	<11	916	<11	939	3.16	0.32	31.00
Oral cleft	<11	916	<11	939	0.56	0.05	6.46
Gastrointestinal	<11	916	<11	939	0.56	0.17	1.90
Genital	<11	916	<11	939	1.34	0.35	5.05
Urinary	<11	916	<11	939	0.72	0.25	2.02
Musculoskeletal	<11	916	11	939	0.72	0.28	1.89
Limb defects	<11	916	<11	939	0.22	0.03	1.90
Other	<11	916	<11	939	2.05	0.29	14.51

Outcome	Exposed		Reference		RR	95% CI lower	95% CI upper
	Events	N	Events	N			
Any Congenital Malformation	149	2,904	17,032	420,806	1.20	1.03	1.41
Central Nervous System	<11	2,904	830	420,806	0.82	0.34	1.97
Eye Anomalies	<11	2,904	182	420,806	0.78	0.11	5.58
Ear Anomalies	<11	2,904	100	420,806	1.31	0.18	9.36
Cardiovascular Anomalies	68	2,904	6,331	420,806	1.49	1.17	1.88
Other vascular	0	2,904	92	420,806			
Respiratory malformations	<11	2,904	1,178	420,806	0.77	0.37	1.62
Oral cleft	<11	2,904	557	420,806	0.73	0.23	2.25
Gastrointestinal	17	2,904	2,104	420,806	1.07	0.67	1.73
Genital	14	2,904	1,816	420,806	1.00	0.59	1.70
Urinary	18	2,904	1,294	420,806	1.92	1.21	3.05
Musculoskeletal	19	2,904	2,263	420,806	1.12	0.71	1.76
Limb defects	<11	2,904	1,804	420,806	0.66	0.33	1.33
Other	<11	2,904	483	420,806	2.35	1.17	4.71
Duloxetine versus SSRI							
Any Congenital Malformation	109	2,214	1,723	40,746	1.12	0.93	1.36
Central Nervous System	<11	2,214	89	40,746	0.93	0.38	2.29
Eye Anomalies	0	2,214	17	40,746			
Ear Anomalies	<11	2,214	12	40,746	1.77	0.23	13.78
Cardiovascular Anomalies	52	2,214	635	40,746	1.40	1.06	1.85
Other vascular	0	2,214	13	40,746			
Respiratory malformations	<11	2,214	139	40,746	0.54	0.20	1.45
Oral cleft	<11	2,214	58	40,746	0.88	0.28	2.82
Gastrointestinal	12	2,214	231	40,746	0.87	0.49	1.55
Genital	10	2,214	184	40,746	1.03	0.55	1.95
Urinary	10	2,214	133	40,746	1.40	0.74	2.66
Musculoskeletal	12	2,214	253	40,746	0.90	0.51	1.61
Limb defects	<11	2,214	132	40,746	1.06	0.50	2.27
Other	<11	2,214	47	40,746	2.09	0.83	5.27
Duloxetine versus Venlafaxine							
Any Congenital Malformation	148	2,811	236	5,253	1.12	0.92	1.36
Central Nervous System	<11	2,811	12	5,253	0.92	0.32	2.69
Eye Anomalies	<11	2,811	<11	5,253	0.35	0.04	2.97

	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Ear Anomalies	<11	2,811	<11	5,253	2.75	0.13	59.94
Cardiovascular Anomalies	67	2,811	85	5,253	1.29	0.95	1.75
Other vascular	0	2,811	<11	5,253			
Respiratory malformations	<11	2,811	24	5,253	0.48	0.21	1.11
Oral cleft	<11	2,811	<11	5,253	0.50	0.14	1.81
Gastrointestinal	17	2,811	31	5,253	1.02	0.57	1.85
Genital	14	2,811	25	5,253	1.07	0.56	2.07
Urinary	18	2,811	13	5,253	2.49	1.23	5.04
Musculoskeletal	19	2,811	43	5,253	0.86	0.50	1.48
Limb defects	<11	2,811	15	5,253	1.18	0.49	2.87
Other	<11	2,811	<11	5,253	1.44	0.57	3.61
Duloxetine versus Duloxetine Discontinuers							
Any Congenital Malformation	133	2,571	72	1,659	1.10	0.84	1.45
Central Nervous System	<11	2,571	<11	1,659	1.34	0.24	7.47
Eye Anomalies	<11	2,571	<11	1,659	0.57	0.04	8.34
Ear Anomalies	<11	2,571	0	1,659			
Cardiovascular Anomalies	62	2,571	24	1,659	1.62	1.02	2.57
Other vascular	0	2,571	<11	1,659			
Respiratory malformations	<11	2,571	<11	1,659	0.81	0.27	2.47
Oral cleft	<11	2,571	<11	1,659	1.13	0.17	7.33
Gastrointestinal	13	2,571	12	1,659	0.57	0.27	1.19
Genital	14	2,571	<11	1,659	1.05	0.45	2.45
Urinary	15	2,571	<11	1,659	1.31	0.54	3.14
Musculoskeletal	14	2,571	14	1,659	0.62	0.30	1.30
Limb defects	<11	2,571	<11	1,659	1.23	0.31	4.81
Other	<11	2,571	<11	1,659	6.36	0.55	72.93
Adjusted: Restricted + PS2 (All covariates)	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Duloxetine versus Unexposed							
Any Congenital Malformation	149	2,902	16,031	391,885	1.11	0.95	1.30
Central Nervous System	<11	2,902	775	391,885	0.79	0.33	1.90
Eye Anomalies	<11	2,902	172	391,885	0.83	0.12	5.89

Outcome	Exposed		Reference		RR	95% CI lower	95% CI upper
	Events	N	Events	N			
Ear Anomalies	<11	2,902	95	391,885	1.39	0.19	9.99
Cardiovascular Anomalies	68	2,902	5,966	391,885	1.30	1.02	1.64
Other vascular	0	2,902	84	391,885			
Respiratory malformations	<11	2,902	1,113	391,885	0.75	0.36	1.57
Oral cleft	<11	2,902	530	391,885	0.61	0.20	1.90
Gastrointestinal	17	2,902	1,999	391,885	1.02	0.64	1.65
Genital	14	2,902	1,702	391,885	0.98	0.58	1.65
Urinary	18	2,902	1,222	391,885	1.75	1.10	2.78
Musculoskeletal	19	2,902	2,153	391,885	1.04	0.66	1.63
Limb defects	<11	2,902	1,650	391,885	0.75	0.37	1.49
Other	<11	2,902	454	391,885	2.47	1.23	4.97
Duloxetine versus SSRI							
Any Congenital Malformation	109	2,211	1,676	39,548	1.05	0.87	1.26
Central Nervous System	<11	2,211	84	39,548	0.95	0.39	2.34
Eye Anomalies	0	2,211	17	39,548			
Ear Anomalies	<11	2,211	12	39,548	2.21	0.28	17.66
Cardiovascular Anomalies	52	2,211	621	39,548	1.28	0.97	1.70
Other vascular	0	2,211	12	39,548			
Respiratory malformations	<11	2,211	136	39,548	0.55	0.20	1.48
Oral cleft	<11	2,211	57	39,548	0.72	0.23	2.28
Gastrointestinal	12	2,211	227	39,548	0.84	0.47	1.49
Genital	<11	2,211	173	39,548	0.93	0.49	1.75
Urinary	<11	2,211	129	39,548	1.30	0.69	2.47
Musculoskeletal	12	2,211	248	39,548	0.82	0.46	1.46
Limb defects	<11	2,211	127	39,548	0.97	0.45	2.08
Other	<11	2,211	47	39,548	2.71	1.06	6.92
Duloxetine versus Venlafaxine							
Any Congenital Malformation	146	2,805	230	5,125	1.05	0.86	1.28
Central Nervous System	<11	2,805	12	5,125	0.87	0.30	2.54
Eye Anomalies	<11	2,805	<11	5,125	0.35	0.04	3.00
Ear Anomalies	<11	2,805	<11	5,125	10.11	0.07	1513.52
Cardiovascular Anomalies	65	2,805	83	5,125	1.11	0.82	1.51
Other vascular	0	2,805	<11	5,125			

	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Respiratory malformations	<11	2,805	23	5,125	0.43	0.19	0.98
Oral cleft	<11	2,805	<11	5,125	0.63	0.17	2.32
Gastrointestinal	17	2,805	31	5,125	0.97	0.54	1.75
Genital	14	2,805	25	5,125	1.14	0.59	2.22
Urinary	18	2,805	12	5,125	1.90	0.98	3.66
Musculoskeletal	19	2,805	41	5,125	0.84	0.49	1.44
Limb defects	<11	2,805	15	5,125	1.43	0.57	3.60
Other	<11	2,805	<11	5,125	2.78	0.92	8.33
Duloxetine versus Duloxetine Discontinuers							
Any Congenital Malformation	131	2,548	72	1,647	1.13	0.86	1.50
Central Nervous System	<11	2,548	<11	1,647	1.13	0.22	5.72
Eye Anomalies	<11	2,548	<11	1,647	0.24	0.02	2.32
Ear Anomalies	<11	2,548	0	1,647			
Cardiovascular Anomalies	61	2,548	24	1,647	1.59	1.00	2.53
Other vascular	0	2,548	<11	1,647			
Respiratory malformations	<11	2,548	<11	1,647	0.57	0.21	1.58
Oral cleft	<11	2,548	<11	1,647	1.16	0.18	7.68
Gastrointestinal	13	2,548	12	1,647	0.79	0.35	1.76
Genital	14	2,548	<11	1,647	1.00	0.44	2.31
Urinary	15	2,548	<11	1,647	1.31	0.54	3.14
Musculoskeletal	13	2,548	14	1,647	0.64	0.30	1.37
Limb defects	<11	2,548	<11	1,647	1.11	0.30	4.14
Other	<11	2,548	<11	1,647	5.35	0.56	51.09

[illegible]

Outcome	Exposed		Reference		RR	95% CI lower	95% CI upper
	Events	N	Events	N			
Any Congenital Malformation	19	304	788	18,029	1.40	0.90	2.17
Central Nervous System	<11	304	38	18,029	2.14	0.29	15.70
Eye Anomalies	0	304	<11	18,029			
Ear Anomalies	<11	304	<11	18,029	8.65	1.06	70.29
Cardiovascular Anomalies	<11	304	302	18,029	1.60	0.83	3.07
Other vascular	0	304	<11	18,029			
Respiratory malformations	0	304	64	18,029			
Oral cleft	0	304	24	18,029			
Gastrointestinal	<11	304	97	18,029	1.44	0.36	5.84
Genital	<11	304	87	18,029	0.65	0.09	4.62
Urinary	<11	304	62	18,029	4.23	1.54	11.59
Musculoskeletal	<11	304	87	18,029	1.13	0.28	4.55
Limb defects	<11	304	84	18,029	0.82	0.11	5.88
Other	<11	304	18	18,029	10.90	3.20	37.14
Duloxetine versus SSRI							
Any Congenital Malformation	13	229	104	1,841	0.94	0.54	1.65
Central Nervous System	<11	229	<11	1,841	0.82	0.11	6.39
Eye Anomalies	0	229	0	1,841			
Ear Anomalies	<11	229	0	1,841			
Cardiovascular Anomalies	<11	229	39	1,841	0.97	0.39	2.43
Other vascular	0	229	0	1,841			
Respiratory malformations	0	229	<11	1,841			
Oral cleft	0	229	<11	1,841			
Gastrointestinal	<11	229	15	1,841	0.89	0.21	3.81
Genital	<11	229	<11	1,841	1.08	0.13	8.65
Urinary	<11	229	<11	1,841	3.05	0.60	15.45
Musculoskeletal	<11	229	14	1,841	0.50	0.07	3.75
Limb defects	<11	229	<11	1,841	1.66	0.19	14.26
Other	<11	229	<11	1,841	18.20	0.53	626.20
Duloxetine versus Venlafaxine							
Any Congenital Malformation	19	293	15	274	0.95	0.51	1.76
Central Nervous System	<11	293	0	274			
Eye Anomalies	0	293	0	274			

	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Ear Anomalies	<11	293	0	274			
Cardiovascular Anomalies	<11	293	<11	274	0.79	0.33	1.88
Other vascular	0	293	0	274			
Respiratory malformations	0	293	<11	274			
Oral cleft	0	293	0	274			
Gastrointestinal	<11	293	<11	274	1.36	0.16	11.81
Genital	<11	293	<11	274	0.47	0.04	5.16
Urinary	<11	293	<11	274	5.21	0.42	63.84
Musculoskeletal	<11	293	<11	274	1.39	0.16	12.30
Limb defects	<11	293	0	274			
Other	<11	293	<11	274	1.41	0.24	8.40
Duloxetine versus Duloxetine Discontinuers							
Any Congenital Malformation	19	304	13	221	1.03	0.52	2.03
Central Nervous System	<11	304	0	221			
Eye Anomalies	0	304	0	221			
Ear Anomalies	<11	304	0	221			
Cardiovascular Anomalies	<11	304	<11	221	1.25	0.43	3.62
Other vascular	0	304	0	221			
Respiratory malformations	0	304	0	221			
Oral cleft	0	304	0	221			
Gastrointestinal	<11	304	<11	221	0.53	0.09	3.26
Genital	<11	304	<11	221	0.92	0.05	17.37
Urinary	<11	304	<11	221	2.99	0.33	27.24
Musculoskeletal	<11	304	<11	221	0.60	0.09	3.88
Limb defects	<11	304	<11	221	0.58	0.04	8.06
Other	<11	304	0	221			
Adjusted: Restricted + PS2 (All covariates)	Exposed		Reference				
Duloxetine versus Unexposed							
Any Congenital Malformation	18	302	635	14,016	1.06	0.68	1.67
Central Nervous System	<11	302	31	14,016	1.55	0.21	11.34
Eye Anomalies	0	302	<11	14,016			
Ear Anomalies	<11	302	<11	14,016	2.28	0.31	16.89

Outcome	Exposed		Reference		RR	95% CI lower	95% CI upper
	Events	N	Events	N			
Cardiovascular Anomalies	<11	302	239	14,016	1.14	0.60	2.19
Other vascular	0	302	<11	14,016			
Respiratory malformations	0	302	56	14,016			
Oral cleft	0	302	23	14,016			
Gastrointestinal	<11	302	76	14,016	0.76	0.11	5.43
Genital	<11	302	74	14,016	0.58	0.08	4.17
Urinary	<11	302	57	14,016	2.34	0.86	6.35
Musculoskeletal	<11	302	78	14,016	1.09	0.27	4.39
Limb defects	<11	302	56	14,016	0.47	0.07	3.34
Other	<11	302	15	14,016	8.59	2.52	29.27
Duloxetine versus SSRI							
Any Congenital Malformation	13	222	88	1,517	0.98	0.56	1.72
Central Nervous System	<11	222	<11	1,517	1.52	0.18	13.22
Eye Anomalies	0	222	0	1,517			
Ear Anomalies	<11	222	0	1,517			
Cardiovascular Anomalies	<11	222	31	1,517	0.72	0.29	1.78
Other vascular	0	222	0	1,517			
Respiratory malformations	0	222	<11	1,517			
Oral cleft	0	222	<11	1,517			
Gastrointestinal	<11	222	15	1,517	1.13	0.26	5.03
Genital	<11	222	<11	1,517	0.90	0.11	7.25
Urinary	<11	222	<11	1,517	12.50	1.22	128.10
Musculoskeletal	<11	222	11	1,517	1.19	0.14	9.93
Limb defects	<11	222	<11	1,517	0.73	0.09	5.67
Other	<11	222	<11	1,517	34.75	0.28	4363.67
Duloxetine versus Venlafaxine							
Any Congenital Malformation	13	209	15	220	0.58	0.30	1.12
Central Nervous System	0	209	0	220			
Eye Anomalies	0	209	0	220			
Ear Anomalies	0	209	0	220			
Cardiovascular Anomalies	<11	209	<11	220	0.41	0.17	0.95
Other vascular	0	209	0	220			
Respiratory malformations	0	209	<11	220			

Outcome	Exposed		Reference				
	Events	N	Events	N	RR	95% CI lower	95% CI upper
Oral cleft	0	209	0	220			
Gastrointestinal	<11	209	<11	220	0.73	0.12	4.43
Genital	0	209	0	220			
Urinary	<11	209	<11	220	1.60	0.34	7.49
Musculoskeletal	<11	209	<11	220	0.80	0.13	4.98
Limb defects	0	209	0	220			
Other	<11	209	<11	220	7.20	0.30	170.18
Duloxetine versus Duloxetine Discontinuers							
Any Congenital Malformation	12	219	10	197	1.01	0.45	2.24
Central Nervous System	<11	219	0	197			
Eye Anomalies	0	219	0	197			
Ear Anomalies	0	219	0	197			
Cardiovascular Anomalies	<11	219	<11	197	1.83	0.46	7.30
Other vascular	0	219	0	197			
Respiratory malformations	0	219	0	197			
Oral cleft	0	219	0	197			
Gastrointestinal	<11	219	<11	197	0.50	0.04	5.79
Genital	0	219	<11	197			
Urinary	<11	219	<11	197	11.20	0.31	405.40
Musculoskeletal	<11	219	<11	197	0.20	0.02	1.73
Limb defects	<11	219	<11	197	1.00	0.06	17.14
Other	<11	219	0	197			

15.1. 21. Malformations- Sensitivity Analyses #4: Correct relative risks for outcome misclassification

Outcome- Any Congenital Malformation

Target PPV= 78 (CI: 66-86)

Distribution for bias parameters: Sensitivity: Min=0.5, Mode 1=0.75, Mode 2=0.75, Max=1.0; Specificity: Min=0.995, Mode 1=0.997, Mode 2=0.997, Max=0.999

Exposure	Reference	1:1 PS matched analysis			Total Error Analysis					
		Odds ratio	95% CI lower	95% CI upper	Odds ratio	95% CI lower	95% CI upper	Width CI	% change in CI width over traditional	% change in OR
Duloxetine	Unexposed	1.28	0.96	1.69	1.30	0.97	1.72	1.77	3%	1.98%
Duloxetine	SSRI	1.11	0.81	1.51	1.11	0.81	1.50	1.85	1%	0.66%
Duloxetine	Venlafaxine	1.09	0.82	1.44	1.10	0.82	1.44	1.77	1%	0.78%
Duloxetine	Duloxetine Discontinuers	1.11	0.81	1.51	1.12	0.82	1.54	1.86	1%	1.27%

Outcome- Cardiovascular Anomalies

Target PPV= 78 (CI: 66-86)

Distribution for bias parameters: Sensitivity: Min=0.5, Mode 1=0.75, Mode 2=0.75, Max=1.0; Specificity: Min=0.995, Mode 1=0.997, Mode 2=0.997, Max=0.999

Exposure	Reference	1:1 PS matched analysis			Total Error Analysis					
		Odds ratio	95% CI lower	95% CI upper	Odds ratio	95% CI lower	95% CI upper	Width CI	% change in CI width over traditional	% change in OR
Duloxetine	Unexposed	1.30	0.86	1.96	1.36	0.90	2.19	2.44	9%	4.71%
Duloxetine	SSRI	1.39	0.86	2.25	1.46	0.89	2.54	2.87	10%	4.91%
Duloxetine	Venlafaxine	1.20	0.79	1.84	1.26	0.78	2.09	2.68	14%	4.22%
Duloxetine	Duloxetine Discontinuers	1.55	0.94	2.55	1.69	0.99	3.14	3.18	20%	8.93%

15.1. 22. Malformations- Sensitivity Analyses #5: Redefine outcome based on claims profile review

	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Definition #1: if outcome likely occurred							
Any Congenital Malformation	102	2,058	103	2,058	0.99	0.76	1.29
Central Nervous System	<11	2,016	20	10,080	0.75	0.22	2.52
Eye Anomalies	<11	2,016	<11	10,080	2.50	0.23	27.56
Ear Anomalies	<11	2,016	<11	10,080	5.00	0.31	79.90
Cardiovascular Anomalies	44	2,016	190	10,080	1.16	0.84	1.60
Other vascular	0	2,016	<11	10,080	.	.	.
Respiratory malformations	<11	2,016	30	10,080	0.67	0.24	1.89
Oral cleft	<11	2,016	17	10,080	0.88	0.26	3.01
Gastrointestinal	<11	2,016	59	10,080	0.85	0.43	1.65
Genital	11	2,016	48	10,080	1.15	0.60	2.20
Urinary	15	2,016	31	10,080	2.42	1.31	4.47
Musculoskeletal	<11	2,016	59	10,080	0.59	0.27	1.30
Limb defects	<11	2,016	30	10,080	0.67	0.24	1.89
Other	<11	2,016	<11	10,080	3.33	0.94	11.80
Definition #2: if outcome “likely occurred” or “probably occurred”							
Any Congenital Malformation	107	2,058	104	2,058	1.03	0.79	1.34
Central Nervous System	<11	2,016	23	10,080	0.65	0.20	2.17
Eye Anomalies	<11	2,016	<11	10,080	1.67	0.17	16.01
Ear Anomalies	<11	2,016	<11	10,080	5.00	0.31	79.90
Cardiovascular Anomalies	47	2,016	197	10,080	1.19	0.87	1.63
Other vascular	0	2,016	<11	10,080	.	.	.
Respiratory malformations	<11	2,016	31	10,080	0.81	0.31	2.07
Oral cleft	<11	2,016	17	10,080	0.88	0.26	3.01
Gastrointestinal	<11	2,016	62	10,080	0.81	0.41	1.57
Genital	11	2,016	50	10,080	1.10	0.57	2.11
Urinary	15	2,016	32	10,080	2.34	1.27	4.32
Musculoskeletal	<11	2,016	60	10,080	0.58	0.27	1.27
Limb defects	<11	2,016	32	10,080	0.63	0.22	1.77
Other	<11	2,016	<11	10,080	3.75	1.30	10.80

Outcome	Exposed		Reference		RR	95% CI lower	95% CI upper
	Events	N	Events	N			
Any Congenital Malformation	98	1,823	13,066	320,188	1.14	0.94	1.39
Central Nervous System	<11	1,823	632	320,188	0.79	0.25	2.45
Eye Anomalies	<11	1,823	142	320,188	1.07	0.15	7.65
Ear Anomalies	<11	1,823	73	320,188	2.53	0.35	18.17
Cardiovascular Anomalies	44	1,823	4,787	320,188	1.30	0.97	1.74
Other vascular	0	1,823	70	320,188			
Respiratory malformations	<11	1,823	908	320,188	0.76	0.28	2.02
Oral cleft	<11	1,823	455	320,188	0.58	0.14	2.31
Gastrointestinal	<11	1,823	1,656	320,188	0.96	0.52	1.79
Genital	<11	1,823	1,412	320,188	1.00	0.52	1.93
Urinary	13	1,823	1,009	320,188	1.87	1.09	3.23
Musculoskeletal	<11	1,823	1,788	320,188	0.66	0.33	1.32
Limb defects	<11	1,823	1,315	320,188	0.43	0.14	1.34
Other	<11	1,823	368	320,188	2.40	0.99	5.79
Duloxetine versus SSRI							
Any Congenital Malformation	75	1,398	1,384	32,774	1.11	0.89	1.39
Central Nervous System	<11	1,398	73	32,774	0.83	0.26	2.62
Eye Anomalies	0	1,398	13	32,774			
Ear Anomalies	<11	1,398	<11	32,774	3.66	0.45	30.13
Cardiovascular Anomalies	34	1,398	509	32,774	1.31	0.93	1.84
Other vascular	0	1,398	<11	32,774			
Respiratory malformations	<11	1,398	109	32,774	0.68	0.22	2.14
Oral cleft	<11	1,398	53	32,774	0.61	0.15	2.46
Gastrointestinal	<11	1,398	182	32,774	1.05	0.54	2.03
Genital	<11	1,398	143	32,774	1.12	0.55	2.26
Urinary	<11	1,398	113	32,774	1.21	0.53	2.74
Musculoskeletal	<11	1,398	202	32,774	0.65	0.29	1.46
Limb defects	<11	1,398	106	32,774	0.64	0.20	2.01
Other	<11	1,398	37	32,774	2.86	0.86	9.47
Duloxetine versus Venlafaxine							
Any Congenital Malformation	97	1,772	196	4,388	1.14	0.90	1.44
Central Nervous System	<11	1,772	12	4,388	0.89	0.24	3.31
Eye Anomalies	<11	1,772	<11	4,388	1.41	0.12	16.44

	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Ear Anomalies	<11	1,772	<11	4,388	15.06	0.08	2770.68
Cardiovascular Anomalies	43	1,772	70	4,388	1.32	0.92	1.91
Other vascular	0	1,772	<11	4,388			
Respiratory malformations	<11	1,772	18	4,388	0.39	0.14	1.11
Oral cleft	<11	1,772	<11	4,388	0.54	0.12	2.48
Gastrointestinal	<11	1,772	27	4,388	0.81	0.40	1.64
Genital	<11	1,772	23	4,388	1.11	0.51	2.44
Urinary	13	1,772	<11	4,388	2.23	1.05	4.70
Musculoskeletal	<11	1,772	34	4,388	0.54	0.25	1.15
Limb defects	<11	1,772	14	4,388	0.72	0.20	2.60
Other	<11	1,772	<11	4,388	3.28	0.86	12.48
Duloxetine versus Duloxetine Discontinuers							
Any Congenital Malformation	98	1,810	70	1,604	1.28	0.94	1.72
Central Nervous System	<11	1,810	<11	1,604	2.10	0.26	16.81
Eye Anomalies	<11	1,810	0	1,604			
Ear Anomalies	<11	1,810	0	1,604			
Cardiovascular Anomalies	44	1,810	22	1,604	1.84	1.10	3.08
Other vascular	0	1,810	0	1,604			
Respiratory malformations	<11	1,810	<11	1,604	0.87	0.22	3.47
Oral cleft	<11	1,810	<11	1,604	1.22	0.14	10.32
Gastrointestinal	<11	1,810	11	1,604	0.91	0.38	2.20
Genital	<11	1,810	<11	1,604	1.38	0.49	3.90
Urinary	13	1,810	<11	1,604	1.28	0.55	2.99
Musculoskeletal	<11	1,810	16	1,604	0.40	0.18	0.93
Limb defects	<11	1,810	<11	1,604	0.63	0.14	2.79
Other	<11	1,810	<11	1,604	8.47	0.49	146.12

15.1. 24. Malformations- Sensitivity Analyses #8: Redefine outcome based on infant claims only

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Outcome	Exposed		Reference		RR	95% CI lower	95% CI upper
	Events	N	Events	N			
Any Congenital Malformation	112	2,223	14,564	392,928	1.15	0.96	1.38
Central Nervous System	<11	2,223	700	392,928	0.87	0.33	2.33
Eye Anomalies	<11	2,223	161	392,928	1.03	0.14	7.38
Ear Anomalies	<11	2,223	83	392,928	2.01	0.28	14.40
Cardiovascular Anomalies	51	2,223	5,288	392,928	1.35	1.03	1.77
Other vascular	0	2,223	73	392,928			
Respiratory malformations	<11	2,223	1,073	392,928	0.74	0.31	1.78
Oral cleft	<11	2,223	503	392,928	0.76	0.25	2.37
Gastrointestinal	11	2,223	1,903	392,928	0.89	0.49	1.60
Genital	11	2,223	1,499	392,928	1.08	0.60	1.96
Urinary	14	2,223	1,094	392,928	1.94	1.15	3.28
Musculoskeletal	<11	2,223	2,018	392,928	0.74	0.40	1.37
Limb defects	<11	2,223	1,477	392,928	0.62	0.26	1.48
Other	<11	2,223	396	392,928	3.36	1.59	7.09
Duloxetine versus SSRI							
Any Congenital Malformation	84	1,703	1,545	39,395	1.12	0.91	1.39
Central Nervous System	<11	1,703	78	39,395	1.08	0.40	2.94
Eye Anomalies	0	1,703	17	39,395			
Ear Anomalies	<11	1,703	11	39,395	3.01	0.37	24.16
Cardiovascular Anomalies	38	1,703	566	39,395	1.31	0.95	1.81
Other vascular	0	1,703	11	39,395			
Respiratory malformations	<11	1,703	134	39,395	0.73	0.27	1.98
Oral cleft	<11	1,703	54	39,395	0.96	0.30	3.05
Gastrointestinal	<11	1,703	218	39,395	0.96	0.51	1.81
Genital	<11	1,703	155	39,395	1.11	0.55	2.26
Urinary	<11	1,703	114	39,395	1.33	0.62	2.85
Musculoskeletal	<11	1,703	230	39,395	0.56	0.25	1.25
Limb defects	<11	1,703	115	39,395	0.92	0.38	2.26
Other	<11	1,703	39	39,395	3.49	1.22	9.97
Duloxetine versus Venlafaxine							
Any Congenital Malformation	110	2,160	214	5,085	1.12	0.89	1.39
Central Nervous System	<11	2,160	11	5,085	1.09	0.33	3.56
Eye Anomalies	<11	2,160	<11	5,085	0.66	0.07	6.06

Outcome	Exposed		Reference		RR	95% CI lower	95% CI upper
	Events	N	Events	N			
Ear Anomalies	<11	2,160	<11	5,085	13.02	0.09	1950.26
Cardiovascular Anomalies	49	2,160	74	5,085	1.23	0.88	1.73
Other vascular	0	2,160	<11	5,085			
Respiratory malformations	<11	2,160	22	5,085	0.43	0.17	1.12
Oral cleft	<11	2,160	<11	5,085	0.73	0.20	2.65
Gastrointestinal	11	2,160	31	5,085	0.90	0.45	1.79
Genital	11	2,160	23	5,085	1.37	0.65	2.88
Urinary	14	2,160	11	5,085	2.26	1.09	4.69
Musculoskeletal	<11	2,160	37	5,085	0.57	0.29	1.14
Limb defects	<11	2,160	14	5,085	1.32	0.44	3.93
Other	<11	2,160	<11	5,085	3.45	1.08	11.04
Duloxetine versus Duloxetine Discontinuers							
Any Congenital Malformation	112	2,215	85	1,978	1.09	0.83	1.43
Central Nervous System	<11	2,215	<11	1,978	0.67	0.18	2.42
Eye Anomalies	<11	2,215	<11	1,978	1.00	0.06	17.34
Ear Anomalies	<11	2,215	0	1,978			
Cardiovascular Anomalies	51	2,215	28	1,978	1.46	0.94	2.27
Other vascular	0	2,215	<11	1,978			
Respiratory malformations	<11	2,215	<11	1,978	0.74	0.23	2.42
Oral cleft	<11	2,215	<11	1,978	1.30	0.22	7.64
Gastrointestinal	11	2,215	16	1,978	0.67	0.31	1.45
Genital	11	2,215	<11	1,978	1.19	0.48	2.94
Urinary	14	2,215	<11	1,978	1.03	0.48	2.23
Musculoskeletal	<11	2,215	18	1,978	0.47	0.22	1.00
Limb defects	<11	2,215	<11	1,978	0.48	0.16	1.42
Other	<11	2,215	<11	1,978	1.33	0.41	4.28

15.1. 25. Malformations- Sensitivity Analyses #9: Restrict outcome to inpatient diagnoses only

[illegible]

Outcome	Exposed		Reference		RR	95% CI lower	95% CI upper
	Events	N	Events	N			
Any Congenital Malformation	76	2,223	9,047	392,928	1.23	0.99	1.54
Central Nervous System	<11	2,223	575	392,928	0.79	0.25	2.45
Eye Anomalies	<11	2,223	55	392,928	1.98	0.28	14.19
Ear Anomalies	0	2,223	43	392,928			
Cardiovascular Anomalies	40	2,223	3,772	392,928	1.45	1.07	1.98
Other vascular	0	2,223	70	392,928			
Respiratory malformations	<11	2,223	563	392,928	1.15	0.43	3.08
Oral cleft	<11	2,223	311	392,928	0.83	0.21	3.31
Gastrointestinal	<11	2,223	1,541	392,928	0.81	0.40	1.61
Genital	<11	2,223	757	392,928	1.05	0.47	2.34
Urinary	<11	2,223	694	392,928	1.71	0.85	3.42
Musculoskeletal	<11	2,223	969	392,928	0.64	0.24	1.71
Limb defects	<11	2,223	661	392,928	0.63	0.16	2.50
Other	<11	2,223	302	392,928	3.63	1.62	8.14
Duloxetine versus SSRI							
Any Congenital Malformation	58	1,703	937	39,395	1.27	0.98	1.65
Central Nervous System	<11	1,703	61	39,395	0.88	0.28	2.78
Eye Anomalies	0	1,703	<11	39,395			
Ear Anomalies	0	1,703	<11	39,395			
Cardiovascular Anomalies	31	1,703	385	39,395	1.56	1.09	2.24
Other vascular	0	1,703	<11	39,395			
Respiratory malformations	<11	1,703	81	39,395	0.95	0.30	3.01
Oral cleft	<11	1,703	34	39,395	0.87	0.21	3.57
Gastrointestinal	<11	1,703	172	39,395	0.89	0.42	1.89
Genital	<11	1,703	78	39,395	1.14	0.42	3.10
Urinary	<11	1,703	77	39,395	1.13	0.41	3.07
Musculoskeletal	<11	1,703	100	39,395	0.47	0.12	1.92
Limb defects	<11	1,703	50	39,395	0.84	0.21	3.44
Other	<11	1,703	26	39,395	4.97	1.69	14.61
Duloxetine versus Venlafaxine							
Any Congenital Malformation	74	2,160	131	5,085	1.20	0.91	1.58
Central Nervous System	<11	2,160	<11	5,085	0.99	0.26	3.82
Eye Anomalies	<11	2,160	<11	5,085	0.87	0.09	8.67

Outcome	Exposed		Reference		RR	95% CI lower	95% CI upper
	Events	N	Events	N			
Ear Anomalies	<11	2,160	<11	5,085			
Cardiovascular Anomalies	38	2,160	53	5,085	1.43	0.96	2.14
Other vascular	0	2,160	<11	5,085			
Respiratory malformations	<11	2,160	<11	5,085	0.76	0.25	2.35
Oral cleft	<11	2,160	<11	5,085	0.71	0.15	3.46
Gastrointestinal	<11	2,160	27	5,085	0.72	0.33	1.59
Genital	<11	2,160	12	5,085	1.40	0.51	3.85
Urinary	<11	2,160	<11	5,085	2.06	0.80	5.33
Musculoskeletal	<11	2,160	17	5,085	0.46	0.16	1.33
Limb defects	<11	2,160	<11	5,085	2.21	0.32	15.24
Other	<11	2,160	<11	5,085	3.75	1.04	13.60
Duloxetine versus Duloxetine Discontinuers							
Any Congenital Malformation	76	2,215	46	1,978	1.50	1.04	2.16
Central Nervous System	<11	2,215	<11	1,978	0.50	0.12	2.05
Eye Anomalies	<11	2,215	<11	1,978	1.00	0.06	17.34
Ear Anomalies	0	2,215	0	1,978			
Cardiovascular Anomalies	40	2,215	18	1,978	1.73	1.02	2.93
Other vascular	0	2,215	<11	1,978			
Respiratory malformations	<11	2,215	<11	1,978	1.10	0.26	4.78
Oral cleft	<11	2,215	<11	1,978	2.11	0.17	26.85
Gastrointestinal	<11	2,215	12	1,978	0.74	0.29	1.90
Genital	<11	2,215	<11	1,978	2.97	0.56	15.68
Urinary	<11	2,215	<11	1,978	2.22	0.61	8.11
Musculoskeletal	<11	2,215	<11	1,978	0.36	0.11	1.16
Limb defects	<11	2,215	<11	1,978	0.50	0.09	2.82
Other	<11	2,215	<11	1,978	1.50	0.41	5.55

Outcome	Exposed		Reference		RR	95% CI lower	95% CI upper
	Events	N	Events	N			
Any Congenital Malformation	150	1,965	364	5,238	1.10	0.91	1.32
Central Nervous System	<11	1,965	23	5,238	0.81	0.35	1.89
Eye Anomalies	<11	1,965	<11	5,238	0.59	0.13	2.74
Ear Anomalies	<11	1,965	<11	5,238	2.67	0.38	18.91
Cardiovascular Anomalies	53	1,965	118	5,238	1.20	0.87	1.65
Other vascular	0	1,965	<11	5,238			
Respiratory malformations	<11	1,965	34	5,238	0.78	0.39	1.58
Oral cleft	<11	1,965	<11	5,238	1.07	0.33	3.40
Gastrointestinal	14	1,965	30	5,238	1.24	0.66	2.34
Genital	23	1,965	41	5,238	1.50	0.90	2.49
Urinary	14	1,965	19	5,238	1.96	0.99	3.91
Musculoskeletal	33	1,965	109	5,238	0.81	0.55	1.19
Limb defects	<11	1,965	21	5,238	1.02	0.45	2.29
Other	<11	1,965	<11	5,238	2.96	1.21	7.28
Duloxetine versus Duloxetine Discontinuers							
Any Congenital Malformation	153	2,018	134	1,921	1.09	0.87	1.36
Central Nervous System	<11	2,018	12	1,921	0.56	0.22	1.41
Eye Anomalies	<11	2,018	<11	1,921	0.63	0.11	3.79
Ear Anomalies	<11	2,018	0	1,921			
Cardiovascular Anomalies	54	2,018	41	1,921	1.25	0.84	1.87
Other vascular	0	2,018	0	1,921			
Respiratory malformations	11	2,018	<11	1,921	1.31	0.53	3.25
Oral cleft	<11	2,018	<11	1,921	1.90	0.35	10.38
Gastrointestinal	14	2,018	15	1,921	0.89	0.43	1.84
Genital	23	2,018	17	1,921	1.29	0.69	2.40
Urinary	14	2,018	13	1,921	1.03	0.48	2.18
Musculoskeletal	34	2,018	38	1,921	0.85	0.54	1.35
Limb defects	<11	2,018	<11	1,921	1.09	0.40	2.99
Other	<11	2,018	<11	1,921	3.17	0.87	11.51
Adjusted: Restricted + PS2 (All covariates)							
Duloxetine versus Unexposed							
Any Congenital Malformation	134	1,759	20,565	325,903	1.02	0.87	1.20
Central Nervous System	<11	1,759	1,150	325,903	0.98	0.47	2.05

Outcome	Exposed		Reference		RR	95% CI lower	95% CI upper
	Events	N	Events	N			
Eye Anomalies	<11	1,759	301	325,903	0.49	0.07	3.45
Ear Anomalies	<11	1,759	106	325,903	1.99	0.28	14.28
Cardiovascular Anomalies	49	1,759	6,286	325,903	1.19	0.90	1.57
Other vascular	0	1,759	116	325,903			
Respiratory malformations	11	1,759	1,752	325,903	1.02	0.57	1.85
Oral cleft	<11	1,759	509	325,903	0.83	0.27	2.59
Gastrointestinal	13	1,759	1,801	325,903	1.09	0.63	1.87
Genital	19	1,759	2,626	325,903	1.15	0.73	1.80
Urinary	14	1,759	1,352	325,903	1.73	1.02	2.92
Musculoskeletal	29	1,759	4,857	325,903	0.86	0.60	1.24
Limb defects	<11	1,759	1,877	325,903	0.69	0.33	1.45
Other	<11	1,759	565	325,903	2.37	1.18	4.76
Duloxetine versus SSRI							
Any Congenital Malformation	98	1,340	2,162	32,403	0.98	0.81	1.19
Central Nervous System	<11	1,340	114	32,403	0.91	0.37	2.23
Eye Anomalies	0	1,340	31	32,403			
Ear Anomalies	<11	1,340	17	32,403	2.00	0.26	15.32
Cardiovascular Anomalies	40	1,340	637	32,403	1.23	0.90	1.69
Other vascular	0	1,340	14	32,403			
Respiratory malformations	<11	1,340	201	32,403	0.82	0.39	1.74
Oral cleft	<11	1,340	56	32,403	0.88	0.28	2.79
Gastrointestinal	11	1,340	201	32,403	1.12	0.61	2.04
Genital	14	1,340	241	32,403	1.15	0.68	1.96
Urinary	<11	1,340	140	32,403	0.80	0.33	1.95
Musculoskeletal	16	1,340	608	32,403	0.64	0.39	1.05
Limb defects	<11	1,340	158	32,403	1.14	0.54	2.43
Other	<11	1,340	52	32,403	1.88	0.68	5.20
Duloxetine versus Venlafaxine							
Any Congenital Malformation	130	1,708	298	4,194	0.97	0.80	1.18
Central Nervous System	<11	1,708	18	4,194	1.31	0.53	3.28
Eye Anomalies	<11	1,708	<11	4,194	0.18	0.02	1.33
Ear Anomalies	<11	1,708	<11	4,194	2.76	0.16	48.12
Cardiovascular Anomalies	47	1,708	98	4,194	1.00	0.72	1.40

Outcome	Exposed		Reference		RR	95% CI lower	95% CI upper
	Events	N	Events	N			
Other vascular	0	1,708	<11	4,194			
Respiratory malformations	<11	1,708	30	4,194	0.60	0.30	1.20
Oral cleft	<11	1,708	<11	4,194	0.65	0.18	2.34
Gastrointestinal	13	1,708	26	4,194	1.31	0.67	2.56
Genital	19	1,708	31	4,194	1.51	0.85	2.66
Urinary	14	1,708	11	4,194	2.76	1.29	5.92
Musculoskeletal	28	1,708	92	4,194	0.76	0.50	1.16
Limb defects	<11	1,708	17	4,194	1.27	0.51	3.16
Other	<11	1,708	<11	4,194	2.93	1.05	8.15
Duloxetine versus Duloxetine Discontinuers							
Any Congenital Malformation	134	1,752	105	1,542	1.10	0.86	1.41
Central Nervous System	<11	1,752	<11	1,542	0.46	0.19	1.15
Eye Anomalies	<11	1,752	<11	1,542	0.45	0.04	4.95
Ear Anomalies	<11	1,752	0	1,542			
Cardiovascular Anomalies	49	1,752	28	1,542	1.43	0.91	2.24
Other vascular	0	1,752	<11	1,542			
Respiratory malformations	11	1,752	<11	1,542	1.01	0.42	2.38
Oral cleft	<11	1,752	<11	1,542	1.67	0.24	11.46
Gastrointestinal	13	1,752	14	1,542	0.76	0.36	1.58
Genital	19	1,752	12	1,542	2.06	0.91	4.66
Urinary	14	1,752	11	1,542	0.95	0.45	2.01
Musculoskeletal	29	1,752	31	1,542	0.87	0.52	1.44
Limb defects	<11	1,752	<11	1,542	1.25	0.40	3.97
Other	<11	1,752	<11	1,542	2.79	0.68	11.48

15.2. 1. Preterm/SGA- Baseline characteristics of duloxetine exposed vs. unexposed women- early exposure: unadjusted

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Total	2,903	100.00	1,364,247	100.00	
Demographics					
Age, mean (SD)	27.75	5.50	25.0	5.4	0.51
Age categorical, N (%)					
<=19	146	5.03	210,287	15.41	-0.35
20-24	736	25.35	527,221	38.65	-0.29
25-29	989	34.07	361,462	26.50	0.17
30-34	658	22.67	175,472	12.86	0.26
35-39	294	10.13	73,279	5.37	0.18
>=40	80	2.76	16,526	1.21	0.11
Race, N (%)					
White	2,287	78.78	550,487	40.35	0.85
Black or African American	258	8.89	423,318	31.03	-0.58
Hispanic or Latino	87	3.00	196,311	14.39	-0.41
Asian or Other Pacific Islander	40	1.38	59,467	4.36	-0.18
American Indian	39	1.34	22,416	1.64	-0.02
Other	127	4.37	78,854	5.78	-0.06
Unknown	65	2.24	33,394	2.45	-0.01
Chronic comorbid conditions, N (%)					
Hypertension	261	8.99	45,119	3.31	0.24
Diabetes	208	7.17	43,444	3.18	0.18
Renal Disease	33	1.14	6,786	0.50	0.07
Obesity Overweight	225	7.75	47,588	3.49	0.19
Comorbidity Index Q1	999	34.41	723,961	53.07	-0.38
Comorbidity Index Q2	723	24.91	334,859	24.55	0.01
Comorbidity Index Q3	493	16.98	160,033	11.73	0.15
Comorbidity Index Q4	688	23.70	145,394	10.66	0.35
Infections, N (%)					
Toxoplasmosis	0	0.00	244	0.02	-0.02
Rubella	0	0.00	182	0.01	-0.02
Cytomegalovirus	0	0.00	72	0.01	-0.01

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Herpes	57	1.96	13,627	1.00	0.08
Syphilis	<11	0.03	1,589	0.12	-0.03
Varicella	<11	0.03	321	0.02	0.01
Parvovirus B19	0	0.00	67	0.00	-0.01
Zika virus other mosquito	0	0.00	0	0.00	0.00
Lymphocytic choriomeningitis	<11	0.03	12	0.00	0.03
Influenza	28	0.96	11,488	0.84	0.01
Chlamydia	15	0.52	11,819	0.87	-0.04
Human papilloma virus	31	1.07	8,753	0.64	0.05
Gonorrhea	17	0.59	13,216	0.97	-0.04
HIV	<11	0.34	5,184	0.38	-0.01
Trichomoniasis	28	0.96	22,259	1.63	-0.06
Indications for duloxetine, N (%)					
Depression	1,484	51.12	93,278	6.84	1.12
Anxiety	921	31.73	62,081	4.55	0.75
Neuropathic Pain	340	11.71	25,466	1.87	0.40
Fibromyalgia	331	11.40	14,627	1.07	0.44
Non neuropathic Pain	1,550	53.39	244,767	17.94	0.80
Other psychiatric conditions, N (%)					
Sleep disorder	181	6.23	12,414	0.91	0.29
Bipolar disorder	415	14.30	21,564	1.58	0.48
Psychosis	31	1.07	3,291	0.24	0.10
Schizophrenia	31	1.07	2,717	0.20	0.11
Personality disorder	64	2.20	3,280	0.24	0.18
Adjustment disorder	36	1.24	5,954	0.44	0.09
Tobacco use, N (%)	379	13.06	67,524	4.95	0.29
Alcohol abuse or dependence, N (%)	43	1.48	5,672	0.42	0.11
Drug abuse or dependence, N (%)	107	3.69	14,495	1.06	0.17
Other medication exposures, N (%)					
Benzodiazepines	1,130	38.93	52,390	3.84	0.95
Other hypnotics	761	26.21	62,355	4.57	0.63
Barbiturates	195	6.72	23,022	1.69	0.25

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Anxiolytics	169	5.82	7,282	0.53	0.30
Anticonvulsants	754	25.97	33,251	2.44	0.72
Antipsychotics	601	20.70	21,718	1.59	0.64
SSRIs	914	31.48	104,160	7.63	0.63
SNRIs	124	4.27	11,881	0.87	0.22
Other Antidep	833	28.69	47,100	3.45	0.73
Stimulants	232	7.99	12,076	0.89	0.35
Antidiabetic	117	4.03	16,019	1.17	0.18
Insulin	103	3.55	16,679	1.22	0.15
Antihyperten	457	15.74	49,435	3.62	0.42
Opioid analgesics	1,898	65.38	372,339	27.29	0.83
Triptans	212	7.30	17,545	1.29	0.30
NSAIDs	1,107	38.13	243,893	17.88	0.46
Obstetric conditions, N (%)					
Multifetal gestation Flag	97	3.34	50,468	3.70	-0.02
Markers of healthcare utilization					
Number of distinct 3 digit ICD 9 codes=0	143	4.93	406,380	29.79	-0.69
Number of distinct 3 digit ICD 9 codes: tertile 1 for number >0	555	19.12	404,414	29.64	-0.25
Number of distinct 3 digit ICD 9 codes: tertile 2 for number >0	625	21.53	246,531	18.07	0.09
Number of distinct 3 digit ICD 9 codes: tertile 3 for number >0	1,580	54.43	306,922	22.50	0.69
Number of ED visits=0	1,803	62.11	1,063,726	77.97	-0.35
Number of ED visits=1	617	21.25	199,938	14.66	0.17
Number of ED visits=2	253	8.72	63,564	4.66	0.16
Number of ED visits>2	230	7.92	37,019	2.71	0.23
Number of non-duloxetine generics dispensed=0	202	6.96	600,687	44.03	-0.94
Number of non-duloxetine generics dispensed: tertile 1 for number >0	214	7.37	209,458	15.35	-0.25
Number of non-duloxetine generics dispensed: tertile 2 for number >0	616	21.22	296,355	21.72	-0.01
Number of non-duloxetine generics dispensed: tertile 3 for number >0	1,871	64.45	257,747	18.89	1.04
Number of hospital admissions=0	2,785	95.94	1,315,440	96.42	-0.03

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Number of hospital admissions=1	103	3.55	43,789	3.21	0.02
Number of hospital admissions=2	13	0.45	4,508	0.33	0.02
Number of hospital admissions>2	<11	0.07	510	0.04	0.01
Number of outpatient visits=0	268	9.23	505,899	37.08	-0.70
Number of outpatient visits: tertile 1 for number >0	318	10.95	273,744	20.07	-0.25
Number of outpatient visits: tertile 2 for number >0	715	24.63	311,504	22.83	0.04
Number of outpatient visits: tertile 3 for number >0	1,602	55.18	273,100	20.02	0.78
Number of psychiatric hospitalizations Q1	2,815	96.97	1,356,297	99.42	-0.18
Number of psychiatric hospitalizations Q2	77	2.65	7,205	0.53	0.17
Number of psychiatric hospitalizations Q3	<11	0.31	632	0.05	0.06
Number of psychiatric hospitalizations Q4	<11	0.07	113	0.01	0.03
Number of psychiatrist visits=0	1,265	43.58	1,230,011	90.16	-1.14
Number of psychiatrist visits=1	603	20.77	68,278	5.00	0.48
Number of psychiatrist visits=2	309	10.64	23,349	1.71	0.38
Number of psychiatrist visits>2	726	25.01	42,609	3.12	0.66
Geographic region					
Arkansas	PPD		1,044	0.08	0.01
Alabama	PPD		5,693	0.42	-0.01
California	205	7.06	272,169	19.95	-0.38
Colorado	PPD		5,196	0.38	-0.04
District of Columbia	PPD		637	0.05	0.02
Delaware	76	2.62	12,132	0.89	0.13
Florida	24	0.83	30,026	2.20	-0.11
Georgia	15	0.52	30,237	2.22	-0.15
Hawaii	PPD		8,989	0.66	-0.09
Iowa	29	1.00	8,208	0.60	0.04
Idaho	PPD		1,374	0.10	0.02
Illinois	314	10.82	131,835	9.66	0.04
Indiana	266	9.16	47,036	3.45	0.24
Kansas	44	1.52	10,651	0.78	0.07
Kentucky	48	1.65	25,822	1.89	-0.02
Louisiana	109	3.75	30,490	2.23	0.09

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Massachusetts	PPD		7,814	0.57	-0.05
Maryland	38	1.31	26,038	1.91	-0.05
Maine	PPD		3,678	0.27	0.01
Minnesota	166	5.72	49,451	3.62	0.10
Missouri	152	5.24	37,852	2.77	0.13
Mississippi	14	0.48	21,337	1.56	-0.11
North Carolina	66	2.27	17,106	1.25	0.08
North Dakota	26	0.90	3,598	0.26	0.08
Nebraska	31	1.07	5,558	0.41	0.08
New Hampshire	PPD		3,388	0.25	0.01
New Jersey	0	0.00	14,268	1.05	-0.15
New Mexico	25	0.86	19,872	1.46	-0.06
Nevada	PPD		1,302	0.10	-0.01
New York	510	17.57	227,228	16.66	0.02
Ohio	51	1.76	21,670	1.59	0.01
Oklahoma	33	1.14	17,820	1.31	-0.02
Oregon	57	1.96	11,626	0.85	0.09
Pennsylvania	19	0.65	19,752	1.45	-0.08
Rhode Island	PPD		2,495	0.18	0.00
South Carolina			1,786	0.13	0.01
South Dakota	18	0.62	5,744	0.42	0.03
Tennessee	172	5.92	106,643	7.82	-0.07
Texas	PPD		4,670	0.34	-0.02
Utah	71	2.45	7,568	0.55	0.16
Virginia	75	2.58	28,760	2.11	0.03
Vermont	30	1.03	7,861	0.58	0.05
Washington	PPD		1,487	0.11	-0.01
Wisconsin	130	4.48	63,482	4.65	-0.01
West Virginia	PPD		1,778	0.13	0.04
Wyoming			1,076	0.08	0.02
Opioids					
buprenorphine	74	2.55	4,126	0.30	0.19

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
butorphanol	<11	0.17	184	0.01	0.05
codeine	527	18.15	132,022	9.68	0.25
fentanyl	40	1.38	972	0.07	0.15
hydrocodone	1,295	44.61	220,145	16.14	0.65
hydromorphone	40	1.38	1,811	0.13	0.14
levorphanol	0	0.00	0	0.00	0.00
meperidine	<11	0.28	1,268	0.09	0.04
methadone	36	1.24	1,248	0.09	0.14
morphine	54	1.86	1,297	0.10	0.18
oxycodone	504	17.36	56,117	4.11	0.44
oxymorphone	<11	0.14	124	0.01	0.05
pentazocine	<11	0.10	344	0.03	0.03
propoxyphene	193	6.65	34,563	2.53	0.20
tapentadol	<11	0.21	90	0.01	0.06
tramadol	484	16.67	42,737	3.13	0.47
Healthcare Utilization, mean (SD)					
Comorbidity Index	1.60	1.86	0.93	1.41	0.41
Morphine equivalents	19914.85	465801.64	880.16	71830.69	0.06
Number of diagnoses	5.99	4.70	2.81	3.35	0.78
Number of ED visits	0.75	1.74	0.35	0.89	0.29
Number of non-duloxetine generics dispensed	5.69	4.28	1.82	2.49	1.11
Number of hospitalizations	0.05	0.24	0.04	0.22	0.03
Number of outpatient visits	5.64	6.60	2.13	3.48	0.67
Number of psychiatric hospitalizations	0.04	0.22	0.01	0.09	0.17
Number of psychiatrist visits	2.28	4.88	0.33	2.17	0.52

15.2. 2. Preterm/SGA- Baseline characteristics of duloxetine exposed vs. SSRI exposed women- early exposure: unadjusted

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Total	1,989	100	67,222	100	
Demographics					
Age, mean (SD)	27.76	5.47	26.1	5.4	0.32
Age categorical, N (%)					
<=19	107	5.38	6,389	9.50	-0.16
20-24	492	24.74	23,496	34.95	-0.22
25-29	679	34.14	20,822	30.97	0.07
30-34	461	23.18	10,937	16.27	0.17
35-39	195	9.80	4,627	6.88	0.11
>=40	55	2.77	951	1.41	0.09
Race, N (%)					
White	1,560	78.43	48,541	72.21	0.14
Black/African American	189	9.50	8,570	12.75	-0.10
Hispanic/Latino	57	2.87	4,410	6.56	-0.17
Asian or Other Pacific	28	1.41	711	1.06	0.03
American Indian	28	1.41	1,099	1.63	-0.02
Other	85	4.27	2,357	3.51	0.04
Unknown	42	2.11	1,534	2.28	-0.01
Chronic comorbid conditions, N (%)					
Hypertension	177	8.90	3,954	5.88	0.12
Diabetes	143	7.19	3,424	5.09	0.09
Renal Disease	20	1.01	544	0.81	0.02
Obesity Overweight	155	7.79	3,433	5.11	0.11
Comorbidity Index Q1	704	35.39	29,089	43.27	-0.16
Comorbidity Index Q2	497	24.99	17,199	25.59	-0.01
Comorbidity Index Q3	326	16.39	10,253	15.25	0.03
Comorbidity Index Q4	462	23.23	10,681	15.89	0.19
Infections, N (%)					
Toxoplasmosis	0	0.00	13	0.02	-0.02
Rubella	0	0.00	<11	0.01	-0.01
Cytomegalovirus	0	0.00	0	0.00	-0.01

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Herpes	39	1.96	1,020	1.52	0.03
Syphilis	<11	0.05	66	0.10	-0.02
Varicella	<11	0.05	20	0.03	0.01
Parvovirus B19	0	0.00	<11	0.01	-0.01
Zika virus other mosquito	0	0.00	0	0.00	
Lymphocytic choriomeningitis	<11	0.05	0	0.00	0.03
Influenza	18	0.90	861	1.28	-0.04
Chlamydia	11	0.55	396	0.59	0.00
Human papilloma virus	17	0.85	601	0.89	0.00
Gonorrhea	13	0.65	429	0.64	0.00
HIV	<11	0.40	285	0.42	0.00
Trichomoniasis	21	1.06	837	1.25	-0.02
Indications for duloxetine, N (%)					
Depression	929	46.71	29,548	43.96	0.06
Anxiety	569	28.61	17,747	26.40	0.05
Neuropathic Pain	218	10.96	3,370	5.01	0.22
Fibromyalgia	217	10.91	1,841	2.74	0.33
Non neuropathic Pain	1,059	53.24	23,150	34.44	0.39
Other psychiatric conditions, N (%)					
Sleep disorder	113	5.68	2,842	4.23	0.07
Bipolar disorder	269	13.52	5,921	8.81	0.15
Psychosis	19	0.96	749	1.11	-0.02
Schizophrenia	19	0.96	757	1.13	-0.02
Personality disorder	32	1.61	1,021	1.52	0.01
Adjustment disorder	23	1.16	869	1.29	-0.01
Tobacco use, N (%)	253	12.72	7,183	10.69	0.06
Alcohol abuse or dependence, N (%)	22	1.11	1,077	1.60	-0.04
Drug abuse or dependence, N (%)	61	3.07	2,341	3.48	-0.02
Other medication exposures, N (%)					
Benzodiazepines	719	36.15	15,636	23.26	0.28
Other hypnotics	469	23.58	10,763	16.01	0.19
Barbiturates	116	5.83	3,002	4.47	0.06

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Anxiolytics	100	5.03	2,477	3.68	0.07
Anticonvulsants	502	25.24	7,591	11.29	0.37
Antipsychotics	370	18.60	7,814	11.62	0.20
SSRIs	0	0.00	67,222	100.00	
SNRIs	73	3.67	2,322	3.45	0.01
Other Antidep	535	26.90	12,517	18.62	0.20
Stimulants	166	8.35	3,014	4.48	0.16
Antidiabetic	85	4.27	1,656	2.46	0.10
Insulin	73	3.67	1,502	2.23	0.08
Antihyperten	302	15.18	5,995	8.92	0.19
Opioid analgesics	1,292	64.96	33,382	49.66	0.31
Triptans	137	6.89	2,689	4.00	0.13
NSAIDs	738	37.10	19,394	28.85	0.18
Obstetric conditions, N (%)					
Multifetal gestation Flag	73	3.67	2,675	3.98	-0.02
Markers of healthcare utilization					
Number of distinct 3 digit ICD 9 codes=0	114	5.73	7,456	11.09	-0.19
Number of distinct 3 digit ICD 9 codes: tertile 1 for number >0	395	19.86	15,512	23.08	-0.08
Number of distinct 3 digit ICD 9 codes: tertile 2 for number >0	436	21.92	14,584	21.70	0.01
Number of distinct 3 digit ICD 9 codes: tertile 3 for number >0	1,044	52.49	29,670	44.14	0.17
Number of ED visits=0	1,232	61.94	44,806	66.65	-0.10
Number of ED visits=1	447	22.47	13,023	19.37	0.08
Number of ED visits=2	169	8.50	5,171	7.69	0.03
Number of ED visits>2	141	7.09	4,222	6.28	0.03
Number of non-duloxetine generics dispensed=0	169	8.50	7,961	11.84	-0.11
Number of non-duloxetine generics dispensed: tertile 1 for number >0	156	7.84	7,645	11.37	-0.12
Number of non-duloxetine generics dispensed: tertile 2 for number >0	445	22.37	17,678	26.30	-0.09
Number of non-duloxetine generics dispensed: tertile 3 for number >0	1,219	61.29	33,938	50.49	0.22
Number of hospital admissions=0	1,925	96.78	63,813	94.93	0.09

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Number of hospital admissions=1	57	2.87	3,065	4.56	-0.09
Number of hospital admissions=2	<11	0.35	286	0.43	-0.01
Number of hospital admissions>2	<11	0.00	58	0.09	-0.04
Number of outpatient visits=0	207	10.41	10,599	15.77	-0.16
Number of outpatient visits: tertile 1 for number >0	230	11.56	10,619	15.80	-0.12
Number of outpatient visits: tertile 2 for number >0	492	24.74	17,563	26.13	-0.03
Number of outpatient visits: tertile 3 for number >0	1,060	53.29	28,441	42.31	0.22
Number of psychiatric hospitalizations Q1	1,944	97.74	65,677	97.70	0.00
Number of psychiatric hospitalizations Q2	41	2.06	1,350	2.01	0.00
Number of psychiatric hospitalizations Q3	<11	0.20	155	0.23	-0.01
Number of psychiatric hospitalizations Q4	<11	0.00	40	0.06	-0.03
Number of psychiatrist visits=0	928	46.66	37,971	56.49	-0.20
Number of psychiatrist visits=1	429	21.57	12,221	18.18	0.08
Number of psychiatrist visits=2	201	10.11	5,794	8.62	0.05
Number of psychiatrist visits>2	431	21.67	11,236	16.71	0.13
Geographic region					
Arkansas	0	0.00	49	0.07	-0.04
Alabama	PPD		434	0.65	-0.09
California	151	7.59	6,052	9.00	-0.05
Colorado	PPD		344	0.51	-0.05
District of Columbia			26	0.04	0.02
Delaware	53	2.66	702	1.04	0.12
Florida	14	0.70	1,211	1.80	-0.10
Georgia	PPD		1,324	1.97	-0.14
Hawaii			93	0.14	-0.01
Iowa	16	0.80	819	1.22	-0.04
Idaho	0	0.00	195	0.29	-0.08
Illinois	203	10.21	5,669	8.43	0.06
Indiana	199	10.01	3,296	4.90	0.20
Kansas	30	1.51	722	1.07	0.04
Kentucky	27	1.36	1,880	2.80	-0.10
Louisiana	74	3.72	1,225	1.82	0.12

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Massachusetts	PPD		634	0.94	-0.09
Maryland	24	1.21	1,077	1.60	-0.03
Maine	PPD		400	0.60	-0.04
Minnesota	102	5.13	4,334	6.45	-0.06
Missouri	103	5.18	2,642	3.93	0.06
Mississippi	PPD		818	1.22	-0.08
North Carolina	45	2.26	858	1.28	0.07
North Dakota	19	0.96	344	0.51	0.05
Nebraska	17	0.85	468	0.70	0.02
New Hampshire	PPD		444	0.66	-0.04
New Jersey			323	0.48	-0.10
New Mexico	15	0.75	1,039	1.55	-0.07
Nevada	PPD		128	0.19	-0.04
New York	380	19.11	7,049	10.49	0.24
Ohio	30	1.51	1,956	2.91	-0.10
Oklahoma	14	0.70	956	1.42	-0.07
Oregon	39	1.96	1,099	1.63	0.02
Pennsylvania	PPD		2,030	3.02	-0.18
Rhode Island			190	0.28	-0.02
South Carolina			135	0.20	0.01
South Dakota			347	0.52	0.01
Tennessee	125	6.28	6,363	9.47	-0.12
Texas	PPD		210	0.31	-0.01
Utah	44	2.21	898	1.34	0.07
Virginia	57	2.87	1,600	2.38	0.03
Vermont	24	1.21	977	1.45	-0.02
Washington	0	0.00	160	0.24	-0.07
Wisconsin	89	4.47	5,390	8.02	-0.15
West Virginia	PPD		224	0.33	0.01
Wyoming			88	0.13	-0.01
Opioids					
buprenorphine	52	2.61	937	1.39	0.09

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
butorphanol	<11	0.15	29	0.04	0.03
codeine	339	17.04	11,471	17.06	0.00
fentanyl	23	1.16	187	0.28	0.10
hydrocodone	870	43.74	21,607	32.14	0.24
hydromorphone	28	1.41	275	0.41	0.11
levorphanol	0	0.00	0	0.00	-0.01
meperidine	<11	0.30	180	0.27	0.01
methadone	23	1.16	278	0.41	0.08
morphine	38	1.91	269	0.40	0.14
oxycodone	330	16.59	6,504	9.68	0.21
oxymorphone	<11	0.20	23	0.03	0.05
pentazocine	<11	0.10	60	0.09	0.00
propoxyphene	122	6.13	4,339	6.45	-0.01
tapentadol	<11	0.20	22	0.03	0.05
tramadol	317	15.94	5,718	8.51	0.23
Healthcare Utilization, mean (SD)					
Comorbidity Index	1.56	1.80	1.23	1.60	0.19
Morphine equivalents	25312.82	558921.39	3242.10	148734.73	0.05
Number of diagnoses	5.76	4.52	4.93	4.38	0.19
Number of ED visits	0.73	1.87	0.63	1.40	0.06
Number of non-duloxetine generics dispensed	5.29	4.08	4.31	3.65	0.25
Number of hospitalizations	0.04	0.20	0.06	0.26	-0.09
Number of outpatient visits	5.29	6.32	4.24	5.42	0.18
Number of psychiatric hospitalizations	0.02	0.17	0.03	0.20	-0.01
Number of psychiatrist visits	2.01	4.70	1.60	4.38	0.09

15.2. 3. Preterm/SGA- Baseline characteristics of duloxetine exposed vs. venlafaxine exposed women- early exposure: unadjusted

	Duloxetine	Duloxetine	Venlafaxine	Venlafaxine	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Total	2,779	100.00	7,258	100.00	
Demographics					
Age, mean (SD)	27.74	5.50	26.8	5.3	0.18
Age categorical, N (%)					
<=19	142	5.11	463	6.38	-0.05
20-24	703	25.30	2,301	31.70	-0.14
25-29	950	34.18	2,414	33.26	0.02
30-34	624	22.45	1,405	19.36	0.08
35-39	284	10.22	561	7.73	0.09
>=40	76	2.73	114	1.57	0.08
Race, N (%)					
White	2,189	78.77	5,808	80.02	-0.03
Black/African American	247	8.89	549	7.56	0.05
Hispanic/Latino	83	2.99	333	4.59	-0.08
Asian or Other Pacific	35	1.26	93	1.28	0.00
American Indian	38	1.37	92	1.27	0.01
Other	126	4.53	219	3.02	0.08
Unknown	61	2.20	164	2.26	0.00
Chronic comorbid conditions, N (%)					
Hypertension	250	9.00	420	5.79	0.12
Diabetes	202	7.27	350	4.82	0.10
Renal Disease	31	1.12	55	0.76	0.04
Obesity Overweight	217	7.81	379	5.22	0.10
Comorbidity Index Q1	950	34.18	2,924	40.29	-0.13
Comorbidity Index Q2	688	24.76	1,848	25.46	-0.02
Comorbidity Index Q3	480	17.27	1,168	16.09	0.03
Comorbidity Index Q4	661	23.79	1,318	18.16	0.14
Infections, N (%)					
Toxoplasmosis	0	0.00	<11	0.03	-0.02
Rubella	0	0.00	0	0.00	
Cytomegalovirus	0	0.00	0	0.00	

	Duloxetine	Duloxetine	Venlafaxine	Venlafaxine	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Herpes	54	1.94	106	1.46	0.04
Syphilis	<11	0.04	<11	0.07	-0.01
Varicella	<11	0.04	<11	0.03	0.00
Parvovirus B19	0	0.00	0	0.00	
Zika virus other mosquito	0	0.00	0	0.00	
Lymphocytic choriomeningitis	<11	0.04	0	0.00	0.03
Influenza	26	0.94	89	1.23	-0.03
Chlamydia	15	0.54	40	0.55	0.00
Human papilloma virus	29	1.04	62	0.85	0.02
Gonorrhea	17	0.61	33	0.45	0.02
HIV	<11	0.36	32	0.44	-0.01
Trichomoniasis	28	1.01	85	1.17	-0.02
Indications for duloxetine, N (%)					
Depression	1,416	50.95	3,705	51.05	0.00
Anxiety	867	31.20	2,146	29.57	0.04
Neuropathic Pain	317	11.41	449	6.19	0.19
Fibromyalgia	315	11.34	270	3.72	0.29
Non neuropathic Pain	1,481	53.29	2,793	38.48	0.30
Other psychiatric conditions, N (%)					
Sleep disorder	168	6.05	404	5.57	0.02
Bipolar disorder	400	14.39	836	11.52	0.09
Psychosis	29	1.04	77	1.06	0.00
Schizophrenia	29	1.04	84	1.16	-0.01
Personality disorder	60	2.16	146	2.01	0.01
Adjustment disorder	33	1.19	94	1.30	-0.01
Tobacco use, N (%)	362	13.03	808	11.13	0.06
Alcohol abuse or dependence, N (%)	42	1.51	135	1.86	-0.03
Drug abuse or dependence, N (%)	99	3.56	330	4.55	-0.05
Other medication exposures, N (%)					
Benzodiazepines	1,067	38.40	2,326	32.05	0.13
Other hypnotics	713	25.66	1,409	19.41	0.15
Barbiturates	182	6.55	367	5.06	0.06

	Duloxetine	Duloxetine	Venlafaxine	Venlafaxine	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Anxiolytics	158	5.69	356	4.90	0.03
Anticonvulsants	718	25.84	1,207	16.63	0.23
Antipsychotics	567	20.40	1,213	16.71	0.10
SSRIs	863	31.05	2,073	28.56	0.05
SNRIs	0	0.00	7,258	100.00	
Other Antidep	785	28.25	1,818	25.05	0.07
Stimulants	222	7.99	457	6.30	0.07
Antidiabetic	115	4.14	208	2.87	0.07
Insulin	102	3.67	169	2.33	0.08
Antihyperten	437	15.73	764	10.53	0.15
Opioid analgesics	1,809	65.10	3,904	53.79	0.23
Triptans	205	7.38	412	5.68	0.07
NSAIDs	1,059	38.11	2,199	30.30	0.17
Obstetric conditions, N (%)					
Multifetal gestation Flag	95	3.42	279	3.84	-0.02
Markers of healthcare utilization					
Number of distinct 3 digit ICD 9 codes=0	139	5.00	628	8.65	-0.15
Number of distinct 3 digit ICD 9 codes: tertile 1 for number >0	532	19.14	1,618	22.29	-0.08
Number of distinct 3 digit ICD 9 codes: tertile 2 for number >0	603	21.70	1,633	22.50	-0.02
Number of distinct 3 digit ICD 9 codes: tertile 3 for number >0	1,505	54.16	3,379	46.56	0.15
Number of ED visits=0	1,736	62.47	4,912	67.68	-0.11
Number of ED visits=1	586	21.09	1,356	18.68	0.06
Number of ED visits=2	241	8.67	527	7.26	0.05
Number of ED visits>2	216	7.77	463	6.38	0.05
Number of non-duloxetine generics dispensed=0	201	7.23	414	5.70	0.06
Number of non-duloxetine generics dispensed: tertile 1 for number >0	210	7.56	650	8.96	-0.05
Number of non-duloxetine generics dispensed: tertile 2 for number >0	587	21.12	1,832	25.24	-0.10
Number of non-duloxetine generics dispensed: tertile 3 for number >0	1,781	64.09	4,362	60.10	0.08
Number of hospital admissions=0	2,669	96.04	6,940	95.62	0.02

	Duloxetine	Duloxetine	Venlafaxine	Venlafaxine	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Number of hospital admissions=1	96	3.45	281	3.87	-0.02
Number of hospital admissions=2	12	0.43	30	0.41	0.00
Number of hospital admissions>2	<11	0.07	<11	0.10	-0.01
Number of outpatient visits=0	259	9.32	935	12.88	-0.11
Number of outpatient visits: tertile 1 for number >0	306	11.01	1,041	14.34	-0.10
Number of outpatient visits: tertile 2 for number >0	689	24.79	1,899	26.16	-0.03
Number of outpatient visits: tertile 3 for number >0	1,525	54.88	3,383	46.61	0.17
Number of psychiatric hospitalizations Q1	2,698	97.09	7,060	97.27	-0.01
Number of psychiatric hospitalizations Q2	70	2.52	167	2.30	0.01
Number of psychiatric hospitalizations Q3	<11	0.32	24	0.33	0.00
Number of psychiatric hospitalizations Q4	<11	0.07	<11	0.10	-0.01
Number of psychiatrist visits=0	1,220	43.90	3,396	46.79	-0.06
Number of psychiatrist visits=1	584	21.01	1,478	20.36	0.02
Number of psychiatrist visits=2	297	10.69	792	10.91	-0.01
Number of psychiatrist visits>2	678	24.40	1,592	21.93	0.06
Geographic region					
Arkansas	PPD		PPD		0.00
Alabama			21	0.29	0.01
California	198	7.12	577	7.95	-0.03
Colorado	PPD		34	0.47	-0.07
District of Columbia			PPD		0.03
Delaware	73	2.63	87	1.20	0.10
Florida	23	0.83	95	1.31	-0.05
Georgia	14	0.50	129	1.78	-0.12
Hawaii	PPD		PPD		0.00
Iowa	28	1.01	133	1.83	-0.07
Idaho	PPD		44	0.61	-0.08
Illinois	307	11.05	547	7.54	0.12
Indiana	260	9.36	363	5.00	0.17
Kansas	43	1.55	82	1.13	0.04
Kentucky	46	1.66	158	2.18	-0.04
Louisiana	106	3.81	150	2.07	0.10

	Duloxetine	Duloxetine	Venlafaxine	Venlafaxine	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Massachusetts	PPD		38	0.52	-0.05
Maryland	37	1.33	108	1.49	-0.01
Maine	PPD		48	0.66	-0.05
Minnesota	155	5.58	472	6.50	-0.04
Missouri	144	5.18	343	4.73	0.02
Mississippi	14	0.50	123	1.69	-0.11
North Carolina	65	2.34	81	1.12	0.09
North Dakota	25	0.90	37	0.51	0.05
Nebraska	30	1.08	61	0.84	0.02
New Hampshire	PPD		40	0.55	-0.03
New Jersey			37	0.51	-0.10
New Mexico	22	0.79	103	1.42	-0.06
Nevada	PPD		13	0.18	-0.03
New York	496	17.85	802	11.05	0.19
Ohio	47	1.69	306	4.22	-0.15
Oklahoma	31	1.12	92	1.27	-0.01
Oregon	55	1.98	126	1.74	0.02
Pennsylvania	19	0.68	326	4.49	-0.24
Rhode Island	PPD		21	0.29	-0.02
South Carolina			19	0.26	-0.02
South Dakota	18	0.65	43	0.59	0.01
Tennessee	155	5.58	627	8.64	-0.12
Texas	PPD		15	0.21	0.00
Utah	67	2.41	94	1.30	0.08
Virginia	69	2.48	152	2.09	0.03
Vermont	29	1.04	74	1.02	0.00
Washington	PPD		16	0.22	-0.04
Wisconsin	121	4.35	563	7.76	-0.14
West Virginia	PPD		25	0.34	0.00
Wyoming			16	0.22	-0.02
Opioids					
buprenorphine	69	2.48	134	1.85	0.04

	Duloxetine	Duloxetine	Venlafaxine	Venlafaxine	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
butorphanol	<11	0.18	<11	0.08	0.03
codeine	503	18.10	1,362	18.77	-0.02
fentanyl	39	1.40	47	0.65	0.08
hydrocodone	1,236	44.48	2,547	35.09	0.19
hydromorphone	35	1.26	36	0.50	0.08
Levorphanol	0	0.00	0	0.00	
meperidine	<11	0.25	24	0.33	-0.01
methadone	33	1.19	46	0.63	0.06
morphine	50	1.80	55	0.76	0.09
oxycodone	475	17.09	777	10.71	0.19
oxymorphone	<11	0.14	<11	0.11	0.01
pentazocine	<11	0.11	12	0.17	-0.02
propoxyphene	181	6.51	543	7.48	-0.04
tapentadol	<11	0.22	<11	0.01	0.06
tramadol	460	16.55	747	10.29	0.18
Healthcare Utilization, mean (SD)					
Comorbidity Index	1.60	1.84	1.33	1.65	0.16
Morphine equivalents	20513.26	476013.12	4523.68	218539.96	0.04
Number of diagnoses	5.95	4.64	5.19	4.43	0.17
Number of ED visits	0.74	1.74	0.63	1.40	0.07
Number of non-duloxetine generics dispensed	5.62	4.24	5.18	3.94	0.11
Number of hospitalizations	0.05	0.24	0.05	0.25	-0.02
Number of outpatient visits	5.56	6.36	4.69	5.81	0.14
Number of psychiatric hospitalizations	0.03	0.21	0.03	0.21	0.01
Number of psychiatrist visits	2.25	4.77	2.04	4.71	0.04

15.2. 4. Preterm/SGA- Baseline characteristics of duloxetine exposed vs. unexposed women - early exposure: adjusted for treatment indications

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Total	2,548	100.00	448,960	100.00	
Demographics					
Age, mean (SD)	27.8	5.53	25.63	5.41	0.40
Age categorical, N (%)					
<=19	122	4.79	53,219	11.85	-0.26
20-24	648	25.43	162,886	36.28	-0.24
25-29	867	34.03	131,576	29.31	0.10
30-34	574	22.53	67,349	15	0.19
35-39	263	10.32	27,521	6.13	0.15
>=40	74	2.9	6,409	1.43	0.10
Race, N (%)					
White	2,011	78.92	265,575	59.15	0.44
Black or African American	228	8.95	95,826	21.34	-0.35
Hispanic or Latino	73	2.86	37,604	8.38	-0.24
Asian or Other Pacific Islander	38	1.49	9,100	2.03	-0.04
American Indian	33	1.3	9,465	2.11	-0.06
Other	110	4.32	21,053	4.69	-0.02
Unknown	55	2.16	10,335	2.3	-0.01
Chronic comorbid conditions, N (%)					
Hypertension	236	9.26	27,511	6.13	0.12
Diabetes	184	7.22	23,322	5.19	0.08
Renal Disease	31	1.22	4,853	1.08	0.01
Obesity Overweight	204	8.01	28,856	6.43	0.06
Comorbidity Index Q1	857	33.63	194,373	43.29	-0.20
Comorbidity Index Q2	626	24.57	115,724	25.78	-0.03
Comorbidity Index Q3	437	17.15	66,569	14.83	0.06
Comorbidity Index Q4	628	24.65	72,293	16.1	0.21
Infections, N (%)					
Toxoplasmosis	<11	0	135	0.03	-0.02
Rubella	<11	0	40	0.01	-0.01
Cytomegalovirus	<11	0	31	0.01	-0.01

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Herpes	49	1.92	7,822	1.74	0.01
Syphilis	<11	0.04	571	0.13	-0.03
Varicella	<11	0	183	0.04	-0.03
Parvovirus B19	<11	0	47	0.01	-0.01
Zika virus other mosquito	<11	0	<11	0	
Lymphocytic choriomeningitis	<11	0.04	<11	0	0.03
Influenza	26	1.02	6,413	1.43	-0.04
Chlamydia	13	0.51	3,860	0.86	-0.04
Human papilloma virus	26	1.02	3,861	0.86	0.02
Gonorrhea	14	0.55	4,268	0.95	-0.05
HIV	<11	0.35	2,206	0.49	-0.02
Trichomoniasis	26	1.02	7,765	1.73	-0.06
Indications for duloxetine, N (%)					
Depression	1,484	58.24	270,980	60.36	-0.04
Anxiety	921	36.15	154,255	34.36	0.04
Neuropathic Pain	340	13.34	73,784	16.43	-0.09
Fibromyalgia	331	12.99	60,580	13.49	-0.01
Non neuropathic Pain	1,550	60.83	275,500	61.36	-0.01
Other psychiatric conditions, N (%)					
Sleep disorder	172	6.75	18,884	4.21	0.11
Bipolar disorder	365	14.32	32,341	7.2	0.23
Psychosis	30	1.18	5,795	1.29	-0.01
Schizophrenia	29	1.14	4,149	0.92	0.02
Personality disorder	62	2.43	7,191	1.6	0.06
Adjustment disorder	33	1.3	6,814	1.52	-0.02
Tobacco use, N (%)	360	14.13	53,775	11.98	0.06
Alcohol abuse or dependence, N (%)	39	1.53	6,548	1.46	0.01
Drug abuse or dependence, N (%)	100	3.92	14,849	3.31	0.03
Other medication exposures, N (%)					
Benzodiazepines	1,046	41.05	88,862	19.79	0.47
Other hypnotics	699	27.43	61,262	13.65	0.35
Barbiturates	174	6.83	18,030	4.02	0.12

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Anxiolytics	158	6.2	14,288	3.18	0.14
Anticonvulsants	696	27.32	48,961	10.91	0.43
Antipsychotics	547	21.47	38,477	8.57	0.37
SSRIs	833	32.69	164,664	36.68	-0.08
SNRIs	112	4.4	23,070	5.14	-0.03
Other Antidep	770	30.22	76,202	16.97	0.32
Stimulants	203	7.97	16,169	3.6	0.19
Antidiabetic	101	3.96	9,328	2.08	0.11
Insulin	91	3.57	9,564	2.13	0.09
Antihyperten	402	15.78	34,829	7.76	0.25
Opioid analgesics	1,737	68.17	236,049	52.58	0.32
Triptans	197	7.73	16,283	3.63	0.18
NSAIDs	1,027	40.31	152,947	34.07	0.13
Obstetric conditions, N (%)					
Multifetal gestation Flag	87	3.41	18,147	4.04	-0.03
Markers of healthcare utilization					
Number of distinct 3 digit ICD 9 codes=0	82	3.22	31,311	6.97	-0.17
Number of distinct 3 digit ICD 9 codes: tertile 1 for number >0	438	17.19	80,080	17.84	-0.02
Number of distinct 3 digit ICD 9 codes: tertile 2 for number >0	543	21.31	93,669	20.86	0.01
Number of distinct 3 digit ICD 9 codes: tertile 3 for number >0	1,485	58.28	243,901	54.33	0.08
Number of ED visits=0	1,519	59.62	264,481	58.91	0.01
Number of ED visits=1	563	22.1	98,808	22.01	0.00
Number of ED visits=2	242	9.5	43,249	9.63	0.00
Number of ED visits>2	224	8.79	42,422	9.45	-0.02
Number of non-duloxetine generics dispensed=0	155	6.08	77,775	17.32	-0.36
Number of non-duloxetine generics dispensed: tertile 1 for number >0	172	6.75	50,509	11.25	-0.16
Number of non-duloxetine generics dispensed: tertile 2 for number >0	515	20.21	108,639	24.2	-0.10
Number of non-duloxetine generics dispensed: tertile 3 for number >0	1,706	66.95	212,037	47.23	0.41
Number of hospital admissions=0	2,439	95.72	422,833	94.18	0.07

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Number of hospital admissions=1	94	3.69	22,753	5.07	-0.07
Number of hospital admissions=2	13	0.51	2,812	0.63	-0.02
Number of hospital admissions>2	<11	0.08	562	0.13	-0.01
Number of outpatient visits=0	181	7.1	51,907	11.56	-0.15
Number of outpatient visits: tertile 1 for number >0	243	9.54	59,462	13.24	-0.12
Number of outpatient visits: tertile 2 for number >0	628	24.65	110,503	24.61	0.00
Number of outpatient visits: tertile 3 for number >0	1,496	58.71	227,087	50.58	0.16
Number of psychiatric hospitalizations Q1	2,462	96.62	434,303	96.74	-0.01
Number of psychiatric hospitalizations Q2	75	2.94	12,741	2.84	0.01
Number of psychiatric hospitalizations Q3	<11	0.35	1,553	0.35	0.00
Number of psychiatric hospitalizations Q4	<11	0.08	363	0.08	0.00
Number of psychiatrist visits=0	975	38.27	210,626	46.91	-0.18
Number of psychiatrist visits=1	586	23	98,442	21.93	0.03
Number of psychiatrist visits=2	298	11.7	47,287	10.53	0.04
Number of psychiatrist visits>2	689	27.04	92,605	20.63	0.15
Geographic region					
Arkansas	PPD		450	0.1	0.01
Alabama	PPD		2,446	0.54	-0.02
California	171	6.71	51,510	11.47	-0.17
Colorado	PPD		1,385	0.31	-0.04
District of Columbia	PPD		281	0.06	0.02
Delaware	63	2.47	3,848	0.86	0.13
Florida	18	0.71	6,207	1.38	-0.07
Georgia	13	0.51	7,883	1.76	-0.12
Hawaii	PPD		2,048	0.46	-0.06
Iowa	27	1.06	3,596	0.8	0.03
Idaho	PPD		835	0.19	0.00
Illinois	269	10.56	33,263	7.41	0.11
Indiana	241	9.46	23,098	5.14	0.17
Kansas	39	1.53	3,852	0.86	0.06
Kentucky	41	1.61	12,800	2.85	-0.08
Louisiana	95	3.73	7,893	1.76	0.12

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Massachusetts	PPD		2,616	0.58	-0.05
Maryland	33	1.3	9,971	2.22	-0.07
Maine	PPD		2,652	0.59	-0.04
Minnesota	160	6.28	29,775	6.63	-0.01
Missouri	131	5.14	12,400	2.76	0.12
Mississippi	PPD		7,249	1.61	-0.12
North Carolina	59	2.32	7,330	1.63	0.05
North Dakota	25	0.98	2,413	0.54	0.05
Nebraska	26	1.02	2,734	0.61	0.05
New Hampshire	PPD		2,998	0.67	-0.04
New Jersey			2,828	0.63	-0.11
New Mexico	25	0.98	7,613	1.7	-0.06
Nevada	PPD		716	0.16	-0.02
New York	429	16.84	54,633	12.17	0.13
Ohio	46	1.81	11,848	2.64	-0.06
Oklahoma	32	1.26	5,785	1.29	0.00
Oregon	53	2.08	6,526	1.45	0.05
Pennsylvania	17	0.67	9,841	2.19	-0.13
Rhode Island	PPD		1,341	0.3	-0.02
South Carolina			837	0.19	0.00
South Dakota	16	0.63	2,801	0.62	0.00
Tennessee	155	6.08	43,383	9.66	-0.13
Texas	PPD		1,127	0.25	-0.01
Utah	58	2.28	3,260	0.73	0.13
Virginia	69	2.71	12,266	2.73	0.00
Vermont	29	1.14	5,413	1.21	-0.01
Washington	PPD		530	0.12	-0.01
Wisconsin	116	4.55	34,836	7.76	-0.13
West Virginia	PPD		1,318	0.29	0.00
Wyoming			524	0.12	0.01
Opioids					
buprenorphine	63	2.47	4,603	1.03	0.11

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
butorphanol	<11	0.2	296	0.07	0.04
codeine	484	19	78,856	17.56	0.04
fentanyl	35	1.37	2,014	0.45	0.10
hydrocodone	1,198	47.02	156,907	34.95	0.25
hydromorphone	37	1.45	2,705	0.6	0.08
levorphanol	<11	0	<11	0	0.00
meperidine	<11	0.31	1,315	0.29	0.00
methadone	35	1.37	2,434	0.54	0.09
morphine	49	1.92	2,939	0.65	0.11
oxycodone	474	18.6	52,651	11.73	0.19
oxymorphone	<11	0.12	351	0.08	0.01
pentazocine	<11	0.12	422	0.09	0.01
propoxyphene	179	7.03	28,412	6.33	0.03
tapentadol	<11	0.24	210	0.05	0.05
tramadol	457	17.94	47,031	10.48	0.21
Healthcare Utilization, mean (SD)					
Comorbidity Index	1.65	1.89	1.25	1.73	0.22
Morphine equivalents	21852.39	496327.68	3839.25	139576.33	0.05
Number of diagnoses	6.38	4.75	6.04	5	0.07
Number of ED visits	0.81	1.8	0.85	1.67	-0.02
Number of non-duloxetine generics dispensed	5.94	4.35	4.1	3.81	0.45
Number of hospitalizations	0.05	0.25	0.07	0.3	-0.07
Number of outpatient visits	6.03	6.82	5.05	5.89	0.15
Number of psychiatric hospitalizations	0.04	0.23	0.04	0.23	0.00
Number of psychiatrist visits	2.48	5.02	1.89	4.36	0.12

15.2. 5. Preterm/SGA- Baseline characteristics of duloxetine exposed vs. SSRI exposed women - early exposure: adjusted for treatment indications

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Total	1,715	100.00	51,847	100.00	
Demographics					
Age, mean (SD)	27.81	5.49	26.3	5.43	0.28
Age categorical, N (%)					
<=19	88	5.13	4,488	8.66	-0.14
20-24	423	24.66	17,503	33.76	-0.20
25-29	588	34.29	16,314	31.47	0.06
30-34	395	23.03	8,861	17.09	0.15
35-39	171	9.97	3,858	7.44	0.09
>=40	50	2.92	823	1.59	0.09
Race, N (%)					
White	1,349	78.66	37,952	73.2	0.13
Black/African American	164	9.56	6,229	12.01	-0.08
Hispanic/Latino	46	2.68	3,158	6.09	-0.17
Asian or Other Pacific	26	1.52	609	1.17	0.03
American Indian	24	1.4	929	1.79	-0.03
Other	72	4.2	1,771	3.42	0.04
Unknown	34	1.98	1,199	2.31	-0.02
Chronic comorbid conditions, N (%)					
Hypertension	159	9.27	3,566	6.88	0.09
Diabetes	125	7.29	2,997	5.78	0.06
Renal Disease	19	1.11	567	1.09	0.00
Obesity Overweight	137	7.99	3,222	6.21	0.07
Comorbidity Index Q1	597	34.81	20,856	40.23	-0.11
Comorbidity Index Q2	417	24.31	13,314	25.68	-0.03
Comorbidity Index Q3	283	16.5	8,309	16.03	0.01
Comorbidity Index Q4	418	24.37	9,368	18.07	0.15
Infections, N (%)					
Toxoplasmosis	<11	0	12	0.02	-0.02
Rubella	<11	0	<11	0.01	-0.01
Cytomegalovirus	<11	0	<11	0.01	-0.01

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Herpes	32	1.87	917	1.77	0.01
Syphilis	<11	0.06	66	0.13	-0.02
Varicella	<11	0	25	0.05	-0.03
Parvovirus B19	<11	0	<11	0.01	-0.01
Zika virus other mosquito	<11	0	<11	0	.
Lymphocytic choriomeningitis	<11	0.06	<11	0	0.03
Influenza	16	0.93	772	1.49	-0.05
Chlamydia	<11	0.58	332	0.64	-0.01
Human papilloma virus	12	0.7	476	0.92	-0.02
Gonorrhea	<11	0.58	396	0.76	-0.02
HIV	<11	0.41	216	0.42	0.00
Trichomoniasis	19	1.11	678	1.31	-0.02
Indications for duloxetine, N (%)					
Depression	929	54.17	28,056	54.11	0.00
Anxiety	569	33.18	17,783	34.3	-0.02
Neuropathic Pain	218	12.71	6,877	13.26	-0.02
Fibromyalgia	217	12.65	7,256	13.99	-0.04
Non neuropathic Pain	1,059	61.75	32,515	62.71	-0.02
Other psychiatric conditions, N (%)					
Sleep disorder	109	6.36	2,882	5.56	0.03
Bipolar disorder	234	13.64	5,254	10.13	0.11
Psychosis	18	1.05	679	1.31	-0.02
Schizophrenia	17	0.99	640	1.24	-0.02
Personality disorder	30	1.75	966	1.86	-0.01
Adjustment disorder	21	1.22	781	1.51	-0.02
Tobacco use, N (%)	235	13.7	6,820	13.15	0.02
Alcohol abuse or dependence, N (%)	19	1.11	883	1.7	-0.05
Drug abuse or dependence, N (%)	57	3.32	2,071	4	-0.04
Other medication exposures, N (%)					
Benzodiazepines	660	38.48	14,990	28.91	0.20
Other hypnotics	422	24.61	9,988	19.26	0.13
Barbiturates	100	5.83	2,807	5.41	0.02

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Anxiolytics	91	5.31	2,362	4.55	0.03
Anticonvulsants	459	26.76	7,954	15.34	0.28
Antipsychotics	331	19.3	6,964	13.43	0.16
SSRIs	<11	0	51,847	100	.
SNRIs	65	3.79	2,125	4.1	-0.02
Other Antidep	493	28.75	11,737	22.64	0.14
Stimulants	144	8.4	2,675	5.16	0.13
Antidiabetic	69	4.02	1,441	2.78	0.07
Insulin	61	3.56	1,287	2.48	0.06
Antihyperten	260	15.16	5,385	10.39	0.14
Opioid analgesics	1,168	68.1	31,335	60.44	0.16
Triptans	126	7.35	2,564	4.95	0.10
NSAIDs	673	39.24	19,552	37.71	0.03
Obstetric conditions, N (%)					
Multifetal gestation Flag	65	3.79	2,109	4.07	-0.01
Markers of healthcare utilization					
Number of distinct 3 digit ICD 9 codes=0	62	3.62	3,160	6.09	-0.12
Number of distinct 3 digit ICD 9 codes: tertile 1 for number >0	304	17.73	8,861	17.09	0.02
Number of distinct 3 digit ICD 9 codes: tertile 2 for number >0	379	22.1	10,691	20.62	0.04
Number of distinct 3 digit ICD 9 codes: tertile 3 for number >0	970	56.56	29,135	56.19	0.01
Number of ED visits=0	1,013	59.07	30,462	58.75	0.01
Number of ED visits=1	406	23.67	11,263	21.72	0.05
Number of ED visits=2	160	9.33	5,053	9.75	-0.01
Number of ED visits>2	136	7.93	5,069	9.78	-0.07
Number of non-duloxetine generics dispensed=0	130	7.58	4,462	8.61	-0.04
Number of non-duloxetine generics dispensed: tertile 1 for number >0	123	7.17	4,454	8.59	-0.05
Number of non-duloxetine generics dispensed: tertile 2 for number >0	365	21.28	11,769	22.7	-0.03
Number of non-duloxetine generics dispensed: tertile 3 for number >0	1,097	63.97	31,163	60.11	0.08
Number of hospital admissions=0	1,656	96.56	49,001	94.51	0.10

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Number of hospital admissions=1	52	3.03	2,522	4.87	-0.09
Number of hospital admissions=2	<11	0.41	271	0.52	-0.02
Number of hospital admissions>2	<11	0	53	0.1	-0.05
Number of outpatient visits=0	135	7.87	5,013	9.67	-0.06
Number of outpatient visits: tertile 1 for number >0	172	10.03	6,510	12.56	-0.08
Number of outpatient visits: tertile 2 for number >0	428	24.96	12,811	24.71	0.01
Number of outpatient visits: tertile 3 for number >0	980	57.14	27,513	53.07	0.08
Number of psychiatric hospitalizations Q1	1,672	97.49	50,341	97.1	0.02
Number of psychiatric hospitalizations Q2	39	2.27	1,308	2.52	-0.02
Number of psychiatric hospitalizations Q3	<11	0.23	160	0.31	-0.01
Number of psychiatric hospitalizations Q4	<11	0	38	0.07	-0.04
Number of psychiatrist visits=0	700	40.82	24,854	47.94	-0.14
Number of psychiatrist visits=1	416	24.26	10,962	21.14	0.07
Number of psychiatrist visits=2	192	11.2	5,364	10.35	0.03
Number of psychiatrist visits>2	407	23.73	10,667	20.57	0.08
Geographic region					
Arkansas	PPD		47	0.09	-0.04
Alabama	PPD		360	0.69	-0.09
California	121	7.06	4,212	8.12	-0.04
Colorado	PPD		225	0.43	-0.06
District of Columbia	PPD		18	0.03	0.03
Delaware	43	2.51	501	0.97	0.12
Florida	PPD		854	1.65	-0.10
Georgia	PPD		997	1.92	-0.13
Hawaii	PPD		63	0.12	0.00
Iowa	14	0.82	608	1.17	-0.04
Idaho	PPD		157	0.3	-0.08
Illinois	166	9.68	4,044	7.8	0.07
Indiana	178	10.38	2,771	5.35	0.19
Kansas	25	1.46	471	0.91	0.05
Kentucky	24	1.4	1,573	3.03	-0.11
Louisiana	62	3.62	895	1.73	0.12

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Massachusetts	PPD		418	0.81	-0.07
Maryland	21	1.22	874	1.69	-0.04
Maine	PPD		299	0.58	-0.04
Minnesota	98	5.71	3,630	7	-0.05
Missouri	90	5.25	1,838	3.54	0.08
Mississippi	PPD		627	1.21	-0.09
North Carolina	40	2.33	709	1.37	0.07
North Dakota	18	1.05	302	0.58	0.05
Nebraska	15	0.87	373	0.72	0.02
New Hampshire	PPD		380	0.73	-0.04
New Jersey			210	0.41	-0.09
New Mexico	15	0.87	846	1.63	-0.07
Nevada	PPD		112	0.22	-0.04
New York	312	18.19	4,988	9.62	0.25
Ohio	25	1.46	1,588	3.06	-0.11
Oklahoma	14	0.82	634	1.22	-0.04
Oregon	37	2.16	855	1.65	0.04
Pennsylvania	PPD		1,571	3.03	-0.18
Rhode Island			152	0.29	-0.01
South Carolina			109	0.21	0.02
South Dakota			304	0.59	0.00
Tennessee	111	6.47	5,353	10.32	-0.14
Texas	PPD		130	0.25	-0.02
Utah	37	2.16	627	1.21	0.07
Virginia	53	3.09	1,356	2.61	0.03
Vermont	23	1.34	739	1.43	-0.01
Washington	PPD		109	0.21	-0.06
Wisconsin	80	4.66	4,658	8.98	-0.17
West Virginia	PPD		193	0.37	0.01
Wyoming			67	0.13	0.00
Opioids					
buprenorphine	42	2.45	779	1.5	0.07

