PASS Information

Title	Observational Studies to Assess Maternal and Fetal Outcomes Following Exposure to Duloxetine - F1J-MC-B057
Version identifier	5
Date of last version	10/26/2016
EU PAS Register No:	EUPAS15946
Active substance	ATC code N06AX21, duloxetine
Medicinal product(s):	Cymbalta, Ariclaim, Xeristar, Yentreve, Duloxetine Lilly
Product reference:	LY248686
Procedure number:	N/A
Marketing authorisation holder(s)	Eli Lilly and Company
Joint PASS	No
Research question and objectives	To assess the risk of major congenital malformations, preterm delivery, small for gestational age, and preeclampsia associated with duloxetine use in pregnancy.
Country(-ies) of study	United States
Author	Krista Huybrechts, MS PhD (Brigham and Women's Hospital, Harvard Medical School) Sonia Hernandez-Diaz, MD DrPH (Harvard T.H. Chan

	School of Public Health) Brian Bateman, MD MS (Brigham and Women's Hospital, Massachusetts General Hospital, Harvard Medical School)

Marketing Authorisation Holder

Marketing authorisation holder (MAH)	Eli Lilly and Company
MAH contact person	Hu Li, MD PhD Global Patient Safety Eli Lilly and Company Lilly Corporate Center Phone: 317-665-3095 Email: li_hu_hl@lilly.com Elizabeth Heaviside, DPhil Global Regulatory Affairs Eli Lilly and Company Erl Wood Manor Windlesham, Surrey, GU20 6PH United Kingdom Phone: +44 (0)1276 483054 FAX: +44 (0)1276 483378 Email: heaviside_elizabeth@lilly.com

1. Table of Contents

Section **Page**

List of Tables

List of Figures

List of Annexes

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 hemorrhage
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. Responsible Parties

Not applicable.

4. Abstract

F1J-MC-B057: Observational Studies to Assess Maternal and Fetal Outcomes Following Exposure to Duloxetine. Protocol v5 – July 15, 2016

Brian Bateman, MD MS (Brigham and Women's Hospital, Massachusetts General Hospital, Harvard Medical School), Sonia Hernandez-Diaz, MD DrPH (Harvard T.H. Chan School of Public Health), Krista Huybrechts, MS PhD (Brigham and Women's Hospital, Harvard Medical School)

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 preeclampsia, postpartum hemorrhage, major congential malformations, cardiac malformations, preterm birth, and small for gestational age.

Study design: Retrospective cohort study

Population: Medicaid insured pregnant women 18 to 55 years of age.

Variables: 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.

Data sources: Medicaid Analytic eXtract (MAX) for 2004-2013

Study size: Approximately 1500 pregnancies exposed to duloxetine during the first trimester, and 300-500 pregnancies exposed in late pregnancy are projected. The reference groups will consist 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.

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

residual confounding by controlling for proxies of unmeasured confounders. Sensitivity analyses will be conducted to test the robustness of the findings. Exploratory analyses will be conducted to examine the risk of stillbirth and spontaneous abortion.

Milestones: Analyses are expected to start by November 1st, 2016 and will be completed by October 31, 2018.

5. Amendments and Updates

Not applicable.

6. Milestones

Milestone	Planned date
Start of data collection	1 November 2016
End of data collection	30 April 2018
Final report of study results	31 October 2018

7. Rationale and Background

7.1. 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 may increase the 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 remained 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]

Most women experience some kind of pain during pregnancy. Many of these women require pharmacologic treatment. Some antidepressants are used in the management of migraine headaches, as well as for analgesic purposes in chronic pain states. 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 pain killers may be risk factors for adverse pregnancy outcomes. For instance, some studies have found a significant association between migraine and preeclampsia,[43,44] and preeclampsia is known to be associated with intrauterine growth retardation and prematurity. First trimester exposure to opioids has been associated with the risk of oral clefts, neural tube and cardiac defects,[45-47] and chronic opioid use in pregnancy has also been associated with Cesarean delivery, postpartum hemorrhage due to uterine atony, fetal growth restriction, and other adverse neonatal outcomes.[48] Triptans have been associated with postpartum haemorrhage[49] and low birth weight.[50] Therefore, specific pain indications and concomitant analgesics should be considered as potential risk factors when evaluating the safety of antidepressants during pregnancy.

7.2. 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.[51] In some studies, first trimester exposure to certain SSRIs has been associated with some specific birth defects,[52-56] while SSRI use late in pregnancy has been associated with pulmonary hypertension of the newborn (PPHN),[57] prematurity,[58-60] low birth weight,[59,60] small size for gestational age,[61] and various neonatal complications.[58,59,62,63] However, other studies have not found these association. 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. For some outcomes such as PPHN further studies demonstrated that the increase risk initially suggested is modest and the absolute risk is small and therefore difficult to define beyond the current confidence intervals for the association.[64] Data regarding the safety of SNRIs during pregnancy is sparse. We therefore propose to focus on evaluating the association between maternal use of one specific SNRI, duloxetine, during pregnancy and the risk of relatively common adverse pregnancy outcomes for which there is literature that reports an association with other antidepressants.

Major Congenital Malformations

One of the most concerning adverse effects of medications during pregnancy is teratogenicity.[65] In the US, more than 150,000 infants (3% of all infants) are born with serious birth defects each year.[66] Deaths due to birth defects account for more than 21% of all infant deaths, making them the leading cause of infant mortality.[65] 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 rare birth defects occur 2-3.5 times more frequently among infants of women treated with paroxetine or fluoxetine early in pregnancy.[67 68] However, other studies have found no association after accounting for depression severity.[69-71] Some of the more recent evidence on this topic has clearly demonstrated the impact of confounding by the underlying indication of depression using a variety of different methodological approaches: restriction of the cohort to women with a depression diagnosis,[69] sibling controlled analyses,[70] and comparison between pregnancies with exposure to SSRIs during the first trimester versus pregnancies with paused SSRI treatment.[72] 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.[73,74] 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.[75]

Low Birth Weight, Preterm Delivery and Small for Gestational Age

These outcomes are leading causes of maternal and/or perinatal mortality and morbidity.[76-79] Low birth weight can be the result of prematurity or of fetal growth retardation or restriction. Prematurity (< 37 weeks of gestation) accounts for approximately 10 percent of all births and is the leading cause of perinatal deaths[76] and long term disabilities.[76] Fetuses with growth restriction are born smaller than their peers with the same gestational age at birth. Based on the distribution of birth weights within levels of gestational age, a newborn with a birth weight below the 10th percentile is considered small for gestational age (SGA). Infants SGA may be term or preterm. Infants SGA are also at a greater risk of death and are more likely to develop diabetes, cardiovascular disease, schizophrenia and other serious conditions.[76,77] Maternal use of SSRIs during pregnancy has been associated with prematurity,[58-60,62] low birth weight,[59,60] and SGA.[59,80] However, evidence is conflicting.[81] Some studies have also reported an increased risk of prematurity and SGA in patients treated with non-SSRI antidepressants,[59,62] 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.[29,82,83] Whether these risks extend to SNRIs remains unclear.

Other fetal outcomes

Stillbirths and clinically recognized spontaneous abortions are captured in this data source, but no well-validated algorithms for defining the LMP in association with pregnancies that end in nonlive births are currently available. Analyses involving these outcomes should therefore be considered exploratory. In addition, we will conduct sensitivity analyses to quantify the potential impact of missing terminations and stillbirths in our evaluation of teratogenic effects.

Elective terminations are not reliably captured in the data and we can therefore not evaluate them.

Preeclampsia

Preeclampsia, clinically recognized by hypertension and proteinuria, is a leading cause of morbidity and mortality in pregnancy.[78,79] It causes intrauterine growth restriction and is a major cause of medically indicated preterm deliveries.[84,85] Along with various vascular disorders, psychological conditions such as stress,[86] 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.[25,82] Alternatively, ADs could potentially increase the risk of preeclampsia through their vascular effects.[87,88] SNRIs can cause elevations of diastolic blood pressure, probably due to their noradrenergic effects.[89]

Postpartum Hemorrhage

Primary postpartum hemorrhage (PPH) occurs within the first 24 hours of delivery and is known to affect 1 to 5% of deliveries.[90] It is responsible for 25% of maternal deaths related to pregnancy worldwide, and is still the second leading cause of pregnancy-related maternal death

in the United States.[90] Serotonin is crucial for platelet aggregation and blood clotting.[91] Bleeding is more common in users of serotonergic AD.[92,93,94,95] 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 is largely unknown.

7.3. 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.[96] 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.[97] Two cases reported in the literature described infants with neonatal withdrawal symptoms.[98,99] Another two exposed cases reported had no signs of toxicity.[100,101] 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.[102] 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).[103]

A recent review concluded that the evidence for duloxetine is limited but does not suggest a clinically important increased risk of major congenital malformations.[104] 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.

7.4 Research Question and Objectives

The objective of this study is to provide a systematic evaluation on the safety of duloxetine in pregnant women. Therefore, we will quantify 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). To test the hypothesis that exposure to duloxetine during specific gestational periods is associated with an increased risk of pre-specified major adverse maternal and fetal outcomes, we will estimate the relative risk of major adverse events in pregnancies exposed during etiologically relevant periods relative to a cohort of women with similar underlying disease, but not treated with duloxetine.

The study objectives are:

- 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.

- 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 hemorrhage in relation to exposure to duloxetine in the last month of pregnancy.

8. Research Methods

8.1. Study design

We will conduct a cohort study nested in the nationwide Medicaid Analytic eXtract for the period 2004-2013. Completed pregnancies in women 18 to 55 years of age will be linked to liveborn infants. We have developed a linkage algorithm based on state, Medicaid case number (which identifies family units), date of delivery, and birth hospital which have been used to accurately link mother-infant data files in the MAX.[105] Several steps of data cleaning are implemented to ensure accurate linkage and avoid duplication of pregnancies. Strict eligibility criteria are then applied to ensure complete claim information for the mother and infant. Although the linkage proportion varied tremendously by state, the efficiency of linkage of delivery admissions to infants for most states was over 80%.[105] To ensure complete ascertainment of claims submitted to Medicaid, the cohort is restricted to women without restricted benefits, private insurance, or certain capitated managed care programs that underreport claims to MAX.

Maternal use of duloxetine and other medications will be determined based on pharmacy dispensing records. Exposure will be defined based on a dispensed prescription for duloxetine during the etiologically relevant window.