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
butorphanol	<11	0.17	31	0.06	0.03
codeine	304	17.73	10,554	20.36	-0.07
fentanyl	21	1.22	301	0.58	0.07
hydrocodone	795	46.36	21,702	41.86	0.09
hydromorphone	25	1.46	360	0.7	0.07
levorphanol	<11	0	<11	0	-0.01
meperidine	<11	0.35	169	0.33	0.00
methadone	22	1.28	423	0.81	0.05
morphine	34	1.98	486	0.94	0.09
oxycodone	312	18.19	7,375	14.22	0.11
oxymorphone	<11	0.17	47	0.09	0.02
pentazocine	<11	0.12	75	0.15	-0.01
propoxyphene	111	6.47	4,369	8.43	-0.07
tapentadol	<11	0.23	28	0.05	0.05
tramadol	296	17.26	6,801	13.12	0.12
Healthcare Utilization, mean (SD)					
Comorbidity Index	1.61	1.85	1.34	1.68	0.15
Morphine equivalents	28937.13	601665.27	3340.59	99156.57	0.06
Number of diagnoses	6.18	4.58	6.23	5.1	-0.01
Number of ED visits	0.8	1.95	0.87	1.71	-0.04
Number of non-duloxetine generics dispensed	5.53	4.16	5.21	4.09	0.08
Number of hospitalizations	0.04	0.21	0.06	0.28	-0.10
Number of outpatient visits	5.7	6.56	5.32	5.99	0.06
Number of psychiatric hospitalizations	0.03	0.18	0.03	0.22	-0.03
Number of psychiatrist visits	2.21	4.87	1.89	4.46	0.07

15.2. 6. Preterm/SGA- Baseline characteristics of duloxetine exposed vs. venlafaxine exposed women - early exposure: adjusted for treatment indications

	Duloxetine	Duloxetine	Venlafaxine	Venlafaxine	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Total	2,436	100.00	5,954	100.00	
Demographics					
Age, mean (SD)	27.8	5.54	26.97	5.3	0.15
Age categorical, N (%)					
<=19	119	4.89	342	5.74	-0.04
20-24	618	25.37	1,837	30.85	-0.12
25-29	831	34.11	1,984	33.33	0.02
30-34	543	22.29	1,195	20.08	0.05
35-39	254	10.43	500	8.39	0.07
>=40	71	2.91	96	1.61	0.09
Race, N (%)					
White	1,921	78.86	4,791	80.47	-0.04
Black/African American	219	8.99	434	7.28	0.06
Hispanic/Latino	71	2.91	258	4.33	-0.08
Asian or Other Pacific	33	1.35	85	1.43	-0.01
American Indian	32	1.31	77	1.29	0.00
Other	109	4.47	180	3.02	0.08
Unknown	51	2.09	131	2.19	-0.01
Chronic comorbid conditions, N (%)					
Hypertension	226	9.28	400	6.71	0.09
Diabetes	178	7.31	322	5.41	0.08
Renal Disease	29	1.19	47	0.79	0.04
Obesity Overweight	197	8.09	365	6.14	0.08
Comorbidity Index Q1	814	33.42	2,295	38.55	-0.11
Comorbidity Index Q2	594	24.38	1,522	25.57	-0.03
Comorbidity Index Q3	426	17.49	980	16.45	0.03
Comorbidity Index Q4	602	24.71	1,157	19.43	0.13
Infections, N (%)					
Toxoplasmosis	<11	0	<11	0.03	-0.03

	Duloxetine	Duloxetine	Venlafaxine	Venlafaxine	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Rubella	<11	0	<11	0	
Cytomegalovirus	<11	0	<11	0	
Herpes	46	1.89	93	1.56	0.03
Syphilis	<11	0.04	<11	0.1	-0.02
Varicella	<11	0	<11	0.01	-0.01
Parvovirus B19	<11	0	<11	0	
Zika virus other mosquito	<11	0	<11	0	
Lymphocytic choriomeningitis	<11	0.04	<11	0	0.03
Influenza	24	0.99	82	1.38	-0.04
Chlamydia	13	0.53	31	0.52	0.00
Human papilloma virus	24	0.99	50	0.83	0.02
Gonorrhea	14	0.57	29	0.49	0.01
HIV	<11	0.37	33	0.55	-0.03
Trichomoniasis	26	1.07	77	1.29	-0.02
Indications for duloxetine, N (%)					
Depression	1,416	58.13	3,467	58.23	0.00
Anxiety	867	35.59	2,098	35.24	0.01
Neuropathic Pain	317	13.01	898	15.09	-0.06
Fibromyalgia	315	12.93	747	12.55	0.01
Non neuropathic Pain	1,481	60.8	3,640	61.13	-0.01
Other psychiatric conditions, N (%)					
Sleep disorder	159	6.53	388	6.51	0.00
Bipolar disorder	352	14.45	734	12.33	0.06
Psychosis	28	1.15	71	1.2	0.00
Schizophrenia	27	1.11	72	1.21	-0.01
Personality disorder	58	2.38	132	2.22	0.01
Adjustment disorder	30	1.23	88	1.48	-0.02
Tobacco use, N (%)	343	14.08	746	12.53	0.05
Alcohol abuse or dependence, N (%)	38	1.56	113	1.89	-0.03
Drug abuse or dependence, N (%)	93	3.82	292	4.91	-0.05
Other medication exposures, N (%)					
Benzodiazepines	986	40.48	2,176	36.54	0.08

	Duloxetine	Duloxetine	Venlafaxine	Venlafaxine	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Other hypnotics	652	26.77	1,340	22.51	0.10
Barbiturates	161	6.61	365	6.13	0.02
Anxiolytics	148	6.08	333	5.6	0.02
Anticonvulsants	660	27.09	1,230	20.65	0.15
Antipsychotics	516	21.18	1,093	18.35	0.07
SSRIs	786	32.27	1,801	30.25	0.04
SNRIs	<11	0	5,954	100	.
Other Antidep	724	29.72	1,661	27.9	0.04
Stimulants	193	7.92	404	6.79	0.04
Antidiabetic	99	4.06	187	3.13	0.05
Insulin	90	3.69	161	2.71	0.06
Antihyperten	383	15.72	692	11.62	0.12
Opioid analgesics	1,653	67.86	3,750	62.98	0.10
Triptans	190	7.8	416	6.98	0.03
NSAIDs	981	40.27	2,225	37.37	0.06
Obstetric conditions, N (%)					
Multifetal gestation Flag	85	3.49	254	4.27	-0.04
Markers of healthcare utilization					
Number of distinct 3 digit ICD 9 codes=0	79	3.24	319	5.36	-0.10
Number of distinct 3 digit ICD 9 codes: tertile 1 for number >0	420	17.24	1,019	17.11	0.00
Number of distinct 3 digit ICD 9 codes: tertile 2 for number >0	524	21.51	1,273	21.37	0.00
Number of distinct 3 digit ICD 9 codes: tertile 3 for number >0	1,413	58	3,344	56.16	0.04
Number of ED visits=0	1,463	60.06	3,706	62.25	-0.04
Number of ED visits=1	533	21.88	1,170	19.66	0.05
Number of ED visits=2	230	9.44	547	9.18	0.01
Number of ED visits>2	210	8.62	530	8.91	-0.01
Number of non-duloxetine generics dispensed=0	154	6.32	279	4.69	0.07
Number of non-duloxetine generics dispensed: tertile 1 for number >0	170	6.98	398	6.69	0.01
Number of non-duloxetine generics dispensed: tertile 2 for number >0	491	20.16	1,269	21.32	-0.03

	Duloxetine	Duloxetine	Venlafaxine	Venlafaxine	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Number of non-duloxetine generics dispensed: tertile 3 for number >0	1,621	66.54	4,007	67.31	-0.02
Number of hospital admissions=0	2,335	95.85	5,651	94.91	0.05
Number of hospital admissions=1	87	3.57	265	4.45	-0.04
Number of hospital admissions=2	12	0.49	32	0.54	-0.01
Number of hospital admissions>2	<11	0.08	<11	0.1	-0.01
Number of outpatient visits=0	175	7.18	508	8.53	-0.05
Number of outpatient visits: tertile 1 for number >0	233	9.56	694	11.65	-0.07
Number of outpatient visits: tertile 2 for number >0	607	24.92	1,456	24.45	0.01
Number of outpatient visits: tertile 3 for number >0	1,421	58.33	3,296	55.36	0.06
Number of psychiatric hospitalizations Q1	2,357	96.76	5,762	96.77	0.00
Number of psychiatric hospitalizations Q2	68	2.79	160	2.68	0.01
Number of psychiatric hospitalizations Q3	<11	0.37	27	0.45	-0.01
Number of psychiatric hospitalizations Q4	<11	0.08	<11	0.1	-0.01
Number of psychiatrist visits=0	940	38.59	2,506	42.09	-0.07
Number of psychiatrist visits=1	567	23.28	1,253	21.05	0.05
Number of psychiatrist visits=2	286	11.74	700	11.76	0.00
Number of psychiatrist visits>2	643	26.4	1,494	25.09	0.03
Geographic region					
Arkansas	PPD		PPD		0.00
Alabama			18	0.29	0.01
California	165	6.77	439	7.38	-0.02
Colorado	PPD		25	0.42	-0.08
District of Columbia			PPD		0.03
Delaware	61	2.5	64	1.08	0.11
Florida	17	0.7	75	1.26	-0.06
Georgia	PPD		102	1.72	-0.12
Hawaii			PPD		0.01
Iowa	26	1.07	99	1.66	-0.05
Idaho	PPD		40	0.67	-0.08
Illinois	262	10.76	421	7.07	0.13
Indiana	236	9.69	322	5.41	0.16

	Duloxetine	Duloxetine	Venlafaxine	Venlafaxine	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Kansas	39	1.6	61	1.03	0.05
Kentucky	40	1.64	138	2.32	-0.05
Louisiana	92	3.78	128	2.14	0.10
Massachusetts	PPD		23	0.39	-0.03
Maryland	33	1.35	96	1.61	-0.02
Maine	PPD		38	0.64	-0.04
Minnesota	149	6.12	435	7.31	-0.05
Missouri	124	5.09	278	4.68	0.02
Mississippi	PPD		90	1.52	-0.11
North Carolina	58	2.38	65	1.09	0.10
North Dakota	24	0.99	35	0.58	0.05
Nebraska	25	1.03	45	0.76	0.03
New Hampshire	PPD		32	0.53	-0.02
New Jersey			31	0.51	-0.10
New Mexico	22	0.9	90	1.51	-0.06
Nevada	PPD		PPD		-0.03
New York	416	17.08	615	10.32	0.20
Ohio	42	1.72	271	4.55	-0.16
Oklahoma	30	1.23	68	1.14	0.01
Oregon	51	2.09	105	1.76	0.02
Pennsylvania	17	0.7	246	4.14	-0.23
Rhode Island	PPD		17	0.29	-0.02
South Carolina			17	0.29	-0.02
South Dakota	16	0.66	37	0.62	0.00
Tennessee	141	5.79	524	8.81	-0.12
Texas	PPD		PPD		0.01
Utah	54	2.22	69	1.16	0.08
Virginia	63	2.59	138	2.32	0.02
Vermont	28	1.15	59	0.99	0.02
Washington	PPD		PPD		-0.02
Wisconsin	107	4.39	519	8.71	-0.18
West Virginia	PPD		23	0.38	-0.01

	Duloxetine	Duloxetine	Venlafaxine	Venlafaxine	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Wyoming	PPD		PPD		-0.01
Opioids					
buprenorphine	58	2.38	95	1.6	0.06
butorphanol	<11	0.21	<11	0.15	0.01
codeine	460	18.88	1,293	21.72	-0.07
fentanyl	34	1.4	77	1.29	0.01
hydrocodone	1,142	46.88	2,568	43.13	0.08
hydromorphone	32	1.31	42	0.71	0.06
levorphanol	<11	0	<11	0	.
meperidine	<11	0.29	29	0.48	-0.03
methadone	32	1.31	73	1.23	0.01
morphine	45	1.85	82	1.37	0.04
oxycodone	445	18.27	881	14.8	0.09
oxymorphone	<11	0.12	12	0.2	-0.02
pentazocine	<11	0.12	12	0.21	-0.02
propoxyphene	168	6.9	550	9.24	-0.09
tapentadol	<11	0.25	<11	0.02	0.06
tramadol	434	17.82	860	14.44	0.09
Healthcare Utilization, mean (SD)					
Comorbidity Index	1.65	1.89	1.4	1.69	0.14
Morphine equivalents	22526.59	507532.93	6229.29	232280.62	0.04
Number of diagnoses	6.33	4.69	6.27	4.99	0.01
Number of ED visits	0.8	1.81	0.81	1.67	-0.01
Number of non-duloxetine generics dispensed	5.87	4.3	6	4.41	-0.03
Number of hospitalizations	0.05	0.25	0.06	0.27	-0.04
Number of outpatient visits	5.94	6.57	5.57	5.98	0.06
Number of psychiatric hospitalizations	0.04	0.23	0.04	0.23	0.00
Number of psychiatrist visits	2.44	4.89	2.25	4.7	0.04

15.2. 7. Preterm/SGA- Baseline characteristics of duloxetine exposed vs. unexposed women - early exposure: fully adjusted

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Total	2,547	100.00	433,219	100.00	
Demographics					
Age, mean (SD)	27.8	5.52	27.76	5.56	0.01
Age categorical, N (%)					
<=19	122	4.79	19,551	4.51	0.01
20-24	647	25.4	110,481	25.5	0.00
25-29	867	34.04	149,175	34.43	-0.01
30-34	574	22.54	97,434	22.49	0.00
35-39	263	10.33	44,234	10.21	0.00
>=40	74	2.91	12,344	2.85	0.00
Race, N (%)					
White	2,010	78.92	346,931	80.08	-0.03
Black or African American	228	8.95	35,253	8.14	0.03
Hispanic or Latino	73	2.87	11,034	2.55	0.02
Asian or Other Pacific Islander	38	1.49	6,306	1.46	0.00
American Indian	33	1.3	5,543	1.28	0.00
Other	110	4.32	18,860	4.35	0.00
Unknown	55	2.16	9,291	2.14	0.00
Chronic comorbid conditions, N (%)					
Hypertension	236	9.27	39,080	9.02	0.01
Diabetes	184	7.22	31,290	7.22	0.00
Renal Disease	31	1.22	5,344	1.23	0.00
Obesity Overweight	204	8.01	34,317	7.92	0.00
Comorbidity Index Q1	856	33.61	145,300	33.54	0.00
Comorbidity Index Q2	626	24.58	107,486	24.81	-0.01
Comorbidity Index Q3	437	17.16	75,250	17.37	-0.01
Comorbidity Index Q4	628	24.66	105,182	24.28	0.01
Infections, N (%)					
Toxoplasmosis	<11	0	<11	0	
Rubella	<11	0	<11	0	
Cytomegalovirus	<11	0	<11	0	

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Herpes	49	1.92	8,278	1.91	0.00
Syphilis	<11	0.04	159	0.04	0.00
Varicella	<11	0	<11	0	
Parvovirus B19	<11	0	<11	0	
Zika virus other mosquito	<11	0	<11	0	
Lymphocytic choriomeningitis	<11	0	19	0	-0.01
Influenza	26	1.02	4,401	1.02	0.00
Chlamydia	13	0.51	2,252	0.52	0.00
Human papilloma virus	26	1.02	4,391	1.01	0.00
Gonorrhea	14	0.55	2,325	0.54	0.00
HIV	<11	0.35	1,538	0.35	0.00
Trichomoniasis	26	1.02	4,320	1	0.00
Indications for duloxetine, N (%)					
Depression	1,483	58.23	258,369	59.64	-0.03
Anxiety	920	36.12	158,176	36.51	-0.01
Neuropathic Pain	340	13.35	56,221	12.98	0.01
Fibromyalgia	330	12.96	50,508	11.66	0.04
Non neuropathic Pain	1,549	60.82	257,574	59.46	0.03
Other psychiatric conditions, N (%)					
Sleep disorder	172	6.75	28,944	6.68	0.00
Bipolar disorder	365	14.33	61,035	14.09	0.01
Psychosis	30	1.18	5,114	1.18	0.00
Schizophrenia	29	1.14	4,894	1.13	0.00
Personality disorder	62	2.43	10,393	2.4	0.00
Adjustment disorder	32	1.26	5,568	1.29	0.00
Tobacco use, N (%)	360	14.13	61,742	14.25	0.00
Alcohol abuse or dependence, N (%)	39	1.53	6,703	1.55	0.00
Drug abuse or dependence, N (%)	100	3.93	17,402	4.02	0.00
Other medication exposures, N (%)					
Benzodiazepines	1,045	41.03	176,819	40.82	0.00
Other hypnotics	698	27.4	116,200	26.82	0.01
Barbiturates	174	6.83	29,399	6.79	0.00

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Anxiolytics	157	6.16	25,727	5.94	0.01
Anticonvulsants	695	27.29	112,236	25.91	0.03
Antipsychotics	547	21.48	88,738	20.48	0.02
SSRIs	833	32.71	149,858	34.59	-0.04
SNRIs	112	4.4	20,154	4.65	-0.01
Other Antidepressants	769	30.19	129,790	29.96	0.01
Stimulants	203	7.97	33,317	7.69	0.01
Antidiabetic	101	3.97	16,698	3.85	0.01
Insulin	91	3.57	15,362	3.55	0.00
Antihypertensives	402	15.78	65,991	15.23	0.02
Opioid analgesics	1,736	68.16	296,258	68.39	0.00
Triptans	197	7.73	32,913	7.6	0.01
NSAIDs	1,027	40.32	173,981	40.16	0.00
Obstetric conditions, N (%)					
Multifetal gestation Flag	87	3.42	14,784	3.41	0.00
Markers of healthcare utilization					
Number of distinct 3 digit ICD 9 codes=0	82	3.22	12,064	2.78	0.03
Number of distinct 3 digit ICD 9 codes: tertile 1 for number >0	438	17.2	73,950	17.07	0.00
Number of distinct 3 digit ICD 9 codes: tertile 2 for number >0	543	21.32	94,012	21.7	-0.01
Number of distinct 3 digit ICD 9 codes: tertile 3 for number >0	1,484	58.26	253,193	58.44	0.00
Number of ED visits=0	1,519	59.64	259,588	59.92	-0.01
Number of ED visits=1	562	22.07	95,174	21.97	0.00
Number of ED visits=2	242	9.5	40,716	9.4	0.00
Number of ED visits>2	224	8.79	37,741	8.71	0.00
Number of non-duloxetine generics dispensed=0	155	6.09	21,869	5.05	0.05
Number of non-duloxetine generics dispensed: tertile 1 for number >0	172	6.75	27,736	6.4	0.01
Number of non-duloxetine generics dispensed: tertile 2 for number >0	515	20.22	90,091	20.8	-0.01
Number of non-duloxetine generics dispensed: tertile 3 for number >0	1,705	66.94	293,523	67.75	-0.02
Number of hospital admissions=0	2,438	95.72	415,096	95.82	0.00

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Number of hospital admissions=1	94	3.69	15,561	3.59	0.01
Number of hospital admissions=2	13	0.51	2,183	0.5	0.00
Number of hospital admissions>2	<11	0.08	379	0.09	0.00
Number of outpatient visits=0	181	7.11	28,485	6.58	0.02
Number of outpatient visits: tertile 1 for number >0	243	9.54	39,873	9.2	0.01
Number of outpatient visits: tertile 2 for number >0	628	24.66	108,421	25.03	-0.01
Number of outpatient visits: tertile 3 for number >0	1,495	58.7	256,440	59.19	-0.01
Number of psychiatric hospitalizations Q1	2,461	96.62	419,143	96.75	-0.01
Number of psychiatric hospitalizations Q2	75	2.94	12,182	2.81	0.01
Number of psychiatric hospitalizations Q3	<11	0.35	1,528	0.35	0.00
Number of psychiatric hospitalizations Q4	<11	0.08	366	0.08	0.00
Number of psychiatrist visits=0	975	38.28	158,467	36.58	0.04
Number of psychiatrist visits=1	586	23.01	104,167	24.04	-0.02
Number of psychiatrist visits=2	298	11.7	52,392	12.09	-0.01
Number of psychiatrist visits>2	688	27.01	118,194	27.28	-0.01
Geographic region					
Arkansas	PPD		513	0.12	0.00
Alabama			1,733	0.4	0.00
California	171	6.71	27,795	6.42	0.01
Colorado	PPD		453	0.1	0.00
District of Columbia			505	0.12	0.00
Delaware	63	2.47	10,433	2.41	0.00
Florida	18	0.71	2,948	0.68	0.00
Georgia	13	0.51	2,159	0.5	0.00
Hawaii	PPD		456	0.11	0.00
Iowa	27	1.06	4,754	1.1	0.00
Idaho	PPD		910	0.21	0.00
Illinois	268	10.52	45,631	10.53	0.00
Indiana	241	9.46	41,253	9.52	0.00
Kansas	39	1.53	6,711	1.55	0.00
Kentucky	41	1.61	6,875	1.59	0.00
Louisiana	95	3.73	16,028	3.7	0.00

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Massachusetts	PPD		1,176	0.27	0.00
Maryland	33	1.3	5,515	1.27	0.00
Maine	PPD		1,382	0.32	0.00
Minnesota	160	6.28	27,682	6.39	0.00
Missouri	131	5.14	22,656	5.23	0.00
Mississippi	PPD		1,645	0.38	0.00
North Carolina	59	2.32	9,813	2.27	0.00
North Dakota	25	0.98	4,144	0.96	0.00
Nebraska	26	1.02	4,484	1.03	0.00
New Hampshire	PPD		1,571	0.36	0.00
New Jersey			PPD		
New Mexico	25	0.98	4,199	0.97	0.00
Nevada	PPD		365	0.08	0.00
New York	429	16.84	73,529	16.97	0.00
Ohio	46	1.81	8,055	1.86	0.00
Oklahoma	32	1.26	5,544	1.28	0.00
Oregon	53	2.08	9,214	2.13	0.00
Pennsylvania	17	0.67	2,770	0.64	0.00
Rhode Island	PPD		845	0.19	0.00
South Carolina			899	0.21	0.00
South Dakota	16	0.63	2,637	0.61	0.00
Tennessee	155	6.09	26,654	6.15	0.00
Texas	PPD		844	0.19	0.00
Utah	58	2.28	9,616	2.22	0.00
Virginia	69	2.71	11,695	2.7	0.00
Vermont	29	1.14	5,108	1.18	0.00
Washington	PPD		345	0.08	0.00
Wisconsin	116	4.55	19,531	4.51	0.00
West Virginia	PPD		1,428	0.33	0.00
Wyoming			718	0.17	0.00
Opioids					
buprenorphine	63	2.47	10,081	2.33	0.01

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
butorphanol	<11	0.2	712	0.16	0.01
codeine	484	19	82,984	19.16	0.00
fentanyl	35	1.37	5,164	1.19	0.02
hydrocodone	1,198	47.04	205,497	47.43	-0.01
hydromorphone	37	1.45	5,883	1.36	0.01
levorphanol	<11	0	<11	0	
meperidine	<11	0.31	1,380	0.32	0.00
methadone	35	1.37	5,564	1.28	0.01
morphine	49	1.92	6,827	1.58	0.03
oxycodone	474	18.61	78,318	18.08	0.01
oxymorphone	<11	0.12	542	0.13	0.00
pentazocine	<11	0.12	536	0.12	0.00
propoxyphene	179	7.03	31,295	7.22	-0.01
tapentadol	<11	0.24	759	0.18	0.01
tramadol	456	17.9	76,310	17.61	0.01
Healthcare Utilization, mean (SD)					
Comorbidity Index	1.65	1.89	1.64	1.86	0.01
Morphine equivalents	21859.43	496424.98	18544.59	386820.12	0.01
Number of diagnoses	6.38	4.75	6.47	4.84	-0.02
Number of ED visits	0.81	1.8	0.83	1.72	-0.01
Number of non-duloxetine generics dispensed	5.94	4.35	5.91	4.27	0.01
Number of hospitalizations	0.05	0.25	0.05	0.26	0.00
Number of outpatient visits	6.03	6.82	5.98	6.45	0.01
Number of psychiatric hospitalizations	0.04	0.23	0.04	0.23	0.00
Number of psychiatrist visits	2.47	5.02	2.48	5.07	0.00

15.2. 8. Preterm/SGA- Baseline characteristics of duloxetine exposed vs. SSRI exposed women - early exposure: fully adjusted

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Total	1,713	100.00	50,616	100.00	
Demographics					
Age, mean (SD)	27.81	5.49	27.81	5.57	0.00
Age categorical, N (%)					
<=19	88	5.14	2,545	5.03	0.01
20-24	422	24.64	12,409	24.52	0.00
25-29	588	34.33	17,403	34.38	0.00
30-34	395	23.06	11,719	23.15	0.00
35-39	170	9.92	5,038	9.95	0.00
>=40	50	2.92	1,502	2.97	0.00
Race, N (%)					
White	1,347	78.63	39,841	78.71	0.00
Black/African American	164	9.57	4,789	9.46	0.00
Hispanic/Latino	46	2.69	1,333	2.63	0.00
Asian or Other Pacific	26	1.52	811	1.6	-0.01
American Indian	24	1.4	713	1.41	0.00
Other	72	4.2	2,129	4.21	0.00
Unknown	34	1.98	999	1.97	0.00
Chronic comorbid conditions, N (%)					
Hypertension	159	9.28	4,724	9.33	0.00
Diabetes	125	7.3	3,724	7.36	0.00
Renal Disease	19	1.11	565	1.12	0.00
Obesity Overweight	136	7.94	4,041	7.98	0.00
Comorbidity Index Q1	596	34.79	17,588	34.75	0.00
Comorbidity Index Q2	417	24.34	12,246	24.19	0.00
Comorbidity Index Q3	282	16.46	8,422	16.64	0.00
Comorbidity Index Q4	418	24.4	12,361	24.42	0.00
Infections, N (%)					
Toxoplasmosis	<11	0	<11	0	0.00
Rubella	<11	0	<11	0	
Cytomegalovirus	<11	0	<11	0	

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Herpes	32	1.87	937	1.85	0.00
Syphilis	<11	0.06	28	0.06	0.00
Varicella	<11	0	<11	0	
Parvovirus B19	<11	0	<11	0	
Zika virus other mosquito	<11	0	<11	0	
Lymphocytic choriomeningitis	<11	0	<11	0	
Influenza	16	0.93	449	0.89	0.01
Chlamydia	<11	0.58	305	0.6	0.00
Human papilloma virus	12	0.7	340	0.67	0.00
Gonorrhea	<11	0.58	294	0.58	0.00
HIV	<11	0.41	215	0.42	0.00
Trichomoniasis	19	1.11	549	1.08	0.00
Indications for duloxetine, N (%)					
Depression	928	54.17	27,509	54.35	0.00
Anxiety	568	33.16	16,933	33.45	-0.01
Neuropathic Pain	217	12.67	6,363	12.57	0.00
Fibromyalgia	215	12.55	5,901	11.66	0.03
Non neuropathic Pain	1,057	61.7	31,314	61.86	0.00
Other psychiatric conditions, N (%)					
Sleep disorder	109	6.36	3,197	6.32	0.00
Bipolar disorder	233	13.6	6,984	13.8	-0.01
Psychosis	18	1.05	534	1.05	0.00
Schizophrenia	17	0.99	518	1.02	0.00
Personality disorder	30	1.75	931	1.84	-0.01
Adjustment disorder	20	1.17	580	1.15	0.00
Tobacco use, N (%)	235	13.72	7,008	13.84	0.00
Alcohol abuse or dependence, N (%)	19	1.11	543	1.07	0.00
Drug abuse or dependence, N (%)	57	3.33	1,684	3.33	0.00
Other medication exposures, N (%)					
Benzodiazepines	658	38.41	19,589	38.7	-0.01
Other hypnotics	420	24.52	12,446	24.59	0.00
Barbiturates	100	5.84	2,941	5.81	0.00

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Anxiolytics	90	5.25	2,714	5.36	0.00
Anticonvulsants	457	26.68	13,306	26.29	0.01
Antipsychotics	330	19.26	9,856	19.47	-0.01
SSRIs	<11	0	50,616	100	
SNRIs	65	3.79	1,951	3.85	0.00
Other Antidep	491	28.66	14,548	28.74	0.00
Stimulants	144	8.41	4,200	8.3	0.00
Antidiabetic	69	4.03	2,049	4.05	0.00
Insulin	61	3.56	1,814	3.58	0.00
Antihyperten	259	15.12	7,600	15.01	0.00
Opioid analgesics	1,166	68.07	34,569	68.3	0.00
Triptans	126	7.36	3,695	7.3	0.00
NSAIDs	672	39.23	19,989	39.49	-0.01
Obstetric conditions, N (%)					
Multifetal gestation Flag	65	3.79	1,933	3.82	0.00
Markers of healthcare utilization					
Number of distinct 3 digit ICD 9 codes=0	62	3.62	1,786	3.53	0.00
Number of distinct 3 digit ICD 9 codes: tertile 1 for number >0	304	17.75	8,897	17.58	0.00
Number of distinct 3 digit ICD 9 codes: tertile 2 for number >0	379	22.12	11,348	22.42	-0.01
Number of distinct 3 digit ICD 9 codes: tertile 3 for number >0	968	56.51	28,584	56.47	0.00
Number of ED visits=0	1,012	59.08	29,790	58.85	0.00
Number of ED visits=1	405	23.64	11,996	23.7	0.00
Number of ED visits=2	160	9.34	4,762	9.41	0.00
Number of ED visits>2	136	7.94	4,068	8.04	0.00
Number of non-duloxetine generics dispensed=0	130	7.59	3,849	7.6	0.00
Number of non-duloxetine generics dispensed: tertile 1 for number >0	123	7.18	3,605	7.12	0.00
Number of non-duloxetine generics dispensed: tertile 2 for number >0	365	21.31	10,765	21.27	0.00
Number of non-duloxetine generics dispensed: tertile 3 for number >0	1,095	63.92	32,397	64.01	0.00
Number of hospital admissions=0	1,654	96.56	48,864	96.54	0.00

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Number of hospital admissions=1	52	3.04	1,543	3.05	0.00
Number of hospital admissions=2	<11	0.41	208	0.41	0.00
Number of hospital admissions>2	<11	0	<11	0	-0.01
Number of outpatient visits=0	135	7.88	3,931	7.77	0.00
Number of outpatient visits: tertile 1 for number >0	172	10.04	4,993	9.87	0.01
Number of outpatient visits: tertile 2 for number >0	428	24.99	12,716	25.12	0.00
Number of outpatient visits: tertile 3 for number >0	978	57.09	28,976	57.25	0.00
Number of psychiatric hospitalizations Q1	1,670	97.49	49,354	97.51	0.00
Number of psychiatric hospitalizations Q2	39	2.28	1,139	2.25	0.00
Number of psychiatric hospitalizations Q3	<11	0.23	122	0.24	0.00
Number of psychiatric hospitalizations Q4	<11	0	<11	0	-0.01
Number of psychiatrist visits=0	700	40.86	20,497	40.49	0.01
Number of psychiatrist visits=1	416	24.28	12,326	24.35	0.00
Number of psychiatrist visits=2	191	11.15	5,616	11.1	0.00
Number of psychiatrist visits>2	406	23.7	12,177	24.06	-0.01
Geographic region					
Arkansas	PPD		PPD		0.00
Alabama			56	0.11	0.00
California	120	7.01	3,557	7.03	0.00
Colorado	PPD		56	0.11	0.00
District of Columbia			60	0.12	0.00
Delaware	43	2.51	1,264	2.5	0.00
Florida	PPD		294	0.58	0.00
Georgia			231	0.46	0.00
Hawaii			60	0.12	0.00
Iowa	14	0.82	403	0.8	0.00
Idaho	PPD		PPD		0.00
Illinois	165	9.63	4,817	9.52	0.00
Indiana	178	10.39	5,260	10.39	0.00
Kansas	25	1.46	747	1.48	0.00
Kentucky	24	1.4	695	1.37	0.00
Louisiana	62	3.62	1,869	3.69	0.00

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Massachusetts	PPD		145	0.29	0.00
Maryland	21	1.23	617	1.22	0.00
Maine	PPD		143	0.28	0.00
Minnesota	98	5.72	2,890	5.71	0.00
Missouri	90	5.25	2,723	5.38	-0.01
Mississippi	PPD		204	0.4	0.00
North Carolina	40	2.34	1,190	2.35	0.00
North Dakota	18	1.05	526	1.04	0.00
Nebraska	15	0.88	438	0.87	0.00
New Hampshire	PPD		206	0.41	0.00
New Jersey			PPD		0.00
New Mexico	15	0.88	434	0.86	0.00
Nevada	PPD		28	0.06	0.00
New York	312	18.21	9,316	18.41	0.00
Ohio	25	1.46	740	1.46	0.00
Oklahoma	14	0.82	409	0.81	0.00
Oregon	37	2.16	1,096	2.16	0.00
Pennsylvania	PPD		314	0.62	0.00
Rhode Island			110	0.22	0.00
South Carolina			153	0.3	0.00
South Dakota			291	0.57	0.00
Tennessee	111	6.48	3,235	6.39	0.00
Texas	PPD		83	0.16	0.00
Utah	37	2.16	1,115	2.2	0.00
Virginia	53	3.09	1,571	3.1	0.00
Vermont	23	1.34	683	1.35	0.00
Washington	PPD		PPD		0.00
Wisconsin	80	4.67	2,317	4.58	0.00
West Virginia	PPD		211	0.42	0.00
Wyoming			57	0.11	0.00
Opioids					
buprenorphine	42	2.45	1,192	2.35	0.01

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
butorphanol	<11	0.18	82	0.16	0.00
codeine	304	17.75	9,009	17.8	0.00
fentanyl	21	1.23	590	1.16	0.01
hydrocodone	794	46.35	23,737	46.9	-0.01
hydromorphone	25	1.46	704	1.39	0.01
levorphanol	<11	0	<11	0	
meperidine	<11	0.35	187	0.37	0.00
methadone	22	1.28	637	1.26	0.00
morphine	33	1.93	888	1.75	0.01
oxycodone	312	18.21	9,163	18.1	0.00
oxymorphone	<11	0.18	96	0.19	0.00
pentazocine	<11	0.12	61	0.12	0.00
propoxyphene	111	6.48	3,353	6.62	-0.01
tapentadol	<11	0.23	109	0.21	0.00
tramadol	294	17.16	8,746	17.28	0.00
Healthcare Utilization, mean (SD)					
Comorbidity Index	1.61	1.85	1.62	1.86	0.00
Morphine equivalents	28948.06	602016.08	14919.87	319322.93	0.03
Number of diagnoses	6.18	4.58	6.19	4.67	0.00
Number of ED visits	0.8	1.96	0.81	1.65	-0.01
Number of non-duloxetine generics dispensed	5.53	4.16	5.91	4.51	-0.09
Number of hospitalizations	0.04	0.21	0.04	0.21	0.00
Number of outpatient visits	5.69	6.56	5.65	6.12	0.01
Number of psychiatric hospitalizations	0.03	0.18	0.03	0.18	0.00
Number of psychiatrist visits	2.2	4.87	2.18	4.62	0.00

15.2. 9. Preterm/SGA- Baseline characteristics of duloxetine exposed vs. venlafaxine exposed women - early exposure: fully adjusted

	Duloxetine	Duloxetine	Venlafaxine	Venlafaxine	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Total	2,429	100.00	5,864	100.00	
Demographics					
Age, mean (SD)	27.78	5.51	27.79	5.52	0.00
Age categorical, N (%)					
<=19	119	4.9	279	4.75	0.01
20-24	616	25.36	1,491	25.43	0.00
25-29	830	34.17	2,011	34.29	0.00
30-34	543	22.35	1,309	22.32	0.00
35-39	254	10.46	595	10.14	0.01
>=40	67	2.76	180	3.06	-0.02
Race, N (%)					
White	1,915	78.84	4,620	78.79	0.00
Black/African American	219	9.02	518	8.84	0.01
Hispanic/Latino	71	2.92	162	2.76	0.01
Asian or Other Pacific	33	1.36	91	1.56	-0.02
American Indian	32	1.32	80	1.37	0.00
Other	108	4.45	269	4.59	-0.01
Unknown	51	2.1	123	2.1	0.00
Chronic comorbid conditions, N (%)					
Hypertension	224	9.22	556	9.49	-0.01
Diabetes	176	7.25	450	7.67	-0.02
Renal Disease	29	1.19	70	1.19	0.00
Obesity Overweight	196	8.07	485	8.27	-0.01
Comorbidity Index Q1	813	33.47	1,990	33.94	-0.01
Comorbidity Index Q2	594	24.45	1,430	24.39	0.00
Comorbidity Index Q3	425	17.5	1,030	17.57	0.00
Comorbidity Index Q4	597	24.58	1,413	24.1	0.01
Infections, N (%)					
Toxoplasmosis	<11	0	<11	0	
Rubella	<11	0	<11	0	
Cytomegalovirus	<11	0	<11	0	

	Duloxetine	Duloxetine	Venlafaxine	Venlafaxine	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Herpes	46	1.89	99	1.69	0.02
Syphilis	<11	0.04	<11	0.04	0.00
Varicella	<11	0	<11	0	
Parvovirus B19	<11	0	<11	0	
Zika virus other mosquito	<11	0	<11	0	
Lymphocytic choriomeningitis	<11	0	<11	0	
Influenza	24	0.99	53	0.9	0.01
Chlamydia	13	0.54	34	0.58	-0.01
Human papilloma virus	24	0.99	55	0.95	0.00
Gonorrhea	14	0.58	30	0.51	0.01
HIV	<11	0.37	26	0.44	-0.01
Trichomoniasis	26	1.07	65	1.11	0.00
Indications for duloxetine, N (%)					
Depression	1,413	58.17	3,489	59.49	-0.03
Anxiety	865	35.61	2,157	36.79	-0.02
Neuropathic Pain	313	12.89	757	12.91	0.00
Fibromyalgia	309	12.72	707	12.05	0.02
Non neuropathic Pain	1,475	60.72	3,553	60.59	0.00
Other psychiatric conditions, N (%)					
Sleep disorder	159	6.55	388	6.61	0.00
Bipolar disorder	350	14.41	879	15	-0.02
Psychosis	28	1.15	70	1.2	0.00
Schizophrenia	27	1.11	67	1.13	0.00
Personality disorder	58	2.39	149	2.54	-0.01
Adjustment disorder	29	1.19	76	1.3	-0.01
Tobacco use, N (%)	341	14.04	833	14.2	0.00
Alcohol abuse or dependence, N (%)	38	1.56	93	1.59	0.00
Drug abuse or dependence, N (%)	93	3.83	230	3.92	0.00
Other medication exposures, N (%)					
Benzodiazepines	981	40.39	2,449	41.76	-0.03
Other hypnotics	649	26.72	1,618	27.59	-0.02
Barbiturates	159	6.55	388	6.61	0.00

	Duloxetine	Duloxetine	Venlafaxine	Venlafaxine	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Anxiolytics	146	6.01	375	6.4	-0.02
Anticonvulsants	655	26.97	1,539	26.24	0.02
Antipsychotics	516	21.24	1,277	21.77	-0.01
SSRIs	781	32.15	1,918	32.7	-0.01
SNRIs	<11	0	5,864	100	
Other Antidep	721	29.68	1,766	30.11	-0.01
Stimulants	192	7.9	474	8.08	-0.01
Antidiabetic	99	4.08	236	4.03	0.00
Insulin	88	3.62	228	3.9	-0.01
Antihyperten	381	15.69	913	15.57	0.00
Opioid analgesics	1,646	67.76	3,964	67.59	0.00
Triptans	189	7.78	468	7.98	-0.01
NSAIDs	977	40.22	2,360	40.24	0.00
Obstetric conditions, N (%)					
Multifetal gestation Flag	85	3.5	205	3.5	0.00
Markers of healthcare utilization					
Number of distinct 3 digit ICD 9 codes=0	79	3.25	191	3.25	0.00
Number of distinct 3 digit ICD 9 codes: tertile 1 for number >0	420	17.29	995	16.97	0.01
Number of distinct 3 digit ICD 9 codes: tertile 2 for number >0	523	21.53	1,286	21.92	-0.01
Number of distinct 3 digit ICD 9 codes: tertile 3 for number >0	1,407	57.93	3,393	57.85	0.00
Number of ED visits=0	1,460	60.11	3,527	60.15	0.00
Number of ED visits=1	531	21.86	1,229	20.95	0.02
Number of ED visits=2	228	9.39	562	9.59	-0.01
Number of ED visits>2	210	8.65	545	9.3	-0.02
Number of non-duloxetine generics dispensed=0	152	6.26	392	6.68	-0.02
Number of non-duloxetine generics dispensed: tertile 1 for number >0	170	7	402	6.86	0.01
Number of non-duloxetine generics dispensed: tertile 2 for number >0	491	20.21	1,163	19.84	0.01
Number of non-duloxetine generics dispensed: tertile 3 for number >0	1,616	66.53	3,907	66.62	0.00
Number of hospital admissions=0	2,328	95.84	5,617	95.79	0.00

	Duloxetine	Duloxetine	Venlafaxine	Venlafaxine	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Number of hospital admissions=1	87	3.58	211	3.61	0.00
Number of hospital admissions=2	12	0.49	32	0.54	-0.01
Number of hospital admissions>2	<11	0.08	<11	0.07	0.00
Number of outpatient visits=0	175	7.2	420	7.16	0.00
Number of outpatient visits: tertile 1 for number >0	233	9.59	544	9.27	0.01
Number of outpatient visits: tertile 2 for number >0	607	24.99	1,480	25.24	-0.01
Number of outpatient visits: tertile 3 for number >0	1,414	58.21	3,420	58.33	0.00
Number of psychiatric hospitalizations Q1	2,351	96.79	5,682	96.9	-0.01
Number of psychiatric hospitalizations Q2	67	2.76	152	2.6	0.01
Number of psychiatric hospitalizations Q3	<11	0.37	25	0.43	-0.01
Number of psychiatric hospitalizations Q4	<11	0.08	<11	0.07	0.00
Number of psychiatrist visits=0	937	38.58	2,236	38.13	0.01
Number of psychiatrist visits=1	566	23.3	1,355	23.1	0.00
Number of psychiatrist visits=2	285	11.73	674	11.5	0.01
Number of psychiatrist visits>2	641	26.39	1,599	27.27	-0.02
Geographic region					
Arkansas	PPD		PPD		-0.01
Alabama			24	0.41	-0.01
California	165	6.79	390	6.65	0.01
Colorado	PPD		PPD		0.00
District of Columbia					0.00
Delaware	61	2.51	139	2.36	0.01
Florida	17	0.7	34	0.58	0.01
Georgia	PPD		29	0.49	0.00
Hawaii			PPD		0.00
Iowa	26	1.07	64	1.1	0.00
Idaho	PPD		PPD		0.00
Illinois	261	10.75	613	10.46	0.01
Indiana	233	9.59	566	9.65	0.00
Kansas	39	1.61	102	1.74	-0.01
Kentucky	40	1.65	93	1.59	0.00
Louisiana	92	3.79	221	3.77	0.00

	Duloxetine	Duloxetine	Venlafaxine	Venlafaxine	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Massachusetts	PPD		17	0.29	-0.01
Maryland	33	1.36	84	1.43	-0.01
Maine	PPD		19	0.32	0.00
Minnesota	149	6.13	377	6.43	-0.01
Missouri	124	5.1	303	5.17	0.00
Mississippi	PPD		23	0.4	0.00
North Carolina	58	2.39	140	2.38	0.00
North Dakota	24	0.99	54	0.92	0.01
Nebraska	25	1.03	59	1	0.00
New Hampshire	PPD		21	0.36	0.00
New Jersey			PPD		
New Mexico	22	0.91	50	0.86	0.01
Nevada	PPD		PPD		0.00
New York	414	17.04	1,015	17.32	-0.01
Ohio	42	1.73	105	1.79	0.00
Oklahoma	30	1.24	68	1.17	0.01
Oregon	51	2.1	118	2.01	0.01
Pennsylvania	17	0.7	42	0.71	0.00
Rhode Island	PPD		PPD		0.01
South Carolina					0.01
South Dakota	16	0.66	36	0.62	0.00
Tennessee	141	5.8	342	5.84	0.00
Texas	PPD		PPD		0.01
Utah	54	2.22	149	2.53	-0.02
Virginia	62	2.55	157	2.68	-0.01
Vermont	28	1.15	68	1.16	0.00
Washington	PPD		PPD		0.00
Wisconsin	107	4.41	239	4.08	0.02
West Virginia	PPD		21	0.36	0.00
Wyoming			PPD		0.00
Opioids					
buprenorphine	58	2.39	144	2.46	0.00

	Duloxetine	Duloxetine	Venlafaxine	Venlafaxine	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
butorphanol	<11	0.21	14	0.24	-0.01
codeine	460	18.94	1,116	19.03	0.00
fentanyl	34	1.4	93	1.59	-0.02
hydrocodone	1,140	46.93	2,781	47.43	-0.01
hydromorphone	29	1.19	73	1.24	0.00
levorphanol	<11	0	<11	0	
meperidine	<11	0.29	17	0.29	0.00
methadone	31	1.28	82	1.41	-0.01
morphine	45	1.85	114	1.94	-0.01
oxycodone	443	18.24	1,066	18.17	0.00
oxymorphone	<11	0.12	<11	0.13	0.00
pentazocine	<11	0.12	<11	0.12	0.00
propoxyphene	168	6.92	417	7.11	-0.01
tapentadol	<11	0.16	<11	0.1	0.02
tramadol	430	17.7	1,034	17.64	0.00
Healthcare Utilization, mean (SD)					
Comorbidity Index	1.65	1.88	1.61	1.8	0.02
Morphine equivalents	22568.16	508263.05	18118.59	491222.65	0.01
Number of diagnoses	6.32	4.69	6.44	4.99	-0.02
Number of ED visits	0.8	1.81	0.86	1.72	-0.04
Number of non-duloxetine generics dispensed	5.86	4.3	6.38	4.86	-0.11
Number of hospitalizations	0.05	0.25	0.05	0.26	-0.01
Number of outpatient visits	5.93	6.56	5.89	6.02	0.01
Number of psychiatric hospitalizations	0.04	0.23	0.04	0.23	0.00
Number of psychiatrist visits	2.44	4.89	2.42	4.74	0.00

15.2. 10. Preterm/SGA- Baseline characteristics of duloxetine exposed vs. unexposed women - late exposure: unadjusted

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Total	880	100.00	1,364,101	100.00	
Demographics					
Age, mean (SD)	28.47	5.52	24.96	5.37	0.64
Age categorical, N (%)					
<=19	39	4.43	210,275	15.41	-0.37
20-24	183	20.80	527,166	38.65	-0.40
25-29	305	34.66	361,427	26.50	0.18
30-34	215	24.43	175,448	12.86	0.30
35-39	111	12.61	73,262	5.37	0.26
>=40	27	3.07	16,523	1.21	0.13
Race, N (%)					
White	703	79.89	550,387	40.35	0.88
Black or African American	78	8.86	423,293	31.03	-0.58
Hispanic or Latino	23	2.61	196,304	14.39	-0.43
Asian or Other Pacific Islander	15	1.70	59,463	4.36	-0.16
American Indian	17	1.93	22,412	1.64	0.02
Other	27	3.07	78,849	5.78	-0.13
Unknown	17	1.93	33,393	2.45	-0.04
Chronic comorbid conditions, N (%)					
Hypertension	121	13.75	70,915	5.20	0.30
Diabetes	161	18.30	145,182	10.64	0.22
Renal Disease	16	1.82	13,091	0.96	0.07
Obesity Overweight	94	10.68	69,073	5.06	0.21
Comorbidity Index Q1	275	31.25	723,914	53.07	-0.45
Comorbidity Index Q2	206	23.41	334,820	24.55	-0.03
Comorbidity Index Q3	145	16.48	160,009	11.73	0.14
Comorbidity Index Q4	254	28.86	145,358	10.66	0.47
Infections, N (%)					
Toxoplasmosis	<11	0.00	342	0.03	-0.02
Rubella	<11	0.11	223	0.02	0.04
Cytomegalovirus	<11	0.00	135	0.01	-0.01

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Herpes	20	2.27	20,011	1.47	0.06
Syphilis	<11	0.11	2,391	0.18	-0.02
Varicella	<11	0.11	466	0.03	0.03
Parvovirus B19	<11	0.00	145	0.01	-0.01
Zika virus other mosquito	<11	0.00	<11	0.00	0.00
Lymphocytic choriomeningitis	<11	0.00	15	0.00	0.00
Influenza	12	1.36	16,899	1.24	0.01
Chlamydia	<11	0.45	15,239	1.12	-0.08
Human papilloma virus	<11	1.14	10,411	0.76	0.04
Gonorrhea	<11	0.80	16,404	1.20	-0.04
HIV	<11	0.57	6,133	0.45	0.02
Trichomoniasis	<11	0.91	29,847	2.19	-0.10
Indications for duloxetine, N (%)					
Depression	504	57.27	111,783	8.19	1.23
Anxiety	347	39.43	72,699	5.33	0.90
Neuropathic Pain	128	14.55	36,921	2.71	0.43
Fibromyalgia	102	11.59	18,556	1.36	0.42
Non neuropathic Pain	519	58.98	328,770	24.10	0.76
Other psychiatric conditions, N (%)					
Sleep disorder	62	7.05	14,583	1.07	0.31
Bipolar disorder	148	16.82	25,008	1.83	0.53
Psychosis	17	1.93	4,125	0.30	0.16
Schizophrenia	<11	1.14	3,299	0.24	0.11
Personality disorder	28	3.18	4,044	0.30	0.22
Adjustment disorder	13	1.48	7,863	0.58	0.09
Tobacco use, N (%)	186	21.14	93,807	6.88	0.42
Alcohol abuse or dependence, N (%)	14	1.59	6,808	0.50	0.11
Drug abuse or dependence, N (%)	33	3.75	19,434	1.42	0.15
Other medication exposures, N (%)					
Benzodiazepines	388	44.09	55,340	4.06	1.06
Other hypnotics	315	35.80	95,923	7.03	0.75
Barbiturates	76	8.64	30,525	2.24	0.28

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Anxiolytics	77	8.75	8,735	0.64	0.39
Anticonvulsants	242	27.50	35,072	2.57	0.74
Antipsychotics	210	23.86	23,218	1.70	0.70
SSRIs	259	29.43	119,733	8.78	0.54
SNRIs	52	5.91	12,354	0.91	0.28
Other Antidep	267	30.34	52,644	3.86	0.75
Stimulants	82	9.32	12,532	0.92	0.39
Antidiabetic	49	5.57	27,968	2.05	0.18
Insulin	59	6.70	29,733	2.18	0.22
Antihyperten	206	23.41	83,411	6.11	0.50
Opioid analgesics	634	72.05	452,778	33.19	0.84
Triptans	68	7.73	18,526	1.36	0.31
NSAIDs	337	38.30	268,090	19.65	0.42
Obstetric conditions, N (%)					
Multifetal gestation Flag	34	3.86	50,460	3.70	0.01
Markers of healthcare utilization					
Number of distinct 3 digit ICD 9 codes=0	50	5.68	406,370	29.79	-0.67
Number of distinct 3 digit ICD 9 codes: tertile 1 for number >0	171	19.43	404,378	29.64	-0.24
Number of distinct 3 digit ICD 9 codes: tertile 2 for number >0	197	22.39	246,494	18.07	0.11
Number of distinct 3 digit ICD 9 codes: tertile 3 for number >0	462	52.50	306,859	22.50	0.65
Number of ED visits=0	551	62.61	1,063,640	77.97	-0.34
Number of ED visits=1	178	20.23	199,901	14.65	0.15
Number of ED visits=2	73	8.30	63,554	4.66	0.15
Number of ED visits>2	78	8.86	37,006	2.71	0.27
Number of non-duloxetine generics dispensed=0	<11	0.45	176,545	12.94	-0.52
Number of non-duloxetine generics dispensed: tertile 1 for number >0	59	6.70	327,385	24.00	-0.49
Number of non-duloxetine generics dispensed: tertile 2 for number >0	121	13.75	432,252	31.69	-0.44
Number of non-duloxetine generics dispensed: tertile 3 for number >0	696	79.09	427,919	31.37	1.09
Number of hospital admissions=0	791	89.89	1,280,287	93.86	-0.15

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Number of hospital admissions=1	68	7.73	69,900	5.12	0.11
Number of hospital admissions=2	18	2.05	10,766	0.79	0.11
Number of hospital admissions>2	<11	0.34	3,148	0.23	0.02
Number of outpatient visits=0	93	10.57	505,877	37.09	-0.65
Number of outpatient visits: tertile 1 for number >0	95	10.80	273,726	20.07	-0.26
Number of outpatient visits: tertile 2 for number >0	217	24.66	311,462	22.83	0.04
Number of outpatient visits: tertile 3 for number >0	475	53.98	273,036	20.02	0.75
Number of psychiatric hospitalizations Q1	852	96.82	1,356,154	99.42	-0.19
Number of psychiatric hospitalizations Q2	24	2.73	7,203	0.53	0.17
Number of psychiatric hospitalizations Q3	<11	0.45	631	0.05	0.08
Number of psychiatric hospitalizations Q4	<11	0.00	113	0.01	-0.01
Number of psychiatrist visits=0	379	43.07	1,229,927	90.16	-1.15
Number of psychiatrist visits=1	200	22.73	68,252	5.00	0.53
Number of psychiatrist visits=2	89	10.11	23,336	1.71	0.36
Number of psychiatrist visits>2	212	24.09	42,586	3.12	0.64
Geographic region					
Arkansas	PPD		1,044	0.08	-0.04
Alabama	PPD		5,693	0.42	-0.01
California	61	6.93	272,154	19.95	-0.39
Colorado	PPD		5,195	0.38	-0.03
District of Columbia	PPD		637	0.05	-0.03
Delaware	24	2.73	12,128	0.89	0.14
Florida	PPD		30,025	2.20	-0.10
Georgia	PPD		30,232	2.22	-0.11
Hawaii	PPD		8,989	0.66	-0.09
Iowa	PPD		8,207	0.60	0.04
Idaho	PPD		1,374	0.10	-0.04
Illinois	74	8.41	131,825	9.66	-0.04
Indiana	82	9.32	47,025	3.45	0.24
Kansas	PPD		10,649	0.78	0.05
Kentucky	19	2.16	25,813	1.89	0.02
Louisiana	26	2.95	30,486	2.23	0.05

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Massachusetts	PPD		7,814	0.57	-0.05
Maryland	13	1.48	26,036	1.91	-0.03
Maine	PPD		3,678	0.27	0.06
Minnesota	78	8.86	49,437	3.62	0.22
Missouri	50	5.68	37,840	2.77	0.14
Mississippi	PPD		21,335	1.56	-0.08
North Carolina	20	2.27	17,102	1.25	0.08
North Dakota	PPD		3,598	0.26	0.03
Nebraska			5,556	0.41	0.07
New Hampshire			3,387	0.25	0.03
New Jersey			14,266	1.05	-0.10
New Mexico			19,871	1.46	-0.03
Nevada			1,302	0.10	-0.04
New York	130	14.77	227,209	16.66	-0.05
Ohio	13	1.48	21,667	1.59	-0.01
Oklahoma	PPD		17,818	1.31	-0.01
Oregon	17	1.93	11,625	0.85	0.09
Pennsylvania	PPD		19,752	1.45	-0.09
Rhode Island			2,495	0.18	-0.02
South Carolina			1,785	0.13	0.04
South Dakota			5,744	0.42	-0.03
Tennessee	40	4.55	106,641	7.82	-0.14
Texas	PPD		4,670	0.34	-0.05
Utah	34	3.86	7,564	0.55	0.23
Virginia	32	3.64	28,754	2.11	0.09
Vermont	PPD		7,861	0.58	0.07
Washington			1,487	0.11	0.00
Wisconsin	44	5.00	63,478	4.65	0.02
West Virginia	PPD		1,777	0.13	0.02
Wyoming			1,076	0.08	0.04
Opioids					
buprenorphine	34	3.86	4,610	0.34	0.25

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
butorphanol	<11	0.00	236	0.02	-0.02
codeine	214	24.32	192,507	14.11	0.26
fentanyl	20	2.27	1,112	0.08	0.20
hydrocodone	422	47.95	258,949	18.98	0.64
hydromorphone	19	2.16	2,548	0.19	0.18
levorphanol	<11	0.00	<11	0.00	0.00
meperidine	<11	0.34	1,925	0.14	0.04
methadone	11	1.25	1,502	0.11	0.14
morphine	25	2.84	1,538	0.11	0.23
oxycodone	206	23.41	77,601	5.69	0.52
oxymorphone	<11	0.34	133	0.01	0.08
pentazocine	<11	0.23	383	0.03	0.06
propoxyphene	75	8.52	43,741	3.21	0.23
tapentadol	<11	0.00	94	0.01	-0.01
tramadol	157	17.84	45,080	3.30	0.49
Healthcare Utilization, mean (SD)					
Comorbidity Index	1.79	1.96	0.93	1.41	0.51
Morphine equivalents	7801.9	37570.8	1206.61	85267.33	0.10
Number of diagnoses	5.91	4.75	2.81	3.35	0.75
Number of ED visits	0.76	1.44	0.35	0.89	0.34
Number of non-duloxetine generics dispensed	10.5	6.29	4.49	4	1.14
Number of hospitalizations	0.13	0.42	0.08	0.34	0.14
Number of outpatient visits	5.72	7.66	2.13	3.48	0.60
Number of psychiatric hospitalizations	0.04	0.21	0.01	0.09	0.18
Number of psychiatrist visits	2.33	5.11	0.33	2.17	0.51

15.2. 11. Preterm/SGA- Baseline characteristics of duloxetine exposed vs. SSRI exposed women - late exposure: unadjusted

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Total	621	100.00	46,098	100.00	
Demographics					
Age, mean (SD)	28.41	5.31	25.99	5.34	0.46
Age categorical, N (%)					
<=19	30	4.83	4,312	9.35	-0.18
20-24	118	19.00	16,590	35.99	-0.39
25-29	224	36.07	14,068	30.52	0.12
30-34	161	25.93	7,398	16.05	0.24
35-39	72	11.59	3,106	6.74	0.17
>=40	16	2.58	624	1.35	0.09
Race, N (%)					
White	504	81.16	33,196	72.01	0.22
Black/African American	53	8.53	6,371	13.82	-0.17
Hispanic/Latino	15	2.42	2,615	5.67	-0.17
Asian or Other Pacific	PPD		414	0.90	0.05
American Indian	PPD		895	1.94	0.00
Other	18	2.90	1,488	3.23	-0.02
Unknown	PPD		1,119	2.43	-0.06
Chronic comorbid conditions, N (%)					
Hypertension	86	13.85	3,655	7.93	0.19
Diabetes	108	17.39	6,467	14.03	0.09
Renal Disease	<11	1.45	717	1.56	-0.01
Obesity Overweight	63	10.14	3,121	6.77	0.12
Comorbidity Index Q1	196	31.56	20,058	43.51	-0.25
Comorbidity Index Q2	152	24.48	11,627	25.22	-0.02
Comorbidity Index Q3	99	15.94	6,982	15.15	0.02
Comorbidity Index Q4	174	28.02	7,431	16.12	0.29
Infections, N (%)					
Toxoplasmosis	<11	0.00	11	0.02	-0.02
Rubella	<11	0.00	<11	0.01	-0.01
Cytomegalovirus	<11	0.00	<11	0.02	-0.02

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Herpes	15	2.42	1,015	2.20	0.01
Syphilis	<11	0.16	59	0.13	0.01
Varicella	<11	0.16	22	0.05	0.04
Parvovirus B19	<11	0.00	<11	0.02	-0.02
Zika virus other mosquito	<11	0.00	<11	0.00	
Lymphocytic choriomeningitis	<11	0.00	<11	0.00	-0.01
Influenza	<11	1.29	890	1.93	-0.05
Chlamydia	<11	0.32	346	0.75	-0.06
Human papilloma virus	<11	0.97	472	1.02	-0.01
Gonorrhea	<11	0.81	352	0.76	0.00
HIV	<11	0.64	205	0.44	0.03
Trichomoniasis	<11	0.81	802	1.74	-0.08
Indications for duloxetine, N (%)					
Depression	329	52.98	21,062	45.69	0.15
Anxiety	231	37.20	12,041	26.12	0.24
Neuropathic Pain	78	12.56	2,938	6.37	0.21
Fibromyalgia	65	10.47	1,426	3.09	0.30
Non neuropathic Pain	351	56.52	18,878	40.95	0.32
Other psychiatric conditions, N (%)					
Sleep disorder	40	6.44	1,859	4.03	0.11
Bipolar disorder	102	16.43	4,402	9.55	0.21
Psychosis	<11	1.29	593	1.29	0.00
Schizophrenia	<11	1.13	617	1.34	-0.02
Personality disorder	20	3.22	853	1.85	0.09
Adjustment disorder	<11	1.61	716	1.55	0.00
Tobacco use, N (%)	135	21.74	6,946	15.07	0.17
Alcohol abuse or dependence, N (%)	<11	1.29	903	1.96	-0.05
Drug abuse or dependence, N (%)	17	2.74	2,026	4.39	-0.09
Other medication exposures, N (%)					
Benzodiazepines	254	40.90	9,710	21.06	0.44
Other hypnotics	212	34.14	9,496	20.60	0.31
Barbiturates	45	7.25	2,584	5.61	0.07

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Anxiolytics	46	7.41	1,707	3.70	0.16
Anticonvulsants	167	26.89	4,801	10.41	0.43
Antipsychotics	143	23.03	5,023	10.90	0.33
SSRIs	<11	0.00	46,098	100.00	
SNRIs	32	5.15	1,876	4.07	0.05
Other Antidep	177	28.50	8,114	17.60	0.26
Stimulants	61	9.82	1,924	4.17	0.22
Antidiabetic	34	5.48	1,595	3.46	0.10
Insulin	42	6.76	1,706	3.70	0.14
Antihyperten	139	22.38	5,669	12.30	0.27
Opioid analgesics	433	69.73	26,388	57.24	0.26
Triptans	39	6.28	1,719	3.73	0.12
NSAIDs	226	36.39	13,557	29.41	0.15
Obstetric conditions, N (%)					
Multifetal gestation Flag	25	4.03	2,001	4.34	-0.02
Markers of healthcare utilization					
Number of distinct 3 digit ICD 9 codes=0	42	6.76	6,480	14.06	-0.24
Number of distinct 3 digit ICD 9 codes: tertile 1 for number >0	130	20.93	10,990	23.84	-0.07
Number of distinct 3 digit ICD 9 codes: tertile 2 for number >0	139	22.38	9,600	20.83	0.04
Number of distinct 3 digit ICD 9 codes: tertile 3 for number >0	310	49.92	19,028	41.28	0.17
Number of ED visits=0	396	63.77	31,057	67.37	-0.08
Number of ED visits=1	129	20.77	8,739	18.96	0.05
Number of ED visits=2	49	7.89	3,447	7.48	0.02
Number of ED visits>2	47	7.57	2,855	6.19	0.05
Number of non-duloxetine generics dispensed=0	<11	0.48	1,164	2.53	-0.17
Number of non-duloxetine generics dispensed: tertile 1 for number >0	50	8.05	4,539	9.85	-0.06
Number of non-duloxetine generics dispensed: tertile 2 for number >0	97	15.62	11,565	25.09	-0.24
Number of non-duloxetine generics dispensed: tertile 3 for number >0	471	75.85	28,830	62.54	0.29
Number of hospital admissions=0	578	93.08	41,758	90.59	0.09

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Number of hospital admissions=1	36	5.80	3,521	7.64	-0.07
Number of hospital admissions=2	<11	0.97	577	1.25	-0.03
Number of hospital admissions>2	<11	0.16	242	0.52	-0.06
Number of outpatient visits=0	77	12.40	8,862	19.22	-0.19
Number of outpatient visits: tertile 1 for number >0	71	11.43	7,525	16.32	-0.14
Number of outpatient visits: tertile 2 for number >0	158	25.44	11,795	25.59	0.00
Number of outpatient visits: tertile 3 for number >0	315	50.72	17,916	38.87	0.24
Number of psychiatric hospitalizations Q1	611	98.39	45,121	97.88	0.04
Number of psychiatric hospitalizations Q2	<11	1.61	868	1.88	-0.02
Number of psychiatric hospitalizations Q3	<11	0.00	86	0.19	-0.06
Number of psychiatric hospitalizations Q4	<11	0.00	23	0.05	-0.03
Number of psychiatrist visits=0	284	45.73	29,237	63.42	-0.36
Number of psychiatrist visits=1	147	23.67	7,187	15.59	0.20
Number of psychiatrist visits=2	59	9.50	3,256	7.06	0.09
Number of psychiatrist visits>2	131	21.10	6,418	13.92	0.19
Geographic region					
Arkansas	PPD		43	0.09	-0.04
Alabama	PPD		288	0.62	-0.11
California	46	7.41	3,485	7.56	-0.01
Colorado	PPD		283	0.61	-0.04
District of Columbia	PPD		16	0.03	-0.03
Delaware	14	2.25	416	0.90	0.11
Florida	PPD		852	1.85	-0.07
Georgia	PPD		937	2.03	-0.16
Hawaii	PPD		47	0.10	0.02
Iowa	PPD		634	1.38	-0.07
Idaho	PPD		184	0.40	-0.09
Illinois	51	8.21	3,939	8.54	-0.01
Indiana	63	10.14	2,360	5.12	0.19
Kansas	PPD		584	1.27	0.03
Kentucky	PPD		1,118	2.43	-0.05
Louisiana	19	3.06	757	1.64	0.09

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Massachusetts	PPD		447	0.97	-0.08
Maryland			701	1.52	-0.01
Maine			300	0.65	0.02
Minnesota	59	9.50	3,410	7.40	0.08
Missouri	33	5.31	1,766	3.83	0.07
Mississippi	PPD		490	1.06	-0.03
North Carolina	15	2.42	734	1.59	0.06
North Dakota	PPD		275	0.60	0.01
Nebraska			356	0.77	0.00
New Hampshire			366	0.79	-0.02
New Jersey			215	0.47	-0.10
New Mexico			717	1.56	-0.04
Nevada			73	0.16	-0.06
New York	97	15.62	4,479	9.72	0.18
Ohio	PPD		1,339	2.90	-0.16
Oklahoma			772	1.67	-0.10
Oregon			923	2.00	-0.01
Pennsylvania			1,277	2.77	-0.16
Rhode Island			187	0.41	-0.05
South Carolina			88	0.19	0.05
South Dakota			285	0.62	-0.07
Tennessee	28	4.51	3,879	8.41	-0.16
Texas	PPD		143	0.31	-0.03
Utah	19	3.06	795	1.72	0.09
Virginia	23	3.70	1,115	2.42	0.07
Vermont	PPD		688	1.49	0.01
Washington	34	5.48	116	0.25	-0.07
Wisconsin			3,998	8.67	-0.12
West Virginia			157	0.34	-0.04
Wyoming	PPD		64	0.14	0.01
Opioids					
buprenorphine	26	4.19	614	1.33	0.17

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
butorphanol	<11	0.00	22	0.05	-0.03
codeine	136	21.90	11,388	24.70	-0.07
fentanyl	13	2.09	145	0.31	0.16
hydrocodone	288	46.38	16,947	36.76	0.20
hydromorphone	15	2.42	294	0.64	0.15
levorphanol	<11	0.00	<11	0.00	-0.01
meperidine	<11	0.16	208	0.45	-0.05
methadone	<11	0.81	215	0.47	0.04
morphine	16	2.58	204	0.44	0.18
oxycodone	134	21.58	6,291	13.65	0.21
oxymorphone	<11	0.48	14	0.03	0.09
pentazocine	<11	0.16	39	0.08	0.02
propoxyphene	40	6.44	3,703	8.03	-0.06
tapentadol	<11	0.00	11	0.02	-0.02
tramadol	105	16.91	3,741	8.12	0.27
Healthcare Utilization, mean (SD)					
Comorbidity Index	1.73	1.88	1.24	1.63	0.28
Morphine equivalents	8208.62	43083.78	3931.6	167001.13	0.04
Number of diagnoses	5.55	4.47	4.65	4.35	0.21
Number of ED visits	0.71	1.4	0.61	1.43	0.07
Number of non-duloxetine generics dispensed	9.68	5.69	7.99	5.4	0.31
Number of hospitalizations	0.08	0.32	0.12	0.45	-0.10
Number of outpatient visits	5.2	7.17	3.93	5.3	0.20
Number of psychiatric hospitalizations	0.02	0.13	0.02	0.18	-0.05
Number of psychiatrist visits	1.99	4.82	1.35	4.05	0.14

15.2. 12. Preterm/SGA- Baseline characteristics of duloxetine exposed vs. venlafaxine exposed women - late exposure: unadjusted

	Duloxetine	Duloxetine	Venlafaxine	Venlafaxine	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Total	828	100.00	2,770	100.00	
Demographics					
Age, mean (SD)	28.53	5.53	27.19	5.34	0.25
Age categorical, N (%)					
<=19	38	4.59	161	5.81	-0.06
20-24	165	19.93	814	29.39	-0.22
25-29	291	35.14	910	32.85	0.05
30-34	203	24.52	600	21.66	0.07
35-39	106	12.80	241	8.70	0.13
>=40	25	3.02	44	1.59	0.10
Race, N (%)					
White	660	79.71	2,264	81.73	-0.05
Black/African American	73	8.82	194	7.00	0.07
Hispanic/Latino	23	2.78	102	3.68	-0.05
Asian or Other Pacific	14	1.69	40	1.44	0.02
American Indian	17	2.05	36	1.30	0.06
Other	26	3.14	62	2.24	0.06
Unknown	15	1.81	72	2.60	-0.05
Chronic comorbid conditions, N (%)					
Hypertension	114	13.77	256	9.24	0.14
Diabetes	152	18.36	444	16.03	0.06
Renal Disease	14	1.69	26	0.94	0.07
Obesity Overweight	92	11.11	176	6.35	0.17
Comorbidity Index Q1	262	31.64	1,074	38.77	-0.15
Comorbidity Index Q2	191	23.07	690	24.91	-0.04
Comorbidity Index Q3	137	16.55	430	15.52	0.03
Comorbidity Index Q4	238	28.74	576	20.79	0.18
Infections, N (%)					
Toxoplasmosis	<11	0.00	<11	0.00	
Rubella	<11	0.00	<11	0.00	
Cytomegalovirus	<11	0.00	<11	0.00	

	Duloxetine	Duloxetine	Venlafaxine	Venlafaxine	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Herpes	18	2.17	43	1.55	0.05
Syphilis	<11	0.12	<11	0.11	0.00
Varicella	<11	0.12	<11	0.04	0.03
Parvovirus B19	<11	0.00	<11	0.00	
Zika virus other mosquito	<11	0.00	<11	0.00	
Lymphocytic choriomeningitis	<11	0.00	<11	0.00	
Influenza	11	1.33	55	1.99	-0.05
Chlamydia	<11	0.48	11	0.40	0.01
Human papilloma virus	<11	1.09	26	0.94	0.01
Gonorrhea	<11	0.72	16	0.58	0.02
HIV	<11	0.60	15	0.54	0.01
Trichomoniasis	<11	0.97	38	1.37	-0.04
Indications for duloxetine, N (%)					
Depression	471	56.88	1,503	54.26	0.05
Anxiety	321	38.77	895	32.31	0.14
Neuropathic Pain	116	14.01	252	9.10	0.15
Fibromyalgia	95	11.47	134	4.84	0.24
Non neuropathic Pain	486	58.70	1,272	45.92	0.26
Other psychiatric conditions, N (%)					
Sleep disorder	56	6.76	154	5.56	0.05
Bipolar disorder	139	16.79	366	13.21	0.10
Psychosis	16	1.93	37	1.34	0.05
Schizophrenia	<11	1.21	34	1.23	0.00
Personality disorder	25	3.02	68	2.45	0.03
Adjustment disorder	11	1.33	39	1.41	-0.01
Tobacco use, N (%)	174	21.01	435	15.70	0.14
Alcohol abuse or dependence, N (%)	12	1.45	61	2.20	-0.06
Drug abuse or dependence, N (%)	29	3.50	155	5.60	-0.10
Other medication exposures, N (%)					
Benzodiazepines	364	43.96	927	33.47	0.22
Other hypnotics	287	34.66	638	23.03	0.26
Barbiturates	68	8.21	199	7.18	0.04

	Duloxetine	Duloxetine	Venlafaxine	Venlafaxine	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Anxiolytics	69	8.33	143	5.16	0.13
Anticonvulsants	228	27.54	486	17.55	0.24
Antipsychotics	198	23.91	504	18.19	0.14
SSRIs	239	28.86	664	23.97	0.11
SNRIs	<11	0.00	2,770	100.00	
Other Antidep	241	29.11	711	25.67	0.08
Stimulants	78	9.42	188	6.79	0.10
Antidiabetic	45	5.43	118	4.26	0.05
Insulin	55	6.64	144	5.20	0.06
Antihyperten	193	23.31	439	15.85	0.19
Opioid analgesics	593	71.62	1,705	61.55	0.21
Triptans	63	7.61	166	5.99	0.06
NSAIDs	323	39.01	910	32.85	0.13
Obstetric conditions, N (%)					
Multifetal gestation Flag	32	3.86	139	5.02	-0.06
Markers of healthcare utilization					
Number of distinct 3 digit ICD 9 codes=0	46	5.56	283	10.22	-0.17
Number of distinct 3 digit ICD 9 codes: tertile 1 for number >0	165	19.93	648	23.39	-0.08
Number of distinct 3 digit ICD 9 codes: tertile 2 for number >0	187	22.58	598	21.59	0.02
Number of distinct 3 digit ICD 9 codes: tertile 3 for number >0	430	51.93	1,241	44.80	0.14
Number of ED visits=0	526	63.53	1,857	67.04	-0.07
Number of ED visits=1	164	19.81	530	19.13	0.02
Number of ED visits=2	68	8.21	215	7.76	0.02
Number of ED visits>2	70	8.45	168	6.06	0.09
Number of non-duloxetine generics dispensed=0	<11	0.48	27	0.97	-0.06
Number of non-duloxetine generics dispensed: tertile 1 for number >0	57	6.88	184	6.64	0.01
Number of non-duloxetine generics dispensed: tertile 2 for number >0	118	14.25	583	21.05	-0.18
Number of non-duloxetine generics dispensed: tertile 3 for number >0	649	78.38	1,976	71.34	0.16
Number of hospital admissions=0	748	90.34	2,515	90.79	-0.02

	Duloxetine	Duloxetine	Venlafaxine	Venlafaxine	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Number of hospital admissions=1	61	7.37	201	7.26	0.00
Number of hospital admissions=2	16	1.93	36	1.30	0.05
Number of hospital admissions>2	<11	0.36	18	0.65	-0.04
Number of outpatient visits=0	86	10.39	420	15.16	-0.14
Number of outpatient visits: tertile 1 for number >0	94	11.35	408	14.73	-0.10
Number of outpatient visits: tertile 2 for number >0	204	24.64	709	25.60	-0.02
Number of outpatient visits: tertile 3 for number >0	444	53.62	1,233	44.51	0.18
Number of psychiatric hospitalizations Q1	802	96.86	2,706	97.69	-0.05
Number of psychiatric hospitalizations Q2	22	2.66	57	2.06	0.04
Number of psychiatric hospitalizations Q3	<11	0.48	<11	0.18	0.05
Number of psychiatric hospitalizations Q4	<11	0.00	<11	0.07	-0.04
Number of psychiatrist visits=0	360	43.48	1,416	51.12	-0.15
Number of psychiatrist visits=1	191	23.07	527	19.03	0.10
Number of psychiatrist visits=2	87	10.51	274	9.89	0.02
Number of psychiatrist visits>2	190	22.95	553	19.96	0.07
Geographic region					
Arkansas	PPD		PPD		-0.05
Alabama					0.02
California	56	6.76	199	7.18	-0.02
Colorado	PPD		15	0.54	-0.07
District of Columbia			PPD		-0.05
Delaware	24	2.90	32	1.16	0.12
Florida	PPD		34	1.23	-0.03
Georgia			62	2.24	-0.15
Hawaii			PPD		0.03
Iowa			40	1.44	-0.04
Idaho			23	0.83	-0.13
Illinois	70	8.45	198	7.15	0.05
Indiana	79	9.54	133	4.80	0.18
Kansas	PPD		33	1.19	0.01
Kentucky	16	1.93	49	1.77	0.01
Louisiana	26	3.14	44	1.59	0.10

	Duloxetine	Duloxetine	Venlafaxine	Venlafaxine	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Massachusetts	PPD		17	0.61	-0.08
Maryland	13	1.57	33	1.19	0.03
Maine	PPD		27	0.97	-0.03
Minnesota	66	7.97	228	8.23	-0.01
Missouri	49	5.92	117	4.22	0.08
Mississippi	PPD		48	1.73	-0.09
North Carolina	20	2.42	33	1.19	0.09
North Dakota	PPD		PPD		0.01
Nebraska	PPD		27	0.97	0.01
New Hampshire	PPD		20	0.72	-0.03
New Jersey	PPD		PPD		-0.02
New Mexico	PPD		42	1.52	-0.03
Nevada	PPD		PPD		-0.06
New York	123	14.86	270	9.75	0.16
Ohio	13	1.57	117	4.22	-0.16
Oklahoma	PPD		36	1.30	-0.01
Oregon	15	1.81	60	2.17	-0.03
Pennsylvania	PPD		117	4.22	-0.24
Rhode Island	PPD		PPD		-0.03
South Carolina	PPD		PPD		0.01
South Dakota	PPD		17	0.61	-0.06
Tennessee	38	4.59	211	7.62	-0.13
Texas	PPD		PPD		-0.01
Utah	31	3.74	52	1.88	0.11
Virginia	30	3.62	60	2.17	0.09
Vermont	PPD		37	1.34	-0.01
Washington	PPD		PPD		-0.02
Wisconsin	44	5.31	254	9.17	-0.15
West Virginia	PPD		13	0.47	-0.04
Wyoming	PPD		PPD		0.01
Opioids					
buprenorphine	30	3.62	66	2.38	0.07

	Duloxetine	Duloxetine	Venlafaxine	Venlafaxine	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
butorphanol	<11	0.00	<11	0.18	-0.06
codeine	202	24.40	691	24.95	-0.01
fentanyl	20	2.42	21	0.76	0.13
hydrocodone	393	47.46	1,132	40.87	0.13
hydromorphone	17	2.05	22	0.79	0.11
levorphanol	<11	0.00	<11	0.00	
meperidine	<11	0.36	11	0.40	-0.01
methadone	<11	1.21	24	0.87	0.03
morphine	23	2.78	26	0.94	0.14
oxycodone	187	22.58	419	15.13	0.19
oxymorphone	<11	0.36	<11	0.07	0.06
pentazocine	<11	0.12	<11	0.22	-0.02
propoxyphene	69	8.33	271	9.78	-0.05
tapentadol	<11	0.00	<11	0.04	-0.03
tramadol	144	17.39	286	10.32	0.21
Healthcare Utilization, mean (SD)					
Comorbidity Index	1.79	1.96	1.48	1.84	0.16
Morphine equivalents	7484.74	36131.64	10276.38	389155.06	-0.01
Number of diagnoses	5.84	4.69	4.98	4.39	0.19
Number of ED visits	0.74	1.44	0.62	1.34	0.08
Number of non-duloxetine generics dispensed	10.36	6.24	9.31	5.87	0.17
Number of hospitalizations	0.12	0.41	0.12	0.47	0.00
Number of outpatient visits	5.7	7.78	4.63	6.37	0.15
Number of psychiatric hospitalizations	0.04	0.21	0.03	0.2	0.04
Number of psychiatrist visits	2.32	5.21	2.01	5.64	0.06

15.2. 13. Preterm/SGA- Baseline characteristics of duloxetine exposed vs. unexposed women - late exposure: adjusted for treatment indications

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Total	764	100.00	448,839	100.00	
Demographics					
Age, mean (SD)	28.51	5.52	25.62	5.39	0.53
Age categorical, N (%)					
<=19	33	4.32	52,739	11.75	-0.28
20-24	156	20.42	163,123	36.34	-0.36
25-29	268	35.08	132,014	29.41	0.12
30-34	187	24.48	67,223	14.98	0.24
35-39	96	12.57	27,509	6.13	0.22
>=40	24	3.14	6,231	1.39	0.12
Race, N (%)					
White	617	80.76	269,652	60.08	0.47
Black or African American	63	8.25	93,593	20.85	-0.36
Hispanic or Latino	17	2.23	36,281	8.08	-0.27
Asian or Other Pacific Islander	13	1.7	8,325	1.85	-0.01
American Indian	13	1.7	10,046	2.24	-0.04
Other	25	3.27	20,721	4.62	-0.07
Unknown	16	2.09	10,221	2.28	-0.01
Chronic comorbid conditions, N (%)					
Hypertension	105	13.74	40,008	8.91	0.15
Diabetes	139	18.19	62,865	14.01	0.11
Renal Disease	16	2.09	8,327	1.86	0.02
Obesity Overweight	87	11.39	38,618	8.6	0.09
Comorbidity Index Q1	233	30.5	190,901	42.53	-0.25
Comorbidity Index Q2	168	21.99	115,057	25.63	-0.09
Comorbidity Index Q3	131	17.15	68,113	15.18	0.05
Comorbidity Index Q4	232	30.37	74,767	16.66	0.33
Infections, N (%)					
Toxoplasmosis	<11	0	181	0.04	-0.03
Rubella	<11	0.13	47	0.01	0.05
Cytomegalovirus	<11	0	50	0.01	-0.01

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Herpes	18	2.36	11,199	2.49	-0.01
Syphilis	<11	0.13	747	0.17	-0.01
Varicella	<11	0	236	0.05	-0.03
Parvovirus B19	<11	0	57	0.01	-0.02
Zika virus other mosquito	<11	0	<11	0	
Lymphocytic choriomeningitis	<11	0	<11	0	0.00
Influenza	11	1.44	9,382	2.09	-0.05
Chlamydia	<11	0.52	4,931	1.1	-0.06
Human papilloma virus	<11	1.05	4,679	1.04	0.00
Gonorrhea	<11	0.79	5,065	1.13	-0.04
HIV	<11	0.52	2,465	0.55	0.00
Trichomoniasis	<11	0.79	10,080	2.25	-0.12
Indications for duloxetine, N (%)					
Depression	504	65.97	292,124	65.08	0.02
Anxiety	347	45.42	202,825	45.19	0.00
Neuropathic Pain	128	16.75	91,467	20.38	-0.09
Fibromyalgia	102	13.35	69,870	15.57	-0.06
Non neuropathic Pain	519	67.93	306,731	68.34	-0.01
Other psychiatric conditions, N (%)					
Sleep disorder	61	7.98	22,950	5.11	0.12
Bipolar disorder	135	17.67	39,729	8.85	0.26
Psychosis	14	1.83	7,097	1.58	0.02
Schizophrenia	<11	1.31	5,014	1.12	0.02
Personality disorder	26	3.4	9,106	2.03	0.08
Adjustment disorder	13	1.7	8,721	1.94	-0.02
Tobacco use, N (%)	174	22.77	74,262	16.55	0.16
Alcohol abuse or dependence, N (%)	14	1.83	7,550	1.68	0.01
Drug abuse or dependence, N (%)	30	3.93	18,762	4.18	-0.01
Other medication exposures, N (%)					
Benzodiazepines	360	47.12	100,531	22.4	0.54
Other hypnotics	284	37.17	87,155	19.42	0.40
Barbiturates	66	8.64	24,352	5.43	0.13

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Anxiolytics	69	9.03	18,092	4.03	0.20
Anticonvulsants	219	28.66	52,827	11.77	0.43
Antipsychotics	188	24.61	42,224	9.41	0.41
SSRIs	240	31.41	184,538	41.11	-0.20
SNRIs	47	6.15	23,877	5.32	0.04
Other Antidep	248	32.46	83,504	18.6	0.32
Stimulants	67	8.77	17,747	3.95	0.20
Antidiabetic	36	4.71	14,406	3.21	0.08
Insulin	50	6.54	15,863	3.53	0.14
Antihyperten	176	23.04	53,404	11.9	0.30
Opioid analgesics	572	74.87	267,819	59.67	0.33
Triptans	65	8.51	17,784	3.96	0.19
NSAIDs	309	40.45	158,750	35.37	0.10
Obstetric conditions, N (%)					
Multifetal gestation Flag	30	3.93	18,535	4.13	-0.01
Markers of healthcare utilization					
Number of distinct 3 digit ICD 9 codes=0	27	3.53	35,070	7.81	-0.19
Number of distinct 3 digit ICD 9 codes: tertile 1 for number >0	127	16.62	79,625	17.74	-0.03
Number of distinct 3 digit ICD 9 codes: tertile 2 for number >0	168	21.99	90,232	20.1	0.05
Number of distinct 3 digit ICD 9 codes: tertile 3 for number >0	442	57.85	243,911	54.34	0.07
Number of ED visits=0	449	58.77	263,367	58.68	0.00
Number of ED visits=1	166	21.73	98,257	21.89	0.00
Number of ED visits=2	73	9.55	43,050	9.59	0.00
Number of ED visits>2	76	9.95	44,165	9.84	0.00
Number of non-duloxetine generics dispensed=0	<11	0.39	15,448	3.44	-0.22
Number of non-duloxetine generics dispensed: tertile 1 for number >0	46	6.02	43,997	9.8	-0.14
Number of non-duloxetine generics dispensed: tertile 2 for number >0	92	12.04	102,241	22.78	-0.29
Number of non-duloxetine generics dispensed: tertile 3 for number >0	623	81.54	287,153	63.98	0.40
Number of hospital admissions=0	684	89.53	397,213	88.5	0.03

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Number of hospital admissions=1	60	7.85	39,664	8.84	-0.04
Number of hospital admissions=2	17	2.23	7,903	1.76	0.03
Number of hospital admissions>2	<11	0.39	4,058	0.9	-0.06
Number of outpatient visits=0	56	7.33	55,842	12.44	-0.17
Number of outpatient visits: tertile 1 for number >0	74	9.69	58,725	13.08	-0.11
Number of outpatient visits: tertile 2 for number >0	187	24.48	107,730	24	0.01
Number of outpatient visits: tertile 3 for number >0	447	58.51	226,541	50.47	0.16
Number of psychiatric hospitalizations Q1	737	96.47	434,680	96.85	-0.02
Number of psychiatric hospitalizations Q2	23	3.01	12,314	2.74	0.02
Number of psychiatric hospitalizations Q3	<11	0.52	1,513	0.34	0.03
Number of psychiatric hospitalizations Q4	<11	0	333	0.07	-0.04
Number of psychiatrist visits=0	280	36.65	211,376	47.09	-0.21
Number of psychiatrist visits=1	194	25.39	97,440	21.71	0.09
Number of psychiatrist visits=2	88	11.52	47,280	10.53	0.03
Number of psychiatrist visits>2	202	26.44	92,743	20.66	0.14
Geographic region					
Arkansas	PPD		444	0.1	-0.04
Alabama	PPD		2,210	0.49	-0.02
California	49	6.41	48,057	10.71	-0.15
Colorado	PPD		1,356	0.3	-0.01
District of Columbia	PPD		313	0.07	-0.04
Delaware	18	2.36	3,906	0.87	0.12
Florida	PPD		5,923	1.32	-0.07
Georgia	PPD		7,843	1.75	-0.09
Hawaii	PPD		2,091	0.47	-0.06
Iowa	PPD		3,699	0.82	0.01
Idaho	PPD		832	0.19	-0.06
Illinois	63	8.25	33,096	7.37	0.03
Indiana	74	9.69	23,847	5.31	0.17
Kansas	PPD		3,826	0.85	0.04
Kentucky	16	2.09	13,032	2.9	-0.05
Louisiana	21	2.75	7,527	1.68	0.07

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Massachusetts	PPD		2,720	0.61	-0.05
Maryland			10,048	2.24	-0.06
Maine	PPD		2,793	0.62	0.00
Minnesota			31,526	7.02	0.10
Missouri	43	5.63	12,015	2.68	0.15
Mississippi	PPD		6,948	1.55	-0.10
North Carolina			7,708	1.72	0.04
North Dakota	PPD		2,678	0.6	-0.01
Nebraska			2,808	0.63	0.05
New Hampshire	PPD		3,158	0.7	-0.04
New Jersey			2,654	0.59	-0.05
New Mexico	PPD		8,302	1.85	-0.04
Nevada			696	0.15	-0.06
New York	112	14.66	53,239	11.86	0.08
Ohio	13	1.7	11,692	2.6	-0.06
Oklahoma	PPD		5,746	1.28	0.01
Oregon			6,973	1.55	0.05
Pennsylvania	PPD		9,607	2.14	-0.14
Rhode Island			1,506	0.34	-0.04
South Carolina	PPD		882	0.2	0.01
South Dakota			2,863	0.64	-0.06
Tennessee	38	4.97	43,412	9.67	-0.18
Texas	PPD		999	0.22	-0.02
Utah			3,322	0.74	0.18
Virginia	25	3.27	12,253	2.73	0.06
Vermont	29	3.8	5,798	1.29	0.00
Washington	PPD		518	0.12	0.00
Wisconsin			36,113	8.05	-0.14
West Virginia	PPD		1,353	0.3	-0.01
Wyoming			505	0.11	0.03
Opioids					
buprenorphine	29	3.8	5,605	1.25	0.16

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
butorphanol	<11	0	353	0.08	-0.04
codeine	193	25.26	111,871	24.92	0.01
fentanyl	19	2.49	2,726	0.61	0.15
hydrocodone	390	51.05	179,225	39.93	0.22
hydromorphone	18	2.36	4,055	0.9	0.11
levorphanol	<11	0	0	0	0.00
meperidine	<11	0.26	1,918	0.43	-0.03
methadone	11	1.44	3,272	0.73	0.07
morphine	24	3.14	3,648	0.81	0.17
oxycodone	190	24.87	69,719	15.53	0.23
oxymorphone	<11	0.39	428	0.1	0.06
pentazocine	<11	0.26	536	0.12	0.03
propoxyphene	72	9.42	34,383	7.66	0.06
tapentadol	<11	0	333	0.07	-0.04
tramadol	148	19.37	49,703	11.07	0.23
Healthcare Utilization, mean (SD)					
Comorbidity Index	1.85	1.98	1.28	1.74	0.30
Morphine equivalents	8505.83	39972.94	5218.02	168194.12	0.03
Number of diagnoses	6.38	4.77	6.05	5.06	0.07
Number of ED visits	0.83	1.41	0.87	1.7	-0.02
Number of non-duloxetine generics dispensed	10.93	6.39	8.31	5.74	0.43
Number of hospitalizations	0.13	0.43	0.17	0.69	-0.06
Number of outpatient visits	6.18	7.96	5.07	5.98	0.16
Number of psychiatric hospitalizations	0.04	0.22	0.04	0.22	0.02
Number of psychiatrist visits	2.55	5.25	1.89	4.38	0.14

15.2. 14. Preterm/SGA- Baseline characteristics of duloxetine exposed vs. SSRI exposed women - late exposure: adjusted for treatment indications

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Total	524	100.00	34,081	100.00	
Demographics					
Age, mean (SD)	28.44	5.28	26.28	5.39	0.40
Age categorical, N (%)					
<=19	25	4.77	2,871	8.42	-0.15
20-24	97	18.51	11,717	34.38	-0.37
25-29	193	36.83	10,687	31.36	0.12
30-34	136	25.95	5,768	16.92	0.22
35-39	59	11.26	2,506	7.35	0.13
>=40	14	2.67	532	1.56	0.08
Race, N (%)					
White	432	82.44	24,931	73.15	0.22
Black/African American	41	7.82	4,375	12.84	-0.17
Hispanic/Latino			1,764	5.18	-0.18
Asian or Other Pacific			342	1	0.03
American Indian			727	2.13	-0.03
Other	16	3.05	1,111	3.26	-0.01
Unknown			831	2.44	-0.05
Chronic comorbid conditions, N (%)					
Hypertension	73	13.93	3,172	9.31	0.14
Diabetes	88	16.79	5,243	15.38	0.04
Renal Disease	<11	1.72	644	1.89	-0.01
Obesity Overweight	57	10.88	2,815	8.26	0.09
Comorbidity Index Q1	166	31.68	13,593	39.88	-0.17
Comorbidity Index Q2	116	22.14	8,534	25.04	-0.07
Comorbidity Index Q3	86	16.41	5,548	16.28	0.00
Comorbidity Index Q4	156	29.77	6,407	18.8	0.26
Infections, N (%)					
Toxoplasmosis	<11	0	15	0.04	-0.03
Rubella	<11	0	<11	0	-0.01
Cytomegalovirus	<11	0	<11	0.03	-0.02

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Herpes	13	2.48	868	2.55	0.00
Syphilis	<11	0.19	52	0.15	0.01
Varicella	<11	0	24	0.07	-0.04
Parvovirus B19	<11	0	<11	0.01	-0.02
Zika virus other mosquito	<11	0	<11	0	
Lymphocytic choriomeningitis	<11	0	<11	0	
Influenza	<11	1.34	758	2.22	-0.07
Chlamydia	<11	0.38	281	0.82	-0.06
Human papilloma virus	<11	0.76	371	1.09	-0.03
Gonorrhea	<11	0.76	289	0.85	-0.01
HIV	<11	0.57	154	0.45	0.02
Trichomoniasis	<11	0.76	603	1.77	-0.09
Indications for duloxetine, N (%)					
Depression	329	62.79	21,589	63.35	-0.01
Anxiety	231	44.08	14,356	42.12	0.04
Neuropathic Pain	78	14.89	4,838	14.19	0.02
Fibromyalgia	65	12.4	4,748	13.93	-0.05
Non neuropathic Pain	351	66.98	23,604	69.26	-0.05
Other psychiatric conditions, N (%)					
Sleep disorder	40	7.63	1,999	5.86	0.07
Bipolar disorder	93	17.75	4,096	12.02	0.16
Psychosis	<11	1.15	582	1.71	-0.05
Schizophrenia	<11	1.34	551	1.62	-0.02
Personality disorder	18	3.44	887	2.6	0.05
Adjustment disorder	<11	1.91	641	1.88	0.00
Tobacco use, N (%)	124	23.66	6,289	18.45	0.13
Alcohol abuse or dependence, N (%)	<11	1.53	803	2.36	-0.06
Drug abuse or dependence, N (%)	14	2.67	1,820	5.34	-0.14
Other medication exposures, N (%)					
Benzodiazepines	232	44.27	9,970	29.25	0.32
Other hypnotics	186	35.5	8,884	26.07	0.21
Barbiturates	37	7.06	2,355	6.91	0.01

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Anxiolytics	39	7.44	1,700	4.99	0.10
Anticonvulsants	150	28.63	5,048	14.81	0.34
Antipsychotics	125	23.85	4,716	13.84	0.26
SSRIs	<11	0	34,081	100	
SNRIs	28	5.34	1,781	5.23	0.01
Other Antidep	163	31.11	7,887	23.14	0.18
Stimulants	49	9.35	1,824	5.35	0.15
Antidiabetic	22	4.2	1,335	3.92	0.01
Insulin	33	6.3	1,454	4.27	0.09
Antihyperten	118	22.52	4,989	14.64	0.20
Opioid analgesics	380	72.52	22,706	66.62	0.13
Triptans	36	6.87	1,695	4.97	0.08
NSAIDs	204	38.93	12,696	37.25	0.03
Obstetric conditions, N (%)					
Multifetal gestation Flag	22	4.2	1,434	4.21	0.00
Markers of healthcare utilization					
Number of distinct 3 digit ICD 9 codes=0	20	3.82	2,608	7.65	-0.17
Number of distinct 3 digit ICD 9 codes: tertile 1 for number >0	94	17.94	6,051	17.76	0.00
Number of distinct 3 digit ICD 9 codes: tertile 2 for number >0	116	22.14	6,868	20.15	0.05
Number of distinct 3 digit ICD 9 codes: tertile 3 for number >0	294	56.11	18,554	54.44	0.03
Number of ED visits=0	311	59.35	20,160	59.15	0.00
Number of ED visits=1	118	22.52	7,274	21.34	0.03
Number of ED visits=2	49	9.35	3,295	9.67	-0.01
Number of ED visits>2	46	8.78	3,352	9.83	-0.04
Number of non-duloxetine generics dispensed=0	<11	0.38	441	1.29	-0.10
Number of non-duloxetine generics dispensed: tertile 1 for number >0	37	7.06	2,114	6.2	0.03
Number of non-duloxetine generics dispensed: tertile 2 for number >0	73	13.93	6,483	19.02	-0.14
Number of non-duloxetine generics dispensed: tertile 3 for number >0	412	78.63	25,043	73.48	0.12
Number of hospital admissions=0	488	93.13	30,153	88.47	0.16

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Number of hospital admissions=1	29	5.53	3,086	9.06	-0.14
Number of hospital admissions=2	<11	1.15	556	1.63	-0.04
Number of hospital admissions>2	<11	0.19	286	0.84	-0.09
Number of outpatient visits=0	43	8.21	3,981	11.68	-0.12
Number of outpatient visits: tertile 1 for number >0	51	9.73	4,447	13.05	-0.10
Number of outpatient visits: tertile 2 for number >0	137	26.15	8,346	24.49	0.04
Number of outpatient visits: tertile 3 for number >0	293	55.92	17,307	50.78	0.10
Number of psychiatric hospitalizations Q1	515	98.28	33,047	96.97	0.09
Number of psychiatric hospitalizations Q2	<11	1.72	896	2.63	-0.06
Number of psychiatric hospitalizations Q3	<11	0	104	0.31	-0.08
Number of psychiatric hospitalizations Q4	<11	0	34	0.1	-0.04
Number of psychiatrist visits=0	197	37.6	17,282	50.71	-0.27
Number of psychiatrist visits=1	144	27.48	6,709	19.69	0.18
Number of psychiatrist visits=2	58	11.07	3,331	9.77	0.04
Number of psychiatrist visits>2	125	23.85	6,758	19.83	0.10
Geographic region					
Arkansas	PPD		40	0.12	-0.05
Alabama			204	0.6	-0.11
California	34	6.49	2,218	6.51	0.00
Colorado			PPD		-0.02
District of Columbia	PPD				-0.02
Delaware			274	0.81	0.10
Florida			522	1.53	-0.07
Georgia			649	1.9	-0.17
Hawaii			35	0.1	0.02
Iowa			426	1.25	-0.07
Idaho			141	0.41	-0.09
Illinois	41	7.82	2,643	7.76	0.00
Indiana	56	10.69	1,917	5.62	0.19
Kansas	PPD		375	1.1	0.05
Kentucky			865	2.54	-0.07
Louisiana	15	2.86	481	1.41	0.10

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Massachusetts	PPD		286	0.84	-0.06
Maryland			543	1.59	-0.02
Maine			229	0.67	0.01
Minnesota	57	10.88	2,972	8.72	0.07
Missouri	29	5.53	1,130	3.32	0.11
Mississippi	PPD		348	1.02	-0.05
North Carolina	13	2.48	577	1.69	0.06
North Dakota	PPD		280	0.82	-0.01
Nebraska			286	0.84	0.01
New Hampshire			328	0.96	-0.04
New Jersey			124	0.36	-0.09
New Mexico			536	1.57	-0.02
Nevada			55	0.16	-0.06
New York	81	15.46	3,023	8.87	0.20
Ohio	PPD		1,067	3.13	-0.15
Oklahoma			427	1.25	-0.05
Oregon			694	2.03	0.02
Pennsylvania			916	2.69	-0.15
Rhode Island			173	0.51	-0.05
South Carolina			82	0.24	0.03
South Dakota			246	0.72	-0.08
Tennessee	26	4.96	3,045	8.93	-0.16
Texas	PPD		74	0.22	-0.01
Utah			534	1.57	0.05
Virginia	20	3.82	876	2.57	0.07
Vermont	PPD		550	1.61	0.01
Washington			63	0.18	-0.06
Wisconsin	26	4.96	3,454	10.14	-0.20
West Virginia	PPD		132	0.39	-0.04
Wyoming			53	0.16	0.01
Opioids					
buprenorphine	21	4.01	524	1.54	0.15

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
butorphanol	<11	0	22	0.07	-0.04
codeine	120	22.9	10,052	29.49	-0.15
fentanyl	12	2.29	243	0.71	0.13
hydrocodone	260	49.62	15,680	46.01	0.07
hydromorphone	14	2.67	372	1.09	0.12
levorphanol	<11	0	<11	0	-0.01
meperidine	<11	0.19	184	0.54	-0.06
methadone	<11	0.95	308	0.9	0.01
morphine	15	2.86	357	1.05	0.13
oxycodone	121	23.09	6,406	18.8	0.11
oxymorphone	<11	0.57	29	0.09	0.08
pentazocine	<11	0.19	47	0.14	0.01
propoxyphene	38	7.25	3,439	10.09	-0.10
tapentadol	<11	0	11	0.03	-0.03
tramadol	98	18.7	4,208	12.35	0.18
Healthcare Utilization, mean (SD)					
Comorbidity Index	1.79	1.93	1.38	1.72	0.23
Morphine equivalents	9062.51	46467.8	4502.44	118467.65	0.05
Number of diagnoses	6.1	4.49	6.04	5.01	0.01
Number of ED visits	0.78	1.34	0.86	1.64	-0.05
Number of non-duloxetine generics dispensed	10.1	5.77	9.65	6.02	0.08
Number of hospitalizations	0.08	0.33	0.16	0.53	-0.16
Number of outpatient visits	5.74	7.58	5.17	6.08	0.08
Number of psychiatric hospitalizations	0.02	0.13	0.04	0.22	-0.10
Number of psychiatrist visits	2.26	5.12	1.83	4.42	0.09

15.2. 15. Preterm/SGA- Baseline characteristics of duloxetine exposed vs. venlafaxine exposed women - late exposure: adjusted for treatment

indications

	Duloxetine	Duloxetine	Venlafaxine	Venlafaxine	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Total	717	100.00	2,230	100.00	
Demographics					
Age, mean (SD)	28.57	5.53	27.4	5.3	0.22
Age categorical, N (%)					
<=19	32	4.46	114	5.1	-0.03
20-24	140	19.53	633	28.37	-0.21
25-29	256	35.7	730	32.73	0.06
30-34	175	24.41	514	23.04	0.03
35-39	92	12.83	210	9.43	0.11
>=40	22	3.07	30	1.32	0.12
Race, N (%)					
White	578	80.61	1,805	80.92	-0.01
Black/African American	59	8.23	143	6.42	0.07
Hispanic/Latino	PPD		78	3.51	-0.07
Asian or Other Pacific			42	1.9	-0.02
American Indian	13	1.81	34	1.54	0.02
Other	24	3.35	58	2.6	0.04
Unknown	14	1.95	69	3.1	-0.07
Chronic comorbid conditions, N (%)					
Hypertension	98	13.67	219	9.82	0.12
Diabetes	131	18.27	372	16.69	0.04
Renal Disease	14	1.95	19	0.86	0.09
Obesity Overweight	85	11.85	173	7.75	0.14
Comorbidity Index Q1	221	30.82	839	37.62	-0.14
Comorbidity Index Q2	157	21.9	558	25.01	-0.07
Comorbidity Index Q3	123	17.15	332	14.91	0.06
Comorbidity Index Q4	216	30.13	501	22.47	0.17
Infections, N (%)					
Toxoplasmosis	<11	0	<11	0	

	Duloxetine	Duloxetine	Venlafaxine	Venlafaxine	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Rubella	<11	0	<11	0	
Cytomegalovirus	<11	0	<11	0	
Herpes	16	2.23	34	1.54	0.05
Syphilis	<11	0.14	<11	0.09	0.02
Varicella	<11	0	<11	0.03	-0.02
Parvovirus B19	<11	0	<11	0	
Zika virus other mosquito	<11	0	<11	0	
Lymphocytic choriomeningitis	<11	0	<11	0	
Influenza	<11	1.39	45	2.02	-0.05
Chlamydia	<11	0.56	<11	0.28	0.04
Human papilloma virus	<11	0.98	23	1.02	0.00
Gonorrhea	<11	0.7	<11	0.41	0.04
HIV	<11	0.56	12	0.54	0.00
Trichomoniasis	<11	0.84	28	1.26	-0.04
Indications for duloxetine, N (%)					
Depression	471	65.69	1,499	67.21	-0.03
Anxiety	321	44.77	1,023	45.89	-0.02
Neuropathic Pain	116	16.18	425	19.06	-0.08
Fibromyalgia	95	13.25	311	13.95	-0.02
Non neuropathic Pain	486	67.78	1,494	66.99	0.02
Other psychiatric conditions, N (%)					
Sleep disorder	55	7.67	161	7.2	0.02
Bipolar disorder	127	17.71	310	13.92	0.10
Psychosis	13	1.81	38	1.69	0.01
Schizophrenia	<11	1.39	29	1.31	0.01
Personality disorder	23	3.21	64	2.87	0.02
Adjustment disorder	11	1.53	40	1.77	-0.02
Tobacco use, N (%)	162	22.59	394	17.65	0.12
Alcohol abuse or dependence, N (%)	12	1.67	46	2.05	-0.03
Drug abuse or dependence, N (%)	26	3.63	143	6.4	-0.13
Other medication exposures, N (%)					
Benzodiazepines	337	47	915	41.04	0.12

	Duloxetine	Duloxetine	Venlafaxine	Venlafaxine	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Other hypnotics	260	36.26	600	26.91	0.20
Barbiturates	60	8.37	188	8.43	0.00
Anxiolytics	63	8.79	132	5.93	0.11
Anticonvulsants	206	28.73	473	21.21	0.17
Antipsychotics	178	24.83	463	20.77	0.10
SSRIs	221	30.82	577	25.89	0.11
SNRIs	<11	0	2,230	100	
Other Antidep	224	31.24	640	28.68	0.06
Stimulants	63	8.79	168	7.53	0.05
Antidiabetic	33	4.6	92	4.11	0.02
Insulin	46	6.42	120	5.39	0.04
Antihyperten	164	22.87	376	16.87	0.15
Opioid analgesics	534	74.48	1,520	68.14	0.14
Triptans	60	8.37	155	6.95	0.05
NSAIDs	295	41.14	858	38.49	0.05
Obstetric conditions, N (%)					
Multifetal gestation Flag	28	3.91	109	4.87	-0.05
Markers of healthcare utilization					
Number of distinct 3 digit ICD 9 codes=0	25	3.49	138	6.19	-0.13
Number of distinct 3 digit ICD 9 codes: tertile 1 for number >0	122	17.02	393	17.62	-0.02
Number of distinct 3 digit ICD 9 codes: tertile 2 for number >0	159	22.18	452	20.26	0.05
Number of distinct 3 digit ICD 9 codes: tertile 3 for number >0	411	57.32	1,247	55.94	0.03
Number of ED visits=0	427	59.55	1,395	62.55	-0.06
Number of ED visits=1	154	21.48	443	19.88	0.04
Number of ED visits=2	68	9.48	213	9.57	0.00
Number of ED visits>2	68	9.48	178	8	0.05
Number of non-duloxetine generics dispensed=0	<11	0.42	19	0.84	-0.05
Number of non-duloxetine generics dispensed: tertile 1 for number >0	45	6.28	94	4.21	0.09
Number of non-duloxetine generics dispensed: tertile 2 for number >0	89	12.41	375	16.82	-0.13

	Duloxetine	Duloxetine	Venlafaxine	Venlafaxine	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Number of non-duloxetine generics dispensed: tertile 3 for number >0	580	80.89	1,742	78.13	0.07
Number of hospital admissions=0	645	89.96	1,997	89.55	0.01
Number of hospital admissions=1	54	7.53	178	7.96	-0.02
Number of hospital admissions=2	15	2.09	36	1.59	0.04
Number of hospital admissions>2	<11	0.42	20	0.89	-0.06
Number of outpatient visits=0	51	7.11	228	10.22	-0.11
Number of outpatient visits: tertile 1 for number >0	73	10.18	243	10.91	-0.02
Number of outpatient visits: tertile 2 for number >0	175	24.41	525	23.52	0.02
Number of outpatient visits: tertile 3 for number >0	418	58.3	1,234	55.35	0.06
Number of psychiatric hospitalizations Q1	692	96.51	2,168	97.21	-0.04
Number of psychiatric hospitalizations Q2	21	2.93	55	2.45	0.03
Number of psychiatric hospitalizations Q3	<11	0.56	<11	0.25	0.05
Number of psychiatric hospitalizations Q4	<11	0	<11	0.09	-0.04
Number of psychiatrist visits=0	265	36.96	899	40.32	-0.07
Number of psychiatrist visits=1	185	25.8	498	22.35	0.08
Number of psychiatrist visits=2	86	11.99	263	11.78	0.01
Number of psychiatrist visits>2	181	25.24	570	25.55	-0.01
Geographic region					
Arkansas	PPD		PPD		-0.06
Alabama	PPD		PPD		0.03
California	45	6.28	137	6.14	0.01
Colorado	PPD		PPD		-0.05
District of Columbia	PPD		PPD		-0.05
Delaware	18	2.51	35	1.56	0.07
Florida	PPD		24	1.06	-0.04
Georgia	PPD		49	2.21	-0.16
Hawaii	PPD		PPD		0.05
Iowa	PPD		38	1.69	-0.06
Idaho	PPD		16	0.72	-0.12
Illinois	59	8.23	152	6.79	0.05
Indiana	72	10.04	106	4.74	0.20

	Duloxetine	Duloxetine	Venlafaxine	Venlafaxine	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Kansas	PPD		20	0.89	0.05
Kentucky	14	1.95	44	1.97	0.00
Louisiana	21	2.93	39	1.77	0.08
Massachusetts	PPD		18	0.83	-0.10
Maryland	PPD		31	1.37	0.01
Maine			20	0.88	-0.02
Minnesota	62	8.65	220	9.86	-0.04
Missouri	42	5.86	85	3.81	0.10
Mississippi	PPD		32	1.42	-0.09
North Carolina	17	2.37	33	1.49	0.06
North Dakota	PPD		13	0.57	0.00
Nebraska	PPD		18	0.81	0.03
New Hampshire			19	0.87	-0.06
New Jersey			PPD		
New Mexico			29	1.3	0.01
Nevada			PPD		
New York	105	14.64	204	9.15	0.17
Ohio	13	1.81	91	4.07	-0.13
Oklahoma	PPD		23	1.04	0.03
Oregon	15	2.09	48	2.17	-0.01
Pennsylvania	PPD		84	3.74	-0.22
Rhode Island	PPD		PPD		
South Carolina					
South Dakota			15	0.67	-0.06
Tennessee	37	5.16	185	8.29	-0.13
Texas	PPD		PPD		
Utah	22	3.07	43	1.92	0.07
Virginia	27	3.77	48	2.17	0.09
Vermont	PPD		34	1.52	-0.02
Washington			PPD		
Wisconsin	36	5.02	212	9.52	-0.17
West Virginia	PPD		PPD		

	Duloxetine	Duloxetine	Venlafaxine	Venlafaxine	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Wyoming	PPD		PPD		0.02
Opioids					
buprenorphine	25	3.49	47	2.12	0.08
butorphanol	<11	0	5	0.21	-0.06
codeine	182	25.38	619	27.75	-0.05
fentanyl	19	2.65	30	1.32	0.10
hydrocodone	362	50.49	1,070	47.99	0.05
hydromorphone	16	2.23	21	0.93	0.10
levorphanol	<11	0	<11	0	
meperidine	<11	0.28	<11	0.32	-0.01
methadone	<11	1.39	28	1.26	0.01
morphine	22	3.07	37	1.68	0.09
oxycodone	173	24.13	427	19.13	0.12
oxymorphone	<11	0.42	<11	0.19	0.04
pentazocine	<11	0.14	10	0.43	-0.05
propoxyphene	68	9.48	234	10.51	-0.03
tapentadol	<11	0	<11	0.06	-0.04
tramadol	136	18.97	296	13.28	0.16
Healthcare Utilization, mean (SD)					
Comorbidity Index	1.84	1.98	1.54	1.9	0.16
Morphine equivalents	8140.83	38454.1	21185.5	491961.74	-0.04
Number of diagnoses	6.31	4.71	6.06	4.84	0.05
Number of ED visits	0.81	1.4	0.78	1.6	0.02
Number of non-duloxetine generics dispensed	10.79	6.34	10.48	6.14	0.05
Number of hospitalizations	0.13	0.42	0.15	0.52	-0.03
Number of outpatient visits	6.17	8.1	5.77	6.95	0.05
Number of psychiatric hospitalizations	0.04	0.22	0.03	0.22	0.03
Number of psychiatrist visits	2.55	5.36	2.47	5.86	0.01

15.2. 16. Preterm/SGA- Baseline characteristics of duloxetine exposed vs. unexposed women - late exposure: fully adjusted

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Total	764	100.00	391,641	100.00	
Demographics					
Age, mean (SD)	28.51	5.52	28.39	5.57	0.02
Age categorical, N (%)					
<=19	33	4.32	15,932	4.07	0.01
20-24	156	20.42	79,866	20.39	0.00
25-29	268	35.08	138,782	35.44	-0.01
30-34	187	24.48	95,942	24.5	0.00
35-39	96	12.57	49,024	12.52	0.00
>=40	24	3.14	12,096	3.09	0.00
Race, N (%)					
White	617	80.76	319,546	81.59	-0.02
Black or African American	63	8.25	29,896	7.63	0.02
Hispanic or Latino	17	2.23	7,716	1.97	0.02
Asian or Other Pacific Islander	13	1.7	6,688	1.71	0.00
American Indian	13	1.7	6,703	1.71	0.00
Other	25	3.27	12,898	3.29	0.00
Unknown	16	2.09	8,195	2.09	0.00
Chronic comorbid conditions, N (%)					
Hypertension	105	13.74	53,100	13.56	0.01
Diabetes	139	18.19	71,236	18.19	0.00
Renal Disease	16	2.09	8,026	2.05	0.00
Obesity Overweight	87	11.39	43,888	11.21	0.01
Comorbidity Index Q1	233	30.5	118,506	30.26	0.01
Comorbidity Index Q2	168	21.99	88,082	22.49	-0.01
Comorbidity Index Q3	131	17.15	68,083	17.38	-0.01
Comorbidity Index Q4	232	30.37	116,970	29.87	0.01
Infections, N (%)					
Toxoplasmosis	<11	0	<11	0	
Rubella	<11	0.13	537	0.14	0.00
Cytomegalovirus	<11	0	<11	0	

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Herpes	18	2.36	9,083	2.32	0.00
Syphilis	<11	0.13	486	0.12	0.00
Varicella	<11	0	<11	0	0.00
Parvovirus B19	<11	0	<11	0	
Zika virus other mosquito	<11	0	<11	0	
Lymphocytic choriomeningitis	<11	0	<11	0	
Influenza	11	1.44	5,403	1.38	0.01
Chlamydia	<11	0.52	2,084	0.53	0.00
Human papilloma virus	<11	1.05	4,016	1.03	0.00
Gonorrhea	<11	0.79	3,046	0.78	0.00
HIV	<11	0.52	2,057	0.53	0.00
Trichomoniasis	<11	0.79	3,045	0.78	0.00
Indications for duloxetine, N (%)					
Depression	504	65.97	263,298	67.23	-0.03
Anxiety	347	45.42	179,031	45.71	-0.01
Neuropathic Pain	128	16.75	63,951	16.33	0.01
Fibromyalgia	102	13.35	47,553	12.14	0.04
Non neuropathic Pain	519	67.93	260,023	66.39	0.03
Other psychiatric conditions, N (%)					
Sleep disorder	61	7.98	30,684	7.83	0.01
Bipolar disorder	135	17.67	68,103	17.39	0.01
Psychosis	14	1.83	6,875	1.76	0.01
Schizophrenia	<11	1.31	5,169	1.32	0.00
Personality disorder	26	3.4	13,115	3.35	0.00
Adjustment disorder	13	1.7	6,803	1.74	0.00
Tobacco use, N (%)	174	22.77	90,051	22.99	-0.01
Alcohol abuse or dependence, N (%)	14	1.83	7,621	1.95	-0.01
Drug abuse or dependence, N (%)	30	3.93	16,064	4.1	-0.01
Other medication exposures, N (%)					
Benzodiazepines	360	47.12	185,419	47.34	0.00
Other hypnotics	284	37.17	145,172	37.07	0.00
Barbiturates	66	8.64	34,063	8.7	0.00

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Anxiolytics	69	9.03	34,439	8.79	0.01
Anticonvulsants	219	28.66	107,963	27.57	0.02
Antipsychotics	188	24.61	92,815	23.7	0.02
SSRIs	240	31.41	128,791	32.88	-0.03
SNRIs	47	6.15	24,957	6.37	-0.01
Other Antidep	248	32.46	127,619	32.59	0.00
Stimulants	67	8.77	32,953	8.41	0.01
Antidiabetic	36	4.71	18,226	4.65	0.00
Insulin	50	6.54	25,277	6.45	0.00
Antihyperten	176	23.04	87,865	22.44	0.01
Opioid analgesics	572	74.87	294,052	75.08	0.00
Triptans	65	8.51	32,274	8.24	0.01
NSAIDs	309	40.45	158,406	40.45	0.00
Obstetric conditions, N (%)					
Multifetal gestation Flag	30	3.93	15,701	4.01	0.00
Markers of healthcare utilization					
Number of distinct 3 digit ICD 9 codes=0	27	3.53	12,431	3.17	0.02
Number of distinct 3 digit ICD 9 codes: tertile 1 for number >0	127	16.62	65,453	16.71	0.00
Number of distinct 3 digit ICD 9 codes: tertile 2 for number >0	168	21.99	86,870	22.18	0.00
Number of distinct 3 digit ICD 9 codes: tertile 3 for number >0	442	57.85	226,887	57.93	0.00
Number of ED visits=0	449	58.77	231,125	59.01	0.00
Number of ED visits=1	166	21.73	84,736	21.64	0.00
Number of ED visits=2	73	9.55	37,167	9.49	0.00
Number of ED visits>2	76	9.95	38,612	9.86	0.00
Number of non-duloxetine generics dispensed=0	<11	0.39	1,059	0.27	0.02
Number of non-duloxetine generics dispensed: tertile 1 for number >0	46	6.02	22,277	5.69	0.01
Number of non-duloxetine generics dispensed: tertile 2 for number >0	92	12.04	45,126	11.52	0.02
Number of non-duloxetine generics dispensed: tertile 3 for number >0	623	81.54	323,178	82.52	-0.03
Number of hospital admissions=0	684	89.53	350,452	89.48	0.00

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Number of hospital admissions=1	60	7.85	30,727	7.85	0.00
Number of hospital admissions=2	17	2.23	8,896	2.27	0.00
Number of hospital admissions>2	<11	0.39	1,566	0.4	0.00
Number of outpatient visits=0	56	7.33	27,141	6.93	0.02
Number of outpatient visits: tertile 1 for number >0	74	9.69	37,418	9.55	0.00
Number of outpatient visits: tertile 2 for number >0	187	24.48	96,484	24.64	0.00
Number of outpatient visits: tertile 3 for number >0	447	58.51	230,597	58.88	-0.01
Number of psychiatric hospitalizations Q1	737	96.47	377,873	96.48	0.00
Number of psychiatric hospitalizations Q2	23	3.01	11,690	2.98	0.00
Number of psychiatric hospitalizations Q3	<11	0.52	2,077	0.53	0.00
Number of psychiatric hospitalizations Q4	<11	0	<11	0	0.00
Number of psychiatrist visits=0	280	36.65	138,068	35.25	0.03
Number of psychiatrist visits=1	194	25.39	102,619	26.2	-0.02
Number of psychiatrist visits=2	88	11.52	46,184	11.79	-0.01
Number of psychiatrist visits>2	202	26.44	104,769	26.75	-0.01
Geographic region					
Arkansas	PPD		PPD		0.00
Alabama			1,608	0.41	0.00
California	49	6.41	23,926	6.11	0.01
Colorado	PPD		1,013	0.26	0.00
District of Columbia			PPD		0.00
Delaware	18	2.36	8,896	2.27	0.01
Florida	PPD		2,490	0.64	0.00
Georgia			3,029	0.77	0.00
Hawaii			471	0.12	0.00
Iowa			3,649	0.93	0.00
Idaho			PPD		0.00
Illinois	63	8.25	32,373	8.27	0.00
Indiana	74	9.69	38,025	9.71	0.00
Kansas	PPD		5,212	1.33	0.00
Kentucky	16	2.09	8,024	2.05	0.00
Louisiana	21	2.75	11,098	2.83	-0.01

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Massachusetts	PPD		1,024	0.26	0.00
Maryland			5,697	1.45	0.00
Maine			2,573	0.66	0.00
Minnesota	74	9.69	38,925	9.94	-0.01
Missouri	43	5.63	22,158	5.66	0.00
Mississippi	PPD		1,993	0.51	0.00
North Carolina	17	2.23	8,778	2.24	0.00
North Dakota	PPD		2,220	0.57	-0.01
Nebraska			4,109	1.05	0.00
New Hampshire			1,613	0.41	0.00
New Jersey	PPD		1,016	0.26	0.00
New Mexico			5,188	1.32	0.00
Nevada			PPD		0.00
New York	112	14.66	57,160	14.6	0.00
Ohio	13	1.7	6,887	1.76	0.00
Oklahoma	PPD		5,905	1.51	-0.01
Oregon	17	2.23	8,953	2.29	0.00
Pennsylvania	PPD		1,961	0.5	0.00
Rhode Island			471	0.12	0.00
South Carolina			1,054	0.27	0.00
South Dakota	PPD		1,042	0.27	0.00
Tennessee			19,652	5.02	0.00
Texas			505	0.13	0.00
Utah	25	3.27	11,938	3.05	0.01
Virginia	29	3.8	14,706	3.76	0.00
Vermont	PPD		5,174	1.32	0.00
Washington	PPD		558	0.14	0.00
Wisconsin			18,546	4.74	0.00
West Virginia			1,133	0.29	-0.01
Wyoming	PPD		889	0.23	0.01
Opioids					
buprenorphine	29	3.8	14,185	3.62	0.01

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
	<11	0	<11	0	0.00
codeine	193	25.26	100,637	25.7	-0.01
fentanyl	19	2.49	7,997	2.04	0.03
hydrocodone	390	51.05	200,798	51.27	0.00
hydromorphone	18	2.36	8,169	2.09	0.02
levorphanol	<11	0	<11	0	
meperidine	<11	0.26	1,006	0.26	0.00
methadone	11	1.44	5,372	1.37	0.01
morphine	24	3.14	10,398	2.66	0.03
oxycodone	190	24.87	95,616	24.41	0.01
oxymorphone	<11	0.39	1,484	0.38	0.00
pentazocine	<11	0.26	969	0.25	0.00
propoxyphene	72	9.42	37,964	9.69	-0.01
tapentadol	<11	0	<11	0	0.00
tramadol	148	19.37	73,973	18.89	0.01
Healthcare Utilization, mean (SD)					
Comorbidity Index	1.85	1.98	1.86	1.98	0.00
Morphine equivalents	8505.83	39972.94	8618.54	142506.69	0.00
Number of diagnoses	6.38	4.77	6.56	5	-0.04
Number of ED visits	0.83	1.41	0.87	1.74	-0.03
Number of non-duloxetine generics dispensed	10.93	6.39	10.93	6.33	0.00
Number of hospitalizations	0.13	0.43	0.14	0.51	-0.01
Number of outpatient visits	6.18	7.96	6.07	6.76	0.02
Number of psychiatric hospitalizations	0.04	0.22	0.04	0.22	0.00
Number of psychiatrist visits	2.55	5.25	2.48	5.11	0.02

15.2. 17. Preterm/SGA- Baseline characteristics of duloxetine exposed vs. SSRI exposed women - late exposure: fully adjusted

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Total	523	100.00	34,076	100.00	
Demographics					
Age, mean (SD)	28.42	5.27	28.29	5.44	0.02
Age categorical, N (%)					
<=19	25	4.78	1,645	4.83	0.00
20-24	97	18.55	6,619	19.42	-0.02
25-29	193	36.9	12,385	36.35	0.01
30-34	136	26	8,626	25.31	0.02
35-39	58	11.09	3,936	11.55	-0.01
>=40	14	2.68	866	2.54	0.01
Race, N (%)					
White	431	82.41	27,799	81.58	0.02
Black/African American	41	7.84	2,797	8.21	-0.01
Hispanic/Latino			733	2.15	-0.02
Asian or Other Pacific			469	1.38	0.00
American Indian			578	1.7	0.00
Other	16	3.06	1,129	3.31	-0.01
Unknown			571	1.68	0.00
Chronic comorbid conditions, N (%)					
Hypertension	73	13.96	4,819	14.14	-0.01
Diabetes	88	16.83	5,847	17.16	-0.01
Renal Disease	<11	1.72	667	1.96	-0.02
Obesity Overweight	56	10.71	3,676	10.79	0.00
Comorbidity Index Q1	166	31.74	10,580	31.05	0.01
Comorbidity Index Q2	116	22.18	7,752	22.75	-0.01
Comorbidity Index Q3	85	16.25	5,828	17.1	-0.02
Comorbidity Index Q4	156	29.83	9,916	29.1	0.02
Infections, N (%)					
Toxoplasmosis	<11	0	<11	0.01	-0.01
Rubella	<11	0	<11	0	0.00
Cytomegalovirus	<11	0	<11	0	-0.01

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Herpes	13	2.49	859	2.52	0.00
Syphilis	<11	0.19	56	0.16	0.01
Varicella	<11	0	11	0.03	-0.03
Parvovirus B19	<11	0	<11	0	-0.01
Zika virus other mosquito	<11	0	<11	0	
Lymphocytic choriomeningitis	<11	0	<11	0	
Influenza	<11	1.34	572	1.68	-0.03
Chlamydia	<11	0.38	146	0.43	-0.01
Human papilloma virus	<11	0.76	212	0.62	0.02
Gonorrhea	<11	0.76	259	0.76	0.00
HIV	<11	0.57	217	0.64	-0.01
Trichomoniasis	<11	0.76	276	0.81	0.00
Indications for duloxetine, N (%)					
Depression	329	62.91	21,481	63.04	0.00
Anxiety	231	44.17	15,237	44.71	-0.01
Neuropathic Pain	77	14.72	5,269	15.46	-0.02
Fibromyalgia	64	12.24	4,311	12.65	-0.01
Non neuropathic Pain	350	66.92	23,026	67.57	-0.01
Other psychiatric conditions, N (%)					
Sleep disorder	40	7.65	2,640	7.75	0.00
Bipolar disorder	92	17.59	6,216	18.24	-0.02
Psychosis	<11	1.15	398	1.17	0.00
Schizophrenia	<11	1.34	516	1.51	-0.01
Personality disorder	18	3.44	1,252	3.67	-0.01
Adjustment disorder	<11	1.91	603	1.77	0.01
Tobacco use, N (%)	124	23.71	8,138	23.88	0.00
Alcohol abuse or dependence, N (%)	<11	1.53	582	1.71	-0.01
Drug abuse or dependence, N (%)	14	2.68	1,201	3.52	-0.05
Other medication exposures, N (%)					
Benzodiazepines	231	44.17	15,469	45.4	-0.02
Other hypnotics	185	35.37	12,271	36.01	-0.01
Barbiturates	37	7.07	2,522	7.4	-0.01

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Anxiolytics	39	7.46	2,634	7.73	-0.01
Anticonvulsants	149	28.49	10,019	29.4	-0.02
Antipsychotics	124	23.71	8,325	24.43	-0.02
SSRIs	<11	0	34,076	100	
SNRIs	28	5.35	1,962	5.76	-0.02
Other Antidep	162	30.98	10,827	31.77	-0.02
Stimulants	49	9.37	3,501	10.27	-0.03
Antidiabetic	22	4.21	1,437	4.22	0.00
Insulin	33	6.31	2,129	6.25	0.00
Antihyperten	117	22.37	7,808	22.91	-0.01
Opioid analgesics	379	72.47	24,993	73.34	-0.02
Triptans	36	6.88	2,438	7.15	-0.01
NSAIDs	203	38.81	13,641	40.03	-0.02
Obstetric conditions, N (%)					
Multifetal gestation Flag	22	4.21	1,493	4.38	-0.01
Markers of healthcare utilization					
Number of distinct 3 digit ICD 9 codes=0	20	3.82	1,276	3.74	0.00
Number of distinct 3 digit ICD 9 codes: tertile 1 for number >0	94	17.97	5,835	17.12	0.02
Number of distinct 3 digit ICD 9 codes: tertile 2 for number >0	116	22.18	7,400	21.72	0.01
Number of distinct 3 digit ICD 9 codes: tertile 3 for number >0	293	56.02	19,565	57.42	-0.03
Number of ED visits=0	310	59.27	19,907	58.42	0.02
Number of ED visits=1	118	22.56	7,562	22.19	0.01
Number of ED visits=2	49	9.37	3,240	9.51	0.00
Number of ED visits>2	46	8.8	3,367	9.88	-0.04
Number of non-duloxetine generics dispensed=0	<11	0.38	145	0.42	-0.01
Number of non-duloxetine generics dispensed: tertile 1 for number >0	37	7.07	2,238	6.57	0.02
Number of non-duloxetine generics dispensed: tertile 2 for number >0	73	13.96	4,303	12.63	0.04
Number of non-duloxetine generics dispensed: tertile 3 for number >0	411	78.59	27,390	80.38	-0.04
Number of hospital admissions=0	487	93.12	31,334	91.95	0.04

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Number of hospital admissions=1	29	5.54	2,055	6.03	-0.02
Number of hospital admissions=2	<11	1.15	444	1.3	-0.01
Number of hospital admissions>2	<11	0.19	243	0.71	-0.08
Number of outpatient visits=0	43	8.22	2,709	7.95	0.01
Number of outpatient visits: tertile 1 for number >0	51	9.75	3,193	9.37	0.01
Number of outpatient visits: tertile 2 for number >0	137	26.2	8,784	25.78	0.01
Number of outpatient visits: tertile 3 for number >0	292	55.83	19,390	56.9	-0.02
Number of psychiatric hospitalizations Q1	514	98.28	33,384	97.97	0.02
Number of psychiatric hospitalizations Q2	<11	1.72	623	1.83	-0.01
Number of psychiatric hospitalizations Q3	<11	0	38	0.11	-0.05
Number of psychiatric hospitalizations Q4	<11	0	31	0.09	-0.04
Number of psychiatrist visits=0	197	37.67	12,669	37.18	0.01
Number of psychiatrist visits=1	144	27.53	9,169	26.91	0.01
Number of psychiatrist visits=2	57	10.9	3,669	10.77	0.00
Number of psychiatrist visits>2	125	23.9	8,569	25.15	-0.03
Geographic region					
Arkansas	PPD		PPD		-0.02
Alabama			53	0.15	-0.06
California	33	6.31	2,061	6.05	0.01
Colorado			125	0.37	0.00
District of Columbia	PPD		PPD		-0.01
Delaware			666	1.96	0.00
Florida			290	0.85	-0.01
Georgia			200	0.59	-0.06
Hawaii			66	0.19	0.00
Iowa			190	0.56	0.00
Idaho			32	0.1	-0.04
Illinois	41	7.84	2,537	7.45	0.01
Indiana	56	10.71	3,580	10.51	0.01
Kansas	PPD		538	1.58	0.01
Kentucky			521	1.53	0.00
Louisiana	15	2.87	934	2.74	0.01

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Massachusetts	PPD		141	0.41	-0.01
Maryland			449	1.32	0.00
Maine			252	0.74	0.00
Minnesota	57	10.9	3,613	10.6	0.01
Missouri	29	5.54	1,936	5.68	-0.01
Mississippi	PPD		202	0.59	0.00
North Carolina	13	2.49	852	2.5	0.00
North Dakota	PPD		256	0.75	0.00
Nebraska			310	0.91	0.00
New Hampshire			211	0.62	-0.01
New Jersey	PPD		34	0.1	-0.04
New Mexico			426	1.25	0.01
Nevada			PPD		-0.03
New York	81	15.49	5,057	14.84	0.02
Ohio	PPD		441	1.29	-0.03
Oklahoma			247	0.72	0.00
Oregon			757	2.22	0.00
Pennsylvania	PPD		377	1.11	-0.04
Rhode Island			70	0.2	0.00
South Carolina			117	0.34	0.01
South Dakota	PPD		110	0.32	-0.03
Tennessee			1,733	5.09	-0.01
Texas			55	0.16	0.01
Utah	PPD		765	2.24	0.00
Virginia	20	3.82	1,271	3.73	0.00
Vermont	PPD		579	1.7	0.00
Washington	PPD		14	0.04	-0.03
Wisconsin			1,848	5.42	-0.02
West Virginia			70	0.21	0.00
Wyoming	PPD		66	0.19	0.00
Opioids					
buprenorphine	21	4.02	1,510	4.43	-0.02

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
butorphanol	<11	0	<11	0.02	-0.02
codeine	120	22.94	8,472	24.86	-0.05
fentanyl	12	2.29	939	2.75	-0.03
hydrocodone	259	49.52	17,523	51.42	-0.04
hydromorphone	14	2.68	1,021	3	-0.02
levorphanol	<11	0	<11	0	0.00
meperidine	<11	0.19	98	0.29	-0.02
methadone	<11	0.96	354	1.04	-0.01
morphine	14	2.68	1,034	3.03	-0.02
oxycodone	121	23.14	8,390	24.62	-0.03
oxymorphone	<11	0.57	<11	0	0.11
pentazocine	<11	0.19	64	0.19	0.00
propoxyphene	38	7.27	2,658	7.8	-0.02
tapentadol	<11	0	<11	0.01	-0.01
tramadol	97	18.55	6,427	18.86	-0.01
Healthcare Utilization, mean (SD)					
Comorbidity Index	1.79	1.93	1.83	1.98	-0.02
Morphine equivalents	8991.64	46483.9	10440.85	172330.66	-0.01
Number of diagnoses	6.1	4.49	6.38	4.89	-0.06
Number of ED visits	0.79	1.34	0.88	1.69	-0.06
Number of non-duloxetine generics dispensed	10.09	5.78	11.31	6.74	-0.19
Number of hospitalizations	0.08	0.33	0.11	0.49	-0.07
Number of outpatient visits	5.74	7.59	5.87	6.61	-0.02
Number of psychiatric hospitalizations	0.02	0.13	0.02	0.18	-0.04
Number of psychiatrist visits	2.26	5.12	2.28	4.55	0.00

15.2. 18. Preterm/SGA- Baseline characteristics of duloxetine exposed vs. venlafaxine exposed women - late exposure: fully adjusted

	Duloxetine	Duloxetine	Venlafaxine	Venlafaxine	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Total	713	100.00	2,152	100.00	
Demographics					
Age, mean (SD)	28.55	5.5	28.54	5.68	0.00
Age categorical, N (%)					
<=19	32	4.49	109	5.07	-0.03
20-24	139	19.5	423	19.68	0.00
25-29	255	35.76	758	35.22	0.01
30-34	175	24.54	495	22.98	0.04
35-39	91	12.76	285	13.26	-0.01
>=40	21	2.95	82	3.79	-0.05
Race, N (%)					
White	575	80.65	1,723	80.07	0.01
Black/African American	59	8.27	181	8.41	0.00
Hispanic/Latino	17	2.38	45	2.09	0.02
Asian or Other Pacific	PPD		36	1.69	-0.01
American Indian			55	2.57	-0.05
Other	24	3.37	76	3.51	-0.01
Unknown	14	1.96	36	1.66	0.02
Chronic comorbid conditions, N (%)					
Hypertension	96	13.46	297	13.79	-0.01
Diabetes	130	18.23	409	19	-0.02
Renal Disease	14	1.96	44	2.04	-0.01
Obesity Overweight	83	11.64	228	10.6	0.03
Comorbidity Index Q1	220	30.86	664	30.85	0.00
Comorbidity Index Q2	157	22.02	484	22.5	-0.01
Comorbidity Index Q3	123	17.25	357	16.58	0.02
Comorbidity Index Q4	213	29.87	647	30.07	0.00
Infections, N (%)					
Toxoplasmosis	<11	0	<11	0	
Rubella	<11	0	<11	0	
Cytomegalovirus	<11	0	<11	0	

	Duloxetine	Duloxetine	Venlafaxine	Venlafaxine	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Herpes	16	2.24	38	1.76	0.03
Syphilis	<11	0.14	<11	0.11	0.01
Varicella	<11	0	<11	0	
Parvovirus B19	<11	0	<11	0	
Zika virus other mosquito	<11	0	<11	0	
Lymphocytic choriomeningitis	<11	0	<11	0	
Influenza	<11	1.4	23	1.05	0.03
Chlamydia	<11	0.56	14	0.67	-0.01
Human papilloma virus	<11	0.98	18	0.84	0.01
Gonorrhea	<11	0.7	14	0.64	0.01
HIV	<11	0.56	13	0.59	0.00
Trichomoniasis	<11	0.84	22	1.01	-0.02
Indications for duloxetine, N (%)					
Depression	469	65.78	1,434	66.64	-0.02
Anxiety	320	44.88	977	45.41	-0.01
Neuropathic Pain	114	15.99	339	15.73	0.01
Fibromyalgia	92	12.9	269	12.49	0.01
Non neuropathic Pain	482	67.6	1,435	66.68	0.02
Other psychiatric conditions, N (%)					
Sleep disorder	55	7.71	186	8.65	-0.03
Bipolar disorder	126	17.67	401	18.62	-0.02
Psychosis	12	1.68	42	1.97	-0.02
Schizophrenia	<11	1.26	29	1.33	-0.01
Personality disorder	23	3.23	79	3.69	-0.03
Adjustment disorder	11	1.54	45	2.08	-0.04
Tobacco use, N (%)	161	22.58	528	24.54	-0.05
Alcohol abuse or dependence, N (%)	12	1.68	40	1.85	-0.01
Drug abuse or dependence, N (%)	26	3.65	75	3.49	0.01
Other medication exposures, N (%)					
Benzodiazepines	334	46.84	1,008	46.84	0.00
Other hypnotics	259	36.33	788	36.6	-0.01
Barbiturates	60	8.42	162	7.53	0.03

	Duloxetine	Duloxetine	Venlafaxine	Venlafaxine	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Anxiolytics	62	8.7	174	8.07	0.02
Anticonvulsants	204	28.61	590	27.43	0.03
Antipsychotics	178	24.96	551	25.59	-0.01
SSRIs	219	30.72	641	29.81	0.02
SNRIs	<11	0	2,152	100	
Other Antidep	223	31.28	705	32.76	-0.03
Stimulants	62	8.7	199	9.27	-0.02
Antidiabetic	33	4.63	86	4	0.03
Insulin	46	6.45	155	7.19	-0.03
Antihyperten	162	22.72	503	23.38	-0.02
Opioid analgesics	530	74.33	1,599	74.28	0.00
Triptans	59	8.27	186	8.64	-0.01
NSAIDs	293	41.09	881	40.93	0.00
Obstetric conditions, N (%)					
Multifetal gestation Flag	28	3.93	92	4.26	-0.02
Markers of healthcare utilization					
Number of distinct 3 digit ICD 9 codes=0	25	3.51	78	3.61	-0.01
Number of distinct 3 digit ICD 9 codes: tertile 1 for number >0	122	17.11	364	16.89	0.01
Number of distinct 3 digit ICD 9 codes: tertile 2 for number >0	158	22.16	486	22.59	-0.01
Number of distinct 3 digit ICD 9 codes: tertile 3 for number >0	408	57.22	1,225	56.91	0.01
Number of ED visits=0	424	59.47	1,275	59.25	0.00
Number of ED visits=1	154	21.6	449	20.87	0.02
Number of ED visits=2	68	9.54	209	9.73	-0.01
Number of ED visits>2	67	9.4	218	10.15	-0.03
Number of non-duloxetine generics dispensed=0	<11	0.42	<11	0.39	0.01
Number of non-duloxetine generics dispensed: tertile 1 for number >0	45	6.31	144	6.67	-0.01
Number of non-duloxetine generics dispensed: tertile 2 for number >0	88	12.34	256	11.9	0.01
Number of non-duloxetine generics dispensed: tertile 3 for number >0	577	80.93	1,744	81.04	0.00
Number of hospital admissions=0	641	89.9	1,908	88.65	0.04

	Duloxetine	Duloxetine	Venlafaxine	Venlafaxine	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Number of hospital admissions=1	54	7.57	192	8.93	-0.05
Number of hospital admissions=2	15	2.1	45	2.11	0.00
Number of hospital admissions>2	<11	0.42	<11	0.31	0.02
Number of outpatient visits=0	51	7.15	163	7.57	-0.02
Number of outpatient visits: tertile 1 for number >0	73	10.24	207	9.63	0.02
Number of outpatient visits: tertile 2 for number >0	175	24.54	526	24.44	0.00
Number of outpatient visits: tertile 3 for number >0	414	58.06	1,256	58.37	-0.01
Number of psychiatric hospitalizations Q1	688	96.49	2,064	95.93	0.03
Number of psychiatric hospitalizations Q2	21	2.95	79	3.68	-0.04
Number of psychiatric hospitalizations Q3	<11	0.56	<11	0.4	0.02
Number of psychiatric hospitalizations Q4	<11	0	<11	0	
Number of psychiatrist visits=0	264	37.03	793	36.83	0.00
Number of psychiatrist visits=1	184	25.81	543	25.23	0.01
Number of psychiatrist visits=2	86	12.06	256	11.91	0.00
Number of psychiatrist visits>2	179	25.11	560	26.04	-0.02
Geographic region					
Arkansas	PPD		PPD		
Alabama					0.02
California	45	6.31	132	6.16	0.01
Colorado	PPD		PPD		0.00
District of Columbia					
Delaware	18	2.52	45	2.11	0.03
Florida	PPD		17	0.77	-0.01
Georgia	PPD		PPD		-0.01
Hawaii					
Iowa			15	0.7	0.03
Idaho			PPD		
Illinois	59	8.27	173	8.06	0.01
Indiana	71	9.96	208	9.68	0.01
Kansas	PPD		34	1.56	-0.01
Kentucky	14	1.96	42	1.93	0.00
Louisiana	21	2.95	59	2.73	0.01

	Duloxetine	Duloxetine	Venlafaxine	Venlafaxine	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Massachusetts	PPD		PPD		0.00
Maryland	PPD		31	1.43	0.01
Maine	PPD		PPD		0.02
Minnesota	62	8.7	211	9.79	-0.04
Missouri	42	5.89	152	7.07	-0.05
Mississippi	PPD		PPD		0.00
North Carolina	17	2.38	54	2.49	-0.01
North Dakota	PPD		14	0.67	-0.01
Nebraska	PPD		18	0.85	0.03
New Hampshire	PPD		PPD		0.00
New Jersey	PPD		PPD		0.01
New Mexico	PPD		26	1.21	0.02
Nevada	PPD		PPD		
New York	104	14.59	317	14.73	0.00
Ohio	13	1.82	37	1.7	0.01
Oklahoma	PPD		26	1.21	0.02
Oregon	15	2.1	43	2	0.01
Pennsylvania	PPD		PPD		0.00
Rhode Island	PPD		PPD		0.02
South Carolina	PPD		PPD		0.01
South Dakota	PPD		PPD		0.00
Tennessee	37	5.19	103	4.81	0.02
Texas	PPD		PPD		0.02
Utah	21	2.95	64	2.99	0.00
Virginia	27	3.79	87	4.06	-0.01
Vermont	PPD		30	1.39	-0.01
Washington	PPD		PPD		-0.01
Wisconsin	36	5.05	112	5.22	-0.01
West Virginia	PPD		PPD		0.00
Wyoming	PPD		PPD		0.02
Opioids					
buprenorphine	25	3.51	78	3.64	-0.01

	Duloxetine	Duloxetine	Venlafaxine	Venlafaxine	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
butorphanol	<11	0	<11	0	
codeine	181	25.39	540	25.1	0.01
fentanyl	18	2.52	54	2.49	0.00
hydrocodone	359	50.35	1,079	50.12	0.00
hydromorphone	15	2.1	42	1.95	0.01
levorphanol	<11	0	<11	0	
meperidine	<11	0.28	<11	0.25	0.01
methadone	<11	1.4	32	1.51	-0.01
morphine	21	2.95	51	2.38	0.04
oxycodone	172	24.12	518	24.06	0.00
oxymorphone	<11	0.42	<11	0.48	-0.01
pentazocine	<11	0.14	<11	0.22	-0.02
propoxyphene	68	9.54	210	9.77	-0.01
tapentadol	<11	0	<11	0	
tramadol	134	18.79	395	18.34	0.01
Healthcare Utilization, mean (SD)					
Comorbidity Index	1.84	1.98	1.89	2.05	-0.02
Morphine equivalents	7982.9	38362.2	7226.48	167409.41	0.01
Number of diagnoses	6.3	4.72	6.31	5	0.00
Number of ED visits	0.81	1.4	0.87	1.62	-0.04
Number of non-duloxetine generics dispensed	10.77	6.33	11.4	6.55	-0.10
Number of hospitalizations	0.13	0.43	0.15	0.47	-0.03
Number of outpatient visits	6.16	8.11	5.91	6.53	0.03
Number of psychiatric hospitalizations	0.04	0.22	0.04	0.23	-0.02
Number of psychiatrist visits	2.55	5.37	2.49	5.53	0.01

15.2. 19. Preterm/SGA- Absolute risks for early exposure

	Exposed					Reference							
Outcome	Events	N	Risk (/1,000)	95% CI		Events	N	Risk (/1,000)	95% CI		RR	95% CI	
				lower	upper				lower	upper		lower	upper
Duloxetine versus Unexposed													
Preterm	417	2,903	143.6	131.1	156.9	147,034	1,364,247	107.8	107.3	108.3	1.33	1.22	1.46
Small for gestational age	86	2,903	29.6	23.8	36.5	27,767	1,364,247	20.4	20.1	20.6	1.46	1.18	1.79
Duloxetine versus SSRI													
Preterm	282	1,989	141.8	126.7	157.9	9,013	67,222	134.1	131.5	136.7	1.06	0.95	1.18
Small for gestational age	60	1,989	30.2	23.1	38.7	1,697	67,222	25.2	24.1	26.5	1.19	0.93	1.54
Duloxetine versus Venlafaxine													
Preterm	402	2,779	144.7	131.8	158.3	1,008	7,258	138.9	131	147.1	1.04	0.94	1.16
Small for gestational age	79	2,779	28.4	22.6	35.3	166	7,258	22.9	19.6	26.6	1.24	0.95	1.62

15.2. 20. Preterm/SGA- Absolute risks for late exposure

	Exposed					Reference							
Outcome	Events	N	Risk (/1,000)	95% CI		Events	N	Risk (/1,000)	95% CI		RR	95% CI	
				lower	upper				lower	upper		lower	upper
Duloxetine versus Unexposed													
Preterm	179	880	203.4	177.3	231.5	147,007	1,364,101	107.8	107.2	108.3	1.89	1.66	2.15
Small for gestational age	29	880	33.0	22.2	47.0	27,762	1,364,101	20.4	20.1	20.6	1.62	1.13	2.32
Duloxetine versus SSRI													
Preterm	128	621	206.1	175.0	240.1	7,685	46,098	166.7	163.3	170.1	1.24	1.06	1.44
Small for gestational age	18	621	29.0	17.3	45.4	1,189	46,098	25.8	24.4	27.3	1.12	0.71	1.78
Duloxetine versus Venlafaxine													
Preterm	167	828	201.7	174.9	230.7	559	2,770	201.8	187	217.2	1.00	0.86	1.17
Small for gestational age	26	828	31.4	20.6	45.7	61	2,770	22	16.9	28.2	1.43	0.91	2.24

15.2. 21. Preterm/SGA- Relative risks for duloxetine exposed vs. unexposed women

15.2.21.1 Unadjusted Analyses

	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Early							
Preterm	28.51	5.52	28.39	5.57	28.51	5.52	28.39
Small for gestational age	28.51	5.52	28.39	5.57	28.51	5.52	28.39
Late							
Preterm	179	880	147,007	1,364,101	1.89	1.66	2.15
Small for gestational age	29	880	27,762	1,364,101	1.62	1.13	2.32

15.2.21.2 Adjusted: Restricted + PS1 (indications)

	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Early							
Preterm	374	2,548	53,716	448,960	1.11	1.01	1.22
Small for gestational age	80	2,548	10,387	448,960	1.26	1.01	1.56
Late							
Preterm	155	764	53,694	448,839	1.44	1.25	1.66
Small for gestational age	28	764	10,382	448,839	1.40	0.97	2.01

15.2.21.3 Adjusted: Restricted + PS2 (All covariates)

	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Early							
Preterm	374	2,547	51,748	433,219	1.01	0.92	1.10
Small for gestational age	80	2,547	10,030	433,219	1.14	0.92	1.41
Late							
Preterm	155	764	47,773	391,641	1.19	1.04	1.37

	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Small for gestational age	28	764	9,188	391,641	1.20	0.83	1.72

15.2.21.4 Adjusted: Restricted + hdPS

	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Early							
Preterm	373	2,543	51,209	429,290	0.99	0.90	1.09
Small for gestational age	80	2,543	9,939	429,290	1.10	0.89	1.37
Late							
Preterm	154	760	48,374	407,136	1.13	0.98	1.31
Small for gestational age	28	760	9,469	407,136	1.12	0.78	1.61

15.2. 22. Preterm/SGA- Relative risks for duloxetine exposed vs. SSRI exposed women

15.2.22.1 Unadjusted Analyses

	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Early							
Preterm	282	1,989	9,013	67,222	1.06	0.95	1.18
Small for gestational age	60	1,989	1,697	67,222	1.19	0.93	1.54
Late							
Preterm	128	621	7,685	46,098	1.24	1.06	1.44
Small for gestational age	18	621	1,189	46,098	1.12	0.71	1.78

15.2.22.2 Adjusted: Restricted + PS1 (Indications)

	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Early							
Preterm	251	1,715	7,144	51,847	1.03	0.92	1.16
Small for gestational age	56	1,715	1,354	51,847	1.24	0.95	1.61
Late							
Preterm	110	524	5,610	34,081	1.21	1.02	1.43
Small for gestational age	17	524	897	34,081	1.20	0.75	1.93

15.2.22.3 Adjusted: Restricted + PS2 (All covariates)

	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Early							
Preterm	251	1,713	6,953	50,616	0.95	0.84	1.06
Small for gestational age	56	1,713	1,320	50,616	1.26	0.97	1.64
Late							
Preterm	110	523	5,609	34,076	1.02	0.87	1.21
Small for gestational age	17	523	897	34,076	1.17	0.73	1.88

15.2.22.4 Adjusted: Restricted + hdPS

	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Early							
Preterm	250	1,712	7,142	51,845	0.92	0.82	1.04
Small for gestational age	55	1,712	1,353	51,845	1.19	0.91	1.55
Late							
Preterm	109	521	5,364	33,133	1.05	0.88	1.24
Small for gestational age	16	521	870	33,133	0.98	0.60	1.59

15.2. 23. Preterm/SGA- Relative risks for duloxetine exposed vs. venlafaxine exposed women

15.2.23.1 Unadjusted Analyses

	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Early							
Preterm	402	2,779	1,008	7,258	1.04	0.94	1.16
Small for gestational age	79	2,779	166	7,258	1.24	0.95	1.62
Late							
Preterm	167	828	559	2,770	1.00	0.86	1.17
Small for gestational age	26	828	61	2,770	1.43	0.91	2.24

15.2.23.2 Adjusted: Restricted + PS1 (indications)

	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Early							
Preterm	360	2,436	837	5,954	1.01	0.90	1.13
Small for gestational age	73	2,436	135	5,954	1.25	0.95	1.65
Late							
Preterm	144	717	454	2,230	0.98	0.83	1.16
Small for gestational age	25	717	49	2,230	1.60	0.99	2.57

15.2.23.3 Adjusted: Restricted + PS2 (All covariates)

	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Early							
Preterm	358	2,429	826	5,864	0.94	0.84	1.06
Small for gestational age	72	2,429	133	5,864	1.18	0.90	1.56
Late							
Preterm	144	713	439	2,152	0.88	0.75	1.04
Small for gestational age	25	713	48	2,152	1.32	0.83	2.09

15.2.23.4 Adjusted: Restricted + hdPS

	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Early							
Preterm	353	2,414	798	5,658	0.95	0.84	1.06
Small for gestational age	73	2,414	124	5,658	1.57	1.17	2.11
Late							
Preterm	130	669	419	2,106	0.80	0.67	0.94
Small for gestational age	24	669	45	2,106	1.33	0.83	2.13

15.2. 24. Preterm/SGA- Sensitivity Analyses #1: Re-define exposure as having filled ≥ 2 prescriptions

15.2.24.1 Unadjusted Analysis

	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Duloxetine versus Unexposed							
Early							
Preterm	222	1,322	147,034	1,364,247	1.56	1.38	1.76
Small for gestational age	43	1,322	27,767	1,364,247	1.60	1.19	2.14
Late							
Preterm	111	567	147,007	1,364,101	1.82	1.54	2.15
Small for gestational age	19	567	27,762	1,364,101	1.65	1.06	2.56
Duloxetine versus SSRI							
Early							
Preterm	154	947	4,991	35,730	1.16	1.01	1.35
Small for gestational age	28	947	895	35,730	1.18	0.81	1.71
Late							
Preterm	79	421	4,381	27,206	1.17	0.95	1.42
Small for gestational age	14	421	666	27,206	1.36	0.81	2.29
Duloxetine versus Venlafaxine							
Early							
Preterm	212	1,268	563	3,723	1.11	0.96	1.28
Small for gestational age	38	1,268	78	3,723	1.43	0.98	2.10
Late							
Preterm	106	545	384	1,937	0.98	0.81	1.19
Small for gestational age	19	545	40	1,937	1.69	0.99	2.89

15.2.24.2 Adjusted: Restricted + PS1 (indications)

	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Duloxetine versus Unexposed							
Early							

Preterm	199	1,176	53,716	448,960	1.27	1.12	1.44
Small for gestational age	43	1,176	10,387	448,960	1.44	1.07	1.93
Late							
Preterm	98	496	53,694	448,839	1.40	1.17	1.67
Small for gestational age	19	496	10,382	448,839	1.45	0.94	2.26
Duloxetine versus SSRI							
Early							
Preterm	138	826	4,062	28,225	1.14	0.98	1.33
Small for gestational age	28	826	715	28,225	1.29	0.89	1.87
Late							
Preterm	69	363	3,367	20,645	1.10	0.89	1.36
Small for gestational age	14	363	511	20,645	1.47	0.87	2.47
Duloxetine versus Venlafaxine							
Early							
Preterm	190	1,124	473	3,075	1.11	0.95	1.29
Small for gestational age	38	1,124	63	3,075	1.53	1.03	2.26
Late							
Preterm	93	476	321	1,571	0.97	0.79	1.19
Small for gestational age	19	476	33	1,571	1.78	1.03	3.07

15.2.24.3 Adjusted: Restricted + PS2 Indications

	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Duloxetine versus Unexposed							
Early							
Preterm	199	1,176	49,746	414,742	1.11	0.97	1.26
Small for gestational age	43	1,176	9,650	414,742	1.30	0.97	1.74
Late							
Preterm	98	496	42,079	339,806	1.12	0.93	1.33
Small for gestational age	19	496	8,018	339,806	1.26	0.81	1.96
Duloxetine versus SSRI							
Early							
Preterm	138	825	3,954	27,591	1.04	0.89	1.21
Small for gestational age	28	825	703	27,591	1.32	0.91	1.91

Late							
Preterm	69	359	3,108	19,186	0.95	0.77	1.17
Small for gestational age	14	359	470	19,186	1.34	0.79	2.25
Duloxetine versus Venlafaxine							
Early							
Preterm	189	1,122	464	2,988	0.95	0.81	1.10
Small for gestational age	37	1,122	61	2,988	1.35	0.92	2.00
Late							
Preterm	91	465	288	1,389	0.76	0.62	0.93
Small for gestational age	19	465	30	1,389	2.18	1.22	3.90

15.2. 25. Preterm/SGA- Sensitivity Analyses #2: Re-define exposure as days supply overlap

15.2.25.1 Unadjusted Analyses

	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Duloxetine versus Unexposed							
Early							
Preterm	540	3,724	147,034	1,364,247	1.35	1.24	1.45
Small for gestational age	101	3,724	27,767	1,364,247	1.33	1.10	1.62
Late							
Preterm	196	1,003	147,007	1,364,101	1.81	1.60	2.06
Small for gestational age	37	1,003	27,762	1,364,101	1.81	1.32	2.49
Duloxetine versus SSRI							
Early							
Preterm	370	2,574	9,013	67,222	1.07	0.97	1.18
Small for gestational age	70	2,574	1,697	67,222	1.08	0.85	1.36
Late							
Preterm	136	700	7,685	46,098	1.17	1.00	1.36
Small for gestational age	22	700	1,189	46,098	1.22	0.80	1.85
Duloxetine versus Venlafaxine							
Early							
Preterm	520	3,561	1,008	7,258	1.05	0.95	1.16
Small for gestational age	94	3,561	166	7,258	1.15	0.90	1.48
Late							
Preterm	184	942	559	2,770	0.97	0.83	1.12
Small for gestational age	31	942	61	2,770	1.49	0.98	2.29

15.2.25.2 Adjusted: Restricted + PS1 (indications)

	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Duloxetine versus Unexposed							
Early							
Preterm	484	3,261	53,716	448,960	1.12	1.03	1.21

Preterm	118	590	5,306	32,644	1.01	0.86	1.19
Small for gestational age	21	590	854	32,644	1.36	0.89	2.08
Duloxetine versus Venlafaxine							
Early							
Preterm	464	3,106	825	5,832	0.95	0.86	1.05
Small for gestational age	83	3,106	131	5,832	1.14	0.87	1.49
Late							
Preterm	158	811	438	2,131	0.84	0.71	0.98
Small for gestational age	30	811	48	2,131	1.40	0.90	2.16

15.2. 26. Preterm/SGA- Sensitivity Analyses #3: Restrict cohort to women with a recorded diagnosis of fibromyalgia

15.2.26.1 Unadjusted Analyses

	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Duloxetine versus Unexposed							
Early							
Preterm	334	2,368	119,876	1,130,713	1.33	1.20	1.47
Small for gestational age	74	2,368	23,249	1,130,713	1.52	1.21	1.90
Late							
Preterm	144	708	119,854	1,130,598	1.92	1.66	2.22
Small for gestational age	26	708	23,246	1,130,598	1.79	1.22	2.61
Duloxetine versus SSRI							
Early							
Preterm	231	1,615	7,410	55,649	1.07	0.95	1.21
Small for gestational age	51	1,615	1,412	55,649	1.24	0.95	1.64
Late							
Preterm	108	496	6,305	38,209	1.32	1.12	1.56
Small for gestational age	15	496	996	38,209	1.16	0.70	1.92
Duloxetine versus Venlafaxine							
Early							
Preterm	324	2,267	856	6,211	1.04	0.92	1.17
Small for gestational age	67	2,267	142	6,211	1.29	0.97	1.72
Late							
Preterm	135	668	480	2,370	1.00	0.84	1.18
Small for gestational age	24	668	51	2,370	1.67	1.04	2.69

15.2.26.2 Adjusted: Restricted + PS1 (indications)

	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Duloxetine versus Unexposed							
Early							
Preterm	49	360	2,560	19,262	0.91	0.70	1.19

Preterm	12	49	114	768	1.37	0.82	2.29
Small for gestational age	<11	49	20	768	2.61	0.80	8.56
Duloxetine versus Venlafaxine							
Early							
Preterm	35	265	37	264	0.62	0.42	0.91
Small for gestational age	11	265	<11	264	1.28	0.53	3.08
Late							
Preterm	<11	18	14	64	0.95	0.41	2.19
Small for gestational age	0	18	0	64	-	-	-

15.2. 27. Preterm/SGA- Sensitivity Analyses #4: Correct relative risks for outcome misclassification

For preterm delivery

Target PPV= 78 (CI: 65-88)

Distribution for bias parameters: Sensitivity: Min=0.5, Mode 1=0.75, Mode 2=0.75, Max=1.0; Specificity: Min=0.97, Mode 1=0.98, Mode 2=0.99, Max=0.996

Outcome- Preterm										
Early										
		1:1 PS matched analysis			Total Error Analysis					
Exposure	Reference	Odds ratio	95% CI lower	95% CI upper	Odds ratio	95% CI lower	95% CI upper	Width CI	% change in CI width over traditional	% change in OR
Duloxetine	Unexposed	0.89	0.76	1.03	0.87	0.74	1.04	1.41	5%	-1.99%
Duloxetine	SSRI	0.87	0.72	1.04	0.84	0.69	1.04	1.49	4%	-2.87%
Duloxetine	Venlafaxine	0.98	0.83	1.15	0.98	0.82	1.16	1.42	2%	-0.09%
Late										
Exposure	Reference	Odds ratio	95% CI lower	95% CI upper	Odds ratio	95% CI lower	95% CI upper	Width CI	% change in CI width over traditional	% change in OR
Duloxetine	Unexposed	1.44	1.10	1.87	1.53	1.13	2.03	1.79	6%	6.51%
Duloxetine	SSRI	1.07	0.79	1.45	1.08	0.80	1.50	1.88	3%	0.54%
Duloxetine	Venlafaxine	0.86	0.67	1.12	0.84	0.63	1.09	1.72	0%	-3.27%

For Small for gestational age

Target PPV= 84 (CI: 72-92)

Distribution for bias parameters: Sensitivity: Min=0.2, Mode 1=0.3, Mode 2=0.3, Max=0.4; Specificity: Min=0.99, Mode 1=0.993, Mode 2=0.993, Max=0.996

Outcome- Small for gestational age										
Early										
		1:1 PS matched analysis			Total Error Analysis					
Exposure	Reference	Odds ratio	95% CI lower	95% CI upper	Odds ratio	95% CI lower	95% CI upper	Width CI	% change in CI width over traditional	% change in OR
Duloxetine	Unexposed	1.00	0.73	1.37	1.00	0.76	1.30	1.71	-8%	-0.11%

Duloxetine	SSRI	1.53	1.01	2.33	1.83	1.28	2.64	2.07	-7%	19.81%
Duloxetine	Venlafaxine	1.32	0.93	1.90	1.50	1.08	2.03	1.88	-5%	13.31%
Late										
Exposure	Reference	Odds ratio	95% CI lower	95% CI upper	Odds ratio	95% CI lower	95% CI upper	Width CI	% change in CI width over traditional	% change in OR
Duloxetine	Unexposed	1.08	0.63	1.86	1.11	0.72	1.77	2.47	-17%	3.11%
Duloxetine	SSRI	1.43	0.68	3.03	1.69	0.87	3.39	3.91	-14%	18.21%
Duloxetine	Venlafaxine	1.43	0.76	2.68	1.63	0.97	2.92	3.02	-18%	14.30%

15.2. 28. Preterm/SGA- Sensitivity Analyses #5: Redefine outcome based on claims profile review

Duloxetine versus Unexposed							
		Exposed		Reference			
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Definition #1: if outcome likely occurred							
Early							
Preterm	270	2548	298	2548	0.91	0.78	1.06
Small for gestational age	58	2548	51	2548	1.14	0.78	1.65
Late							
Preterm	107	764	82	764	1.30	1.00	1.71
Small for gestational age	19	764	19	764	1.00	0.53	1.87
Definition #2: if outcome "likely occurred" or "probably occurred"							
Early							
Preterm	308	2548	332	2548	0.93	0.80	1.07
Small for gestational age	74	2548	75	2548	0.99	0.72	1.35
Late							
Preterm	123	764	87	764	1.41	1.09	1.83
Small for gestational age	27	764	23	764	1.17	0.68	2.03

15.2. 29. Preterm/SGA- Sensitivity Analyses #6: Restrict cohort to the first pregnancy occurring within the study period

15.2.29.1 Adjusted: Restricted + PS1 (indications)

	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Duloxetine versus Unexposed							
Early							
Preterm	293	2,063	43,260	366,707	1.09	0.98	1.21
Small for gestational age	70	2,063	8,576	366,707	1.35	1.07	1.69
Late							
Preterm	123	607	43,242	366,611	1.46	1.25	1.71
Small for gestational age	25	607	8,573	366,611	1.54	1.05	2.26
Duloxetine versus SSRI							
Early							
Preterm	202	1,383	5,854	42,698	1.03	0.91	1.17
Small for gestational age	49	1,383	1,119	42,698	1.32	0.99	1.74
Late							
Preterm	92	413	4,578	28,090	1.30	1.08	1.56
Small for gestational age	14	413	735	28,090	1.24	0.74	2.08
Duloxetine versus Venlafaxine							
Early							
Preterm	284	1,972	708	5,082	1.01	0.89	1.15
Small for gestational age	63	1,972	114	5,082	1.37	1.01	1.84
Late							
Preterm	115	571	391	1,914	0.98	0.81	1.18
Small for gestational age	23	571	40	1,914	1.93	1.16	3.19

15.2.29.2 Adjusted: Restricted + PS2 (All)

	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Duloxetine versus Unexposed							
Early							
Preterm	293	2,062	41,213	349,242	0.98	0.88	1.09
Small for gestational age	70	2,062	8,197	349,242	1.21	0.96	1.52
Late							
Preterm	123	607	36,753	303,870	1.21	1.03	1.41
Small for gestational age	25	607	7,292	303,870	1.29	0.88	1.90
Duloxetine versus SSRI							
Early							
Preterm	202	1,382	5,713	41,799	0.94	0.83	1.07
Small for gestational age	49	1,382	1,095	41,799	1.34	1.01	1.77
Late							
Preterm	92	412	4,578	28,086	1.07	0.90	1.29
Small for gestational age	14	412	735	28,086	1.13	0.67	1.90
Duloxetine versus Venlafaxine							
Early							
Preterm	282	1,965	700	4,985	0.93	0.82	1.05
Small for gestational age	62	1,965	111	4,985	1.45	1.07	1.98
Late							
Preterm	115	567	368	1,797	0.84	0.70	1.01
Small for gestational age	23	567	37	1,797	2.05	1.22	3.43

15.3. 1. Preeclampsia- Baseline characteristics of duloxetine exposed vs. unexposed women- early exposure: unadjusted

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Total	3,059	.	1,447,644	.	.
Demographics					
Age, mean (SD)	27.78	5.48	24.97	5.38	0.52
Age categorical, N (%)					
<=19	150	4.9	222,754	15.39	-0.35
20-24	767	25.07	558,716	38.59	-0.29
25-29	1,051	34.36	383,699	26.51	0.17
30-34	697	22.79	186,743	12.9	0.26
35-39	311	10.17	78,147	5.4	0.18
>=40	83	2.71	17,585	1.21	0.11
Race, N (%)					
White	2,417	79.01	578,936	39.99	0.87
Black/African American	264	8.63	448,412	30.98	-0.58
Hispanic/Latino	96	3.14	216,254	14.94	-0.42
Asian or Other Pacific	40	1.31	63,328	4.37	-0.19
American Indian	41	1.34	23,377	1.61	-0.02
Other	131	4.28	81,123	5.6	-0.06
Unknown	70	2.29	36,214	2.5	-0.01
Chronic comorbid conditions, N (%)					
Hypertension	277	9.06	47,747	3.3	0.24
Diabetes	217	7.09	46,027	3.18	0.18
Renal Disease	35	1.14	7,165	0.49	0.07
Obesity Overweight	234	7.65	49,898	3.45	0.18
Comorbidity Index Q1	1,051	34.36	768,585	53.09	-0.38
Comorbidity Index Q2	753	24.62	355,512	24.56	0.00
Comorbidity Index Q3	533	17.42	169,465	11.71	0.16
Comorbidity Index Q4	722	23.6	154,082	10.64	0.35
Infections, N (%)					
Toxoplasmosis	0	0	257	0.02	-0.02
Rubella	0	0	199	0.01	-0.02
Cytomegalovirus	0	0	76	0.01	-0.01

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Herpes	59	1.93	14,359	0.99	0.08
Syphilis	<11	0.07	1,704	0.12	-0.02
Varicella	<11	0.03	343	0.02	0.01
Parvovirus B19	0	0	71	0	-0.01
Zika virus other mosquito	0	0	0	0	0.00
Lymphocytic choriomeningitis	<11	0.03	12	0	0.02
Influenza	28	0.92	12,096	0.84	0.01
Chlamydia	15	0.49	12,511	0.86	-0.05
Human papilloma virus	33	1.08	9,293	0.64	0.05
Gonorrhea	18	0.59	14,236	0.98	-0.04
HIV	11	0.36	5,451	0.38	0.00
Trichomoniasis	29	0.95	23,897	1.65	-0.06
Indications for duloxetine, N (%)	.	.	.	.	.
Depression	1,551	50.7	98,385	6.8	1.11
Anxiety	969	31.68	65,689	4.54	0.75
Neuropathic Pain	354	11.57	26,823	1.85	0.40
Fibromyalgia	343	11.21	15,415	1.06	0.43
Non neuropathic Pain	1,633	53.38	258,385	17.85	0.80
Other psychiatric conditions, N (%)	.	.	.	.	.
Sleep disorder	187	6.11	13,117	0.91	0.29
Bipolar disorder	442	14.45	22,838	1.58	0.49
Psychosis	32	1.05	3,553	0.25	0.10
Schizophrenia	33	1.08	2,920	0.2	0.11
Personality disorder	72	2.35	3,467	0.24	0.19
Adjustment disorder	38	1.24	6,268	0.43	0.09
Tobacco use, N (%)	405	13.24	70,896	4.9	0.29
Alcohol abuse or dependence, N (%)	46	1.5	6,001	0.41	0.11
Drug abuse or dependence, N (%)	110	3.6	15,502	1.07	0.17
Other medication exposures, N (%)	.	.	.	.	.
Benzodiazepines	1,204	39.36	55,793	3.85	0.96
Other hypnotics	814	26.61	66,077	4.56	0.64
Barbiturates	211	6.9	24,291	1.68	0.26

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Anxiolytics	181	5.92	7,729	0.53	0.31
Anticonvulsants	807	26.38	35,489	2.45	0.72
Antipsychotics	641	20.95	23,013	1.59	0.64
SSRIs	955	31.22	109,933	7.59	0.63
SNRIs	132	4.32	12,489	0.86	0.22
Other Antidep	872	28.51	49,950	3.45	0.73
Stimulants	251	8.21	12,862	0.89	0.36
Antidiabetic	129	4.22	16,868	1.17	0.19
Insulin	109	3.56	17,644	1.22	0.15
Antihyperten	479	15.66	52,440	3.62	0.42
Opioid analgesics	1,999	65.35	395,337	27.31	0.83
Triptans	221	7.22	18,518	1.28	0.30
NSAIDs	1,162	37.99	258,459	17.85	0.46
Obstetric conditions, N (%)	.	.	.	.	.
Multifetal gestation Flag	104	3.4	54,470	3.76	-0.02
Markers of healthcare utilization	.	.	.	.	.
Number of distinct 3 digit ICD 9 codes=0	158	5.17	436,920	30.18	-0.69
Number of distinct 3 digit ICD 9 codes: tertile 1 for number >0	572	18.7	427,035	29.5	-0.25
Number of distinct 3 digit ICD 9 codes: tertile 2 for number >0	656	21.44	259,969	17.96	0.09
Number of distinct 3 digit ICD 9 codes: tertile 3 for number >0	1,673	54.69	323,720	22.36	0.70
Number of ED visits=0	1,899	62.08	1,129,223	78	-0.35
Number of ED visits=1	653	21.35	211,751	14.63	0.18
Number of ED visits=2	267	8.73	67,396	4.66	0.16
Number of ED visits>2	240	7.85	39,274	2.71	0.23
Number of non-duloxetine generics dispensed=0	211	6.9	640,389	44.24	-0.95
Number of non-duloxetine generics dispensed: tertile 1 for number >0	223	7.29	221,349	15.29	-0.25
Number of non-duloxetine generics dispensed: tertile 2 for number >0	650	21.25	313,532	21.66	-0.01
Number of non-duloxetine generics dispensed: tertile 3 for number >0	1,975	64.56	272,374	18.81	1.05
Number of hospital admissions=0	2,930	95.78	1,395,739	96.41	-0.03

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Number of hospital admissions=1	114	3.73	46,566	3.22	0.03
Number of hospital admissions=2	13	0.42	4,778	0.33	0.02
Number of hospital admissions>2	<11	0.07	561	0.04	0.01
Number of outpatient visits=0	287	9.38	541,102	37.38	-0.70
Number of outpatient visits: tertile 1 for number >0	329	10.76	290,152	20.04	-0.26
Number of outpatient visits: tertile 2 for number >0	757	24.75	328,732	22.71	0.05
Number of outpatient visits: tertile 3 for number >0	1,686	55.12	287,658	19.87	0.78
Number of psychiatric hospitalizations Q1	2,964	96.89	1,439,269	99.42	-0.19
Number of psychiatric hospitalizations Q2	84	2.75	7,589	0.52	0.18
Number of psychiatric hospitalizations Q3	<11	0.29	662	0.05	0.06
Number of psychiatric hospitalizations Q4	<11	0.07	124	0.01	0.03
Number of psychiatrist visits=0	1,338	43.74	1,305,598	90.19	-1.14
Number of psychiatrist visits=1	631	20.63	72,204	4.99	0.48
Number of psychiatrist visits=2	329	10.76	24,716	1.71	0.38
Number of psychiatrist visits>2	761	24.88	45,126	3.12	0.66
Geographic region					
Arkansas	PPD		1,227	0.08	0.01
Alabama	23	0.75	9,535	0.66	0.01
California	229	7.49	308,681	21.32	-0.40
Colorado	PPD		5,500	0.38	-0.03
District of Columbia			682	0.05	0.02
Delaware	76	2.48	12,486	0.86	0.13
Florida	24	0.78	31,773	2.19	-0.12
Georgia	16	0.52	32,305	2.23	-0.15
Hawaii	PPD		9,847	0.68	-0.09
Iowa	29	0.95	8,381	0.58	0.04
Idaho	PPD		1,593	0.11	0.04
Illinois	325	10.62	135,576	9.37	0.04
Indiana	267	8.73	47,687	3.29	0.23
Kansas	44	1.44	10,920	0.75	0.07
Kentucky	49	1.6	26,521	1.83	-0.02
Louisiana	110	3.6	31,053	2.15	0.09

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Massachusetts	PPD		10,666	0.74	-0.07
Maryland	40	1.31	26,482	1.83	-0.04
Maine	PPD		3,945	0.27	0.00
Minnesota	178	5.82	50,852	3.51	0.11
Missouri	153	5	38,231	2.64	0.12
Mississippi	14	0.46	22,007	1.52	-0.11
North Carolina	67	2.19	17,308	1.2	0.08
North Dakota	28	0.92	3,809	0.26	0.09
Nebraska	31	1.01	5,628	0.39	0.07
New Hampshire	PPD		3,451	0.24	0.01
New Jersey	0	0	15,256	1.05	-0.15
New Mexico	25	0.82	20,185	1.39	-0.06
Nevada	PPD		1,461	0.1	0.00
New York	521	17.03	232,253	16.04	0.03
Ohio	55	1.8	22,415	1.55	0.02
Oklahoma	33	1.08	18,238	1.26	-0.02
Oregon	58	1.9	11,839	0.82	0.09
Pennsylvania	20	0.65	20,171	1.39	-0.07
Rhode Island	PPD		2,917	0.2	0.00
South Carolina			1,805	0.12	0.01
South Dakota	18	0.59	5,814	0.4	0.03
Tennessee	180	5.88	115,610	7.99	-0.08
Texas	PPD		4,756	0.33	-0.02
Utah	76	2.48	7,776	0.54	0.16
Virginia	81	2.65	29,667	2.05	0.04
Vermont	30	0.98	8,351	0.58	0.05
Washington	PPD		1,784	0.12	-0.02
Wisconsin	136	4.45	66,610	4.6	-0.01
West Virginia	43	1.41	3,441	0.24	0.13
Wyoming	PPD		1,149	0.08	0.02
Opioids	.	.	.	.	.
buprenorphine	79	2.58	4,396	0.3	0.19

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
butorphanol	<11	0.16	197	0.01	0.05
codeine	550	17.98	140,363	9.7	0.24
fentanyl	44	1.44	1,010	0.07	0.16
hydrocodone	1,364	44.59	233,907	16.16	0.65
hydromorphone	43	1.41	1,924	0.13	0.15
Levorphanol	0	0	0	0	0.00
meperidine	<11	0.26	1,333	0.09	0.04
methadone	41	1.34	1,357	0.09	0.15
morphine	56	1.83	1,366	0.09	0.18
oxycodone	532	17.39	59,011	4.08	0.44
oxymorphone	<11	0.16	132	0.01	0.05
pentazocine	<11	0.1	367	0.03	0.03
propoxyphene	204	6.67	36,161	2.5	0.20
tapentadol	<11	0.23	90	0.01	0.07
tramadol	508	16.61	45,188	3.12	0.46
Healthcare Utilization, mean (SD)					
Comorbidity Index	1.60	1.85	0.93	1.41	0.41
Morphine equivalents	8006.09	126913.25	401.711	26465.28	0.08
Number of diagnoses	6	4.7	2.796	3.35	0.79
Number of ED visits	0.75	1.74	0.348	0.9	0.29
Number of non-duloxetine generics dispensed	5.72	4.31	1.81	2.49	1.11
Number of hospitalizations	0.05	0.24	0.04	0.22	0.03
Number of outpatient visits	5.65	6.61	2.118	3.48	0.67
Number of psychiatric hospitalizations	0.04	0.21	0.006	0.09	0.18
Number of psychiatrist visits	2.3	4.95	0.333	2.17	0.51

15.3. 2. Preeclampsia- Baseline characteristics of duloxetine exposed vs. SSRI exposed women- early exposure: unadjusted

	Duloxetine N/Mean	Duloxetine %/SD	SSRI N/Mean	SSRI %/SD	Standardized Difference
Total	2,104	.	70,926	.	.
Demographics	.	.	.	.	.
Age, mean (SD)	27.80	5.43	26.08	5.38	0.32
Age categorical, N (%)					
<=19	108	5.13	6,671	9.41	-0.17
20-24	512	24.33	24,698	34.82	-0.23
25-29	728	34.6	21,982	30.99	0.08
30-34	491	23.34	11,619	16.38	0.17
35-39	208	9.89	4,952	6.98	0.10
>=40	57	2.71	1,004	1.42	0.09
Race, N (%)					
White	1,655	78.66	51,124	72.08	0.15
Black/African American	194	9.22	9,062	12.78	-0.11
Hispanic/Latino	63	2.99	4,773	6.73	-0.17
Asian or Other Pacific	28	1.33	760	1.07	0.02
American Indian	30	1.43	1,151	1.62	-0.02
Other	88	4.18	2,417	3.41	0.04
Unknown	46	2.19	1,639	2.31	-0.01
Chronic comorbid conditions, N (%)	.	.	.	.	.
Hypertension	192	9.13	4,206	5.93	0.12
Diabetes	150	7.13	3,626	5.11	0.08
Renal Disease	22	1.05	580	0.82	0.02
Obesity Overweight	164	7.79	3,587	5.06	0.11
Comorbidity Index Q1	739	35.12	30,617	43.17	-0.17
Comorbidity Index Q2	521	24.76	18,167	25.61	-0.02
Comorbidity Index Q3	356	16.92	10,848	15.29	0.04
Comorbidity Index Q4	488	23.19	11,294	15.92	0.18
Infections, N (%)					
Toxoplasmosis	0	0	13	0.02	-0.02
Rubella	0	0	<11	0.01	-0.02

	Duloxetine N/Mean	Duloxetine %/SD	SSRI N/Mean	SSRI %/SD	Standardized Difference
Cytomegalovirus	0	0	0	0	-0.01
Herpes	40	1.9	1,081	1.52	0.03
Syphilis	<11	0.1	68	0.1	0.00
Varicella	<11	0.05	21	0.03	0.01
Parvovirus B19	0	0	<11	0.01	-0.01
Zika virus other mosquito	0	0	0	0	.
Lymphocytic choriomeningitis	<11	0.05	0	0	0.03
Influenza	18	0.86	900	1.27	-0.04
Chlamydia	11	0.52	418	0.59	-0.01
Human papilloma virus	19	0.9	633	0.89	0.00
Gonorrhea	14	0.67	459	0.65	0.00
HIV	<11	0.43	296	0.42	0.00
Trichomoniasis	21	1	890	1.25	-0.02
Indications for duloxetine, N (%)					
Depression	971	46.15	31,049	43.78	0.05
Anxiety	602	28.61	18,718	26.39	0.05
Neuropathic Pain	227	10.79	3,542	4.99	0.22
Fibromyalgia	226	10.74	1,944	2.74	0.32
Non neuropathic Pain	1,120	53.23	24,403	34.41	0.39
Other psychiatric conditions, N (%)	.	.	.	.	.
Sleep disorder	115	5.47	2,991	4.22	0.06
Bipolar disorder	288	13.69	6,257	8.82	0.15
Psychosis	19	0.9	800	1.13	-0.02
Schizophrenia	21	1	812	1.14	-0.01
Personality disorder	35	1.66	1,075	1.52	0.01
Adjustment disorder	25	1.19	918	1.29	-0.01
Tobacco use, N (%)	272	12.93	7,546	10.64	0.07
Alcohol abuse or dependence, N (%)	24	1.14	1,142	1.61	-0.04
Drug abuse or dependence, N (%)	62	2.95	2,468	3.48	-0.03
Other medication exposures, N (%)	.	.	.	.	.
Benzodiazepines	769	36.55	16,620	23.43	0.29
Other hypnotics	506	24.05	11,408	16.08	0.20

	Duloxetine N/Mean	Duloxetine %/SD	SSRI N/Mean	SSRI %/SD	Standardized Difference
Barbiturates	126	5.99	3,182	4.49	0.07
Anxiolytics	108	5.13	2,627	3.7	0.07
Anticonvulsants	541	25.71	8,110	11.43	0.37
Antipsychotics	396	18.82	8,266	11.65	0.20
SSRIs	<11	0	70,926	100	.
SNRIs	79	3.75	2,439	3.44	0.02
Other Antidep	561	26.66	13,259	18.69	0.19
Stimulants	179	8.51	3,223	4.54	0.16
Antidiabetic	95	4.52	1,755	2.47	0.11
Insulin	78	3.71	1,603	2.26	0.09
Antihyperten	318	15.11	6,390	9.01	0.19
Opioid analgesics	1,369	65.07	35,296	49.76	0.31
Triptans	141	6.7	2,852	4.02	0.12
NSAIDs	773	36.74	20,452	28.84	0.17
Obstetric conditions, N (%)					
Multifetal gestation Flag	78	3.71	2,881	4.06	-0.02
Markers of healthcare utilization					
Number of distinct 3 digit ICD 9 codes=0	125	5.94	7,921	11.17	-0.19
Number of distinct 3 digit ICD 9 codes: tertile 1 for number >0	409	19.44	16,362	23.07	-0.09
Number of distinct 3 digit ICD 9 codes: tertile 2 for number >0	459	21.82	15,378	21.68	0.00
Number of distinct 3 digit ICD 9 codes: tertile 3 for number >0	1,111	52.8	31,265	44.08	0.18
Number of ED visits=0	1,303	61.93	47,268	66.64	-0.10
Number of ED visits=1	474	22.53	13,723	19.35	0.08
Number of ED visits=2	178	8.46	5,451	7.69	0.03
Number of ED visits>2	149	7.08	4,484	6.32	0.03
Number of non-duloxetine generics dispensed=0	176	8.37	8,403	11.85	-0.12
Number of non-duloxetine generics dispensed: tertile 1 for number >0	165	7.84	8,042	11.34	-0.12
Number of non-duloxetine generics dispensed: tertile 2 for number >0	474	22.53	18,605	26.23	-0.09
Number of non-duloxetine generics dispensed: tertile 3 for number >0	1,289	61.26	35,876	50.58	0.22

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Number of hospital admissions=0	2,033	96.63	67,370	94.99	0.08
Number of hospital admissions=1	64	3.04	3,195	4.5	-0.08
Number of hospital admissions=2	<11	0.33	298	0.42	-0.01
Number of hospital admissions>2	0	0	63	0.09	-0.04
Number of outpatient visits=0	222	10.55	11,211	15.81	-0.16
Number of outpatient visits: tertile 1 for number >0	240	11.41	11,227	15.83	-0.13
Number of outpatient visits: tertile 2 for number >0	522	24.81	18,554	26.16	-0.03
Number of outpatient visits: tertile 3 for number >0	1,120	53.23	29,934	42.2	0.22
Number of psychiatric hospitalizations Q1	2,054	97.62	69,315	97.73	-0.01
Number of psychiatric hospitalizations Q2	46	2.19	1,407	1.98	0.01
Number of psychiatric hospitalizations Q3	<11	0.19	161	0.23	-0.01
Number of psychiatric hospitalizations Q4	0	0	43	0.06	-0.03
Number of psychiatrist visits=0	984	46.77	40,038	56.45	-0.19
Number of psychiatrist visits=1	452	21.48	12,944	18.25	0.08
Number of psychiatrist visits=2	214	10.17	6,103	8.6	0.05
Number of psychiatrist visits>2	454	21.58	11,841	16.69	0.12
Geographic region					
Arkansas	PPD		61	0.09	-0.01
Alabama	PPD		737	1.04	-0.07
California	169	8.03	6,865	9.68	-0.06
Colorado	PPD		360	0.51	-0.04
District of Columbia	PPD		26	0.04	0.02
Delaware	53	2.52	722	1.02	0.11
Florida	14	0.67	1,260	1.78	-0.10
Georgia	PPD		1,420	2	-0.14
Hawaii	PPD		105	0.15	-0.02
Iowa	16	0.76	840	1.18	-0.04
Idaho	PPD		239	0.34	-0.07
Illinois	211	10.03	5,797	8.17	0.06
Indiana	200	9.51	3,359	4.74	0.19
Kansas	30	1.43	747	1.05	0.03
Kentucky	28	1.33	1,932	2.72	-0.10

	Duloxetine N/Mean	Duloxetine %/SD	SSRI N/Mean	SSRI %/SD	Standardized Difference
Louisiana	75	3.56	1,257	1.77	0.11
Massachusetts	PPD		841	1.19	-0.11
Maryland	26	1.24	1,084	1.53	-0.03
Maine	PPD		431	0.61	-0.05
Minnesota	111	5.28	4,478	6.31	-0.04
Missouri	104	4.94	2,667	3.76	0.06
Mississippi	PPD		842	1.19	-0.08
North Carolina	45	2.14	870	1.23	0.07
North Dakota	21	1	368	0.52	0.06
Nebraska	17	0.81	473	0.67	0.02
New Hampshire	PPD		455	0.64	-0.04
New Jersey			342	0.48	-0.10
New Mexico	15	0.71	1,053	1.48	-0.07
Nevada	PPD		148	0.21	-0.05
New York	388	18.44	7,209	10.16	0.24
Ohio	33	1.57	2,041	2.88	-0.09
Oklahoma	14	0.67	972	1.37	-0.07
Oregon	40	1.9	1,123	1.58	0.02
Pennsylvania	PPD		2,075	2.93	-0.18
Rhode Island			219	0.31	-0.01
South Carolina			137	0.19	0.01
South Dakota			355	0.5	0.01
Tennessee	132	6.27	6,798	9.58	-0.12
Texas	PPD		214	0.3	-0.01
Utah	48	2.28	928	1.31	0.07
Virginia	62	2.95	1,637	2.31	0.04
Vermont	24	1.14	1,049	1.48	-0.03
Washington	PPD		192	0.27	-0.07
Wisconsin	93	4.42	5,676	8	-0.15
West Virginia	33	1.57	429	0.6	0.09
Wyoming	PPD		93	0.13	0.00
Opioids	.	.	.	.	.