Outcomes will be defined based on the presence of inpatient and/or outpatient diagnoses and procedures. The primary study outcomes will include: overall and organ-specific malformations, preterm delivery, SGA, preeclampsia, and postpartum hemorrhage. In order to ensure complete capture of exposure, outcomes, and covariates recorded in the claims, we will impose requirements for Medicaid eligibility that will be applied to both the mother and the offspring. The last menstral period (LMP) will be defined using a validated algorithm based on delivery date and diagnostic codes indicative of pre-term delivery in the maternal and infant records.[66] The eligibility requirements vary based on the outcome being considered and are delineated below (Table 1). Four different reference groups will be 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 will be 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 hemorrhage, the hypothesized mechanism by which duloxetine and similar drugs might increase the risk is by depleting platelet serotonin.[106,107] 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 placentation, 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 hemorrhage	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
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

Rationale for the design and datasource

Generally, both the efficacy and the most common adverse effects of medications in adults and children are identified in clinical trials conducted before a given drug is approved for marketing. When it comes to pregnancy safety, however, the situation is reversed. Since pregnant women are excluded from clinical trials, we learn about most maternal and fetal toxicities only after a drug has been marketed, and of course, only after it has been used by pregnant women. In the post-marketing setting, health care utilization databases such as the Medicaid Analytic eXtract (MAX) have become a standard source of information. They provide prospectively collected information for large populations and allow the study of multiple outcomes. The populations represented in Medicaid data often include vulnerable populations such as patients who are racial and ethnic minorities, low-income and/or disabled, who tend to be excluded from clinical trials or registered cohorts. The large size of these datasets often generates enough statistical power to examine rare outcomes and important subgroups. While studies emerging from these databases lack the benefits of randomization, if carefully designed, the results have been shown to be valid and informative, particularly when evaluating unintended drug effects.[108] The MAX pregnancy cohort is one of the largest databases available for pharmacoepidemiology studies in pregnancy. It has been used to study the safety of drug exposures during pregnancy with respect to a wide variety of important fetal and maternal outcomes including congenital malformations,[69] persistent pulmonary hypertension of the newborn,[64] neonatal abstinence syndrome,[109] neonatal seizures,[110] preeclampsia,[111] and postpartum hemorrhage.[107,112]

8.2. Setting

Study Population

All analyses will be conducted using data from the MAX pregnancy cohort. For details on the creation of the MAX pregnancy cohort, see the manuscript by Palmsten et al[105] (attached as a supplement to the protocol).

I. Analyses of major congenital malformations.

a. Inclusion criteria:
    i. Base cohort to include 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 will be 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, lithum and thalidomine from LMP through LMP plus 90 days (i.e., days of exposure overlap with 1st trimester)
v. Pregnancies in which duloxetine is 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. Analysis of postpartum hemorrhage

a. This cohort will be 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 eligbility period for the mother will be different, given that the exposure window is during the final month of pregnancy. Finally, for this maternal outcome, no eligibility criteria will be imposed on the offspring.
b. Inclusion criteria:
    i. Base cohort to include 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 is dispensed in the 4 months prior to the delivery but not during the final month of pregnancy.

III. Analyses of preterm delivery, SGA, and preeclampsia

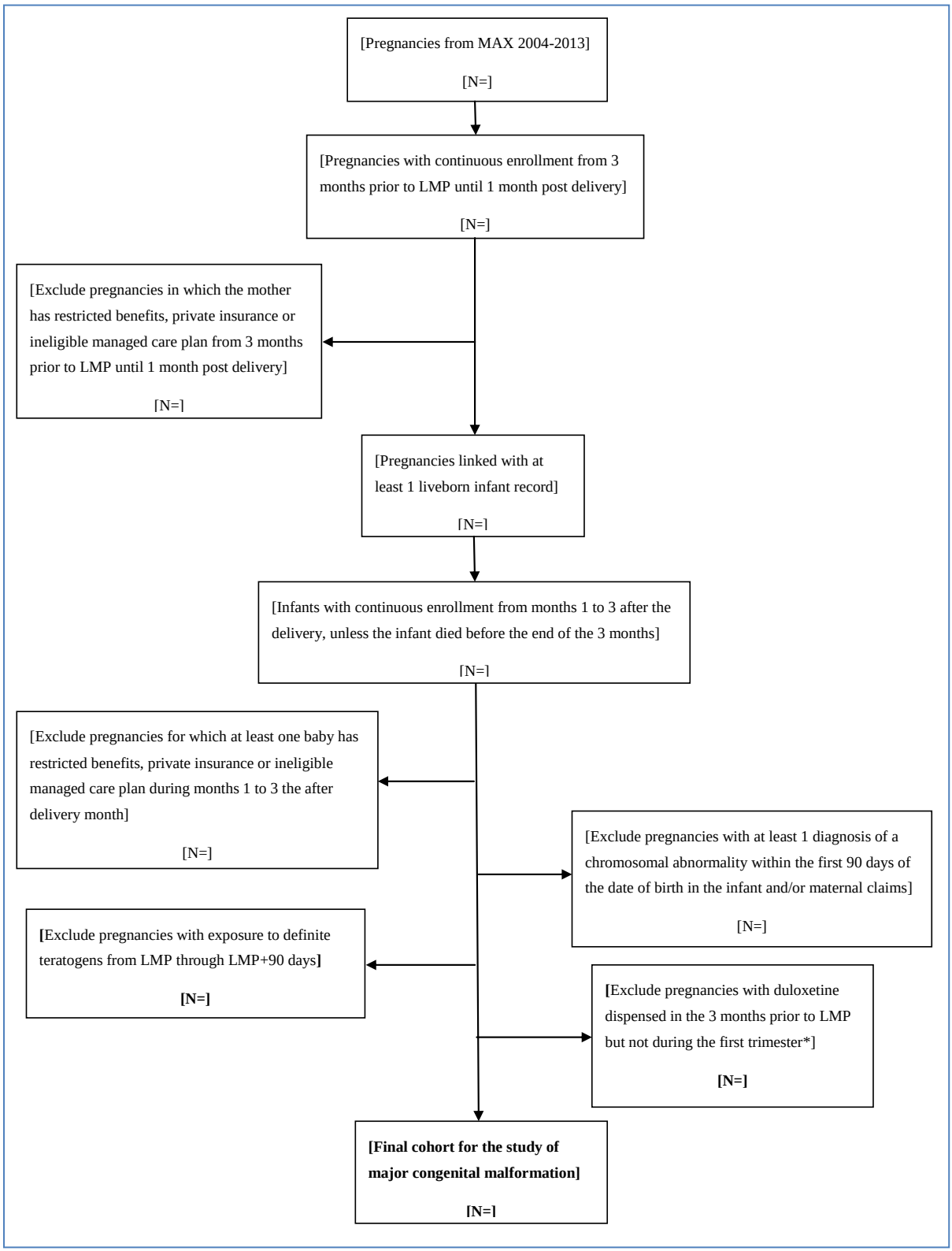
a. This cohort will be similar to that used to study major congenital malformations, with the exception of the exclusions for chromosomal abnormalities and 1st trimester teratogenic medication exposures (which are not necessary when considering these outcomes) and the required eligibility period for infants.
b. Inclusion criteria:

i. Base cohort to include 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 will require 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 will be permitted. Note, that infant eligibility is 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 will exclude pregnancies in which duloxetine is dispensed in the 3 months prior to the LMP but not during pregnancy itself.

The flowcharts of cohort selection are illustrated in Figure 1 to Figure 3.

Figure 1 Flow diagram showing the composition of the study population for the major congenital malformations outcome



*: Except in the analyses using duloxetine discontinuers as the reference group

Figure 2 Flow diagram showing the composition of the study population for preeclampsia and postpartum hemorrhage

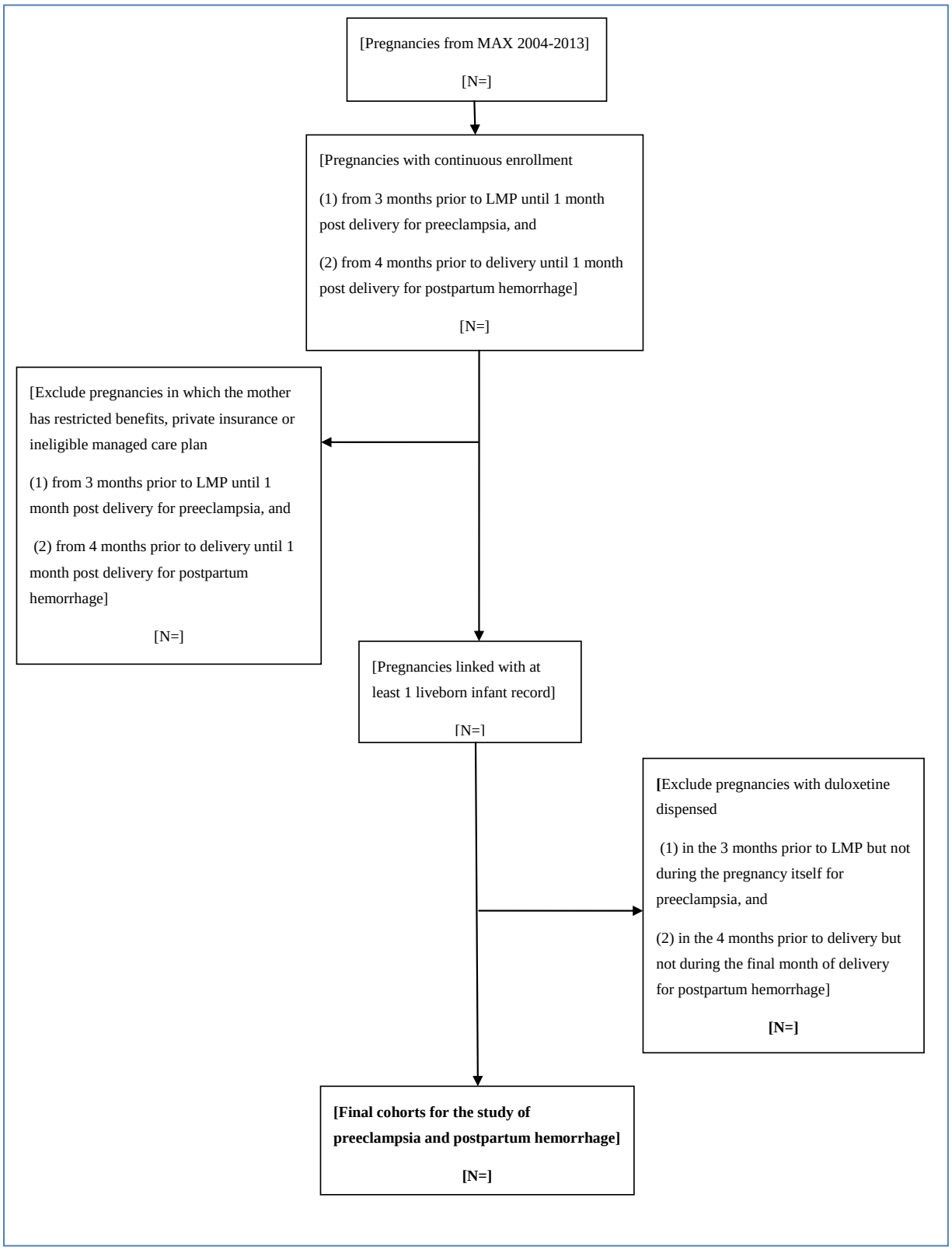
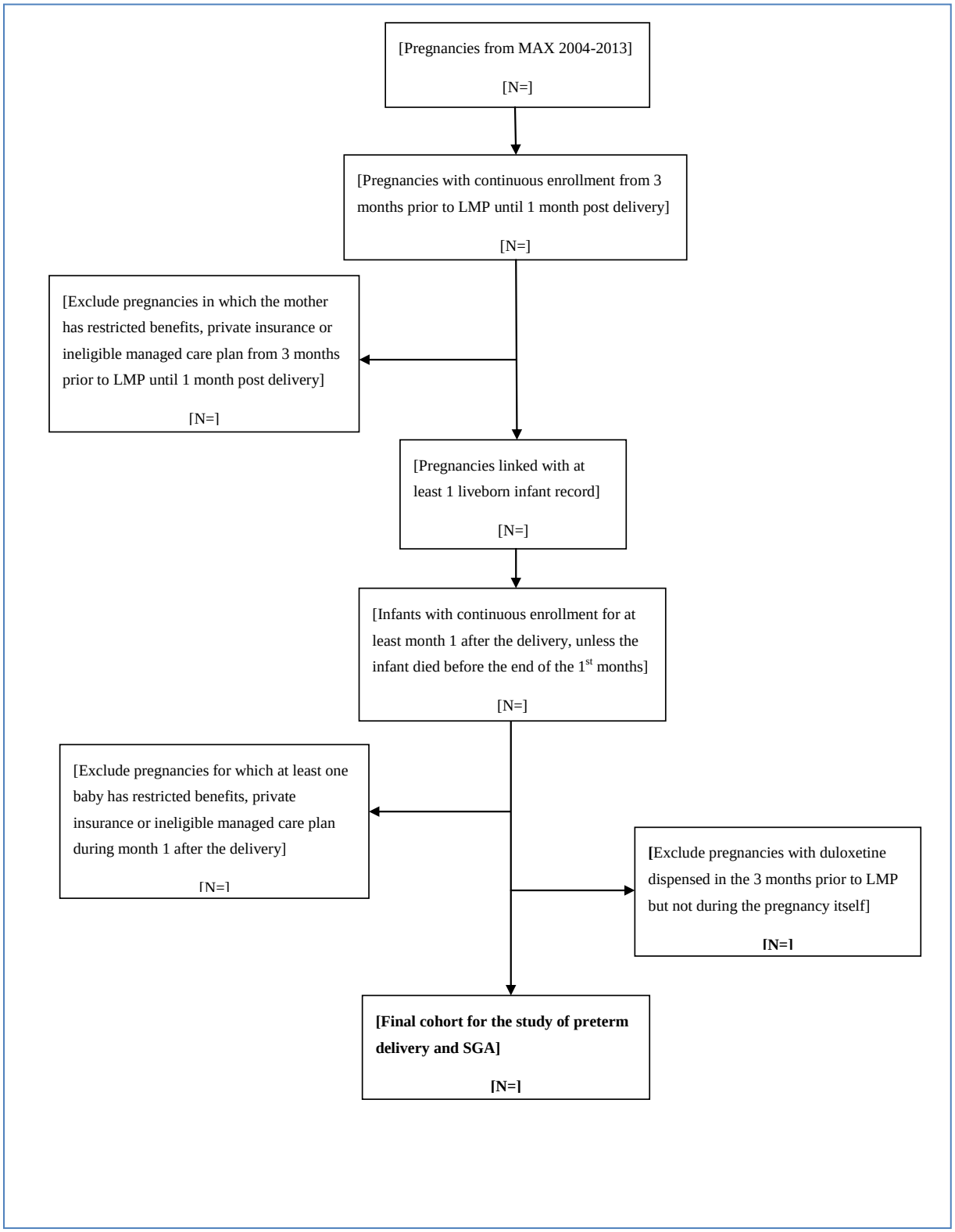


Figure 3 Flow diagram showing the composition of the study population for the preterm delivery and SGA



8.3. Variables

Exposure

Maternal exposure to duloxetine will be 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 the gold standard of drug exposure compared to self-reported information[113] or prescribing records in outpatient medical records.[114] Pharmacists fill prescriptions with little room for interpretations, and are reimbursed by insurers on the basis of detailed, complete, and accurate claims submitted electronically. [115-117] Patient non-response and recall bias are absent from healthcare utilization databases since all data recording is independent of a patient's memory or agreement to participate in a research study.[118-121] While the expectation is that patients will generally take medications that they are dispensed, it is possible that in some instances the patients will discontinue the medication or be non-compliant with the prescription. This potential limitation will be addressed in sensitivity analyses in which exposure to duloxetine will be defined by multiple filled prescriptions during the etiologically relevant window, on the assumption that patients who refill the medication are likely to be taking it regularly. We will also conduct sensitivity analyses in which exposure will be defined based on days supply that overlaps with the etiologically relevant time window (to reduce the likelihood of misclassifying as unexposed women who had medication from earlier dispensings available).

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 discontinue because of their pregnancy might be more comparable to women who continue during pregnancy than women who were never treated with duloxetine. We will therefore also compare 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 will 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 will have limited power because of the size of the exposed and reference group.

I. **Unexposed reference group**

a. **Analyses of major congenital malformations**: Exposure will be defined by one or more dispensed prescriptions for duloxetine from the LMP to day 90 of pregnancy. The

reference group will consist of pregnancies without exposure to duloxetine from 90 days prior to the LMP to day 90 of pregnancy.

b. **Postpartum hemorrhage**: Exposure will be defined by one or more dispensed prescriptions for duloxetine during the final 30 days of pregnancy. The reference group will consist of pregnancies without exposure to duloxetine from 90 days prior to the LMP to delivery.

c. **Analyses of Preeclampsia, SGA, and Preterm delivery**

   i. **Associated with early pregnancy exposure**: Exposure will be defined by one or more dispensed prescriptions for duloxetine from the LMP to day 140 of pregnancy. The reference group will consist 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 will be defined by one or more dispensed prescriptions for duloxetine from day 141 of pregnancy to day 245 of pregnancy. The reference group will consist of pregnancies without exposure to duloxetine from 90 days prior to the LMP to day 245 of pregnancy.

II. **Women exposed to SSRIs as reference group:**

a. **Analyses of major congenital malformations**: Exposure will be defined by one or more dispensed prescriptions for duloxetine from the LMP to day 90 of pregnancy. The reference group will be 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 will be excluded.

b. **Postpartum hemorrhage**: Exposure will be defined by one or more dispensed prescriptions for duloxetine during the final 30 days of pregnancy. The reference group will be 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 will be excluded.

c. **Analyses of Preeclampsia, SGA, and Preterm delivery**

   i. **Associated with early pregnancy exposure**: Exposure will be defined by one or more dispensed prescriptions for duloxetine from the LMP to day 140 of pregnancy. The reference group will be 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 will be excluded.

   ii. **Associated with late pregnancy exposure**: Exposure will be defined by one or more dispensed prescriptions for duloxetine from day 141 of pregnancy to day 245 of pregnancy. The reference group will be 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 will be excluded.

III. **Women exposed to venlafaxine as reference group**:

a. **Analyses of major congenital malformations**: Exposure will be defined by one or more dispensed prescriptions for duloxetine from the LMP to day 90 of pregnancy. The reference group will be 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 will be excluded.
b. **Postpartum hemorrhage**: Exposure will be defined by one or more dispensed prescriptions for duloxetine during the final 30 days of pregnancy. The reference group will be 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 will be excluded.
c. **Analyses of Preeclampsia, SGA, and Preterm delivery**
   i. **Associated with early pregnancy exposure**: Exposure will be defined by one or more dispensed prescriptions for duloxetine from the LMP to day 140 of pregnancy. The reference group will be 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 will be excluded.
   ii. **Associated with late pregnancy exposure:** Exposure will be defined by one or more dispensed prescriptions for duloxetine from day 141 of pregnancy to day 245 of pregnancy. The reference group will be 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 will be excluded.

IV. **Duloxetine discontinuers as reference group**:

a. **Analyses of major congenital malformations**: Exposure will be defined by one or more dispensed prescriptions for duloxetine from the LMP to day 90 of pregnancy. The reference group will be 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 hemorrhage**: not applicable
c. **Analyses of Preeclampsia, SGA, and Preterm delivery**: not applicable

Outcomes

I. **Major congenital malformations**
a. We first define the presence of one of 13 organ-specific malformations based on the following criteria, using the ICD-9 and CPT codes shown in the Table below. Claims from both the infant and maternal record will be 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 is >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 is 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 is 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 are no codes in the infant record between delivery and delivery+90 (i.e., only maternal codes between delivery and delivery+30), then the assumption will be made that the malformation is maternal and we will consider the infant as being unaffected.
c. If an infant has one or more of the 13 organ specific malformations, then we will consider them as having a major malformation overall.
d. Analyses will be conducted examining the association between first trimester duloxetine exposure with malformations overall and with the 13 organ specific malformations.

Table 2 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 hemorrhage**: 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 below) in the mother or infant record between delivery and delivery + 30 days

Table 3 ICD-9 and CPT codes for preterm delivery

ICD-9	Description
644.2x	early onset of delivery
774.2x	neonatal jaundice associated with preterm 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 765.20, 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 algorithmns were previously validated for preeclampsia and cardiac defects. For full details of this validation study, see Palmsten et al, *Pharmacoepidemiology and Drug Safety*, 2014.[122] 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 included in the present study will be validated as described in Section 8.7 (Validation Study).

Covariates

In the analyses, we will account for conditions that are expected to confound the association between duloxetine exposure and each of the outcomes of interest. For a condition to be a confounder, it needs to be associated with the exposure (i.e., imbalanced between the exposed and unexposed) and associated with the outcome (i.e., risk factor for the outcome).