	Duloxetine N/Mean	Duloxetine %/SD	SSRI N/Mean	SSRI %/SD	Standardized Difference
buprenorphine	55	2.61	1,003	1.41	0.09
butorphanol	<11	0.14	31	0.04	0.03
codeine	356	16.92	12,119	17.09	0.00
fentanyl	27	1.28	194	0.27	0.12
hydrocodone	919	43.68	22,881	32.26	0.24
hydromorphone	31	1.47	288	0.41	0.11
Levorphanol	0	0	0	0	-0.01
meperidine	<11	0.29	189	0.27	0.00
methadone	26	1.24	302	0.43	0.09
morphine	38	1.81	289	0.41	0.13
oxycodone	350	16.63	6,836	9.64	0.21
oxymorphone	<11	0.24	23	0.03	0.06
pentazocine	<11	0.1	64	0.09	0.00
propoxyphene	131	6.23	4,530	6.39	-0.01
tapentadol	<11	0.24	22	0.03	0.06
tramadol	335	15.92	6,040	8.52	0.23
Healthcare Utilization, mean (SD)					
Comorbidity Index	1.56	1.79	1.23	1.60	0.20
Morphine equivalents	8361.51	139342.8	1214.6	39953.35	0.07
Number of diagnoses	5.77	4.51	4.92	4.38	0.19
Number of ED visits	0.72	1.83	0.63	1.4	0.06
Number of non-duloxetine generics dispensed	5.31	4.1	4.32	3.66	0.26
Number of hospitalizations	0.04	0.21	0.06	0.26	-0.08
Number of outpatient visits	5.28	6.28	4.23	5.42	0.18
Number of psychiatric hospitalizations	0.03	0.17	0.03	0.2	-0.01
Number of psychiatrist visits	2.01	4.65	1.6	4.38	0.09

15.3. 3. Preeclampsia- Baseline characteristics of duloxetine exposed vs. venlafaxine exposed women- early exposure: unadjusted

	Duloxetine	Duloxetine	Venlafaxine	Venlafaxine	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Total	2,927	.	7,642	.	.
Demographics	.	.	.	.	.
Age, mean (SD)	27.78	5.48	26.80	5.29	0.18
Age categorical, N (%)					
<=19	145	4.95	476	6.23	-0.06
20-24	731	24.97	2,412	31.56	-0.15
25-29	1,011	34.54	2,541	33.25	0.03
30-34	660	22.55	1,495	19.56	0.07
35-39	301	10.28	598	7.83	0.09
>=40	79	2.7	120	1.57	0.08
Race, N (%)					
White	2,312	78.99	6,112	79.98	-0.02
Black/African American	252	8.61	575	7.52	0.04
Hispanic/Latino	92	3.14	364	4.76	-0.08
Asian or Other Pacific	35	1.2	95	1.24	0.00
American Indian	40	1.37	93	1.22	0.01
Other	130	4.44	226	2.96	0.08
Unknown	66	2.25	177	2.32	0.00
Chronic comorbid conditions, N (%)					
Hypertension	265	9.05	460	6.02	0.12
Diabetes	211	7.21	369	4.83	0.10
Renal Disease	32	1.09	57	0.75	0.04
Obesity Overweight	226	7.72	404	5.29	0.10
Comorbidity Index Q1	999	34.13	3,048	39.88	-0.12
Comorbidity Index Q2	718	24.53	1,954	25.57	-0.02
Comorbidity Index Q3	516	17.63	1,244	16.28	0.04
Comorbidity Index Q4	694	23.71	1,396	18.27	0.13
Infections, N (%)					
Toxoplasmosis	0	0	<11	0.03	-0.02
Rubella	0	0	0	0	
Cytomegalovirus	0	0	0	0	

	Duloxetine	Duloxetine	Venlafaxine	Venlafaxine	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Herpes	56	1.91	111	1.45	0.04
Syphilis	<11	0.07	<11	0.07	0.00
Varicella	<11	0.03	<11	0.03	0.00
Parvovirus B19	0	0	0	0	
Zika virus other mosquito	0	0	0	0	
Lymphocytic choriomeningitis	<11	0.03	0	0	0.03
Influenza	26	0.89	93	1.22	-0.03
Chlamydia	15	0.51	41	0.54	0.00
Human papilloma virus	31	1.06	64	0.84	0.02
Gonorrhea	18	0.61	35	0.46	0.02
HIV	11	0.38	33	0.43	-0.01
Trichomoniasis	29	0.99	92	1.2	-0.02
Indications for duloxetine, N (%)					
Depression	1,477	50.46	3,890	50.9	-0.01
Anxiety	913	31.19	2,263	29.61	0.03
Neuropathic Pain	330	11.27	472	6.18	0.18
Fibromyalgia	327	11.17	279	3.65	0.29
Non neuropathic Pain	1,560	53.3	2,921	38.22	0.31
Other psychiatric conditions, N (%)					
Sleep disorder	174	5.94	428	5.6	0.01
Bipolar disorder	425	14.52	881	11.53	0.09
Psychosis	30	1.02	84	1.1	-0.01
Schizophrenia	31	1.06	91	1.19	-0.01
Personality disorder	67	2.29	155	2.03	0.02
Adjustment disorder	35	1.2	95	1.24	0.00
Tobacco use, N (%)	386	13.19	846	11.07	0.06
Alcohol abuse or dependence, N (%)	45	1.54	145	1.9	-0.03
Drug abuse or dependence, N (%)	101	3.45	348	4.55	-0.06
Other medication exposures, N (%)					
Benzodiazepines	1,137	38.85	2,444	31.98	0.14
Other hypnotics	761	26	1,493	19.54	0.15
Barbiturates	197	6.73	386	5.05	0.07

	Duloxetine	Duloxetine	Venlafaxine	Venlafaxine	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Anxiolytics	169	5.77	374	4.89	0.04
Anticonvulsants	769	26.27	1,293	16.92	0.23
Antipsychotics	604	20.64	1,268	16.59	0.10
SSRIs	902	30.82	2,177	28.49	0.05
SNRIs	<11	0	7,642	100	
Other Antidep	821	28.05	1,927	25.22	0.06
Stimulants	238	8.13	487	6.37	0.07
Antidiabetic	127	4.34	217	2.84	0.08
Insulin	108	3.69	181	2.37	0.08
Antihyperten	457	15.61	828	10.83	0.14
Opioid analgesics	1,904	65.05	4,113	53.82	0.23
Triptans	214	7.31	437	5.72	0.06
NSAIDs	1,110	37.92	2,309	30.21	0.16
Obstetric conditions, N (%)					
Multifetal gestation Flag	102	3.48	293	3.83	-0.02
Markers of healthcare utilization					
Number of distinct 3 digit ICD 9 codes=0	154	5.26	667	8.73	-0.14
Number of distinct 3 digit ICD 9 codes: tertile 1 for number >0	547	18.69	1,700	22.25	-0.09
Number of distinct 3 digit ICD 9 codes: tertile 2 for number >0	632	21.59	1,712	22.4	-0.02
Number of distinct 3 digit ICD 9 codes: tertile 3 for number >0	1,594	54.46	3,563	46.62	0.16
Number of ED visits=0	1,826	62.38	5,166	67.6	-0.11
Number of ED visits=1	622	21.25	1,426	18.66	0.06
Number of ED visits=2	254	8.68	556	7.28	0.05
Number of ED visits>2	225	7.69	494	6.46	0.05
Number of non-duloxetine generics dispensed=0	210	7.17	434	5.68	0.06
Number of non-duloxetine generics dispensed: tertile 1 for number >0	219	7.48	683	8.94	-0.05
Number of non-duloxetine generics dispensed: tertile 2 for number >0	621	21.22	1,914	25.05	-0.09

	Duloxetine	Duloxetine	Venlafaxine	Venlafaxine	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Number of non-duloxetine generics dispensed: tertile 3 for number >0	1,877	64.13	4,611	60.34	0.08
Number of hospital admissions=0	2,808	95.93	7,313	95.69	0.01
Number of hospital admissions=1	105	3.59	292	3.82	-0.01
Number of hospital admissions=2	12	0.41	30	0.39	0.00
Number of hospital admissions>2	<11	0.07	<11	0.09	-0.01
Number of outpatient visits=0	278	9.5	989	12.94	-0.11
Number of outpatient visits: tertile 1 for number >0	317	10.83	1,100	14.39	-0.11
Number of outpatient visits: tertile 2 for number >0	729	24.91	2,010	26.3	-0.03
Number of outpatient visits: tertile 3 for number >0	1,603	54.77	3,543	46.36	0.17
Number of psychiatric hospitalizations Q1	2,840	97.03	7,436	97.3	-0.02
Number of psychiatric hospitalizations Q2	76	2.6	175	2.29	0.02
Number of psychiatric hospitalizations Q3	<11	0.31	24	0.31	0.00
Number of psychiatric hospitalizations Q4	<11	0.07	<11	0.09	-0.01
Number of psychiatrist visits=0	1,291	44.11	3,598	47.08	-0.06
Number of psychiatrist visits=1	611	20.87	1,545	20.22	0.02
Number of psychiatrist visits=2	317	10.83	838	10.97	0.00
Number of psychiatrist visits>2	708	24.19	1,661	21.74	0.06
Geographic region					
Arkansas	PPD		PPD		0.00
Alabama	21	0.72	40	0.52	0.02
California	221	7.55	666	8.71	-0.04
Colorado	PPD		38	0.5	-0.06
District of Columbia	PPD		PPD		0.03
Delaware	73	2.49	90	1.18	0.10
Florida	23	0.79	99	1.3	-0.05
Georgia	15	0.51	135	1.77	-0.12
Hawaii	PPD		PPD		-0.01
Iowa	28	0.96	135	1.77	-0.07
Idaho	PPD		47	0.62	-0.05
Illinois	318	10.86	559	7.31	0.12
Indiana	261	8.92	372	4.87	0.16

	Duloxetine	Duloxetine	Venlafaxine	Venlafaxine	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Kansas	43	1.47	84	1.1	0.03
Kentucky	47	1.61	160	2.09	-0.04
Louisiana	107	3.66	152	1.99	0.10
Massachusetts	PPD		58	0.76	-0.07
Maryland	39	1.33	111	1.45	-0.01
Maine	PPD		53	0.69	-0.05
Minnesota	167	5.71	490	6.41	-0.03
Missouri	145	4.95	344	4.5	0.02
Mississippi	14	0.48	127	1.66	-0.12
North Carolina	65	2.22	82	1.07	0.09
North Dakota	27	0.92	40	0.52	0.05
Nebraska	30	1.02	61	0.8	0.02
New Hampshire	PPD		40	0.52	-0.03
New Jersey	0	0	38	0.5	-0.10
New Mexico	22	0.75	103	1.35	-0.06
Nevada	PPD		14	0.18	-0.02
New York	507	17.32	827	10.82	0.19
Ohio	51	1.74	315	4.12	-0.14
Oklahoma	31	1.06	96	1.26	-0.02
Oregon	56	1.91	128	1.67	0.02
Pennsylvania	20	0.68	331	4.33	-0.23
Rhode Island	PPD		25	0.33	-0.02
South Carolina			19	0.25	-0.02
South Dakota	18	0.61	43	0.56	0.01
Tennessee	163	5.57	656	8.58	-0.12
Texas	PPD		15	0.2	0.00
Utah	72	2.46	97	1.27	0.09
Virginia	75	2.56	160	2.09	0.03
Vermont	29	0.99	78	1.02	0.00
Washington	PPD		21	0.27	-0.05
Wisconsin	126	4.3	603	7.89	-0.15
West Virginia	40	1.37	52	0.68	0.07

	Duloxetine	Duloxetine	Venlafaxine	Venlafaxine	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Wyoming	PPD		19	0.25	-0.03
Opioids					
buprenorphine	74	2.53	143	1.87	0.04
butorphanol	<11	0.17	<11	0.08	0.03
codeine	525	17.94	1,431	18.73	-0.02
fentanyl	42	1.43	49	0.64	0.08
hydrocodone	1,299	44.38	2,686	35.15	0.19
hydromorphone	38	1.3	37	0.48	0.09
Levorphanol	0	0	0	0	
meperidine	<11	0.24	25	0.33	-0.02
methadone	37	1.26	50	0.65	0.06
morphine	52	1.78	56	0.73	0.09
oxycodone	502	17.15	824	10.78	0.18
oxymorphone	<11	0.17	<11	0.1	0.02
pentazocine	<11	0.1	12	0.16	-0.02
propoxyphene	192	6.56	564	7.38	-0.03
tapentadol	<11	0.24	<11	0.01	0.06
tramadol	483	16.5	789	10.32	0.18
Healthcare Utilization, mean (SD)					
Comorbidity Index	1.60	1.84	1.35	1.66	0.15
Morphine equivalents	8124.68	129529.96	1170.84	15504.18	0.08
Number of diagnoses	5.96	4.65	5.18	4.43	0.17
Number of ED visits	0.74	1.74	0.63	1.39	0.07
Number of non-duloxetine generics dispensed	5.65	4.27	5.2	3.94	0.11
Number of hospitalizations	0.05	0.24	0.05	0.25	-0.01
Number of outpatient visits	5.57	6.39	4.68	5.79	0.15
Number of psychiatric hospitalizations	0.03	0.21	0.03	0.21	0.01
Number of psychiatrist visits	2.26	4.84	2.04	4.73	0.05

15.3. 4. Preeclampsia- Baseline characteristics of duloxetine exposed vs. unexposed women - early exposure: adjusted for treatment indications

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Total	2,679	.	474,139	.	.
Demographics	.	.	.	.	.
Age, mean (SD)	27.82	5.5	25.66	5.41	0.40
Age categorical, N (%)					
<=19	125	4.67	55,560	11.72	-0.26
20-24	675	25.20	171,400	36.15	-0.24
25-29	922	34.42	139,450	29.41	0.11
30-34	604	22.55	71,624	15.11	0.19
35-39	276	10.30	29,335	6.19	0.15
>=40	77	2.87	6,771	1.43	0.10
Race, N (%)					
White	2,121	79.17	281,425	59.35	0.44
Black or African American	232	8.66	100,044	21.10	-0.36
Hispanic or Latino	80	2.99	40,829	8.61	-0.24
Asian or Other Pacific Islander	38	1.42	9,571	2.02	-0.05
American Indian	35	1.31	9,832	2.07	-0.06
Other	114	4.26	21,383	4.51	-0.01
Unknown	59	2.20	11,055	2.33	-0.01
Chronic comorbid conditions, N (%)	.	.	.	.	.
Hypertension	250	9.33	29,527	6.23	0.12
Diabetes	192	7.17	24,755	5.22	0.08
Renal Disease	32	1.19	5,200	1.10	0.01
Obesity Overweight	212	7.91	30,411	6.41	0.06
Comorbidity Index Q1	904	33.74	204,503	43.13	-0.19
Comorbidity Index Q2	650	24.26	122,380	25.81	-0.04
Comorbidity Index Q3	471	17.58	70,559	14.88	0.07
Comorbidity Index Q4	654	24.41	76,697	16.18	0.21
Infections, N (%)	.	.	.	.	.
Toxoplasmosis	0	0.00	136	0.03	-0.02
Rubella	0	0.00	49	0.01	-0.01
Cytomegalovirus	0	0.00	35	0.01	-0.01

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Herpes	51	1.90	8,180	1.73	0.01
Syphilis	<11	0.07	594	0.13	-0.02
Varicella	0	0.00	194	0.04	-0.03
Parvovirus B19	0	0.00	49	0.01	-0.01
Zika virus other mosquito	0	0.00	0	0.00	.
Lymphocytic choriomeningitis	<11	0.04	0	0.00	0.03
Influenza	26	0.97	6,791	1.43	-0.04
Chlamydia	13	0.49	4,056	0.86	-0.05
Human papilloma virus	28	1.05	4,100	0.86	0.02
Gonorrhea	15	0.56	4,551	0.96	-0.05
HIV	<11	0.34	2,254	0.48	-0.02
Trichomoniasis	27	1.01	8,273	1.74	-0.06
Indications for duloxetine, N (%)	.	.	.	.	.
Depression	1,551	57.89	273,298	57.64	0.01
Anxiety	969	36.17	175,712	37.06	-0.02
Neuropathic Pain	354	13.21	74,673	15.75	-0.07
Fibromyalgia	343	12.80	67,460	14.23	-0.04
Non neuropathic Pain	1,633	60.96	300,424	63.36	-0.05
Other psychiatric conditions, N (%)	.	.	.	.	.
Sleep disorder	178	6.64	20,329	4.29	0.10
Bipolar disorder	385	14.37	34,477	7.27	0.23
Psychosis	31	1.16	6,170	1.30	-0.01
Schizophrenia	31	1.16	4,344	0.92	0.02
Personality disorder	69	2.58	7,551	1.59	0.07
Adjustment disorder	35	1.31	7,070	1.49	-0.02
Tobacco use, N (%)	385	14.37	57,007	12.02	0.07
Alcohol abuse or dependence, N (%)	42	1.57	6,803	1.43	0.01
Drug abuse or dependence, N (%)	103	3.84	15,577	3.29	0.03
Other medication exposures, N (%)	.	.	.	.	.
Benzodiazepines	1,114	41.58	97,881	20.64	0.46
Other hypnotics	747	27.88	65,656	13.85	0.35
Barbiturates	188	7.02	19,397	4.09	0.13

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Anxiolytics	170	6.35	15,553	3.28	0.14
Anticonvulsants	742	27.70	52,572	11.09	0.43
Antipsychotics	580	21.65	40,618	8.57	0.37
SSRIs	870	32.47	172,325	36.34	-0.08
SNRIs	119	4.44	24,006	5.06	-0.03
Other Antidep	803	29.97	80,504	16.98	0.31
Stimulants	218	8.14	17,446	3.68	0.19
Antidiabetic	112	4.18	9,822	2.07	0.12
Insulin	96	3.58	10,042	2.12	0.09
Antihyperten	421	15.71	37,556	7.92	0.24
Opioid analgesics	1,827	68.20	253,085	53.38	0.31
Triptans	202	7.54	17,444	3.68	0.17
NSAIDs	1,078	40.24	164,070	34.60	0.12
Obstetric conditions, N (%)	.	.	.	.	.
Multifetal gestation Flag	92	3.43	19,546	4.12	-0.04
Markers of healthcare utilization	.	.	.	.	.
Number of distinct 3 digit ICD 9 codes=0	93	3.47	32,893	6.94	-0.16
Number of distinct 3 digit ICD 9 codes: tertile 1 for number >0	450	16.80	83,012	17.51	-0.02
Number of distinct 3 digit ICD 9 codes: tertile 2 for number >0	565	21.09	98,302	20.73	0.01
Number of distinct 3 digit ICD 9 codes: tertile 3 for number >0	1,571	58.64	259,932	54.82	0.08
Number of ED visits=0	1,593	59.46	276,600	58.34	0.02
Number of ED visits=1	597	22.28	104,778	22.10	0.00
Number of ED visits=2	255	9.52	46,532	9.81	-0.01
Number of ED visits>2	234	8.73	46,229	9.75	-0.04
Number of non-duloxetine generics dispensed=0	162	6.05	80,889	17.06	-0.35
Number of non-duloxetine generics dispensed: tertile 1 for number >0	177	6.61	52,659	11.11	-0.16
Number of non-duloxetine generics dispensed: tertile 2 for number >0	542	20.23	113,988	24.04	-0.09
Number of non-duloxetine generics dispensed: tertile 3 for number >0	1,798	67.11	226,603	47.79	0.40
Number of hospital admissions=0	2,560	95.56	446,769	94.23	0.06

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Number of hospital admissions=1	104	3.88	23,821	5.02	-0.06
Number of hospital admissions=2	13	0.49	2,930	0.62	-0.02
Number of hospital admissions>2	<11	0.07	620	0.13	-0.02
Number of outpatient visits=0	196	7.32	54,423	11.48	-0.14
Number of outpatient visits: tertile 1 for number >0	251	9.37	62,371	13.15	-0.12
Number of outpatient visits: tertile 2 for number >0	662	24.71	116,489	24.57	0.00
Number of outpatient visits: tertile 3 for number >0	1,570	58.60	240,856	50.80	0.16
Number of psychiatric hospitalizations Q1	2,586	96.53	458,825	96.77	-0.01
Number of psychiatric hospitalizations Q2	82	3.06	13,286	2.80	0.02
Number of psychiatric hospitalizations Q3	<11	0.34	1,606	0.34	0.00
Number of psychiatric hospitalizations Q4	<11	0.07	422	0.09	-0.01
Number of psychiatrist visits=0	1,031	38.48	221,999	46.82	-0.17
Number of psychiatrist visits=1	610	22.77	104,798	22.10	0.02
Number of psychiatrist visits=2	317	11.83	50,356	10.62	0.04
Number of psychiatrist visits>2	721	26.91	96,986	20.46	0.15
Geographic region					
Arkansas	PPD		575	0.12	0.01
Alabama	21	0.78	4,411	0.93	-0.02
California	191	7.13	58,293	12.29	-0.18
Colorado	PPD		1,451	0.31	-0.02
District of Columbia			279	0.06	0.02
Delaware	63	2.35	3,901	0.82	0.12
Florida	18	0.67	6,592	1.39	-0.07
Georgia	14	0.52	8,593	1.81	-0.12
Hawaii	PPD		2,202	0.46	-0.07
Iowa	27	1.01	3,635	0.77	0.03
Idaho	PPD		1,053	0.22	0.02
Illinois	277	10.34	33,972	7.17	0.11
Indiana	242	9.03	23,668	4.99	0.16
Kansas	39	1.46	3,894	0.82	0.06
Kentucky	42	1.57	13,364	2.82	-0.09
Louisiana	96	3.58	8,247	1.74	0.11

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Massachusetts	PPD		3,473	0.73	-0.06
Maryland	33	1.23	9,951	2.10	-0.07
Maine	PPD		2,846	0.60	-0.05
Minnesota	171	6.38	30,363	6.40	0.00
Missouri	132	4.93	12,520	2.64	0.12
Mississippi	PPD		7,526	1.59	-0.12
North Carolina	60	2.24	7,452	1.57	0.05
North Dakota	27	1.01	2,602	0.55	0.05
Nebraska	26	0.97	2,744	0.58	0.04
New Hampshire	PPD		3,116	0.66	-0.05
New Jersey			2,955	0.62	-0.11
New Mexico	25	0.93	7,746	1.63	-0.06
Nevada	PPD		838	0.18	-0.02
New York	440	16.42	55,258	11.65	0.14
Ohio	48	1.79	12,345	2.60	-0.06
Oklahoma	32	1.19	5,954	1.26	-0.01
Oregon	54	2.02	6,641	1.40	0.05
Pennsylvania	18	0.67	10,035	2.12	-0.12
Rhode Island	PPD		1,569	0.33	-0.02
South Carolina			859	0.18	0.00
South Dakota	16	0.60	2,828	0.60	0.00
Tennessee	159	5.94	46,973	9.91	-0.15
Texas	PPD		1,134	0.24	-0.01
Utah	62	2.31	3,407	0.72	0.13
Virginia	75	2.80	12,612	2.66	0.01
Vermont	29	1.08	5,759	1.21	-0.01
Washington	PPD		636	0.13	-0.02
Wisconsin	121	4.52	36,581	7.72	-0.13
West Virginia	37	1.38	2,731	0.58	0.08
Wyoming	PPD		555	0.12	0.02
Opioids	.	.	.	.	.
buprenorphine	67	2.50	5,007	1.06	0.11

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
butorphanol	<11	0.19	320	0.07	0.03
codeine	505	18.85	84,275	17.77	0.03
fentanyl	39	1.46	2,170	0.46	0.10
hydrocodone	1,261	47.07	169,310	35.71	0.23
hydromorphone	39	1.46	2,996	0.63	0.08
levorphanol	<11	0.00	<11	0.00	0.00
meperidine	<11	0.30	1,419	0.30	0.00
methadone	40	1.49	2,791	0.59	0.09
morphine	51	1.90	3,172	0.67	0.11
oxycodone	498	18.59	56,416	11.90	0.19
oxymorphone	<11	0.15	379	0.08	0.02
pentazocine	<11	0.11	523	0.11	0.00
propoxyphene	187	6.98	30,257	6.38	0.02
tapentadol	<11	0.26	213	0.05	0.06
tramadol	481	17.95	50,955	10.75	0.21
Healthcare Utilization, mean (SD)					
Comorbidity Index	1.64	1.88	1.26	1.74	0.21
Morphine equivalents	20959.52	484060.73	3780.67	136261.92	0.05
Number of diagnoses	6.39	4.75	6.09	5.04	0.06
Number of ED visits	0.81	1.81	0.87	1.7	-0.03
Number of non-duloxetine generics dispensed	5.97	4.37	4.15	3.84	0.44
Number of hospitalizations	0.05	0.25	0.07	0.31	-0.06
Number of outpatient visits	6.05	6.83	5.07	5.91	0.15
Number of psychiatric hospitalizations	0.04	0.23	0.04	0.23	0.01
Number of psychiatrist visits	2.5	5.1	1.88	4.36	0.13

15.3. 5. Preeclampsia- Baseline characteristics of duloxetine exposed vs. SSRI exposed women - early exposure: adjusted for treatment indications

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Total	1,809	.	54,630	.	.
Demographics	.	.	.	.	.
Age, mean (SD)	27.85	5.46	26.33	5.44	0.28
Age categorical, N (%)					
<=19	89	4.92	4,686	8.58	-0.15
20-24	439	24.27	18,403	33.69	-0.21
25-29	630	34.83	17,195	31.48	0.07
30-34	417	23.05	9,363	17.14	0.15
35-39	182	10.06	4,116	7.53	0.09
>=40	52	2.87	867	1.59	0.09
Race, N (%)					
White	1,427	78.88	39,892	73.02	0.14
Black/African American	167	9.23	6,592	12.07	-0.09
Hispanic/Latino	51	2.82	3,403	6.23	-0.16
Asian or Other Pacific	26	1.44	648	1.19	0.02
American Indian	26	1.44	1,002	1.83	-0.03
Other	75	4.15	1,829	3.35	0.04
Unknown	37	2.05	1,265	2.31	-0.02
Chronic comorbid conditions, N (%)	.	.	.	.	.
Hypertension	172	9.51	3,767	6.89	0.10
Diabetes	132	7.30	3,191	5.84	0.06
Renal Disease	20	1.11	592	1.08	0.00
Obesity Overweight	145	8.02	3,404	6.23	0.07
Comorbidity Index Q1	628	34.72	21,938	40.16	-0.11
Comorbidity Index Q2	436	24.10	14,016	25.66	-0.04
Comorbidity Index Q3	308	17.03	8,783	16.08	0.03
Comorbidity Index Q4	437	24.16	9,893	18.11	0.15
Infections, N (%)	.	.	.	.	.
Toxoplasmosis	0	0.00	13	0.02	-0.02
Rubella	0	0.00	<11	0.01	-0.02
Cytomegalovirus	0	0.00	<11	0.01	-0.01

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Herpes	33	1.82	964	1.77	0.00
Syphilis	<11	0.11	66	0.12	0.00
Varicella	0	0.00	25	0.05	-0.03
Parvovirus B19	0	0.00	0	0.00	-0.01
Zika virus other mosquito	0	0.00	0	0.00	.
Lymphocytic choriomeningitis	<11	0.06	0	0.00	0.03
Influenza	16	0.88	808	1.48	-0.06
Chlamydia	<11	0.55	356	0.65	-0.01
Human papilloma virus	14	0.77	495	0.91	-0.01
Gonorrhea	11	0.61	418	0.77	-0.02
HIV	<11	0.39	232	0.42	-0.01
Trichomoniasis	19	1.05	713	1.31	-0.02
Indications for duloxetine, N (%)	.	.	.	.	.
Depression	971	53.68	30,196	55.27	-0.03
Anxiety	602	33.28	18,963	34.71	-0.03
Neuropathic Pain	227	12.55	7,307	13.38	-0.02
Fibromyalgia	226	12.49	7,640	13.99	-0.04
Non neuropathic Pain	1,120	61.91	34,217	62.63	-0.01
Other psychiatric conditions, N (%)	.	.	.	.	.
Sleep disorder	111	6.14	3,051	5.58	0.02
Bipolar disorder	249	13.76	5,593	10.24	0.11
Psychosis	18	1.00	731	1.34	-0.03
Schizophrenia	19	1.05	680	1.24	-0.02
Personality disorder	32	1.77	1,028	1.88	-0.01
Adjustment disorder	23	1.27	827	1.51	-0.02
Tobacco use, N (%)	253	13.99	7,197	13.17	0.02
Alcohol abuse or dependence, N (%)	21	1.16	958	1.75	-0.05
Drug abuse or dependence, N (%)	58	3.21	2,187	4.00	-0.04
Other medication exposures, N (%)	.	.	.	.	.
Benzodiazepines	707	39.08	15,986	29.26	0.21
Other hypnotics	456	25.21	10,626	19.45	0.14
Barbiturates	108	5.97	2,977	5.45	0.02

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Anxiolytics	99	5.47	2,539	4.65	0.04
Anticonvulsants	494	27.31	8,500	15.56	0.29
Antipsychotics	353	19.51	7,373	13.50	0.16
SSRIs	0	0.00	54,630	100.00	.
SNRIs	70	3.87	2,262	4.14	-0.01
Other Antidep	515	28.47	12,524	22.93	0.13
Stimulants	154	8.51	2,881	5.27	0.13
Antidiabetic	79	4.37	1,522	2.79	0.09
Insulin	66	3.65	1,371	2.51	0.07
Antihyperten	274	15.15	5,735	10.50	0.14
Opioid analgesics	1,235	68.27	33,139	60.66	0.16
Triptans	128	7.08	2,714	4.97	0.09
NSAIDs	704	38.92	20,669	37.84	0.02
Obstetric conditions, N (%)	.	.	.	.	.
Multifetal gestation Flag	69	3.81	2,264	4.14	-0.02
Markers of healthcare utilization	.	.	.	.	.
Number of distinct 3 digit ICD 9 codes=0	70	3.87	3,310	6.06	-0.10
Number of distinct 3 digit ICD 9 codes: tertile 1 for number >0	314	17.36	9,248	16.93	0.01
Number of distinct 3 digit ICD 9 codes: tertile 2 for number >0	394	21.78	11,214	20.53	0.03
Number of distinct 3 digit ICD 9 codes: tertile 3 for number >0	1,031	56.99	30,858	56.48	0.01
Number of ED visits=0	1,066	58.93	32,035	58.64	0.01
Number of ED visits=1	431	23.83	11,825	21.65	0.05
Number of ED visits=2	168	9.29	5,334	9.76	-0.02
Number of ED visits>2	144	7.96	5,437	9.95	-0.07
Number of non-duloxetine generics dispensed=0	135	7.46	4,656	8.52	-0.04
Number of non-duloxetine generics dispensed: tertile 1 for number >0	128	7.08	4,656	8.52	-0.05
Number of non-duloxetine generics dispensed: tertile 2 for number >0	387	21.39	12,317	22.55	-0.03
Number of non-duloxetine generics dispensed: tertile 3 for number >0	1,159	64.07	33,001	60.41	0.08
Number of hospital admissions=0	1,744	96.41	51,643	94.53	0.09

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Number of hospital admissions=1	58	3.21	2,645	4.84	-0.08
Number of hospital admissions=2	<11	0.39	287	0.52	-0.02
Number of hospital admissions>2	0	0.00	55	0.10	-0.04
Number of outpatient visits=0	147	8.13	5,238	9.59	-0.05
Number of outpatient visits: tertile 1 for number >0	180	9.95	6,826	12.50	-0.08
Number of outpatient visits: tertile 2 for number >0	452	24.99	13,472	24.66	0.01
Number of outpatient visits: tertile 3 for number >0	1,030	56.94	29,094	53.26	0.07
Number of psychiatric hospitalizations Q1	1,761	97.35	53,034	97.08	0.02
Number of psychiatric hospitalizations Q2	44	2.43	1,386	2.54	-0.01
Number of psychiatric hospitalizations Q3	<11	0.22	169	0.31	-0.02
Number of psychiatric hospitalizations Q4	<11	0.00	41	0.07	-0.04
Number of psychiatrist visits=0	741	40.96	25,652	46.96	-0.12
Number of psychiatrist visits=1	436	24.10	11,803	21.61	0.06
Number of psychiatrist visits=2	204	11.28	5,795	10.61	0.02
Number of psychiatrist visits>2	428	23.66	11,381	20.83	0.07
Geographic region					
Arkansas	PPD		58	0.11	-0.02
Alabama			628	1.15	-0.07
California	135	7.46	4,738	8.67	-0.04
Colorado	PPD		230	0.42	-0.04
District of Columbia			17	0.03	0.03
Delaware	43	2.38	505	0.92	0.11
Florida	PPD		883	1.62	-0.10
Georgia			1,064	1.95	-0.13
Hawaii	PPD		75	0.14	-0.01
Iowa			623	1.14	-0.04
Idaho	PPD		188	0.34	-0.08
Illinois			4,147	7.59	0.07
Indiana	179	9.89	2,814	5.15	0.18
Kansas	25	1.38	489	0.89	0.05
Kentucky	25	1.38	1,605	2.94	-0.11
Louisiana	63	3.48	917	1.68	0.11

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Massachusetts	PPD		536	0.98	-0.09
Maryland	21	1.16	883	1.62	-0.04
Maine	PPD		321	0.59	-0.05
Minnesota	106	5.86	3,747	6.86	-0.04
Missouri	91	5.03	1,849	3.38	0.08
Mississippi	PPD		651	1.19	-0.09
North Carolina	40	2.21	724	1.33	0.07
North Dakota	20	1.11	329	0.60	0.05
Nebraska	15	0.83	371	0.68	0.02
New Hampshire	PPD		397	0.73	-0.05
New Jersey	0	0.00	220	0.40	-0.09
New Mexico	15	0.83	850	1.56	-0.07
Nevada	PPD		135	0.25	-0.05
New York	320	17.69	5,128	9.39	0.24
Ohio	27	1.49	1,650	3.02	-0.10
Oklahoma	14	0.77	648	1.19	-0.04
Oregon	38	2.10	875	1.60	0.04
Pennsylvania	PPD		1,608	2.94	-0.18
Rhode Island			183	0.34	-0.01
South Carolina			110	0.20	0.02
South Dakota			302	0.55	0.00
Tennessee	114	6.30	5,676	10.39	-0.15
Texas	PPD		132	0.24	-0.02
Utah	40	2.21	641	1.17	0.08
Virginia	58	3.21	1,382	2.53	0.04
Vermont	23	1.27	786	1.44	-0.01
Washington	0	0.00	132	0.24	-0.07
Wisconsin	83	4.59	4,922	9.01	-0.18
West Virginia	28	1.55	387	0.71	0.08
Wyoming	PPD		72	0.13	0.01
Opioids	.	.	.	.	.
buprenorphine	44	2.43	819	1.50	0.07

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
butorphanol	<11	0.17	37	0.07	0.03
codeine	319	17.63	11,194	20.49	-0.07
fentanyl	25	1.38	298	0.55	0.09
hydrocodone	839	46.38	22,982	42.07	0.09
hydromorphone	27	1.49	384	0.70	0.08
Levorphanol	0	0.00	0	0.00	0.00
meperidine	<11	0.33	176	0.32	0.00
methadone	25	1.38	455	0.83	0.05
morphine	34	1.88	518	0.95	0.08
oxycodone	329	18.19	7,769	14.22	0.11
oxymorphone	<11	0.22	49	0.09	0.03
pentazocine	<11	0.11	82	0.15	-0.01
propoxyphene	117	6.47	4,590	8.40	-0.07
tapentadol	<11	0.28	28	0.05	0.06
tramadol	314	17.36	7,229	13.23	0.11
Healthcare Utilization, mean (SD)					
Comorbidity Index	1.61	1.84	1.35	1.69	0.15
Morphine equivalents	27609.72	585855.47	3338.28	99920.67	0.06
Number of diagnoses	6.19	4.58	6.27	5.13	-0.02
Number of ED visits	0.79	1.92	0.89	1.75	-0.05
Number of non-duloxetine generics dispensed	5.56	4.17	5.25	4.11	0.08
Number of hospitalizations	0.04	0.21	0.06	0.28	-0.09
Number of outpatient visits	5.7	6.53	5.35	5.99	0.06
Number of psychiatric hospitalizations	0.03	0.18	0.03	0.22	-0.03
Number of psychiatrist visits	2.21	4.83	1.92	4.48	0.06

15.3. 6. Preeclampsia- Baseline characteristics of duloxetine exposed vs. venlafaxine exposed women - early exposure: adjusted for treatment

indications

	Duloxetine N/Mean	Duloxetine %/SD	Venlafaxine N/Mean	Venlafaxine %/SD	Standardized Difference
Total	2,560	.	6,254	.	.
Demographics	.	.	.	.	.
Age, mean (SD)	27.82	5.51	27	5.3	0.15
Age categorical, N (%)					
<=19	121	4.73	349	5.58	-0.04
20-24	642	25.08	1,926	30.80	-0.13
25-29	886	34.61	2,082	33.29	0.03
30-34	570	22.27	1,266	20.24	0.05
35-39	267	10.43	527	8.43	0.07
>=40	74	2.89	104	1.66	0.08
Race, N (%)					
White	2,025	79.10	5,032	80.45	-0.03
Black/African American	222	8.67	456	7.28	0.05
Hispanic/Latino	78	3.05	277	4.43	-0.07
Asian or Other Pacific	33	1.29	84	1.35	-0.01
American Indian	34	1.33	77	1.23	0.01
Other	113	4.41	188	3.01	0.07
Unknown	55	2.15	140	2.24	-0.01
Chronic comorbid conditions, N (%)	.	.	.	.	.
Hypertension	239	9.34	442	7.07	0.08
Diabetes	186	7.27	338	5.40	0.08
Renal Disease	29	1.13	50	0.79	0.03
Obesity Overweight	205	8.01	397	6.34	0.06
Comorbidity Index Q1	858	33.52	2,394	38.28	-0.10
Comorbidity Index Q2	618	24.14	1,586	25.36	-0.03
Comorbidity Index Q3	457	17.85	1,051	16.81	0.03
Comorbidity Index Q4	627	24.49	1,223	19.55	0.12
Infections, N (%)	.	.	.	.	.
Toxoplasmosis	0	0.00	<11	0.03	-0.02

	Duloxetine N/Mean	Duloxetine %/SD	Venlafaxine N/Mean	Venlafaxine %/SD	Standardized Difference
Rubella	0	0.00	0	0.00	.
Cytomegalovirus	0	0.00	0	0.00	.
Herpes	48	1.88	99	1.58	0.02
Syphilis	<11	0.08	<11	0.09	-0.01
Varicella	0	0.00	<11	0.01	-0.01
Parvovirus B19	0	0.00	0	0.00	.
Zika virus other mosquito	0	0.00	0	0.00	.
Lymphocytic choriomeningitis	<11	0.04	0	0.00	0.03
Influenza	24	0.94	90	1.44	-0.05
Chlamydia	13	0.51	33	0.52	0.00
Human papilloma virus	26	1.02	49	0.78	0.02
Gonorrhea	15	0.59	28	0.45	0.02
HIV	<11	0.35	32	0.52	-0.02
Trichomoniasis	27	1.05	82	1.31	-0.02
Indications for duloxetine, N (%)	.	.	.	.	.
Depression	1,477	57.70	3,576	57.18	0.01
Anxiety	913	35.66	2,261	36.16	-0.01
Neuropathic Pain	330	12.89	943	15.08	-0.06
Fibromyalgia	327	12.77	786	12.57	0.01
Non neuropathic Pain	1,560	60.94	3,823	61.13	0.00
Other psychiatric conditions, N (%)	.	.	.	.	.
Sleep disorder	165	6.45	415	6.63	-0.01
Bipolar disorder	370	14.45	763	12.19	0.07
Psychosis	29	1.13	80	1.28	-0.01
Schizophrenia	29	1.13	79	1.26	-0.01
Personality disorder	64	2.50	145	2.32	0.01
Adjustment disorder	32	1.25	90	1.43	-0.02
Tobacco use, N (%)	366	14.30	776	12.40	0.06
Alcohol abuse or dependence, N (%)	41	1.60	119	1.90	-0.02
Drug abuse or dependence, N (%)	95	3.71	307	4.91	-0.06
Other medication exposures, N (%)	.	.	.	.	.
Benzodiazepines	1,050	41.02	2,287	36.57	0.09

	Duloxetine N/Mean	Duloxetine %/SD	Venlafaxine N/Mean	Venlafaxine %/SD	Standardized Difference
Other hypnotics	695	27.15	1,422	22.73	0.10
Barbiturates	174	6.80	377	6.03	0.03
Anxiolytics	159	6.21	352	5.63	0.02
Anticonvulsants	704	27.50	1,302	20.82	0.16
Antipsychotics	546	21.33	1,120	17.90	0.09
SSRIs	821	32.07	1,877	30.01	0.04
SNRIs	<11	0.00	6,254	100.00	.
Other Antidep	754	29.45	1,763	28.19	0.03
Stimulants	205	8.01	430	6.88	0.04
Antidiabetic	110	4.30	190	3.04	0.07
Insulin	95	3.71	170	2.72	0.06
Antihyperten	400	15.63	749	11.97	0.11
Opioid analgesics	1,738	67.89	3,940	63.00	0.10
Triptans	195	7.62	435	6.95	0.03
NSAIDs	1,028	40.16	2,335	37.33	0.06
Obstetric conditions, N (%)	.	.	.	.	.
Multifetal gestation Flag	90	3.52	262	4.18	-0.03
Markers of healthcare utilization	.	.	.	.	.
Number of distinct 3 digit ICD 9 codes=0	90	3.52	318	5.08	-0.08
Number of distinct 3 digit ICD 9 codes: tertile 1 for number >0	431	16.84	1,067	17.06	-0.01
Number of distinct 3 digit ICD 9 codes: tertile 2 for number >0	544	21.25	1,355	21.67	-0.01
Number of distinct 3 digit ICD 9 codes: tertile 3 for number >0	1,495	58.40	3,514	56.19	0.04
Number of ED visits=0	1,532	59.84	3,872	61.92	-0.04
Number of ED visits=1	567	22.15	1,244	19.89	0.06
Number of ED visits=2	242	9.45	572	9.15	0.01
Number of ED visits>2	219	8.55	566	9.05	-0.02
Number of non-duloxetine generics dispensed=0	161	6.29	288	4.61	0.07
Number of non-duloxetine generics dispensed: tertile 1 for number >0	175	6.84	410	6.55	0.01
Number of non-duloxetine generics dispensed: tertile 2 for number >0	518	20.23	1,325	21.19	-0.02

	Duloxetine N/Mean	Duloxetine %/SD	Venlafaxine N/Mean	Venlafaxine %/SD	Standardized Difference
Number of non-duloxetine generics dispensed: tertile 3 for number >0	1,706	66.64	4,231	67.65	-0.02
Number of hospital admissions=0	2,451	95.74	5,944	95.04	0.03
Number of hospital admissions=1	95	3.71	274	4.38	-0.03
Number of hospital admissions=2	12	0.47	30	0.49	0.00
Number of hospital admissions>2	<11	0.08	<11	0.09	-0.01
Number of outpatient visits=0	190	7.42	522	8.34	-0.03
Number of outpatient visits: tertile 1 for number >0	241	9.41	730	11.67	-0.07
Number of outpatient visits: tertile 2 for number >0	640	25.00	1,550	24.78	0.01
Number of outpatient visits: tertile 3 for number >0	1,489	58.16	3,452	55.20	0.06
Number of psychiatric hospitalizations Q1	2,475	96.68	6,056	96.84	-0.01
Number of psychiatric hospitalizations Q2	74	2.89	167	2.67	0.01
Number of psychiatric hospitalizations Q3	<11	0.35	25	0.39	-0.01
Number of psychiatric hospitalizations Q4	<11	0.08	<11	0.10	-0.01
Number of psychiatrist visits=0	995	38.87	2,624	41.96	-0.06
Number of psychiatrist visits=1	590	23.05	1,338	21.39	0.04
Number of psychiatrist visits=2	305	11.91	748	11.96	0.00
Number of psychiatrist visits>2	670	26.17	1,544	24.69	0.03
Geographic region					
Arkansas	PPD		PPD		0.01
Alabama	20	0.78	34	0.55	0.03
California	184	7.19	508	8.13	-0.04
Colorado	PPD		28	0.45	-0.06
District of Columbia			PPD		0.03
Delaware	61	2.38	68	1.08	0.10
Florida	17	0.66	77	1.22	-0.06
Georgia	13	0.51	110	1.76	-0.12
Hawaii	PPD		PPD		0.00
Iowa	26	1.02	98	1.57	-0.05
Idaho	PPD		44	0.70	-0.06
Illinois	270	10.55	425	6.80	0.13
Indiana	237	9.26	331	5.30	0.15

	Duloxetine N/Mean	Duloxetine %/SD	Venlafaxine N/Mean	Venlafaxine %/SD	Standardized Difference
Kansas	39	1.52	62	0.99	0.05
Kentucky	41	1.60	140	2.24	-0.05
Louisiana	93	3.63	132	2.12	0.09
Massachusetts	PPD		32	0.51	-0.04
Maryland	33	1.29	102	1.63	-0.03
Maine	PPD		41	0.65	-0.05
Minnesota	160	6.25	449	7.18	-0.04
Missouri	125	4.88	279	4.46	0.02
Mississippi	PPD		94	1.50	-0.12
North Carolina	58	2.27	66	1.06	0.09
North Dakota	26	1.02	35	0.55	0.05
Nebraska	25	0.98	46	0.74	0.03
New Hampshire	PPD		31	0.50	-0.02
New Jersey	0	0.00	30	0.48	-0.10
New Mexico	22	0.86	86	1.38	-0.05
Nevada	PPD		13	0.20	-0.02
New York	427	16.68	642	10.26	0.19
Ohio	44	1.72	280	4.47	-0.16
Oklahoma	30	1.17	70	1.12	0.00
Oregon	52	2.03	109	1.74	0.02
Pennsylvania	18	0.70	245	3.92	-0.22
Rhode Island	PPD		21	0.33	-0.02
South Carolina			17	0.28	-0.02
South Dakota	16	0.63	36	0.57	0.01
Tennessee	145	5.66	550	8.80	-0.12
Texas	PPD		PPD		0.01
Utah	58	2.27	70	1.11	0.09
Virginia	69	2.70	151	2.41	0.02
Vermont	28	1.09	65	1.03	0.01
Washington	PPD		PPD		-0.03
Wisconsin	111	4.34	544	8.69	-0.18
West Virginia	34	1.33	43	0.69	0.06

	Duloxetine N/Mean	Duloxetine %/SD	Venlafaxine N/Mean	Venlafaxine %/SD	Standardized Difference
Wyoming	PPD		14	0.22	-0.02
Opioids	.	.	.	.	.
buprenorphine	62	2.42	104	1.67	0.05
butorphanol	<11	0.20	<11	0.15	0.01
codeine	480	18.75	1,341	21.44	-0.07
fentanyl	37	1.45	76	1.22	0.02
hydrocodone	1,200	46.88	2,691	43.03	0.08
hydromorphone	34	1.33	42	0.67	0.07
Levorphanol	0	0.00	0	0.00	.
meperidine	<11	0.27	29	0.47	-0.03
methadone	36	1.41	76	1.21	0.02
morphine	47	1.84	85	1.35	0.04
oxycodone	468	18.28	930	14.87	0.09
oxymorphone	<11	0.16	12	0.19	-0.01
pentazocine	<11	0.12	13	0.20	-0.02
propoxyphene	176	6.88	573	9.17	-0.08
tapentadol	<11	0.27	<11	0.02	0.07
tramadol	457	17.85	909	14.53	0.09
Healthcare Utilization, mean (SD)					
Comorbidity Index	1.65	1.87	1.41	1.7	0.13
Morphine equivalents	21599.87	495108.91	6068.69	225607.37	0.04
Number of diagnoses	6.34	4.7	6.25	4.92	0.02
Number of ED visits	0.8	1.81	0.81	1.64	-0.01
Number of non-duloxetine generics dispensed	5.89	4.33	6.01	4.39	-0.03
Number of hospitalizations	0.05	0.25	0.06	0.27	-0.03
Number of outpatient visits	5.96	6.6	5.56	5.99	0.06
Number of psychiatric hospitalizations	0.04	0.23	0.04	0.23	0.00
Number of psychiatrist visits	2.46	4.99	2.26	4.83	0.04

15.3. 7. Preeclampsia- Baseline characteristics of duloxetine exposed vs. unexposed women - early exposure: fully adjusted

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Total	2,678	.	457,232	.	.
Demographics	.	.	.	.	.
Age, mean (SD)	28	5.5	28	5.54	0.01
Age categorical, N (%)					
<=19	125	4.67	20,047	4.38	0.01
20-24	674	25.17	115,487	25.26	0.00
25-29	922	34.43	159,309	34.84	-0.01
30-34	604	22.55	102,885	22.50	0.00
35-39	276	10.31	46,575	10.19	0.00
>=40	77	2.88	12,929	2.83	0.00
Race, N (%)					
White	2,120	79.16	367,446	80.36	-0.03
Black or African American	232	8.66	35,859	7.84	0.03
Hispanic or Latino	80	2.99	12,093	2.64	0.02
Asian or Other Pacific Islander	38	1.42	6,285	1.37	0.00
American Indian	35	1.31	5,880	1.29	0.00
Other	114	4.26	19,682	4.30	0.00
Unknown	59	2.20	9,987	2.18	0.00
Chronic comorbid conditions, N (%)	.	.	.	.	.
Hypertension	250	9.34	41,650	9.11	0.01
Diabetes	192	7.17	32,697	7.15	0.00
Renal Disease	32	1.19	5,498	1.20	0.00
Obesity Overweight	212	7.92	35,953	7.86	0.00
Comorbidity Index Q1	903	33.72	153,832	33.64	0.00
Comorbidity Index Q2	650	24.27	112,251	24.55	-0.01
Comorbidity Index Q3	471	17.59	81,192	17.76	0.00
Comorbidity Index Q4	654	24.42	109,957	24.05	0.01
Infections, N (%)	.	.	.	.	.
Toxoplasmosis	0	0.00	0	0.00	.
Rubella	0	0.00	0	0.00	.
Cytomegalovirus	0	0.00	0	0.00	.

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Herpes	51	1.90	8,656	1.89	0.00
Syphilis	<11	0.07	324	0.07	0.00
Varicella	0	0.00	0	0.00	.
Parvovirus B19	0	0.00	0	0.00	.
Zika virus other mosquito	0	0.00	0	0.00	.
Lymphocytic choriomeningitis	0	0.00	18	0.00	-0.01
Influenza	26	0.97	4,379	0.96	0.00
Chlamydia	13	0.49	2,253	0.49	0.00
Human papilloma virus	28	1.05	4,715	1.03	0.00
Gonorrhea	15	0.56	2,509	0.55	0.00
HIV	<11	0.34	1,542	0.34	0.00
Trichomoniasis	27	1.01	4,506	0.99	0.00
Indications for duloxetine, N (%)	.	.	.	.	.
Depression	1,550	57.88	270,704	59.20	-0.03
Anxiety	968	36.15	166,786	36.48	-0.01
Neuropathic Pain	354	13.22	59,090	12.92	0.01
Fibromyalgia	342	12.77	52,682	11.52	0.04
Non neuropathic Pain	1,632	60.94	272,755	59.65	0.03
Other psychiatric conditions, N (%)	.	.	.	.	.
Sleep disorder	178	6.65	30,066	6.58	0.00
Bipolar disorder	385	14.38	64,688	14.15	0.01
Psychosis	31	1.16	5,352	1.17	0.00
Schizophrenia	31	1.16	5,227	1.14	0.00
Personality disorder	69	2.58	11,593	2.54	0.00
Adjustment disorder	34	1.27	5,924	1.30	0.00
Tobacco use, N (%)	385	14.38	66,488	14.54	0.00
Alcohol abuse or dependence, N (%)	42	1.57	7,248	1.59	0.00
Drug abuse or dependence, N (%)	103	3.85	18,044	3.95	-0.01
Other medication exposures, N (%)	.	.	.	.	.
Benzodiazepines	1,113	41.56	189,025	41.34	0.00
Other hypnotics	746	27.86	124,553	27.24	0.01
Barbiturates	188	7.02	31,883	6.97	0.00

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Anxiolytics	169	6.31	27,926	6.11	0.01
Anticonvulsants	741	27.67	120,591	26.37	0.03
Antipsychotics	580	21.66	94,532	20.67	0.02
SSRIs	870	32.49	156,905	34.32	-0.04
SNRIs	119	4.44	21,575	4.72	-0.01
Other Antidep	802	29.95	136,139	29.77	0.00
Stimulants	218	8.14	35,828	7.84	0.01
Antidiabetic	112	4.18	18,540	4.05	0.01
Insulin	96	3.58	16,138	3.53	0.00
Antihyperten	421	15.72	69,288	15.15	0.02
Opioid analgesics	1,826	68.19	313,036	68.46	-0.01
Triptans	202	7.54	33,959	7.43	0.00
NSAIDs	1,078	40.25	183,036	40.03	0.00
Obstetric conditions, N (%)	.	.	.	.	.
Multifetal gestation Flag	92	3.44	15,691	3.43	0.00
Markers of healthcare utilization	.	.	.	.	.
Number of distinct 3 digit ICD 9 codes=0	93	3.47	13,793	3.02	0.03
Number of distinct 3 digit ICD 9 codes: tertile 1 for number >0	450	16.80	76,323	16.69	0.00
Number of distinct 3 digit ICD 9 codes: tertile 2 for number >0	565	21.10	97,999	21.43	-0.01
Number of distinct 3 digit ICD 9 codes: tertile 3 for number >0	1,570	58.63	269,116	58.86	0.00
Number of ED visits=0	1,593	59.48	273,230	59.76	-0.01
Number of ED visits=1	596	22.26	101,377	22.17	0.00
Number of ED visits=2	255	9.52	43,037	9.41	0.00
Number of ED visits>2	234	8.74	39,588	8.66	0.00
Number of non-duloxetine generics dispensed=0	162	6.05	22,811	4.99	0.05
Number of non-duloxetine generics dispensed: tertile 1 for number >0	177	6.61	28,579	6.25	0.01
Number of non-duloxetine generics dispensed: tertile 2 for number >0	542	20.24	95,110	20.80	-0.01
Number of non-duloxetine generics dispensed: tertile 3 for number >0	1,797	67.10	310,732	67.96	-0.02
Number of hospital admissions=0	2,559	95.56	437,243	95.63	0.00

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Number of hospital admissions=1	104	3.88	17,389	3.80	0.00
Number of hospital admissions=2	13	0.49	2,224	0.49	0.00
Number of hospital admissions>2	<11	0.07	377	0.08	0.00
Number of outpatient visits=0	196	7.32	30,909	6.76	0.02
Number of outpatient visits: tertile 1 for number >0	251	9.37	41,381	9.05	0.01
Number of outpatient visits: tertile 2 for number >0	662	24.72	114,919	25.13	-0.01
Number of outpatient visits: tertile 3 for number >0	1,569	58.59	270,024	59.06	-0.01
Number of psychiatric hospitalizations Q1	2,585	96.53	441,961	96.66	-0.01
Number of psychiatric hospitalizations Q2	82	3.06	13,341	2.92	0.01
Number of psychiatric hospitalizations Q3	<11	0.34	1,550	0.34	0.00
Number of psychiatric hospitalizations Q4	<11	0.07	380	0.08	0.00
Number of psychiatrist visits=0	1,031	38.50	168,583	36.87	0.03
Number of psychiatrist visits=1	610	22.78	108,691	23.77	-0.02
Number of psychiatrist visits=2	317	11.84	55,844	12.21	-0.01
Number of psychiatrist visits>2	720	26.89	124,114	27.14	-0.01
Geographic region					
Arkansas	PPD		700	0.15	0.00
Alabama	21	0.78	3,707	0.81	0.00
California	191	7.13	31,080	6.80	0.01
Colorado	PPD		784	0.17	0.00
District of Columbia			516	0.11	0.00
Delaware	63	2.35	10,441	2.28	0.00
Florida	18	0.67	2,940	0.64	0.00
Georgia	14	0.52	2,279	0.50	0.00
Hawaii	PPD		451	0.10	0.00
Iowa	27	1.01	4,735	1.04	0.00
Idaho	PPD		1,442	0.32	0.00
Illinois	276	10.31	47,179	10.32	0.00
Indiana	242	9.04	41,492	9.07	0.00
Kansas	39	1.46	6,778	1.48	0.00
Kentucky	42	1.57	7,111	1.56	0.00
Louisiana	96	3.58	16,366	3.58	0.00

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Massachusetts	PPD		1,346	0.29	0.00
Maryland	33	1.23	5,520	1.21	0.00
Maine	PPD		1,375	0.30	0.00
Minnesota	171	6.39	29,700	6.50	0.00
Missouri	132	4.93	22,940	5.02	0.00
Mississippi	PPD		1,646	0.36	0.00
North Carolina	60	2.24	10,056	2.20	0.00
North Dakota	27	1.01	4,540	0.99	0.00
Nebraska	26	0.97	4,509	0.99	0.00
New Hampshire	PPD		1,586	0.35	0.00
New Jersey	0	0.00	0	0.00	.
New Mexico	25	0.93	4,230	0.93	0.00
Nevada	PPD		535	0.12	0.00
New York	440	16.43	75,949	16.61	0.00
Ohio	48	1.79	8,439	1.85	0.00
Oklahoma	32	1.19	5,536	1.21	0.00
Oregon	54	2.02	9,449	2.07	0.00
Pennsylvania	18	0.67	2,908	0.64	0.00
Rhode Island	PPD		1,034	0.23	0.00
South Carolina			906	0.20	0.00
South Dakota	16	0.60	2,619	0.57	0.00
Tennessee	159	5.94	27,342	5.98	0.00
Texas	PPD		840	0.18	0.00
Utah	62	2.32	10,375	2.27	0.00
Virginia	75	2.80	12,829	2.81	0.00
Vermont	29	1.08	5,119	1.12	0.00
Washington	PPD		334	0.07	0.00
Wisconsin	121	4.52	20,523	4.49	0.00
West Virginia	37	1.38	6,143	1.34	0.00
Wyoming	PPD		903	0.20	0.00
Opioids	.	.	.	.	.
buprenorphine	67	2.50	10,810	2.36	0.01

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
butorphanol	<11	0.19	720	0.16	0.01
codeine	505	18.86	86,930	19.01	0.00
fentanyl	39	1.46	5,708	1.25	0.02
hydrocodone	1,261	47.09	217,340	47.53	-0.01
hydromorphone	39	1.46	6,177	1.35	0.01
Levorphanol	0	0.00	0	0.00	.
meperidine	<11	0.30	1,423	0.31	0.00
methadone	40	1.49	6,292	1.38	0.01
morphine	51	1.90	7,265	1.59	0.02
oxycodone	498	18.60	82,930	18.14	0.01
oxymorphone	<11	0.15	716	0.16	0.00
pentazocine	<11	0.11	546	0.12	0.00
propoxyphene	187	6.98	32,895	7.19	-0.01
tapentadol	<11	0.26	881	0.19	0.01
tramadol	480	17.92	80,808	17.67	0.01
Healthcare Utilization, mean (SD)					
Comorbidity Index	1.64	1.88	1.63	1.86	0.00
Morphine equivalents	20965.89	484150.99	18074.94	381086.3	0.01
Number of diagnoses	6.39	4.76	6.49	4.85	-0.02
Number of ED visits	0.81	1.81	0.83	1.7	-0.01
Number of non-duloxetine generics dispensed	5.97	4.37	5.94	4.28	0.01
Number of hospitalizations	0.05	0.25	0.05	0.26	0.00
Number of outpatient visits	6.04	6.83	5.97	6.44	0.01
Number of psychiatric hospitalizations	0.04	0.23	0.04	0.23	0.00
Number of psychiatrist visits	2.5	5.1	2.47	5.05	0.00

15.3. 8. Preeclampsia- Baseline characteristics of duloxetine exposed vs. SSRI exposed women - early exposure: fully adjusted

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Total	1,807	.	53,409	.	.
Demographics	.	.	.	.	.
Age, mean (SD)	27.85	5.46	27.85	5.54	0.00
Age categorical, N (%)					
<=19	89	4.93	2,561	4.80	0.01
20-24	438	24.24	12,868	24.09	0.00
25-29	630	34.86	18,663	34.94	0.00
30-34	417	23.08	12,402	23.22	0.00
35-39	181	10.02	5,352	10.02	0.00
>=40	52	2.88	1,563	2.93	0.00
Race, N (%)					
White	1,425	78.86	42,098	78.82	0.00
Black or African American	167	9.24	4,913	9.20	0.00
Hispanic or Latino	51	2.82	1,480	2.77	0.00
Asian or Other Pacific Islander	26	1.44	796	1.49	0.00
American Indian	26	1.44	787	1.47	0.00
Other	75	4.15	2,238	4.19	0.00
Unknown	37	2.05	1,098	2.06	0.00
Chronic comorbid conditions, N (%)	.	.	.	.	.
Hypertension	172	9.52	5,112	9.57	0.00
Diabetes	132	7.30	3,911	7.32	0.00
Renal Disease	20	1.11	589	1.10	0.00
Obesity Overweight	144	7.97	4,303	8.06	0.00
Comorbidity Index Q1	627	34.70	18,445	34.53	0.00
Comorbidity Index Q2	436	24.13	12,816	24.00	0.00
Comorbidity Index Q3	307	16.99	9,167	17.16	0.00
Comorbidity Index Q4	437	24.18	12,981	24.30	0.00
Infections, N (%)	.	.	.	.	.
Toxoplasmosis	0	-	0	-	0.00
Rubella	0	-	0	-	.
Cytomegalovirus	0	-	0	-	.

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Herpes	33	1.83	962	1.80	0.00
Syphilis	<11	0.11	59	0.11	0.00
Varicella	0	-	0	-	.
Parvovirus B19	0	-	0	-	.
Zika virus other mosquito	0	-	0	-	.
Lymphocytic choriomeningitis	0	-	0	-	.
Influenza	16	0.89	448	0.84	0.01
Chlamydia	<11	0.55	296	0.55	0.00
Human papilloma virus	14	0.77	406	0.76	0.00
Gonorrhea	11	0.61	320	0.60	0.00
HIV	<11	0.39	208	0.39	0.00
Trichomoniasis	19	1.05	563	1.05	0.00
Indications for duloxetine, N (%)	.	.	.	.	.
Depression	970	53.68	28,728	53.79	0.00
Anxiety	601	33.26	17,959	33.63	0.01
Neuropathic Pain	226	12.51	6,713	12.57	0.00
Fibromyalgia	224	12.40	6,152	11.52	0.03
Non neuropathic Pain	1,118	61.87	33,117	62.01	0.00
Other psychiatric conditions, N (%)	.	.	.	.	.
Sleep disorder	111	6.14	3,288	6.16	0.00
Bipolar disorder	248	13.72	7,461	13.97	0.01
Psychosis	18	1.00	539	1.01	0.00
Schizophrenia	19	1.05	569	1.06	0.00
Personality disorder	32	1.77	989	1.85	0.01
Adjustment disorder	22	1.22	638	1.19	0.00
Tobacco use, N (%)	253	14.00	7,561	14.16	0.00
Alcohol abuse or dependence, N (%)	21	1.16	619	1.16	0.00
Drug abuse or dependence, N (%)	58	3.21	1,727	3.23	0.00
Other medication exposures, N (%)	.	.	.	.	.
Benzodiazepines	705	39.01	21,034	39.38	0.01
Other hypnotics	454	25.12	13,464	25.21	0.00
Barbiturates	108	5.98	3,167	5.93	0.00

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Anxiolytics	98	5.42	2,972	5.57	0.01
Anticonvulsants	492	27.23	14,378	26.92	0.01
Antipsychotics	352	19.48	10,493	19.65	0.00
SSRIs	0	-	53,409	100.00	.
SNRIs	70	3.87	2,085	3.90	0.00
Other Antidep	513	28.39	15,176	28.42	0.00
Stimulants	154	8.52	4,508	8.44	0.00
Antidiabetic	79	4.37	2,316	4.34	0.00
Insulin	66	3.65	1,939	3.63	0.00
Antihyperten	273	15.11	7,989	14.96	0.00
Opioid analgesics	1,233	68.23	36,580	68.49	0.01
Triptans	128	7.08	3,727	6.98	0.00
NSAIDs	703	38.90	20,921	39.17	0.01
Obstetric conditions, N (%)	.	.	.	.	.
Multifetal gestation Flag	69	3.82	2,074	3.88	0.00
Markers of healthcare utilization	.	.	.	.	.
Number of distinct 3 digit ICD 9 codes=0	70	3.87	1,998	3.74	0.01
Number of distinct 3 digit ICD 9 codes: tertile 1 for number >0	314	17.38	9,212	17.25	0.00
Number of distinct 3 digit ICD 9 codes: tertile 2 for number >0	394	21.80	11,780	22.06	0.01
Number of distinct 3 digit ICD 9 codes: tertile 3 for number >0	1,029	56.95	30,418	56.95	0.00
Number of ED visits=0	1,065	58.94	31,478	58.94	0.00
Number of ED visits=1	430	23.80	12,681	23.74	0.00
Number of ED visits=2	168	9.30	4,942	9.25	0.00
Number of ED visits>2	144	7.97	4,309	8.07	0.00
Number of non-duloxetine generics dispensed=0	135	7.47	4,002	7.49	0.00
Number of non-duloxetine generics dispensed: tertile 1 for number >0	128	7.08	3,725	6.97	0.00
Number of non-duloxetine generics dispensed: tertile 2 for number >0	387	21.42	11,386	21.32	0.00
Number of non-duloxetine generics dispensed: tertile 3 for number >0	1,157	64.03	34,295	64.21	0.00
Number of hospital admissions=0	1,742	96.40	51,474	96.38	0.00

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Number of hospital admissions=1	58	3.21	1,726	3.23	0.00
Number of hospital admissions=2	<11	0.39	207	0.39	0.00
Number of hospital admissions>2	0	-	0	-	0.01
Number of outpatient visits=0	147	8.14	4,243	7.94	0.01
Number of outpatient visits: tertile 1 for number >0	180	9.96	5,234	9.80	0.01
Number of outpatient visits: tertile 2 for number >0	452	25.01	13,462	25.21	0.00
Number of outpatient visits: tertile 3 for number >0	1,028	56.89	30,470	57.05	0.00
Number of psychiatric hospitalizations Q1	1,759	97.34	51,993	97.35	0.00
Number of psychiatric hospitalizations Q2	44	2.43	1,295	2.43	0.00
Number of psychiatric hospitalizations Q3	<11	0.22	120	0.22	0.00
Number of psychiatric hospitalizations Q4	0	-	0	-	0.01
Number of psychiatrist visits=0	741	41.01	21,732	40.69	0.01
Number of psychiatrist visits=1	436	24.13	12,880	24.12	0.00
Number of psychiatrist visits=2	203	11.23	5,966	11.17	0.00
Number of psychiatrist visits>2	427	23.63	12,831	24.02	0.01
Geographic region	.	.	.	.	.
Arkansas	PPD		31	0.06	0.00
Alabama	PPD		264	0.49	0.00
California	134	7.42	3,930	7.36	0.00
Colorado	PPD		113	0.21	0.00
District of Columbia	PPD		60	0.11	0.00
Delaware	43	2.38	1,264	2.37	0.00
Florida	PPD		289	0.54	0.00
Georgia	PPD		252	0.47	0.00
Hawaii	PPD		57	0.11	0.00
Iowa	14	0.77	407	0.76	0.00
Idaho	0	-	0	-	0.01
Illinois	172	9.52	5,018	9.40	0.00
Indiana	179	9.91	5,284	9.89	0.00
Kansas	25	1.38	757	1.42	0.00
Kentucky	25	1.38	726	1.36	0.00
Louisiana	63	3.49	1,864	3.49	0.00

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Massachusetts	PPD		143	0.27	0.00
Maryland	21	1.16	625	1.17	0.00
Maine	PPD		143	0.27	0.00
Minnesota	106	5.87	3,133	5.87	0.00
Missouri	91	5.04	2,737	5.12	0.00
Mississippi	PPD		202	0.38	0.00
North Carolina	40	2.21	1,211	2.27	0.00
North Dakota	20	1.11	600	1.12	0.00
Nebraska	15	0.83	427	0.80	0.00
New Hampshire	PPD		209	0.39	0.00
New Jersey	0	-	0	-	0.00
New Mexico	15	0.83	442	0.83	0.00
Nevada	PPD		31	0.06	0.00
New York	320	17.71	9,645	18.06	0.01
Ohio	27	1.49	798	1.49	0.00
Oklahoma	14	0.77	406	0.76	0.00
Oregon	38	2.10	1,124	2.10	0.00
Pennsylvania	PPD		311	0.58	0.00
Rhode Island			136	0.25	0.00
South Carolina			144	0.27	0.00
South Dakota			296	0.55	0.00
Tennessee	114	6.31	3,324	6.22	0.00
Texas	PPD		85	0.16	0.00
Utah	40	2.21	1,201	2.25	0.00
Virginia	58	3.21	1,708	3.20	0.00
Vermont	23	1.27	683	1.28	0.00
Washington	0	-	0	-	0.00
Wisconsin	83	4.59	2,428	4.55	0.00
West Virginia	28	1.55	809	1.51	0.00
Wyoming	PPD		92	0.17	0.00
Opioids	.	.	.	.	.
buprenorphine	44	2.43	1,298	2.43	0.00

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
butorphanol	<11	0.17	85	0.16	0.00
codeine	319	17.65	9,465	17.72	0.00
fentanyl	25	1.38	704	1.32	0.01
hydrocodone	838	46.38	25,023	46.85	0.01
hydromorphone	27	1.49	761	1.42	0.01
Levorphanol	0	-	0	-	.
meperidine	<11	0.33	181	0.34	0.00
methadone	25	1.38	738	1.38	0.00
morphine	33	1.83	915	1.71	0.01
oxycodone	329	18.21	9,732	18.22	0.00
oxymorphone	<11	0.22	111	0.21	0.00
pentazocine	<11	0.11	63	0.12	0.00
propoxyphene	117	6.47	3,551	6.65	0.01
tapentadol	<11	0.28	135	0.25	0.00
tramadol	312	17.27	9,265	17.35	0.00
Healthcare Utilization, mean (SD)					
Comorbidity Index	1.61	1.84	1.62	1.85	-0.01
Morphine equivalents	27618.62	586179.31	11529.41	259494.31	0.04
Number of diagnoses	6.19	4.58	6.22	4.69	-0.01
Number of ED visits	0.79	1.92	0.81	1.65	-0.01
Number of non-duloxetine generics dispensed	5.56	4.17	5.93	4.5	-0.09
Number of hospitalizations	0.04	0.21	0.04	0.22	0.00
Number of outpatient visits	5.7	6.53	5.68	6.21	0.00
Number of psychiatric hospitalizations	0.03	0.18	0.03	0.18	0.00
Number of psychiatrist visits	2.21	4.82	2.2	4.78	0.00

15.3. 9. Preeclampsia- Baseline characteristics of duloxetine exposed vs. venlafaxine exposed women - early exposure: fully adjusted

	Duloxetine N/Mean	Duloxetine %/SD	Venlafaxine N/Mean	Venlafaxine %/SD	Standardized Difference
Total	2,553	.	6,219	.	.
Demographics	.	.	.	.	.
Age, mean (SD)	28	5.49	28	5.52	0.00
Age categorical, N (%)					
<=19	121	4.74	286	4.60	0.01
20-24	640	25.07	1,569	25.22	0.00
25-29	884	34.63	2,149	34.55	0.00
30-34	570	22.33	1,395	22.42	0.00
35-39	267	10.46	629	10.11	0.01
>=40	71	2.78	192	3.08	-0.02
Race, N (%)					
White	2,019	79.08	4,923	79.15	0.00
Black or African American	222	8.70	525	8.45	0.01
Hispanic or Latino	78	3.06	177	2.84	0.01
Asian or Other Pacific Islander	33	1.29	87	1.40	-0.01
American Indian	34	1.33	86	1.39	0.00
Other	112	4.39	286	4.59	-0.01
Unknown	55	2.15	135	2.18	0.00
Chronic comorbid conditions, N (%)	.	.	.	.	.
Hypertension	237	9.28	597	9.60	-0.01
Diabetes	184	7.21	470	7.55	-0.01
Renal Disease	29	1.14	71	1.15	0.00
Obesity Overweight	204	7.99	519	8.34	-0.01
Comorbidity Index Q1	857	33.57	2,094	33.67	0.00
Comorbidity Index Q2	618	24.21	1,505	24.20	0.00
Comorbidity Index Q3	455	17.82	1,135	18.25	-0.01
Comorbidity Index Q4	623	24.40	1,485	23.88	0.01
Infections, N (%)	.	.	.	.	.
Toxoplasmosis	0	0.00	0	0.00	.
Rubella	0	0.00	0	0.00	.
Cytomegalovirus	0	0.00	0	0.00	.

	Duloxetine	Duloxetine	Venlafaxine	Venlafaxine	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Herpes	48	1.88	103	1.66	0.02
Syphilis	<11	0.08	<11	0.07	0.00
Varicella	0	0.00	0	0.00	.
Parvovirus B19	0	0.00	0	0.00	.
Zika virus other mosquito	0	0.00	0	0.00	.
Lymphocytic choriomeningitis	0	0.00	0	0.00	.
Influenza	24	0.94	56	0.91	0.00
Chlamydia	13	0.51	37	0.60	-0.01
Human papilloma virus	26	1.02	58	0.93	0.01
Gonorrhea	15	0.59	34	0.55	0.01
HIV	<11	0.35	26	0.42	-0.01
Trichomoniasis	27	1.06	68	1.10	0.00
Indications for duloxetine, N (%)	.	.	.	.	.
Depression	1,473	57.70	3,659	58.83	-0.02
Anxiety	911	35.68	2,286	36.76	-0.02
Neuropathic Pain	326	12.77	805	12.94	-0.01
Fibromyalgia	322	12.61	737	11.86	0.02
Non neuropathic Pain	1,554	60.87	3,762	60.49	0.01
Other psychiatric conditions, N (%)	.	.	.	.	.
Sleep disorder	165	6.46	413	6.64	-0.01
Bipolar disorder	369	14.45	923	14.85	-0.01
Psychosis	29	1.14	73	1.17	0.00
Schizophrenia	29	1.14	77	1.24	-0.01
Personality disorder	64	2.51	169	2.71	-0.01
Adjustment disorder	31	1.21	83	1.34	-0.01
Tobacco use, N (%)	364	14.26	911	14.65	-0.01
Alcohol abuse or dependence, N (%)	41	1.61	109	1.75	-0.01
Drug abuse or dependence, N (%)	95	3.72	237	3.81	0.00
Other medication exposures, N (%)	.	.	.	.	.
Benzodiazepines	1,044	40.89	2,634	42.36	-0.03
Other hypnotics	692	27.11	1,753	28.20	-0.02
Barbiturates	172	6.74	410	6.59	0.01

	Duloxetine	Duloxetine	Venlafaxine	Venlafaxine	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Anxiolytics	157	6.15	408	6.56	-0.02
Anticonvulsants	700	27.42	1,681	27.03	0.01
Antipsychotics	546	21.39	1,367	21.99	-0.01
SSRIs	816	31.96	2,027	32.60	-0.01
SNRIs	0	0.00	6,219	100.00	.
Other Antidep	751	29.42	1,875	30.15	-0.02
Stimulants	203	7.95	510	8.20	-0.01
Antidiabetic	110	4.31	266	4.27	0.00
Insulin	93	3.64	239	3.84	-0.01
Antihyperten	397	15.55	990	15.92	-0.01
Opioid analgesics	1,731	67.80	4,219	67.83	0.00
Triptans	194	7.60	495	7.96	-0.01
NSAIDs	1,024	40.11	2,515	40.44	-0.01
Obstetric conditions, N (%)	.	.	.	.	.
Multifetal gestation Flag	90	3.53	218	3.50	0.00
Markers of healthcare utilization	.	.	.	.	.
Number of distinct 3 digit ICD 9 codes=0	90	3.53	224	3.60	0.00
Number of distinct 3 digit ICD 9 codes: tertile 1 for number >0	430	16.84	1,019	16.39	0.01
Number of distinct 3 digit ICD 9 codes: tertile 2 for number >0	543	21.27	1,338	21.52	-0.01
Number of distinct 3 digit ICD 9 codes: tertile 3 for number >0	1,490	58.36	3,638	58.50	0.00
Number of ED visits=0	1,528	59.85	3,711	59.67	0.00
Number of ED visits=1	565	22.13	1,339	21.52	0.01
Number of ED visits=2	241	9.44	604	9.72	-0.01
Number of ED visits>2	219	8.58	565	9.09	-0.02
Number of non-duloxetine generics dispensed=0	160	6.27	412	6.62	-0.01
Number of non-duloxetine generics dispensed: tertile 1 for number >0	174	6.82	420	6.75	0.00
Number of non-duloxetine generics dispensed: tertile 2 for number >0	518	20.29	1,221	19.63	0.02
Number of non-duloxetine generics dispensed: tertile 3 for number >0	1,701	66.63	4,167	67.01	-0.01
Number of hospital admissions=0	2,444	95.73	5,948	95.64	0.00

	Duloxetine	Duloxetine	Venlafaxine	Venlafaxine	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Number of hospital admissions=1	95	3.72	235	3.78	0.00
Number of hospital admissions=2	12	0.47	32	0.52	-0.01
Number of hospital admissions>2	<11	0.08	<11	0.06	0.01
Number of outpatient visits=0	189	7.40	459	7.37	0.00
Number of outpatient visits: tertile 1 for number >0	241	9.44	565	9.08	0.01
Number of outpatient visits: tertile 2 for number >0	640	25.07	1,570	25.25	0.00
Number of outpatient visits: tertile 3 for number >0	1,483	58.09	3,625	58.29	0.00
Number of psychiatric hospitalizations Q1	2,469	96.71	6,025	96.88	-0.01
Number of psychiatric hospitalizations Q2	73	2.86	166	2.67	0.01
Number of psychiatric hospitalizations Q3	<11	0.35	24	0.39	-0.01
Number of psychiatric hospitalizations Q4	<11	0.08	<11	0.07	0.00
Number of psychiatrist visits=0	991	38.82	2,400	38.59	0.00
Number of psychiatrist visits=1	589	23.07	1,411	22.69	0.01
Number of psychiatrist visits=2	305	11.95	731	11.75	0.01
Number of psychiatrist visits>2	668	26.17	1,677	26.96	-0.02
Geographic region	.	.	.	.	.
Arkansas	PPD		PPD		-0.01
Alabama	20	0.78	53	0.85	-0.01
California	184	7.21	438	7.04	0.01
Colorado	PPD		PPD		0.01
District of Columbia	PPD		PPD		0.00
Delaware	61	2.39	139	2.23	0.01
Florida	17	0.67	35	0.56	0.01
Georgia	13	0.51	30	0.48	0.00
Hawaii	PPD		PPD		0.00
Iowa	26	1.02	66	1.05	0.00
Idaho	PPD		15	0.24	0.01
Illinois	269	10.54	636	10.23	0.01
Indiana	235	9.20	583	9.37	-0.01
Kansas	39	1.53	103	1.65	-0.01
Kentucky	41	1.61	99	1.59	0.00
Louisiana	93	3.64	230	3.70	0.00

	Duloxetine N/Mean	Duloxetine %/SD	Venlafaxine N/Mean	Venlafaxine %/SD	Standardized Difference
Massachusetts	PPD		18	0.29	0.00
Maryland	33	1.29	85	1.37	-0.01
Maine	PPD		18	0.29	0.00
Minnesota	160	6.27	395	6.35	0.00
Missouri	125	4.90	305	4.90	0.00
Mississippi	PPD		23	0.37	0.00
North Carolina	58	2.27	138	2.22	0.00
North Dakota	26	1.02	60	0.96	0.01
Nebraska	25	0.98	65	1.05	-0.01
New Hampshire	PPD		23	0.37	0.00
New Jersey	0	0.00	0	0.00	.
New Mexico	22	0.86	50	0.80	0.01
Nevada	PPD		PPD		0.01
New York	424	16.61	1,026	16.50	0.00
Ohio	44	1.72	110	1.76	0.00
Oklahoma	30	1.18	68	1.09	0.01
Oregon	52	2.04	124	2.00	0.00
Pennsylvania	18	0.71	49	0.79	-0.01
Rhode Island	PPD		14	0.22	0.00
South Carolina			PPD		0.01
South Dakota	16	0.63	40	0.64	0.00
Tennessee	145	5.68	361	5.81	-0.01
Texas	PPD		PPD		0.01
Utah	58	2.27	162	2.61	-0.02
Virginia	68	2.66	178	2.86	-0.01
Vermont	28	1.10	70	1.12	0.00
Washington	PPD		PPD		0.00
Wisconsin	111	4.35	253	4.06	0.01
West Virginia	34	1.33	89	1.44	-0.01
Wyoming	PPD		PPD		0.01
Opioids	.	.	.	.	.
buprenorphine	62	2.43	155	2.49	0.00

	Duloxetine	Duloxetine	Venlafaxine	Venlafaxine	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
butorphanol	<11	0.20	15	0.24	-0.01
codeine	480	18.80	1,201	19.31	-0.01
fentanyl	37	1.45	96	1.54	-0.01
hydrocodone	1,197	46.89	2,966	47.69	-0.02
hydromorphone	31	1.21	76	1.22	0.00
Levorphanol	0	0.00	0	0.00	.
meperidine	<11	0.27	18	0.28	0.00
methadone	35	1.37	87	1.41	0.00
morphine	47	1.84	110	1.77	0.01
oxycodone	466	18.25	1,120	18.02	0.01
oxymorphone	<11	0.16	12	0.19	-0.01
pentazocine	<11	0.12	<11	0.12	0.00
propoxyphene	176	6.89	436	7.02	0.00
tapentadol	<11	0.16	<11	0.09	0.02
tramadol	454	17.78	1,098	17.66	0.00
Healthcare Utilization, mean (SD)					
Comorbidity Index	1.64	1.87	1.62	1.81	0.01
Morphine equivalents	21576.82	495779.7	19123.27	515619.74	0.00
Number of diagnoses	6.34	4.7	6.46	5	-0.03
Number of ED visits	0.8	1.82	0.85	1.7	-0.03
Number of non-duloxetine generics dispensed	5.88	4.33	6.4	4.82	-0.11
Number of hospitalizations	0.05	0.25	0.05	0.26	-0.01
Number of outpatient visits	5.95	6.6	5.89	6.08	0.01
Number of psychiatric hospitalizations	0.04	0.23	0.04	0.23	0.01
Number of psychiatrist visits	2.46	4.99	2.44	4.88	0.00

15.3. 10. Preeclampsia- Baseline characteristics of duloxetine exposed vs. unexposed women - late exposure: unadjusted

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Total	933	.	1,447,493	.	.
Demographics	.	.	.	.	.
Age, mean (SD)	28.51	5.51	24.97	5.38	0.65
Age categorical, N (%)					
<=19	40	4.29	222,742	15.39	-0.38
20-24	192	20.58	558,660	38.6	-0.40
25-29	323	34.62	383,662	26.51	0.18
30-34	231	24.76	186,718	12.9	0.31
35-39	118	12.65	78,129	5.4	0.26
>=40	29	3.11	17,582	1.21	0.13
Race, N (%)					
White	745	79.85	578,832	39.99	0.89
Black or African American	81	8.68	448,387	30.98	-0.58
Hispanic or Latino	25	2.68	216,247	14.94	-0.44
Asian or Other Pacific Islander	16	1.71	63,324	4.37	-0.16
American Indian	20	2.14	23,372	1.61	0.04
Other	27	2.89	81,118	5.6	-0.13
Unknown	19	2.04	36,213	2.5	-0.03
Chronic comorbid conditions, N (%)	.	.	.	.	.
Hypertension	129	13.83	74,940	5.18	0.30
Diabetes	169	18.11	153,603	10.61	0.22
Renal Disease	17	1.82	13,798	0.95	0.07
Obesity Overweight	99	10.61	72,355	5	0.21
Comorbidity Index Q1	294	31.51	768,536	53.09	-0.45
Comorbidity Index Q2	217	23.26	355,472	24.56	-0.03
Comorbidity Index Q3	153	16.4	169,441	11.71	0.14
Comorbidity Index Q4	269	28.83	154,044	10.64	0.47
Infections, N (%)	.	.	.	.	.
Toxoplasmosis	0	0	356	0.02	-0.02
Rubella	<11	0.11	245	0.02	0.04
Cytomegalovirus	0	0	139	0.01	-0.01

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Herpes	20	2.14	21,100	1.46	0.05
Syphilis	<11	0.11	2,553	0.18	-0.02
Varicella	<11	0.11	494	0.03	0.03
Parvovirus B19	0	0	154	0.01	-0.01
Zika virus other mosquito	0	0	0	0	0.00
Lymphocytic choriomeningitis	0	0	15	0	0.00
Influenza	13	1.39	17,818	1.23	0.01
Chlamydia	<11	0.43	16,155	1.12	-0.08
Human papilloma virus	<11	1.07	11,075	0.77	0.03
Gonorrhea	<11	0.75	17,662	1.22	-0.05
HIV	<11	0.54	6,443	0.45	0.01
Trichomoniasis	<11	0.86	31,954	2.21	-0.11
Indications for duloxetine, N (%)	.	.	.	.	.
Depression	523	56.06	117,885	8.14	1.20
Anxiety	363	38.91	76,889	5.31	0.88
Neuropathic Pain	130	13.93	38,894	2.69	0.42
Fibromyalgia	108	11.58	19,553	1.35	0.42
Non neuropathic Pain	555	59.49	347,051	23.98	0.77
Other psychiatric conditions, N (%)	.	.	.	.	.
Sleep disorder	64	6.86	15,403	1.06	0.30
Bipolar disorder	160	17.15	26,473	1.83	0.54
Psychosis	17	1.82	4,448	0.31	0.15
Schizophrenia	<11	1.07	3,540	0.24	0.10
Personality disorder	31	3.32	4,274	0.3	0.23
Adjustment disorder	14	1.5	8,250	0.57	0.09
Tobacco use, N (%)	198	21.22	98,493	6.8	0.42
Alcohol abuse or dependence, N (%)	16	1.71	7,200	0.5	0.12
Drug abuse or dependence, N (%)	35	3.75	20,761	1.43	0.15
Other medication exposures, N (%)	.	.	.	.	.
Benzodiazepines	413	44.27	58,952	4.07	1.06
Other hypnotics	338	36.23	101,517	7.01	0.76
Barbiturates	80	8.57	32,226	2.23	0.28

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Anxiolytics	82	8.79	9,258	0.64	0.39
Anticonvulsants	264	28.3	37,455	2.59	0.76
Antipsychotics	225	24.12	24,595	1.7	0.71
SSRIs	271	29.05	126,391	8.73	0.54
SNRIs	54	5.79	12,991	0.9	0.27
Other Antidep	276	29.58	55,813	3.86	0.73
Stimulants	87	9.32	13,345	0.92	0.39
Antidiabetic	54	5.79	29,470	2.04	0.19
Insulin	61	6.54	31,444	2.17	0.22
Antihyperten	216	23.15	88,352	6.1	0.50
Opioid analgesics	669	71.7	480,356	33.19	0.84
Triptans	69	7.4	19,542	1.35	0.30
NSAIDs	358	38.37	283,883	19.61	0.42
Obstetric conditions, N (%)	.	.	.	.	.
Multifetal gestation Flag	39	4.18	54,461	3.76	0.02
Markers of healthcare utilization	.	.	.	.	.
Number of distinct 3 digit ICD 9 codes=0	57	6.11	436,908	30.18	-0.66
Number of distinct 3 digit ICD 9 codes: tertile 1 for number >0	177	18.97	426,998	29.5	-0.25
Number of distinct 3 digit ICD 9 codes: tertile 2 for number >0	209	22.4	259,931	17.96	0.11
Number of distinct 3 digit ICD 9 codes: tertile 3 for number >0	490	52.52	323,656	22.36	0.66
Number of ED visits=0	591	63.34	1,129,132	78.01	-0.33
Number of ED visits=1	186	19.94	211,714	14.63	0.14
Number of ED visits=2	76	8.15	67,386	4.66	0.14
Number of ED visits>2	80	8.57	39,261	2.71	0.26
Number of non-duloxetine generics dispensed=0	<11	0.64	189,749	13.11	-0.51
Number of non-duloxetine generics dispensed: tertile 1 for number >0	60	6.43	347,729	24.02	-0.50
Number of non-duloxetine generics dispensed: tertile 2 for number >0	127	13.61	458,129	31.65	-0.44
Number of non-duloxetine generics dispensed: tertile 3 for number >0	740	79.31	451,886	31.22	1.10
Number of hospital admissions=0	838	89.82	1,358,409	93.85	-0.15

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Number of hospital admissions=1	73	7.82	74,302	5.13	0.11
Number of hospital admissions=2	18	1.93	11,416	0.79	0.10
Number of hospital admissions>2	<11	0.43	3,366	0.23	0.03
Number of outpatient visits=0	100	10.72	541,078	37.38	-0.66
Number of outpatient visits: tertile 1 for number >0	100	10.72	290,133	20.04	-0.26
Number of outpatient visits: tertile 2 for number >0	235	25.19	328,689	22.71	0.06
Number of outpatient visits: tertile 3 for number >0	498	53.38	287,593	19.87	0.74
Number of psychiatric hospitalizations Q1	902	96.68	1,439,121	99.42	-0.20
Number of psychiatric hospitalizations Q2	27	2.89	7,587	0.52	0.18
Number of psychiatric hospitalizations Q3	<11	0.43	661	0.05	0.08
Number of psychiatric hospitalizations Q4	0	0	124	0.01	-0.01
Number of psychiatrist visits=0	402	43.09	1,305,511	90.19	-1.15
Number of psychiatrist visits=1	211	22.62	72,177	4.99	0.53
Number of psychiatrist visits=2	97	10.4	24,703	1.71	0.37
Number of psychiatrist visits>2	223	23.9	45,102	3.12	0.64
Geographic region	.	.	.	.	.
Arkansas	0	0	1,227	0.08	-0.04
Alabama	PPD		9,535	0.66	0.04
California	67	7.18	308,666	21.32	-0.41
Colorado	PPD		5,499	0.38	-0.01
District of Columbia	0	0	682	0.05	-0.03
Delaware	24	2.57	12,482	0.86	0.13
Florida	PPD		31,772	2.19	-0.11
Georgia	PPD		32,300	2.23	-0.10
Hawaii	PPD		9,847	0.68	-0.09
Iowa	PPD		8,380	0.58	0.03
Idaho	PPD		1,593	0.11	0.03
Illinois	77	8.25	135,566	9.37	-0.04
Indiana	83	8.9	47,675	3.29	0.24
Kansas	PPD		10,918	0.75	0.04
Kentucky	19	2.04	26,512	1.83	0.01
Louisiana	26	2.79	31,049	2.15	0.04

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Massachusetts	PPD		10,666	0.74	-0.08
Maryland	15	1.61	26,480	1.83	-0.02
Maine	PPD		3,945	0.27	0.05
Minnesota	86	9.22	50,838	3.51	0.24
Missouri	51	5.47	38,219	2.64	0.14
Mississippi	PPD		22,005	1.52	-0.08
North Carolina	20	2.14	17,304	1.2	0.07
North Dakota	PPD		3,809	0.26	0.04
Nebraska	PPD		5,626	0.39	0.07
New Hampshire	PPD		3,450	0.24	0.03
New Jersey	PPD		15,254	1.05	-0.11
New Mexico	PPD		20,184	1.39	-0.03
Nevada	PPD		1,461	0.1	0.00
New York	133	14.26	232,233	16.04	-0.05
Ohio	13	1.39	22,412	1.55	-0.01
Oklahoma	PPD		18,236	1.26	-0.01
Oregon	17	1.82	11,838	0.82	0.09
Pennsylvania	PPD		20,171	1.39	-0.09
Rhode Island	PPD		2,917	0.2	-0.02
South Carolina	PPD		1,804	0.12	0.04
South Dakota	PPD		5,814	0.4	-0.03
Tennessee	42	4.5	115,608	7.99	-0.14
Texas	PPD		4,756	0.33	-0.05
Utah	34	3.64	7,772	0.54	0.22
Virginia	32	3.43	29,661	2.05	0.08
Vermont	PPD		8,351	0.58	0.06
Washington	PPD		1,783	0.12	0.02
Wisconsin	46	4.93	66,606	4.6	0.02
West Virginia	13	1.39	3,438	0.24	0.13
Wyoming	PPD		1,149	0.08	0.04
Opioids	.	.	.	.	.
buprenorphine	36	3.86	4,924	0.34	0.25

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Butorphanol	0	0	253	0.02	-0.02
codeine	222	23.79	204,447	14.12	0.25
fentanyl	22	2.36	1,161	0.08	0.21
hydrocodone	446	47.8	275,075	19	0.64
hydromorphone	20	2.14	2,702	0.19	0.18
Levorphanol	0	0	<11	0	0.00
meperidine	<11	0.32	2,037	0.14	0.04
methadone	12	1.29	1,628	0.11	0.14
morphine	26	2.79	1,623	0.11	0.23
oxycodone	215	23.04	81,555	5.63	0.51
oxymorphone	<11	0.32	143	0.01	0.08
pentazocine	<11	0.21	408	0.03	0.05
propoxyphene	78	8.36	45,705	3.16	0.22
Tapentadol	0	0	94	0.01	-0.01
tramadol	164	17.58	47,665	3.29	0.48
Healthcare Utilization, mean (SD)					
Comorbidity Index	1.79	1.96	0.93	1.41	0.51
Morphine equivalents	5460.04	34277.93	537.141	30335.83	0.15
Number of diagnoses	5.88	4.71	2.796	3.35	0.76
Number of ED visits	0.74	1.42	0.348	0.9	0.33
Number of non-duloxetine generics dispensed	10.49	6.37	4.471	4	1.13
Number of hospitalizations	0.13	0.43	0.076	0.34	0.14
Number of outpatient visits	5.67	7.55	2.117	3.47	0.61
Number of psychiatric hospitalizations	0.04	0.21	0.006	0.09	0.19
Number of psychiatrist visits	2.37	5.29	0.333	2.17	0.50

15.3. 11. Preeclampsia- Baseline characteristics of duloxetine exposed vs. SSRI exposed women - late exposure: unadjusted

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Total	662	.	48,672	.	.
Demographics	.	.	.	.	.
Age, mean (SD)	28.47	5.31	26.01	5.35	0.46
Age categorical, N (%)					
<=19	30	4.53	4,527	9.3	-0.19
20-24	126	19.03	17,426	35.8	-0.38
25-29	237	35.8	14,901	30.62	0.11
30-34	173	26.13	7,832	16.09	0.25
35-39	78	11.78	3,322	6.83	0.17
>=40	18	2.72	664	1.36	0.10
Race, N (%)					
White	536	80.97	35,014	71.94	0.21
Black/African American	56	8.46	6,689	13.74	-0.17
Hispanic/Latino	17	2.57	2,854	5.86	-0.16
Asian or Other Pacific	PPD		443	0.91	0.05
American Indian	14	2.11	938	1.93	0.01
Other	18	2.72	1,536	3.16	-0.03
Unknown	PPD		1,198	2.46	-0.06
Chronic comorbid conditions, N (%)	.	.	.	.	.
Hypertension	92	13.9	3,891	7.99	0.19
Diabetes	115	17.37	6,809	13.99	0.09
Renal Disease	<11	1.51	763	1.57	0.00
Obesity Overweight	68	10.27	3,261	6.7	0.13
Comorbidity Index Q1	212	32.02	21,165	43.48	-0.24
Comorbidity Index Q2	162	24.47	12,237	25.14	-0.02
Comorbidity Index Q3	104	15.71	7,394	15.19	0.01
Comorbidity Index Q4	184	27.79	7,876	16.18	0.28
Infections, N (%)	.	.	.	.	.
Toxoplasmosis	0	0	11	0.02	-0.02
Rubella	0	0	<11	0.01	-0.01
Cytomegalovirus	0	0	<11	0.01	-0.02

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Herpes	15	2.27	1062	2.18	0.01
Syphilis	<11	0.15	61	0.13	0.01
Varicella	<11	0.15	23	0.05	0.03
Parvovirus B19	0	0	<11	0.02	-0.02
Zika virus other mosquito	0	0	0	0	.
Lymphocytic choriomeningitis	0	0	0	0	-0.01
Influenza	<11	1.36	926	1.9	-0.04
Chlamydia	<11	0.3	365	0.75	-0.06
Human papilloma virus	<11	0.91	495	1.02	-0.01
Gonorrhea	<11	0.76	374	0.77	0.00
HIV	<11	0.6	212	0.44	0.02
Trichomoniasis	<11	0.76	845	1.74	-0.09
Indications for duloxetine, N (%)	.	.	.	.	.
Depression	343	51.81	22,159	45.53	0.13
Anxiety	243	36.71	12,696	26.08	0.23
Neuropathic Pain	80	12.08	3,116	6.4	0.20
Fibromyalgia	71	10.73	1,503	3.09	0.30
Non neuropathic Pain	380	57.4	19,958	41.01	0.33
Other psychiatric conditions, N (%)	.	.	.	.	.
Sleep disorder	41	6.19	1,976	4.06	0.10
Bipolar disorder	110	16.62	4,652	9.56	0.21
Psychosis	<11	1.21	636	1.31	-0.01
Schizophrenia	<11	1.06	668	1.37	-0.03
Personality disorder	22	3.32	891	1.83	0.09
Adjustment disorder	11	1.66	752	1.55	0.01
Tobacco use, N (%)	144	21.75	7,295	14.99	0.18
Alcohol abuse or dependence, N (%)	<11	1.51	959	1.97	-0.04
Drug abuse or dependence, N (%)	18	2.72	2,152	4.42	-0.09
Other medication exposures, N (%)	.	.	.	.	.
Benzodiazepines	274	41.39	10,320	21.2	0.45
Other hypnotics	230	34.74	10,050	20.65	0.32
Barbiturates	48	7.25	2,749	5.65	0.07

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Anxiolytics	49	7.4	1,823	3.75	0.16
Anticonvulsants	185	27.95	5,116	10.51	0.45
Antipsychotics	153	23.11	5,287	10.86	0.33
SSRIs	<11	0	48,672	100	.
SNRIs	33	4.98	1,966	4.04	0.05
Other Antidep	184	27.79	8,607	17.68	0.24
Stimulants	63	9.52	2,047	4.21	0.21
Antidiabetic	38	5.74	1,682	3.46	0.11
Insulin	44	6.65	1,800	3.7	0.13
Antihyperten	144	21.75	6,045	12.42	0.25
Opioid analgesics	461	69.64	27,895	57.31	0.26
Triptans	40	6.04	1,832	3.76	0.11
NSAIDs	242	36.56	14,344	29.47	0.15
Obstetric conditions, N (%)	.	.	.	.	.
Multifetal gestation Flag	28	4.23	2,165	4.45	-0.01
Markers of healthcare utilization	.	.	.	.	.
Number of distinct 3 digit ICD 9 codes=0	47	7.1	6,865	14.1	-0.23
Number of distinct 3 digit ICD 9 codes: tertile 1 for number >0	135	20.39	11,590	23.81	-0.08
Number of distinct 3 digit ICD 9 codes: tertile 2 for number >0	149	22.51	10,153	20.86	0.04
Number of distinct 3 digit ICD 9 codes: tertile 3 for number >0	331	50	20,064	41.22	0.18
Number of ED visits=0	427	64.5	32,773	67.33	-0.06
Number of ED visits=1	136	20.54	9,218	18.94	0.04
Number of ED visits=2	50	7.55	3,642	7.48	0.00
Number of ED visits>2	49	7.4	3,039	6.24	0.05
Number of non-duloxetine generics dispensed=0	<11	0.76	1,220	2.51	-0.14
Number of non-duloxetine generics dispensed: tertile 1 for number >0	51	7.7	4,816	9.89	-0.08
Number of non-duloxetine generics dispensed: tertile 2 for number >0	102	15.41	12,233	25.13	-0.24
Number of non-duloxetine generics dispensed: tertile 3 for number >0	504	76.13	30,403	62.47	0.30
Number of hospital admissions=0	614	92.75	44,082	90.57	0.08

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Number of hospital admissions=1	40	6.04	3,715	7.63	-0.06
Number of hospital admissions=2	<11	0.91	611	1.26	-0.03
Number of hospital admissions>2	<11	0.3	264	0.54	-0.04
Number of outpatient visits=0	82	12.39	9,380	19.27	-0.19
Number of outpatient visits: tertile 1 for number >0	76	11.48	7,957	16.35	-0.14
Number of outpatient visits: tertile 2 for number >0	172	25.98	12,459	25.6	0.01
Number of outpatient visits: tertile 3 for number >0	332	50.15	18,876	38.78	0.23
Number of psychiatric hospitalizations Q1	649	98.04	47,644	97.89	0.01
Number of psychiatric hospitalizations Q2	13	1.96	913	1.88	0.01
Number of psychiatric hospitalizations Q3	<11	0	92	0.19	-0.06
Number of psychiatric hospitalizations Q4	<11	0	23	0.05	-0.03
Number of psychiatrist visits=0	303	45.77	30,875	63.43	-0.36
Number of psychiatrist visits=1	156	23.56	7,610	15.64	0.20
Number of psychiatrist visits=2	65	9.82	3,431	7.05	0.10
Number of psychiatrist visits>2	138	20.85	6,756	13.88	0.18
Geographic region	.	.	.	.	.
Arkansas	0	0	54	0.11	-0.05
Alabama	PPD		482	0.99	-0.04
California	51	7.7	4,018	8.26	-0.02
Colorado	PPD		297	0.61	-0.02
District of Columbia	0	0	16	0.03	-0.03
Delaware	14	2.11	430	0.88	0.10
Florida	PPD		888	1.82	-0.08
Georgia	PPD		1,000	2.05	-0.14
Hawaii	PPD		52	0.11	0.01
Iowa	PPD		653	1.34	-0.08
Idaho	PPD		219	0.45	-0.05
Illinois	53	8.01	4,024	8.27	-0.01
Indiana	64	9.67	2,410	4.95	0.18
Kansas	PPD		605	1.24	0.02
Kentucky	PPD		1,147	2.36	-0.05
Louisiana	19	2.87	781	1.6	0.09

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Massachusetts	PPD		578	1.19	-0.10
Maryland			711	1.46	0.02
Maine			324	0.67	0.01
Minnesota	65	9.82	3,524	7.24	0.09
Missouri	34	5.14	1,790	3.68	0.07
Mississippi	PPD		506	1.04	-0.03
North Carolina	15	2.27	742	1.52	0.05
North Dakota	PPD		287	0.59	0.02
Nebraska			362	0.74	0.00
New Hampshire			373	0.77	-0.02
New Jersey			230	0.47	-0.10
New Mexico			731	1.5	-0.04
Nevada			88	0.18	-0.06
New York	100	15.11	4,582	9.41	0.17
Ohio	PPD		1,392	2.86	-0.16
Oklahoma	12	1.81	789	1.62	-0.10
Oregon			951	1.95	-0.01
Pennsylvania			1,312	2.7	-0.16
Rhode Island	PPD		212	0.44	-0.05
South Carolina			90	0.18	0.05
South Dakota			295	0.61	-0.07
Tennessee	30	4.53	4,158	8.54	-0.16
Texas	PPD		146	0.3	-0.03
Utah	19	2.87	823	1.69	0.08
Virginia	23	3.47	1,147	2.36	0.07
Vermont	PPD		737	1.51	0.00
Washington	36	5.44	138	0.28	-0.08
Wisconsin			4,222	8.67	-0.13
West Virginia			288	0.59	0.09
Wyoming	PPD		68	0.14	0.00
Opioids	.	.	.	.	.
buprenorphine	27	4.08	652	1.34	0.17

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
butorphanol	<11	0	25	0.05	-0.03
codeine	142	21.45	12,045	24.75	-0.08
fentanyl	15	2.27	149	0.31	0.17
hydrocodone	305	46.07	17,938	36.85	0.19
hydromorphone	16	2.42	311	0.64	0.15
Levorphanol	0	0	0	0	-0.01
meperidine	<11	0.15	222	0.46	-0.06
methadone	<11	0.91	236	0.48	0.05
morphine	17	2.57	217	0.45	0.17
oxycodone	140	21.15	6,651	13.66	0.20
oxymorphone	<11	0.45	16	0.03	0.09
pentazocine	<11	0.15	43	0.09	0.02
propoxyphene	42	6.34	3,880	7.97	-0.06
Tapentadol	0	0	11	0.02	-0.02
tramadol	112	16.92	3,984	8.19	0.27
Healthcare Utilization, mean (SD)					
Comorbidity Index	1.71	1.87	1.24	1.63	0.27
Morphine equivalents	5655.53	39415.59	1488.56	39406.14	0.11
Number of diagnoses	5.54	4.42	4.65	4.36	0.20
Number of ED visits	0.68	1.37	0.62	1.43	0.05
Number of non-duloxetine generics dispensed	9.66	5.77	7.99	5.41	0.30
Number of hospitalizations	0.09	0.36	0.12	0.45	-0.08
Number of outpatient visits	5.15	7.03	3.93	5.33	0.19
Number of psychiatric hospitalizations	0.02	0.14	0.02	0.18	-0.03
Number of psychiatrist visits	1.98	4.74	1.36	4.1	0.14

15.3. 12. Preeclampsia- Baseline characteristics of duloxetine exposed vs. venlafaxine exposed women - late exposure: unadjusted

	Duloxetine N/Mean	Duloxetine %/SD	Venlafaxine N/Mean	Venlafaxine %/SD	Standardized Difference
Total	879	.	2,943	.	.
Demographics	.	.	.	.	.
Age, mean (SD)	28.57	5.52	27.25	5.35	0.24
Age categorical, N (%)					
<=19	39	4.44	169	5.74	-0.06
20-24	174	19.8	855	29.05	-0.22
25-29	308	35.04	965	32.79	0.05
30-34	218	24.8	644	21.88	0.07
35-39	113	12.86	262	8.9	0.13
>=40	27	3.07	48	1.63	0.10
Race, N (%)					
White	700	79.64	2,407	81.79	-0.05
Black/African American	76	8.65	205	6.97	0.06
Hispanic/Latino	25	2.84	111	3.77	-0.05
Asian or Other Pacific	15	1.71	40	1.36	0.03
American Indian	20	2.28	37	1.26	0.08
Other	26	2.96	64	2.17	0.05
Unknown	17	1.93	79	2.68	-0.05
Chronic comorbid conditions, N (%)	.	.	.	.	.
Hypertension	121	13.77	279	9.48	0.13
Diabetes	160	18.2	471	16	0.06
Renal Disease	15	1.71	29	0.99	0.06
Obesity Overweight	97	11.04	193	6.56	0.16
Comorbidity Index Q1	281	31.97	1,134	38.53	-0.14
Comorbidity Index Q2	202	22.98	735	24.97	-0.05
Comorbidity Index Q3	144	16.38	460	15.63	0.02
Comorbidity Index Q4	252	28.67	614	20.86	0.18
Infections, N (%)	.	.	.	.	.
Toxoplasmosis	0	0	0	0	.
Rubella	0	0	0	0	.
Cytomegalovirus	0	0	0	0	.