The underlying indications for treatment are expected to be important confounders, either due to a direct effect of the conditions or due to lifestyle or other factors associated with the conditions. Indications for therapy will therefore be measured using diagnosis claims and accounted for in the analyses via restriction and balancing through the use of propensity scores. We will also attempt to account for the severity of the underlying indications (e.g., depression) through the use of surrogate measures (co-prescribed medications and measures of healthcare use intensity such as the number of visits to a psychiatrist). Other important potential confounders include chronic comorbid conditions (on the assumption that those with a higher burden of comorbid illness may be more likely to use a SNRI) including for example diabetes, hypertension, and renal disease. These will be measured directly using diagnosis claims for these conditions. We will also measure exposure to medications used as treatments for these conditions (e.g., antihypertensive medications, insulin, oral diabetes medications) as markers of their severity, as well as measures of healthcare utilization which may be markers for overall health status. Patient demographic characteristics, to the degree to which they are assocated with treatment and outcome, may also be important confounders and will be accounted for in our analyses.

Therefore, we will consider 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 will be selected because they are potential risk factors for the outcomes or potential proxies for such risk factors.

We will also assess 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 will also assess the use of suspected teratogenic medications.

Table 4 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
Maternal demographics characteristics Age, Race/ethnicity, Geographic region				
	n/a	n/a	n/a	n/a
Chronic comorbid conditions 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
Infections 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
Indications for duloxetine 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
Other psychiatric conditions 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
Tobacco use, alcohol abuse or dependence, drug abuse or dependence				
	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
Markers of healthcare utilization 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
Other medication exposures (markers of comorbidity) 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
Obstetrical conditions Multifetal gestation				

Covariate assessment window				
	Congenital malformations	PPH	Preterm, SGA, preeclampsia	
			Early exposure	Late exposure
	LMP to delivery	LMP to delivery	LMP to delivery	LMP to delivery
Potentially teratogenic medication exposures ACEI, Danazol, Progestins, Methimazole, Propylthiouracil, Corticosteroids, Fluconazole				
	Days supply overlapping T1	n/a	n/a	n/a

Table 5 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[123]; validated in Metcalfe et al.[124]
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, 714.0x, 714.1x, 714.2x, 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 (excluding 714.0x-2x), 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

Covariate	ICD 9 codes
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, 357.5x, 425.5x, 571.0x - 571.3x, 649.0x, V15.82, E860.0, E860.0, E860.0, V11.3
Alcohol abuse or dependence	291.xx, 303.xx, 305.0x, 357.5x, 425.5x, E860.0, V11.3
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**
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, ethotoin, 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, Tranylcypropine, Bupropion, Mirtazapine, Nefazodone, Trazodone, Vilazodone, Vortioxetine
Stimulants	Amphetamine, amphetamine/dextroamphetamine, dextroamphetamine, methamphetamine, lisdexamfetamine, methyphenidate, dexmethylphenidate, 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.)

Covariate	ICD 9 codes
Triptans	Sumatriptan, rizatriptan, naratriptan, zolmitriptan, eletriptan, almotriptan, frovatriptan, avitriptan, donitriptan
NSAIDs	Aspirin, Celecoxib, Diclofenac, Diflunisal, Etodolac, Fenoprofen, Flurbirofen, Ibuprofen, Indomethacin, Ketroprofen, Ketorolac, Mefenamic Acid, Meloxicam, Nabumetone, Naproxen, Oxaprozin, Piroxicam, Sulindac, Tolmetin
Obstetrical conditions	
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
Potentially teratogenic medication exposures	
Danazol	
Progestins	drospirenone/estradiol, estradiol/norethindrone, hydroxyprogesterone, leuprolide, medroxyprogesterone, medroxyprogesterone, norethindrone, progesterone
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.

In Table 6, we present known or suspected risk factors for the study outcomes that are either unmeasured or poorly measured in the MAX data. These factors are unlikely to be important confounders for the planned analyses. To bias the results, the risk factor would need to be imbalanced between the duloxetine exposed and unexposed, within the levels of the measured covariates included in the propensity score or high-dimensional propensity score (which include a large number of comorbid conditions and markers of their severity, maternal demographic characteristics, and measures of healthcare utilization). The most concerning as potential sources of residual confounding in the planned analyses are smoking status, alcohol use, drug abuse and maternal BMI (all are associated with several of the outcomes of interest). The impact of these missing confounders will be assessed through an external adjustment analysis (informed by data from NHANES), as described below in section 8.7.2. The other unmeasured or poorly measured risk factors are not recognized determinants of treatment with a SNRI, making this scenario unlikely. However, to address the potential for residual confounding by these and other factors not accounted for by measured covariates, we will use comparator groups (in addition to a non-exposed comparator) in the analyses that are more likely to be exchangeable with the duxoletine user group including women exposed to venlafaxine, SSRIs, and women who discontinue duloxetine prior to pregnancy.

Table 6 Risk factors for study outcome that are unmeasured or poorly measured in the MAX database[97]

Preeclampsia	Postpartum hemorrhage	Major congenital malformations	Preterm birth	Small for gestational age
• Preeclampsia in a previous pregnancy • Family history of preeclampsia • Obesity* • Fetal growth restriction, placental abruption, or fetal demise in a previous pregnancy • Prolonged interpregnancy interval if the previous pregnancy was normotensive. If the previous pregnancy was preeclamptic, a short interpregnancy interval increases the risk of recurrence. • Partner related factors (new partner, limited sperm exposure [eg, previous use of barrier contraception])	• Large for gestational age newborn • Personal or family history of previous PPH • Obesity* • Inherited or acquired bleeding diathesis • Inpatient use of uterine relaxants or drugs that affect coagulation	• Obesity*; • Infections: Toxoplasmosis; Rubella; Cytomegalovirus; Herpes; Syphilis; Varicella; Parvovirus B19; Zika virus; Lymphocytic choriomeningitis virus (LCMV); Influenza; • Physical and environmental agents: Lead; Ionizing radiation; Fever/ hyperthermia; Fish consumption related methylmercury exposure • Family history • Smoking* • Alcohol use*	• Not living with partner • Low socioeconomic status • Life events (divorce, separation, death) • Occupational risk factors • Uterine anomaly, including diethylstilbestrol-induced changes in uterus and leiomyomas • History of second-trimester abortion • History of cervical surgery • Sexually transmitted infections • Bacteriuria • Periodontal disease • Vaginal bleeding, especially in more than one trimester • Previous preterm delivery • Substance abuse • Smoking* • Poor nutrition and low body mass index* • Low level of educational achievement • Family history of preterm birth, especially maternal first-degree family history of spontaneous preterm birth, particularly if the pregnant woman	• Fetal infection • Confined placental mosaicism • Family history • Assisted reproductive technologies • Low prepregnancy weight • Poor gestational weight gain • Malabsorption • Malnutrition • Residing at high altitude • Short interpregnancy interval

Preeclampsia	Postpartum hemorrhage	Major congenital malformations	Preterm birth	Small for gestational age
			herself was born preterm • Environmental factors (eg, heat, air pollution)	

*Most important potential confounding variables

8.4. Data Sources

I. Appropriateness of Data Source in Addressing Safety Questions of Interest

The datasource that will be employed for the study is the Medicaid Analytic eXtract (MAX). For details regarding the creation of the MAX pregnancy cohort, please see the manuscript by Palmsten et al[105] (attached as a supplement to the protocol). As noted above, this cohort has been used extensively for studies of the safety of medications in pregnancy. The strengths of this datasource for studying the safety of duloxetine include the following: (1) The MAX is a large, population-based cohort. It includes information on over 1 million pregnancies including (based on preliminary analyses) approximately 1,500 exposed to duloxetine during the first trimester. (2) It allows for objective assessment of drug exposure: Drug exposure will be defined by filled prescriptions during etiologically relevant periods. In contrast to many studies of drug exposures during pregnancy, this approach is not subject to recall bias. An additional strength of our data is that we can explore dose using precise dispensing information. (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.

II. Enrolment and Comprehensive Capture of Care

We require that women be eligible for Medicaid during the baseline, exposure window, and follow up period. We further require that the offspring be eligible for Medicaid during the relevant follow up period. The eligbility 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 is restricted to women without restricted benefits, private insurance, or certain capitated managed care programs that underreport claims to MAX.

III. Country of Origin and Health System

The data are drawn from U.S. Medicaid claims. Medicaid covers approximately half of all births in the U.S.

IV. **Selection of Study Population**

Please see section 8.2 for a detailed description of the selection of the study population.

V. **Quality Assurance (QA) and Quality Control (QC)**

All aspects of data analysis will be 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 will be conducted by a primary analyst and validated by a separate analyst (validation analyst). For all data processing and analysis steps, the validation analyst will review the program along with input and output data sets, and for select steps of the project will employ double programming techniques to reduce the potential for programming errors.

VI. **Study Time Frame and Lag Time Issues**

Data will be drawn from MAX claims from 2004 to 2013. There is a several years delay in CMS releasing complete, nationwide Medicaid claims.

8.5. Study Size

Based on preliminary analyses of women eligible from 3 months prior to the LMP to delivery included in the linked cohort, we project about 1500 patients exposed to duloxetine during the first trimester. The frequency of exposure decreases during pregnancy such that we project 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 hemorrhage), 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

	RR					RR				
Exposed	**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

8.6. Data Management

The research team operates a secure, state-of-the-art computing environment hosted at Partners Healthcare' 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 will be conducted in SAS 9.4.

8.7. Data Analyses

Main Analyses

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

The reference groups will consist 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 will compare the distributions of socio-demographic, clinical and healthcare utilization characteristics during the relevant baseline period for the duloxetine exposed and reference group. Balance will be assessed using the standardized mean difference. An absolute standardized difference greater than 0.1 will be considered an indicator for substantial imbalances between the two exposure groups.[125] Absolute risks for the outcome and unadjusted relative risks with their 95% confidence interval (CI) will be calculated.

Results will be 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 confounders[126], 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.[127]

PS will be derived from the predicted probability of treatment estimated in a logistic regression model, which will contain all covariates without additional variable selection. In case of model convergence problems, we will use lasso regression to aid with variable selection.[128] We will trim 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. The number of exposed women trimmed this way will depend on the outcome studied and will be reported. We will create 50 equally sized PS-strata

based on the distribution among the duloxetine treated women.[129] In the outcome models, the untreated observations will be weighted using the distribution of the treated among PS-strata. Adjusted relative risks will be estimated using generalized linear models (SAS PROC GENMOD with a weight statement and loglink function). Balance of baseline characteristics in this weighted population will be 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) will be combined with the investigator-identified covariates described above to further improve confounding adjustment and thus validity.[127]

Sensitivity Analyses

Sensitivity analyses will be conducted to test the robustness of the findings. The pre-specified sensitivity analyses for each outcome are summarized in Table 8. The overall findings will be interpreted in light of the results of these pre-specified sensitivity analyses.

Table 8 Pre-specified Sensitivity Analyses

Outcome	Sensitivity Analyses
All outcomes	• Re-define exposure as having filled ≥2 prescriptions for duloxetine during the etiologically relevant time window • Redefine exposure as days supply that overlaps with the etiologically relevant time window • Restrict population to women with a recorded diagnosis of fibromyalgia • Correct relative risks for outcome misclassification using sensitivities and specificities consistent with the PPV estimated in the internal validation study • Assess impact of excluding outcomes designated as "probably occurred" or "likely did not occur" based on review of claims profiles • Restrict cohort to the first pregnancy occurring within the study period • External adjustment of the relative risk*
Neonatal outcomes	
Congenital malformations[69]	• Re-define outcome based on infant claims only • Restrict outcome to inpatient diagnoses only • Extend infant follow-up to 1 year • 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-eclampsia[111]	N/A
Post partum hemorrhage[107]	• Days supply of duloxetine overlapping the date of delivery • 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. Briefly, in addition to adjusting for measured confounders by PS stratification, and for proxies of unmeasured factors by hdPS stratification, we will explore 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 will use publicly-available files from the National Health and Nutrition Examination Survey (NHANES) for 1999-2010, restrict the sample to women of childbearing age, stratify them based on insurance (Medicaid vs. private), and assess the association between use of duloxetine and potential confounders (e.g., BMI, alcohol, and smoking). Information from the literature will be 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, will be quantified using bias analyses. This can be 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.[130] 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 will evaluate the potential impact of selection bias due to the restriction of our cohort to live births, using methods proposed by Greenland and Khoury.[131,132] These methods have been previously described in detail by our group[69]). Briefly, we model a range of non-livebirth frequencies for malformed infants in the unexposed and exposed and then calculate "corrected" relative risk estimates based on these inputs and the adjusted relative risk estimate from the main analysis. As such, we conduct a formal quantification of the potential impact of the selection bias.

For these pre-specified analyses, no adjustments will be made for multiple comparisons, but all results ("negative" or "non-significant" and "positive" or "significant") will be reported.[133-135]

Validation Study

For outcomes where no validation study is currently available (major congenital malformations other than cardiac, post partum hemorrhage, preterm delivery, SGA), medical record validation will be conducted.

We will link 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). Up to 50 medical records from pregnancies defined with these codes will then be retrieved for each outcome. Two physicians who are blinded to the drug exposure status will review the charts based on established clinical criteria and classify the outcome as present or absent. The PPV (and 95% CI) of the claims-based algorithm will be calculated.[122] The

algorithms will be refined based on the findings from the validation study, and these revised algorithms will be used in final analyses. The PPV defined based on these algorithms will be used to inform a probabilistic bias analysis which will generate corrected relative risk estimates.

In a sensitivity analysis, we will match exposed to non-exposed women (from the primary analysis for each outcome) in a 1:5 ratio using a nearest neighbor algorithm. De-identified claims profiles of mothers or infants with the outcome of interest as defined using the algorithms will be generated for all cases in the matched cohort. Expert clinicians will review the profiles, blinded to the exposure status, and will "adjudicate" 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 will be assessed.

Exploratory Analyses

Stillbirths: Most stillbirths will occur during hospitalization for delivery, and are captured in MAX using distinct ICD 9 diagnostic codes (V27.1, V27.3, V27.4, V27.6, V27.7, 656.4x, V32.x, V35.x, V36.x). No well-validated algorithm for defining the LMP in association with pregnancies that end in stillbirth is currently available. We do know, however, that stillbirths occur from 20 weeks of gestation onwards. We will therefore conduct exploratory analyses, defining algorithms to assign gestational age at the time of stillbirth based on the distribution observed in Lombardy, Italy during 2005-2010, a dataset our group has access to which contains information on gestational age for stillbirths.

The HealthCare Utilization (HUC) database of Lombardy enables us to link all pregnancy identified in the Certificates of Delivery Assistance registry from 1st January 2005 to 31st December 2010 (i.e., the so called CeDAP), to the hospital discharges registry (reporting all diagnoses released from public or private hospitals), and to the outpatient drug prescriptions registry (reporting all dispensations of National Health Service-reimbursable drugs). In Italy, the entire population benefits from healthcare assistance provided by the National Health Service (NHS), which in Lombardy - an Italian Region with about 16% of the country's population (almost ten million inhabitants) - has been associated since 1997 with an automated system of databases. Information from the NHS registers is linked through a single anonymous identification code preserving individuals' privacy.

Different scenarios will be considered, including the use of a predictive algorithm that includes proximate etiologies and maternal risk factors; such predictive algorithm will be developed in the Lombardy data and validated in the MAX-Partners linked cohort. Livebirths will be obtained from the linked pregnancy cohort and women will be required to meet the Medicaid elibility criteria from 3 months before LMP to delivery. Stillbirths in women ≥18 years will be identified in the MAX source population using the ICD 9 diagnostic codes specified above. The Medicaid eligibility criteria will be imposed from 3 months before the assigned LMP to stillbirth. Exposure will be assessed during the first 20 weeks of pregnancy to avoid differential opportunity of exposure for stillbirths and livebirths. Adjusted analyses will be conducted using the covariates

identified in Table 4 assessed from 3 months before LMP to LMP+140. Measures of healthcare utilization will be assessed during the 3 months before LMP. These analyses will be presented for each of the 3 comparator groups.

Spontaneous abortion: We will explore the risk of clinically recognized spontaneous abortions following a similar approach. Different scenarios will be considered to assign gestational age, including the use of a predictive algorithm that uses information on healthcare utilization from MAX (e.g., ultrasound) combined with data from the Research Patient Data Registry (RPDR), which is the centralized clinical data registry/warehouse for hospitals that are part of Partners Healthcare and contains the medical records for patients treated at these hospitals (the Lombardy data do not contain information on gestational age for spontaneous abortions). Spontaneous abortions in women ≥18 years will be identified in the MAX source population using ICD 9 634.xx. The Medicaid eligibility criteria will be imposed from 3 months before the assigned LMP to spontaneous abortion. Exposure will be assessed during the first 4 weeks of pregnancy to avoid differential opportunity of exposure for spontaneous abortions and livebirths. Adjusted analyses will be conducted using the covariates identified in Table 4 assessed from 3 months before LMP to LMP+28. Measures of healthcare utilization will be assessed during the 3 months before LMP. These analyses will be presented for each of the 3 comparator groups.

If at any point during these exploratory analyses, the validity of the analyses becomes questionable (e.g., poor predictive algorithm for gestational age at stillbirth, indication of differential misclassification of the spontaneous abortion outcome), we will not proceed with analyses beyond that point.

8.8. Quality Control

All aspects of data analysis will be 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 will be conducted by a primary analyst and validated by a separate analyst (validation analyst). For all data processing steps, the validation analyst will review the program along with input and output data sets. For the analysis steps of the project, we will employ double programming techniques to reduce the potential for programming errors.

8.9. Limitations of the Research Methods

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

- Selection bias. Claims databases only include 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 frequencies are the same in both the exposed and unexposed, then the estimates of relative risk in the analysis based on liveborns would be unbiased. However, if non-livebirth of offspring with malformations occurs with greater frequency among women with exposure compared to the non-exposed (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 medication exposure. We will perform sensitivity analyses to assess the potential impact of missing non-livebirth on the risk estimate for duloxetine and malformations.

- Exposure misclassification. To guard against exposure misclassification (i.e., false positives), we will favor 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 will require 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 will explore 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.
- Outcome misclassification. We will use highly specific outcome definitions, since this will result in unbiased estimates of the relative risk as long as the sensitivity is non-differential. We will use validated outcome definitions with high PPV. To further increase confidence in the validity of the outcome definitions, we will replicate 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/dependance) 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 will conduct 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 do 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 will have limited statistical power to detect small increases in risk.

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 these factors are not expected to affect the biologic relations studied.[136]

8.10. Other Aspects

Not applicable

9. Protection of Human Subjects

This study will be submitted to the Institutional Review Board (IRB) of the Brigham & Women's Hospital.

10. Management and Reporting of Adverse Events/Adverse Reactions

Adverse Events

During the course of secondary use of data in observational research, information pertaining to adverse reactions (ARs) will not be discovered because the study does not involve identifiable patient data associated with a Lilly product. Data in this study are being analysed in aggregate only.

11. Plans for Disseminating and Communicating Study Results

The final report will be shared with the US Food and Drug Administration and European Medicines Agency (EMA). Manuscripts describing this work will be submitted for publication in peer-review journals. Findings may also be submitted for presentation at scientific conferences. Results will be disclosed on ENCePP.