	Duloxetine N/Mean	Duloxetine %/SD	Venlafaxine N/Mean	Venlafaxine %/SD	Standardized Difference
Herpes	18	2.05	47	1.6	0.03
Syphilis	<11	0.11	<11	0.1	0.00
Varicella	<11	0.11	<11	0.03	0.03
Parvovirus B19	0	0	0	0	.
Zika virus other mosquito	0	0	0	0	.
Lymphocytic choriomeningitis	0	0	0	0	.
Influenza	12	1.37	57	1.94	-0.04
Chlamydia	<11	0.46	11	0.37	0.01
Human papilloma virus	<11	1.02	27	0.92	0.01
Gonorrhea	<11	0.68	17	0.58	0.01
HIV	<11	0.57	15	0.51	0.01
Trichomoniasis	<11	0.91	41	1.39	-0.05
Indications for duloxetine, N (%)	.	.	.	.	.
Depression	489	55.63	1,592	54.09	0.03
Anxiety	337	38.34	947	32.18	0.13
Neuropathic Pain	118	13.42	263	8.94	0.14
Fibromyalgia	101	11.49	143	4.86	0.24
Non neuropathic Pain	521	59.27	1,338	45.46	0.28
Other psychiatric conditions, N (%)	.	.	.	.	.
Sleep disorder	58	6.6	161	5.47	0.05
Bipolar disorder	150	17.06	388	13.18	0.11
Psychosis	16	1.82	42	1.43	0.03
Schizophrenia	<11	1.14	36	1.22	-0.01
Personality disorder	28	3.19	72	2.45	0.04
Adjustment disorder	12	1.37	40	1.36	0.00
Tobacco use, N (%)	185	21.05	459	15.6	0.14
Alcohol abuse or dependence, N (%)	14	1.59	68	2.31	-0.05
Drug abuse or dependence, N (%)	31	3.53	171	5.81	-0.11
Other medication exposures, N (%)	.	.	.	.	.
Benzodiazepines	388	44.14	984	33.44	0.22
Other hypnotics	309	35.15	679	23.07	0.27
Barbiturates	72	8.19	209	7.1	0.04

	Duloxetine N/Mean	Duloxetine %/SD	Venlafaxine N/Mean	Venlafaxine %/SD	Standardized Difference
Anxiolytics	74	8.42	148	5.03	0.14
Anticonvulsants	249	28.33	518	17.6	0.26
Antipsychotics	212	24.12	525	17.84	0.15
SSRIs	250	28.44	706	23.99	0.10
SNRIs	<11	0	2,943	100	.
Other Antidep	250	28.44	759	25.79	0.06
Stimulants	83	9.44	207	7.03	0.09
Antidiabetic	50	5.69	124	4.21	0.07
Insulin	57	6.48	154	5.23	0.05
Antihyperten	202	22.98	475	16.14	0.17
Opioid analgesics	626	71.22	1,809	61.47	0.21
Triptans	64	7.28	171	5.81	0.06
NSAIDs	343	39.02	958	32.55	0.14
Obstetric conditions, N (%)	.	.	.	.	.
Multifetal gestation Flag	37	4.21	142	4.83	-0.03
Markers of healthcare utilization	.	.	.	.	.
Number of distinct 3 digit ICD 9 codes=0	53	6.03	303	10.3	-0.16
Number of distinct 3 digit ICD 9 codes: tertile 1 for number >0	170	19.34	690	23.45	-0.10
Number of distinct 3 digit ICD 9 codes: tertile 2 for number >0	199	22.64	630	21.41	0.03
Number of distinct 3 digit ICD 9 codes: tertile 3 for number >0	457	51.99	1,320	44.85	0.14
Number of ED visits=0	565	64.28	1,982	67.35	-0.06
Number of ED visits=1	172	19.57	558	18.96	0.02
Number of ED visits=2	70	7.96	224	7.61	0.01
Number of ED visits>2	72	8.19	179	6.08	0.08
Number of non-duloxetine generics dispensed=0	<11	0.68	28	0.95	-0.03
Number of non-duloxetine generics dispensed: tertile 1 for number >0	58	6.6	199	6.76	-0.01
Number of non-duloxetine generics dispensed: tertile 2 for number >0	124	14.11	620	21.07	-0.18
Number of non-duloxetine generics dispensed: tertile 3 for number >0	691	78.61	2,096	71.22	0.17
Number of hospital admissions=0	794	90.33	2,674	90.86	-0.02

	Duloxetine N/Mean	Duloxetine %/SD	Venlafaxine N/Mean	Venlafaxine %/SD	Standardized Difference
Number of hospital admissions=1	65	7.39	212	7.2	0.01
Number of hospital admissions=2	16	1.82	38	1.29	0.04
Number of hospital admissions>2	<11	0.46	19	0.65	-0.03
Number of outpatient visits=0	93	10.58	453	15.39	-0.14
Number of outpatient visits: tertile 1 for number >0	99	11.26	436	14.81	-0.11
Number of outpatient visits: tertile 2 for number >0	221	25.14	754	25.62	-0.01
Number of outpatient visits: tertile 3 for number >0	466	53.01	1,300	44.17	0.18
Number of psychiatric hospitalizations Q1	851	96.81	2,875	97.69	-0.05
Number of psychiatric hospitalizations Q2	24	2.73	61	2.07	0.04
Number of psychiatric hospitalizations Q3	<11	0.46	<11	0.17	0.05
Number of psychiatric hospitalizations Q4	<11	0	<11	0.07	-0.04
Number of psychiatrist visits=0	382	43.46	1,508	51.24	-0.16
Number of psychiatrist visits=1	202	22.98	558	18.96	0.10
Number of psychiatrist visits=2	95	10.81	298	10.13	0.02
Number of psychiatrist visits>2	200	22.75	579	19.67	0.08
Geographic region	.	.	.	.	.
Arkansas	0	0	PPD		-0.05
Alabama	PPD		14	0.48	0.06
California	62	7.05	231	7.85	-0.03
Colorado	PPD		19	0.65	-0.06
District of Columbia	0	0	PPD		-0.05
Delaware	24	2.73	34	1.16	0.11
Florida	PPD		36	1.22	-0.03
Georgia	PPD		64	2.17	-0.14
Hawaii	PPD		PPD		0.03
Iowa	PPD		40	1.36	-0.04
Idaho	PPD		25	0.85	-0.09
Illinois	73	8.3	203	6.9	0.05
Indiana	80	9.1	137	4.66	0.18
Kansas	PPD		33	1.12	0.01
Kentucky	16	1.82	49	1.66	0.01
Louisiana	26	2.96	44	1.5	0.10

	Duloxetine N/Mean	Duloxetine %/SD	Venlafaxine N/Mean	Venlafaxine %/SD	Standardized Difference
Massachusetts	PPD		24	0.82	-0.10
Maryland	15	1.71	34	1.16	0.05
Maine	PPD		30	1.02	-0.04
Minnesota	74	8.42	240	8.15	0.01
Missouri	50	5.69	118	4.01	0.08
Mississippi	PPD		50	1.7	-0.09
North Carolina	20	2.28	33	1.12	0.09
North Dakota	PPD		15	0.51	0.01
Nebraska			27	0.92	0.01
New Hampshire			20	0.68	-0.03
New Jersey			PPD		-0.02
New Mexico	PPD		43	1.46	-0.03
Nevada			PPD		-0.01
New York			126	14.33	0.15
Ohio			13	1.48	-0.16
Oklahoma	PPD		36	1.22	-0.01
Oregon	15	1.71	61	2.07	-0.03
Pennsylvania	PPD		118	4.01	-0.23
Rhode Island			PPD		-0.04
South Carolina					0.01
South Dakota			17	0.58	-0.06
Tennessee	40	4.55	226	7.68	-0.13
Texas	PPD		PPD		-0.01
Utah	31	3.53	55	1.87	0.10
Virginia	30	3.41	62	2.11	0.08
Vermont	PPD		39	1.33	-0.02
Washington			PPD		-0.01
Wisconsin	46	5.23	281	9.55	-0.17
West Virginia	PPD		22	0.75	0.06
Wyoming			PPD		-0.01
Opioids	.	.	.	.	.
buprenorphine	32	3.64	70	2.38	0.07

	Duloxetine	Duloxetine	Venlafaxine	Venlafaxine	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
butorphanol	<11	0	<11	0.17	-0.06
codeine	209	23.78	734	24.94	-0.03
fentanyl	22	2.5	21	0.71	0.14
hydrocodone	415	47.21	1,198	40.71	0.13
hydromorphone	18	2.05	26	0.88	0.10
levorphanol	<11	0	<11	0	.
meperidine	<11	0.34	11	0.37	-0.01
methadone	11	1.25	27	0.92	0.03
morphine	24	2.73	26	0.88	0.14
oxycodone	196	22.3	444	15.09	0.19
oxymorphone	<11	0.34	<11	0.07	0.06
pentazocine	<11	0.11	<11	0.2	-0.02
propoxyphene	72	8.19	287	9.75	-0.05
Tapentadol	0	0	<11	0.03	-0.03
tramadol	151	17.18	297	10.09	0.21
Healthcare Utilization, mean (SD)					
Comorbidity Index	1.78	1.96	1.48	1.85	0.16
Morphine equivalents	5150.66	32646.39	1681	23180.5	0.12
Number of diagnoses	5.81	4.65	4.96	4.37	0.19
Number of ED visits	0.72	1.41	0.62	1.32	0.07
Number of non-duloxetine generics dispensed	10.35	6.33	9.27	5.84	0.18
Number of hospitalizations	0.13	0.42	0.12	0.47	0.00
Number of outpatient visits	5.65	7.67	4.6	6.33	0.15
Number of psychiatric hospitalizations	0.04	0.21	0.03	0.2	0.05
Number of psychiatrist visits	2.36	5.39	2.01	5.66	0.06

15.3. 13. Preeclampsia- Baseline characteristics of duloxetine exposed vs. unexposed women - late exposure: adjusted for treatment indications

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Total	808	.	474,014	.	.
Demographics	.	.	.	.	.
Age, mean (SD)	28.59	5.5	25.56	5.38	0.56
Age categorical, N (%)					
<=19	33	4.08	56,897	12.00	-0.29
20-24	162	20.05	173,503	36.60	-0.37
25-29	284	35.15	138,407	29.20	0.13
30-34	201	24.88	70,136	14.80	0.25
35-39	102	12.62	28,649	6.04	0.23
>=40	26	3.22	6,422	1.35	0.12
Race, N (%)					
White	651	80.57	280,903	59.26	0.48
Black/African American	65	8.04	101,671	21.45	-0.38
Hispanic/Latino	19	2.35	39,638	8.36	-0.27
Asian or Other Pacific	14	1.73	8,934	1.88	-0.01
American Indian	16	1.98	10,434	2.20	-0.02
Other	25	3.09	21,417	4.52	-0.07
Unknown	18	2.23	11,016	2.32	-0.01
Chronic comorbid conditions, N (%)	.	.	.	.	.
Hypertension	113	13.99	41,488	8.75	0.17
Diabetes	147	18.19	65,301	13.78	0.12
Renal Disease	16	1.98	8,656	1.83	0.01
Obesity Overweight	90	11.14	39,781	8.39	0.09
Comorbidity Index Q1	249	30.82	203,524	42.94	-0.25
Comorbidity Index Q2	177	21.91	121,348	25.60	-0.09
Comorbidity Index Q3	137	16.96	71,414	15.07	0.05
Comorbidity Index Q4	245	30.32	77,729	16.40	0.33
Infections, N (%)	.	.	.	.	.
Toxoplasmosis	0	0.00	180	0.04	-0.03
Rubella	<11	0.12	63	0.01	0.04
Cytomegalovirus	0	0.00	54	0.01	-0.02

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Herpes	18	2.23	11,655	2.46	-0.02
Syphilis	<11	0.12	778	0.16	-0.01
Varicella	0	0.00	245	0.05	-0.03
Parvovirus B19	0	0.00	97	0.02	-0.02
Zika virus other mosquito	0	0.00	0	0.00	.
Lymphocytic choriomeningitis	0	0.00	<11	0.00	0.00
Influenza	12	1.49	9,884	2.09	-0.05
Chlamydia	<11	0.50	5,292	1.12	-0.07
Human papilloma virus	<11	0.99	4,984	1.05	-0.01
Gonorrhea	<11	0.74	5,535	1.17	-0.04
HIV	<11	0.50	2,554	0.54	-0.01
Trichomoniasis	<11	0.74	10,898	2.30	-0.13
Indications for duloxetine, N (%)	.	.	.	.	.
Depression	523	64.73	306,054	64.57	0.00
Anxiety	363	44.93	211,156	44.55	0.01
Neuropathic Pain	130	16.09	76,624	16.16	0.00
Fibromyalgia	108	13.37	80,363	16.95	-0.10
Non neuropathic Pain	555	68.69	325,607	68.69	0.00
Other psychiatric conditions, N (%)	.	.	.	.	.
Sleep disorder	63	7.80	23,773	5.02	0.11
Bipolar disorder	144	17.82	41,215	8.69	0.27
Psychosis	14	1.73	7,648	1.61	0.01
Schizophrenia	<11	1.24	5,259	1.11	0.01
Personality disorder	29	3.59	9,662	2.04	0.09
Adjustment disorder	14	1.73	9,108	1.92	-0.01
Tobacco use, N (%)	186	23.02	76,772	16.20	0.17
Alcohol abuse or dependence, N (%)	16	1.98	7,920	1.67	0.02
Drug abuse or dependence, N (%)	32	3.96	19,625	4.14	-0.01
Other medication exposures, N (%)	.	.	.	.	.
Benzodiazepines	382	47.28	104,439	22.03	0.55
Other hypnotics	305	37.75	90,590	19.11	0.42
Barbiturates	70	8.66	25,464	5.37	0.13

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Anxiolytics	74	9.16	18,753	3.96	0.21
Anticonvulsants	239	29.58	53,760	11.34	0.46
Antipsychotics	198	24.50	44,060	9.30	0.41
SSRIs	250	30.94	191,461	40.39	-0.20
SNRIs	48	5.94	24,625	5.19	0.03
Other Antidep	257	31.81	86,469	18.24	0.32
Stimulants	71	8.79	18,528	3.91	0.20
Antidiabetic	41	5.07	14,789	3.12	0.10
Insulin	52	6.44	16,075	3.39	0.14
Antihyperten	185	22.90	55,559	11.72	0.30
Opioid analgesics	604	74.75	279,404	58.94	0.34
Triptans	66	8.17	18,361	3.87	0.18
NSAIDs	328	40.59	165,592	34.93	0.12
Obstetric conditions, N (%)	.	.	.	.	.
Multifetal gestation Flag	34	4.21	19,799	4.18	0.00
Markers of healthcare utilization	.	.	.	.	.
Number of distinct 3 digit ICD 9 codes=0	33	4.08	38,938	8.21	-0.17
Number of distinct 3 digit ICD 9 codes: tertile 1 for number >0	131	16.21	85,559	18.05	-0.05
Number of distinct 3 digit ICD 9 codes: tertile 2 for number >0	177	21.91	96,198	20.29	0.04
Number of distinct 3 digit ICD 9 codes: tertile 3 for number >0	467	57.80	253,320	53.44	0.09
Number of ED visits=0	480	59.41	279,114	58.88	0.01
Number of ED visits=1	174	21.53	103,587	21.85	-0.01
Number of ED visits=2	76	9.41	45,289	9.55	-0.01
Number of ED visits>2	78	9.65	46,023	9.71	0.00
Number of non-duloxetine generics dispensed=0	<11	0.62	16,883	3.56	-0.21
Number of non-duloxetine generics dispensed: tertile 1 for number >0	46	5.69	47,721	10.07	-0.16
Number of non-duloxetine generics dispensed: tertile 2 for number >0	96	11.88	110,274	23.26	-0.30
Number of non-duloxetine generics dispensed: tertile 3 for number >0	661	81.81	299,136	63.11	0.43
Number of hospital admissions=0	723	89.48	419,647	88.53	0.03

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Number of hospital admissions=1	64	7.92	41,715	8.80	-0.03
Number of hospital admissions=2	17	2.10	8,311	1.75	0.03
Number of hospital admissions>2	<11	0.50	4,340	0.92	-0.05
Number of outpatient visits=0	62	7.67	61,383	12.95	-0.17
Number of outpatient visits: tertile 1 for number >0	79	9.78	63,492	13.39	-0.11
Number of outpatient visits: tertile 2 for number >0	201	24.88	114,858	24.23	0.01
Number of outpatient visits: tertile 3 for number >0	466	57.67	234,281	49.42	0.17
Number of psychiatric hospitalizations Q1	778	96.29	459,194	96.87	-0.03
Number of psychiatric hospitalizations Q2	26	3.22	12,837	2.71	0.03
Number of psychiatric hospitalizations Q3	<11	0.50	1,578	0.33	0.03
Number of psychiatric hospitalizations Q4	0	0.00	406	0.09	-0.04
Number of psychiatrist visits=0	299	37.00	228,312	48.17	-0.23
Number of psychiatrist visits=1	202	25.00	99,607	21.01	0.09
Number of psychiatrist visits=2	95	11.76	49,287	10.40	0.04
Number of psychiatrist visits>2	212	26.24	96,808	20.42	0.14
Geographic region	.	.	.	.	.
Arkansas	0	0.00	565	0.12	-0.05
Alabama	PPD		4,090	0.86	0.03
California	54	6.68	54,763	11.55	-0.17
Colorado	PPD		1,410	0.30	0.01
District of Columbia	0	0.00	320	0.07	-0.04
Delaware	18	2.23	3,880	0.82	0.12
Florida	PPD		6,330	1.34	-0.07
Georgia	PPD		8,559	1.81	-0.08
Hawaii	PPD		2,267	0.48	-0.06
Iowa	PPD		3,691	0.78	0.01
Idaho	PPD		1,060	0.22	-0.02
Illinois	65	8.04	34,095	7.19	0.03
Indiana	74	9.16	24,040	5.07	0.16
Kansas	PPD		3,911	0.83	0.04
Kentucky	16	1.98	13,188	2.78	-0.05
Louisiana	21	2.60	8,026	1.69	0.06

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Massachusetts	PPD		3,508	0.74	-0.07
Maryland			10,196	2.15	-0.06
Maine			2,949	0.62	0.00
Minnesota	82	10.15	32,626	6.88	0.12
Missouri	44	5.45	12,213	2.58	0.15
Mississippi	PPD		7,367	1.55	-0.11
North Carolina	17	2.10	7,937	1.67	0.03
North Dakota	PPD		2,863	0.60	0.00
Nebraska			2,806	0.59	0.04
New Hampshire			3,211	0.68	-0.04
New Jersey			2,836	0.60	-0.05
New Mexico			8,471	1.79	-0.05
Nevada			794	0.17	-0.01
New York	115	14.23	54,655	11.53	0.08
Ohio	13	1.61	12,131	2.56	-0.07
Oklahoma	PPD		5,984	1.26	0.01
Oregon	17	2.10	7,019	1.48	0.05
Pennsylvania	PPD		9,648	2.04	-0.14
Rhode Island			1,742	0.37	-0.05
South Carolina			906	0.19	0.01
South Dakota			2,929	0.62	-0.06
Tennessee	40	4.95	46,182	9.74	-0.18
Texas	PPD		1,030	0.22	-0.02
Utah	25	3.09	3,403	0.72	0.17
Virginia	29	3.59	12,666	2.67	0.05
Vermont	PPD		6,027	1.27	0.00
Washington	38	4.70	622	0.13	0.03
Wisconsin			37,902	8.00	-0.14
West Virginia	PPD		2,651	0.56	0.08
Wyoming			542	0.11	0.03
Opioids	.	.	.	.	.
buprenorphine	31	3.84	5,937	1.25	0.16

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
butorphanol	0	0.00	401	0.08	-0.04
codeine	201	24.88	117,020	24.69	0.00
fentanyl	21	2.60	2,755	0.58	0.16
hydrocodone	412	50.99	186,371	39.32	0.24
hydromorphone	18	2.23	4,156	0.88	0.11
levorphanol	0	0.00	<11	0.00	0.00
meperidine	<11	0.25	2,022	0.43	-0.03
methadone	12	1.49	3,380	0.71	0.07
morphine	25	3.09	3,583	0.76	0.17
oxycodone	198	24.50	71,183	15.02	0.24
oxymorphone	<11	0.37	395	0.08	0.06
pentazocine	<11	0.25	585	0.12	0.03
propoxyphene	75	9.28	35,411	7.47	0.07
tapentadol	0	0.00	304	0.06	-0.04
tramadol	155	19.18	50,934	10.75	0.24
Healthcare Utilization, mean (SD)					
Comorbidity Index	1.85	1.99	1.27	1.73	0.51
Morphine equivalents	8304.52	39001.34	4812.14	159825.5	0.15
Number of diagnoses	6.35	4.73	5.97	5.04	0.76
Number of ED visits	0.81	1.39	0.86	1.69	0.33
Number of non-duloxetine generics dispensed	10.92	6.49	8.2	5.71	1.13
Number of hospitalizations	0.14	0.44	0.17	0.71	0.14
Number of outpatient visits	6.13	7.86	4.97	5.94	0.61
Number of psychiatric hospitalizations	0.04	0.22	0.04	0.23	0.19
Number of psychiatrist visits	2.61	5.47	1.87	4.4	0.50

15.3. 14. Preeclampsia- Baseline characteristics of duloxetine exposed vs. SSRI exposed women - late exposure: adjusted for treatment indications

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Total	558	.	35,933	.	.
Demographics	.	.	.	.	.
Age, mean (SD)	28.53	5.28	26.34	5.4	0.41
Age categorical, N (%)					
<=19	25	4.48	2,988	8.32	-0.16
20-24	102	18.28	12,244	34.08	-0.37
25-29	205	36.74	11,251	31.31	0.11
30-34	146	26.16	6,216	17.30	0.22
35-39	64	11.47	2,686	7.47	0.14
>=40	16	2.87	547	1.52	0.09
Race, N (%)					
White	458	82.08	26,320	73.25	0.21
Black/African American	43	7.71	4,554	12.67	-0.16
Hispanic/Latino			1,903	5.30	-0.17
Asian or Other Pacific			343	0.95	0.04
American Indian			760	2.11	-0.01
Other	16	2.87	1,165	3.24	-0.02
Unknown			889	2.47	-0.05
Chronic comorbid conditions, N (%)	.	.	.	.	.
Hypertension	79	14.16	3,369	9.38	0.15
Diabetes	95	17.03	5,591	15.56	0.04
Renal Disease	<11	1.61	742	2.06	-0.03
Obesity Overweight	60	10.75	2,930	8.15	0.09
Comorbidity Index Q1	179	32.08	14,301	39.80	-0.16
Comorbidity Index Q2	124	22.22	9,006	25.06	-0.07
Comorbidity Index Q3	90	16.13	5,885	16.38	-0.01
Comorbidity Index Q4	165	29.57	6,740	18.76	0.25
Infections, N (%)	.	.	.	.	.
Toxoplasmosis	0	0.00	<11	0.03	-0.02
Rubella	0	0.00	<11	0.00	-0.01

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Cytomegalovirus	0	0.00	<11	0.03	-0.02
Herpes	13	2.33	915	2.55	-0.01
Syphilis	<11	0.18	50	0.14	0.01
Varicella	0	0.00	26	0.07	-0.04
Parvovirus B19	0	0.00	<11	0.01	-0.02
Zika virus other mosquito	0	0.00	0	0.00	.
Lymphocytic choriomeningitis	0	0.00	0	0.00	.
Influenza	<11	1.43	773	2.15	-0.05
Chlamydia	<11	0.36	297	0.83	-0.06
Human papilloma virus	<11	0.72	385	1.07	-0.04
Gonorrhea	<11	0.72	309	0.86	-0.02
HIV	<11	0.54	161	0.45	0.01
Trichomoniasis	<11	0.72	655	1.82	-0.10
Indications for duloxetine, N (%)	.	.	.	.	.
Depression	343	61.47	22,183	61.73	-0.01
Anxiety	243	43.55	15,173	42.23	0.03
Neuropathic Pain	80	14.34	6,328	17.61	-0.09
Fibromyalgia	71	12.72	5,023	13.98	-0.04
Non neuropathic Pain	380	68.10	24,413	67.94	0.00
Other psychiatric conditions, N (%)	.	.	.	.	.
Sleep disorder	41	7.35	2,100	5.84	0.06
Bipolar disorder	99	17.74	4,302	11.97	0.16
Psychosis	<11	1.08	620	1.73	-0.06
Schizophrenia	<11	1.25	583	1.62	-0.03
Personality disorder	20	3.58	912	2.54	0.06
Adjustment disorder	11	1.97	656	1.83	0.01
Tobacco use, N (%)	133	23.84	6,504	18.10	0.14
Alcohol abuse or dependence, N (%)	<11	1.79	842	2.34	-0.04
Drug abuse or dependence, N (%)	15	2.69	1,844	5.13	-0.13
Other medication exposures, N (%)	.	.	.	.	.
Benzodiazepines	249	44.62	10,488	29.19	0.32

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Other hypnotics	202	36.20	9,408	26.18	0.22
Barbiturates	40	7.17	2,488	6.92	0.01
Anxiolytics	42	7.53	1,845	5.13	0.10
Anticonvulsants	167	29.93	5,368	14.94	0.37
Antipsychotics	131	23.48	5,021	13.97	0.25
SSRIs	-	0.00	35,933	100.00	.
SNRIs	29	5.20	1,878	5.23	0.00
Other Antidep	170	30.47	8,288	23.07	0.17
Stimulants	50	8.96	1,916	5.33	0.14
Antidiabetic	26	4.66	1,456	4.05	0.03
Insulin	35	6.27	1,629	4.53	0.08
Antihyperten	122	21.86	5,341	14.86	0.18
Opioid analgesics	406	72.76	24,065	66.97	0.13
Triptans	37	6.63	1,788	4.98	0.07
NSAIDs	218	39.07	13,414	37.33	0.04
Obstetric conditions, N (%)	.	.	.	.	.
Multifetal gestation Flag	25	4.48	1,515	4.22	0.01
Markers of healthcare utilization	.	.	.	.	.
Number of distinct 3 digit ICD 9 codes=0	24	4.30	2,740	7.62	-0.14
Number of distinct 3 digit ICD 9 codes: tertile 1 for number >0	98	17.56	6,383	17.76	-0.01
Number of distinct 3 digit ICD 9 codes: tertile 2 for number >0	124	22.22	7,293	20.30	0.05
Number of distinct 3 digit ICD 9 codes: tertile 3 for number >0	312	55.91	19,517	54.32	0.03
Number of ED visits=0	335	60.04	21,290	59.25	0.02
Number of ED visits=1	125	22.40	7,641	21.27	0.03
Number of ED visits=2	50	8.96	3,479	9.68	-0.02
Number of ED visits>2	48	8.60	3,523	9.80	-0.04
Number of non-duloxetine generics dispensed=0	<11	0.72	456	1.27	-0.06
Number of non-duloxetine generics dispensed: tertile 1 for number >0	37	6.63	2,175	6.05	0.02
Number of non-duloxetine generics dispensed: tertile 2 for number >0	76	13.62	6,829	19.00	-0.15

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Number of non-duloxetine generics dispensed: tertile 3 for number >0	441	79.03	26,474	73.68	0.13
Number of hospital admissions=0	518	92.83	31,781	88.45	0.15
Number of hospital admissions=1	32	5.73	3,236	9.01	-0.13
Number of hospital admissions=2	<11	1.08	618	1.72	-0.06
Number of hospital admissions>2	<11	0.36	297	0.83	-0.06
Number of outpatient visits=0	47	8.42	4,191	11.66	-0.11
Number of outpatient visits: tertile 1 for number >0	56	10.04	4,680	13.02	-0.09
Number of outpatient visits: tertile 2 for number >0	149	26.70	8,846	24.62	0.05
Number of outpatient visits: tertile 3 for number >0	306	54.84	18,215	50.69	0.08
Number of psychiatric hospitalizations Q1	546	97.85	34,878	97.06	0.05
Number of psychiatric hospitalizations Q2	12	2.15	926	2.58	-0.03
Number of psychiatric hospitalizations Q3	0	0.00	103	0.29	-0.08
Number of psychiatric hospitalizations Q4	0	0.00	27	0.07	-0.04
Number of psychiatrist visits=0	213	38.17	18,419	51.26	-0.27
Number of psychiatrist visits=1	151	27.06	7,082	19.71	0.17
Number of psychiatrist visits=2	63	11.29	3,428	9.54	0.06
Number of psychiatrist visits>2	131	23.48	7,004	19.49	0.10
Geographic region	.	.	.	.	.
Arkansas	0	0.00	49	0.14	-0.05
Alabama	PPD		351	0.98	-0.03
California	38	6.81	2,552	7.10	-0.01
Colorado	PPD		186	0.52	0.00
District of Columbia	0	0.00	PPD		-0.02
Delaware	PPD				0.08
Florida	PPD		538	1.50	-0.07
Georgia	PPD		699	1.94	-0.15
Hawaii	PPD		38	0.11	0.02
Iowa	PPD		442	1.23	-0.07
Idaho	0	0.00	183	0.51	-0.10
Illinois	43	7.71	2,733	7.61	0.00
Indiana	56	10.04	1,952	5.43	0.17

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Kansas	PPD		389	1.08	0.05
Kentucky			883	2.46	-0.07
Louisiana	15	2.69	485	1.35	0.10
Massachusetts	PPD		362	1.01	-0.08
Maryland			550	1.53	-0.02
Maine			243	0.68	0.00
Minnesota	63	11.29	3,047	8.48	0.09
Missouri	30	5.38	1,152	3.21	0.11
Mississippi	PPD		368	1.02	-0.06
North Carolina	13	2.33	593	1.65	0.05
North Dakota	PPD		283	0.79	0.01
Nebraska			285	0.79	0.01
New Hampshire			334	0.93	-0.05
New Jersey	0	0.00	128	0.36	-0.08
New Mexico	PPD		534	1.49	-0.02
Nevada	0	0.00	66	0.18	-0.06
New York	84	15.05	3,089	8.60	0.20
Ohio	PPD		1,107	3.08	-0.16
Oklahoma			422	1.17	-0.05
Oregon			704	1.96	0.01
Pennsylvania			952	2.65	-0.15
Rhode Island			212	0.59	-0.07
South Carolina			92	0.26	0.02
South Dakota			251	0.70	-0.08
Tennessee	28	5.02	3,210	8.93	-0.15
Texas	PPD		76	0.21	-0.01
Utah			559	1.56	0.04
Virginia	20	3.58	902	2.51	0.06
Vermont	PPD		609	1.70	-0.01
Washington	0	0.00	82	0.23	-0.07
Wisconsin	28	5.02	3,616	10.06	-0.19
West Virginia	PPD		253	0.70	0.07

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Wyoming	PPD		55	0.15	0.01
Opioids	.	.	.	.	.
buprenorphine	22	3.94	567	1.58	0.14
butorphanol	-	0.00	30	0.08	-0.04
codeine	126	22.58	10,670	29.69	-0.16
fentanyl	14	2.51	245	0.68	0.15
hydrocodone	276	49.46	16,553	46.07	0.07
hydromorphone	14	2.51	388	1.08	0.11
levorphanol	0	0.00	<11	0.00	-0.01
meperidine	<11	0.18	198	0.55	-0.06
methadone	<11	1.08	314	0.87	0.02
morphine	16	2.87	343	0.95	0.14
oxycodone	126	22.58	6,650	18.51	0.10
oxymorphone	<11	0.54	33	0.09	0.08
pentazocine	<11	0.18	57	0.16	0.01
propoxyphene	40	7.17	3,622	10.08	-0.10
tapentadol	0	0.00	11	0.03	-0.02
tramadol	105	18.82	4,433	12.34	0.18
Healthcare Utilization, mean (SD)					
Comorbidity Index	1.78	1.92	1.38	1.73	0.22
Morphine equivalents	8721.13	45066.72	4212.42	110400.92	0.05
Number of diagnoses	6.06	4.45	6.03	5	0.01
Number of ED visits	0.76	1.32	0.86	1.63	-0.06
Number of non-duloxetine generics dispensed	10.09	5.87	9.67	6.02	0.07
Number of hospitalizations	0.09	0.37	0.16	0.53	-0.14
Number of outpatient visits	5.66	7.44	5.13	6.07	0.08
Number of psychiatric hospitalizations	0.02	0.15	0.03	0.21	-0.07
Number of psychiatrist visits	2.25	5.04	1.8	4.43	0.09

15.3. 15. Preeclampsia- Baseline characteristics of duloxetine exposed vs. venlafaxine exposed women - late exposure: adjusted for treatment

indications

	Duloxetine N/Mean	Duloxetine %/SD	Venlafaxine N/Mean	Venlafaxine %/SD	Standardized Difference
Total	760	.	2,364	.	.
Demographics	.	.	.	.	.
Age, mean (SD)	28.64	5.51	27.34	5.3	0.24
Age categorical, N (%)					
<=19	32	4.21	122	5.17	-0.05
20-24	146	19.21	683	28.89	-0.23
25-29	272	35.79	771	32.61	0.07
30-34	188	24.74	534	22.60	0.05
35-39	98	12.89	223	9.43	0.11
>=40	24	3.16	31	1.29	0.13
Race, N (%)					
White	611	80.39	1,924	81.39	-0.03
Black/African American	61	8.03	151	6.40	0.06
Hispanic/Latino	19	2.50	89	3.78	-0.07
Asian or Other Pacific	13	1.71	43	1.82	-0.01
American Indian	16	2.11	36	1.50	0.05
Other	24	3.16	51	2.14	0.06
Unknown	16	2.11	70	2.97	-0.05
Chronic comorbid conditions, N (%)	.	.	.	.	.
Hypertension	105	13.82	247	10.44	0.10
Diabetes	139	18.29	402	17.00	0.03
Renal Disease	14	1.84	22	0.92	0.08
Obesity Overweight	88	11.58	199	8.43	0.11
Comorbidity Index Q1	237	31.18	872	36.89	-0.12
Comorbidity Index Q2	166	21.84	599	25.35	-0.08
Comorbidity Index Q3	129	16.97	375	15.85	0.03
Comorbidity Index Q4	228	30.00	518	21.91	0.19
Infections, N (%)	.	.	.	.	.
Toxoplasmosis	0	0.00	0	0.00	.

	Duloxetine N/Mean	Duloxetine %/SD	Venlafaxine N/Mean	Venlafaxine %/SD	Standardized Difference
Rubella	0	0.00	0	0.00	.
Cytomegalovirus	0	0.00	0	0.00	.
Herpes	16	2.11	34	1.45	0.05
Syphilis	<11	0.13	<11	0.10	0.01
Varicella	0	0.00	<11	0.02	-0.02
Parvovirus B19	0	0.00	0	0.00	.
Zika virus other mosquito	0	0.00	0	0.00	.
Lymphocytic choriomeningitis	0	0.00	0	0.00	.
Influenza	11	1.45	53	2.23	-0.06
Chlamydia	<11	0.53	<11	0.31	0.03
Human papilloma virus	<11	0.92	28	1.20	-0.03
Gonorrhea	<11	0.66	11	0.45	0.03
HIV	<11	0.53	13	0.56	0.00
Trichomoniasis	<11	0.79	30	1.28	-0.05
Indications for duloxetine, N (%)	.	.	.	.	.
Depression	489	64.34	1,502	63.54	0.02
Anxiety	337	44.34	1,074	45.42	-0.02
Neuropathic Pain	118	15.53	363	15.35	0.00
Fibromyalgia	101	13.29	330	13.95	-0.02
Non neuropathic Pain	521	68.55	1,644	69.55	-0.02
Other psychiatric conditions, N (%)	.	.	.	.	.
Sleep disorder	57	7.50	165	6.98	0.02
Bipolar disorder	135	17.76	329	13.93	0.11
Psychosis	13	1.71	43	1.82	-0.01
Schizophrenia	<11	1.32	32	1.34	0.00
Personality disorder	26	3.42	68	2.88	0.03
Adjustment disorder	12	1.58	43	1.80	-0.02
Tobacco use, N (%)	173	22.76	414	17.53	0.13
Alcohol abuse or dependence, N (%)	14	1.84	50	2.13	-0.02
Drug abuse or dependence, N (%)	28	3.68	152	6.44	-0.13
Other medication exposures, N (%)	.	.	.	.	.
Benzodiazepines	358	47.11	961	40.67	0.13

	Duloxetine N/Mean	Duloxetine %/SD	Venlafaxine N/Mean	Venlafaxine %/SD	Standardized Difference
Other hypnotics	280	36.84	652	27.57	0.20
Barbiturates	64	8.42	199	8.43	0.00
Anxiolytics	68	8.95	139	5.90	0.12
Anticonvulsants	225	29.61	496	20.96	0.20
Antipsychotics	187	24.61	479	20.25	0.10
SSRIs	231	30.39	619	26.17	0.09
SNRIs	0	0.00	2,364	100.00	.
Other Antidep	233	30.66	675	28.56	0.05
Stimulants	67	8.82	195	8.23	0.02
Antidiabetic	38	5.00	106	4.50	0.02
Insulin	48	6.32	133	5.62	0.03
Antihyperten	172	22.63	410	17.35	0.13
Opioid analgesics	565	74.34	1,626	68.79	0.12
Triptans	61	8.03	169	7.14	0.03
NSAIDs	313	41.18	932	39.41	0.04
Obstetric conditions, N (%)	.	.	.	.	.
Multifetal gestation Flag	32	4.21	121	5.13	-0.04
Markers of healthcare utilization	.	.	.	.	.
Number of distinct 3 digit ICD 9 codes=0	31	4.08	153	6.49	-0.11
Number of distinct 3 digit ICD 9 codes: tertile 1 for number >0	126	16.58	427	18.06	-0.04
Number of distinct 3 digit ICD 9 codes: tertile 2 for number >0	168	22.11	471	19.91	0.05
Number of distinct 3 digit ICD 9 codes: tertile 3 for number >0	435	57.24	1,313	55.54	0.03
Number of ED visits=0	458	60.26	1,465	61.96	-0.03
Number of ED visits=1	162	21.32	468	19.80	0.04
Number of ED visits=2	70	9.21	232	9.81	-0.02
Number of ED visits>2	70	9.21	199	8.43	0.03
Number of non-duloxetine generics dispensed=0	<11	0.66	12	0.51	0.02
Number of non-duloxetine generics dispensed: tertile 1 for number >0	45	5.92	103	4.36	0.07
Number of non-duloxetine generics dispensed: tertile 2 for number >0	93	12.24	390	16.50	-0.12

	Duloxetine N/Mean	Duloxetine %/SD	Venlafaxine N/Mean	Venlafaxine %/SD	Standardized Difference
Number of non-duloxetine generics dispensed: tertile 3 for number >0	617	81.18	1,859	78.64	0.06
Number of hospital admissions=0	684	90.00	2,109	89.22	0.03
Number of hospital admissions=1	57	7.50	192	8.11	-0.02
Number of hospital admissions=2	15	1.97	41	1.72	0.02
Number of hospital admissions>2	<11	0.53	23	0.95	-0.05
Number of outpatient visits=0	57	7.50	248	10.47	-0.10
Number of outpatient visits: tertile 1 for number >0	78	10.26	274	11.60	-0.04
Number of outpatient visits: tertile 2 for number >0	189	24.87	553	23.41	0.03
Number of outpatient visits: tertile 3 for number >0	436	57.37	1,289	54.51	0.06
Number of psychiatric hospitalizations Q1	733	96.45	2,300	97.28	-0.05
Number of psychiatric hospitalizations Q2	23	3.03	55	2.34	0.04
Number of psychiatric hospitalizations Q3	<11	0.53	<11	0.29	0.04
Number of psychiatric hospitalizations Q4	0	0.00	<11	0.09	-0.04
Number of psychiatrist visits=0	284	37.37	998	42.24	-0.10
Number of psychiatrist visits=1	193	25.39	504	21.30	0.10
Number of psychiatrist visits=2	93	12.24	281	11.90	0.01
Number of psychiatrist visits>2	190	25.00	581	24.56	0.01
Geographic region	.	.	.	.	.
Arkansas	0	0.00	PPD	PPD	-0.06
Alabama	PPD	PPD	PPD	PPD	0.09
California	50	6.58	166	7.02	-0.02
Colorado	PPD	PPD	17	0.71	-0.06
District of Columbia	0	0.00	PPD	PPD	-0.05
Delaware	18	2.37	29	1.22	0.09
Florida	PPD	PPD	28	1.20	-0.06
Georgia	PPD	PPD	49	2.06	-0.14
Hawaii	PPD	PPD	-	0.00	0.05
Iowa	PPD	PPD	35	1.49	-0.05
Idaho	PPD	PPD	22	0.91	-0.11
Illinois	61	8.03	161	6.81	0.05
Indiana	72	9.47	119	5.01	0.17

	Duloxetine N/Mean	Duloxetine %/SD	Venlafaxine N/Mean	Venlafaxine %/SD	Standardized Difference
Kansas	PPD		19	0.80	0.05
Kentucky	14	1.84	48	2.01	-0.01
Louisiana	21	2.76	42	1.77	0.07
Massachusetts	PPD		PPD		-0.06
Maryland	PPD		35	1.47	0.00
Maine	PPD		22	0.93	-0.03
Minnesota	70	9.21	228	9.63	-0.01
Missouri	43	5.66	89	3.76	0.09
Mississippi	PPD		34	1.44	-0.09
North Carolina	17	2.24	33	1.39	0.06
North Dakota	PPD		15	0.64	0.00
Nebraska	PPD		16	0.70	0.04
New Hampshire	PPD		16	0.68	-0.04
New Jersey	PPD		PPD		0.00
New Mexico	PPD		30	1.27	0.00
Nevada	PPD		PPD		-0.02
New York	108	14.21	201	8.48	0.18
Ohio	13	1.71	101	4.26	-0.15
Oklahoma	PPD		23	0.96	0.03
Oregon	15	1.97	44	1.88	0.01
Pennsylvania	PPD		83	3.50	-0.21
Rhode Island	PPD		PPD		-0.04
South Carolina	PPD				0.00
South Dakota	PPD		17	0.71	-0.06
Tennessee	39	5.13	193	8.17	-0.12
Texas	PPD		PPD		0.01
Utah	22	2.89	38	1.61	0.09
Virginia	27	3.55	48	2.04	0.09
Vermont	PPD		38	1.59	-0.03
Washington	PPD		PPD		0.02
Wisconsin	38	5.00	243	10.30	-0.20
West Virginia	PPD		19	0.79	0.05

	Duloxetine	Duloxetine	Venlafaxine	Venlafaxine	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Wyoming	PPD		PPD		0.01
Opioids	.	.	.	.	.
buprenorphine	27	3.55	49	2.06	0.09
butorphanol	0	0.00	<11	0.22	-0.07
codeine	189	24.87	676	28.59	-0.08
fentanyl	21	2.76	32	1.35	0.10
hydrocodone	383	50.39	1,158	48.98	0.03
hydromorphone	16	2.11	27	1.16	0.07
levorphanol	0	0.00	0	0.00	.
meperidine	<11	0.26	<11	0.32	-0.01
methadone	11	1.45	33	1.39	0.00
morphine	23	3.03	42	1.78	0.08
oxycodone	181	23.82	449	18.98	0.12
oxymorphone	<11	0.39	<11	0.19	0.04
pentazocine	<11	0.13	<11	0.34	-0.04
propoxyphene	71	9.34	259	10.97	-0.05
tapentadol	0	0.00	<11	0.06	-0.03
tramadol	143	18.82	324	13.71	0.14
Healthcare Utilization, mean (SD)					
Comorbidity Index	1.84	1.98	1.55	1.91	0.15
Morphine equivalents	7957.96	37493.55	23167.08	613624.83	-0.03
Number of diagnoses	6.27	4.67	6.04	4.87	0.05
Number of ED visits	0.79	1.38	0.79	1.59	0.00
Number of non-duloxetine generics dispensed	10.78	6.45	10.56	6.18	0.04
Number of hospitalizations	0.13	0.44	0.16	0.57	-0.05
Number of outpatient visits	6.11	7.99	5.76	7.08	0.05
Number of psychiatric hospitalizations	0.04	0.22	0.03	0.22	0.04
Number of psychiatrist visits	2.6	5.57	2.49	5.98	0.02

15.3. 16. Preeclampsia- Baseline characteristics of duloxetine exposed vs. unexposed women - late exposure: fully adjusted

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Total	808	.	429,847	.	.
Demographics	.	.	.	.	.
Age, mean (SD)	28.59	5.5	28.47	5.55	0.02
Age categorical, N (%)					
<=19	33	4.08	16,336	3.80	0.01
20-24	162	20.05	85,906	19.99	0.00
25-29	284	35.15	152,971	35.59	-0.01
30-34	201	24.88	107,399	24.99	0.00
35-39	102	12.62	53,604	12.47	0.00
>=40	26	3.22	13,631	3.17	0.00
Race, N (%)					
White	651	80.57	350,298	81.49	-0.02
Black/African American	65	8.04	31,750	7.39	0.02
Hispanic/Latino	19	2.35	8,835	2.06	0.02
Asian or Other Pacific	14	1.73	7,470	1.74	0.00
American Indian	16	1.98	8,537	1.99	0.00
Other	25	3.09	13,234	3.08	0.00
Unknown	18	2.23	9,723	2.26	0.00
Chronic comorbid conditions, N (%)	.	.	.	.	.
Hypertension	113	13.99	59,065	13.74	0.01
Diabetes	147	18.19	78,465	18.25	0.00
Renal Disease	16	1.98	8,436	1.96	0.00
Obesity Overweight	90	11.14	47,405	11.03	0.00
Comorbidity Index Q1	249	30.82	132,033	30.72	0.00
Comorbidity Index Q2	177	21.91	96,234	22.39	-0.01
Comorbidity Index Q3	137	16.96	73,683	17.14	0.00
Comorbidity Index Q4	245	30.32	127,898	29.75	0.01
Infections, N (%)	.	.	.	.	.
Toxoplasmosis	0	0.00	0	0.00	.
Rubella	<11	0.12	623	0.14	-0.01
Cytomegalovirus	0	0.00	0	0.00	.

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Herpes	18	2.23	9,452	2.20	0.00
Syphilis	<11	0.12	495	0.12	0.00
Varicella	0	0.00	0	0.00	.
Parvovirus B19	0	0.00	0	0.00	.
Zika virus other mosquito	0	0.00	0	0.00	.
Lymphocytic choriomeningitis	0	0.00	0	0.00	.
Influenza	12	1.49	6,136	1.43	0.00
Chlamydia	<11	0.50	2,150	0.50	0.00
Human papilloma virus	<11	0.99	4,251	0.99	0.00
Gonorrhea	<11	0.74	3,185	0.74	0.00
HIV	<11	0.50	2,228	0.52	0.00
Trichomoniasis	<11	0.74	2,996	0.70	0.01
Indications for duloxetine, N (%)	.	.	.	.	.
Depression	523	64.73	283,144	65.87	-0.02
Anxiety	363	44.93	194,265	45.19	-0.01
Neuropathic Pain	130	16.09	67,947	15.81	0.01
Fibromyalgia	108	13.37	52,935	12.31	0.03
Non neuropathic Pain	555	68.69	288,615	67.14	0.03
Other psychiatric conditions, N (%)	.	.	.	.	.
Sleep disorder	63	7.80	33,193	7.72	0.00
Bipolar disorder	144	17.82	75,052	17.46	0.01
Psychosis	14	1.73	7,302	1.70	0.00
Schizophrenia	<11	1.24	5,305	1.23	0.00
Personality disorder	29	3.59	14,968	3.48	0.01
Adjustment disorder	14	1.73	7,455	1.73	0.00
Tobacco use, N (%)	186	23.02	99,843	23.23	0.00
Alcohol abuse or dependence, N (%)	16	1.98	8,782	2.04	0.00
Drug abuse or dependence, N (%)	32	3.96	17,861	4.16	-0.01
Other medication exposures, N (%)	.	.	.	.	.
Benzodiazepines	382	47.28	203,934	47.44	0.00
Other hypnotics	305	37.75	161,456	37.56	0.00
Barbiturates	70	8.66	37,558	8.74	0.00

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Anxiolytics	74	9.16	38,234	8.89	0.01
Anticonvulsants	239	29.58	121,508	28.27	0.03
Antipsychotics	198	24.50	101,580	23.63	0.02
SSRIs	250	30.94	138,985	32.33	-0.03
SNRIs	48	5.94	26,669	6.20	-0.01
Other Antidep	257	31.81	137,246	31.93	0.00
Stimulants	71	8.79	36,966	8.60	0.01
Antidiabetic	41	5.07	21,609	5.03	0.00
Insulin	52	6.44	27,302	6.35	0.00
Antihyperten	185	22.90	96,301	22.40	0.01
Opioid analgesics	604	74.75	322,364	75.00	-0.01
Triptans	66	8.17	34,145	7.94	0.01
NSAIDs	328	40.59	174,131	40.51	0.00
Obstetric conditions, N (%)	.	.	.	.	.
Multifetal gestation Flag	34	4.21	18,046	4.20	0.00
Markers of healthcare utilization	.	.	.	.	.
Number of distinct 3 digit ICD 9 codes=0	33	4.08	15,981	3.72	0.02
Number of distinct 3 digit ICD 9 codes: tertile 1 for number >0	131	16.21	69,383	16.14	0.00
Number of distinct 3 digit ICD 9 codes: tertile 2 for number >0	177	21.91	95,667	22.26	-0.01
Number of distinct 3 digit ICD 9 codes: tertile 3 for number >0	467	57.80	248,816	57.88	0.00
Number of ED visits=0	480	59.41	256,759	59.73	-0.01
Number of ED visits=1	174	21.53	92,007	21.40	0.00
Number of ED visits=2	76	9.41	40,246	9.36	0.00
Number of ED visits>2	78	9.65	40,836	9.50	0.01
Number of non-duloxetine generics dispensed=0	<11	0.62	1,963	0.46	0.02
Number of non-duloxetine generics dispensed: tertile 1 for number >0	46	5.69	22,915	5.33	0.02
Number of non-duloxetine generics dispensed: tertile 2 for number >0	96	11.88	48,587	11.30	0.02
Number of non-duloxetine generics dispensed: tertile 3 for number >0	661	81.81	356,383	82.91	-0.03
Number of hospital admissions=0	723	89.48	384,742	89.51	0.00

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Number of hospital admissions=1	64	7.92	33,383	7.77	0.01
Number of hospital admissions=2	17	2.10	9,574	2.23	-0.01
Number of hospital admissions>2	<11	0.50	2,148	0.50	0.00
Number of outpatient visits=0	62	7.67	31,265	7.27	0.02
Number of outpatient visits: tertile 1 for number >0	79	9.78	41,607	9.68	0.00
Number of outpatient visits: tertile 2 for number >0	201	24.88	107,533	25.02	0.00
Number of outpatient visits: tertile 3 for number >0	466	57.67	249,442	58.03	-0.01
Number of psychiatric hospitalizations Q1	778	96.29	414,078	96.33	0.00
Number of psychiatric hospitalizations Q2	26	3.22	13,449	3.13	0.01
Number of psychiatric hospitalizations Q3	<11	0.50	2,319	0.54	-0.01
Number of psychiatric hospitalizations Q4	0	0.00	0	0.00	.
Number of psychiatrist visits=0	299	37.00	153,501	35.71	0.03
Number of psychiatrist visits=1	202	25.00	110,759	25.77	-0.02
Number of psychiatrist visits=2	95	11.76	51,739	12.04	-0.01
Number of psychiatrist visits>2	212	26.24	113,848	26.49	-0.01
Geographic region	.	.	.	.	.
Arkansas	0	0.00	0	0.00	.
Alabama	PPD		5,038	1.17	-0.01
California	54	6.68	27,337	6.36	0.01
Colorado	PPD		1,713	0.40	0.00
District of Columbia	0	0.00	0	0.00	.
Delaware	18	2.23	9,282	2.16	0.00
Florida	PPD		2,563	0.60	0.00
Georgia	PPD		3,711	0.86	0.00
Hawaii	PPD		469	0.11	0.00
Iowa	PPD		3,763	0.88	0.00
Idaho	PPD		527	0.12	0.00
Illinois	65	8.04	34,649	8.06	0.00
Indiana	74	9.16	39,571	9.21	0.00
Kansas	PPD		5,468	1.27	0.00
Kentucky	16	1.98	8,243	1.92	0.00
Louisiana	21	2.60	11,488	2.67	0.00

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Massachusetts	PPD		1,024	0.24	0.00
Maryland			5,958	1.39	0.00
Maine			2,786	0.65	0.00
Minnesota	82	10.15	44,254	10.30	0.00
Missouri	44	5.45	23,586	5.49	0.00
Mississippi	PPD		2,021	0.47	0.00
North Carolina	17	2.10	9,180	2.14	0.00
North Dakota	PPD		2,825	0.66	0.00
Nebraska			4,292	1.00	0.00
New Hampshire			1,630	0.38	0.00
New Jersey			989	0.23	0.00
New Mexico			5,427	1.26	0.00
Nevada			564	0.13	0.00
New York	115	14.23	61,304	14.26	0.00
Ohio	13	1.61	7,080	1.65	0.00
Oklahoma	PPD		6,144	1.43	-0.01
Oregon	17	2.10	9,335	2.17	0.00
Pennsylvania	PPD		2,000	0.47	0.00
Rhode Island			504	0.12	0.00
South Carolina			1,085	0.25	0.00
South Dakota			1,095	0.25	0.00
Tennessee	40	4.95	21,144	4.92	0.00
Texas	PPD		536	0.12	0.00
Utah	25	3.09	12,729	2.96	0.01
Virginia	29	3.59	15,080	3.51	0.00
Vermont	PPD		5,391	1.25	0.00
Washington	38	4.70	1,100	0.26	0.00
Wisconsin			20,143	4.69	0.00
West Virginia			5,819	1.35	0.00
Wyoming	PPD		1,001	0.23	0.00
Opioids	.	.	.	.	.
buprenorphine	31	3.84	15,818	3.68	0.01

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Butorphanol	0	0.00	0	0.00	.
codeine	201	24.88	108,274	25.19	-0.01
fentanyl	21	2.60	9,409	2.19	0.03
hydrocodone	412	50.99	220,323	51.26	-0.01
hydromorphone	18	2.23	8,663	2.02	0.01
levorphanol	0	0.00	0	0.00	.
meperidine	<11	0.25	1,070	0.25	0.00
methadone	12	1.49	6,139	1.43	0.00
morphine	25	3.09	11,441	2.66	0.03
oxycodone	198	24.50	103,904	24.17	0.01
oxymorphone	<11	0.37	1,446	0.34	0.01
pentazocine	<11	0.25	1,029	0.24	0.00
propoxyphene	75	9.28	41,205	9.59	-0.01
tapentadol	0	0.00	0	0.00	.
tramadol	155	19.18	80,393	18.70	0.01
Healthcare Utilization, mean (SD)					
Comorbidity Index	1.85	1.99	1.85	2	0.00
Morphine equivalents	8304.52	39001.34	8246.3	135829.03	0.00
Number of diagnoses	6.35	4.73	6.52	4.96	-0.04
Number of ED visits	0.81	1.39	0.85	1.72	-0.02
Number of non-duloxetine generics dispensed	10.92	6.49	10.91	6.28	0.00
Number of hospitalizations	0.14	0.44	0.14	0.52	-0.01
Number of outpatient visits	6.13	7.86	6.01	6.72	0.02
Number of psychiatric hospitalizations	0.04	0.22	0.04	0.23	0.00
Number of psychiatrist visits	2.61	5.47	2.47	5.11	0.03

15.3. 17. Preeclampsia- Baseline characteristics of duloxetine exposed vs. SSRI exposed women - late exposure: fully adjusted

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Total	558	.	34,433	.	.
Demographics	.	.	.	.	.
Age, mean (SD)	28.53	5.28	28.52	5.47	0.00
Age categorical, N (%)					
<=19	25	4.48	1,509	4.38	0.00
20-24	102	18.28	6,216	18.05	0.01
25-29	205	36.74	12,664	36.78	0.00
30-34	146	26.16	8,961	26.02	0.00
35-39	64	11.47	4,016	11.66	-0.01
>=40	16	2.87	1,067	3.10	-0.01
Race, N (%)					
White	458	82.08	28,258	82.07	0.00
Black/African American	43	7.71	2,639	7.67	0.00
Hispanic/Latino			702	2.04	0.01
Asian or Other Pacific			530	1.54	-0.01
American Indian			692	2.01	0.00
Other	16	2.87	1,005	2.92	0.00
Unknown			607	1.76	0.00
Chronic comorbid conditions, N (%)	.	.	.	.	.
Hypertension	79	14.16	4,841	14.06	0.00
Diabetes	95	17.03	5,905	17.15	0.00
Renal Disease	<11	1.61	536	1.56	0.00
Obesity Overweight	60	10.75	3,652	10.61	0.00
Comorbidity Index Q1	179	32.08	10,964	31.84	0.01
Comorbidity Index Q2	124	22.22	7,693	22.34	0.00
Comorbidity Index Q3	90	16.13	5,595	16.25	0.00
Comorbidity Index Q4	165	29.57	10,180	29.57	0.00
Infections, N (%)	.	.	.	.	.
Toxoplasmosis	0	0.00	0	0.00	.
Rubella	0	0.00	0	0.00	.
Cytomegalovirus	0	0.00	0	0.00	.

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Herpes	13	2.33	772	2.24	0.01
Syphilis	<11	0.18	58	0.17	0.00
Varicella	0	0.00	0	0.00	.
Parvovirus B19	0	0.00	0	0.00	.
Zika virus other mosquito	0	0.00	0	0.00	.
Lymphocytic choriomeningitis	0	0.00	0	0.00	.
Influenza	<11	1.43	471	1.37	0.01
Chlamydia	<11	0.36	123	0.36	0.00
Human papilloma virus	<11	0.72	238	0.69	0.00
Gonorrhea	<11	0.72	251	0.73	0.00
HIV	<11	0.54	201	0.58	-0.01
Trichomoniasis	<11	0.72	235	0.68	0.00
Indications for duloxetine, N (%)	.	.	.	.	.
Depression	343	61.47	21,314	61.90	-0.01
Anxiety	243	43.55	15,108	43.88	-0.01
Neuropathic Pain	80	14.34	4,877	14.16	0.00
Fibromyalgia	71	12.72	4,201	12.20	0.02
Non neuropathic Pain	380	68.10	23,414	68.00	0.00
Other psychiatric conditions, N (%)	.	.	.	.	.
Sleep disorder	41	7.35	2,497	7.25	0.00
Bipolar disorder	99	17.74	6,050	17.57	0.00
Psychosis	<11	1.08	364	1.06	0.00
Schizophrenia	<11	1.25	438	1.27	0.00
Personality disorder	20	3.58	1,258	3.65	0.00
Adjustment disorder	11	1.97	620	1.80	0.01
Tobacco use, N (%)	133	23.84	8,164	23.71	0.00
Alcohol abuse or dependence, N (%)	<11	1.79	613	1.78	0.00
Drug abuse or dependence, N (%)	15	2.69	927	2.69	0.00
Other medication exposures, N (%)	.	.	.	.	.
Benzodiazepines	249	44.62	15,405	44.74	0.00
Other hypnotics	202	36.20	12,374	35.94	0.01
Barbiturates	40	7.17	2,430	7.06	0.00

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Anxiolytics	42	7.53	2,604	7.56	0.00
Anticonvulsants	167	29.93	10,058	29.21	0.02
Antipsychotics	131	23.48	8,059	23.40	0.00
SSRIs	-	0.00	34,433	100.00	.
SNRIs	29	5.20	1,832	5.32	-0.01
Other Antidep	170	30.47	10,607	30.81	-0.01
Stimulants	50	8.96	3,074	8.93	0.00
Antidiabetic	26	4.66	1,565	4.54	0.01
Insulin	35	6.27	2,161	6.28	0.00
Antihyperten	122	21.86	7,369	21.40	0.01
Opioid analgesics	406	72.76	24,964	72.50	0.01
Triptans	37	6.63	2,292	6.66	0.00
NSAIDs	218	39.07	13,455	39.08	0.00
Obstetric conditions, N (%)	.	.	.	.	.
Multifetal gestation Flag	25	4.48	1,523	4.42	0.00
Markers of healthcare utilization	.	.	.	.	.
Number of distinct 3 digit ICD 9 codes=0	24	4.30	1,451	4.21	0.00
Number of distinct 3 digit ICD 9 codes: tertile 1 for number >0	98	17.56	6,102	17.72	0.00
Number of distinct 3 digit ICD 9 codes: tertile 2 for number >0	124	22.22	7,768	22.56	-0.01
Number of distinct 3 digit ICD 9 codes: tertile 3 for number >0	312	55.91	19,112	55.51	0.01
Number of ED visits=0	335	60.04	20,814	60.45	-0.01
Number of ED visits=1	125	22.40	7,547	21.92	0.01
Number of ED visits=2	50	8.96	3,108	9.02	0.00
Number of ED visits>2	48	8.60	2,964	8.61	0.00
Number of non-duloxetine generics dispensed=0	<11	0.72	237	0.69	0.00
Number of non-duloxetine generics dispensed: tertile 1 for number >0	37	6.63	2,325	6.75	0.00
Number of non-duloxetine generics dispensed: tertile 2 for number >0	76	13.62	4,659	13.53	0.00
Number of non-duloxetine generics dispensed: tertile 3 for number >0	441	79.03	27,212	79.03	0.00
Number of hospital admissions=0	518	92.83	31,950	92.79	0.00

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Number of hospital admissions=1	32	5.73	1,985	5.76	0.00
Number of hospital admissions=2	<11	1.08	377	1.10	0.00
Number of hospital admissions>2	<11	0.36	121	0.35	0.00
Number of outpatient visits=0	47	8.42	2,903	8.43	0.00
Number of outpatient visits: tertile 1 for number >0	56	10.04	3,462	10.06	0.00
Number of outpatient visits: tertile 2 for number >0	149	26.70	9,213	26.76	0.00
Number of outpatient visits: tertile 3 for number >0	306	54.84	18,855	54.76	0.00
Number of psychiatric hospitalizations Q1	546	97.85	33,708	97.90	0.00
Number of psychiatric hospitalizations Q2	12	2.15	725	2.10	0.00
Number of psychiatric hospitalizations Q3	0	0.00	0	0.00	.
Number of psychiatric hospitalizations Q4	0	0.00	0	0.00	.
Number of psychiatrist visits=0	213	38.17	13,158	38.21	0.00
Number of psychiatrist visits=1	151	27.06	9,273	26.93	0.00
Number of psychiatrist visits=2	63	11.29	3,818	11.09	0.01
Number of psychiatrist visits>2	131	23.48	8,184	23.77	-0.01
Geographic region	.	.	.	.	.
Arkansas	0	0.00	0	0.00	.
Alabama	PPD		257	0.75	0.00
California	38	6.81	2,275	6.61	0.01
Colorado	PPD		182	0.53	0.00
District of Columbia	0	0.00	0	0.00	.
Delaware	PPD		624	1.81	0.00
Florida	PPD		248	0.72	0.00
Georgia	PPD		129	0.37	0.00
Hawaii	PPD		69	0.20	0.00
Iowa	PPD		185	0.54	0.00
Idaho	0	0.00	0	0.00	.
Illinois	43	7.71	2,651	7.70	0.00
Indiana	56	10.04	3,356	9.75	0.01
Kansas	PPD		573	1.66	0.00
Kentucky	PPD		471	1.37	0.01
Louisiana	15	2.69	952	2.76	0.00

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Massachusetts	PPD		127	0.37	0.00
Maryland			424	1.23	0.00
Maine			241	0.70	0.00
Minnesota	63	11.29	3,953	11.48	-0.01
Missouri	30	5.38	1,852	5.38	0.00
Mississippi	PPD		177	0.51	0.00
North Carolina	13	2.33	812	2.36	0.00
North Dakota	PPD		335	0.97	-0.01
Nebraska			307	0.89	0.00
New Hampshire			188	0.55	0.00
New Jersey	0	0.00	0	0.00	.
New Mexico	PPD		415	1.21	0.00
Nevada	0	0.00	0	0.00	.
New York	84	15.05	5,315	15.44	-0.01
Ohio	PPD		308	0.90	0.00
Oklahoma			242	0.70	0.00
Oregon			744	2.16	0.00
Pennsylvania			244	0.71	0.00
Rhode Island			57	0.17	0.00
South Carolina			130	0.38	0.00
South Dakota			62	0.18	0.00
Tennessee	28	5.02	1,687	4.90	0.01
Texas	PPD		61	0.18	0.00
Utah			758	2.20	0.00
Virginia	20	3.58	1,206	3.50	0.00
Vermont	PPD		566	1.64	0.00
Washington	0	0.00	0	0.00	.
Wisconsin	28	5.02	1,694	4.92	0.00
West Virginia	PPD		497	1.44	0.00
Wyoming			60	0.18	0.00
Opioids	.	.	.	.	.
buprenorphine	22	3.94	1,271	3.69	0.01

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
butorphanol	0	0.00	0	0.00	.
codeine	126	22.58	7,870	22.86	-0.01
fentanyl	14	2.51	797	2.31	0.01
hydrocodone	276	49.46	17,018	49.42	0.00
hydromorphone	14	2.51	882	2.56	0.00
levorphanol	0	0.00	0	0.00	.
meperidine	<11	0.18	57	0.17	0.00
methadone	<11	1.08	366	1.06	0.00
morphine	16	2.87	895	2.60	0.02
oxycodone	126	22.58	7,823	22.72	0.00
oxymorphone	<11	0.54	162	0.47	0.01
pentazocine	<11	0.18	63	0.18	0.00
propoxyphene	40	7.17	2,504	7.27	0.00
tapentadol	0	0.00	0	0.00	.
tramadol	105	18.82	6,357	18.46	0.01
Healthcare Utilization, mean (SD)					
Comorbidity Index	1.78	1.92	1.82	1.99	-0.02
Morphine equivalents	8721.13	45066.72	8767.17	139427.77	0.00
Number of diagnoses	6.06	4.45	6.13	4.66	-0.02
Number of ED visits	0.76	1.32	0.8	1.54	-0.02
Number of non-duloxetine generics dispensed	10.09	5.87	10.97	6.63	-0.14
Number of hospitalizations	0.09	0.37	0.09	0.41	-0.01
Number of outpatient visits	5.66	7.44	5.63	6.43	0.01
Number of psychiatric hospitalizations	0.02	0.15	0.02	0.14	0.00
Number of psychiatrist visits	2.25	5.04	2.2	4.63	0.01

15.3. 18. Preeclampsia- Baseline characteristics of duloxetine exposed vs. venlafaxine exposed women - late exposure: fully adjusted

	Duloxetine N/Mean	Duloxetine %/SD	Venlafaxine N/Mean	Venlafaxine %/SD	Standardized Difference
Total	758	.	2,282	.	.
Demographics	.	.	.	.	.
Age, mean (SD)	28.63	5.51	28.59	5.53	0.01
Age categorical, N (%)					
<=19	32	4.22	99	4.33	-0.01
20-24	146	19.26	440	19.28	0.00
25-29	271	35.75	799	35.01	0.02
30-34	188	24.80	578	25.34	-0.01
35-39	97	12.80	290	12.73	0.00
>=40	24	3.17	76	3.32	-0.01
Race, N (%)					
White	610	80.47	1,832	80.28	0.00
Black/African American	61	8.05	188	8.24	-0.01
Hispanic/Latino			50	2.21	0.02
Asian or Other Pacific			33	1.43	0.01
American Indian	16	2.11	52	2.29	-0.01
Other	24	3.17	76	3.32	-0.01
Unknown	16	2.11	51	2.23	-0.01
Chronic comorbid conditions, N (%)	.	.	.	.	.
Hypertension	105	13.85	327	14.34	-0.01
Diabetes	138	18.21	438	19.18	-0.02
Renal Disease	14	1.85	43	1.89	0.00
Obesity Overweight	88	11.61	268	11.75	0.00
Comorbidity Index Q1	236	31.13	731	32.04	-0.02
Comorbidity Index Q2	166	21.90	508	22.25	-0.01
Comorbidity Index Q3	129	17.02	376	16.45	0.02
Comorbidity Index Q4	227	29.95	668	29.26	0.02
Infections, N (%)	.	.	.	.	.
Toxoplasmosis	0	0.00	0	0.00	.
Rubella	0	0.00	0	0.00	.
Cytomegalovirus	0	0.00	0	0.00	.

	Duloxetine N/Mean	Duloxetine %/SD	Venlafaxine N/Mean	Venlafaxine %/SD	Standardized Difference
Herpes	16	2.11	40	1.74	0.03
Syphilis	<11	0.13	<11	0.05	0.03
Varicella	0	0.00	0	0.00	.
Parvovirus B19	0	0.00	0	0.00	.
Zika virus other mosquito	0	0.00	0	0.00	.
Lymphocytic choriomeningitis	0	0.00	0	0.00	.
Influenza	11	1.45	32	1.41	0.00
Chlamydia	<11	0.53	15	0.64	-0.02
Human papilloma virus	<11	0.92	19	0.82	0.01
Gonorrhea	<11	0.66	15	0.68	0.00
HIV	<11	0.53	13	0.55	0.00
Trichomoniasis	<11	0.79	18	0.78	0.00
Indications for duloxetine, N (%)	.	.	.	.	.
Depression	488	64.38	1,501	65.76	-0.03
Anxiety	337	44.46	1,046	45.85	-0.03
Neuropathic Pain	117	15.44	357	15.64	-0.01
Fibromyalgia	100	13.19	294	12.90	0.01
Non neuropathic Pain	519	68.47	1,540	67.47	0.02
Other psychiatric conditions, N (%)	.	.	.	.	.
Sleep disorder	57	7.52	187	8.21	-0.03
Bipolar disorder	135	17.81	399	17.48	0.01
Psychosis	13	1.72	46	2.02	-0.02
Schizophrenia	<11	1.19	33	1.45	-0.02
Personality disorder	26	3.43	92	4.04	-0.03
Adjustment disorder	12	1.58	36	1.56	0.00
Tobacco use, N (%)	173	22.82	579	25.37	-0.06
Alcohol abuse or dependence, N (%)	14	1.85	47	2.06	-0.02
Drug abuse or dependence, N (%)	28	3.69	82	3.58	0.01
Other medication exposures, N (%)	.	.	.	.	.
Benzodiazepines	357	47.10	1,105	48.43	-0.03
Other hypnotics	279	36.81	843	36.93	0.00
Barbiturates	64	8.44	203	8.90	-0.02

	Duloxetine N/Mean	Duloxetine %/SD	Venlafaxine N/Mean	Venlafaxine %/SD	Standardized Difference
Anxiolytics	68	8.97	209	9.15	-0.01
Anticonvulsants	225	29.68	666	29.18	0.01
Antipsychotics	187	24.67	569	24.92	-0.01
SSRIs	230	30.34	683	29.92	0.01
SNRIs	0	0.00	2,282	100.00	.
Other Antidep	233	30.74	732	32.07	-0.03
Stimulants	67	8.84	216	9.48	-0.02
Antidiabetic	38	5.01	110	4.83	0.01
Insulin	48	6.33	160	6.99	-0.03
Antihyperten	172	22.69	525	23.00	-0.01
Opioid analgesics	563	74.27	1,705	74.72	-0.01
Triptans	60	7.92	192	8.42	-0.02
NSAIDs	312	41.16	944	41.35	0.00
Obstetric conditions, N (%)	.	.	.	.	.
Multifetal gestation Flag	32	4.22	92	4.03	0.01
Markers of healthcare utilization	.	.	.	.	.
Number of distinct 3 digit ICD 9 codes=0	31	4.09	93	4.10	0.00
Number of distinct 3 digit ICD 9 codes: tertile 1 for number >0	126	16.62	387	16.95	-0.01
Number of distinct 3 digit ICD 9 codes: tertile 2 for number >0	167	22.03	488	21.37	0.02
Number of distinct 3 digit ICD 9 codes: tertile 3 for number >0	434	57.26	1,314	57.58	-0.01
Number of ED visits=0	456	60.16	1,373	60.16	0.00
Number of ED visits=1	162	21.37	479	20.98	0.01
Number of ED visits=2	70	9.23	217	9.50	-0.01
Number of ED visits>2	70	9.23	214	9.37	0.00
Number of non-duloxetine generics dispensed=0	<11	0.66	12	0.51	0.02
Number of non-duloxetine generics dispensed: tertile 1 for number >0	45	5.94	144	6.29	-0.01
Number of non-duloxetine generics dispensed: tertile 2 for number >0	92	12.14	262	11.50	0.02
Number of non-duloxetine generics dispensed: tertile 3 for number >0	616	81.27	1,864	81.70	-0.01
Number of hospital admissions=0	682	89.97	2,033	89.10	0.03

	Duloxetine N/Mean	Duloxetine %/SD	Venlafaxine N/Mean	Venlafaxine %/SD	Standardized Difference
Number of hospital admissions=1	57	7.52	190	8.32	-0.03
Number of hospital admissions=2	15	1.98	47	2.08	-0.01
Number of hospital admissions>2	<11	0.53	12	0.51	0.00
Number of outpatient visits=0	57	7.52	175	7.67	-0.01
Number of outpatient visits: tertile 1 for number >0	78	10.29	235	10.28	0.00
Number of outpatient visits: tertile 2 for number >0	189	24.93	540	23.64	0.03
Number of outpatient visits: tertile 3 for number >0	434	57.26	1,333	58.41	-0.02
Number of psychiatric hospitalizations Q1	731	96.44	2,193	96.08	0.02
Number of psychiatric hospitalizations Q2	23	3.03	80	3.52	-0.03
Number of psychiatric hospitalizations Q3	<11	0.53	<11	0.40	0.02
Number of psychiatric hospitalizations Q4	0	0.00	0	0.00	.
Number of psychiatrist visits=0	283	37.34	864	37.87	-0.01
Number of psychiatrist visits=1	193	25.46	570	24.97	0.01
Number of psychiatrist visits=2	93	12.27	266	11.65	0.02
Number of psychiatrist visits>2	189	24.93	582	25.51	-0.01
Geographic region	.	.	.	.	.
Arkansas	-	0.00	-	0.00	.
Alabama	PPD		22	0.96	0.02
California	50	6.60	134	5.85	0.03
Colorado	PPD		PPD		0.01
District of Columbia	0	0.00	0	0.00	.
Delaware	18	2.37	61	2.66	-0.02
Florida	PPD		17	0.73	-0.01
Georgia			13	0.55	0.00
Hawaii	0	0.00	0	0.00	.
Iowa	PPD		18	0.79	0.01
Idaho			PPD		0.01
Illinois	61	8.05	184	8.06	0.00
Indiana	72	9.50	217	9.49	0.00
Kansas	PPD		34	1.49	-0.01
Kentucky	14	1.85	38	1.67	0.01
Louisiana	21	2.77	62	2.72	0.00

	Duloxetine N/Mean	Duloxetine %/SD	Venlafaxine N/Mean	Venlafaxine %/SD	Standardized Difference
Massachusetts	PPD		PPD		0.01
Maryland			32	1.42	0.00
Maine			13	0.55	0.01
Minnesota	70	9.23	230	10.06	-0.03
Missouri	43	5.67	156	6.84	-0.05
Mississippi	PPD		PPD		0.00
North Carolina	17	2.24	55	2.39	-0.01
North Dakota	PPD		20	0.90	-0.03
Nebraska			20	0.90	0.02
New Hampshire			PPD		0.00
New Jersey	PPD				0.00
New Mexico			30	1.30	0.00
Nevada			PPD		0.01
New York	108	14.25	318	13.92	0.01
Ohio	13	1.72	36	1.58	0.01
Oklahoma	PPD		26	1.16	0.01
Oregon	15	1.98	37	1.63	0.03
Pennsylvania	PPD		PPD		0.01
Rhode Island					0.01
South Carolina					0.00
South Dakota					0.01
Tennessee	39	5.15	118	5.16	0.00
Texas	PPD		PPD		0.01
Utah	21	2.77	63	2.77	0.00
Virginia	27	3.56	79	3.46	0.01
Vermont	PPD		29	1.26	-0.01
Washington			PPD		0.01
Wisconsin	38	5.01	117	5.13	-0.01
West Virginia	PPD		29	1.28	0.00
Wyoming			PPD		0.01
Opioids	.	.	.	.	.
buprenorphine	27	3.56	83	3.64	0.00

	Duloxetine N/Mean	Duloxetine %/SD	Venlafaxine N/Mean	Venlafaxine %/SD	Standardized Difference
butorphanol	-	0.00	-	0.00	.
codeine	189	24.93	597	26.18	-0.03
fentanyl	20	2.64	56	2.45	0.01
hydrocodone	381	50.26	1,146	50.23	0.00
hydromorphone	16	2.11	47	2.08	0.00
levorphanol	0	0.00	0	0.00	.
meperidine	<11	0.26	<11	0.16	0.02
methadone	11	1.45	33	1.43	0.00
morphine	22	2.90	64	2.80	0.01
oxycodone	180	23.75	532	23.32	0.01
oxymorphone	<11	0.40	<11	0.43	-0.01
pentazocine	<11	0.13	<11	0.16	-0.01
propoxyphene	71	9.37	224	9.81	-0.01
tapentadol	0	0.00	0	0.00	.
tramadol	142	18.73	397	17.39	0.04
Healthcare Utilization, mean (SD)					
Comorbidity Index	1.84	1.99	1.87	2.08	-0.02
Morphine equivalents	7831	37353.54	6611.55	167695.8	0.01
Number of diagnoses	6.27	4.68	6.38	5.03	-0.02
Number of ED visits	0.79	1.38	0.85	1.64	-0.04
Number of non-duloxetine generics dispensed	10.78	6.44	11.52	6.59	-0.11
Number of hospitalizations	0.13	0.44	0.15	0.55	-0.04
Number of outpatient visits	6.11	7.99	6.02	6.79	0.01
Number of psychiatric hospitalizations	0.04	0.22	0.04	0.22	-0.01
Number of psychiatrist visits	2.59	5.58	2.54	5.76	0.01

15.3. 19. Preeclampsia- Absolute risks for early exposure

	Exposed					Reference							
Outcome	Events	N	Risk (/1,000)	95% CI		Events	N	Risk (/1,000)	95% CI		RR	95% CI	
				lower	upper				lower	upper		lower	upper
Duloxetine versus Unexposed													
Preeclampsia	171	3,059	55.9	48.0	64.6	48,599	1,447,644	33.6	33.3	33.9	1.67	1.44	1.93
Duloxetine versus SSRI													
Preeclampsia	119	2,104	56.6	47.1	67.3	2,540	70,926	35.8	34.5	37.2	1.58	1.32	1.89
Duloxetine versus Venlafaxine													
Preeclampsia	161	2,927	55.0	47.0	63.9	357	7,642	46.7	42.1	51.7	1.18	0.98	1.41

15.3. 20. Preeclampsia- Absolute risks for late exposure

	Exposed					Reference							
Outcome	Events	N	Risk (/1,000)	95% CI		Events	N	Risk (/1,000)	95% CI		RR	95% CI	
				lower	upper				lower	upper		lower	upper
Duloxetine versus Unexposed													
Preeclampsia	58	933	62.2	47.5	79.6	48,593	1,447,493	33.6	33.3	33.9	1.85	1.44	2.38
Duloxetine versus SSRI													
Preeclampsia	42	662	63.4	46.1	84.8	1,835	48,672	37.7	36.0	39.4	1.68	1.25	2.26
Duloxetine versus Venlafaxine													
Preeclampsia	55	879	62.6	47.5	80.7	185	2,943	62.9	54.4	72.2	1.00	0.74	1.33

15.3. 21. Preeclampsia- Relative risks for duloxetine exposed vs. unexposed women

	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Unadjusted Analyses							
Early							
Preeclampsia	171	3,059	48,599	1,447,644	1.67	1.44	1.93
Late							
Preeclampsia	58	933	48,593	1,447,493	1.85	1.44	2.38
Adjusted: Restricted + PS1 (indications)							
Early							
Preeclampsia	152	2,679	17,658	474,139	1.46	1.25	1.70
Late							
Preeclampsia	52	808	17,653	474,014	1.64	1.26	2.13
Adjusted: Restricted + PS2 (All covariates)							
Early							
Preeclampsia	152	2,678	17,241	457,232	1.12	0.96	1.31
Late							
Preeclampsia	52	808	16,683	429,847	1.04	0.80	1.35
Adjusted: Restricted + hdPS							
Early							
Preeclampsia	152	2,673	17,474	467,585	1.12	0.96	1.31
Late							
Preeclampsia	51	804	15,815	413,796	1.02	0.78	1.33

15.3. 22. Preeclampsia- Relative risks for duloxetine exposed vs. SSRI exposed women

	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Unadjusted Analyses							
Early							
Preeclampsia	119	2,104	2,540	70,926	1.58	1.32	1.89
Late							
Preeclampsia	42	662	1,835	48,672	1.68	1.25	2.26
Adjusted: Restricted + PS1 (indications)							
Early							
Preeclampsia	106	1,809	2,018	54,630	1.55	1.29	1.88
Late							
Preeclampsia	37	558	1,436	35,933	1.54	1.13	2.11
Adjusted: Restricted + PS2 (All covariates)							
Early							
Preeclampsia	106	1,807	1,988	53,409	1.16	0.96	1.40
Late							
Preeclampsia	37	558	1,387	34,433	1.05	0.77	1.44
Adjusted: Restricted + hdPS							
Early							
Preeclampsia	106	1,808	2,018	54,628	1.14	0.95	1.38
Late							
Preeclampsia	36	554	1,435	35,932	1.19	0.86	1.63

15.3. 23. Preeclampsia- Relative risks for duloxetine exposed vs. venlafaxine exposed women

	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Unadjusted Analyses							
Early							
Preeclampsia	161	2,927	357	7,642	1.18	0.98	1.41
Late							
Preeclampsia	55	879	185	2,943	1.00	0.74	1.33
Adjusted: Restricted + PS1 (indications)							
Early							
Preeclampsia	142	2,560	293	6,254	1.14	0.94	1.38
Late							
Preeclampsia	49	760	143	2,364	1.06	0.77	1.45
Adjusted: Restricted + PS2 (All covariates)							
Early							
Preeclampsia	142	2,553	291	6,219	0.96	0.80	1.16
Late							
Preeclampsia	49	758	141	2,282	0.80	0.59	1.08
Adjusted: Restricted + hdPS							
Early							
Preeclampsia	141	2,541	285	6,077	0.97	0.80	1.18
Late							
Preeclampsia	43	712	137	2,248	0.87	0.63	1.21

15.3. 24. Preeclampsia- Sensitivity Analyses #1: Re-define exposure as having filled ≥ 2 prescriptions

15.3.24.1 Unadjusted - Early

	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Early							
Duloxetine versus Unexposed							
Preeclampsia	96	1,398	48,599	1,447,644	2.05	1.69	2.48
Duloxetine versus SSRI							
Preeclampsia	71	1,002	1,441	37,754	1.86	1.48	2.34
Duloxetine versus Venlafaxine							
Preeclampsia	88	1,339	210	3,930	1.23	0.97	1.57

15.3.24.2 Unadjusted - Late

	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Late							
Duloxetine versus Unexposed							
Preeclampsia	40	598	48,593	1,447,493	1.99	1.48	2.69
Duloxetine versus SSRI							
Preeclampsia	30	445	1,090	28,748	1.78	1.25	2.52
Duloxetine versus Venlafaxine							
Preeclampsia	39	576	137	2,051	1.01	0.72	1.43

15.3.24.3 Adjusted: Restricted + PS1 (indications) - Early

	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Early							
Duloxetine versus Unexposed							
Preeclampsia	88	1,241	17,658	474,139	1.84	1.50	2.25
Duloxetine versus SSRI							
Preeclampsia	65	873	1,166	29,785	1.89	1.48	2.40
Duloxetine versus Venlafaxine							
Preeclampsia	80	1,185	174	3,238	1.22	0.94	1.57

15.3.24.4 Adjusted: Restricted + PS1 (indications) - Late

	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Late							
Duloxetine versus Unexposed							
Preeclampsia	36	523	17,653	474,014	1.73	1.26	2.37
Duloxetine versus SSRI							
Preeclampsia	27	384	867	21,796	1.74	1.20	2.52
Duloxetine versus Venlafaxine							
Preeclampsia	35	503	110	1,656	1.15	0.79	1.67

15.3.24.5 Adjusted: Restricted + PS2 (All covariates) - Early

	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Early							
Duloxetine versus Unexposed							
Preeclampsia	88	1,241	16,605	433,917	1.27	1.04	1.55
Duloxetine versus SSRI							
Preeclampsia	65	872	1,144	29,112	1.28	1.01	1.63
Duloxetine versus Venlafaxine							
Preeclampsia	80	1,181	172	3,148	1.01	0.78	1.29

15.3.24.6 Adjusted: Restricted + PS2 (All covariates) - Late

	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Late							
Duloxetine versus Unexposed							
Preeclampsia	36	523	14,583	348,407	1.04	0.76	1.43
Duloxetine versus SSRI							
Preeclampsia	27	382	833	20,238	1.03	0.71	1.49
Duloxetine versus Venlafaxine							
Preeclampsia	35	502	109	1,575	0.78	0.55	1.12

15.3. 25. Preeclampsia- Sensitivity Analyses #2: Re-define exposure as days supply overlap

15.3.25.1 Unadjusted - Early

	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Early							
Duloxetine versus Unexposed							
Preeclampsia	209	3,916	48,599	1,447,644	1.59	1.39	1.81
Duloxetine versus SSRI							
Preeclampsia	148	2,720	2,540	70,926	1.52	1.29	1.79
Duloxetine versus Venlafaxine							
Preeclampsia	198	3,743	357	7,642	1.13	0.96	1.34

15.3.25.2 Unadjusted - Late

	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Late							
Duloxetine versus Unexposed							
Preeclampsia	67	1,067	48,593	1,447,493	1.87	1.48	2.36
Duloxetine versus SSRI							
Preeclampsia	50	749	1,835	48,672	1.77	1.35	2.32
Duloxetine versus Venlafaxine							
Preeclampsia	64	1,003	185	2,943	1.02	0.77	1.34

15.3.25.3 Adjusted: Restricted + PS1 (indications) - Early

	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Early							
Duloxetine versus Unexposed							
Preeclampsia	187	3,425	17,658	474,139	1.41	1.23	1.62
Duloxetine versus SSRI							
Preeclampsia	132	2,339	2,018	54,630	1.49	1.25	1.77
Duloxetine versus Venlafaxine							
Preeclampsia	176	3,267	293	6,254	1.07	0.90	1.28

15.3.25.4 Adjusted: Restricted + PS1 (indications) - Late

	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Late							
Duloxetine versus Unexposed							
Preeclampsia	61	927	17,653	474,014	1.67	1.31	2.13
Duloxetine versus SSRI							
Preeclampsia	45	633	1,436	35,933	1.69	1.27	2.25
Duloxetine versus Venlafaxine							
Preeclampsia	58	869	143	2,364	1.13	0.84	1.53

15.3.25.5 Adjusted: Restricted + PS2 (All covariates) - Early

	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Early							
Duloxetine versus Unexposed							
Preeclampsia	187	3,424	17,281	458,961	1.10	0.96	1.27
Duloxetine versus SSRI							
Preeclampsia	131	2,336	1,978	53,230	1.14	0.96	1.35
Duloxetine versus Venlafaxine							
Preeclampsia	176	3,261	291	6,217	0.97	0.81	1.16

15.3.25.6 Adjusted: Restricted + PS2 (All covariates) - Late

	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Late							
Duloxetine versus Unexposed							
Preeclampsia	61	927	16,431	420,631	1.09	0.85	1.39
Duloxetine versus SSRI							
Preeclampsia	45	631	1,397	34,705	1.14	0.86	1.52
Duloxetine versus Venlafaxine							
Preeclampsia	58	864	139	2,272	0.86	0.65	1.15

15.3. 26. Preeclampsia- Sensitivity Analyses #3: Restrict cohort to women with a recorded diagnosis of fibromyalgia

15.3.26.1 Unadjusted - Early

	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Early							
Duloxetine versus Unexposed							
Preeclampsia	148	2,498	41,703	1,200,171	1.71	1.46	1.99
Duloxetine versus SSRI							
Preeclampsia	103	1,711	2,194	58,775	1.61	1.33	1.95
Duloxetine versus Venlafaxine							
Preeclampsia	143	2,392	320	6,540	1.22	1.01	1.48

15.3.26.2 Unadjusted - Late

	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Late							
Duloxetine versus Unexposed							
Preeclampsia	50	754	41,698	1,200,051	1.91	1.46	2.50
Duloxetine versus SSRI							
Preeclampsia	37	532	1,581	40,391	1.78	1.30	2.43
Duloxetine versus Venlafaxine							
Preeclampsia	49	713	170	2,517	1.02	0.75	1.38

15.3.26.3 Adjusted: Restricted + PS1 (indications) - Ealy

	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Early							
Duloxetine versus Unexposed							
Preeclampsia	17	374	832	20,294	1.06	0.66	1.69
Duloxetine versus SSRI							
Preeclampsia	<11	246	81	2,271	1.13	0.60	2.16
Duloxetine versus Venlafaxine							
Preeclampsia	15	350	18	311	0.72	0.37	1.40

15.3.26.4 Adjusted: Restricted + PS1 (Indications) - Late

	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Late							
Duloxetine versus Unexposed							
Preeclampsia	<11	109	803	19,641	0.65	0.21	1.98
Duloxetine versus SSRI							
Preeclampsia	<11	72	60	1,514	0.73	0.18	2.91
Duloxetine versus Venlafaxine							
Preeclampsia	<11	101	11	143	0.34	0.07	1.58

15.3.26.5 Adjusted: Restricted + PS2 (All covariates) - Early

	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Early							
Duloxetine versus Unexposed							
Preeclampsia	17	373	701	17,751	0.98	0.61	1.56
Duloxetine versus SSRI							
Preeclampsia	<11	244	68	1,946	1.03	0.54	1.96
Duloxetine versus Venlafaxine							
Preeclampsia	<11	280	17	284	0.42	0.21	0.87

15.3.26.6 Adjusted: Restricted + PS2 (All covariates) - Late

	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Late							
Duloxetine versus Unexposed							
Preeclampsia	<11	101	397	8,892	0.36	0.09	1.44
Duloxetine versus SSRI							
Preeclampsia	<11	54	34	892	0.60	0.15	2.39
Duloxetine versus Venlafaxine							
Preeclampsia	<11	18	<11	64	0.44	0.06	3.28

15.3. 27. Preeclampsia- Sensitivity Analyses #4: Correct relative risks for outcome misclassification

Target PPV= 86 (CI: 74-94)

Distribution for bias parameters: Sensitivity: Min=0.5, Mode 1=0.75, Mode 2=0.75, Max=1.0; Specificity: Min=0.99, Mode 1=0.996, Mode 2=0.996, Max=0.999

		1:1 PS matched Analysis			Total Error Analysis					
Early Exposure										
Exposure	Reference	Odds ratio	95% CI lower	95% CI upper	Odds ratio	95% CI lower	95% CI upper	Width CI	% change in CI width over traditional	% change in OR
Duloxetine	Unexposed	1.22	0.96	1.55	1.25	0.97	1.64	1.69	4%	2.25%
Duloxetine	SSRI	1.23	0.92	1.65	1.26	0.92	1.75	1.91	7%	2.63%
Duloxetine	Venlafaxine	0.92	0.72	1.17	0.92	0.70	1.17	1.67	5%	0.00%
Late Exposure										
Exposure	Reference	Odds ratio	95% CI lower	95% CI upper	Odds ratio	95% CI lower	95% CI upper	Width CI	% change in CI width over traditional	% change in OR
Duloxetine	Unexposed	1.11	0.74	1.67	1.12	0.74	1.63	2.19	-1%	0.78%
Duloxetine	SSRI	0.83	0.53	1.31	0.81	0.51	1.27	2.47	-4%	-1.89%
Duloxetine	Venlafaxine	1.00	0.66	1.53	0.98	0.64	1.54	2.41	3%	-1.61%

15.3. 28. Preeclampsia- Sensitivity Analyses #5: Redefine outcome based on claims profile review