12. References

1. Evans J, Heron J, Francomb H, Oke S, Golding J. Cohort study of depressed mood during pregnancy and after childbirth. BMJ 2001;323:257-60.
2. Gotlib IH, Whiffen VE, Mount JH, Milne K, Cordy NI. Prevalence rates and demographic characteristics associated with depression in pregnancy and the postpartum. J Consult Clin Psychol 1989;57:269-74.
3. Kendell RE, Wainwright S, Hailey A, Shannon B. The influence of childbirth on psychiatric morbidity. Psychological medicine 1976;6:297-302.
4. Reefhuis J, Rasmussen SA, Friedman JM. Selective serotonin-reuptake inhibitors and persistent pulmonary hypertension of the newborn. N Engl J Med 2006;354:2188-90; author reply -90.
5. Cooper WO, Willy ME, Pont SJ, Ray WA. Increasing use of antidepressants in pregnancy. Am J Obstet Gynecol 2007;196:544 e1-5.
6. Andrade SE, Raebel MA, Brown J, et al. Use of antidepressant medications during pregnancy: a multisite study. Am J Obstet Gynecol 2008;198:194 e1-5.
7. Kaufman DW, Kelly JP, Rosenberg L, Anderson TE, Mitchell AA. Recent patterns of medication use in the ambulatory adult population of the United States. The Slone Survey. Journal of the American Medical Association 2002;287:337-44.
8. Riley EH, Fuentes-Afflick E, Jackson RA, et al. Correlates of prescription drug use during pregnancy. J Womens Health (Larchmt) 2005;14:401-9.
9. Mitchell AA, Gilboa SM, Werler MM, Kelley KE, Louik C, Hernandez-Diaz S. Medication use during pregnancy, with particular focus on prescription drugs: 1976-2008. Am J Obstet Gynecol 2011;205:51 e1-8.
10. Andrade SE, Gurwitz JH, Davis RL, et al. Prescription drug use in pregnancy. Am J Obstet Gynecol 2004;191:398-407.
11. Huybrechts KF, Palmsten K, Mogun H, et al. National trends in antidepressant medication treatment among publicly insured pregnant women. General hospital psychiatry 2013;35:265-71.
12. Moses-Kolko EL, Roth EK. Antepartum and postpartum depression: healthy mom, healthy baby. J Am Med Womens Assoc 2004;59:181-91.
13. Cohen LS, Altshuler LL, Harlow BL, et al. Relapse of major depression during pregnancy in women who maintain or discontinue antidepressant treatment. Jama 2006;295:499-507.
14. Altshuler LL, Cohen LS, Moline ML, et al. Treatment of depression in women: a summary of the expert consensus guidelines. Journal of psychiatric practice 2001;7:185-208.
15. Bonari L, Pinto N, Ahn E, Einarson A, Steiner M, Koren G. Perinatal risks of untreated depression during pregnancy. Can J Psychiatry 2004;49:726-35.
16. Frank E, Kupfer DJ, Perel JM, et al. Three-year outcomes for maintenance therapies in recurrent depression. Arch Gen Psychiatry 1990;47:1093-9.
17. O'Hara MW, Neunaber DJ, Zekoski EM. Prospective study of postpartum depression: prevalence, course, and predictive factors. Journal of abnormal psychology 1984;93:158-71.
18. Hirschfeld RM, Keller MB, Panico S, et al. The National Depressive and Manic-Depressive Association consensus statement on the undertreatment of depression. Jama 1997;277:333-40.
19. Marcus SM, Flynn HA, Blow FC, Barry KL. Depressive symptoms among pregnant women screened in obstetrics settings. J Womens Health (Larchmt) 2003;12:373-80.
20. Flynn HA, Blow FC, Marcus SM. Rates and predictors of depression treatment among pregnant women in hospital-affiliated obstetrics practices. General hospital psychiatry 2006;28:289-95.
21. Scholle SH, Haskett RF, Hanusa BH, Pincus HA, Kupfer DJ. Addressing depression in obstetrics/gynecology practice. General hospital psychiatry 2003;25:83-90.
22. Ververs T, Kaasenbrood H, Visser G, Schobben F, de Jong-van den Berg L, Egberts T. Prevalence and patterns of antidepressant drug use during pregnancy. European journal of clinical pharmacology 2006;62:863-70.
23. Field T, Diego M, Hernandez-Reif M. Prenatal depression effects on the fetus and newborn: a review. Infant behavior & development 2006;29:445-55.

24. Chung TK, Lau TK, Yip AS, Chiu HF, Lee DT. Antepartum depressive symptomatology is associated with adverse obstetric and neonatal outcomes. Psychosomatic medicine 2001;63:830-4.
25. Sandman CA, Wadhwa PD, Chicz-DeMet A, Dunkel-Schetter C, Porto M. Maternal stress, HPA activity, and fetal/infant outcome. Annals of the New York Academy of Sciences 1997;814:266-75.
26. Kurki T, Hiilesmaa VK, Raitasalo R, Mattila H, Ylikorkala O. Depression and anxiety in early pregnancy and risk for preeclampsia. Obstetrics and gynecology 2000;95:487-90.
27. Michel-Wolfromm H. The psychological factor in spontaneous abortion. Journal of psychosomatic research 1968;12:67-71.
28. Preti A, Cardascia L, Zen T, et al. Obstetric complications in patients with depression--a population-based case-control study. Journal of affective disorders 2000;61:101-6.
29. Paarlberg KM, Vingerhoets AJ, Passchier J, Dekker GA, Van Geijn HP. Psychosocial factors and pregnancy outcome: a review with emphasis on methodological issues. Journal of psychosomatic research 1995;39:563-95.
30. Dayan J, Creveuil C, Herlicoviez M, et al. Role of anxiety and depression in the onset of spontaneous preterm labor. American journal of epidemiology 2002;155:293-301.
31. Dayan J, Creveuil C, Marks MN, et al. Prenatal depression, prenatal anxiety, and spontaneous preterm birth: a prospective cohort study among women with early and regular care. Psychosomatic medicine 2006;68:938-46.
32. Orr ST, James SA, Blackmore Prince C. Maternal prenatal depressive symptoms and spontaneous preterm births among African-American women in Baltimore, Maryland. American journal of epidemiology 2002;156:797-802.
33. Weinstock M. Alterations induced by gestational stress in brain morphology and behaviour of the offspring. Progress in neurobiology 2001;65:427-51.
34. McAnarney ER, Stevens-Simon C. Maternal psychological stress/depression and low birth weight. Is there a relationship? American journal of diseases of children (1960) 1990;144:789-92.
35. Steer RA, Scholl TO, Hediger ML, Fischer RL. Self-reported depression and negative pregnancy outcomes. Journal of clinical epidemiology 1992;45:1093-9.
36. Hoffman S, Hatch MC. Depressive symptomatology during pregnancy: evidence for an association with decreased fetal growth in pregnancies of lower social class women. Health Psychol 2000;19:535-43.
37. Field T, Diego M, Hernandez-Reif M, et al. Prenatal anger effects on the fetus and neonate. J Obstet Gynaecol 2002;22:260-6.
38. Zax M, Sameroff AJ, Babigian HM. Birth outcomes in the offspring of mentally disordered women. The American journal of orthopsychiatry 1977;47:218-30.
39. Cohler BJ, Gallant DH, Grunebaum HU, Weiss JL, Gamer E. Pregnancy and birth complications among mentally ill and well mothers and their children. Social biology 1975;22:269-78.
40. Qiu C, Sanchez SE, Lam N, Garcia P, Williams MA. Associations of depression and depressive symptoms with preeclampsia: results from a Peruvian case-control study. BMC women's health 2007;7:15.
41. Zuckerman B, Amaro H, Bauchner H, Cabral H. Depressive symptoms during pregnancy: relationship to poor health behaviors. Am J Obstet Gynecol 1989;160:1107-11.
42. Smedberg J, Lupattelli A, Mardby AC, Overland S, Nordeng H. The relationship between maternal depression and smoking cessation during pregnancy--a cross-sectional study of pregnant women from 15 European countries. Arch Womens Ment Health 2015;18:73-84.
43. Facchinetti F, Allais G, Nappi RE, et al. Migraine is a risk factor for hypertensive disorders in pregnancy: a prospective cohort study. Cephalalgia : an international journal of headache 2009;29:286-92.
44. Adeney KL, Williams MA, Miller RS, Frederick IO, Sorensen TK, Luthy DA. Risk of preeclampsia in relation to maternal history of migraine headaches. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet 2005;18:167-72.
45. Bracken MB. Drug use in pregnancy and congenital heart disease in offspring. New England Journal of Medicine 1986;314:1120.

46. Shaw GM, Malcoe LH, Swan SH, Cummins SK, Schulman J. Congenital cardiac anomalies relative to selected maternal exposures and conditions during early pregnancy. European journal of epidemiology 1992;8:757-60.
47. Broussard CS, Rasmussen SA, Reefhuis J, et al. Maternal treatment with opioid analgesics and risk for birth defects. American journal of obstetrics and gynecology 2011;204:314 e1-11.
48. Nezvalova-Henriksen K, Spigset O, Nordeng H. Effects of codeine on pregnancy outcome: results from a large population-based cohort study. European journal of clinical pharmacology 2011;67:1253-61.
49. Nezvalova-Henriksen K, Spigset O, Nordeng H. Triptan exposure during pregnancy and the risk of major congenital malformations and adverse pregnancy outcomes: results from the Norwegian Mother and Child Cohort Study. Headache 2010;50:563-75.
50. Olesen C, Steffensen FH, Sorensen HT, Nielsen GL, Olsen J. Pregnancy outcome following prescription for sumatriptan. Headache 2000;40:20-4.
51. Stewart DE. Clinical practice. Depression during pregnancy. N Engl J Med 2011;365:1605-11.
52. Louik C, Lin AE, Werler MM, Hernandez-Diaz S, Mitchell AA. First-trimester use of selective serotonin-reuptake inhibitors and the risk of birth defects. N Engl J Med 2007;356:2675-83.
53. Alwan S, Reefhuis J, Rasmussen SA, Olney RS, Friedman JM. Use of selective serotonin-reuptake inhibitors in pregnancy and the risk of birth defects. N Engl J Med 2007;356:2684-92.
54. Berard A, Ramos E, Rey E, Blais L, St-Andre M, Oraichi D. First trimester exposure to paroxetine and risk of cardiac malformations in infants: the importance of dosage. Birth Defects Res B Dev Reprod Toxicol 2007;80:18-27.
55. Cole JA, Ephross SA, Cosmatos IS, Walker AM. Paroxetine in the first trimester and the prevalence of congenital malformations. Pharmacoepidemiol Drug Saf 2007;16:1075-85.
56. Wogelius P, Norgaard M, Gislum M, et al. Maternal use of selective serotonin reuptake inhibitors and risk of congenital malformations. Epidemiology 2006;17:701-4.
57. Chambers CD, Hernandez-Diaz S, Van Marter LJ, et al. Selective serotonin-reuptake inhibitors and risk of persistent pulmonary hypertension of the newborn. N Engl J Med 2006;354:579-87.
58. Chambers CD, Johnson KA, Dick LM, Felix RJ, Jones KL. Birth outcomes in pregnant women taking fluoxetine. New England Journal of Medicine 1996;335:1010-5.
59. Kallen B. Fluoxetine use in early pregnancy. Birth Defects Res B Dev Reprod Toxicol 2004;71:395-6.
60. Wen SW, Yang Q, Garner P, et al. Selective serotonin reuptake inhibitors and adverse pregnancy outcomes. Am J Obstet Gynecol 2006;194:961-6.
61. Oberlander TF, Warburton W, Misri S, Aghajanian J, Hertzman C. Neonatal outcomes after prenatal exposure to selective serotonin reuptake inhibitor antidepressants and maternal depression using population-based linked health data. Arch Gen Psychiatry 2006;63:898-906.
62. Davis EP, Glynn LM, Schetter CD, Hobel C, Chicz-Demet A, Sandman CA. Prenatal exposure to maternal depression and cortisol influences infant temperament. Journal of the American Academy of Child and Adolescent Psychiatry 2007;46:737-46.
63. Costei AM, Kozer E, Ho T, Ito S, Koren G. Perinatal outcome following third trimester exposure to paroxetine. Arch Pediatr Adolesc Med 2002;156:1129-32.
64. Huybrechts KF, Bateman BT, Palmsten K, et al. Antidepressant use late in pregnancy and risk of persistent pulmonary hypertension of the newborn. JAMA 2015;313:2142-51.
65. Centers for Disease Control. Economic cost of birth defects and cerebral palsy- United States, 1992. Morbidity Mortality Weekly Report 1995;44:694-9.
66. Margulis AV, Setoguchi S, Mittleman MA, Glynn RJ, Dormuth CR, Hernandez-Diaz S. Algorithms to estimate the beginning of pregnancy in administrative databases. Pharmacoepidemiol Drug Saf 2013;22:16-24.
67. Reefhuis J, Devine O, Friedman JM, Louik C, Honein MA. Specific SSRIs and birth defects: Bayesian analysis to interpret new data in the context of previous reports. BMJ 2015;351:h3190.
68. Wurst KE, Poole C, Ephross SA, Olshan AF. First trimester paroxetine use and the prevalence of congenital, specifically cardiac, defects: a meta-analysis of epidemiological studies. Birth Defects Res A Clin Mol Teratol 2010;88:159-70.

69. Huybrechts KF, Palmsten K, Avorn J, et al. Antidepressant use in pregnancy and the risk of cardiac defects. N Engl J Med 2014;370:2397-407.
70. Furu K, Kieler H, Haglund B, et al. Selective serotonin reuptake inhibitors and venlafaxine in early pregnancy and risk of birth defects: population based cohort study and sibling design. BMJ 2015;350:h1798.
71. Wemakor A, Casson K, Garne E, et al. Selective serotonin reuptake inhibitor antidepressant use in first trimester pregnancy and risk of specific congenital anomalies: a European register-based study. European journal of epidemiology 2015;30:1187-98.
72. Jimenez-Solem E, Andersen JT, Petersen M, et al. Exposure to selective serotonin reuptake inhibitors and the risk of congenital malformations: a nationwide cohort study. BMJ open 2012;2.
73. Einarson A, Fatoye B, Sarkar M, et al. Pregnancy outcome following gestational exposure to venlafaxine: a multicenter prospective controlled study. Am J Psychiatry 2001;158:1728-30.
74. Oberlander TF, Warburton W, Misri S, Riggs W, Aghajanian J, Hertzman C. Major congenital malformations following prenatal exposure to serotonin reuptake inhibitors and benzodiazepines using population-based health data. Birth Defects Res B Dev Reprod Toxicol 2008;83:68-76.
75. Polen KN, Rasmussen SA, Riehle-Colarusso T, Reefhuis J. Association between reported venlafaxine use in early pregnancy and birth defects, national birth defects prevention study, 1997-2007. Birth defects research Part A, Clinical and molecular teratology 2013;97:28-35.
76. Halbreich U. The association between pregnancy processes, preterm delivery, low birth weight, and postpartum depressions--the need for interdisciplinary integration. Am J Obstet Gynecol 2005;193:1312-22.
77. McIntire DD, Bloom SL, Casey BM, Leveno KJ. Birth weight in relation to morbidity and mortality among newborn infants. N Engl J Med 1999;340:1234-8.
78. Roberts JM. Endothelial Dysfunction in Preeclampsia. Seminars in Reproductive Endocrinology 1998;16:5-15.
79. Mackay AP, Berg CJ, Atrash HK. Pregnancy-related mortality from preeclampsia and eclampsia. Obstetrics and gynecology 2001;97:533-8.
80. Davis RL, Rubanowice D, McPhillips H, et al. Risks of congenital malformations and perinatal events among infants exposed to antidepressant medications during pregnancy. Pharmacoepidemiol Drug Saf 2007;16:1086-94.
81. Huybrechts KF, Sanghani RS, Avorn J, Urato AC. Preterm birth and antidepressant medication use during pregnancy: a systematic review and meta-analysis. PloS one 2014;9:e92778.
82. Chrousos GP, Torpy DJ, Gold PW. Interactions between the hypothalamic-pituitary-adrenal axis and the female reproductive system: clinical implications. Ann Intern Med 1998;129:229-40.
83. Hendricks SK, R SJ, Moore DE, Brown ZA. Oligohydramnios associated with prostaglandin synthetase inhibitors in preterm labor. British Journal of Obstetrics and Gynaecology 1990;97:312-6.
84. Roberts JM, Pearson G, Cutler J, Lindheimer M. Summary of the NHLBI Working Group on Research on Hypertension During Pregnancy. Hypertension 2003;41:437-45.
85. Ananth CV, Getahun D, Peltier MR, Salihu HM, Vintzileos AM. Recurrence of spontaneous versus medically indicated preterm birth. Am J Obstet Gynecol 2006;195:643-50.
86. Klonoff-Cohen HS, Cross J, Pieper C. Job stress and preeclampsia. Epidemiology 1996;7:245-9.
87. Bjoro K, Stray-Pedersen S. In vitro perfusion studies on human umbilical arteries. II. Effects of prostacyclin and a thromboxane A2 mimetic. Acta obstetricia et gynecologica Scandinavica 1986;65:467-71.
88. Haugen G, Bjoro K, Stray-Pedersen S. Vasoactive effects of intra- and extravascular serotonin, PGE2 and PGF2 alpha in human umbilical arteries. Gynecol Obstet Invest 1991;31:208-12.
89. Thase ME. Effects of venlafaxine on blood pressure: a meta-analysis of original data from 3744 depressed patients. J Clin Psychiatry 1998;59:502-8.
90. Magann EF, Evans S, Hutchinson M, Collins R, Howard BC, Morrison JC. Postpartum hemorrhage after vaginal birth: an analysis of risk factors. Southern medical journal 2005;98:419-22.

91. De Abajo F, García Rodríguez L, Montero D. Association between selective serotonin reuptake inhibitors and upper gastrointestinal bleeding: population based case-control study. British Medical Journal 1999;319:1106-9.
92. Aranth J, Lindberg C. Bleeding, a side effect of fluoxetine. Am J Psychiatry 1992;149:412.
93. Yaryura-Tobias JA, Kirschen H, Ninan P, Mosberg HJ. Fluoxetine and bleeding in obsessive-compulsive disorder. Am J Psychiatry 1991;148:949.
94. Movig KL, Janssen MW, de Waal Malefijt J, Kabel PJ, Leufkens HG, Egberts AC. Relationship of serotonergic antidepressants and need for blood transfusion in orthopedic surgical patients. Archives of internal medicine 2003;163:2354-8.
95. Meijer WE, Heerdink ER, Nolen WA, Herings RM, Leufkens HG, Egberts AC. Association of risk of abnormal bleeding with degree of serotonin reuptake inhibition by antidepressants. Archives of internal medicine 2004;164:2367-70.
96. Hudson JI, Wohlreich MM, Kajdasz DK, Mallinckrodt CH, Watkin JG, Martynov OV. Safety and tolerability of duloxetine in the treatment of major depressive disorder: analysis of pooled data from eight placebo-controlled clinical trials. Human psychopharmacology 2005;20:327-41.
97. Hoog SL, Cheng Y, Elpers J, Dowsett SA. Duloxetine and pregnancy outcomes: safety surveillance findings. International journal of medical sciences 2013;10:413-9.
98. Eyal R, Yaeger D. Poor neonatal adaptation after in utero exposure to duloxetine. Am J Psychiatry 2008;165:651.
99. Abdy NA, Gerhart K. Duloxetine withdrawal syndrome in a newborn. Clinical pediatrics 2013;52:976-7.
100. Briggs GG, Ambrose PJ, Ilett KF, Hackett LP, Nageotte MP, Padilla G. Use of duloxetine in pregnancy and lactation. The Annals of pharmacotherapy 2009;43:1898-902.
101. Bellantuono C, Marini A, Lucarelli C. Infant health and neurodevelopmental outcomes following prenatal exposure to duloxetine. Clinical drug investigation 2013;33:685-8.
102. Einarson A, Smart K, Vial T, et al. Rates of major malformations in infants following exposure to duloxetine during pregnancy: a preliminary report. J Clin Psychiatry 2012;73:1471.
103. Kallen B, Borg N, Reis M. The use of central nervous system active drugs during pregnancy. Pharmaceuticals (Basel) 2013;6:1221-86.
104. Lassen D, Ennis ZN, Damkier P. First-Trimester Pregnancy Exposure to Venlafaxine or Duloxetine and Risk of Major Congenital Malformations: A Systematic Review. Basic & clinical pharmacology & toxicology 2016;118:32-6.
105. Palmsten K, Huybrechts KF, Mogun H, et al. Harnessing the Medicaid Analytic eXtract (MAX) to Evaluate Medications in Pregnancy: Design Considerations. PloS one 2013;8:e67405.
106. de Abajo FJ, Rodriguez LA, Montero D. Association between selective serotonin reuptake inhibitors and upper gastrointestinal bleeding: population based case-control study. BMJ 1999;319:1106-9.
107. Palmsten K, Hernandez-Diaz S, Huybrechts KF, et al. Use of antidepressants near delivery and risk of postpartum hemorrhage: cohort study of low income women in the United States. BMJ 2013;347:f4877.
108. Schneeweiss S, Glynn R, Tsai E, Avorn J, Solomon D. Assessment of bias by unmeasured confounders in pharmacoepidemiologic claims data studies using external data. Epidemiology 2005;16:17-24.
109. Desai RJ, Huybrechts KF, Hernandez-Diaz S, et al. Exposure to prescription opioid analgesics in utero and risk of neonatal abstinence syndrome: population based cohort study. BMJ 2015;350:h2102.
110. Bateman BT, Huybrechts KF, Maeda A, et al. Calcium Channel Blocker Exposure in Late Pregnancy and the Risk of Neonatal Seizures. Obstetrics and gynecology 2015;126:271-8.
111. Palmsten K, Huybrechts KF, Michels KB, et al. Antidepressant use and risk for preeclampsia. Epidemiology 2013;24:682-91.
112. Bateman BT, Hernandez-Diaz S, Huybrechts KF, et al. Outpatient calcium-channel blockers and the risk of postpartum haemorrhage: a cohort study. BJOG : an international journal of obstetrics and gynaecology 2013;120:1668-76; dicussion 76-7.
113. West S, Savitz D, Koch G, Strom B, Guess H, Hartzema A. Recall accuracy for prescription medications: self-report compared with database information. American journal of epidemiology 1995;142:1103-12.