Duloxetine versus Unexposed	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Definition #1: if outcome likely occurred							
Early							
Preeclampsia	88	2679	81	2679	1.09	0.81	1.46
Late							
Preeclampsia	31	808	23	808	1.35	0.79	2.29
Definition #2: if outcome "likely occurred" or "probably occurred"							
Early							
Preeclampsia	151	2679	126	2679	1.20	0.95	1.51
Late							
Preeclampsia	52	808	47	808	1.11	0.75	1.62

15.3. 29. Preeclampsia- Sensitivity Analyses #6: Restrict cohort to the first pregnancy occurring within the study period

15.3.29.1 Adjusted: Restricted + PS1 (indications)

	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Duloxetine versus Unexposed							
Early							
Preeclampsia	130	2,171	15,002	387,541	1.49	1.26	1.76
Late							
Preeclampsia	44	644	14,998	387,441	1.68	1.26	2.23
Duloxetine versus SSRI							
Early							
Preeclampsia	90	1,461	1,736	45,047	1.57	1.28	1.92
Late							
Preeclampsia	32	442	1,226	29,650	1.67	1.19	2.34
Duloxetine versus Venlafaxine							
Early							
Preeclampsia	125	2,076	263	5,339	1.16	0.94	1.42
Late							
Preeclampsia	43	608	132	2,028	1.06	0.76	1.47

15.3.29.2 Adjusted: Restricted + PS2 (All covariates)

10.0.20.2 Adjusted: Restricted + PDE (All covariates)							
	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Duloxetine versus Unexposed							
Early							
Preeclampsia	130	2,170	14,496	369,471	1.13	0.96	1.34
Late							
Preeclampsia	44	644	13,532	327,779	1.05	0.79	1.40
Duloxetine versus SSRI							
Early							
Preeclampsia	90	1,459	1,709	44,197	1.16	0.94	1.42
Late							
Preeclampsia	32	442	1,226	29,646	1.06	0.76	1.48
Duloxetine versus Venlafaxine							
Early							
Preeclampsia	125	2,069	261	5,299	1.00	0.82	1.22
Late							
Preeclampsia	43	606	127	1,928	0.77	0.56	1.07

15.4. 1. Postpartum Haemorrhage- Baseline characteristics of duloxetine exposed vs. unexposed women: unadjusted

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Total	955		4,128,460		
Demographics					
Age, mean (SD)	28.34	5.40	24.66	5.27	0.69
Age categorical, N (%)					
<=19	38	3.98	664,657	16.10	-0.41
20-24	206	21.57	1,692,233	40.99	-0.43
25-29	346	36.23	1,031,327	24.98	0.25
30-34	218	22.83	492,095	11.92	0.29
35-39	124	12.98	203,836	4.94	0.28
>=40	23	2.41	44,312	1.07	0.10
Race, N (%)					
White	812	85.03	1,921,982	46.55	0.89
Black or African American	50	5.24	1,018,822	24.68	-0.57
Hispanic or Latino	13	1.36	554,026	13.42	-0.47
Asian or Other Pacific Islander	13	1.36	172,345	4.17	-0.17
American Indian	22	2.30	70,211	1.70	0.04
Other	18	1.88	271,463	6.58	-0.23
Unknown	27	2.83	119,611	2.90	0.00
Chronic comorbid conditions, N (%)					
Hypertension	137	14.35	206,880	5.01	0.32
Diabetes	191	20.00	446,641	10.82	0.26
Renal Disease	<11	0.84	22,689	0.55	0.03
Obesity Overweight	66	6.91	134,186	3.25	0.17
Comorbidity Index Q1	321	33.61	2,364,125	57.26	-0.49
Comorbidity Index Q2	206	21.57	908,302	22.00	-0.01
Comorbidity Index Q3	181	18.95	460,218	11.15	0.22
Comorbidity Index Q4	247	25.86	395,815	9.59	0.44
Indications for duloxetine, N (%)					
Depression	302	31.62	115,411	2.80	0.83
Anxiety	177	18.53	59,928	1.45	0.59

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Neuropathic Pain	45	4.71	44,638	1.08	0.22
Fibromyalgia	45	4.71	13,696	0.33	0.28
Non neuropathic Pain	272	28.48	416,332	10.08	0.48
Other psychiatric conditions, N (%)					
Sleep disorder	21	2.20	9,200	0.22	0.18
Bipolar disorder	95	9.95	28,431	0.69	0.42
Psychosis	<11	0.63	3,262	0.08	0.09
Schizophrenia	<11	0.63	3,651	0.09	0.09
Personality disorder	16	1.68	3,707	0.09	0.17
Adjustment disorder	<11	0.31	8,072	0.20	0.02
Tobacco use, N (%)	123	12.88	203,136	4.92	0.28
Alcohol abuse or dependence, N (%)	<11	0.10	6,990	0.17	-0.02
Drug abuse or dependence, N (%)	19	1.99	33,634	0.81	0.10
Other medication exposures, N (%)					
Benzodiazepines	189	19.79	28,252	0.68	0.66
Other hypnotics	225	23.56	162,520	3.94	0.59
Barbiturates	35	3.66	39,954	0.97	0.18
Anxiolytics	50	5.24	7,285	0.18	0.32
Anticonvulsants	108	11.31	21,759	0.53	0.47
Antipsychotics	120	12.57	12,403	0.30	0.52
SSRIs	86	9.01	125,563	3.04	0.25
SNRIs	<11	0.73	6,045	0.15	0.09
Other Antidep	132	13.82	34,710	0.84	0.51
Stimulants	42	4.40	5,767	0.14	0.29
Antidiabetic	40	4.19	57,303	1.39	0.17
Insulin	62	6.49	78,046	1.89	0.23
Antihyperten	152	15.92	161,606	3.91	0.41
Opioid analgesics	416	43.56	501,535	12.15	0.75
Triptans	18	1.88	4,729	0.11	0.18
NSAIDs	56	5.86	43,604	1.06	0.27
Obstetric conditions, N (%)					
Multifetal gestation Flag	36	3.77	123,041	2.98	0.04

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Markers of healthcare utilization					
Number of distinct 3 digit ICD 9 codes=0	<11	0.94	104,760	2.54	-0.12
Number of distinct 3 digit ICD 9 codes: tertile 1 for number >0	74	7.75	1,078,474	26.12	-0.51
Number of distinct 3 digit ICD 9 codes: tertile 2 for number >0	278	29.11	1,708,473	41.38	-0.26
Number of distinct 3 digit ICD 9 codes: tertile 3 for number >0	594	62.20	1,236,753	29.96	0.68
Number of ED visits=0	707	74.03	3,424,350	82.94	-0.22
Number of ED visits=1	171	17.91	502,819	12.18	0.16
Number of ED visits=2	35	3.66	124,318	3.01	0.04
Number of ED visits>2	42	4.40	76,973	1.86	0.15
Number of non-duloxetine generics dispensed=0	75	7.85	1,314,752	31.85	-0.63
Number of non-duloxetine generics dispensed: tertile 1 for number >0	99	10.37	953,457	23.09	-0.35
Number of non-duloxetine generics dispensed: tertile 2 for number >0	104	10.89	718,059	17.39	-0.19
Number of non-duloxetine generics dispensed: tertile 3 for number >0	677	70.89	1,142,192	27.67	0.96
Number of hospital admissions=0	898	94.03	3,982,918	96.47	-0.12
Number of hospital admissions=1	47	4.92	122,947	2.98	0.10
Number of hospital admissions=2	<11	0.63	18,339	0.44	0.03
Number of hospital admissions>2	<11	0.42	4,256	0.10	0.06
Number of outpatient visits=0	13	1.36	214,618	5.20	-0.22
Number of outpatient visits: tertile 1 for number >0	161	16.86	1,161,216	28.13	-0.27
Number of outpatient visits: tertile 2 for number >0	226	23.66	1,453,039	35.20	-0.26
Number of outpatient visits: tertile 3 for number >0	555	58.12	1,299,587	31.48	0.56
Number of psychiatric hospitalizations Q1	932	97.59	4,113,996	99.65	-0.18
Number of psychiatric hospitalizations Q2	19	1.99	12,881	0.31	0.16
Number of psychiatric hospitalizations Q3	<11	0.42	1,351	0.03	0.08
Number of psychiatric hospitalizations Q4	0	0.00	232	0.01	-0.01
Number of psychiatrist visits=0	559	58.53	3,923,936	95.05	-0.96
Number of psychiatrist visits=1	163	17.07	92,491	2.24	0.52
Number of psychiatrist visits=2	57	5.97	32,600	0.79	0.29
Number of psychiatrist visits>2	176	18.43	79,433	1.92	0.57

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Geographic region					
Arkansas	PPD		9,632	0.23	0.05
Alabama			17,666	0.43	0.04
California	50	5.24	589,940	14.29	-0.31
Colorado	PPD		30,139	0.73	-0.04
District of Columbia			993	0.02	0.03
Delaware	16	1.68	25,984	0.63	0.10
Florida	15	1.57	324,553	7.86	-0.30
Georgia	PPD		167,662	4.06	-0.21
Hawaii			18,872	0.46	-0.10
Iowa			29,402	0.71	0.01
Idaho			3,030	0.07	0.04
Illinois	65	6.81	300,917	7.29	-0.02
Indiana	78	8.17	112,960	2.74	0.24
Kansas	19	1.99	56,256	1.36	0.05
Kentucky	21	2.20	140,273	3.40	-0.07
Louisiana	14	1.47	46,026	1.11	0.03
Massachusetts	PPD		26,378	0.64	-0.03
Maryland			114,729	2.78	-0.04
Maine	PPD		9,848	0.24	0.12
Minnesota			125,671	3.04	0.25
Missouri	41	4.29	92,339	2.24	0.12
Mississippi	PPD		41,747	1.01	-0.10
North Carolina			28,735	0.70	0.09
North Dakota	PPD		14,396	0.35	0.07
Nebraska			23,178	0.56	0.13
New Hampshire	PPD		23,345	0.57	0.05
New Jersey			39,781	0.96	-0.12
New Mexico			34,018	0.82	-0.05
Nevada			5,424	0.13	-0.05
New York	102	10.68	648,082	15.70	-0.15
Ohio	14	1.47	66,983	1.62	-0.01

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Oklahoma	22	2.30	140,066	3.39	-0.07
Oregon	50	5.24	78,951	1.91	0.18
Pennsylvania	PPD		67,151	1.63	-0.11
Rhode Island	0	0.00	4,797	0.12	-0.05
South Carolina	PPD		6,169	0.15	0.05
South Dakota			14,673	0.36	0.01
Tennessee	44	4.61	246,432	5.97	-0.06
Texas	PPD		23,888	0.58	-0.04
Utah	70	7.33	54,973	1.33	0.30
Virginia	35	3.66	141,788	3.43	0.01
Vermont	PPD		19,059	0.46	0.07
Washington			7,253	0.18	0.01
Wisconsin	41	4.29	137,190	3.32	0.05
West Virginia	PPD		11,738	0.28	0.09
Wyoming			5,373	0.13	0.04
Opioids					
buprenorphine	32	3.35	7,710	0.19	0.24
butorphanol	<11	0.1	348	0.01	0.04
codeine	117	12.25	240,274	5.82	0.23
fentanyl	12	1.26	665	0.02	0.16
hydrocodone	237	24.82	222,222	5.38	0.56
hydromorphone	<11	0.84	2,349	0.06	0.12
levorphanol	0	0	0	0	.
meperidine	<11	0.31	2,517	0.06	0.06
methadone	13	1.36	2,287	0.06	0.16
morphine	14	1.47	1,055	0.03	0.17
oxycodone	118	12.36	61,330	1.49	0.44
oxymorphone	<11	0	68	0	-0.01
pentazocine	<11	0.1	154	0	0.04
propoxyphene	28	2.93	39,333	0.95	0.14
Tapentadol	0	0	18	0	0.00
tramadol	38	3.98	12,285	0.3	0.26

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Healthcare Utilization, mean (SD)					
Comorbidity Index	1.69	1.88	0.84	1.36	0.51
Morphine equivalents	902.54	5,462.26	66.51	11,425.48	0.09
Number of diagnoses	7.53	4.44	4.53	3.17	0.78
Number of ED visits	0.47	1.31	0.26	0.83	0.19
Number of non-duloxetine generics dispensed	4.92	3.89	1.82	2.04	1.00
Number of hospitalizations	0.07	0.33	0.04	0.25	0.11
Number of outpatient visits	9.26	9.02	5.47	4.19	0.54
Number of psychiatric hospitalizations	0.03	0.19	0.00	0.07	0.17
Number of psychiatrist visits	2.04	7.52	0.20	1.90	0.34

15.4. 2. Postpartum Haemorrhage- Baseline characteristics of duloxetine exposed vs. SSRI exposed women: unadjusted

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Total	869		65,303		
Demographics					
Age, mean (SD)	28.38	5.40	26.16	5.35	
Age categorical, N (%)					
<=19	34	3.91	5,581	8.55	-0.19
20-24	188	21.63	23,161	35.47	-0.31
25-29	311	35.79	20,118	30.81	0.11
30-34	202	23.25	10,839	16.60	0.17
35-39	112	12.89	4,694	7.19	0.19
>=40	22	2.53	910	1.39	0.08
Race, N (%)					
White	741	85.27	52,950	81.08	0.11
Black or African American	46	5.29	4,622	7.08	-0.07
Hispanic or Latino			2,555	3.91	-0.17
Asian or Other Pacific Islander			457	0.70	0.07
American Indian	19	2.19	1,112	1.70	0.04
Other	14	1.61	1,573	2.41	-0.06
Unknown	26	2.99	2,034	3.11	-0.01
Chronic comorbid conditions, N (%)					
Hypertension	130	14.96	4,862	7.45	0.24
Diabetes	169	19.45	9,315	14.26	0.14
Renal Disease	<11	0.81	531	0.81	0.00
Obesity Overweight	63	7.25	2,466	3.78	0.15
Comorbidity Index Q1	294	33.83	30,415	46.58	-0.26
Comorbidity Index Q2	186	21.40	15,486	23.71	-0.06
Comorbidity Index Q3	161	18.53	9,746	14.92	0.10
Comorbidity Index Q4	228	26.24	9,656	14.79	0.29
Indications for duloxetine, N (%)					
Depression	273	31.42	17,381	26.62	0.11
Anxiety	158	18.18	7,648	11.71	0.18
Neuropathic Pain	33	3.80	1,708	2.62	0.07

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Fibromyalgia	40	4.60	592	0.91	0.23
Non neuropathic Pain	244	28.08	11,930	18.27	0.23
Other psychiatric conditions, N (%)					
Sleep disorder	17	1.96	683	1.05	0.07
Bipolar disorder	82	9.44	3,358	5.14	0.17
Psychosis	<11	0.69	264	0.40	0.04
Schizophrenia	<11	0.69	416	0.64	0.01
Personality disorder	13	1.50	475	0.73	0.07
Adjustment disorder	<11	0.35	334	0.51	-0.03
Tobacco use, N (%)	111	12.77	6,001	9.19	0.11
Alcohol abuse or dependence, N (%)	<11	0.12	521	0.80	-0.10
Drug abuse or dependence, N (%)	15	1.73	1,792	2.74	-0.07
Other medication exposures, N (%)					
Benzodiazepines	163	18.76	4,530	6.94	0.36
Other hypnotics	197	22.67	8,957	13.72	0.23
Barbiturates	33	3.80	2,002	3.07	0.04
Anxiolytics	44	5.06	1,065	1.63	0.19
Anticonvulsants	96	11.05	1,985	3.04	0.32
Antipsychotics	108	12.43	2,675	4.10	0.31
SSRIs	0	0.00	65,303	100.00	.
SNRIs	<11	0.81	301	0.46	0.04
Other Antidep	116	13.35	3,632	5.56	0.27
Stimulants	36	4.14	577	0.88	0.21
Antidiabetic	39	4.49	1,486	2.28	0.12
Insulin	56	6.44	2,153	3.30	0.15
Antihyperten	143	16.46	5,419	8.30	0.25
Opioid analgesics	377	43.38	18,265	27.97	0.33
Triptans	16	1.84	361	0.55	0.12
NSAIDs	50	5.75	1,550	2.37	0.17
Obstetric conditions, N (%)					
Multifetal gestation Flag	35	4.03	2,062	3.16	0.05
Markers of healthcare utilization					

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Number of distinct 3 digit ICD 9 codes=0	<11	1.04	580	0.89	0.02
Number of distinct 3 digit ICD 9 codes: tertile 1 for number >0	68	7.83	9,361	14.33	-0.21
Number of distinct 3 digit ICD 9 codes: tertile 2 for number >0	253	29.11	22,825	34.95	-0.13
Number of distinct 3 digit ICD 9 codes: tertile 3 for number >0	539	62.03	32,537	49.82	0.25
Number of ED visits=0	650	74.80	50,450	77.26	-0.06
Number of ED visits=1	154	17.72	9,777	14.97	0.07
Number of ED visits=2	30	3.45	2,888	4.42	-0.05
Number of ED visits>2	35	4.03	2,188	3.35	0.04
Number of non-duloxetine generics dispensed=0	73	8.40	3,246	4.97	0.14
Number of non-duloxetine generics dispensed: tertile 1 for number >0	91	10.47	9,459	14.48	-0.12
Number of non-duloxetine generics dispensed: tertile 2 for number >0	99	11.39	11,408	17.47	-0.17
Number of non-duloxetine generics dispensed: tertile 3 for number >0	606	69.74	41,190	63.08	0.14
Number of hospital admissions=0	815	93.79	61,792	94.62	-0.04
Number of hospital admissions=1	44	5.06	2,963	4.54	0.02
Number of hospital admissions=2	<11	0.69	443	0.68	0.00
Number of hospital admissions>2	<11	0.46	105	0.16	0.05
Number of outpatient visits=0	13	1.50	1,151	1.76	-0.02
Number of outpatient visits: tertile 1 for number >0	147	16.92	13,867	21.23	-0.11
Number of outpatient visits: tertile 2 for number >0	204	23.48	20,274	31.05	-0.17
Number of outpatient visits: tertile 3 for number >0	505	58.11	30,011	45.96	0.25
Number of psychiatric hospitalizations Q1	847	97.47	63,744	97.61	-0.01
Number of psychiatric hospitalizations Q2	18	2.07	1,372	2.10	0.00
Number of psychiatric hospitalizations Q3	<11	0.46	154	0.24	0.04
Number of psychiatric hospitalizations Q4	<11	0.00	33	0.05	-0.03
Number of psychiatrist visits=0	511	58.80	45,751	70.06	-0.24
Number of psychiatrist visits=1	147	16.92	7,832	11.99	0.14
Number of psychiatrist visits=2	56	6.44	3,457	5.29	0.05
Number of psychiatrist visits>2	155	17.84	8,263	12.65	0.14
Geographic region					

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Arkansas	PPD		165	0.25	0.05
Alabama	PPD		371	0.57	0.02
California	48	5.52	3,382	5.18	0.02
Colorado	PPD		725	1.11	-0.07
District of Columbia	PPD		PPD		0.04
Delaware	15	1.73	PPD		0.11
Florida	PPD		3,459	5.30	-0.22
Georgia	PPD		2,360	3.61	-0.21
Hawaii	0	0.00	50	0.08	-0.04
Iowa	PPD		1,029	1.58	-0.07
Idaho	PPD		219	0.34	-0.05
Illinois	61	7.02	4,315	6.61	0.02
Indiana	72	8.29	2,417	3.70	0.19
Kansas	15	1.73	1,356	2.08	-0.03
Kentucky	20	2.30	2,469	3.78	-0.09
Louisiana	PPD		498	0.76	0.06
Massachusetts	PPD		676	1.04	-0.07
Maryland	17	1.96	1,335	2.04	-0.01
Maine	PPD		445	0.68	0.07
Minnesota	78	8.98	4,225	6.47	0.09
Missouri	40	4.60	2,044	3.13	0.08
Mississippi	PPD		317	0.49	-0.04
North Carolina	16	1.84	549	0.84	0.09
North Dakota	PPD		465	0.71	0.02
Nebraska	17	1.96	602	0.92	0.09
New Hampshire	PPD		942	1.44	-0.03
New Jersey	PPD		283	0.43	-0.09
New Mexico	PPD		515	0.79	-0.04
Nevada	PPD		109	0.17	-0.06
New York	97	11.16	4,696	7.19	0.14
Ohio	13	1.50	1,867	2.86	-0.09
Oklahoma	19	2.19	2,349	3.60	-0.08

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Oregon	45	5.18	2,900	4.44	0.03
Pennsylvania	<11	0.46	1,788	2.74	-0.18
Rhode Island	<11	0.00	178	0.27	-0.07
South Carolina	<11	0.46	159	0.24	0.04
South Dakota	<11	0.46	361	0.55	-0.01
Tennessee	42	4.83	4,234	6.48	-0.07
Texas	<11	0.35	280	0.43	-0.01
Utah	57	6.56	2,552	3.91	0.12
Virginia	31	3.57	2,323	3.56	0.00
Vermont	<11	1.15	764	1.17	0.00
Washington	<11	0.23	240	0.37	-0.03
Wisconsin	36	4.14	4,387	6.72	-0.11
West Virginia	<11	0.92	348	0.53	0.05
Wyoming	<11	0.23	162	0.25	0.00
Opioids					
buprenorphine	29	3.34	514	0.79	0.18
butorphanol	<11	0	21	0.03	-0.03
codeine	102	11.74	7,973	12.21	-0.01
fentanyl	11	1.27	49	0.08	0.15
hydrocodone	213	24.51	9,240	14.15	0.26
hydromorphone	<11	0.81	139	0.21	0.08
Levorphanol	0	0	<11	0	.
meperidine	<11	0.35	121	0.19	0.03
methadone	13	1.5	172	0.26	0.13
morphine	11	1.27	77	0.12	0.14
oxycodone	105	12.08	2,920	4.47	0.28
oxymorphone	<11	0	<11	0	-0.01
pentazocine	<11	0.12	<11	0.02	0.04
propoxyphene	23	2.65	1,741	2.67	0.00
tapentadol	<11	0	<11	0	-0.01
tramadol	36	4.14	786	1.2	0.18
Healthcare Utilization, mean (SD)					

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Comorbidity Index	1.69	1.87	1.16	1.57	0.31
Morphine equivalents	841.49	5,345.66	184.87	3,816.44	0.14
Number of diagnoses	7.48	4.46	6.25	4.02	0.29
Number of ED visits	0.45	1.30	0.41	1.44	0.03
Number of non-duloxetine generics dispensed	4.79	3.82	3.94	2.95	0.25
Number of hospitalizations	0.08	0.34	0.06	0.30	0.04
Number of outpatient visits	9.18	9.04	7.32	5.98	0.24
Number of psychiatric hospitalizations	0.03	0.20	0.03	0.19	0.01
Number of psychiatrist visits	2.01	7.63	1.25	4.23	0.12

15.4. 3. Postpartum Haemorrhage- Baseline characteristics of duloxetine exposed vs. venlafaxine exposed women: unadjusted

	Duloxetine N/Mean	Duloxetine %/SD	Venlafaxine N/Mean	Venlafaxine %/SD	Standardized Difference
Total	948		3,573		
Demographics					
Age, mean (SD)					
Age categorical, N (%)					
<=19	38	4.01	194	5.43	-0.07
20-24	204	21.52	1,046	29.28	-0.18
25-29	343	36.18	1,161	32.49	0.08
30-34	217	22.89	766	21.44	0.03
35-39	124	13.08	353	9.88	0.10
>=40	22	2.32	53	1.48	0.06
Race, N (%)					
White	805	84.92	3,109	87.01	-0.06
Black or African American	50	5.27	126	3.53	0.09
Hispanic or Latino	13	1.37	91	2.55	-0.08
Asian or Other Pacific Islander	13	1.37	29	0.81	0.05
American Indian	22	2.32	28	0.78	0.12
Other	18	1.90	71	1.99	-0.01
Unknown	27	2.85	119	3.33	-0.03
Chronic comorbid conditions, N (%)					
Hypertension	136	14.35	380	10.64	0.11
Diabetes	188	19.83	608	17.02	0.07
Renal Disease	<11	0.74	23	0.64	0.01
Obesity Overweight	65	6.86	122	3.41	0.16
Comorbidity Index Q1	321	33.86	1,435	40.16	-0.13
Comorbidity Index Q2	204	21.52	851	23.82	-0.05
Comorbidity Index Q3	179	18.88	556	15.56	0.09
Comorbidity Index Q4	244	25.74	731	20.46	0.13
Indications for duloxetine, N (%)					
Depression	300	31.65	1,000	27.99	0.08
Anxiety	175	18.46	503	14.08	0.12
Neuropathic Pain	45	4.75	110	3.08	0.09

	Duloxetine N/Mean	Duloxetine %/SD	Venlafaxine N/Mean	Venlafaxine %/SD	Standardized Difference
Fibromyalgia	44	4.64	47	1.32	0.20
Non neuropathic Pain	269	28.38	684	19.14	0.22
Other psychiatric conditions, N (%)					
Sleep disorder	21	2.22	47	1.32	0.07
Bipolar disorder	94	9.92	277	7.75	0.08
Psychosis	<11	0.63	12	0.34	0.04
Schizophrenia	<11	0.63	23	0.64	0.00
Personality disorder	16	1.69	38	1.06	0.05
Adjustment disorder	<11	0.32	11	0.31	0.00
Tobacco use, N (%)	123	12.97	356	9.96	0.09
Alcohol abuse or dependence, N (%)	<11	0.11	36	1.01	-0.12
Drug abuse or dependence, N (%)	19	2.00	114	3.19	-0.07
Other medication exposures, N (%)					
Benzodiazepines	186	19.62	480	13.43	0.17
Other hypnotics	223	23.52	481	13.46	0.26
Barbiturates	33	3.48	115	3.22	0.01
Anxiolytics	49	5.17	88	2.46	0.14
Anticonvulsants	107	11.29	241	6.75	0.16
Antipsychotics	119	12.55	284	7.95	0.15
SSRIs	86	9.07	252	7.05	0.07
SNRIs	0	0.00	3,573	100.00	.
Other Antidep	131	13.82	340	9.52	0.13
Stimulants	42	4.43	62	1.74	0.16
Antidiabetic	39	4.11	110	3.08	0.06
Insulin	62	6.54	171	4.79	0.08
Antihyperten	151	15.93	387	10.83	0.15
Opioid analgesics	411	43.35	1,104	30.90	0.26
Triptans	18	1.90	46	1.29	0.05
NSAIDs	55	5.80	117	3.27	0.12
Obstetric conditions, N (%)					
Multifetal gestation Flag	36	3.80	122	3.41	0.02
Markers of healthcare utilization					

	Duloxetine N/Mean	Duloxetine %/SD	Venlafaxine N/Mean	Venlafaxine %/SD	Standardized Difference
Number of distinct 3 digit ICD 9 codes=0	<11	0.95	27	0.76	0.02
Number of distinct 3 digit ICD 9 codes: tertile 1 for number >0	74	7.81	467	13.07	-0.17
Number of distinct 3 digit ICD 9 codes: tertile 2 for number >0	277	29.22	1,208	33.81	-0.10
Number of distinct 3 digit ICD 9 codes: tertile 3 for number >0	588	62.03	1,871	52.36	0.20
Number of ED visits=0	703	74.16	2,776	77.69	-0.08
Number of ED visits=1	168	17.72	509	14.25	0.09
Number of ED visits=2	35	3.69	152	4.25	-0.03
Number of ED visits>2	42	4.43	136	3.81	0.03
Number of non-duloxetine generics dispensed=0	75	7.91	88	2.46	0.25
Number of non-duloxetine generics dispensed: tertile 1 for number >0	99	10.44	456	12.76	-0.07
Number of non-duloxetine generics dispensed: tertile 2 for number >0	103	10.86	518	14.50	-0.11
Number of non-duloxetine generics dispensed: tertile 3 for number >0	671	70.78	2,511	70.28	0.01
Number of hospital admissions=0	892	94.09	3,386	94.77	-0.03
Number of hospital admissions=1	46	4.85	155	4.34	0.02
Number of hospital admissions=2	<11	0.63	24	0.67	0.00
Number of hospital admissions>2	<11	0.42	<11	0.22	0.03
Number of outpatient visits=0	13	1.37	50	1.40	0.00
Number of outpatient visits: tertile 1 for number >0	160	16.88	739	20.68	-0.10
Number of outpatient visits: tertile 2 for number >0	226	23.84	1,090	30.51	-0.15
Number of outpatient visits: tertile 3 for number >0	549	57.91	1,694	47.41	0.21
Number of psychiatric hospitalizations Q1	925	97.57	3,489	97.65	0.00
Number of psychiatric hospitalizations Q2	19	2.00	72	2.02	0.00
Number of psychiatric hospitalizations Q3	<11	0.42	12	0.34	0.01
Number of psychiatric hospitalizations Q4	0	0.00	<11	0.00	.
Number of psychiatrist visits=0	556	58.65	2,336	65.38	-0.14
Number of psychiatrist visits=1	161	16.98	499	13.97	0.08
Number of psychiatrist visits=2	56	5.91	222	6.21	-0.01
Number of psychiatrist visits>2	175	18.46	516	14.44	0.11
Geographic region					

	Duloxetine N/Mean	Duloxetine %/SD	Venlafaxine N/Mean	Venlafaxine %/SD	Standardized Difference
Arkansas	PPD		PPD		0.03
Alabama					0.08
California	50	5.27	173	4.84	0.02
Colorado	PPD		33	0.92	-0.06
District of Columbia			PPD		0.03
Delaware	16	1.69	28	0.78	0.08
Florida	15	1.58	132	3.69	-0.13
Georgia	PPD		96	2.69	-0.14
Hawaii			PPD		-0.05
Iowa			76	2.13	-0.11
Idaho			21	0.59	-0.06
Illinois	64	6.75	237	6.63	0.00
Indiana	77	8.12	133	3.72	0.19
Kansas	19	2.00	69	1.93	0.01
Kentucky	19	2.00	72	2.02	0.00
Louisiana	14	1.48	39	1.09	0.03
Massachusetts	PPD		22	0.62	-0.03
Maryland	20	2.11	70	1.96	0.01
Maine	PPD		30	0.84	0.04
Minnesota	84	8.86	267	7.47	0.05
Missouri	41	4.32	145	4.06	0.01
Mississippi	PPD		33	0.92	-0.09
North Carolina	16	1.69	29	0.81	0.08
North Dakota	PPD		32	0.90	0.01
Nebraska	20	2.11	37	1.04	0.09
New Hampshire			44	1.23	-0.02
New Jersey	PPD		PPD		-0.04
New Mexico			25	0.70	-0.04
Nevada			PPD		-0.05
New York	102	10.76	309	8.65	0.07
Ohio	PPD		132	3.69	-0.16
Oklahoma	22	2.32	99	2.77	-0.03

	Duloxetine N/Mean	Duloxetine %/SD	Venlafaxine N/Mean	Venlafaxine %/SD	Standardized Difference
Oregon	50	5.27	163	4.56	0.03
Pennsylvania	PPD	PPD	153	4.28	-0.25
Rhode Island			PPD	PPD	-0.07
South Carolina					0.07
South Dakota			21	0.59	-0.02
Tennessee	44	4.64	198	5.54	-0.04
Texas	PPD		PPD		0.01
Utah	69	7.28	135	3.78	0.15
Virginia	35	3.69	88	2.46	0.07
Vermont	PPD		31	0.87	0.02
Washington	PPD	PPD	PPD		-0.01
Wisconsin			296	8.28	-0.16
West Virginia			21	0.59	0.05
Wyoming			14	0.39	-0.01
Opioids					
buprenorphine	32	3.38	52	1.46	0.13
butorphanol	<11	0.11	<11	0.11	0.00
codeine	116	12.24	439	12.29	0.00
fentanyl	12	1.27	<11	0.28	0.11
hydrocodone	233	24.58	575	16.09	0.21
hydromorphone	<11	0.84	<11	0.28	0.08
levorphanol	<11	0	<11	0	.
meperidine	<11	0.32	<11	0.17	0.03
methadone	13	1.37	18	0.5	0.09
morphine	14	1.48	12	0.34	0.12
oxycodone	118	12.45	191	5.35	0.25
oxymorphone	<11	0	<11	0.03	-0.02
pentazocine	<11	0.11	0	0	0.05
propoxyphene	28	2.95	111	3.11	-0.01
Tapentadol	0	0	0	0	.
tramadol	37	3.9	57	1.6	0.14
Healthcare Utilization, mean (SD)					

	Duloxetine	Duloxetine	Venlafaxine	Venlafaxine	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Comorbidity Index	1.68	1.88	1.45	1.83	0.12
Morphine equivalents	905.46	5,482.09	269.65	2,502.78	0.15
Number of diagnoses	7.50	4.42	6.47	4.02	0.24
Number of ED visits	0.47	1.31	0.41	1.20	0.05
Number of non-duloxetine generics dispensed	4.90	3.85	4.50	3.26	0.11
Number of hospitalizations	0.07	0.33	0.06	0.31	0.03
Number of outpatient visits	9.25	9.04	7.49	6.15	0.23
Number of psychiatric hospitalizations	0.03	0.19	0.03	0.18	0.01
Number of psychiatrist visits	2.05	7.55	1.46	4.61	0.09

15.4. 4. Postpartum Haemorrhage- Baseline characteristics of duloxetine exposed vs. unexposed women: adjusted for treatment indications

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Total	739		969,868		
Demographics					
Age, mean (SD)					
Age categorical, N (%)	28.44	5.3	25.154	5.35	0.62
<=19	27	3.65	131,946	13.6	-0.36
20-24	151	20.43	379,096	39.09	-0.42
25-29	274	37.08	262,469	27.06	0.22
30-34	173	23.41	130,076	13.41	0.26
35-39	98	13.26	54,021	5.57	0.27
>=40	16	2.17	12,260	1.26	0.07
Race, N (%)					
White	628	84.98	574,572	59.24	0.60
Black or African American	41	5.55	203,621	20.99	-0.47
Hispanic or Latino			77,137	7.95	-0.33
Asian or Other Pacific Islander			18,592	1.92	-0.02
American Indian	15	2.03	20,490	2.11	-0.01
Other	16	2.17	49,063	5.06	-0.16
Unknown	18	2.44	26,394	2.72	-0.02
Chronic comorbid conditions, N (%)					
Hypertension	112	15.16	74,026	7.63	0.24
Diabetes	141	19.08	125,814	12.97	0.17
Renal Disease	<11	0.95	10,006	1.03	-0.01
Obesity Overweight	54	7.31	51,731	5.33	0.08
Comorbidity Index Q1	231	31.26	456,516	47.07	-0.33
Comorbidity Index Q2	163	22.06	229,727	23.69	-0.04
Comorbidity Index Q3	140	18.94	137,258	14.15	0.13
Comorbidity Index Q4	205	27.74	146,368	15.09	0.31
Indications for duloxetine, N (%)					
Depression	302	40.87	393,832	40.61	0.01
Anxiety	177	23.95	234,456	24.17	-0.01
Neuropathic Pain	45	6.09	59,322	6.12	0.00

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Fibromyalgia	45	6.09	69,214	7.14	-0.04
Non neuropathic Pain	272	36.81	345,083	35.58	0.03
Other psychiatric conditions, N (%)					
Sleep disorder	20	2.71	11,442	1.18	0.11
Bipolar disorder	72	9.74	39,269	4.05	0.23
Psychosis	<11	0.81	5,464	0.56	0.03
Schizophrenia	<11	0.68	4,885	0.5	0.02
Personality disorder	14	1.89	8,665	0.89	0.09
Adjustment disorder	<11	0.41	8,731	0.9	-0.06
Tobacco use, N (%)	107	14.48	103,376	10.66	0.12
Alcohol abuse or dependence, N (%)	0	0	6,054	0.62	-0.11
Drug abuse or dependence, N (%)	14	1.89	22,789	2.35	-0.03
Other medication exposures, N (%)					
Benzodiazepines	166	22.46	51,425	5.3	0.51
Other hypnotics	186	25.17	99,376	10.25	0.40
Barbiturates	30	4.06	21,700	2.24	0.10
Anxiolytics	45	6.09	12,393	1.28	0.26
Anticonvulsants	94	12.72	20,861	2.15	0.41
Antipsychotics	93	12.58	21,588	2.23	0.40
SSRIs	69	9.34	165,069	17.02	-0.23
SNRIs	<11	0.81	9,417	0.97	-0.02
Other Antidep	112	15.16	43,673	4.5	0.36
Stimulants	32	4.33	7,175	0.74	0.23
Antidiabetic	30	4.06	17,555	1.81	0.13
Insulin	46	6.22	28,253	2.91	0.16
Antihyperten	128	17.32	63,802	6.58	0.34
Opioid analgesics	354	47.9	252,482	26.03	0.47
Triptans	17	2.3	3,746	0.39	0.17
NSAIDs	48	6.5	23,430	2.42	0.20
Obstetric conditions, N (%)					
Multifetal gestation Flag	29	3.92	33,497	3.45	0.02
Markers of healthcare utilization					

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Number of distinct 3 digit ICD 9 codes=0	<11	0.41	5,831	0.6	-0.03
Number of distinct 3 digit ICD 9 codes: tertile 1 for number >0	45	6.09	87,544	9.03	-0.11
Number of distinct 3 digit ICD 9 codes: tertile 2 for number >0	182	24.63	292,918	30.2	-0.13
Number of distinct 3 digit ICD 9 codes: tertile 3 for number >0	509	68.88	583,575	60.17	0.18
Number of ED visits=0	528	71.45	665,514	68.62	0.06
Number of ED visits=1	144	19.49	184,941	19.07	0.01
Number of ED visits=2	28	3.79	63,821	6.58	-0.13
Number of ED visits>2	39	5.28	55,593	5.73	-0.02
Number of non-duloxetine generics dispensed=0	48	6.5	172,290	17.76	-0.35
Number of non-duloxetine generics dispensed: tertile 1 for number >0	70	9.47	171,544	17.69	-0.24
Number of non-duloxetine generics dispensed: tertile 2 for number >0	69	9.34	163,424	16.85	-0.22
Number of non-duloxetine generics dispensed: tertile 3 for number >0	552	74.7	462,610	47.7	0.58
Number of hospital admissions=0	688	93.1	895,184	92.3	0.03
Number of hospital admissions=1	42	5.68	59,033	6.09	-0.02
Number of hospital admissions=2	<11	0.68	11,022	1.14	-0.05
Number of hospital admissions>2	<11	0.54	4,629	0.48	0.01
Number of outpatient visits=0	<11	0.41	16,904	1.74	-0.13
Number of outpatient visits: tertile 1 for number >0	103	13.94	153,346	15.81	-0.05
Number of outpatient visits: tertile 2 for number >0	166	22.46	270,467	27.89	-0.13
Number of outpatient visits: tertile 3 for number >0	467	63.19	529,151	54.56	0.18
Number of psychiatric hospitalizations Q1	718	97.16	937,907	96.7	0.03
Number of psychiatric hospitalizations Q2	18	2.44	27,564	2.84	-0.03
Number of psychiatric hospitalizations Q3	<11	0.41	3,446	0.36	0.01
Number of psychiatric hospitalizations Q4	<11	0	951	0.1	-0.04
Number of psychiatrist visits=0	373	50.47	544,477	56.14	-0.11
Number of psychiatrist visits=1	154	20.84	167,223	17.24	0.09
Number of psychiatrist visits=2	54	7.31	74,892	7.72	-0.02
Number of psychiatrist visits>2	158	21.38	183,275	18.9	0.06
Geographic region					

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Arkansas	PPD		2,272	0.23	0.07
Alabama	PPD		6,067	0.63	0.02
California	34	4.6	86,845	8.95	-0.17
Colorado	PPD		5,486	0.57	-0.05
District of Columbia	0	0	439	0.05	-0.03
Delaware	PPD		6,831	0.7	0.06
Florida	PPD		45,325	4.67	-0.24
Georgia	PPD		28,514	2.94	-0.20
Hawaii	0	0	4,227	0.44	-0.09
Iowa	PPD		9,685	1	-0.01
Idaho	PPD		1,329	0.14	0.00
Illinois	51	6.9	63,015	6.5	0.02
Indiana	61	8.25	39,712	4.09	0.17
Kansas	15	2.03	11,969	1.23	0.06
Kentucky	19	2.57	38,291	3.95	-0.08
Louisiana	13	1.76	10,176	1.05	0.06
Massachusetts	PPD		8,025	0.83	-0.05
Maryland	19	2.57	28,553	2.94	-0.02
Maine	PPD		5,900	0.61	0.09
Minnesota	76	10.28	58,407	6.02	0.16
Missouri	32	4.33	21,255	2.19	0.12
Mississippi	0	0	11,299	1.17	-0.15
North Carolina	15	2.03	11,964	1.23	0.06
North Dakota	PPD		6,554	0.68	0.06
Nebraska	14	1.89	7,722	0.8	0.10
New Hampshire	PPD		10,814	1.11	-0.02
New Jersey	PPD		6,085	0.63	-0.08
New Mexico	PPD		11,322	1.17	-0.07
Nevada	0	0	1,526	0.16	-0.06
New York	84	11.37	116,006	11.96	-0.02
Ohio	PPD		21,789	2.25	-0.06
Oklahoma	17	2.3	28,176	2.91	-0.04

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Oregon	37	5.01	25,018	2.58	0.13
Pennsylvania	PPD		20,035	2.07	-0.17
Rhode Island	0	0	2,693	0.28	-0.07
South Carolina	PPD		2,108	0.22	0.01
South Dakota			5,778	0.6	-0.01
Tennessee	32	4.33	69,614	7.18	-0.12
Texas	PPD		3,819	0.39	-0.05
Utah	43	5.82	10,757	1.11	0.26
Virginia	28	3.79	36,909	3.81	0.00
Vermont	PPD		10,470	1.08	0.01
Washington			1,657	0.17	0.02
Wisconsin	33	4.47	59,059	6.09	-0.07
West Virginia	PPD		4,599	0.47	0.07
Wyoming			1,774	0.18	0.02
Opioids					
buprenorphine	25	3.38	6,191	0.64	0.20
Butorphanol	0	0	341	0.04	-0.03
codeine	95	12.86	107,071	11.04	0.06
fentanyl	12	1.62	1,145	0.12	0.16
hydrocodone	204	27.6	128,142	13.21	0.36
hydromorphone	<11	0.81	2,667	0.27	0.07
levorphanol	0	0	0	0	.
meperidine	<11	0.41	1,562	0.16	0.05
methadone	12	1.62	3,080	0.32	0.13
morphine	13	1.76	1,735	0.18	0.16
oxycodone	107	14.48	46,821	4.83	0.33
oxymorphone	0	0	154	0.02	-0.02
pentazocine	<11	0.14	104	0.01	0.05
propoxyphene	20	2.71	19,415	2	0.05
Tapentadol	0	0	14	0	-0.01
tramadol	33	4.47	12,138	1.25	0.19
Healthcare Utilization, mean (SD)					

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Comorbidity Index	1.78	1.93	1.17	1.65	0.34
Morphine equivalents	1116.97	6182.11	300.659	22439.23	0.05
Number of diagnoses	8.15	4.49	7.373	5.43	0.16
Number of ED visits	0.53	1.44	0.596	1.47	-0.04
Number of non-duloxetine generics dispensed	5.28	4	3.045	2.91	0.64
Number of hospitalizations	0.09	0.35	0.103	0.45	-0.04
Number of outpatient visits	9.89	9.18	8.307	6.44	0.20
Number of psychiatric hospitalizations	0.03	0.2	0.039	0.24	-0.03
Number of psychiatrist visits	2.26	7.16	1.717	4.35	0.09

15.4. 5. Postpartum Haemorrhage- Baseline characteristics of duloxetine exposed vs. SSRI exposed women: adjusted for treatment indications

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Total	670		40,430		.
Demographics					.
Age, mean (SD)	28.5	5.32	26.39	5.4	0.39
Age categorical, N (%)					
<=19	24	3.58	3,206	7.93	-0.19
20-24	138	20.6	13,872	34.31	-0.31
25-29	243	36.27	12,617	31.21	0.11
30-34	161	24.03	6,981	17.27	0.17
35-39	88	13.13	3,141	7.77	0.18
>=40	16	2.39	614	1.52	0.06
Race, N (%)					
White	571	85.22	32,405	80.15	0.13
Black or African American	37	5.52	3,025	7.48	-0.08
Hispanic or Latino			1,577	3.9	-0.16
Asian or Other Pacific Islander			305	0.75	0.08
American Indian	13	1.94	772	1.91	0.00
Other			1,102	2.72	-0.06
Unknown	17	2.54	1,244	3.08	-0.03
Chronic comorbid conditions, N (%)					.
Hypertension	106	15.82	3,560	8.81	0.21
Diabetes	126	18.81	6,232	15.41	0.09
Renal Disease	<11	0.9	453	1.12	-0.02
Obesity Overweight	52	7.76	2,038	5.04	0.11
Comorbidity Index Q1	210	31.34	17,278	42.73	-0.24
Comorbidity Index Q2	148	22.09	9,493	23.48	-0.03
Comorbidity Index Q3	124	18.51	6,564	16.23	0.06
Comorbidity Index Q4	188	28.06	7,096	17.55	0.25
Indications for duloxetine, N (%)					.
Depression	273	40.75	16,326	40.38	0.01
Anxiety	158	23.58	9,516	23.54	0.00
Neuropathic Pain	33	4.93	4,648	11.5	-0.24

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Fibromyalgia	40	5.97	2,414	5.97	0.00
Non neuropathic Pain	244	36.42	15,196	37.59	-0.02
Other psychiatric conditions, N (%)					
Sleep disorder	16	2.39	715	1.77	0.04
Bipolar disorder	60	8.96	2,775	6.86	0.08
Psychosis	<11	0.9	238	0.59	0.04
Schizophrenia	<11	0.75	329	0.81	-0.01
Personality disorder	11	1.64	473	1.17	0.04
Adjustment disorder	<11	0.45	251	0.62	-0.02
Tobacco use, N (%)	97	14.48	4,644	11.49	0.09
Alcohol abuse or dependence, N (%)	0	0	400	0.99	-0.14
Drug abuse or dependence, N (%)	<11	1.49	1,400	3.46	-0.13
Other medication exposures, N (%)					.
Benzodiazepines	144	21.49	4,267	10.55	0.30
Other hypnotics	164	24.48	7,203	17.82	0.16
Barbiturates	28	4.18	1,468	3.63	0.03
Anxiolytics	39	5.82	962	2.38	0.17
Anticonvulsants	83	12.39	1,758	4.35	0.29
Antipsychotics	84	12.54	2,341	5.79	0.24
SSRIs	<11	0	40,430	100	.
SNRIs	<11	0.9	248	0.61	0.03
Other Antidep	100	14.93	3,002	7.43	0.24
Stimulants	26	3.88	473	1.17	0.17
Antidiabetic	29	4.33	963	2.38	0.11
Insulin	42	6.27	1,562	3.86	0.11
Antihyperten	120	17.91	3,835	9.49	0.25
Opioid analgesics	321	47.91	14,582	36.07	0.24
Triptans	15	2.24	317	0.78	0.12
NSAIDs	43	6.42	1,447	3.58	0.13
Obstetric conditions, N (%)					.
Multifetal gestation Flag	28	4.18	1,343	3.32	0.05
Markers of healthcare utilization					.

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Number of distinct 3 digit ICD 9 codes=0	<11	0.45	151	0.37	0.01
Number of distinct 3 digit ICD 9 codes: tertile 1 for number >0	40	5.97	3,170	7.84	-0.07
Number of distinct 3 digit ICD 9 codes: tertile 2 for number >0	165	24.63	11,373	28.13	-0.08
Number of distinct 3 digit ICD 9 codes: tertile 3 for number >0	462	68.96	25,736	63.66	0.11
Number of ED visits=0	483	72.09	28,361	70.15	0.04
Number of ED visits=1	130	19.4	7,119	17.61	0.05
Number of ED visits=2	25	3.73	2,563	6.34	-0.12
Number of ED visits>2	32	4.78	2,386	5.9	-0.05
Number of non-duloxetine generics dispensed=0	46	6.87	1,357	3.36	0.16
Number of non-duloxetine generics dispensed: tertile 1 for number >0	64	9.55	4,542	11.23	-0.06
Number of non-duloxetine generics dispensed: tertile 2 for number >0	66	9.85	5,927	14.66	-0.15
Number of non-duloxetine generics dispensed: tertile 3 for number >0	494	73.73	28,605	70.75	0.07
Number of hospital admissions=0	621	92.69	37,481	92.71	0.00
Number of hospital admissions=1	40	5.97	2,399	5.93	0.00
Number of hospital admissions=2	<11	0.75	427	1.06	-0.03
Number of hospital admissions>2	<11	0.6	123	0.3	0.04
Number of outpatient visits=0	<11	0.45	403	1	-0.06
Number of outpatient visits: tertile 1 for number >0	92	13.73	6,072	15.02	-0.04
Number of outpatient visits: tertile 2 for number >0	153	22.84	11,002	27.21	-0.10
Number of outpatient visits: tertile 3 for number >0	422	62.99	22,953	56.77	0.13
Number of psychiatric hospitalizations Q1	650	97.01	38,893	96.2	0.05
Number of psychiatric hospitalizations Q2	17	2.54	1,311	3.24	-0.04
Number of psychiatric hospitalizations Q3	<11	0.45	170	0.42	0.00
Number of psychiatric hospitalizations Q4	0	0	56	0.14	-0.05
Number of psychiatrist visits=0	341	50.9	22,628	55.97	-0.10
Number of psychiatrist visits=1	138	20.6	6,796	16.81	0.10
Number of psychiatrist visits=2	53	7.91	3,113	7.7	0.01
Number of psychiatrist visits>2	138	20.6	7,894	19.52	0.03
Geographic region					.

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Arkansas	PPD		121	0.3	0.06
Alabama	PPD		247	0.61	0.02
California	34	5.07	2,038	5.04	0.00
Colorado	PPD		346	0.86	-0.07
District of Columbia	PPD		PPD		-0.02
Delaware	PPD		PPD		0.08
Florida	PPD		1,563	3.87	-0.21
Georgia	PPD		1,242	3.07	-0.20
Hawaii	0	0	37	0.09	-0.04
Iowa	PPD		690	1.71	-0.07
Idaho	0	0	142	0.35	-0.08
Illinois	48	7.16	2,682	6.63	0.02
Indiana	56	8.36	1,594	3.94	0.18
Kansas	PPD		693	1.71	0.01
Kentucky	18	2.69	1,396	3.45	-0.04
Louisiana	PPD		291	0.72	0.09
Massachusetts	PPD		395	0.98	-0.06
Maryland	16	2.39	831	2.06	0.02
Maine	PPD		316	0.78	0.08
Minnesota	70	10.45	3,333	8.24	0.08
Missouri	31	4.63	1,056	2.61	0.11
Mississippi	0	0	210	0.52	-0.10
North Carolina	15	2.24	434	1.07	0.09
North Dakota	PPD		389	0.96	0.02
Nebraska	PPD		387	0.96	0.07
New Hampshire	PPD		634	1.57	-0.05
New Jersey	PPD		127	0.31	-0.08
New Mexico	PPD		382	0.94	-0.04
Nevada	0	0	64	0.16	-0.06
New York	79	11.79	3,029	7.49	0.15
Ohio	PPD		1,201	2.97	-0.10
Oklahoma	15	2.24	1,019	2.52	-0.02

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Oregon	32	4.78	1,783	4.41	0.02
Pennsylvania	PPD		1,142	2.82	-0.22
Rhode Island	0	0	174	0.43	-0.09
South Carolina	PPD		89	0.22	0.02
South Dakota			280	0.69	-0.01
Tennessee	30	4.48	2,666	6.59	-0.09
Texas	PPD		124	0.31	-0.03
Utah	33	4.93	1,212	3	0.10
Virginia	25	3.73	1,390	3.44	0.02
Vermont	PPD		564	1.4	0.00
Washington			142	0.35	-0.01
Wisconsin	28	4.18	3,410	8.43	-0.18
West Virginia	PPD		236	0.58	0.05
Wyoming			87	0.21	-0.02
Opioids					
buprenorphine	22	3.28	343	0.85	0.17
butorphanol	<11	0	13	0.03	-0.03
codeine	83	12.39	6,278	15.53	-0.09
fentanyl	11	1.64	56	0.14	0.16
hydrocodone	184	27.46	7,902	19.54	0.19
hydromorphone	<11	0.75	170	0.42	0.04
levorphanol	0	0	0	0	
meperidine	<11	0.45	78	0.19	0.05
methadone	12	1.79	224	0.55	0.12
morphine	<11	1.49	127	0.32	0.12
oxycodone	96	14.33	2,991	7.4	0.22
oxymorphone	0	0	0	0	-0.01
pentazocine	<11	0.15	<11	0.02	0.04
propoxyphene	17	2.54	1,324	3.27	-0.04
tapentadol	0	0	0	0	-0.01
tramadol	31	4.63	816	2.02	0.15
Healthcare Utilization, mean (SD)					

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Comorbidity Index	1.77	1.92	1.308	1.69	0.26
Morphine equivalents	1046.7	6062.55	338.098	4613.88	0.13
Number of diagnoses	8.13	4.51	7.738	4.75	0.08
Number of ED visits	0.51	1.43	0.603	1.77	-0.06
Number of non-duloxetine generics dispensed	5.16	3.93	4.648	3.39	0.14
Number of hospitalizations	0.09	0.37	0.092	0.39	0.00
Number of outpatient visits	9.81	9.17	8.83	7	0.12
Number of psychiatric hospitalizations	0.03	0.21	0.046	0.25	-0.05
Number of psychiatrist visits	2.2	7.19	1.85	4.73	0.06

15.4. 6. Postpartum Haemorrhage- Baseline characteristics of duloxetine exposed vs. venlafaxine exposed women: adjusted for treatment indications

	Duloxetine N/Mean	Duloxetine %/SD	Venlafaxine N/Mean	Venlafaxine %/SD	Standardized Difference
Total	733		2,440		.
Demographics					.
Age, mean (SD)	28.44	5.29	27.46	5.39	0.18
Age categorical, N (%)					
<=19	27	3.68	127	5.2	-0.07
20-24	149	20.33	694	28.43	-0.19
25-29	272	37.11	793	32.52	0.10
30-34	172	23.47	531	21.78	0.04
35-39	98	13.37	260	10.66	0.08
>=40	15	2.05	35	1.42	0.05
Race, N (%)					
White	622	84.86	2,120	86.88	-0.06
Black or African American	41	5.59	82	3.35	0.11
Hispanic or Latino			57	2.35	-0.08
Asian or Other Pacific Islander			25	1.02	0.05
American Indian	15	2.05	19	0.8	0.11
Other	16	2.18	56	2.31	-0.01
Unknown	18	2.46	81	3.3	-0.05
Chronic comorbid conditions, N (%)					.
Hypertension	111	15.14	259	10.61	0.14
Diabetes	138	18.83	442	18.11	0.02
Renal Disease	<11	0.82	14	0.56	0.03
Obesity Overweight	53	7.23	90	3.69	0.16
Comorbidity Index Q1	231	31.51	903	37.01	-0.12
Comorbidity Index Q2	162	22.1	589	24.16	-0.05
Comorbidity Index Q3	138	18.83	399	16.36	0.06
Comorbidity Index Q4	202	27.56	548	22.48	0.12
Indications for duloxetine, N (%)					.
Depression	300	40.93	1,031	42.26	-0.03
Anxiety	175	23.87	639	26.19	-0.05
Neuropathic Pain	45	6.14	182	7.44	-0.05

	Duloxetine N/Mean	Duloxetine %/SD	Venlafaxine N/Mean	Venlafaxine %/SD	Standardized Difference
Fibromyalgia	44	6	146	6	0.00
Non neuropathic Pain	269	36.7	901	36.91	0.00
Other psychiatric conditions, N (%)					.
Sleep disorder	20	2.73	47	1.94	0.05
Bipolar disorder	71	9.69	213	8.75	0.03
Psychosis	<11	0.82	12	0.5	0.04
Schizophrenia	<11	0.68	16	0.64	0.00
Personality disorder	14	1.91	36	1.47	0.03
Adjustment disorder	<11	0.41	<11	0.44	0.00
Tobacco use, N (%)	107	14.6	292	11.97	0.08
Alcohol abuse or dependence, N (%)	0	0	29	1.19	-0.16
Drug abuse or dependence, N (%)	14	1.91	94	3.87	-0.12
Other medication exposures, N (%)					.
Benzodiazepines	163	22.24	448	18.38	0.10
Other hypnotics	184	25.1	427	17.48	0.19
Barbiturates	29	3.96	94	3.85	0.01
Anxiolytics	44	6	85	3.46	0.12
Anticonvulsants	93	12.69	206	8.44	0.14
Antipsychotics	92	12.55	248	10.16	0.08
SSRIs	69	9.41	221	9.05	0.01
SNRIs	0	0	2,440	100	.
Other Antidep	111	15.14	283	11.6	0.10
Stimulants	32	4.37	57	2.34	0.11
Antidiabetic	29	3.96	72	2.96	0.05
Insulin	46	6.28	120	4.92	0.06
Antihyperten	127	17.33	282	11.54	0.17
Opioid analgesics	349	47.61	950	38.94	0.18
Triptans	17	2.32	34	1.4	0.07
NSAIDs	47	6.41	108	4.41	0.09
Obstetric conditions, N (%)					.
Multifetal gestation Flag	29	3.96	94	3.87	0.00
Markers of healthcare utilization					.

	Duloxetine N/Mean	Duloxetine %/SD	Venlafaxine N/Mean	Venlafaxine %/SD	Standardized Difference
Number of distinct 3 digit ICD 9 codes=0	<11	0.41	<11	0.31	0.02
Number of distinct 3 digit ICD 9 codes: tertile 1 for number >0	45	6.14	197	8.08	-0.08
Number of distinct 3 digit ICD 9 codes: tertile 2 for number >0	181	24.69	642	26.3	-0.04
Number of distinct 3 digit ICD 9 codes: tertile 3 for number >0	504	68.76	1,594	65.31	0.07
Number of ED visits=0	524	71.49	1,718	70.41	0.02
Number of ED visits=1	142	19.37	433	17.74	0.04
Number of ED visits=2	28	3.82	146	6	-0.10
Number of ED visits>2	39	5.32	143	5.84	-0.02
Number of non-duloxetine generics dispensed=0	48	6.55	40	1.66	0.25
Number of non-duloxetine generics dispensed: tertile 1 for number >0	70	9.55	243	9.96	-0.01
Number of non-duloxetine generics dispensed: tertile 2 for number >0	68	9.28	288	11.79	-0.08
Number of non-duloxetine generics dispensed: tertile 3 for number >0	547	74.62	1,869	76.59	-0.05
Number of hospital admissions=0	683	93.18	2,269	93.01	0.01
Number of hospital admissions=1	41	5.59	144	5.9	-0.01
Number of hospital admissions=2	<11	0.68	21	0.84	-0.02
Number of hospital admissions>2	<11	0.55	<11	0.25	0.05
Number of outpatient visits=0	<11	0.41	20	0.83	-0.05
Number of outpatient visits: tertile 1 for number >0	102	13.92	370	15.15	-0.04
Number of outpatient visits: tertile 2 for number >0	166	22.65	653	26.76	-0.10
Number of outpatient visits: tertile 3 for number >0	462	63.03	1,397	57.25	0.12
Number of psychiatric hospitalizations Q1	712	97.14	2,353	96.44	0.04
Number of psychiatric hospitalizations Q2	18	2.46	75	3.06	-0.04
Number of psychiatric hospitalizations Q3	<11	0.41	12	0.5	-0.01
Number of psychiatric hospitalizations Q4	0	0	0	0	.
Number of psychiatrist visits=0	371	50.61	1,231	50.43	0.00
Number of psychiatrist visits=1	152	20.74	452	18.54	0.06
Number of psychiatrist visits=2	53	7.23	222	9.12	-0.07
Number of psychiatrist visits>2	157	21.42	535	21.91	-0.01
Geographic region					.

	Duloxetine N/Mean	Duloxetine %/SD	Venlafaxine N/Mean	Venlafaxine %/SD	Standardized Difference
Arkansas	PPD		PPD		0.05
Alabama					0.09
California	34	4.64	107	4.39	0.01
Colorado	PPD		17	0.69	-0.06
District of Columbia	0	0	PPD		-0.03
Delaware	PPD		18	0.74	0.06
Florida			61	2.49	-0.13
Georgia			59	2.41	-0.17
Hawaii	0	0	PPD		-0.04
Iowa	PPD		47	1.94	-0.08
Idaho			17	0.7	-0.09
Illinois	50	6.82	153	6.29	0.02
Indiana	61	8.32	101	4.14	0.17
Kansas	15	2.05	35	1.44	0.05
Kentucky	17	2.32	43	1.76	0.04
Louisiana	13	1.77	28	1.14	0.05
Massachusetts	PPD		PPD		0.02
Maryland	19	2.59	48	1.96	0.04
Maine	PPD		21	0.85	0.06
Minnesota	76	10.37	243	9.94	0.01
Missouri	32	4.37	89	3.64	0.04
Mississippi	0	0	22	0.91	-0.14
North Carolina	15	2.05	21	0.86	0.10
North Dakota	PPD		25	1.04	0.02
Nebraska	14	1.91	24	0.98	0.08
New Hampshire	PPD		31	1.29	-0.03
New Jersey			PPD		-0.02
New Mexico			16	0.65	-0.01
Nevada	0	0	PPD		-0.05
New York	84	11.46	219	8.96	0.08
Ohio	PPD		88	3.62	-0.16
Oklahoma	17	2.32	47	1.92	0.03

	Duloxetine	Duloxetine	Venlafaxine	Venlafaxine	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Oregon	37	5.05	113	4.64	0.02
Pennsylvania	PPD		99	4.04	-0.26
Rhode Island	0	0	PPD		-0.08
South Carolina	PPD				0.05
South Dakota			16	0.66	-0.02
Tennessee	32	4.37	145	5.95	-0.07
Texas	PPD		PPD		-0.02
Utah	42	5.73	68	2.77	0.15
Virginia	28	3.82	73	2.98	0.05
Vermont	PPD		24	0.98	0.02
Washington			PPD		0.00
Wisconsin	33	4.5	244	9.99	-0.21
West Virginia	PPD		16	0.65	0.05
Wyoming			PPD		-0.02
Opioids					.
buprenorphine	25	3.41	36	1.48	0.12
butorphanol	0	0	<11	0.16	-0.06
codeine	94	12.82	362	14.84	-0.06
fentanyl	12	1.64	12	0.48	0.11
hydrocodone	200	27.29	520	21.3	0.14
hydromorphone	<11	0.82	<11	0.38	0.06
levorphanol	0	0	<11	0	.
meperidine	<11	0.41	<11	0.25	0.03
methadone	12	1.64	23	0.95	0.06
morphine	13	1.77	18	0.74	0.09
oxycodone	107	14.6	206	8.45	0.19
oxymorphone	0	0	<11	0.07	-0.04
pentazocine	<11	0.14	<11	0	0.05
propoxyphene	20	2.73	95	3.88	-0.06
tapentadol	<11	0	<11	0	.
tramadol	32	4.37	71	2.93	0.08
Healthcare Utilization, mean (SD)					.

	Duloxetine	Duloxetine	Venlafaxine	Venlafaxine	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Comorbidity Index	28.44	5.29	27.46	5.39	0.11
Morphine equivalents	1.77	1.93	1.566	1.89	0.15
Number of diagnoses	1121.27	6206.96	414.85	2964.26	0.09
Number of ED visits	8.13	4.47	7.715	4.4	-0.04
Number of non-duloxetine generics dispensed	0.54	1.44	0.588	1.49	0.03
Number of hospitalizations	5.25	3.96	5.15	3.62	0.00
Number of outpatient visits	0.09	0.35	0.084	0.34	0.15
Number of psychiatric hospitalizations	9.89	9.2	8.661	6.57	-0.04
Number of psychiatrist visits	0.03	0.2	0.041	0.22	0.03

15.4. 7. Postpartum Haemorrhage- Baseline characteristics of duloxetine exposed vs. unexposed women: fully adjusted

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Total	737	.	827,474	.	.
Demographics					
Age, mean (SD)	28.42	5.30	28.36	5.38	0.01
Age categorical, N (%)	.	.	.	.	.
<=19	27	3.66	26,780	3.24	0.02
20-24	151	20.49	163,196	19.72	0.02
25-29	274	37.18	314,832	38.05	-0.02
30-34	172	23.34	195,554	23.63	-0.01
35-39	97	13.16	108,732	13.14	0.00
>=40	16	2.17	18,381	2.22	0.00
Race, N (%)					
White	626	84.94	710,680	85.89	-0.03
Black or African American	41	5.56	41,388	5	0.03
Hispanic or Latino			8,124	0.98	0.02
Asian or Other Pacific Islander			13,306	1.61	0.00
American Indian	15	2.04	16,771	2.03	0.00
Other	16	2.17	16,812	2.03	0.01
Unknown	18	2.44	20,393	2.46	0.00
Chronic comorbid conditions, N (%)	.	.	.	.	.
Hypertension	110	14.93	123,940	14.98	0.00
Diabetes	141	19.13	159,283	19.25	0.00
Renal Disease	<11	0.95	7,840	0.95	0.00
Obesity Overweight	54	7.33	60,584	7.32	0.00
Comorbidity Index Q1	231	31.34	255,396	30.86	0.01
Comorbidity Index Q2	163	22.12	186,592	22.55	-0.01
Comorbidity Index Q3	140	19	159,747	19.31	-0.01
Comorbidity Index Q4	203	27.54	225,739	27.28	0.01
Indications for duloxetine, N (%)	.	.	.	.	.
Depression	300	40.71	346,340	41.86	-0.02
Anxiety	175	23.74	196,057	23.69	0.00
Neuropathic Pain	45	6.11	49,881	6.03	0.00

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Fibromyalgia	43	5.83	43,762	5.29	0.02
Non neuropathic Pain	270	36.64	292,689	35.37	0.03
Other psychiatric conditions, N (%)	.	.	.	.	.
Sleep disorder	20	2.71	20,526	2.48	0.01
Bipolar disorder	71	9.63	76,431	9.24	0.01
Psychosis	<11	0.81	6,188	0.75	0.01
Schizophrenia	<11	0.68	5,580	0.67	0.00
Personality disorder	14	1.9	14,134	1.71	0.01
Adjustment disorder	<11	0.41	3,444	0.42	0.00
Tobacco use, N (%)	106	14.38	118,135	14.28	0.00
Alcohol abuse or dependence, N (%)	0	0	<11	0	.
Drug abuse or dependence, N (%)	14	1.9	16,478	1.99	-0.01
Other medication exposures, N (%)	.	.	.	.	.
Benzodiazepines	165	22.39	177,119	21.4	0.02
Other hypnotics	186	25.24	207,710	25.1	0.00
Barbiturates	30	4.07	33,461	4.04	0.00
Anxiolytics	44	5.97	44,542	5.38	0.03
Anticonvulsants	92	12.48	91,417	11.05	0.04
Antipsychotics	91	12.35	91,793	11.09	0.04
SSRIs	69	9.36	80,354	9.71	-0.01
SNRIs	<11	0.81	7,030	0.85	0.00
Other Antidep	110	14.93	119,826	14.48	0.01
Stimulants	31	4.21	32,937	3.98	0.01
Antidiabetic	30	4.07	33,634	4.06	0.00
Insulin	46	6.24	52,815	6.38	-0.01
Antihyperten	126	17.1	140,712	17	0.00
Opioid analgesics	352	47.76	395,515	47.8	0.00
Triptans	17	2.31	16,476	1.99	0.02
NSAIDs	47	6.38	51,415	6.21	0.01
Obstetric conditions, N (%)	.	.	.	.	.
Multifetal gestation Flag	29	3.93	32,636	3.94	0.00
Markers of healthcare utilization	.	.	.	.	.

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Number of distinct 3 digit ICD 9 codes=0	<11	0.41	3,311	0.4	0.00
Number of distinct 3 digit ICD 9 codes: tertile 1 for number >0	45	6.11	49,250	5.95	0.01
Number of distinct 3 digit ICD 9 codes: tertile 2 for number >0	182	24.69	203,966	24.65	0.00
Number of distinct 3 digit ICD 9 codes: tertile 3 for number >0	507	68.79	570,947	69	0.00
Number of ED visits=0	528	71.64	594,881	71.89	-0.01
Number of ED visits=1	142	19.27	158,563	19.16	0.00
Number of ED visits=2	28	3.8	30,216	3.65	0.01
Number of ED visits>2	39	5.29	43,814	5.29	0.00
Number of non-duloxetine generics dispensed=0	48	6.51	48,805	5.9	0.03
Number of non-duloxetine generics dispensed: tertile 1 for number >0	70	9.5	75,188	9.09	0.01
Number of non-duloxetine generics dispensed: tertile 2 for number >0	69	9.36	75,746	9.15	0.01
Number of non-duloxetine generics dispensed: tertile 3 for number >0	550	74.63	627,736	75.86	-0.03
Number of hospital admissions=0	686	93.08	771,218	93.2	0.00
Number of hospital admissions=1	42	5.7	46,096	5.57	0.01
Number of hospital admissions=2	<11	0.68	5,757	0.7	0.00
Number of hospital admissions>2	<11	0.54	4,403	0.53	0.00
Number of outpatient visits=0	<11	0.41	3,031	0.37	0.01
Number of outpatient visits: tertile 1 for number >0	103	13.98	113,526	13.72	0.01
Number of outpatient visits: tertile 2 for number >0	166	22.52	185,392	22.4	0.00
Number of outpatient visits: tertile 3 for number >0	465	63.09	525,526	63.51	-0.01
Number of psychiatric hospitalizations Q1	716	97.15	804,383	97.21	0.00
Number of psychiatric hospitalizations Q2	18	2.44	19,769	2.39	0.00
Number of psychiatric hospitalizations Q3	<11	0.41	3,322	0.4	0.00
Number of psychiatric hospitalizations Q4	0	0	0	0	.
Number of psychiatrist visits=0	372	50.47	409,133	49.44	0.02
Number of psychiatrist visits=1	154	20.9	179,695	21.72	-0.02
Number of psychiatrist visits=2	54	7.33	62,513	7.55	-0.01
Number of psychiatrist visits>2	157	21.3	176,133	21.29	0.00
Geographic region	.	.	.	.	.

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Arkansas	PPD		5,492	0.66	0.00
Alabama	PPD		7,253	0.88	-0.01
California	34	4.61	36,180	4.37	0.01
Colorado	PPD		2,199	0.27	0.00
District of Columbia	0	0	0	0	.
Delaware	PPD		11,014	1.33	0.00
Florida	PPD		6,091	0.74	0.01
Georgia	PPD		2,898	0.35	0.01
Hawaii	0	0	0	0	.
Iowa	PPD		7,580	0.92	0.00
Idaho	PPD		1,154	0.14	0.00
Illinois	50	6.78	56,225	6.79	0.00
Indiana	61	8.28	67,775	8.19	0.00
Kansas	15	2.04	17,002	2.05	0.00
Kentucky	19	2.58	20,825	2.52	0.00
Louisiana	13	1.76	14,565	1.76	0.00
Massachusetts	PPD		3,393	0.41	0.00
Maryland	19	2.58	21,442	2.59	0.00
Maine	PPD		12,128	1.47	0.00
Minnesota	76	10.31	86,356	10.44	0.00
Missouri	32	4.34	37,370	4.52	-0.01
Mississippi	0	0	0	0	.
North Carolina	15	2.04	16,259	1.96	0.01
North Dakota	PPD		10,900	1.32	-0.01
Nebraska	14	1.9	16,521	2	-0.01
New Hampshire	PPD		7,972	0.96	0.00
New Jersey	PPD		998	0.12	0.00
New Mexico	PPD		4,432	0.54	0.00
Nevada	0	0	0	0	0.00
New York	84	11.4	93,935	11.35	0.00
Ohio	PPD		11,733	1.42	0.01
Oklahoma	17	2.31	19,053	2.3	0.00

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Oregon	37	5.02	41,964	5.07	0.00
Pennsylvania	PPD		1,912	0.23	0.01
Rhode Island	0	0	0	0	.
South Carolina	PPD		2,354	0.28	0.00
South Dakota			4,645	0.56	0.00
Tennessee	32	4.34	35,475	4.29	0.00
Texas	PPD		1,095	0.13	0.00
Utah	42	5.7	47,934	5.79	0.00
Virginia	28	3.8	31,006	3.75	0.00
Vermont	PPD		10,859	1.31	-0.01
Washington			2,353	0.28	0.00
Wisconsin	33	4.48	38,023	4.6	-0.01
West Virginia	PPD		8,812	1.06	0.00
Wyoming			2,296	0.28	0.00
Opioids	.	.	.	.	.
buprenorphine	25	3.39	27,721	3.35	0.00
butorphanol	0	0	0	0	0.00
codeine	95	12.89	106,998	12.93	0.00
fentanyl	11	1.49	9,370	1.13	0.03
hydrocodone	203	27.54	228,834	27.65	0.00
hydromorphone	<11	0.81	5,676	0.69	0.01
levorphanol	0	0	0	0	.
meperidine	<11	0.41	3,365	0.41	0.00
methadone	12	1.63	13,336	1.61	0.00
morphine	13	1.76	11,730	1.42	0.03
oxycodone	106	14.38	115,223	13.92	0.01
oxymorphone	0	0	0	0	0.00
pentazocine	<11	0.14	816	0.1	0.01
propoxyphene	20	2.71	22,777	2.75	0.00
tapentadol	0	0	0	0	.
tramadol	33	4.48	35,651	4.31	0.01
Healthcare Utilization, mean (SD)					

	Duloxetine	Duloxetine	Unexposed	Unexposed	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Comorbidity Index	1.77	1.92	1.79	1.93	-0.01
Morphine equivalents	8.14	4.48	8.26	4.84	-0.03
Number of diagnoses	0.53	1.44	0.53	1.46	0.00
Number of ED visits	5.26	4.00	5.04	3.75	0.06
Number of non-duloxetine generics dispensed	0.09	0.35	0.09	0.39	-0.01
Number of hospitalizations	9.85	9.13	9.57	7.25	0.03
Number of outpatient visits	0.03	0.20	0.03	0.20	0.00
Number of psychiatric hospitalizations	2.23	7.09	1.94	4.44	0.05

15.4. 8. Postpartum Haemorrhage- Baseline characteristics of duloxetine exposed vs. SSRI exposed women: fully adjusted

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Total	668	.	37,266	.	.
Demographics					
Age, mean (SD)	28.42	5.30	28.36	5.38	0.01
Age categorical, N (%)	.	.	.	.	.
<=19	24	3.59	1,276	3.42	0.01
20-24	138	20.66	7,483	20.08	0.01
25-29	243	36.38	13,638	36.6	0.00
30-34	160	23.95	9,058	24.31	-0.01
35-39	87	13.02	4,930	13.23	-0.01
>=40	16	2.4	880	2.36	0.00
Race, N (%)					
White	569	85.18	31,804	85.34	0.00
Black or African American	37	5.54	2,083	5.59	0.00
Hispanic or Latino	PPD		438	1.18	0.02
Asian or Other Pacific Islander			596	1.6	0.00
American Indian	13	1.95	743	1.99	0.00
Other	PPD		667	1.79	0.00
Unknown	17	2.54	934	2.51	0.00
Chronic comorbid conditions, N (%)	.	.	.	.	.
Hypertension	104	15.57	5,851	15.7	0.00
Diabetes	126	18.86	7,003	18.79	0.00
Renal Disease	<11	0.9	323	0.87	0.00
Obesity Overweight	52	7.78	2,801	7.52	0.01
Comorbidity Index Q1	210	31.44	11,705	31.41	0.00
Comorbidity Index Q2	148	22.16	8,354	22.42	-0.01
Comorbidity Index Q3	124	18.56	6,939	18.62	0.00
Comorbidity Index Q4	186	27.84	10,268	27.55	0.01
Indications for duloxetine, N (%)	.	.	.	.	.
Depression	271	40.57	15,244	40.9	-0.01
Anxiety	156	23.35	8,803	23.62	-0.01

	Duloxetine N/Mean	Duloxetine %/SD	SSRI N/Mean	SSRI %/SD	Standardized Difference
Neuropathic Pain	33	4.94	1,864	5	0.00
Fibromyalgia	38	5.69	1,933	5.19	0.02
Non neuropathic Pain	242	36.23	13,297	35.68	0.01
Other psychiatric conditions, N (%)	.	.	.	.	.
Sleep disorder	16	2.4	846	2.27	0.01
Bipolar disorder	59	8.83	3,180	8.53	0.01
Psychosis	<11	0.9	351	0.94	0.00
Schizophrenia	<11	0.75	293	0.79	0.00
Personality disorder	11	1.65	589	1.58	0.01
Adjustment disorder	<11	0.45	153	0.41	0.01
Tobacco use, N (%)	96	14.37	5,377	14.43	0.00
Alcohol abuse or dependence, N (%)	0	0	<11	0	.
Drug abuse or dependence, N (%)	<11	1.5	530	1.42	0.01
Other medication exposures, N (%)	.	.	.	.	.
Benzodiazepines	143	21.41	7,933	21.29	0.00
Other hypnotics	164	24.55	9,233	24.78	-0.01
Barbiturates	28	4.19	1,523	4.09	0.01
Anxiolytics	38	5.69	2,182	5.85	-0.01
Anticonvulsants	81	12.13	4,380	11.75	0.01
Antipsychotics	82	12.28	4,546	12.2	0.00
SSRIs	0	0	37,266	100	.
SNRIs	<11	0.9	327	0.88	0.00
Other Antidep	98	14.67	5,481	14.71	0.00
Stimulants	25	3.74	1,378	3.7	0.00
Antidiabetic	29	4.34	1,513	4.06	0.01
Insulin	42	6.29	2,344	6.29	0.00
Antihyperten	118	17.66	6,665	17.89	-0.01
Opioid analgesics	319	47.75	17,775	47.7	0.00
Triptans	15	2.25	812	2.18	0.00
NSAIDs	42	6.29	2,197	5.89	0.02
Obstetric conditions, N (%)	.	.	.	.	.
Multifetal gestation Flag	28	4.19	1,565	4.2	0.00

	Duloxetine N/Mean	Duloxetine %/SD	SSRI N/Mean	SSRI %/SD	Standardized Difference
Markers of healthcare utilization	.	.	.	.	.
Number of distinct 3 digit ICD 9 codes=0	<11	0.45	167	0.45	0.00
Number of distinct 3 digit ICD 9 codes: tertile 1 for number >0	40	5.99	2,215	5.94	0.00
Number of distinct 3 digit ICD 9 codes: tertile 2 for number >0	165	24.7	9,205	24.7	0.00
Number of distinct 3 digit ICD 9 codes: tertile 3 for number >0	460	68.86	25,679	68.91	0.00
Number of ED visits=0	483	72.31	27,017	72.5	0.00
Number of ED visits=1	128	19.16	7,038	18.89	0.01
Number of ED visits=2	25	3.74	1,442	3.87	-0.01
Number of ED visits>2	32	4.79	1,769	4.75	0.00
Number of non-duloxetine generics dispensed=0	46	6.89	2,740	7.35	-0.02
Number of non-duloxetine generics dispensed: tertile 1 for number >0	64	9.58	3,539	9.5	0.00
Number of non-duloxetine generics dispensed: tertile 2 for number >0	66	9.88	3,588	9.63	0.01
Number of non-duloxetine generics dispensed: tertile 3 for number >0	492	73.65	27,399	73.52	0.00
Number of hospital admissions=0	619	92.66	34,475	92.51	0.01
Number of hospital admissions=1	40	5.99	2,327	6.24	-0.01
Number of hospital admissions=2	<11	0.75	287	0.77	0.00
Number of hospital admissions>2	<11	0.6	177	0.47	0.02
Number of outpatient visits=0	<11	0.45	168	0.45	0.00
Number of outpatient visits: tertile 1 for number >0	92	13.77	5,193	13.93	0.00
Number of outpatient visits: tertile 2 for number >0	153	22.9	8,470	22.73	0.00
Number of outpatient visits: tertile 3 for number >0	420	62.87	23,435	62.89	0.00
Number of psychiatric hospitalizations Q1	648	97.01	36,135	96.97	0.00
Number of psychiatric hospitalizations Q2	17	2.54	961	2.58	0.00
Number of psychiatric hospitalizations Q3	<11	0.45	170	0.46	0.00
Number of psychiatric hospitalizations Q4	0	0	0	0	.
Number of psychiatrist visits=0	340	50.9	18,944	50.83	0.00
Number of psychiatrist visits=1	138	20.66	7,816	20.97	-0.01
Number of psychiatrist visits=2	53	7.93	2,916	7.83	0.00
Number of psychiatrist visits>2	137	20.51	7,590	20.37	0.00
Geographic region	.	.	.	.	.
Arkansas	PPD		247	0.66	0.01
Alabama			314	0.84	-0.01

	Duloxetine N/Mean	Duloxetine %/SD	SSRI N/Mean	SSRI %/SD	Standardized Difference
California	34	5.09	1,857	4.98	0.00
Colorado	PPD		107	0.29	0.00
District of Columbia	0	0	0	0	.
Delaware	PPD		476	1.28	0.01
Florida	PPD		278	0.75	0.00
Georgia	PPD		166	0.44	0.00
Hawaii	0	0	0	0	.
Iowa	PPD		333	0.89	0.00
Idaho	0	0	0	0	.
Illinois	47	7.04	2,624	7.04	0.00
Indiana	56	8.38	3,117	8.36	0.00
Kansas	PPD		671	1.8	0.00
Kentucky	18	2.69	973	2.61	0.01
Louisiana	PPD		660	1.77	-0.01
Massachusetts	PPD		161	0.43	0.00
Maryland	16	2.4	895	2.4	0.00
Maine	PPD		628	1.68	0.00
Minnesota	70	10.48	3,901	10.47	0.00
Missouri	31	4.64	1,793	4.81	-0.01
Mississippi	0	0	0	0	.
North Carolina	15	2.25	816	2.19	0.00
North Dakota	PPD		473	1.27	-0.01
Nebraska	PPD		650	1.74	0.00
New Hampshire	PPD		371	1	0.01
New Jersey	0	0	0	0	.
New Mexico	PPD		228	0.61	0.00
Nevada	0	0	0	0	.
New York	79	11.83	4,524	12.14	-0.01
Ohio	PPD		530	1.42	0.01
Oklahoma	15	2.25	807	2.16	0.01
Oregon	32	4.79	1,806	4.85	0.00
Pennsylvania	PPD		43	0.12	0.01

	Duloxetine N/Mean	Duloxetine %/SD	SSRI N/Mean	SSRI %/SD	Standardized Difference
Rhode Island	0	0	0	0	.
South Carolina	PPD		113	0.3	0.00
South Dakota			226	0.61	0.00
Tennessee	30	4.49	1,619	4.34	0.01
Texas	PPD		51	0.14	0.00
Utah	32	4.79	1,866	5.01	-0.01
Virginia	25	3.74	1,383	3.71	0.00
Vermont	PPD		495	1.33	0.00
Washington			117	0.31	0.00
Wisconsin	28	4.19	1,492	4	0.01
West Virginia	PPD		400	1.07	0.00
Wyoming			59	0.16	0.00
Opioids	.	.	.	.	.
buprenorphine	22	3.29	1,110	2.98	0.02
butorphanol	0	0	0	0	.
codeine	83	12.43	4,775	12.81	-0.01
fentanyl	<11	1.5	358	0.96	0.05
hydrocodone	183	27.4	10,233	27.46	0.00
hydromorphone	<11	0.75	278	0.75	0.00
levorphanol	0	0	0	0	.
meperidine	<11	0.45	154	0.41	0.01
methadone	12	1.8	640	1.72	0.01
morphine	<11	1.5	478	1.28	0.02
oxycodone	95	14.22	5,265	14.13	0.00
oxymorphone	0	0	0	0	.
pentazocine	<11	0.15	34	0.09	0.02
propoxyphene	17	2.54	918	2.46	0.01
tapentadol	<11	0	<11	0	.
tramadol	31	4.64	1,714	4.6	0.00
Healthcare Utilization, mean (SD)					
Comorbidity Index	1.77	1.92	1.81	2.00	-0.02
Morphine equivalents	8.11	4.51	8.11	4.67	0.00

	Duloxetine	Duloxetine	SSRI	SSRI	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Number of diagnoses	0.51	1.43	0.50	1.59	0.00
Number of ED visits	5.15	3.92	5.62	4.34	-0.11
Number of non-duloxetine generics dispensed	0.09	0.37	0.09	0.38	0.00
Number of hospitalizations	9.76	9.12	9.35	7.11	0.05
Number of outpatient visits	0.03	0.21	0.03	0.21	0.00
Number of psychiatric hospitalizations	2.16	7.11	1.86	4.34	0.05

15.4. 9. Postpartum Haemorrhage- Baseline characteristics of duloxetine exposed vs. venlafaxine exposed women: fully adjusted

	Duloxetine N/Mean	Duloxetine %/SD	Venlafaxine N/Mean	Venlafaxine %/SD	Standardized Difference
Total	727	.	2,276	.	.
Demographics					
Age, mean (SD)	28.41	28.43	5.27	28.27	0.00
Age categorical, N (%)	.	.	.	.	.
<=19	27	3.71	80	3.5	0.01
20-24	148	20.36	468	20.58	-0.01
25-29	271	37.28	852	37.44	0.00
30-34	170	23.38	530	23.28	0.00
35-39	96	13.2	297	13.05	0.00
>=40	15	2.06	49	2.15	-0.01
Race, N (%)					
White	618	85.01	1,935	85.01	0.00
Black or African American	40	5.5	138	6.08	-0.02
Hispanic or Latino			18	0.81	0.04
Asian or Other Pacific Islander			36	1.58	-0.01
American Indian	15	2.06	51	2.25	-0.01
Other	16	2.2	51	2.23	0.00
Unknown	18	2.48	47	2.06	0.03
Chronic comorbid conditions, N (%)	.	.	.	.	.
Hypertension	108	14.86	336	14.76	0.00
Diabetes	138	18.98	421	18.48	0.01
Renal Disease	<11	0.83	22	0.95	-0.01
Obesity Overweight	52	7.15	148	6.5	0.03
Comorbidity Index Q1	231	31.77	747	32.83	-0.02
Comorbidity Index Q2	162	22.28	519	22.81	-0.01
Comorbidity Index Q3	135	18.57	420	18.44	0.00
Comorbidity Index Q4	199	27.37	590	25.91	0.03
Indications for duloxetine, N (%)	.	.	.	.	.
Depression	297	40.85	935	41.08	0.00
Anxiety	171	23.52	556	24.42	-0.02
Neuropathic Pain	44	6.05	127	5.6	0.02

	Duloxetine N/Mean	Duloxetine %/SD	Venlafaxine N/Mean	Venlafaxine %/SD	Standardized Difference
Fibromyalgia	40	5.5	123	5.41	0.00
Non neuropathic Pain	263	36.18	805	35.37	0.02
Other psychiatric conditions, N (%)	.	.	.	.	.
Sleep disorder	20	2.75	74	3.26	-0.03
Bipolar disorder	68	9.35	207	9.08	0.01
Psychosis	<11	0.83	17	0.73	0.01
Schizophrenia	<11	0.69	15	0.67	0.00
Personality disorder	14	1.93	35	1.52	0.03
Adjustment disorder	<11	0.41	<11	0.28	0.02
Tobacco use, N (%)	105	14.44	341	14.98	-0.02
Alcohol abuse or dependence, N (%)	0	0	0	0	.
Drug abuse or dependence, N (%)	14	1.93	55	2.4	-0.03
Other medication exposures, N (%)	.	.	.	.	.
Benzodiazepines	159	21.87	532	23.36	-0.04
Other hypnotics	183	25.17	574	25.21	0.00
Barbiturates	28	3.85	112	4.94	-0.05
Anxiolytics	43	5.91	121	5.33	0.03
Anticonvulsants	90	12.38	270	11.85	0.02
Antipsychotics	89	12.24	283	12.45	-0.01
SSRIs	68	9.35	236	10.38	-0.03
SNRIs	<11	0	2,276	100	.
Other Antidep	107	14.72	370	16.25	-0.04
Stimulants	31	4.26	106	4.68	-0.02
Antidiabetic	29	3.99	83	3.66	0.02
Insulin	46	6.33	147	6.46	-0.01
Antihyperten	122	16.78	401	17.62	-0.02
Opioid analgesics	343	47.18	1,071	47.06	0.00
Triptans	16	2.2	51	2.26	0.00
NSAIDs	44	6.05	147	6.47	-0.02
Obstetric conditions, N (%)	.	.	.	.	.
Multifetal gestation Flag	29	3.99	112	4.9	-0.04
Markers of healthcare utilization	.	.	.	.	.

	Duloxetine N/Mean	Duloxetine %/SD	Venlafaxine N/Mean	Venlafaxine %/SD	Standardized Difference
Number of distinct 3 digit ICD 9 codes=0	<11	0.41	<11	0.27	0.03
Number of distinct 3 digit ICD 9 codes: tertile 1 for number >0	45	6.19	147	6.45	-0.01
Number of distinct 3 digit ICD 9 codes: tertile 2 for number >0	181	24.9	544	23.89	0.02
Number of distinct 3 digit ICD 9 codes: tertile 3 for number >0	498	68.5	1,579	69.39	-0.02
Number of ED visits=0	520	71.53	1,646	72.3	-0.02
Number of ED visits=1	140	19.26	420	18.46	0.02
Number of ED visits=2	28	3.85	84	3.7	0.01
Number of ED visits>2	39	5.36	126	5.54	-0.01
Number of non-duloxetine generics dispensed=0	48	6.6	159	6.96	-0.01
Number of non-duloxetine generics dispensed: tertile 1 for number >0	70	9.63	210	9.23	0.01
Number of non-duloxetine generics dispensed: tertile 2 for number >0	68	9.35	190	8.33	0.04
Number of non-duloxetine generics dispensed: tertile 3 for number >0	541	74.42	1,718	75.47	-0.02
Number of hospital admissions=0	677	93.12	2,118	93.04	0.00
Number of hospital admissions=1	41	5.64	137	6.02	-0.02
Number of hospital admissions=2	<11	0.69	13	0.58	0.01
Number of hospital admissions>2	<11	0.55	<11	0.36	0.03
Number of outpatient visits=0	<11	0.41	<11	0.37	0.01
Number of outpatient visits: tertile 1 for number >0	102	14.03	312	13.69	0.01
Number of outpatient visits: tertile 2 for number >0	166	22.83	490	21.53	0.03
Number of outpatient visits: tertile 3 for number >0	456	62.72	1,466	64.41	-0.03
Number of psychiatric hospitalizations Q1	706	97.11	2,210	97.12	0.00
Number of psychiatric hospitalizations Q2	18	2.48	60	2.65	-0.01
Number of psychiatric hospitalizations Q3	<11	0.41	<11	0.23	0.03
Number of psychiatric hospitalizations Q4	<11	0	<11	0	.
Number of psychiatrist visits=0	369	50.76	1,145	50.29	0.01
Number of psychiatrist visits=1	152	20.91	477	20.96	0.00
Number of psychiatrist visits=2	53	7.29	173	7.61	-0.01
Number of psychiatrist visits>2	153	21.05	481	21.14	0.00
Geographic region	.	.	.	.	.

	Duloxetine N/Mean	Duloxetine %/SD	Venlafaxine N/Mean	Venlafaxine %/SD	Standardized Difference
Arkansas	PPD		13	0.55	0.00
Alabama			20	0.89	-0.01
California	34	4.68	102	4.46	0.01
Colorado	PPD		PPD		-0.01
District of Columbia					.
Delaware			30	1.3	0.01
Florida			20	0.88	-0.01
Georgia			PPD		-0.01
Hawaii					.
Iowa			22	0.97	0.00
Idaho			PPD		0.00
Illinois	49	6.74	154	6.79	0.00
Indiana	61	8.39	192	8.44	0.00
Kansas	15	2.06	42	1.83	0.02
Kentucky	17	2.34	51	2.26	0.01
Louisiana	13	1.79	44	1.91	-0.01
Massachusetts	PPD		PPD		0.00
Maryland	19	2.61	46	2	0.04
Maine	PPD		33	1.46	0.00
Minnesota	76	10.45	223	9.81	0.02
Missouri	32	4.4	96	4.23	0.01
Mississippi	PPD		PPD		.
North Carolina	14	1.93	46	2.01	-0.01
North Dakota	PPD		29	1.27	0.00
Nebraska	14	1.93	38	1.66	0.02
New Hampshire			21	0.94	0.00
New Jersey	PPD		PPD		0.00
New Mexico					0.02
Nevada					.
New York	84	11.55	274	12.04	-0.02
Ohio	PPD		32	1.43	-0.02
Oklahoma	17	2.34	50	2.2	0.01

	Duloxetine N/Mean	Duloxetine %/SD	Venlafaxine N/Mean	Venlafaxine %/SD	Standardized Difference
Oregon	37	5.09	106	4.64	0.02
Pennsylvania	PPD		PPD		0.00
Rhode Island					.
South Carolina					-0.02
South Dakota					-0.01
Tennessee	32	4.4	115	5.06	-0.03
Texas	PPD		PPD		0.01
Utah	39	5.36	139	6.09	-0.03
Virginia	28	3.85	89	3.89	0.00
Vermont	PPD		31	1.37	-0.01
Washington			PPD		-0.02
Wisconsin	33	4.54	102	4.49	0.00
West Virginia	PPD		26	1.13	0.00
Wyoming			PPD		0.00
Opioids	.	.	.	.	.
buprenorphine	24	3.3	69	3.04	0.01
butorphanol	<11	0	<11	0	.
codeine	94	12.93	310	13.6	-0.02
fentanyl	<11	1.38	24	1.05	0.03
hydrocodone	197	27.1	619	27.18	0.00
hydromorphone	<11	0.83	16	0.72	0.01
levorphanol	<11	0	<11	0	.
meperidine	<11	0.41	12	0.51	-0.01
methadone	12	1.65	48	2.09	-0.03
morphine	12	1.65	29	1.28	0.03
oxycodone	103	14.17	314	13.79	0.01
oxymorphone	<11	0	<11	0	.
pentazocine	<11	0	<11	0	.
propoxyphene	20	2.75	64	2.81	0.00
tapentadol	<11	0	<11	0	.
tramadol	32	4.4	111	4.88	-0.02
Healthcare Utilization, mean (SD)					

	Duloxetine	Duloxetine	Venlafaxine	Venlafaxine	
	N/Mean	%/SD	N/Mean	%/SD	Standardized Difference
Comorbidity Index	1.76	1.78	1.93	2.01	-0.01
Morphine equivalents	8.09	8.17	4.46	4.47	-0.02
Number of diagnoses	0.54	0.53	1.45	1.36	0.01
Number of ED visits	5.19	5.84	3.89	4.41	-0.16
Number of non-duloxetine generics dispensed	0.09	0.09	0.35	0.43	-0.01
Number of hospitalizations	9.82	9.58	9.17	7.58	0.03
Number of outpatient visits	0.03	0.03	0.2	0.19	0.01
Number of psychiatric hospitalizations	2.22	2.24	7.13	5.66	0.00

15.4. 10. Postpartum Haemorrhage- Absolute risks

Reference group	Exposed					Reference				
	Events	N	Risk (/1,000)	95% CI		Events	N	Risk (/1,000)	95% CI	
				lower	upper				lower	upper
Unexposed	34	955	35.6	24.8	49.4	95,988	4,128,460	23.3	23.1	23.4
SSRI	33	869	38.0	26.3	52.9	1,879	65,303	28.8	27.5	30.1
Venlafaxine	34	948	35.9	25.0	49.8	135	3,573	37.8	31.8	44.6

15.4. 11. Postpartum Haemorrhage- Relative risks for duloxetine exposed vs. unexposed women

Level of adjustment	Exposed		Reference		RR	95% CI lower	95% CI upper
	Events	N	Events	N			
Unadjusted	34	955	95,988	4,128,460	1.53	1.10	2.13
Restricted + PS1 (Indications)	30	739	24,415	969,868	1.55	1.09	2.20
Retricted + PS2 (All covariates)	30	737	21,452	827,474	1.53	1.08	2.18
Restricted + hdPS	30	738	21,026	815,386	1.48	1.04	2.10

15.4. 12. Postpartum Haemorrhage- Relative risks for duloxetine exposed vs. SSRI exposed women

Level of adjustment	Exposed		Reference		RR	95% CI lower	95% CI upper
	Events	N	Events	N			
Unadjusted	33	869	1,879	65,303	1.32	0.94	1.85
Restricted + PS1 (Indications)	29	670	1,222	40,430	1.42	0.99	2.03
Retricted + PS2 (All covariates)	29	668	1,135	37,266	1.48	1.03	2.12
Restricted + hdPS	29	663	1,222	40,430	1.31	0.91	1.87

15.4. 13. Postpartum Haemorrhage- Relative risks for duloxetine exposed vs. venlafaxine exposed women

Level of adjustment	Exposed		Reference		RR	95% CI lower	95% CI upper
	Events	N	Events	N			
Unadjusted	34	948	135	3,573	0.95	0.66	1.37
Restricted + PS1 (Indications)	30	733	94	2,440	1.11	0.74	1.66
Retricted + PS2 (All covariates)	29	727	86	2,276	1.04	0.69	1.56
Restricted + hdPS	29	680	82	2,201	0.98	0.65	1.47

15.4. 14. Postpartum Haemorrhage- Sensitivity Analyses #1: Re-define exposure as having filled ≥ 2 prescriptions

15.4. 14.1 Unadjusted

	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Duloxetine versus Unexposed							
Postpartum Haemorrhage	<11	119	95,988	4,128,460	1.45	0.55	3.79
Duloxetine versus SSRI							
Postpartum Haemorrhage	<11	106	135	3,987	1.11	0.42	2.96
Duloxetine versus Venlafaxine							
Postpartum Haemorrhage	<11	90	7,647	281,022	1.14	0.37	3.46

15.4.14.2 Adjusted: Restricted + PS1 (indications)

	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Duloxetine versus Unexposed							
Postpartum Haemorrhage	<11	92	24,415	969,868	1.21	0.40	3.68
Duloxetine versus SSRI							
Postpartum Haemorrhage	<11	80	91	2,692	1.12	0.36	3.46
Duloxetine versus Venlafaxine							
Postpartum Haemorrhage	<11	88	15	287	0.68	0.20	2.31

15.4.14.3 Adjusted: Restricted + PS2 (All covariates)

	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Duloxetine versus Unexposed							
Postpartum Haemorrhage	<11	90	7,647	281,022	1.14	0.37	3.46
Duloxetine versus SSRI							
Postpartum Haemorrhage	<11	74	91	2,690	1.51	0.49	4.68
Duloxetine versus Venlafaxine							
Postpartum Haemorrhage	<11	44	<11	102	0.73	0.08	6.70

15.4. 15. Postpartum Haemorrhage- Sensitivity Analyses #2: Re-define exposure as days supply overlap

15.4.15.1 Unadjusted

Unadjusted	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Duloxetine versus Unexposed							
Postpartum Haemorrhage	43	1,259	95,988	4,128,460	1.47	1.10	1.97
Duloxetine versus SSRI							
Postpartum Haemorrhage	42	1,173	1,879	65,303	1.24	0.92	1.68
Duloxetine versus Venlafaxine							
Postpartum Haemorrhage	43	1,252	135	3,573	0.91	0.65	1.27

15.4.15.2 Adjusted: Restricted + PS1 (indications)

	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Duloxetine versus Unexposed							
Postpartum Haemorrhage	38	980	24,415	969,868	1.47	1.08	2.01
Duloxetine versus SSRI							
Postpartum Haemorrhage	37	911	1,222	40,430	1.37	0.99	1.89
Duloxetine versus Venlafaxine							
Postpartum Haemorrhage	38	974	94	2,440	1.03	0.71	1.49

15.4.15.3 Adjusted: Restricted + PS2 (All covariates)

	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Duloxetine versus Unexposed							
Postpartum Haemorrhage	38	977	22,113	857,978	1.49	1.09	2.04
Duloxetine versus SSRI							
Postpartum Haemorrhage	37	909	1,222	40,420	1.34	0.98	1.85
Duloxetine versus Venlafaxine							
Postpartum Haemorrhage	38	968	90	2,400	1.05	0.72	1.52

15.4. 16. Postpartum Haemorrhage- Sensitivity Analyses #3: Restrict cohort to women with a recorded diagnosis of fibromyalgia

15.4.16.1 Unadjusted

	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Duloxetine versus Unexposed							
Postpartum Haemorrhage	<11	97	887	35,398	1.65	0.63	4.31
Duloxetine versus SSRI							
Postpartum Haemorrhage	<11	88	32	1,407	2.00	0.72	5.53
Duloxetine versus Venlafaxine							
Postpartum Haemorrhage	<11	95	<11	124	1.31	0.34	5.09

15.4.16.2 Adjusted : Restricted + PS1 (indications)

	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Duloxetine versus Unexposed							
Postpartum Haemorrhage	<11	97	887	35,398	1.54	0.59	4.03
Duloxetine versus SSRI							
Postpartum Haemorrhage	<11	88	31	1,394	1.65	0.60	4.52
Duloxetine versus Venlafaxine							
Postpartum Haemorrhage	<11	93	<11	124	2.00	0.43	9.19

15.4.16.3 Adjusted: Restricted + PS2 (All covariates)

	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Duloxetine versus Unexposed							
Postpartum Haemorrhage	<11	93	559	20,390	1.61	0.62	4.22
Duloxetine versus SSRI							
Postpartum Haemorrhage	<11	67	22	903	2.34	0.70	7.76
Duloxetine versus Venlafaxine							
Postpartum Haemorrhage	0	18	<11	60	-	-	-

15.4. 17. Postpartum Haemorrhage- Sensitivity Analyses #4: Correct relative risks for outcome misclassification

Target PPV= 74 (CI: 61-85), criteria 1

Target PPV= 82 (CI: 70-91), criteria 3

Target PPV= 88 (CI: 77-95), criteria 3

Distribution for bias parameters: Sensitivity: Min=0.5, Mode 1=0.75, Mode 2=0.75, Max=1.0; Specificity: Min=0.985, Mode 1=0.992, Mode 2=0.997, Max=0.999

Exposure	Reference	1:1 PS matched Analysis			Total Error Analysis					
		Odds ratio	95% CI lower	95% CI upper	Odds ratio	95% CI lower	95% CI upper	Width CI	% change in CI width over traditional	% change in OR
Duloxetine	Unexposed	1.12	0.66	1.90	1.15	0.60	2.07	3.46	30%	3.32%
Duloxetine	SSRI	1.22	0.70	2.11	1.29	0.69	2.38	3.47	5%	6.18%
Duloxetine	Venlafaxine	1.27	0.73	2.22	1.34	0.75	2.55	3.38	13%	5.26%

15.4. 18. Postpartum Haemorrhage- Sensitivity Analyses #5: Redefine outcome based on claims profile review

15.4. 18.1 Duloxetine versus Unexposed

	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Definition #1: if outcome likely occurred							
Postpartum Haemorrhage	26	737	26	737	1.00	0.59	1.71
Definition #2: if outcome "likely occurred" or "probably occurred"							
Postpartum Haemorrhage	30	737	27	737	1.11	0.67	1.85

15.4. 19. Postpartum Haemorrhage- Sensitivity Analyses #6: Restrict cohort to the first pregnancy occurring within the study period

15.4.19.1 Unadjusted

	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Duloxetine versus Unexposed							
Postpartum Haemorrhage	23	525	18,765	741,481	1.64	1.10	2.45
Duloxetine versus SSRI							
Postpartum Haemorrhage	23	480	963	31,481	1.58	1.05	2.36
Duloxetine versus Venlafaxine							
Postpartum Haemorrhage	23	519	75	1,941	1.20	0.76	1.90

15.4.19.2 Adjusted : Restricted + PS2 (All covariates)

	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Duloxetine versus Unexposed							
Postpartum Haemorrhage	23	523	15,866	609,626	1.60	1.07	2.39
Duloxetine versus SSRI							
Postpartum Haemorrhage	23	479	887	28,552	1.57	1.05	2.35
Duloxetine versus Venlafaxine							
Postpartum Haemorrhage	22	512	70	1,858	1.23	0.76	1.97

15.4. 20. Postpartum Haemorrhage- Sensitivity Analyses #12: Consider as exposed women with duloxetine dispensing <14 days before delivery

15.4.20.1 Unadjusted

	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Duloxetine versus Unexposed							
Postpartum Haemorrhage	17	485	95,988	4,128,460	1.51	0.95	2.40
Duloxetine versus SSRI							
Postpartum Haemorrhage	16	447	1,879	65,303	1.24	0.77	2.02
Duloxetine versus Venlafaxine							
Postpartum Haemorrhage	17	481	135	3,573	0.94	0.57	1.54

15.4.20.2 Adjusted: Restricted + PS2 (All covariates)

	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Duloxetine versus Unexposed							
Postpartum Haemorrhage	15	373	20,144	775,619	1.54	0.94	2.54
Duloxetine versus SSRI							
Postpartum Haemorrhage	14	340	1,098	35,745	1.36	0.81	2.28
Duloxetine versus Venlafaxine							
Postpartum Haemorrhage	14	363	79	2,148	1.21	0.69	2.12

15.4. 21. Postpartum Haemorrhage- Sensitivity Analyses #13: Consider as exposed women with days supply overlapping delivery date

15.4.21.1 Unadjusted

	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Duloxetine versus Unexposed							
Postpartum Haemorrhage	31	909	95,988	4,128,460	1.47	1.04	2.07
Duloxetine versus SSRI							
Postpartum Haemorrhage	30	831	1,879	65,303	1.25	0.88	1.79
Duloxetine versus Venlafaxine							
Postpartum Haemorrhage	31	904	135	3,573	0.91	0.62	1.33

15.4.21.2 Adjusted : Restricted + PS2 (All covariates)

	Exposed		Reference				
Outcome	Events	N	Events	N	RR	95% CI lower	95% CI upper
Duloxetine versus Unexposed							
Postpartum Haemorrhage	27	702	21,324	824,328	1.45	1.00	2.10
Duloxetine versus SSRI							
Postpartum Haemorrhage	26	639	1,134	37,179	1.37	0.93	2.00
Duloxetine versus Venlafaxine							
Postpartum Haemorrhage	26	694	84	2,264	0.96	0.62	1.47

15.5. 1. Cohort of live and non-live births

Outcome	Number	%
Overall		
Live Birth	1,961,667	83.37
Spontaneous Abortion	220,405	9.37
Stillbirth	17,588	0.75
Termination	153,300	6.52
Restricted to women with recorded indications for duloxetine		
Live Birth	313,377	82.27
Spontaneous Abortion	43,928	11.53
Stillbirth	2,911	0.76
Termination	20,717	5.44

stillb15.5. 2. Risk of stillbirth associated with duloxetine exposure during pregnancy, as compared to unexposed women

	RR	lower bound 95% CI	Upper bound 95% CI	Unexposed events	Unexposed total N	Unexposed risk	Duloxetine exposed events	Duloxetine exposed total N	Duloxetine exposed risk
LMP to LMP + 30 days									
Unadjusted	0.95	0.62	1.45	2,855	310,558	0.92	21	2,410	0.87
Adjusted - Indications	0.94	0.61	1.44	2,855	310,558	0.92	21	2,410	0.87
Adjusted - Fully	0.92	0.60	1.42	2,836	308,701	0.92	21	2,410	0.87
Adjusted - hdPS	0.91	0.59	1.40	2,823	307,509	0.92	21	2,410	0.87
LMP + 30 to LMP + 120 days									
Unadjusted	1.53	1.06	2.20	2,855	310,558	0.92	29	2,064	1.41
Adjusted - Indications	1.49	1.04	2.14	2,855	310,558	0.92	29	2,064	1.41
Adjusted - Fully	1.37	0.95	1.97	2,855	310,554	0.92	29	2,064	1.41
Adjusted - hdPS	1.32	0.92	1.90	2,828	307,635	0.92	29	2,064	1.41
LMP + 120 days to LMP + 196 days									
Unadjusted	1.35	0.80	2.27	2,855	310,558	0.92	14	1,132	1.24
Adjusted - Indications	1.34	0.80	2.26	2,855	310,558	0.92	14	1,132	1.24
Adjusted - Fully	1.31	0.78	2.21	2,831	307,354	0.92	14	1,132	1.24
Adjusted - hdPS	1.28	0.76	2.15	2,841	308,985	0.92	14	1,131	1.24
LMP to LMP + 196 days									
Unadjusted	1.08	0.78	1.51	2,855	310,558	0.92	35	3,512	1.00
Adjusted - Indications	1.08	0.78	1.51	2,855	310,558	0.92	35	3,512	1.00
Adjusted - Fully	1.04	0.75	1.45	2,840	309,257	0.92	35	3,512	1.00
Adjusted - hdPS	0.99	0.71	1.38	2,843	308,554	0.92	35	3,511	1.00

15.5. 3. Risk of spontaneous abortion associated with duloxetine exposure during pregnancy, as compared to unexposed women

	RR	lower bound 95% CI	Upper bound 95% CI	Unexposed events	Unexposed total N	Unexposed risk	Duloxetine exposed events	Duloxetine exposed total N	Duloxetine exposed risk
LMP to LMP + 30 days									
Unadjusted	1.24	1.13	1.35	42,967	353,841	12.14	426	2,836	15.02
Adjusted - Indications	1.18	1.08	1.29	42,967	353,841	12.14	426	2,836	15.02
Adjusted - Fully	1.08	0.99	1.18	42,751	351,675	12.16	426	2,836	15.02
Adjusted - hdPS	1.07	0.98	1.17	42,614	350,414	12.16	426	2,836	15.02
LMP + 30 to LMP + 63 days									
Unadjusted	1.58	1.44	1.73	42,967	353,841	12.14	370	1,929	19.18
Adjusted - Indications	1.50	1.37	1.65	42,967	353,841	12.14	370	1,929	19.18
Adjusted - Fully	1.33	1.21	1.46	40,255	326,791	12.32	370	1,929	19.18
Adjusted - hdPS	1.30	1.19	1.43	40,956	334,165	12.26	369	1,927	19.15
LMP to LMP + 63 days									
Unadjusted	1.31	1.22	1.42	42,967	353,841	12.14	579	3,630	15.95
Adjusted - Indications	1.24	1.15	1.34	42,967	353,841	12.14	579	3,630	15.95
Adjusted - Fully	1.14	1.06	1.23	42,778	351,945	12.15	579	3,629	15.95
Adjusted - hdPS	1.16	1.08	1.25	42,849	352,829	12.14	579	3,629	15.95

15.5. 4. Risk of stillbirth associated with duloxetine exposure during pregnancy, as compared to SSRI exposure

	RR	lower bound 95% CI	Upper bound 95% CI	SSRI exposed events	SSRI exposed total N	SSRI exposed risk	Duloxetine exposed events	Duloxetine exposed total N	Duloxetine exposed risk
LMP to LMP + 30 days									
Unadjusted	0.93	0.58	1.49	270	31,500	0.86	18	2,264	0.80
Adjusted - Indications	0.93	0.58	1.50	270	31,500	0.86	18	2,264	0.80
Adjusted - Fully	1.00	0.62	1.62	262	31,009	0.84	18	2,260	0.80
Adjusted - hdPS	0.99	0.61	1.59	270	31,499	0.86	18	2,233	0.81
LMP + 30 to LMP + 120 days									
Unadjusted	1.19	0.77	1.82	377	35,201	1.07	22	1,731	1.27
Adjusted - Indications	1.19	0.78	1.82	377	35,201	1.07	22	1,731	1.27
Adjusted - Fully	1.10	0.72	1.69	373	34,973	1.07	22	1,729	1.27
Adjusted - hdPS	1.23	0.80	1.89	377	35,200	1.07	22	1,730	1.27
LMP + 120 days to LMP + 196 days									
Unadjusted	1.06	0.58	1.92	281	27,220	1.03	11	1,010	1.09
Adjusted - Indications	1.08	0.59	1.96	281	27,220	1.03	11	1,010	1.09
Adjusted - Fully	1.14	0.63	2.08	278	26,870	1.03	11	1,007	1.09
Adjusted - hdPS	1.09	0.60	1.98	281	27,219	1.03	11	993	1.11
LMP to LMP + 196 days									
Unadjusted	0.82	0.53	1.26	566	56,898	0.99	21	2,584	0.81
Adjusted - Indications	0.82	0.53	1.26	566	56,898	0.99	21	2,584	0.81
Adjusted - Fully	0.74	0.48	1.15	562	56,608	0.99	21	2,577	0.81
Adjusted - hdPS	0.79	0.51	1.22	566	56,897	0.99	21	2,571	0.82

15.5. 5. Risk of spontaneous abortion associated with duloxetine exposure during pregnancy, as compared to SSRI exposure

	RR	lower bound 95% CI	Upper bound 95% CI	SSRI exposed events	SSRI exposed total N	SSRI exposed risk	Duloxetine exposed events	Duloxetine exposed total N	Duloxetine exposed risk
LMP to LMP + 30 days									
Unadjusted	1.17	1.06	1.29	4,614	36,114	12.78	398	2,662	14.95
Adjusted - Indications	1.14	1.04	1.25	4,614	36,114	12.78	398	2,662	14.95
Adjusted - Fully	0.93	0.85	1.03	4,502	35,282	12.76	394	2,652	14.86
Adjusted - hdPS	0.94	0.85	1.03	4,614	36,113	12.78	393	2,643	14.87
LMP + 30 to LMP + 63 days									
Unadjusted	1.36	1.23	1.50	3,854	26,605	14.49	349	1,772	19.70
Adjusted - Indications	1.34	1.21	1.48	3,854	26,605	14.49	349	1,772	19.70
Adjusted - Fully	1.24	1.12	1.37	3,802	26,282	14.47	346	1,762	19.64
Adjusted - hdPS	1.21	1.09	1.33	3,853	26,604	14.48	343	1,735	19.77
LMP to LMP + 63 days									
Unadjusted	1.24	1.15	1.35	6,375	47,882	13.31	522	3,151	16.57
Adjusted - Indications	1.21	1.12	1.32	6,375	47,882	13.31	522	3,151	16.57
Adjusted - Fully	1.05	0.97	1.14	6,332	47,522	13.32	519	3,142	16.52
Adjusted - hdPS	1.09	1.00	1.18	6,375	47,881	13.31	519	3,139	16.53

16. Figures

List of Figures

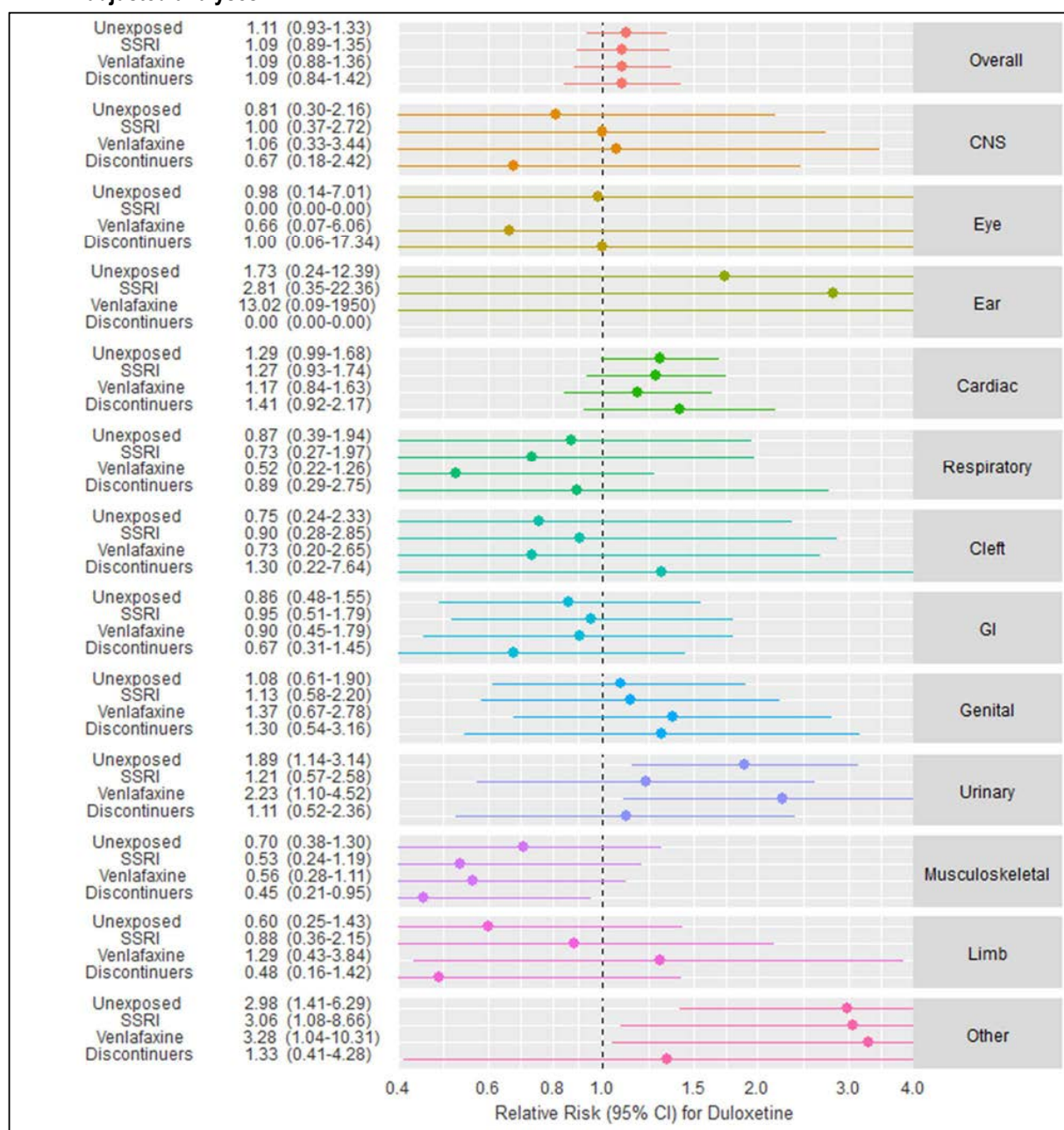
	Page
Legend	541
16.1. 1. Risk of congenital malformations associated with first trimester exposure to duloxetine: fully adjusted analyses	542
16.1. 2. Risk of any malformation associated with first trimester exposure to duloxetine: sensitivity analyses	543
16.1. 3. Risk of any malformation associated with first trimester exposure to duloxetine: sensitivity analyses to address outcome misclassification	544
16.1. 4. Risk of cardiac malformations associated with first trimester exposure to duloxetine: sensitivity analyses	545
16.1. 5. Risk of cardiac malformations associated with first trimester exposure to duloxetine: sensitivity analyses to address outcome misclassification	546
16.1. 6. Any malformation - Sensitivity Analyses #7: External adjustment of the observed relative risk to account for confounding by obesity, smoking, and alcohol using NHANES	547
16.1. 7. Cardiac malformations - Sensitivity Analyses #7: External adjustment of the observed relative risk to account for confounding by obesity, smoking, and alcohol using NHANES	548
16.1. 8. Any malformation - Sensitivity Analyses #7: Rule out approach for residual confounding	549
16.1. 9. Cardiac Malformations - Sensitivity Analyses #7: Rule out approach for residual confounding	550
16.1. 10. Any malformation - Sensitivity Analyses #11: Impact of restriction to live births	551
16.1. 11. Cardiac Malformations - Sensitivity Analyses #11: Impact of restriction to live births	552
16.2. 1. Risk of preterm birth and SGA associated with early and late pregnancy exposure to duloxetine: fully adjusted analyses	553
16.2. 2. Risk of preterm birth associated with early pregnancy exposure to duloxetine: sensitivity analyses	554
16.2. 3. Risk of preterm birth associated with late pregnancy exposure to duloxetine: sensitivity analyses	555
16.2. 4. Risk of SGA associated with early pregnancy exposure to duloxetine: sensitivity analyses	556
16.2. 5. Risk of SGA associated with late pregnancy exposure to duloxetine: sensitivity analyses	557
16.2. 6. Risk of preterm birth associated with early pregnancy exposure to duloxetine: sensitivity analyses to address outcome misclassification	558
16.2. 7. Risk of preterm birth associated with late pregnancy exposure to duloxetine: sensitivity analyses to address outcome misclassification	559
16.2. 8. Risk of SGA associated with early pregnancy exposure to duloxetine: sensitivity analyses to address outcome misclassification	560
16.2. 9. Risk of SGA associated with late pregnancy exposure to duloxetine: sensitivity analyses to address outcome misclassification	561

16.2. 10.	Preterm/SGA - Sensitivity Analyses #7: External adjustment of the observed relative risk to account for confounding by obesity, smoking, and alcohol using NHANES.....	562
16.2. 11.	Preterm/SGA - Sensitivity Analyses #7: Rule out approach for residual confounding	564
16.3. 1.	Risk of preeclampsia associated with early and late pregnancy exposure to duloxetine: fully adjusted analyses.....	569
16.3. 2.	Risk of preeclampsia associated with early pregnancy exposure to duloxetine: sensitivity analyses.....	570
16.3. 3.	Risk of preeclampsia associated with late pregnancy exposure to duloxetine: sensitivity analyses.....	571
16.3. 4.	Risk of preeclampsia associated with early pregnancy exposure to duloxetine: sensitivity analyses to address outcome misclassification	572
16.3. 5.	Risk of preeclampsia associated with late pregnancy exposure to duloxetine: sensitivity analyses to address outcome misclassification	573
16.3. 6.	Preeclampsia - Sensitivity Analyses #7: External adjustment of the observed relative risk to account for confounding by obesity, smoking, and alcohol using NHANES.....	574
16.3. 7.	Preeclampsia - Sensitivity Analyses #7: Rule out approach for residual confounding.....	575
16.4. 1.	Risk of postpartum haemorrhage associated with exposure to duloxetine during the final 30 days of pregnancy: fully adjusted analyses.....	577
16.4. 2.	Risk of postpartum haemorrhage associated with exposure to duloxetine during the final 30 days of pregnancy: sensitivity analyses.....	578
16.4. 3.	Risk of postpartum haemorrhage associated with exposure to duloxetine during the final 30 days of pregnancy: sensitivity analyses to address outcome misclassification	579
16.4. 4.	Postpartum Haemorrhage - Sensitivity Analyses #7: External adjustment of the observed relative risk to account for confounding by obesity, smoking, and alcohol using NHANES	580
16.4. 5.	Postpartum Haemorrhage - Sensitivity Analyses #7: Rule out approach for residual confounding.....	581
16.5. 1.	Risk of stillbirth associated with exposure to duloxetine during pregnancy.....	583
16.5. 2.	Risk of spontaneous abortion associated with exposure to duloxetine during pregnancy	584

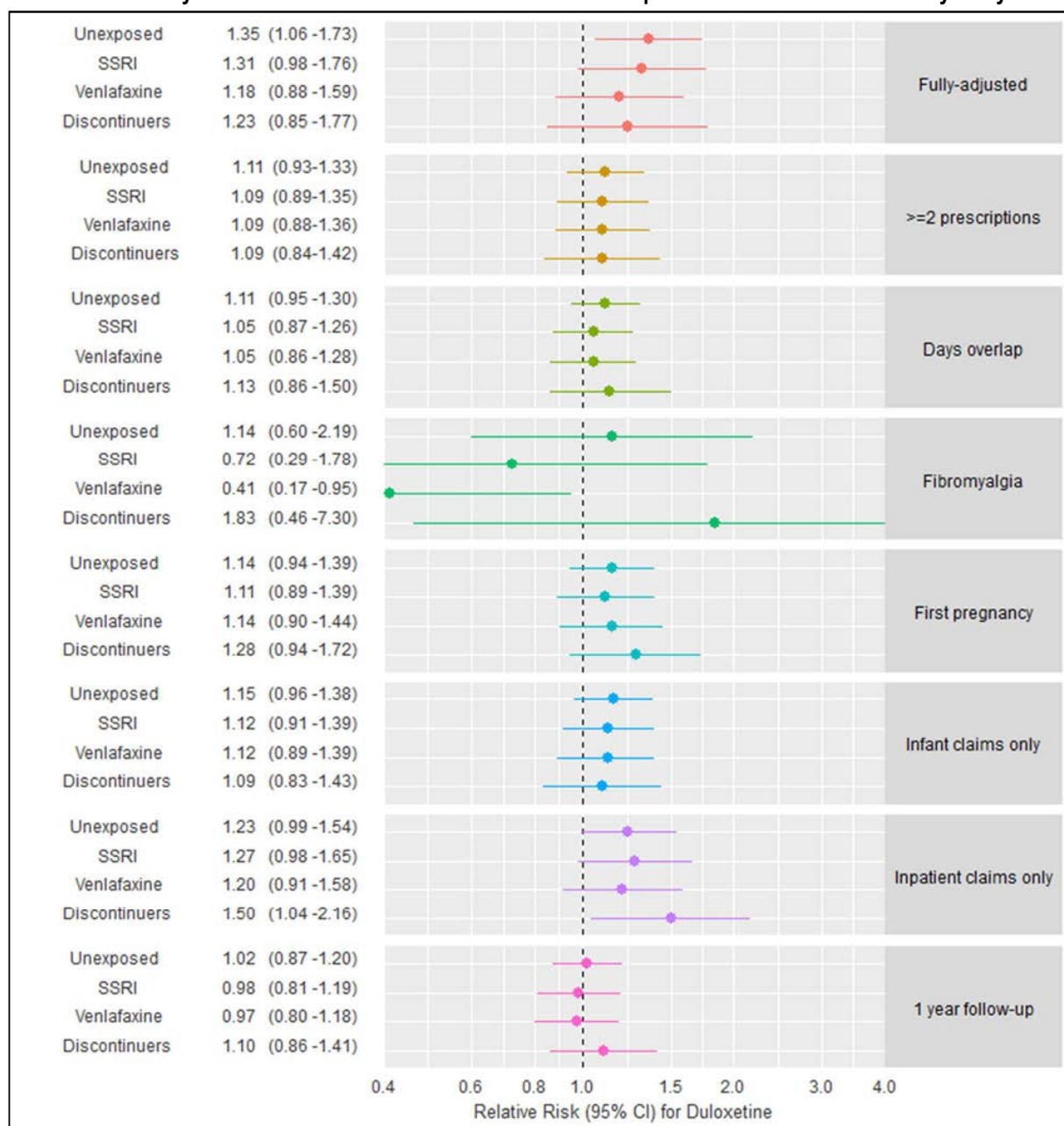
Legend

Term	Definition
RR _{ed}	Exposure-outcome association
RR _{cd}	Confounder-outcome association
OR _{ec}	Exposure-confounder association
P _c	Prevalence of confounder

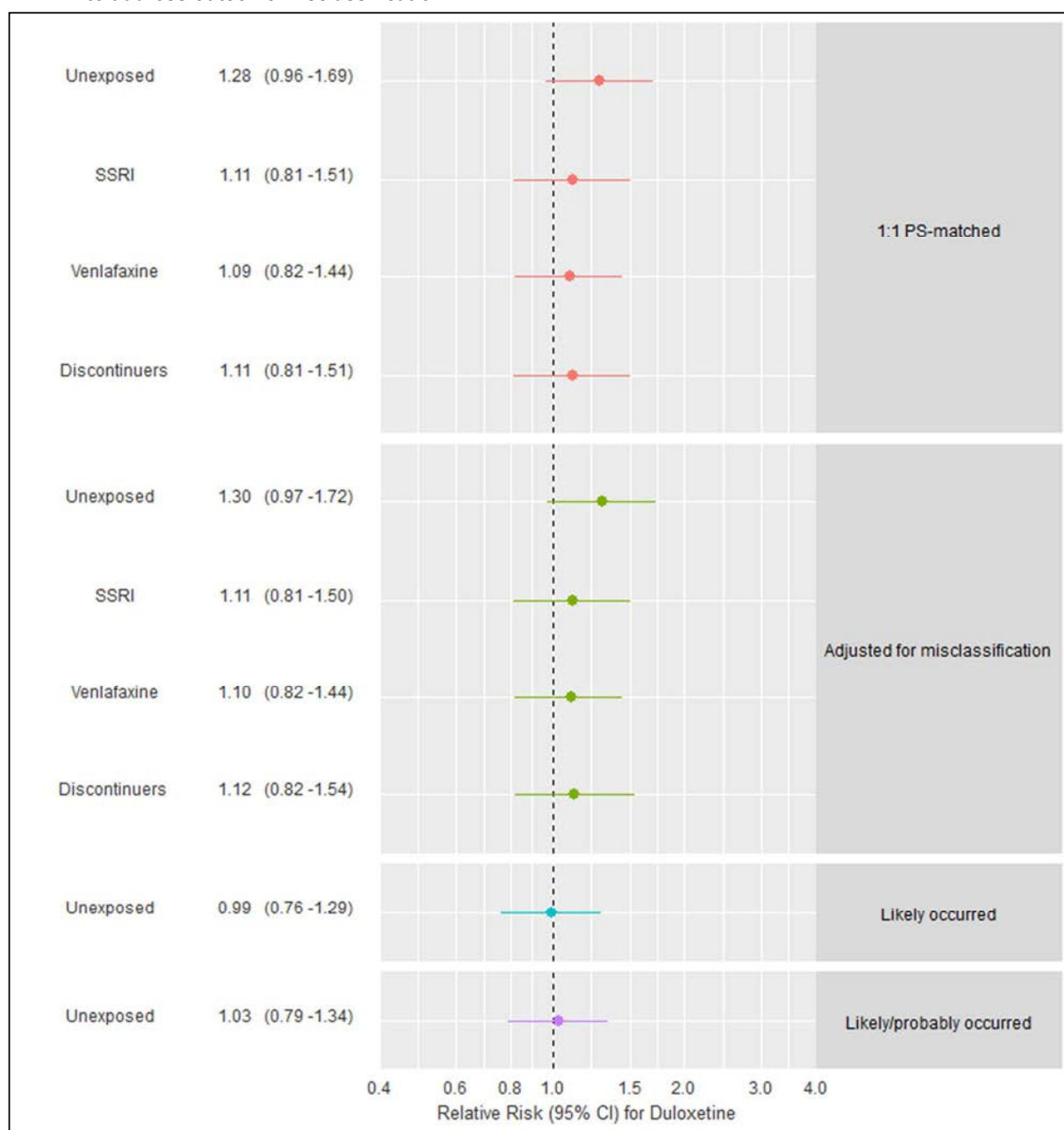
16.1.1. Risk of congenital malformations associated with first trimester exposure to duloxetine: fully adjusted analyses



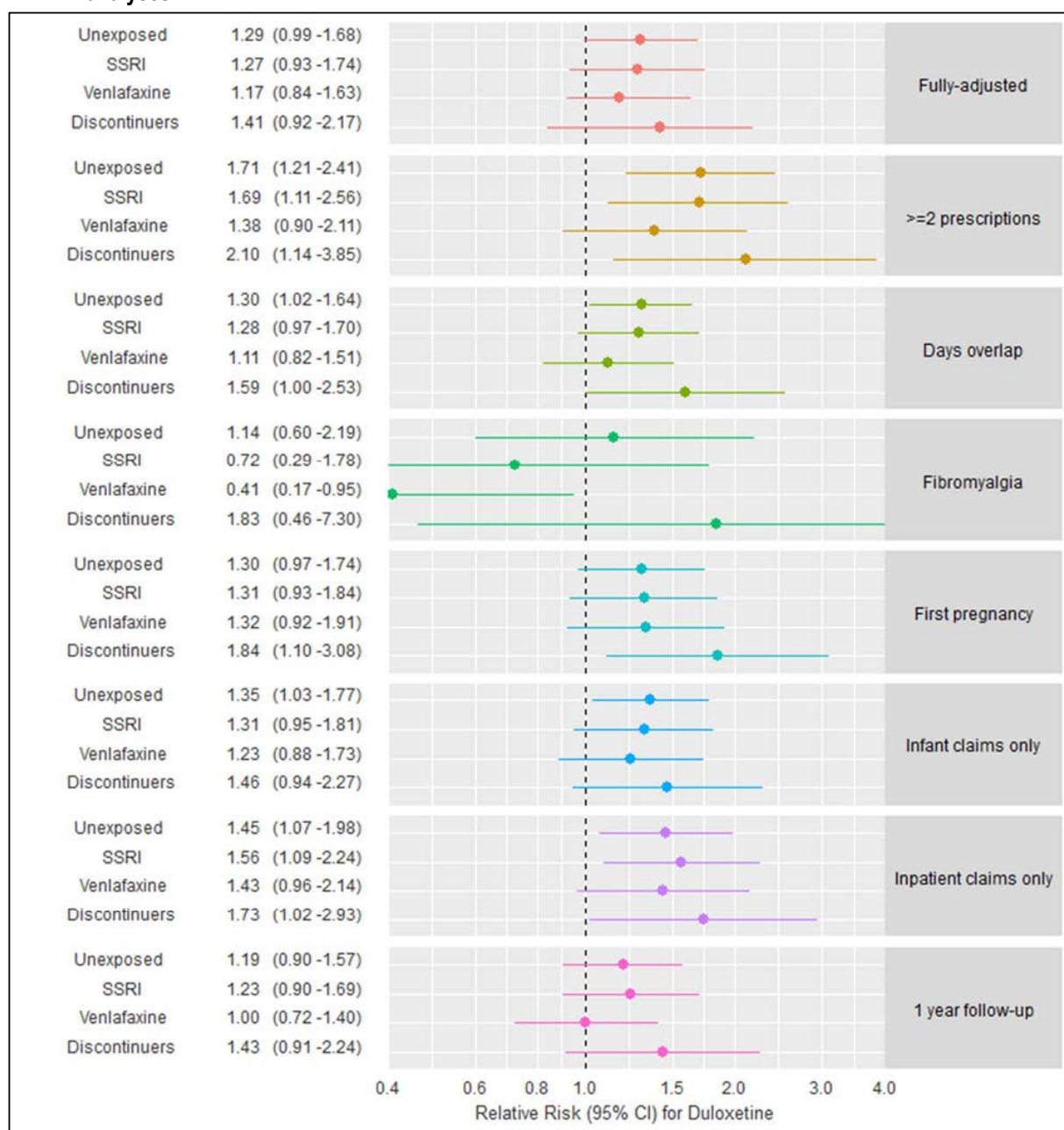
16.1.2. Risk of any malformation associated with first trimester exposure to duloxetine: sensitivity analyses



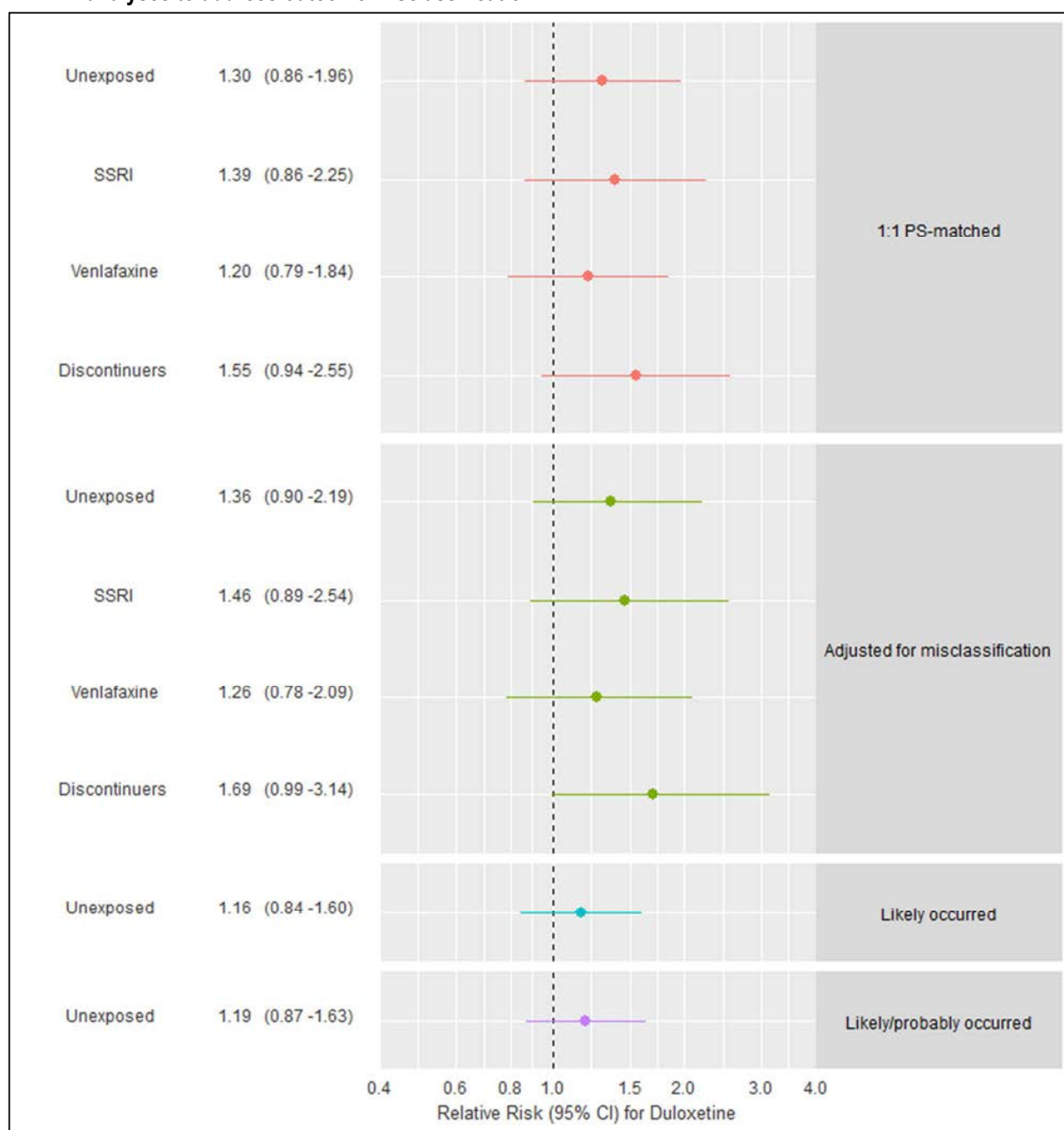
16.1. 3. Risk of any malformation associated with first trimester exposure to duloxetine: sensitivity analyses to address outcome misclassification



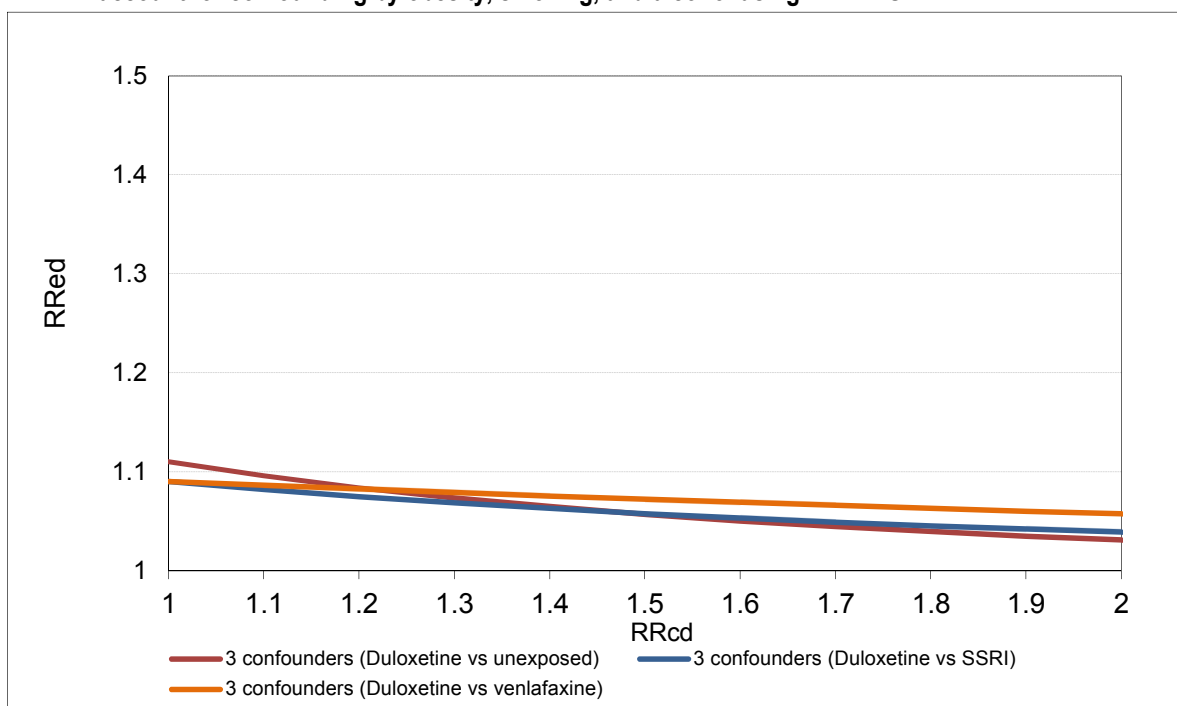
16.1. 4. Risk of cardiac malformations associated with first trimester exposure to duloxetine: sensitivity analyses



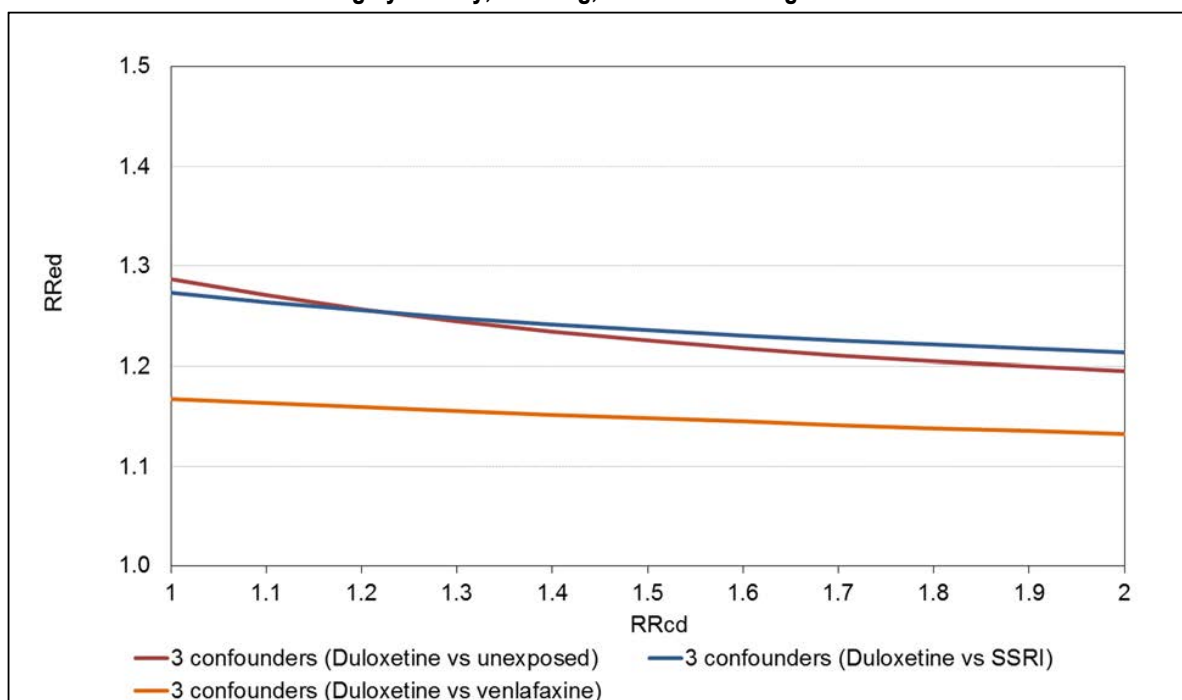
16.1. 5. Risk of cardiac malformations associated with first trimester exposure to duloxetine: sensitivity analyses to address outcome misclassification



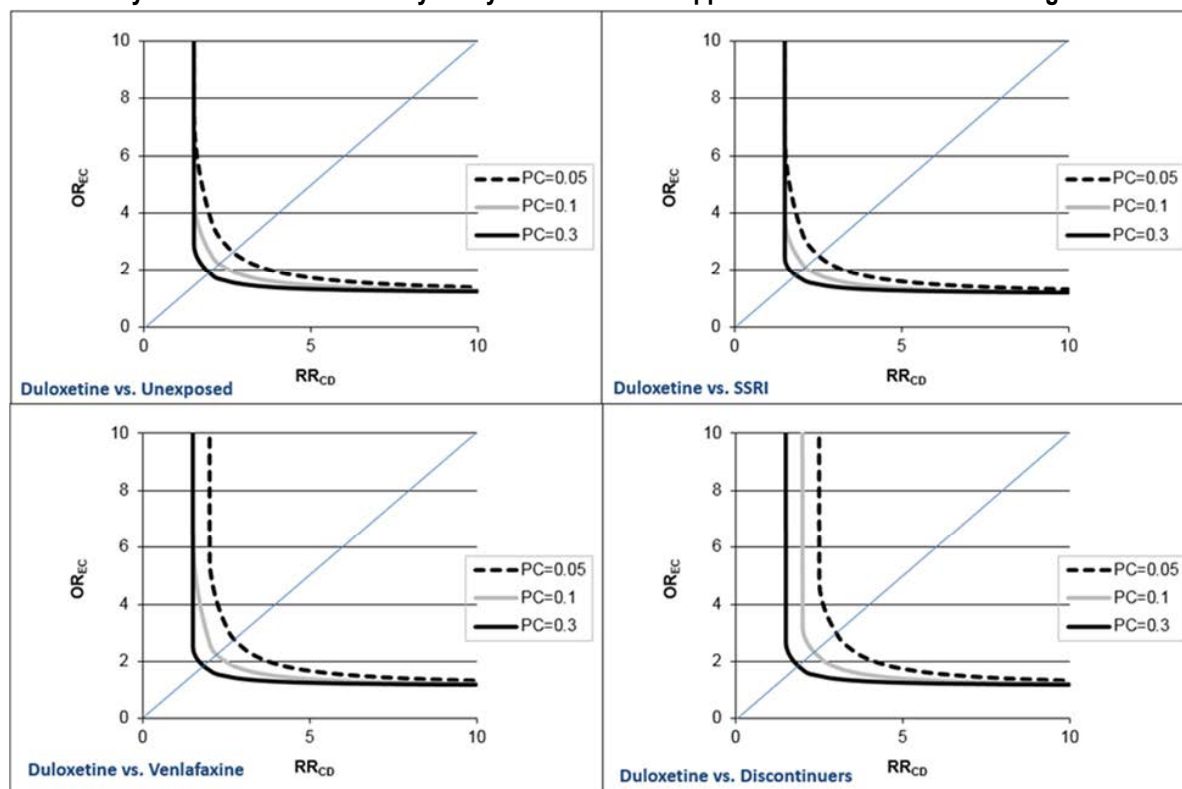
16.1. 6. Any malformation - Sensitivity Analyses #7: External adjustment of the observed relative risk to account for confounding by obesity, smoking, and alcohol using NHANES



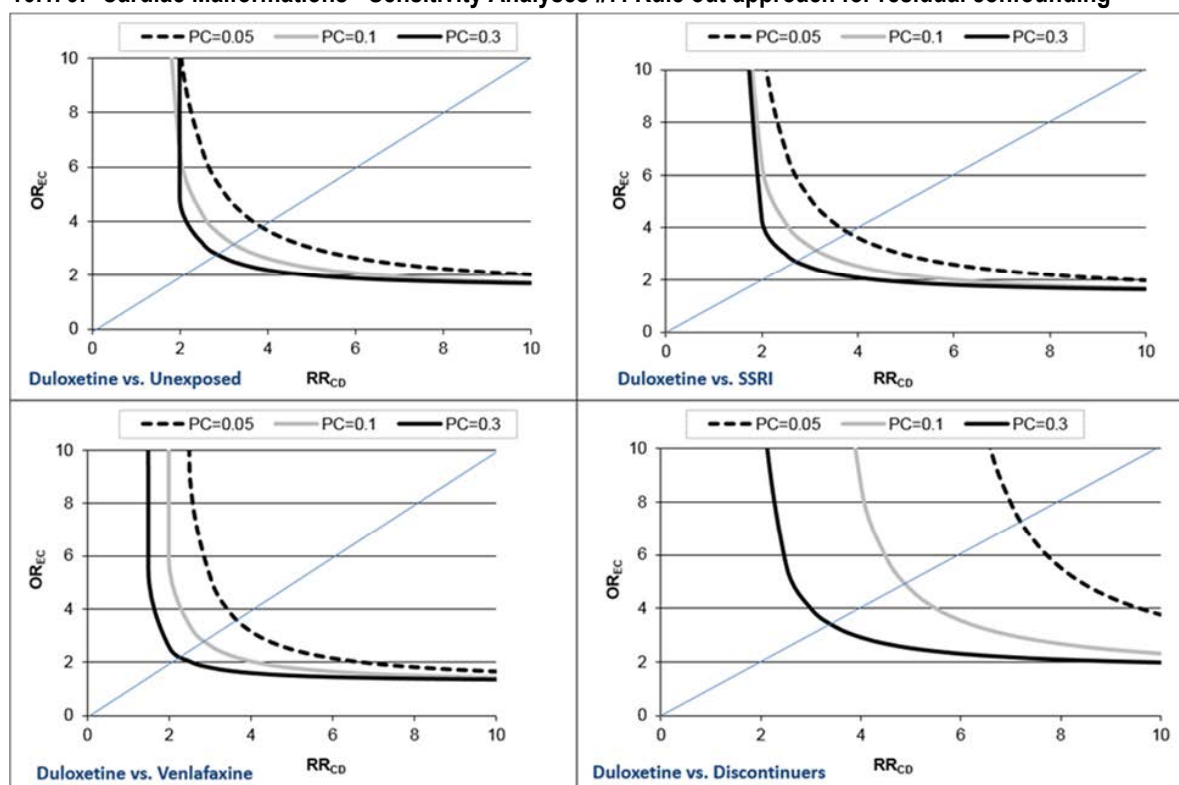
16.1. 7. Cardiac malformations - Sensitivity Analyses #7: External adjustment of the observed relative risk to account for confounding by obesity, smoking, and alcohol using NHANES



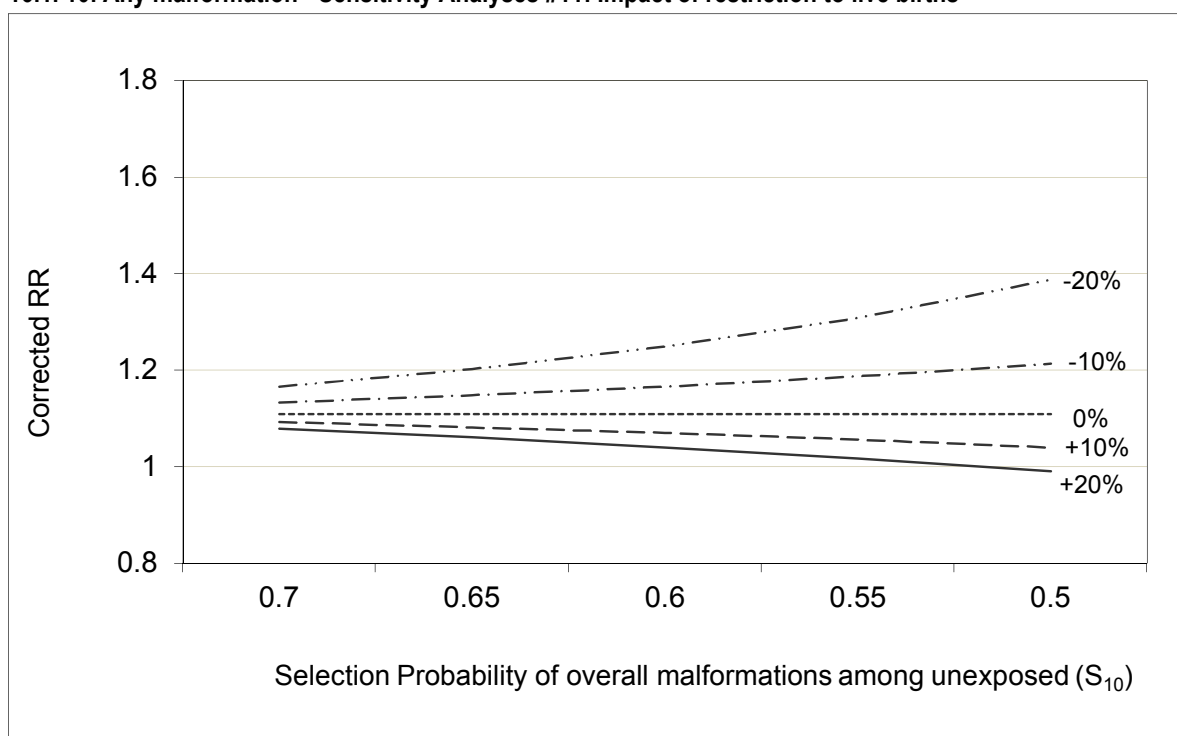
16.1. 8. Any malformation - Sensitivity Analyses #7: Rule out approach for residual confounding



16.1.9. Cardiac Malformations - Sensitivity Analyses #7: Rule out approach for residual confounding

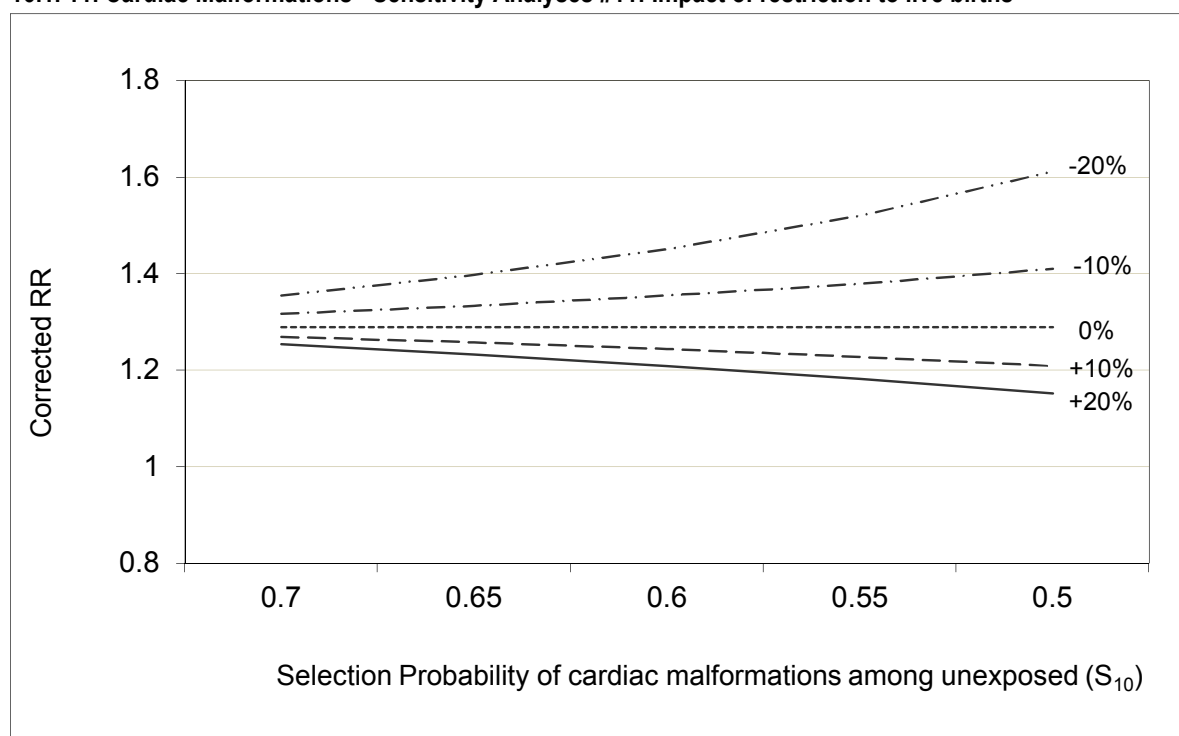


16.1. 10. Any malformation - Sensitivity Analyses #11: Impact of restriction to live births



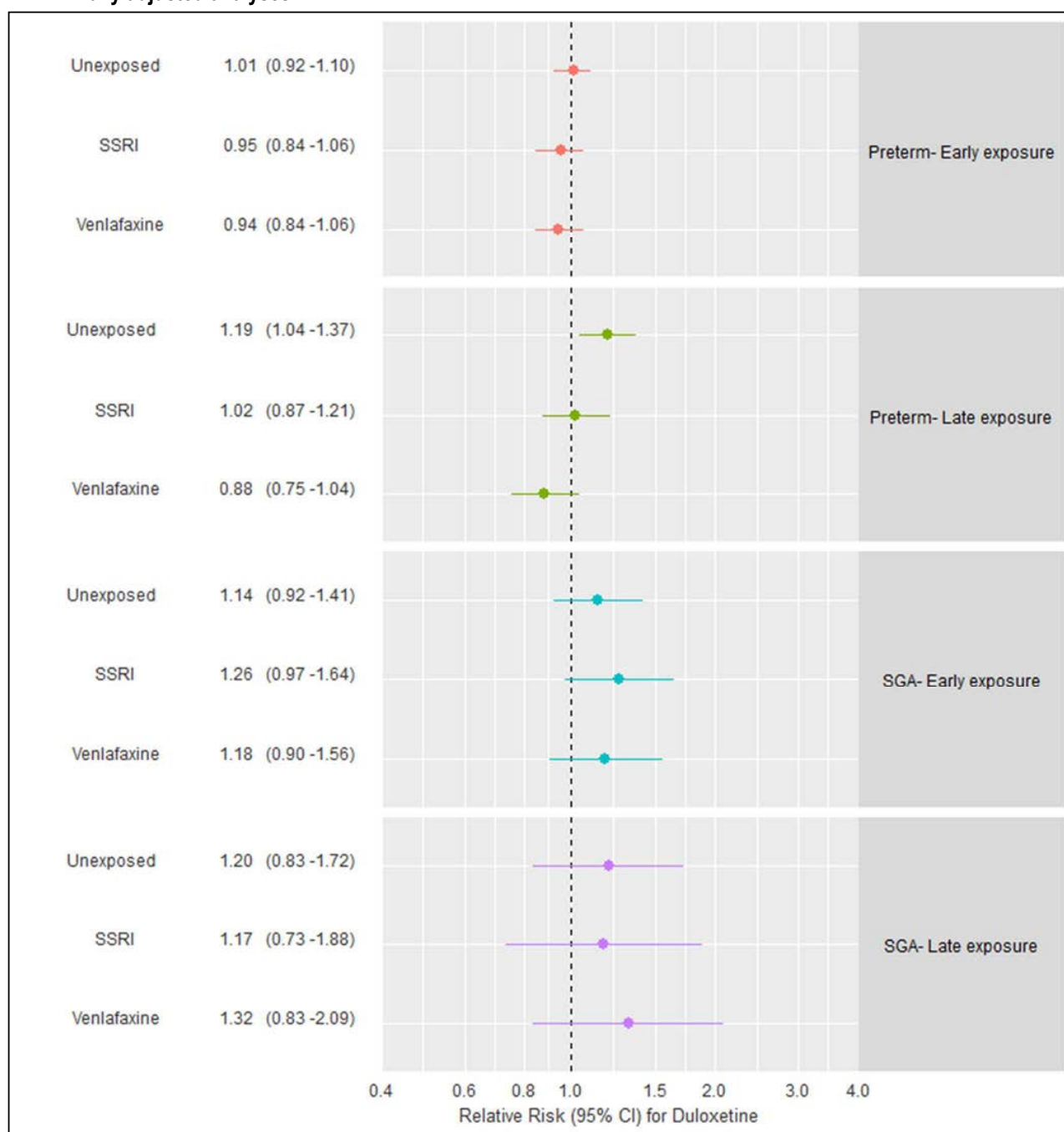
Note: The different lines represent the corrected relative risk for a range of higher or lower selection probabilities among duloxetine users

16.1. 11. Cardiac Malformations - Sensitivity Analyses #11: Impact of restriction to live births

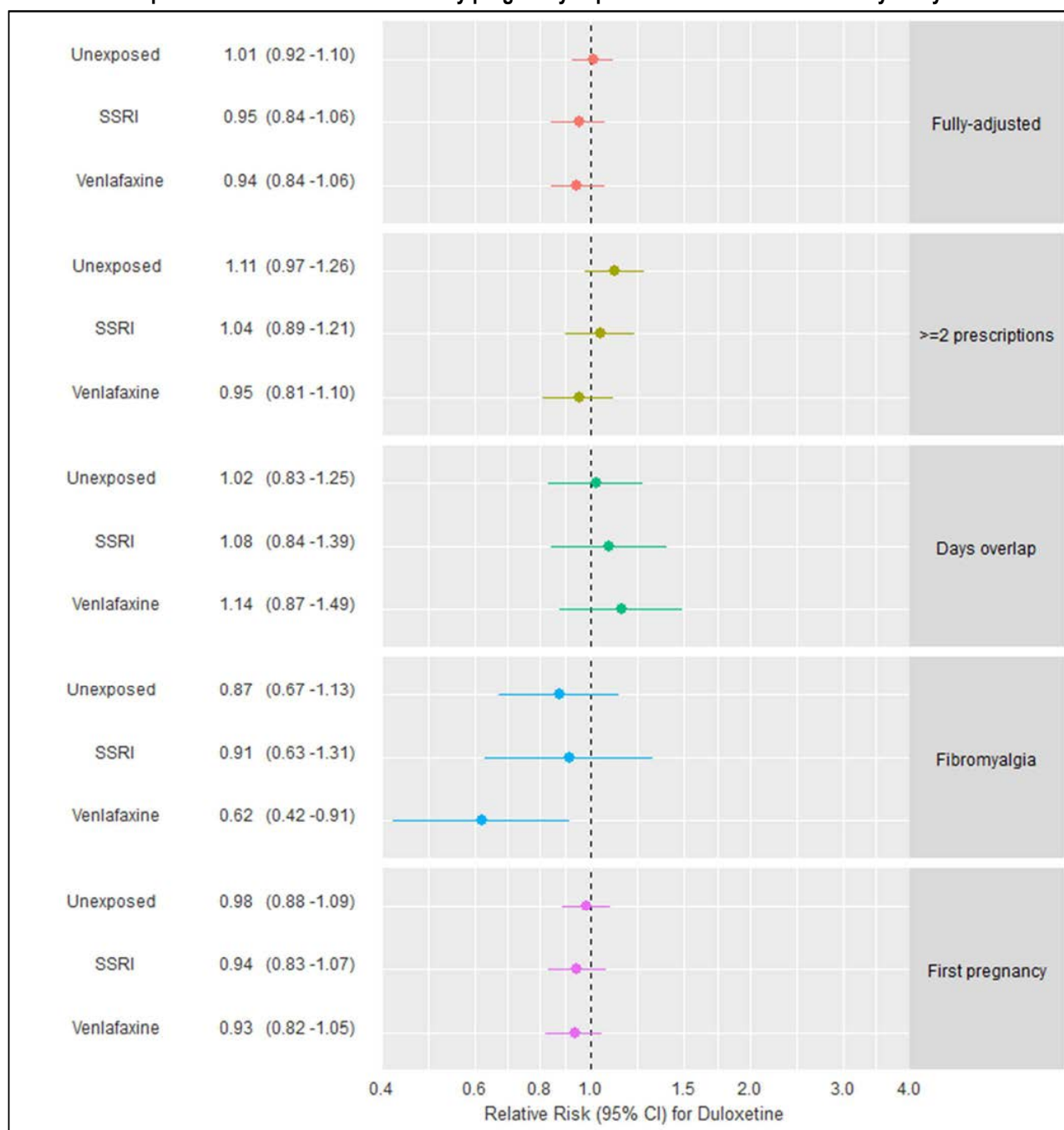


Note: The different lines represent the corrected relative risk for a range of higher or lower selection probabilities among duloxetine users

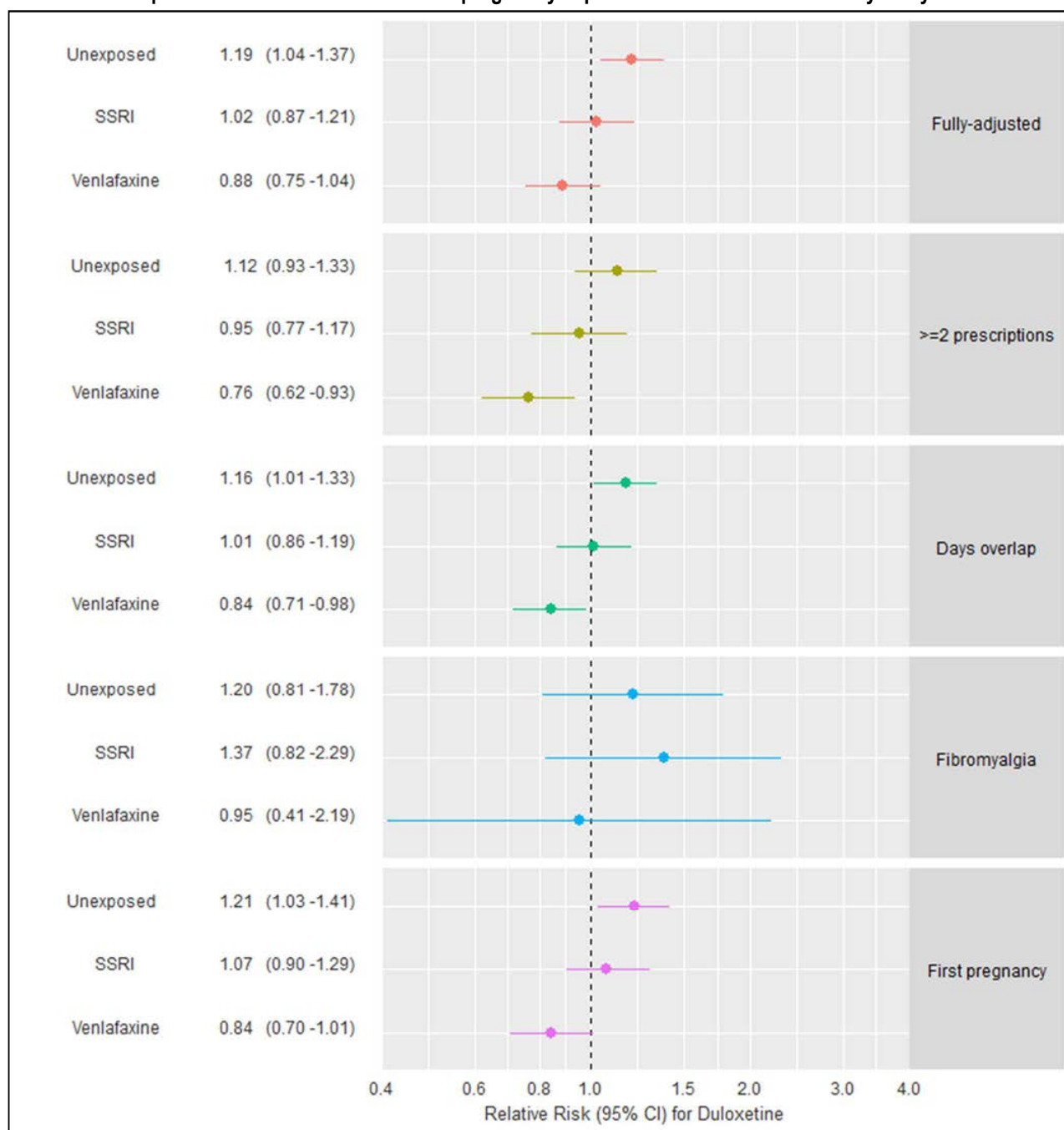
**16.2. 1. Risk of preterm birth and SGA associated with early and late pregnancy exposure to duloxetine:
fully adjusted analyses**



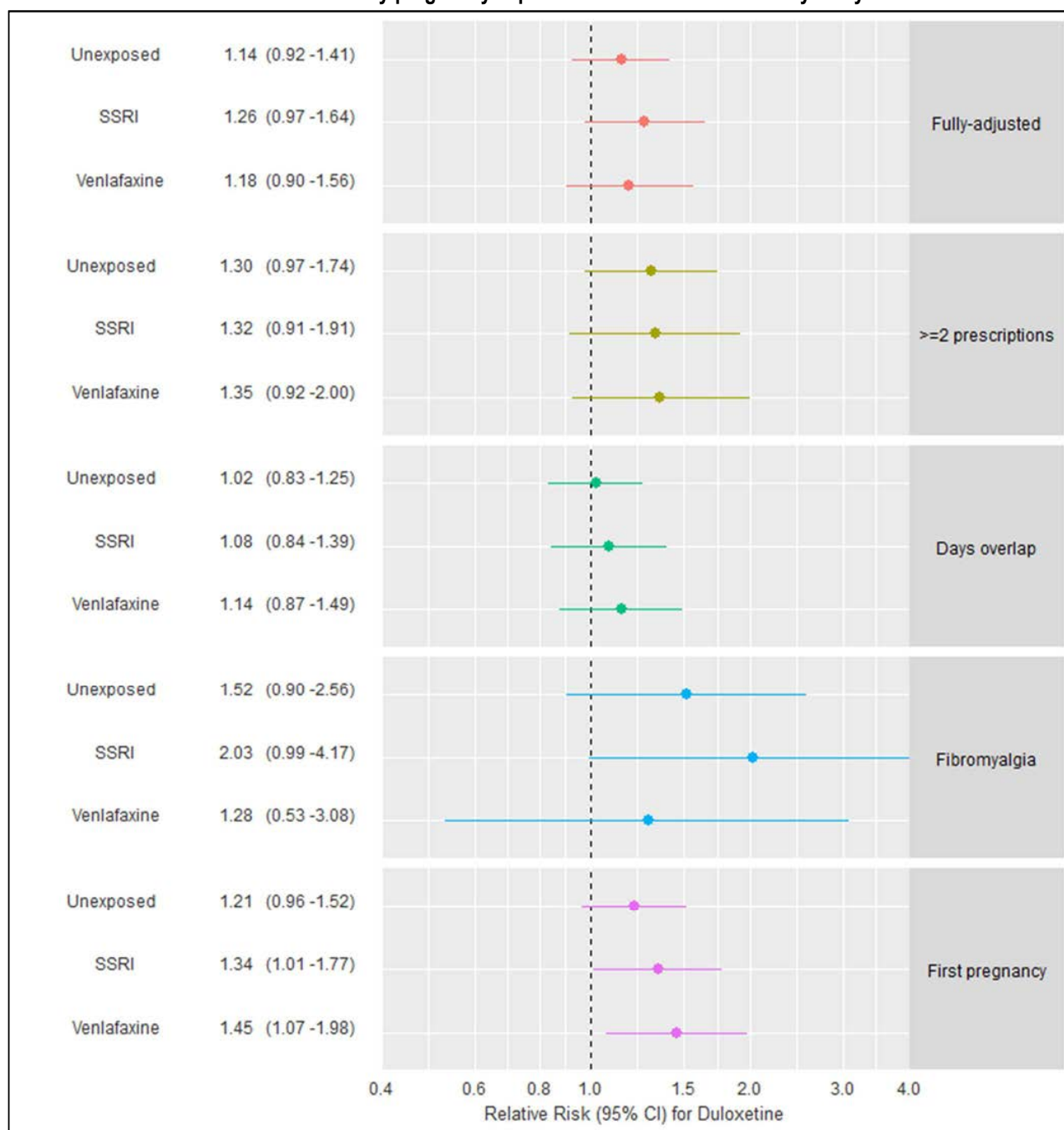
16.2. 2. Risk of preterm birth associated with early pregnancy exposure to duloxetine: sensitivity analyses



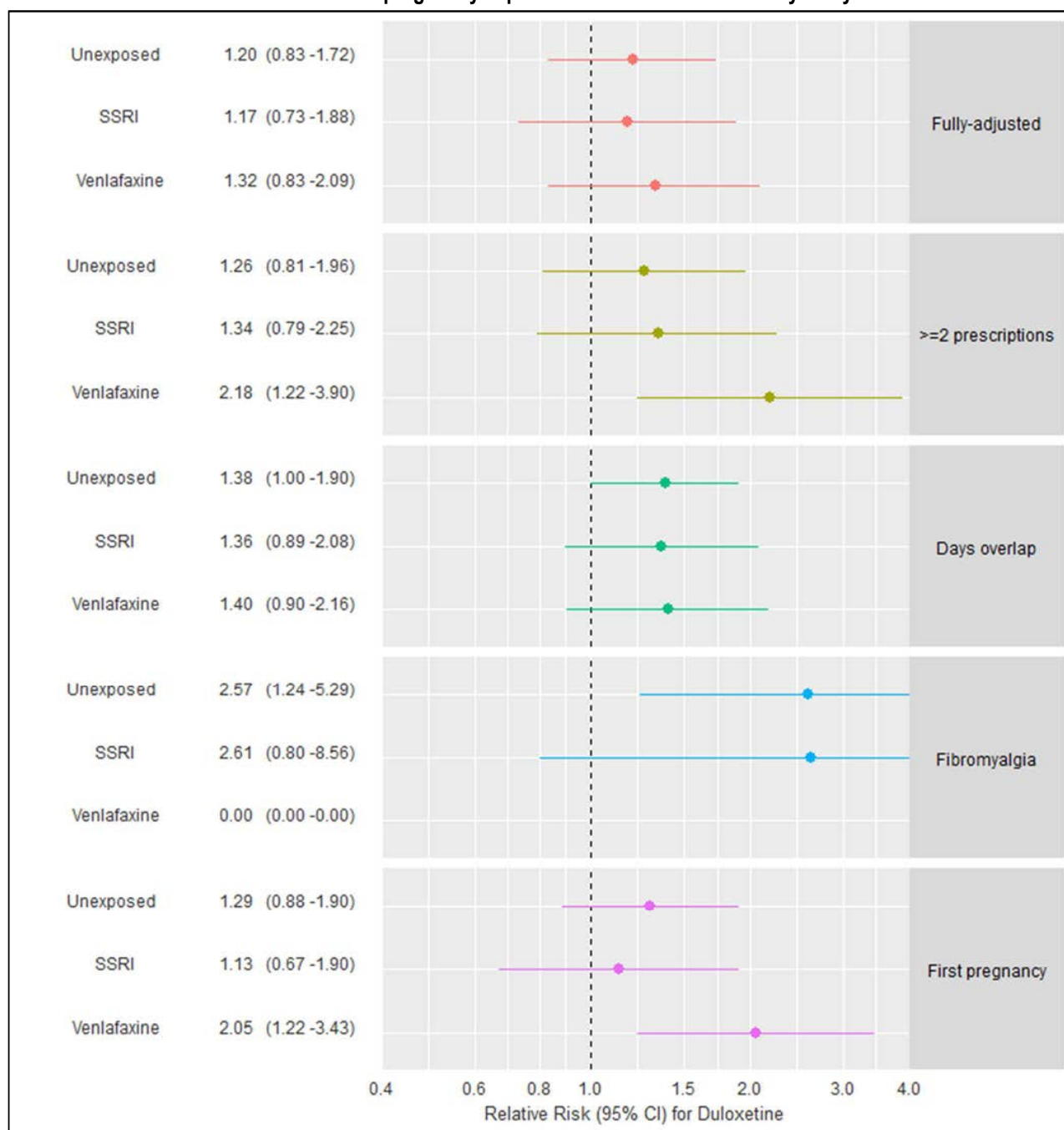
16.2. 3. Risk of preterm birth associated with late pregnancy exposure to duloxetine: sensitivity analyses



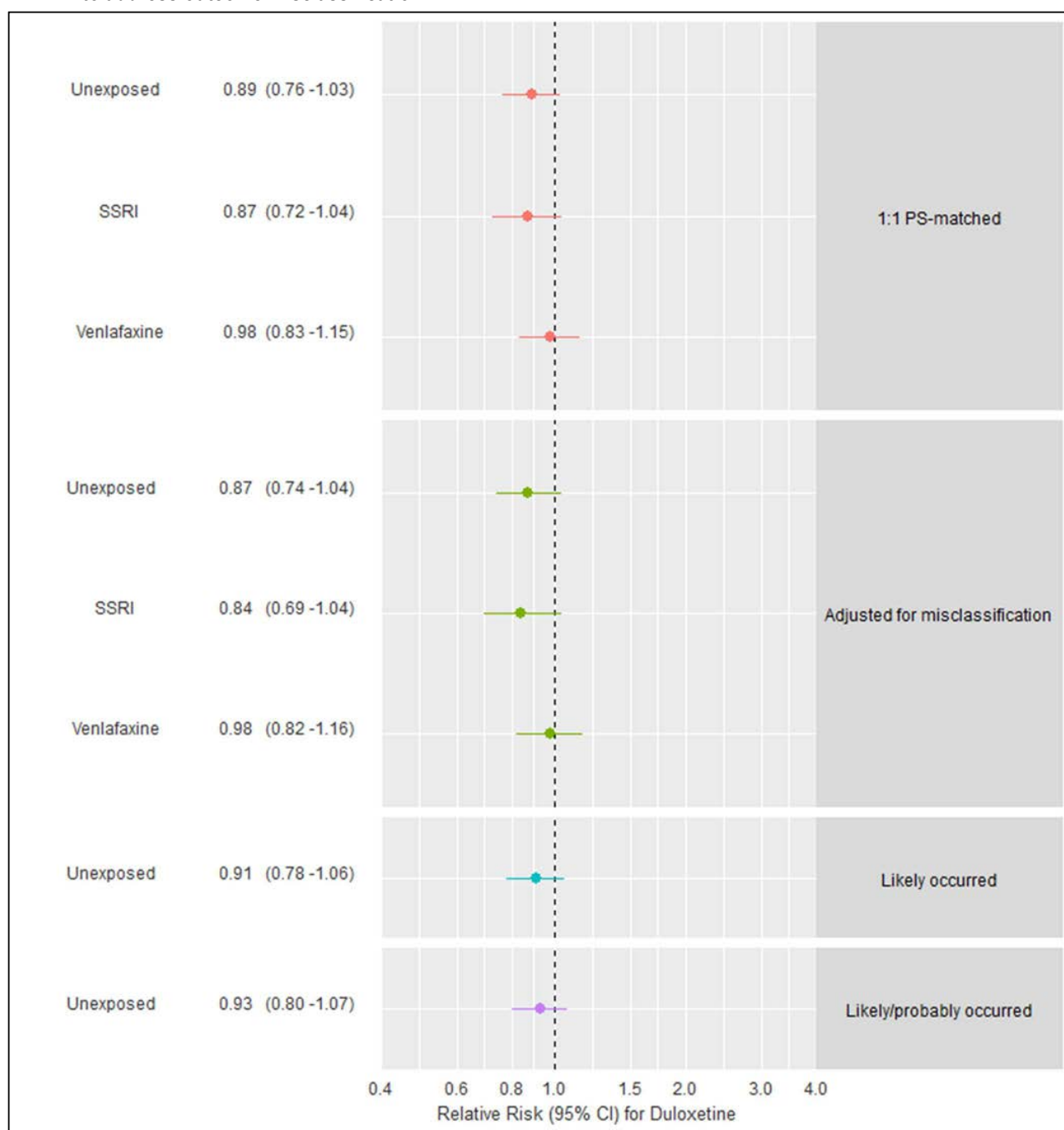
16.2. 4. Risk of SGA associated with early pregnancy exposure to duloxetine: sensitivity analyses



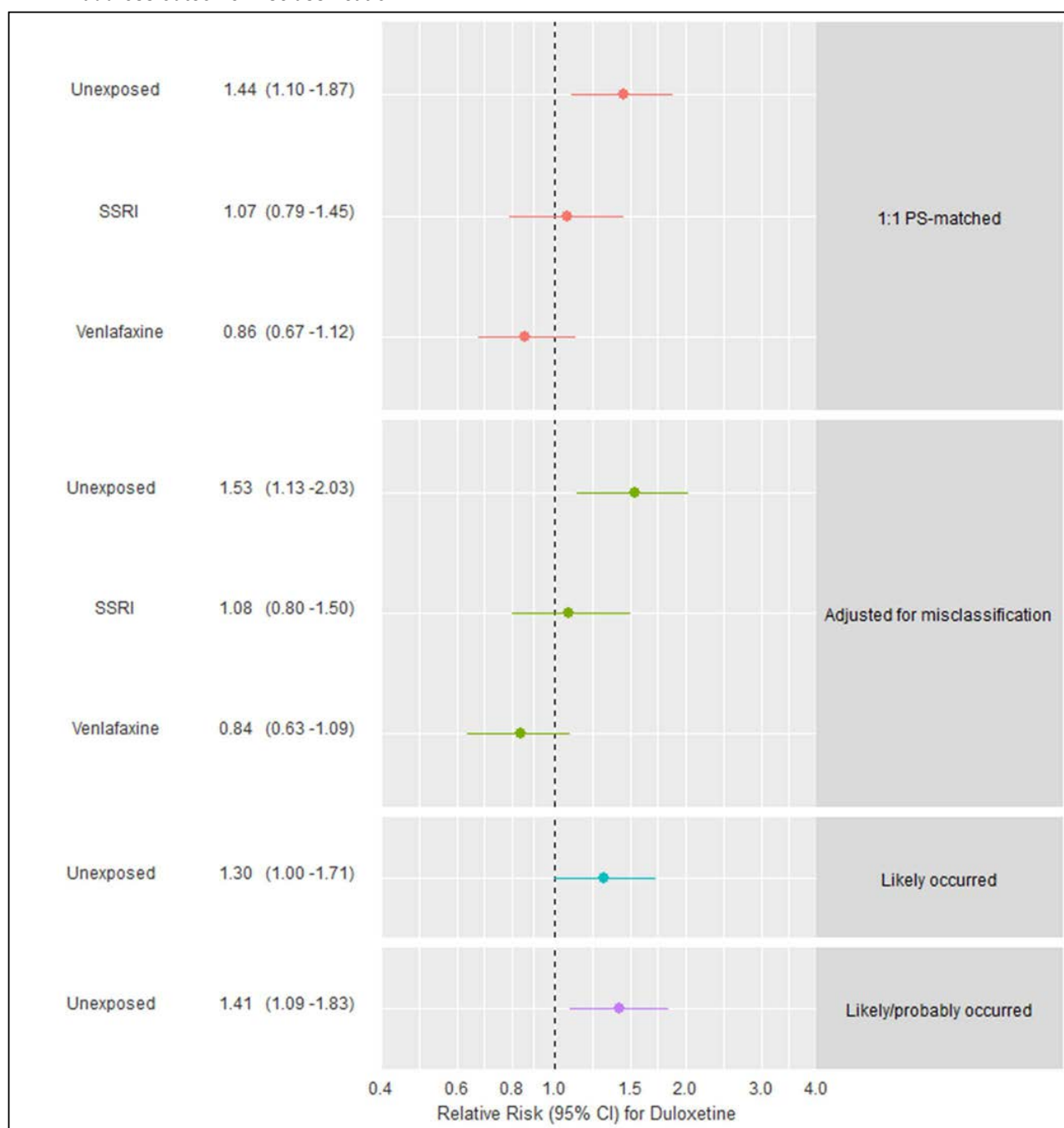
16.2. 5. Risk of SGA associated with late pregnancy exposure to duloxetine: sensitivity analyses



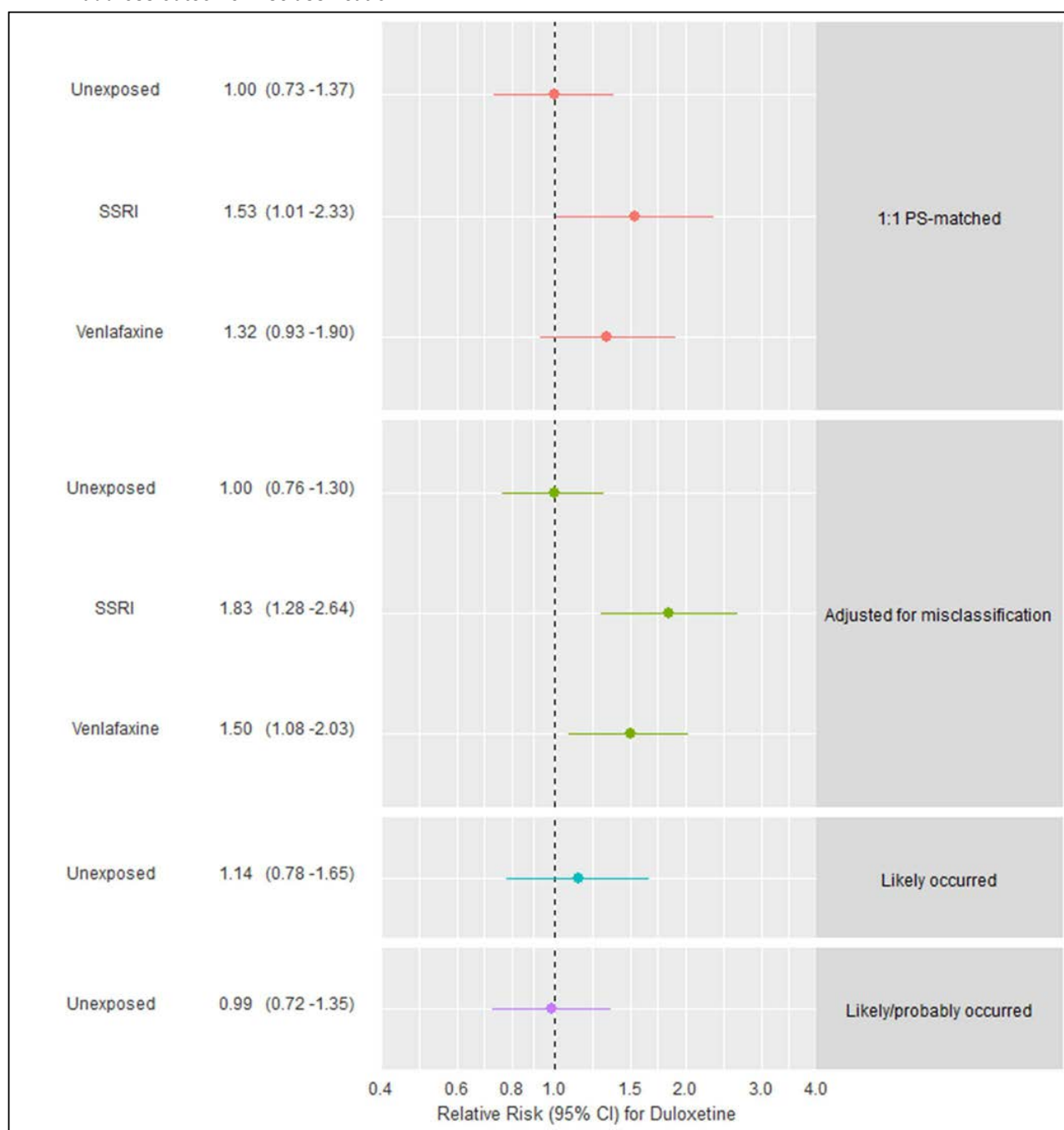
16.2. 6. Risk of preterm birth associated with early pregnancy exposure to duloxetine: sensitivity analyses to address outcome misclassification



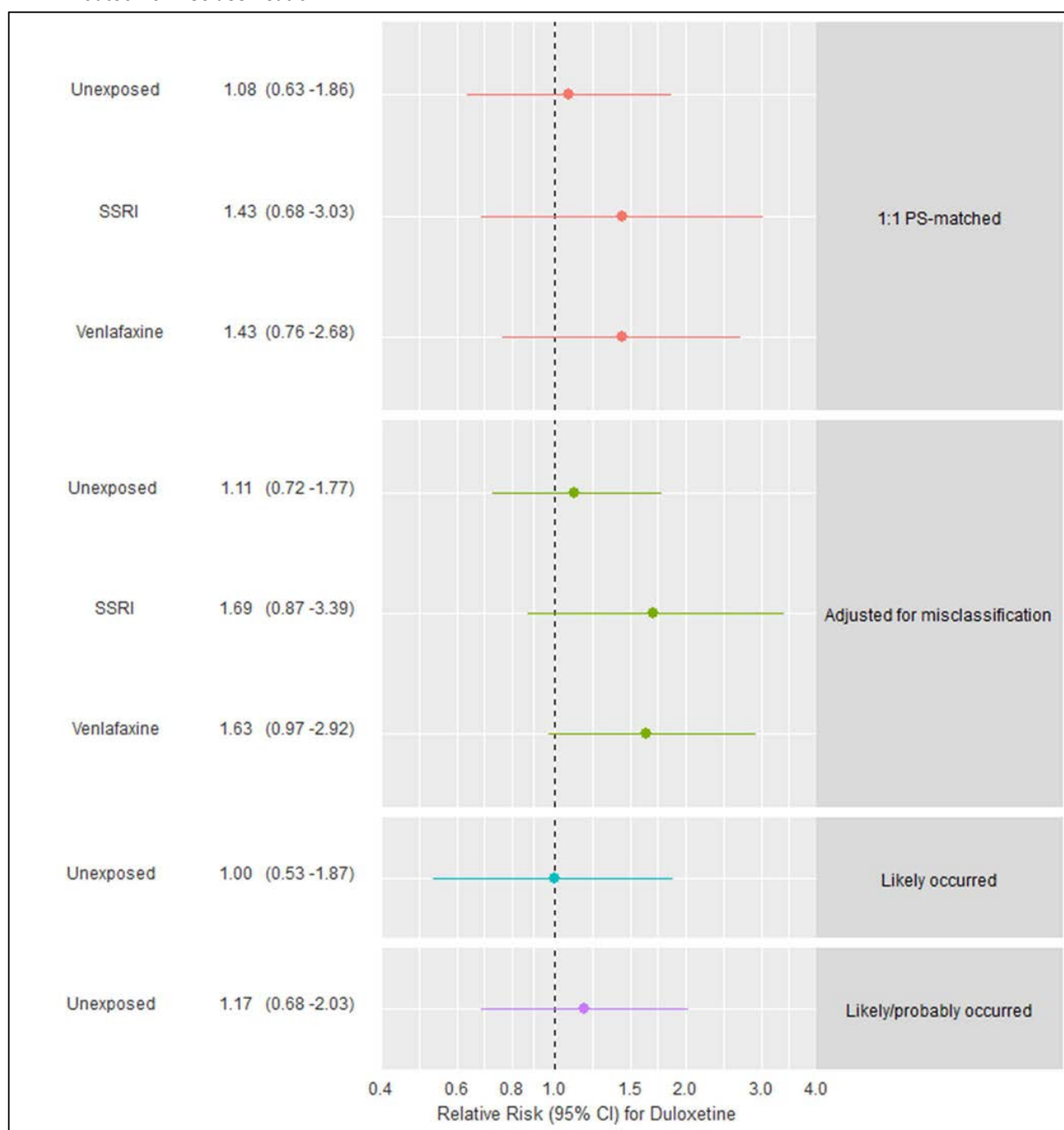
16.2. 7. Risk of preterm birth associated with late pregnancy exposure to duloxetine: sensitivity analyses to address outcome misclassification



16.2. 8. Risk of SGA associated with early pregnancy exposure to duloxetine: sensitivity analyses to address outcome misclassification

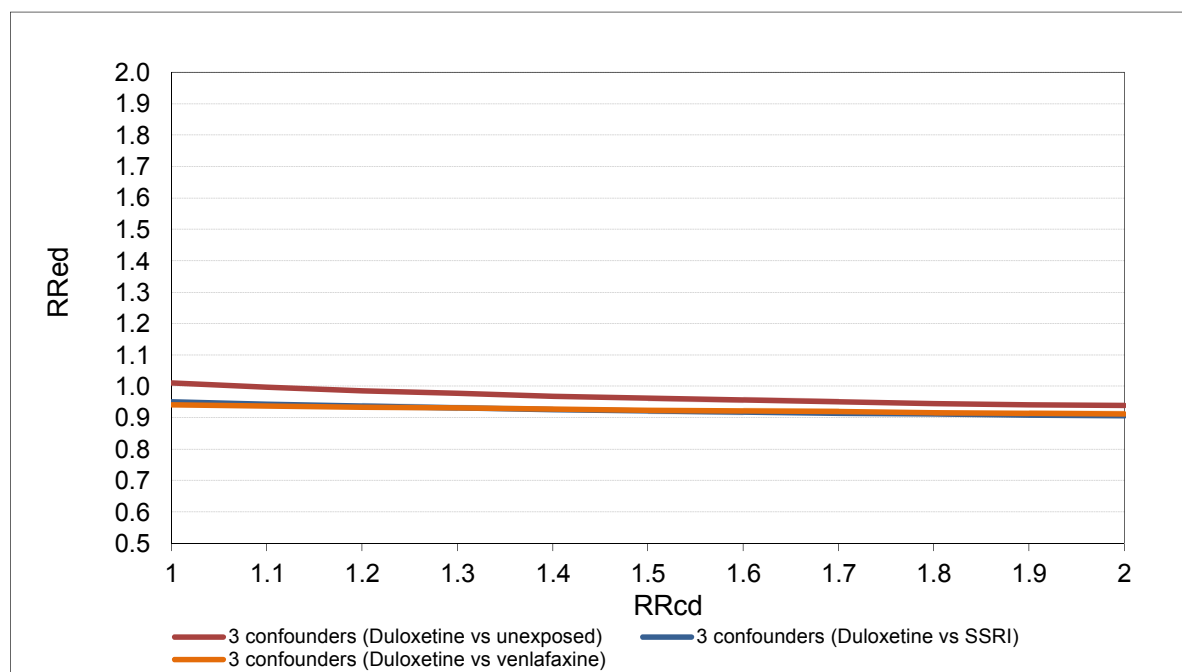


16.2. 9. Risk of SGA associated with late pregnancy exposure to duloxetine: sensitivity analyses to address outcome misclassification

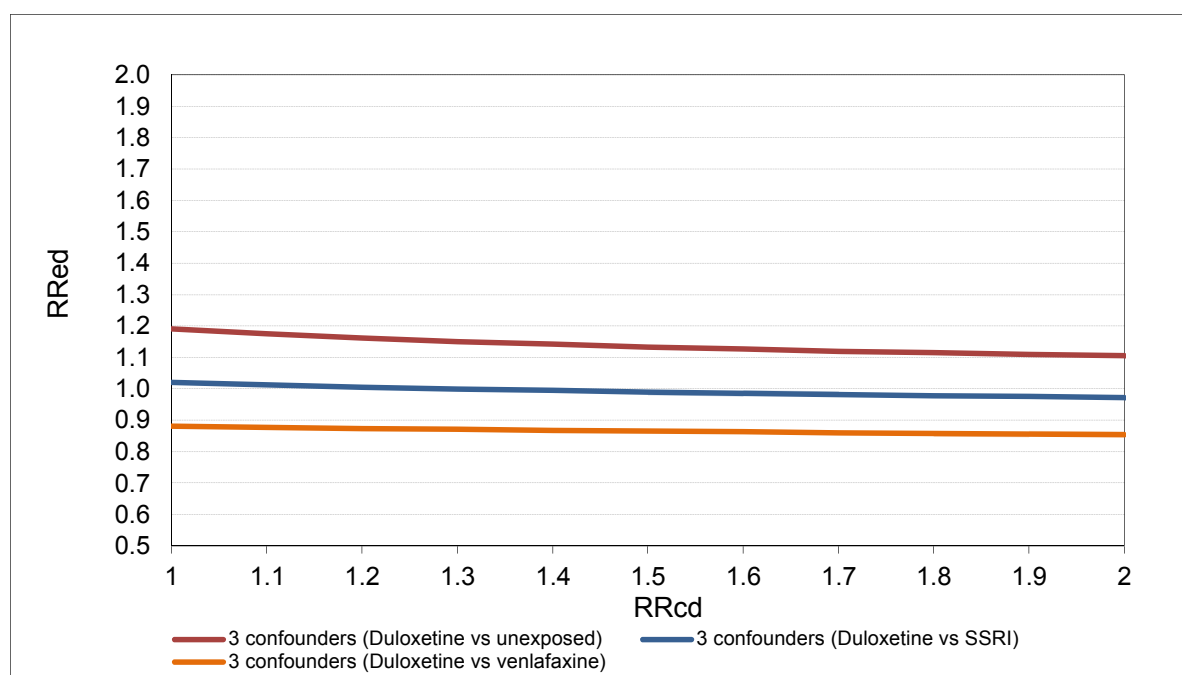


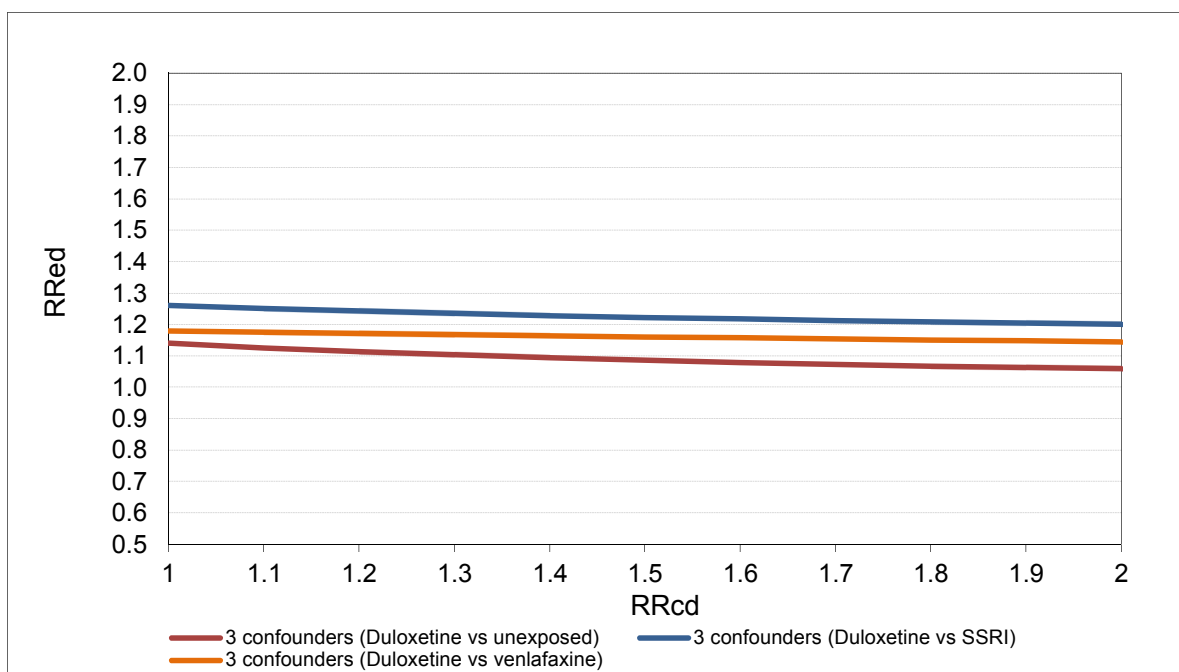
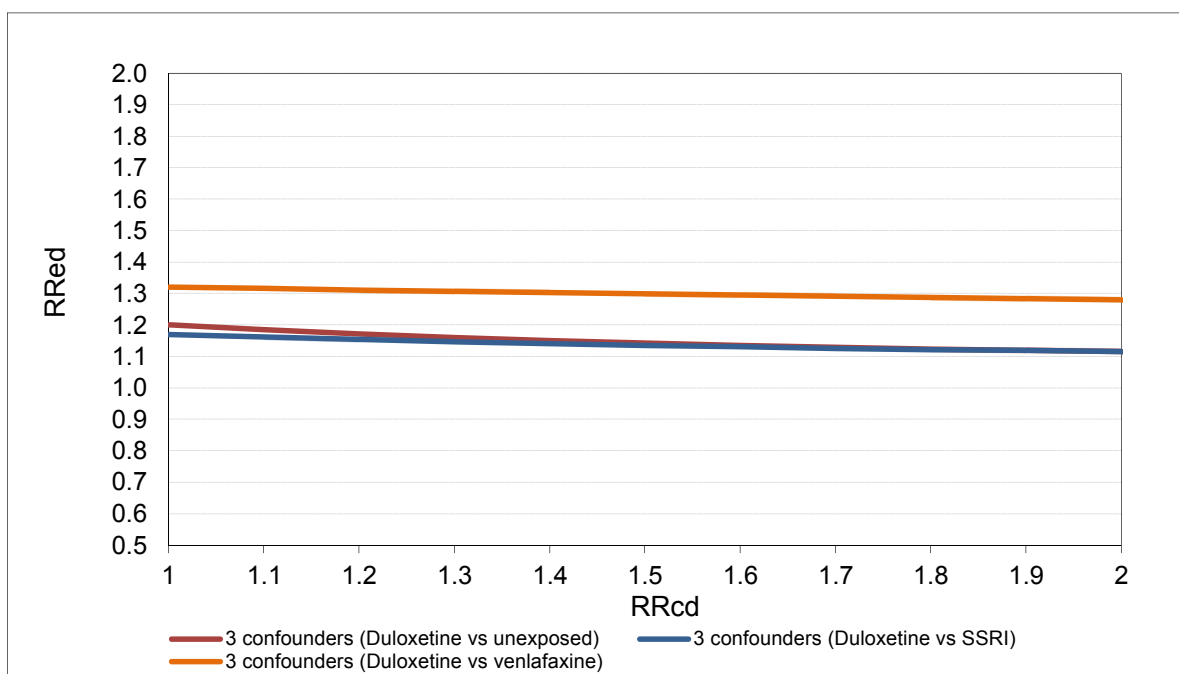
16.2. 10. Preterm/SGA - Sensitivity Analyses #7: External adjustment of the observed relative risk to account for confounding by obesity, smoking, and alcohol using NHANES

Outcome- Preterm (Early exposure period)



Outcome- Preterm (Late exposure period)

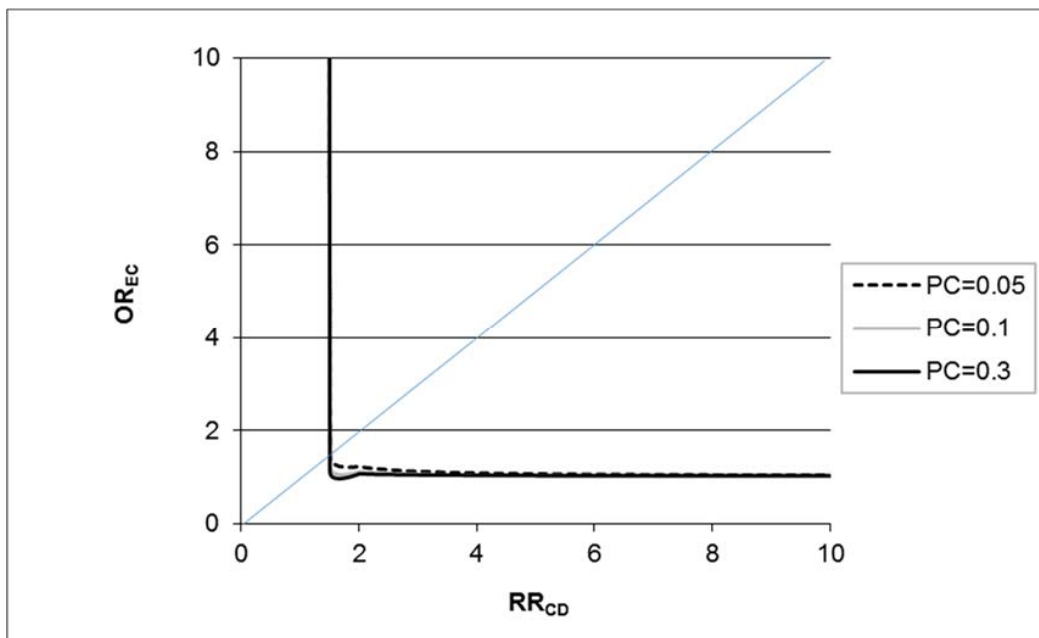


Outcome- SGA (Early exposure period)Outcome- SGA (Late exposure period)

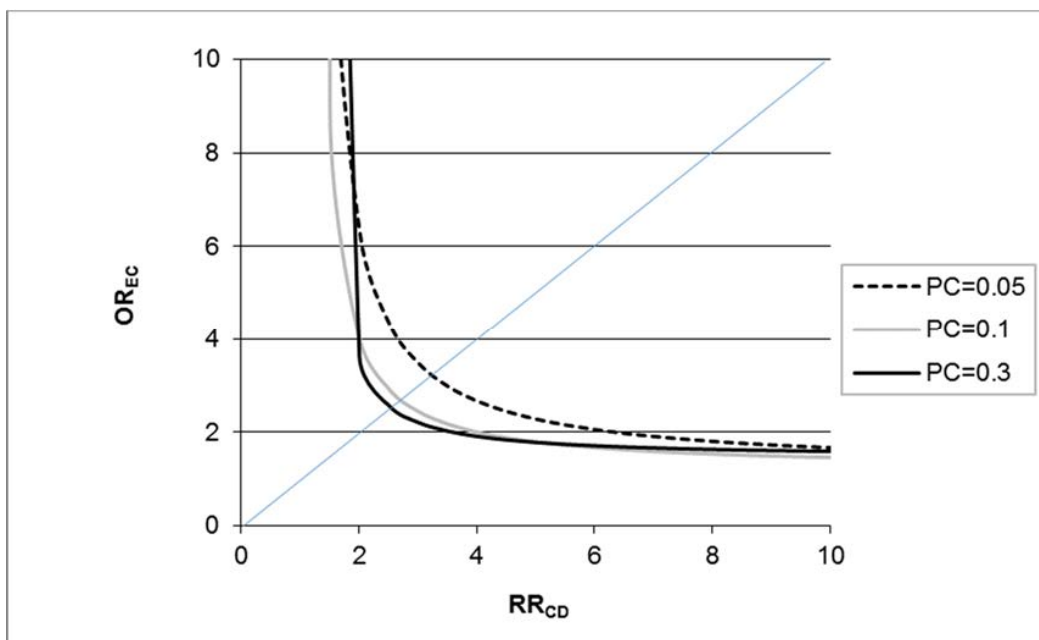
16.2. 11. Preterm/SGA - Sensitivity Analyses #7: Rule out approach for residual confounding

Note: Analyses were only conducted if the estimate from the primary base case analysis showed an increased risk

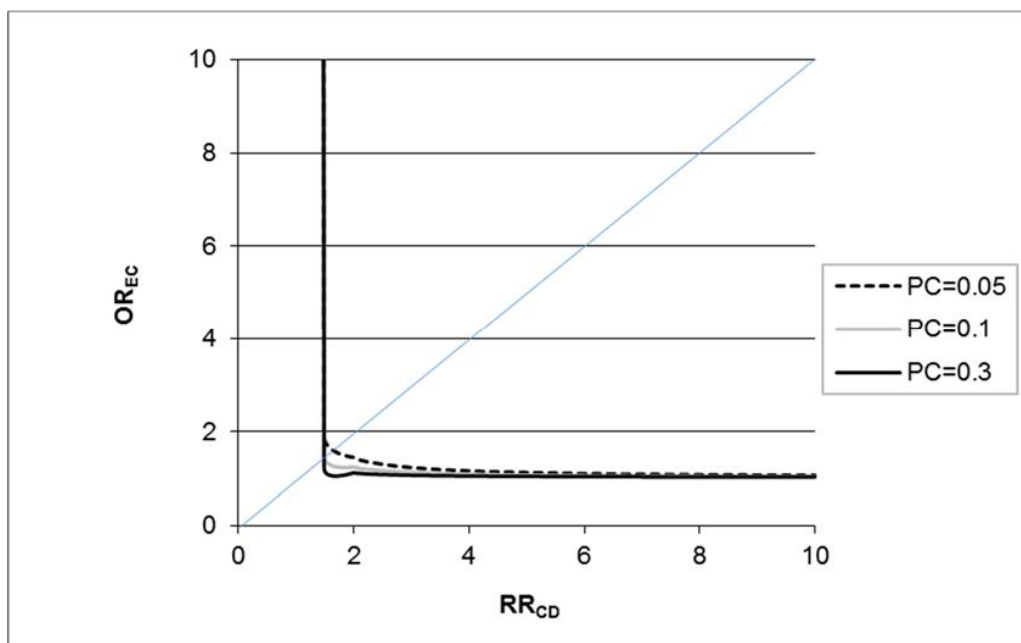
Preterm (Early exposure period)- Duloxetine vs. Unexposed



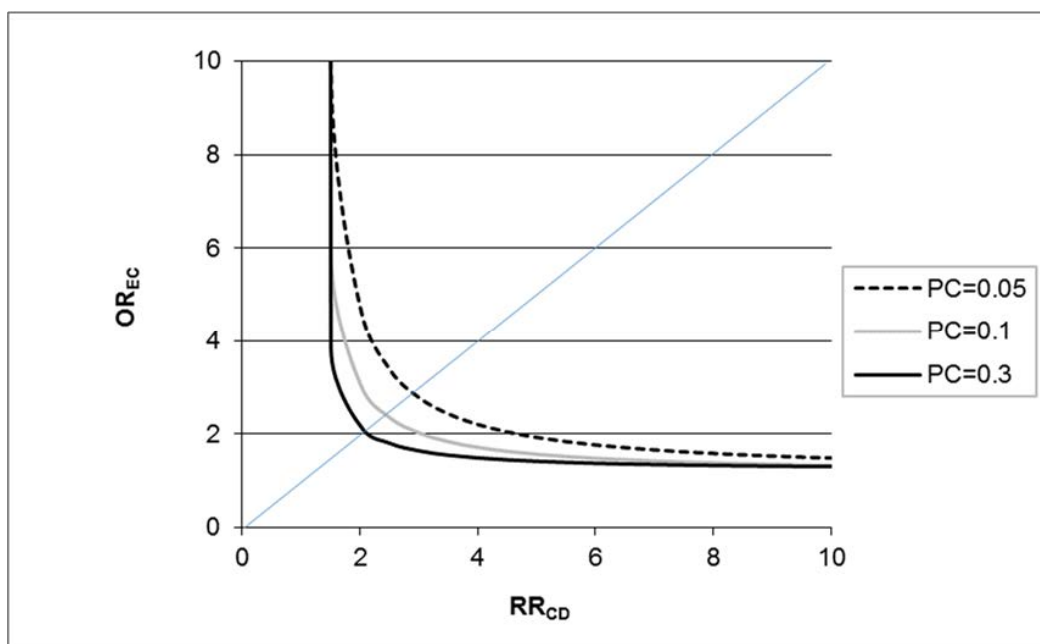
Preterm (Late exposure period)- Duloxetine vs. Unexposed



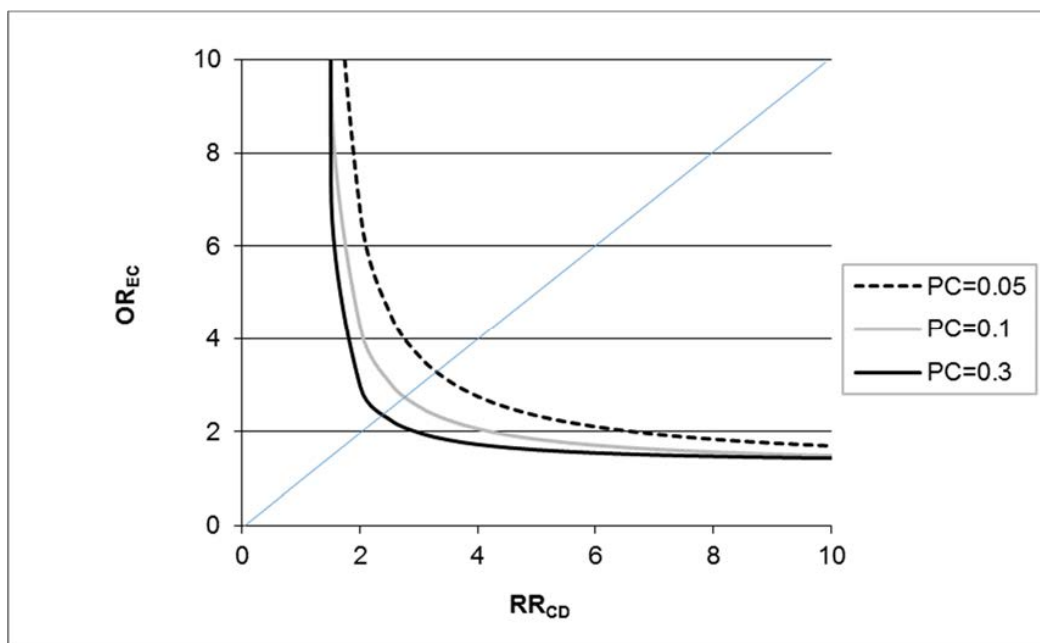
Preterm (Late exposure period)- Duloxetine vs. SSRI



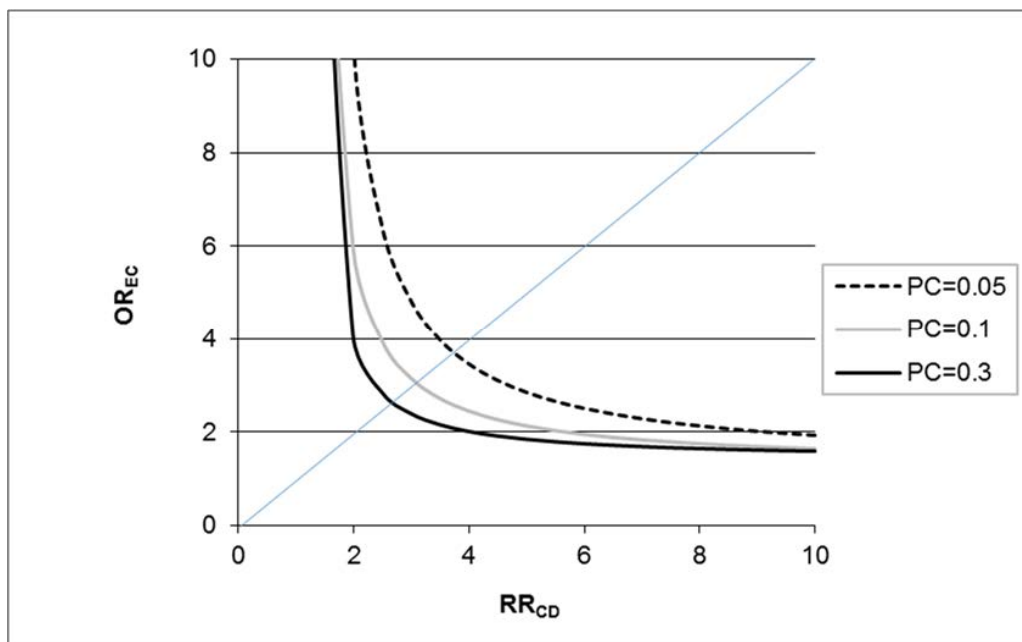
SGA (Early exposure period)- Duloxetine vs. Unexposed



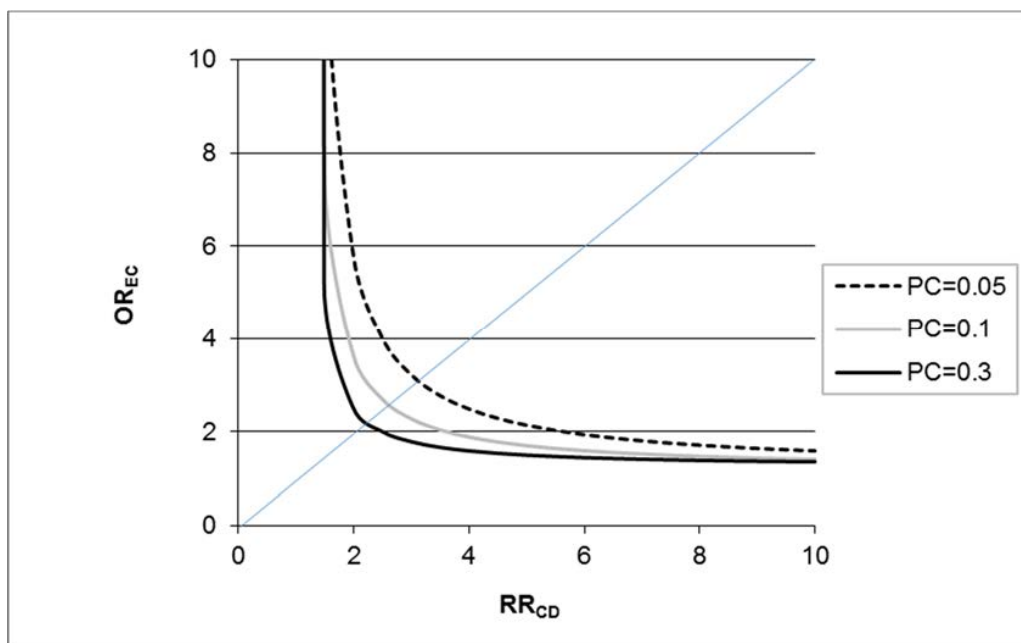
SGA (Late exposure period)- Duloxetine vs. Unexposed



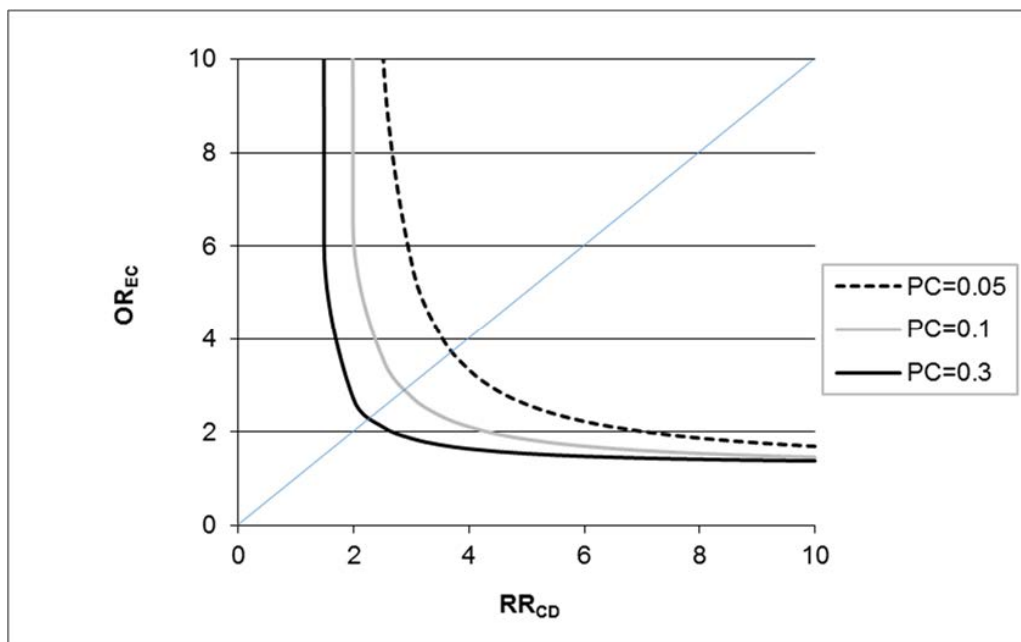
SGA (Early exposure period)- Duloxetine vs. SSRI



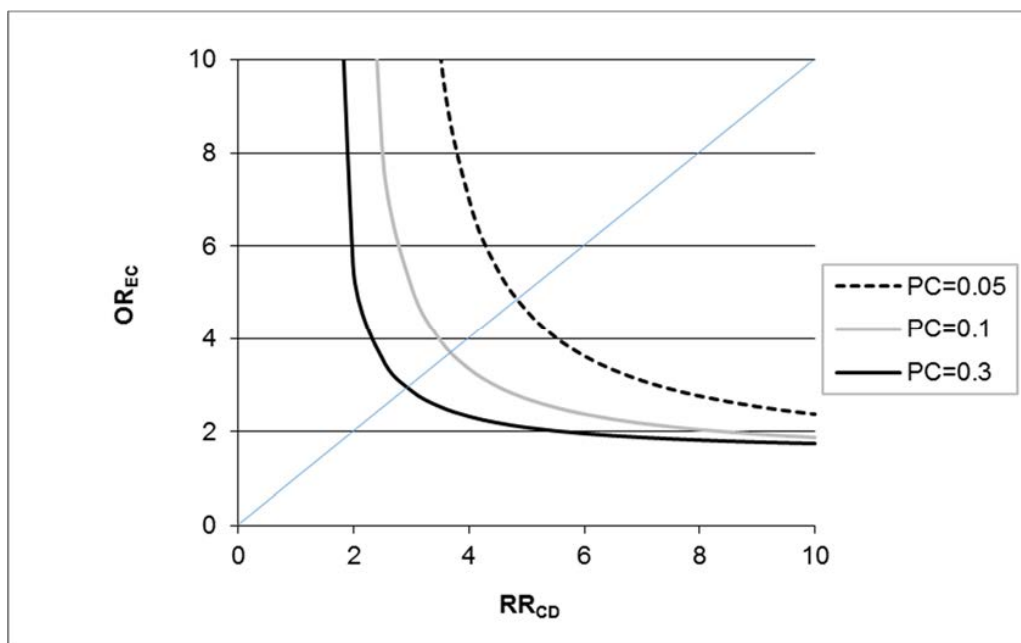
SGA (Late exposure period)- Duloxetine vs. SSRI



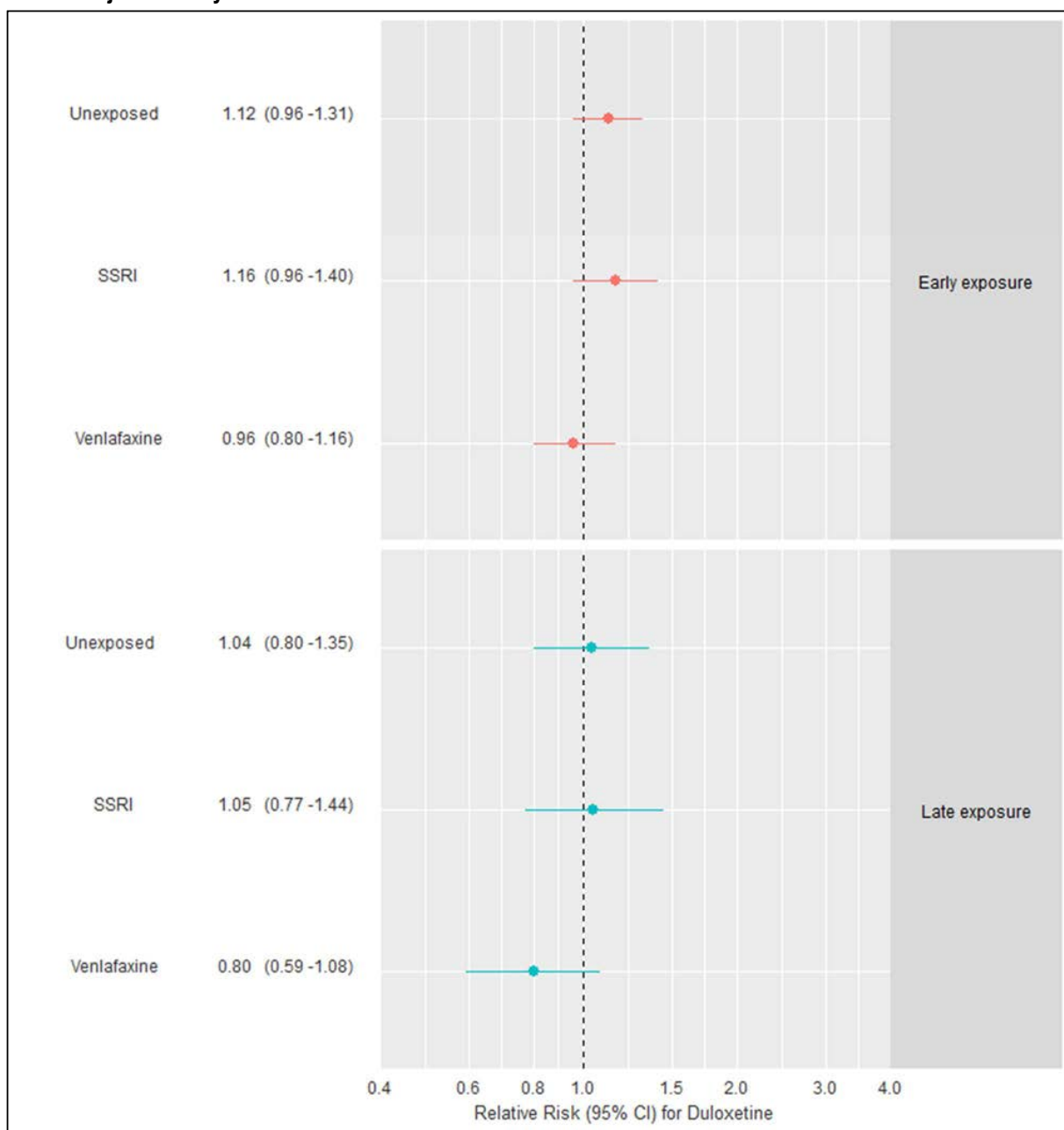
SGA (Early exposure period)- Duloxetine vs. Venlafaxine



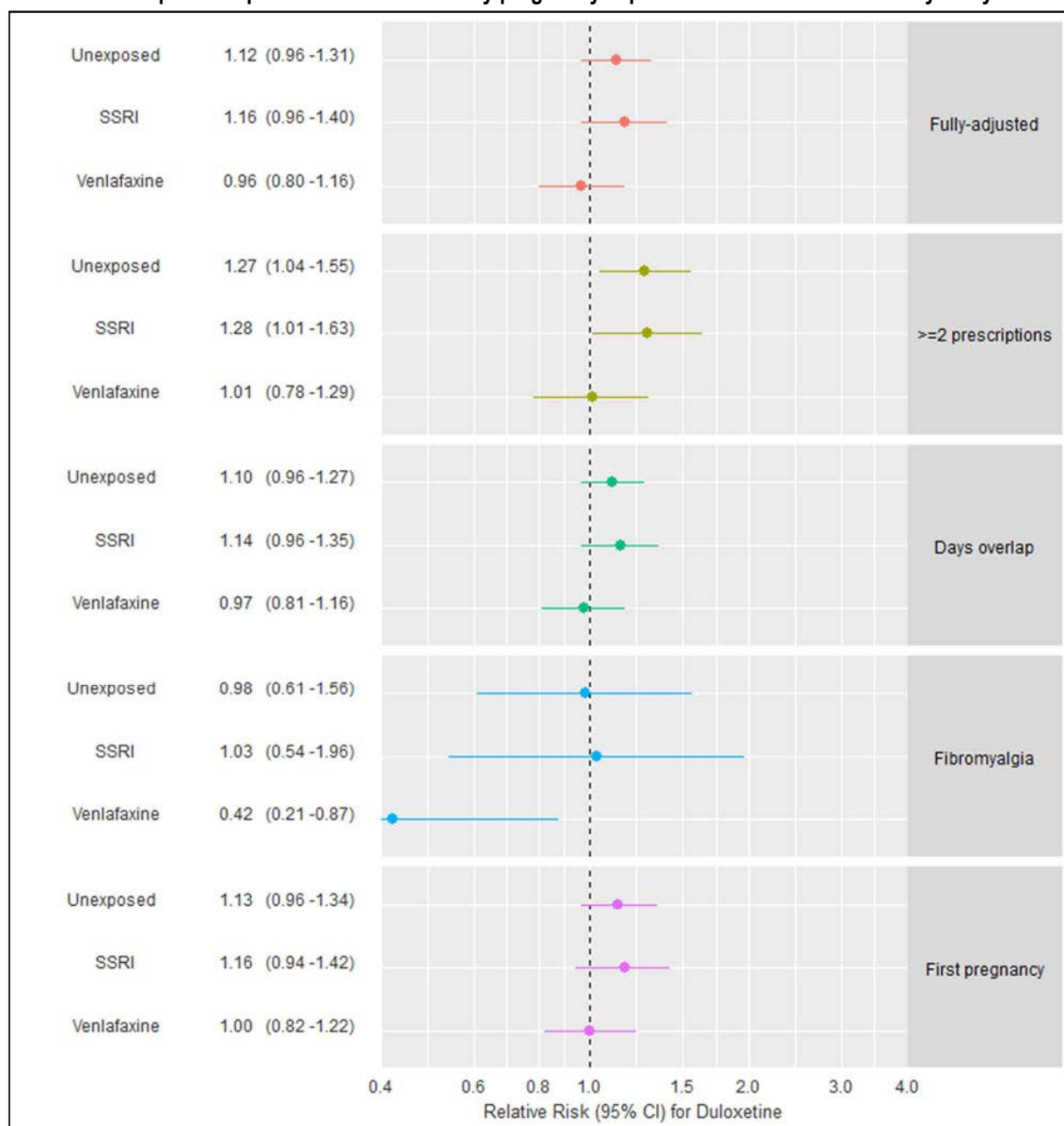
SGA (Late exposure period)- Duloxetine vs. Venlafaxine



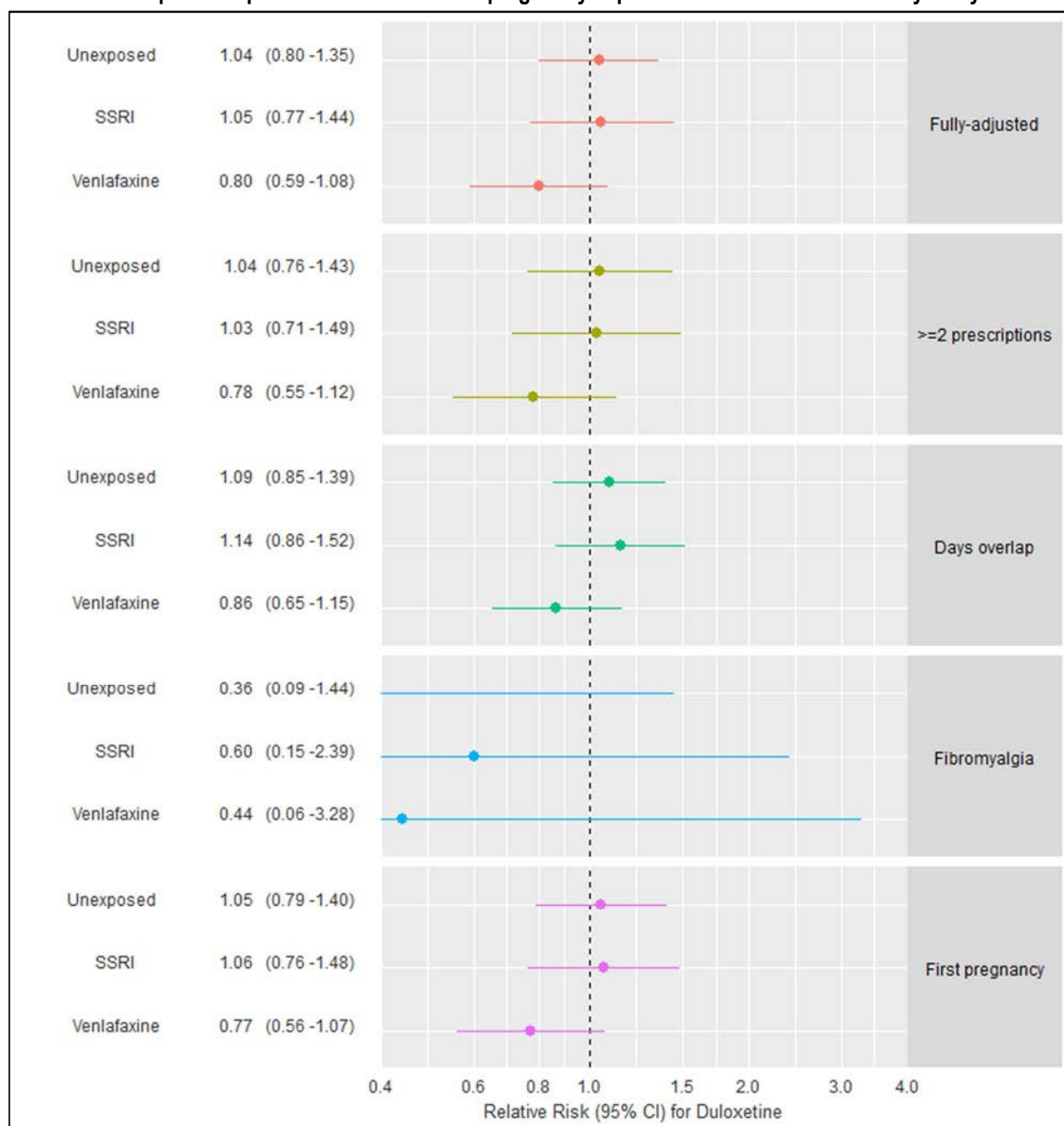
16.3. 1. Risk of preeclampsia associated with early and late pregnancy exposure to duloxetine: fully adjusted analyses



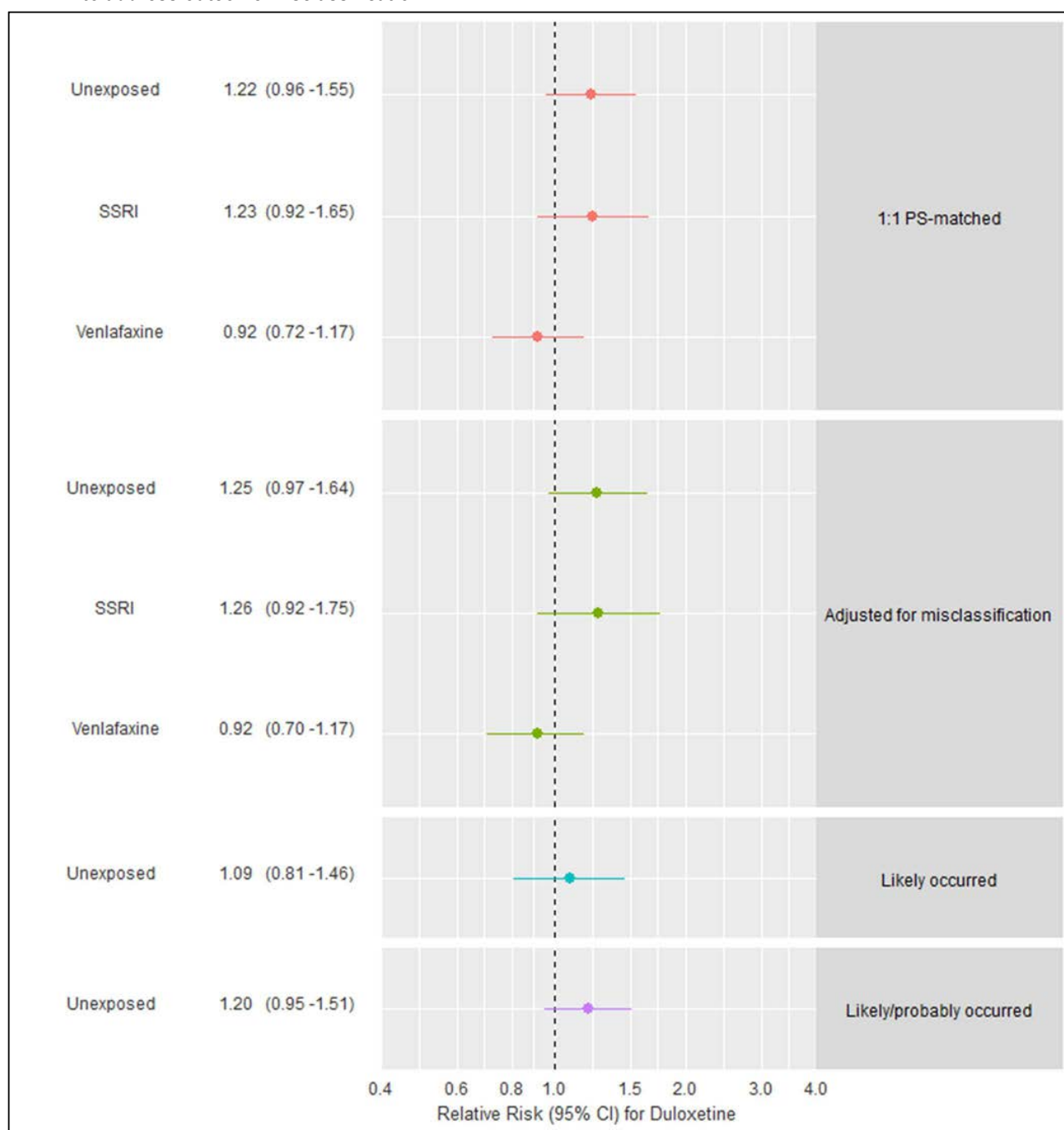
16.3. 2. Risk of preeclampsia associated with early pregnancy exposure to duloxetine: sensitivity analyses



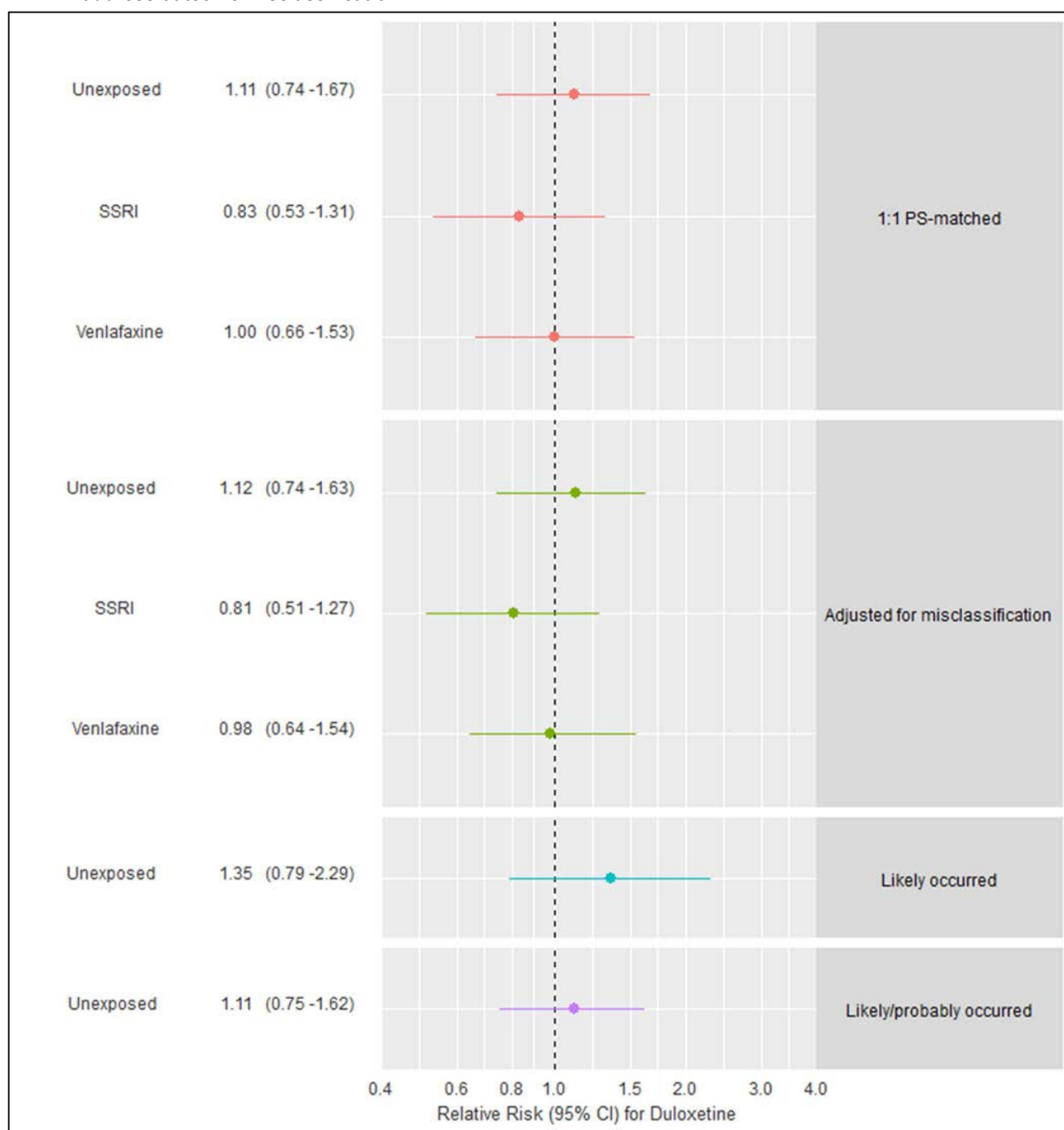
16.3. 3. Risk of preeclampsia associated with late pregnancy exposure to duloxetine: sensitivity analyses



16.3. 4. Risk of preeclampsia associated with early pregnancy exposure to duloxetine: sensitivity analyses to address outcome misclassification

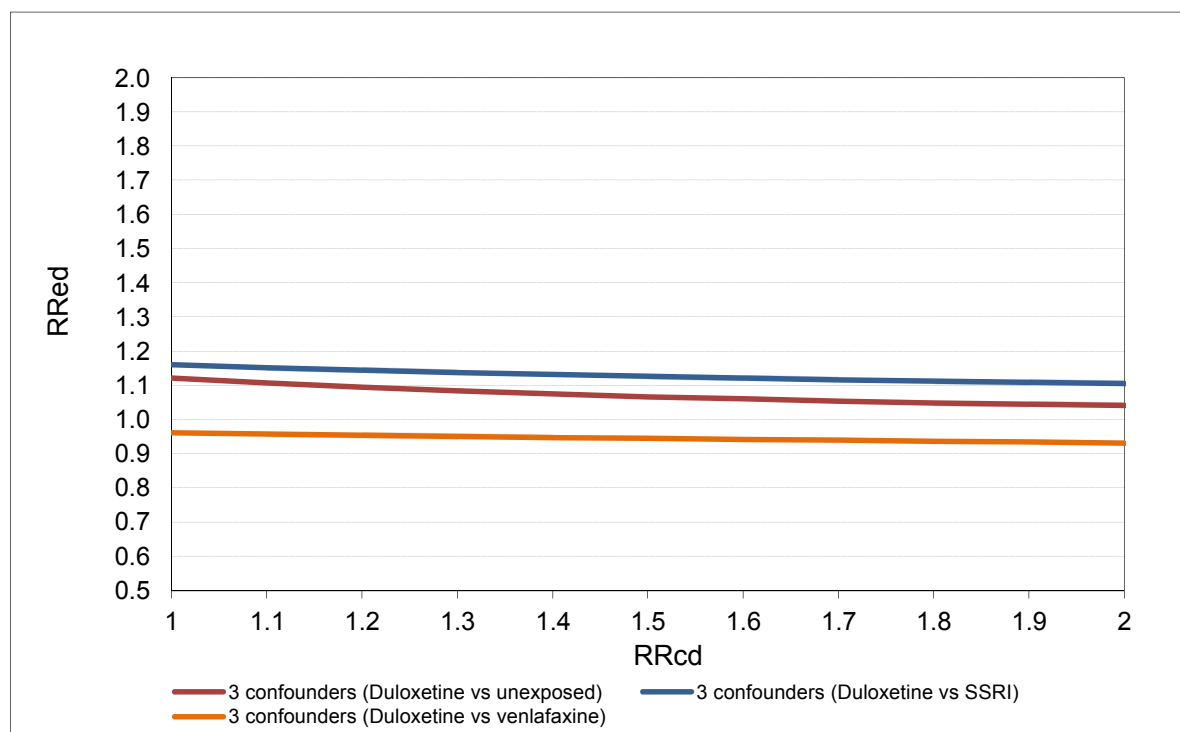


16.3. 5. Risk of preeclampsia associated with late pregnancy exposure to duloxetine: sensitivity analyses to address outcome misclassification

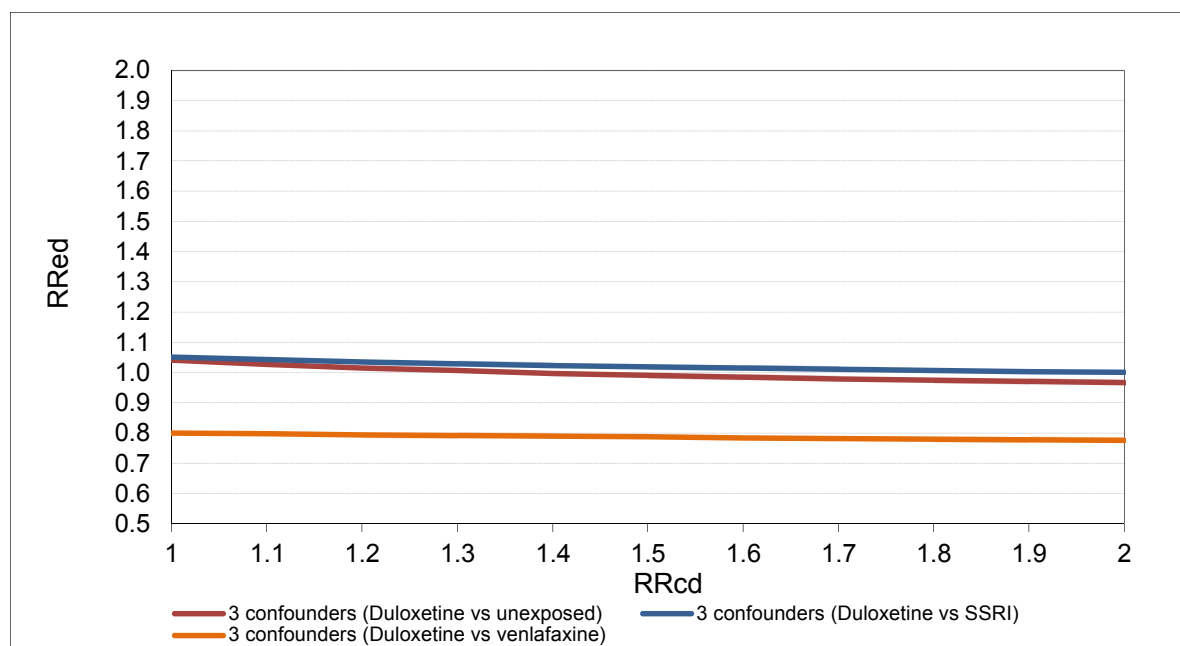


16.3. 6. Preeclampsia - Sensitivity Analyses #7: External adjustment of the observed relative risk to account for confounding by obesity, smoking, and alcohol using NHANES

Preeclampsia (Early exposure period)

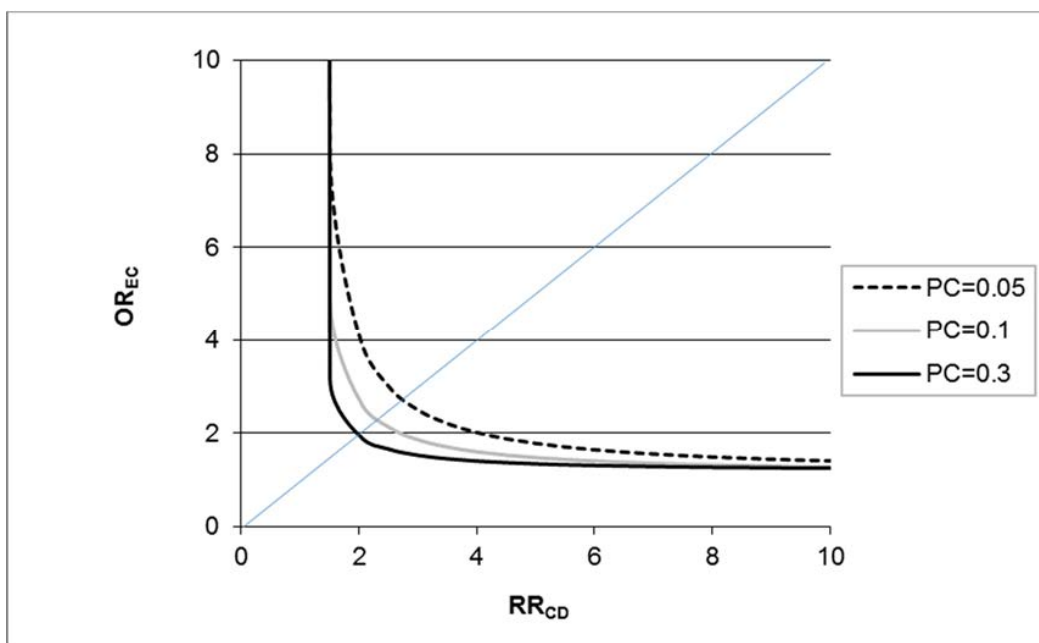


Preeclampsia (Late exposure period)

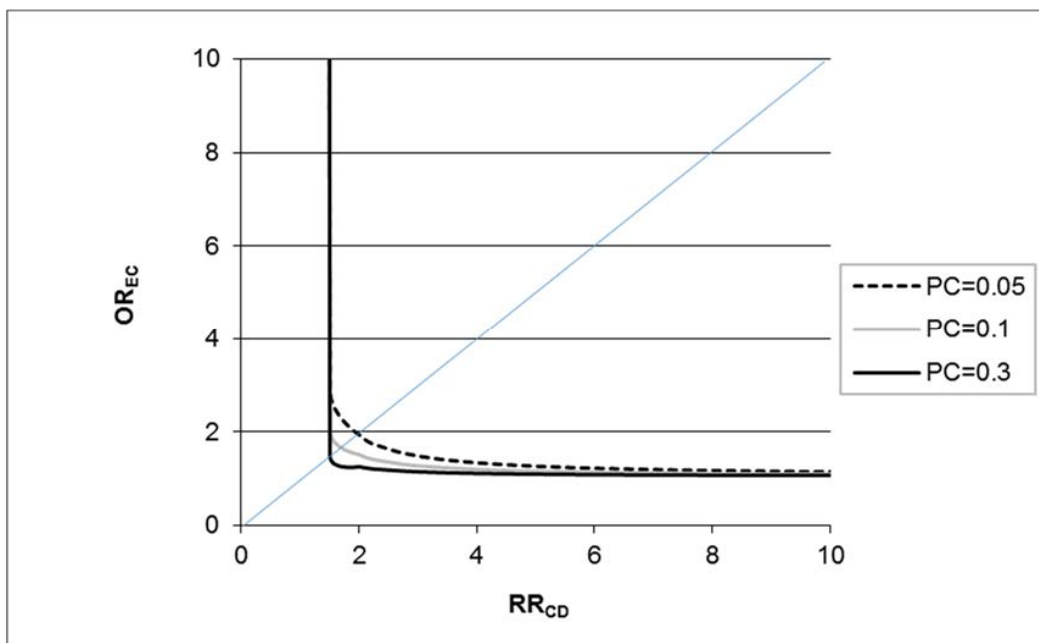


16.3. 7. Preeclampsia - Sensitivity Analyses #7: Rule out approach for residual confounding

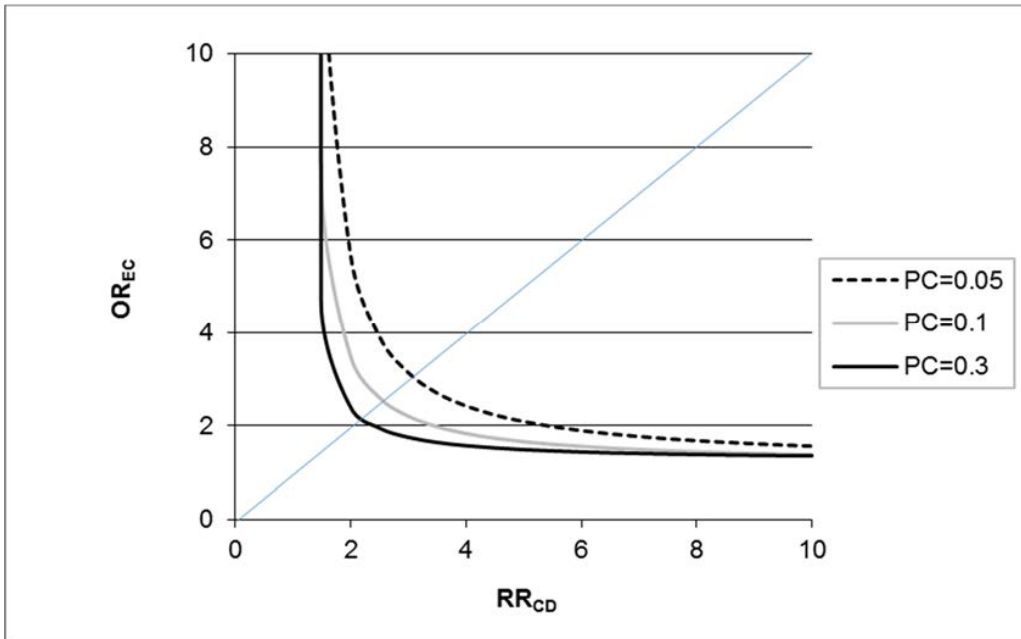
Preeclampsia (Early exposure period)- Duloxetine vs. Unexposed



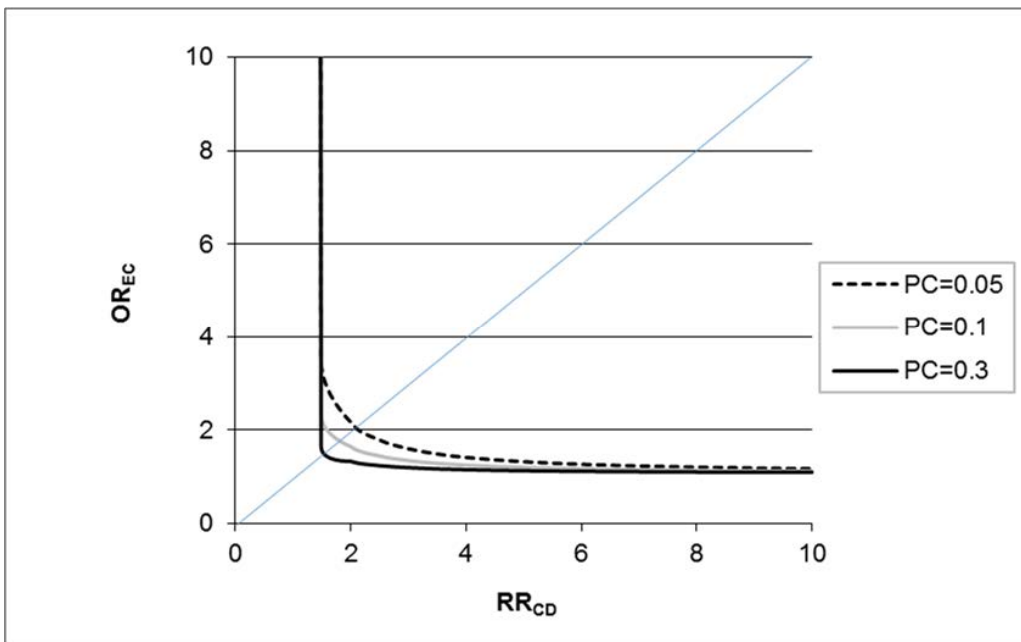
Preeclampsia (Late exposure period)- Duloxetine vs. Unexposed



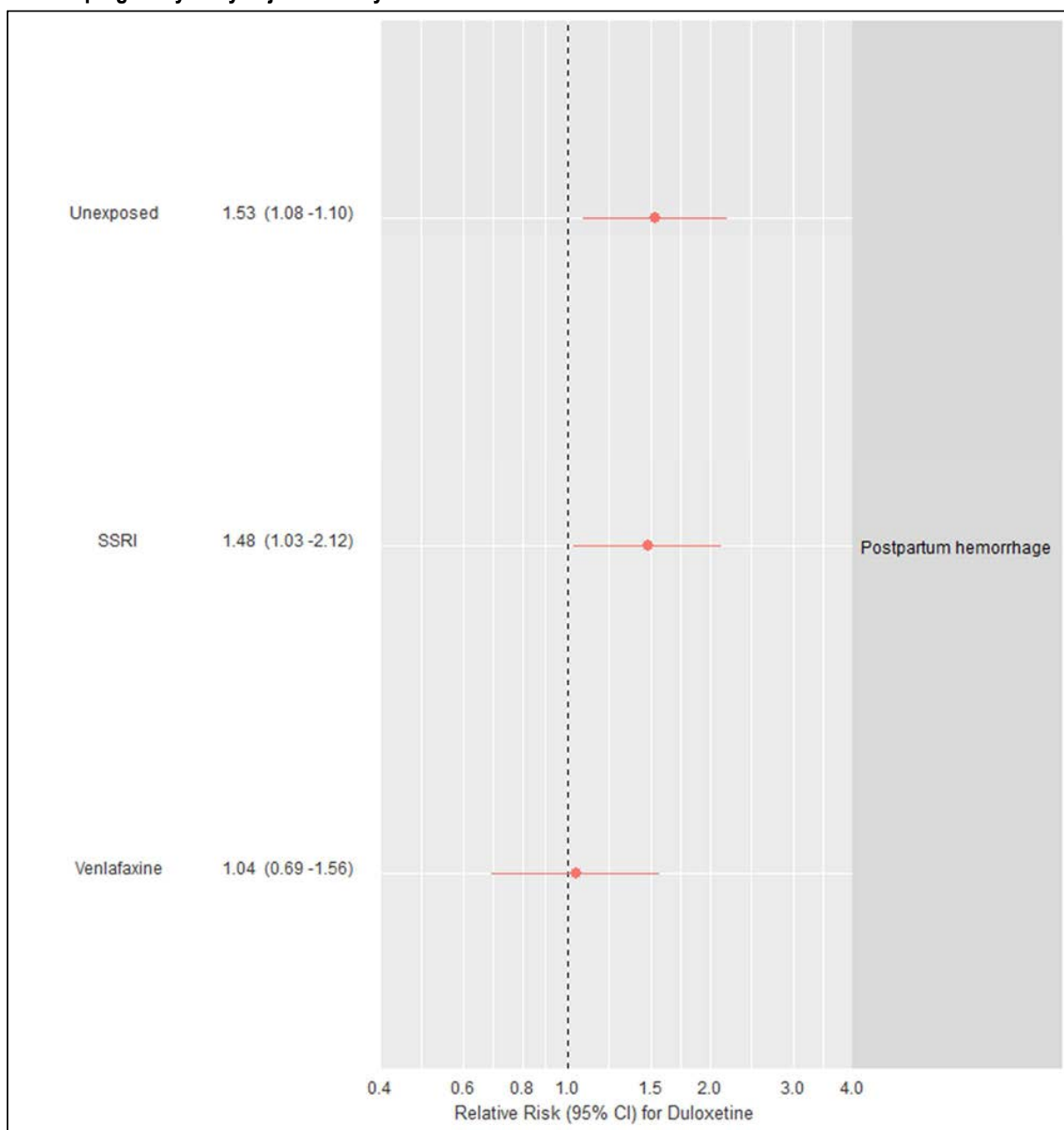
Preeclampsia (Early exposure period)- Duloxetine vs. SSRI



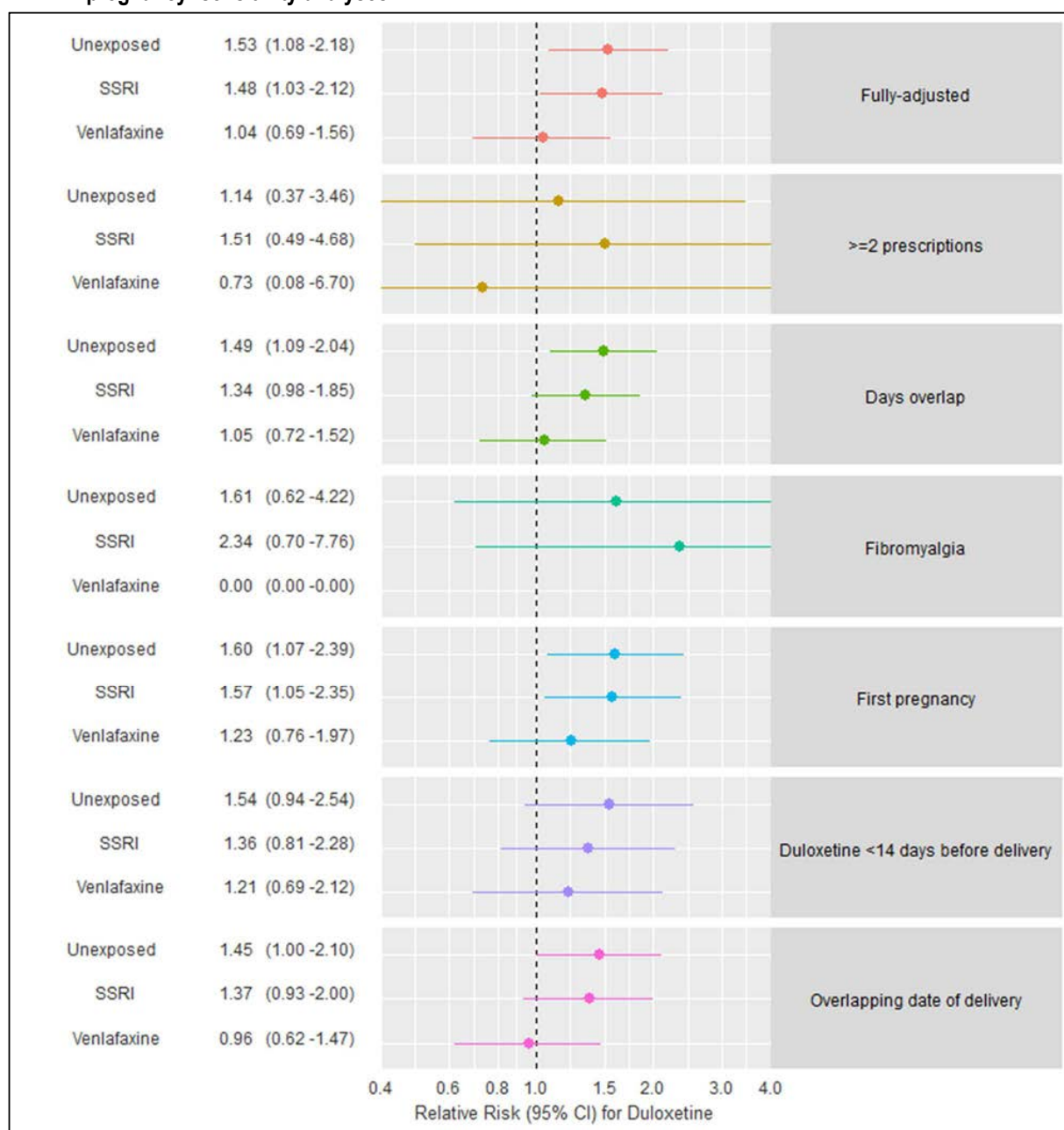
Preeclampsia (Late exposure period)- Duloxetine vs. SSRI



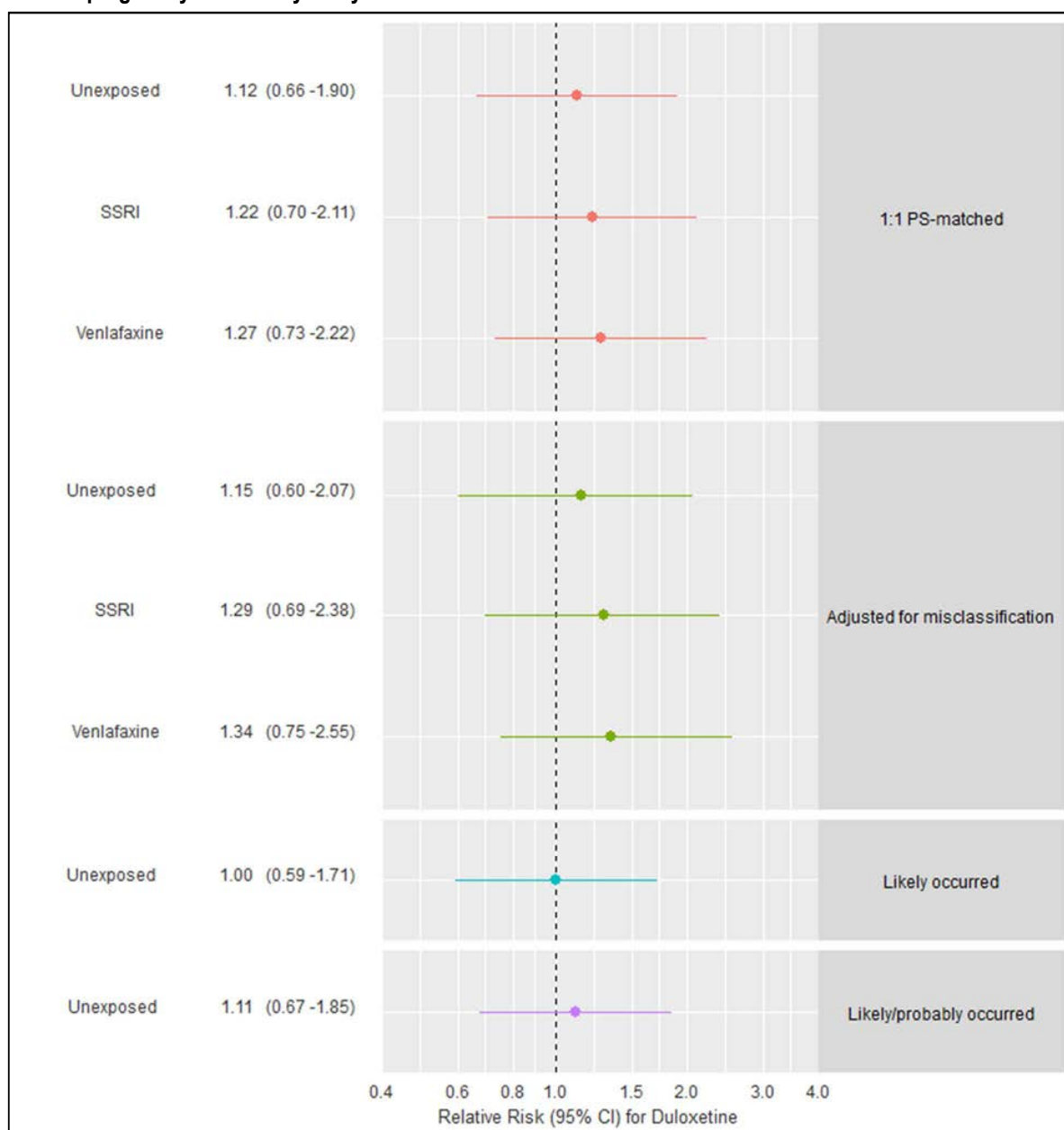
16.4. 1. Risk of postpartum haemorrhage associated with exposure to duloxetine during the final 30 days of pregnancy: fully adjusted analyses



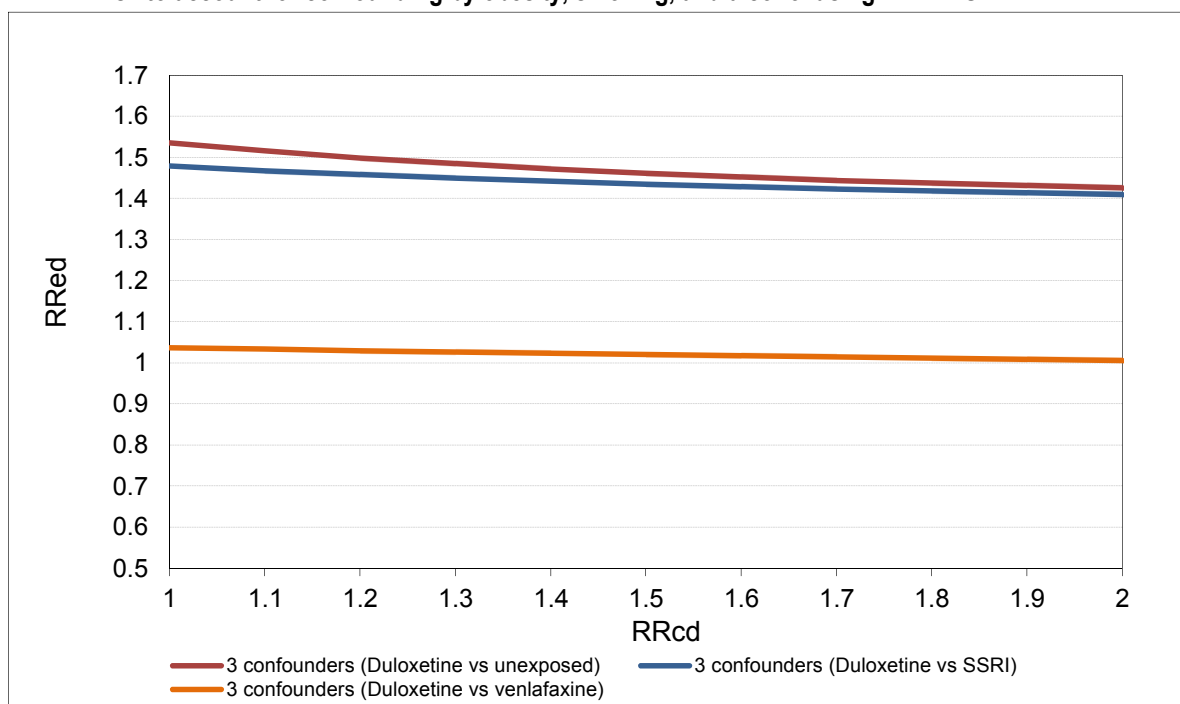
16.4. 2. Risk of postpartum haemorrhage associated with exposure to duloxetine during the final 30 days of pregnancy: sensitivity analyses



16.4. 3. Risk of postpartum haemorrhage associated with exposure to duloxetine during the final 30 days of pregnancy: sensitivity analyses to address outcome misclassification

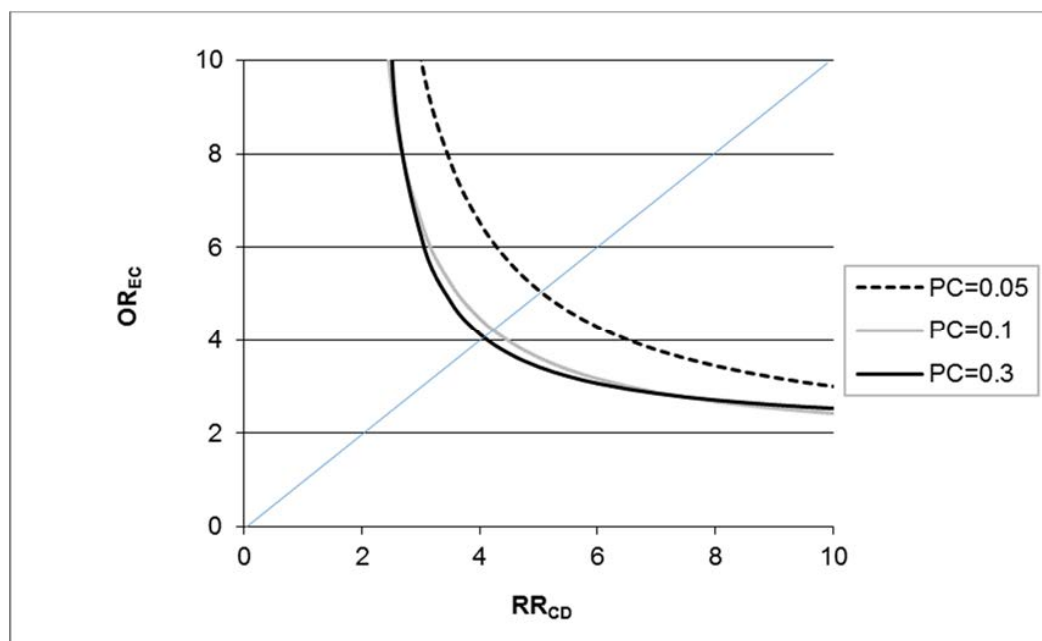


16.4. 4. Postpartum Haemorrhage - Sensitivity Analyses #7: External adjustment of the observed relative risk to account for confounding by obesity, smoking, and alcohol using NHANES

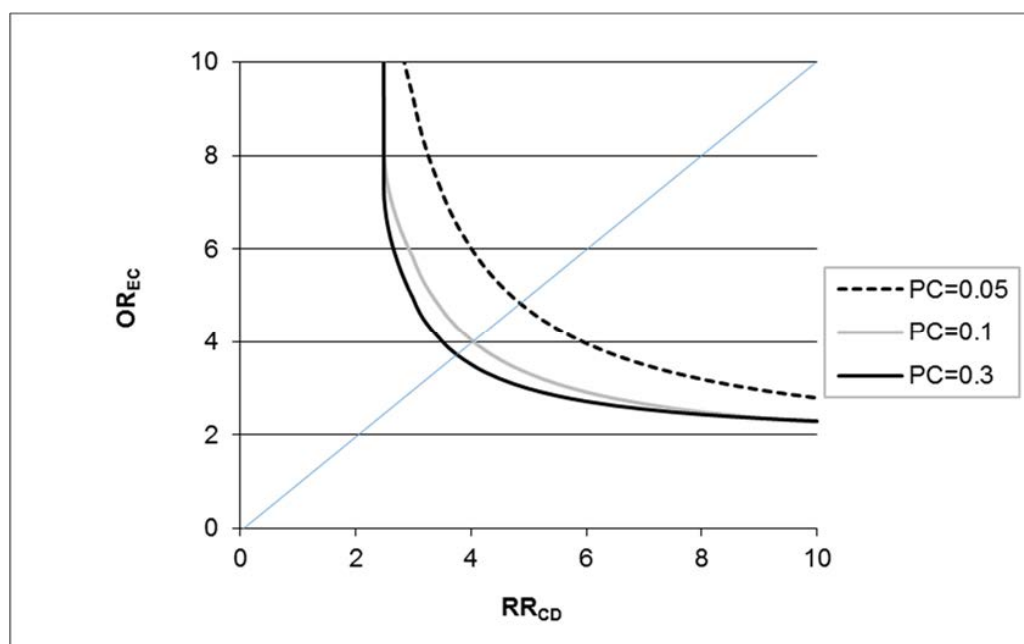


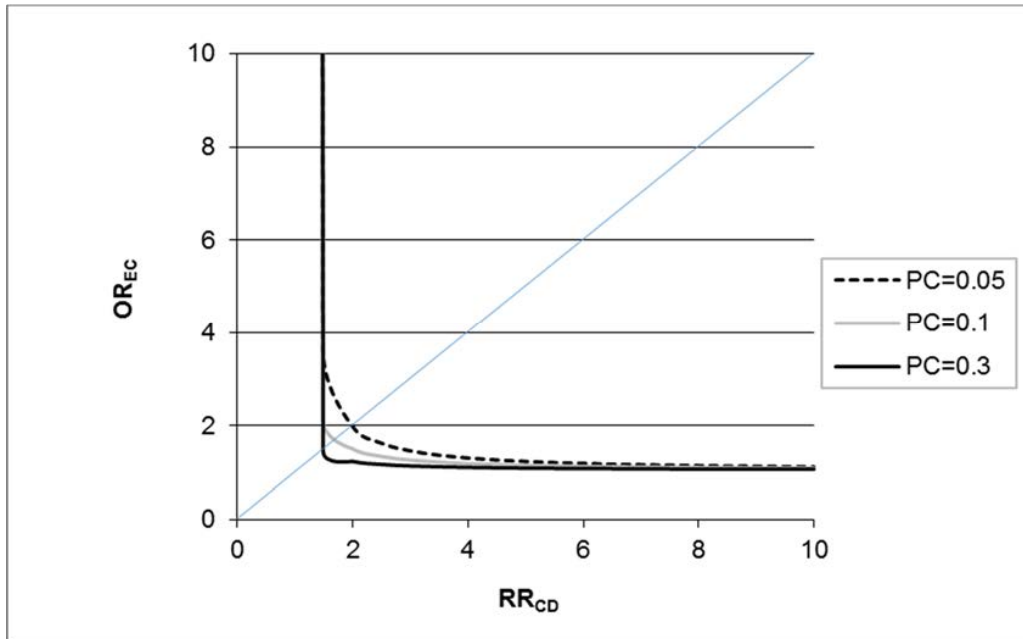
16.4. 5. Postpartum Haemorrhage - Sensitivity Analyses #7: Rule out approach for residual confounding

Postpartum Hemorrhage- Duloxetine vs. Unexposed

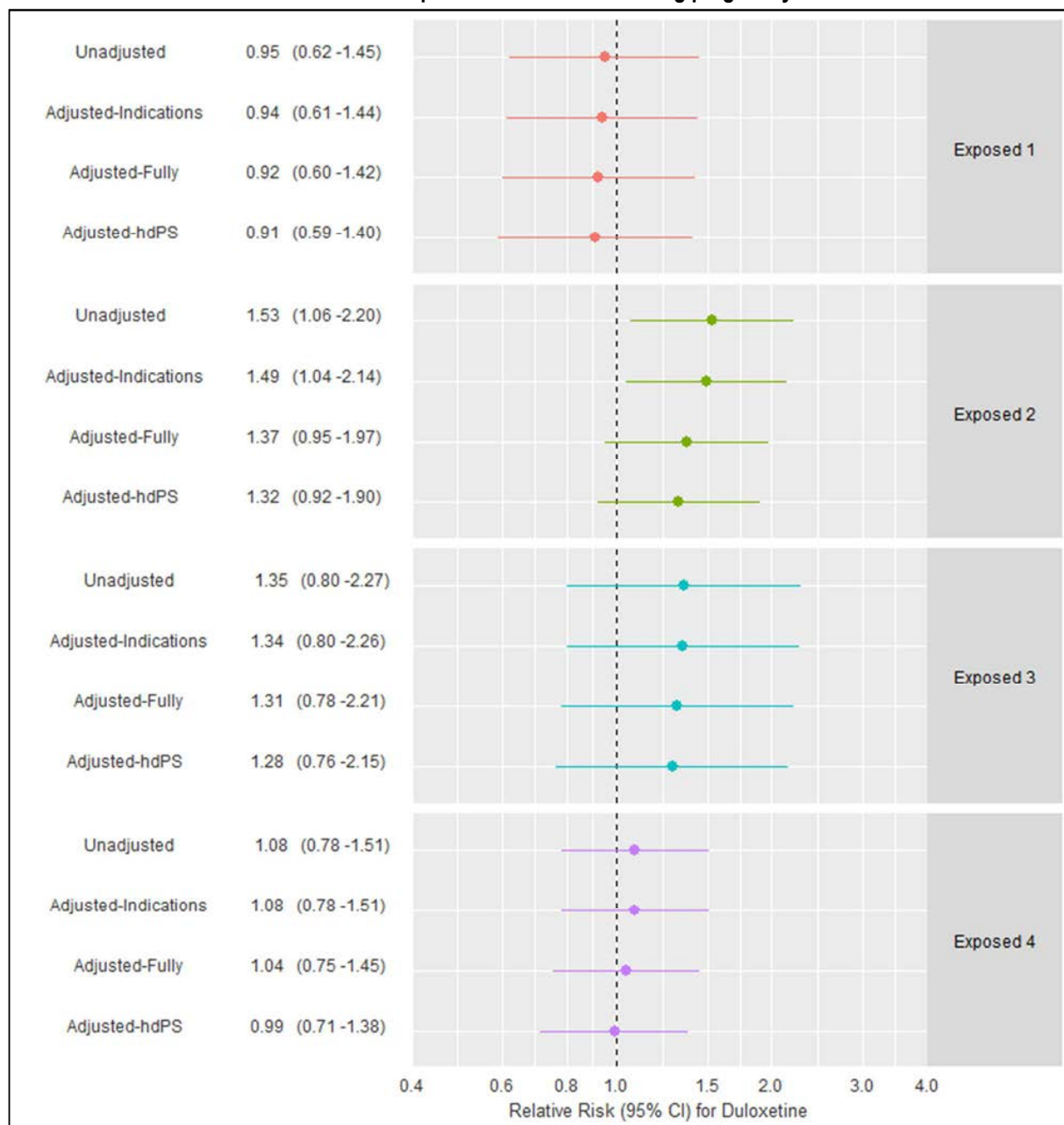


Postpartum Hemorrhage- Duloxetine vs. SSRI



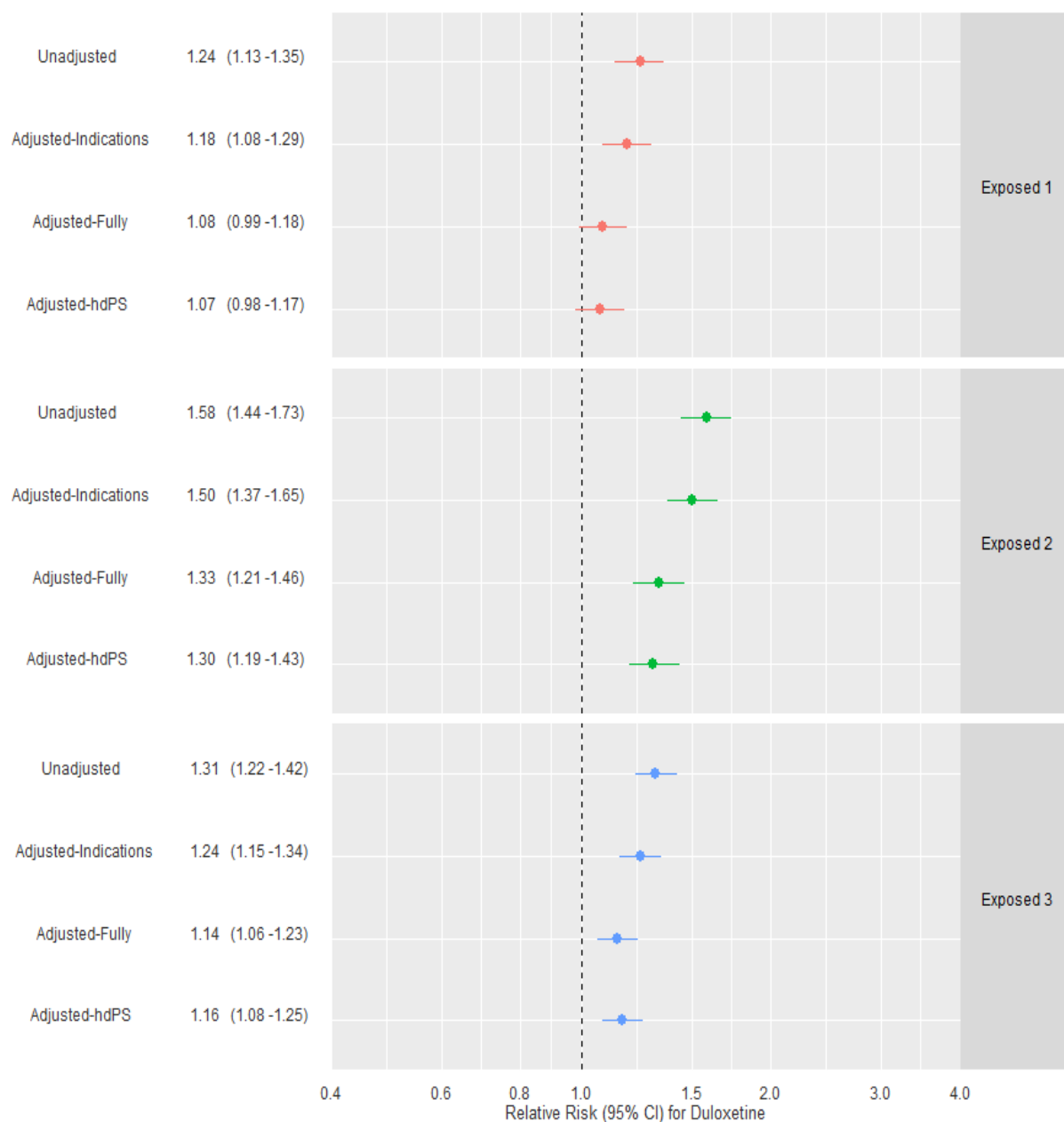
Postpartum Hemorrhage- Duloxetine vs. Venlafaxine

16.5. 1. Risk of stillbirth associated with exposure to duloxetine during pregnancy



Note: Exposed 1 = LMP to LMP + 30 days; Exposed 2 = LMP + 30 days to LMP + 120 days; Exposed 3 = LMP + 120 days to LMP + 196 days; Exposed 4 = LMP to LMP + 196 days

16.5. 2. Risk of spontaneous abortion associated with exposure to duloxetine during pregnancy



Note: Exposed 1 = LMP to LMP + 30 days; Exposed 2 = LMP + 30 days to LMP + 63 days; Exposed 3 = LMP to LMP + 63 days

Annex 1. List of standalone documents

Not applicable.

Annex 2. Additional information

Appendix 1: External adjustment of the observed crude and adjusted relative risk (RR_{ED}) using the NHANES data (1999-2014) to estimate the prevalence of confounders (obesity, smoking and alcohol use) in a similar population.

We identified 15,963 women of childbearing age (18-55 years) who reported prescriptions either for duloxetine (n=68), SSRI (n=979), venlafaxine (n=143), or SNRI (n=209), and those who didn't have prescriptions ("unexposed") for any of these medications (n=14,564) using data from the National Health and Nutrition Examination Survey (NHANES) from the Centers for Disease Control and Prevention for the years 1999-2014 (<https://www.cdc.gov/nchs/nhanes/index.htm>). We assessed the prevalence of obesity (defined as BMI ≥ 30 kg/m²), alcohol use (defined as at least 12 alcohol drinks per year) and smoking (defined by current smoking), stratified by exposure group; these are shown in Table 13. We then modelled a range of strengths of association between these factors and the outcomes of interest (ranging from a relative risk of 1.0 and 2.0) and, based on the difference in the prevalence of these risk factors in each of the contrast being made, calculated corrected relative risks. The corrected relative risk estimates are shown in Figure 16.1.6; Figure 16.1.7; Figure 16.2.10; Figure 16.3.6; Figure 16.4.4.

Table 13 Prevalence of obesity, smoking, and alcohol use by exposure group according to NHANES 1999-2014

	Women 18-55					Women 18-55 with Depression				
	Dulo-xetine	SSRI	Venla-faxine	SNRI	non-exposed	Dulo-xetine	SSRI	Venla-faxine	SNRI	non-exposed
	68	979	143	209	14,564	25	172	29	53	778
Obese (BMI $\geq$ 30)	53.8	42.1	47.6	49.7	31.9	52.7	56.4	60.6	55.2	44.6
Current smoking	33.0	32.0	42.0	39.4	21.6	57.6	43.4	48.1	54.6	43.3
Alcohol use ($\geq$ 12 alcohol drinks/1 yr)	68.2	68.7	75.5	73.7	59.1	77.1	72.9	72.7	73.8	72.2

Appendix 2: Rule out residual confounding

Figure 16.1.8; Figure 16.1.9; Figure 16.2.11; Figure 16.3.7; and Figure 16.4.5 display the strengths of the association (OR) between exposure and a potential unmeasured confounder (OR_{EC}) and the association (RR) between confounder and outcome (RR_{CO}) that would be required to fully explain the observed increase in the outcomes of interest associated with duloxetine use if no such increase existed. We modelled this based on three different hypothetical confounder prevalences in the unexposed (black line: prevalence of confounder (P_c) = 0.30; grey line: P_c = 0.1; black dotted line: P_c = 0.05). Each line splits the area into two. The upper right area represents all combinations of an association (OR) between exposure and confounder (OR_{EC}) and an association between confounder and outcome (RR_{CO}) that would create confounding by an unmeasured factor strong enough to move the point estimate of RR to the null value ($RR=1$) or beyond. The area to the lower left represents all parameter combinations that would not be able to move the estimated RR toward the null.

Appendix 3: Impact of restriction to livebirths

The cohorts for the analysis of congenital malformations contained information on livebirths, and not pregnancies that ended in stillbirth or spontaneous or therapeutic abortions. If livebirth frequency is the same in the duloxetine exposed and unexposed pregnancies, within the levels of the covariates included as potential confounders, then the relative risk estimates obtained from our analyses will be unbiased. However, if non-livebirths occur more frequently in the duloxetine exposed pregnancies then estimates from our main analysis may be biased. We therefore sought to quantify the potential impact of missing non-livebirths using methods previously described in detail and employed in our prior evaluations of the teratogenic potential of medications (see N Engl J Med. 2014 Jun 19;370(25):2397-407; BMJ. 2015 Mar 17;350:h1035). In this sensitivity analysis, we assumed that the frequency of non-livebirth (which included stillbirth and spontaneous or therapeutic abortions) in non-malformed fetuses is 20%. We then modeled a range of livebirth probabilities in the unexposed malformed, ranging from 70% to 50%. We then assessed the potential impact of a 10% to 20% higher and 10% to 20% lower frequency of non-livebirth among the duloxetine exposed (again, within levels of the covariates adjusted for through the use of propensity scores) and generated corrected relative risk estimates based on the risk estimates from the fully adjusted analysis. (Figure 16.1.10; Figure 16.1.11)

Appendix 4: Chart based outcome validation study

To validate claims-based algorithms for identifying study outcomes, we linked a subset of the MAX pregnancy cohort to hospital medical records which were then used to define the positive predictive value (PPV) of these algorithms. Specifically, we linked the medical records of mothers in the MAX pregnancy cohort who delivered between 2000-2010 within Partners HealthCare System. The outcomes of interest validation were small for gestational age (SGA), preeclampsia, non-cardiac congenital malformations, postpartum hemorrhage, and preterm delivery.

A total of 10,899 pregnancies in the MAX cohort were linked to the EHR in Partners. Within this linked cohort, we identified 152 cases of SGA, 574 cases of preeclampsia, 269 cases of non-cardiac congenital malformation, 341 cases of PPH, and 696 cases of preterm delivery based on our claims-based algorithms.

The medical records of 50 randomly sampled cases for each outcome were independently reviewed by physicians to confirm the presence of the condition; disagreements were resolved by a third physician reviewer. We calculated the positive predictive values (PPVs) and 95% confidence intervals (CIs) of pre-specified claims-based algorithms using medical records as the gold standard.

To define the presence of SGA, we determined the percentile of the birthweight of the reviewed cases using a published distribution (*BMC Pediatr.* 2003 Jul 8;3:6). The criteria for validating the presence of SGA included birthweight below the 10th percentile or documented physician diagnosis of SGA/Intrauterine growth restriction (IUGR) with birthweight at less than the 20th percentile. The PPV based on these criteria was 84% (95% CI: 72%, 92%).

The criteria for validating preeclampsia was a diagnosis of preeclampsia recorded in the medical record or evidence of meeting diagnostic criteria for preeclampsia. Based on these criteria, the PPV for preeclampsia was 86% (95% CI: 74%, 94%).

The criteria for validating non-cardiac congenital malformation was a diagnosis of any non-cardiac malformation recorded in the medical record or evidence of meeting diagnostic criteria for any non-cardiac congenital malformation. The PPV based on these criteria was 88% (95% CI: 77%, 95%).

The criteria for validating PPH was a documented diagnosis in the medical record of PPH or an estimated blood loss (EBL) of >500cc for vaginal delivery or >1L for cesarean section. Based on these criteria, the algorithm for defining PPH had a PPV of 74% (95% CI: 61%, 85%). After expanding the validation criteria to include documented atony with treatment of uterotonics, the PPV improved to 82% (95% CI: 70%, 91%). When the criteria were further expanded to include documentation of retained placenta, the PPV was 88% (77%, 95%).

The criteria for validating preterm delivery was a documented or calculated gestational age < 37 completed weeks at the time of delivery. The PPV for preterm delivery based on these criteria was 78% (95% CI: 65%, 88%). If the validation criteria were expanded to include a documented or calculated gestational age from completed 37 to 38 weeks, the PPV increased to 88% (95% CI: 77%, 95%).