114. West S, Strom B, Freundlich B, Normand E, Koch G, Savitz D. Completeness of prescription recording in outpatient medical records from a health maintenance organization. Journal of clinical epidemiology 1994;47:165-7.
115. Stergachis AS. Record linkage studies for postmarketing drug surveillance: data quality and validity considerations. Drug Intell Clin Pharm 1988;22:157-61.
116. Levy AR, O'Brien BJ, Sellors C, Grootendorst P, Willison D. Coding accuracy of administrative drug claims in the Ontario Drug Benefit database. Can J Clin Pharmacol 2003;10:67-71.
117. McKenzie DA, Semradek J, McFarland BH, Mullooly JP, McCamant LE. The validity of medicaid pharmacy claims for estimating drug use among elderly nursing home residents: The Oregon experience. Journal of clinical epidemiology 2000;53:1248-57.
118. Fowles J, Lawthers A, Weiner J, Garnick D, Petrie D, Palmer R. Agreement between physicians' office records and Medicare Part B claims data. Health Care Financ Rev 1995;16:189-99.
119. Romano PS, Mark DH. Bias in the coding of hospital discharge data and its implications for quality assessment. Med Care 1994;32:81-90.
120. Glynn R, Monane M, Gurwitz J, Choodnovskiy I, Avorn J. Agreement between drug treatment data and a discharge diagnosis of diabetes mellitus in the elderly. American Journal of Epidemiology 1999;149:541-9.
121. Fisher ES, Whaley FS, Krushat WM, et al. The accuracy of Medicare's hospital claims data: progress has been made, but problems remain. Am J Public Health 1992;82:243-8.
122. Palmsten K, Huybrechts KF, Kowal MK, Mogun H, Hernandez-Diaz S. Validity of maternal and infant outcomes within nationwide Medicaid data. Pharmacoepidemiol Drug Saf 2014;23:646-55.
123. Bateman BT, Mhyre JM, Hernandez-Diaz S, et al. Development of a comorbidity index for use in obstetric patients. Obstetrics and gynecology 2013;122:957-65.
124. Metcalfe A, Lix LM, Johnson JA, et al. Validation of an obstetric comorbidity index in an external population. BJOG : an international journal of obstetrics and gynaecology 2015;122:1748-55.
125. Austin PC. Using the standardized difference to compare the prevalence of a binary variable between two groups in observational research. Communications in Statistics-Simulation and Computation 2009;38:1228-34.
126. Braitman LE, Rosenbaum PR. Rare outcomes, common treatments: Analytic strategies using propensity scores. Annals of Internal Medicine 2002;137:693-5.
127. Schneeweiss S, Rassen JA, Glynn RJ, Avorn J, Mogun H, Brookhart MA. High-dimensional propensity score adjustment in studies of treatment effects using health care claims data. Epidemiology 2009;20:512-22.
128. Franklin JM, Eddings W, Glynn RJ, Schneeweiss S. Regularized Regression Versus the High-Dimensional Propensity Score for Confounding Adjustment in Secondary Database Analyses. Am J Epidemiol 2015;182:651-9.
129. Desai R, Rothman K, Bateman B, Hernandez-Diaz S, Huybrechts K. Confounding control using propensity scores when the exposure is infrequent: making the case for a fine stratification approach. Pharmacoepidemiol & Drug Safety 2015;24:217.
130. Schneeweiss S. Sensitivity analysis and external adjustment for unmeasured confounders in epidemiologic database studies of therapeutics. Pharmacoepidemiol Drug Saf 2006;15:291-303.
131. Greenland S. Basic methods for sensitivity analysis of biases. Int J Epidemiol 1996;25:1107-16.
132. Khoury MJ, Flanders WD, James LM, Erickson JD. Human teratogens, prenatal mortality, and selection bias. American journal of epidemiology 1989;130:361-70.
133. Rothman KJ, Greenland S, Lash T. Precision and Statistics in Epidemiologic Studies. In: Rothman K, Greenland S, Lash T, eds. Modern Epidemiology. 3 ed. Philadelphia: Lippincott Williams & Wilkins; 2008:148-67.
134. Lang J, Rothman K, Cann C. That confounded p-value. Epidemiology 1998;9:7-8.
135. Poole C. Beyond the confidence interval. American Journal of Public Health 1987;77:195-9.
136. Rothman K, Greenland S, Lash T. Modern Epidemiology. 3rd ed: Philadelphia: Lippincott Williams & Wilkins; 2008.

Annex 1. List of Standalone Documents

Not applicable.

Annex 2. ENCePP Checklist for Study Protocols

Not applicable.

Study title:

Observational Studies to Assess Maternal and Fetal Outcomes Following Exposure to Duloxetine

Study reference number: EUPAS15946

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☑	☐	☐	13
1.1.2 End of data collection[2]	☑	☐	☐	13
1.1.3 Study progress report(s)	☐	☐	☑	
1.1.4 Interim progress report(s)	☐	☐	☑	
1.1.5 Registration in the EU PAS register	☑	☐	☐	1
1.1.6 Final report of study results.	☑	☐	☐	13

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☑	☐	☐	17
2.1.2 The objective(s) of the study?	☑	☐	☐	17-18
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☑	☐	☐	19
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☑	☐	☐	17
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☑	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☑	☐	☐	19
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☑	☐	☐	29-32
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☑	☐	☐	41-42

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☑	☐	☐	19
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☑	☐	☐	19
4.2.2 Age and sex?	☑	☐	☐	19
4.2.3 Country of origin?	☑	☐	☐	38
4.2.4 Disease/indication?	☑	☐	☐	41
4.2.5 Co-morbidity?	☐	☐	☑	
4.2.6 Seasonality?	☐	☐	☑	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☑	☐	☐	21-23

Comments:

At the first level of adjustment, the population will be restricted to those with a recorded indication for duloxetine. Co-morbidity is not a population defining criterion, but will be documented and accounted for in analyses.

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☑	☐	☐	27-29
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☑	☐	☐	27
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☑	☐	☐	27-29
5.4 Is exposure classified based on biological mechanism				

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☑	☐	☐	27-29
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☑	☐	☐	42

Comments:

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☑	☐	☐	29-32
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☑	☐	☐	31-32, 43-44

Comments:

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☑	☐	☐	32-38
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☑	☐	☐	42

Comments:

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☑	☐	☐	19
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☑	☐	☐	19
8.1.3 Covariates?	☑	☐	☐	19
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☑	☐	☐	19
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☑	☐	☐	19
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☑	☐	☐	19
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☑	☐	☐	34-36
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☐	☐	☑	
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☑	☐	☐	35
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☑	☐	☐	19

Comments:

Detailed information on the specifics of the data source are available in Palmsten K et al. PLoS One 2013;8(6):e67405. Endpoints are defined based on ICD-9 codes and CPT codes. Exposure and other medication use is defined based on generic names and corresponding National Drug Codes.

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☑	☐	☐	39-40

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☑	☐	☐	41
10.2 Is the choice of statistical techniques described?	☑	☐	☐	41-42
10.3 Are descriptive analyses included?	☑	☐	☐	41
10.4 Are stratified analyses included?	☑	☐	☐	42
10.5 Does the plan describe methods for adjusting for confounding?	☑	☐	☐	41-42
10.6 Does the plan describe methods addressing effect modification?	☑	☐	☐	42

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☑	☐	☐	38

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☑	☐	☐	40-41
11.3 Are methods of quality assurance described?	☑	☐	☐	39
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☑	☐	☐	44
11.5 Is there a system in place for independent review of study results?	☑	☐	☐	50

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☑	☐	☐	46
12.1.2 Information biases?	☑	☐	☐	46
(e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)				
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☑	☐	☐	39-40
12.3 Does the protocol address other limitations?	☑	☐	☐	45-46

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional	☑	☐	☐	48

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
Review Board approval been described?				
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☑	
13.3 Have data protection requirements been described?	☑	☐	☐	40-41

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☑	☐	☐	12

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☑	☐	☐	50
15.2 Are plans described for disseminating study results externally, including publication?	☑	☐	☐	50

Comments:

Name of the main author of the protocol: _____

Date: / /

Signature: _____

Annex 3. Additional Information

The team has extensive experience evaluating the safety and effectiveness of antidepressants (AD) commonly used for the clinical management of depression in pregnant women using the Medicaid Analytic eXtract (MAX). Specifically, we have assessed the i) comparative maternal safety, ii) comparative fetal safety, and iii) comparative effectiveness of different therapeutic strategies. We have also worked on other therapeutic areas including neurologic (e.g. antipsychotics, anticonvulsants) and non-neurologic areas (e.g. hypertension, pain). Members of the research team also have experience working with Pregnancy Registries, Scandinavian Registries, electronic medical records, other claims health care databases and case-control designs. Investigators are considered experts in the field and are often invited to advice or teach at FDA, NIH, CDC, and international scientific societies and academic institutions. (Please see CVs.)

Overall, within MAX, our work in the past four years has provided evidence to inform therapeutic decisions on the management of depression during pregnancy. First, it has highlighted how commonly antidepressants are prescribed, knowingly or accidentally, to pregnant women. Second, it has put boundaries to the previously suggested increased risk of cardiac malformations in women on certain antidepressants. Our findings suggest that the higher risk among treated women is largely explained by the underlying indication. Further research would be required to understand why women with major depression have an increased risk of malformations in their infants. Third, we shed some light on the controversy regarding the increased risk of persistent pulmonary hypertension of the newborn (PPHN). Our findings suggest that the discrepancies among studies can be partially explained by their methods, mainly the outcome definition. Fourth, we demonstrated how not even the most advanced methods can surpass the strong confounding by indication in comparative effectiveness research on depression treatment in our population. (See references below.)

At the same time, we have developed and promoted valid methods for the production of actionable evidence that will fill current gaps of information on therapeutic decisions in pregnant women. We created the MAX pregnancy linked cohort (RO1: HS018533-03), which represents a very large, unique and powerful database to perform descriptive and comparative safety studies on drugs in pregnancy. In contrast to case-control studies, its longitudinal design allows estimation of absolute risks. We have demonstrated the feasibility of the proposed research in MAX. We have published over 25 manuscripts in four years. These studies won awards such as the 2013 Lilienfeld Prize from the Society of Epidemiologic Research and the 2015 Clinical Research Achievement Award from the Clinical Research Forum. Three of these studies were published in the British Medical Journal, one in the New England Journal of Medicine and one in JAMA. Many of the publications received attention from editors (e.g., commentaries and letters) and lay press.

The successful implementation of these types of studies requires a highly interdisciplinary study team and relies heavily on the expertise being brought by each study member from various fields including pharmacoepidemiology, comparative safety and effectiveness research, reproductive epidemiology, psychiatry, neurology, obstetrics, fetal medicine, epidemiology methods, and clinical pharmacology. The team members have a track record of conducting studies of the highest quality and sophistication. Dr. Sonia Hernandez-Diaz (Harvard T.H. Chan School of Public Health) has contributed several landmark papers on the safety of drugs during pregnancy and has experience conducting pharmaco-epidemiologic studies using Medicaid data and other large healthcare research databases. She has participated in writing safety guidelines for drugs and has received several awards and distinctions for her work on methodology for observational studies. Dr. Krista Huybrechts' (Brigham and Women's Hospital (BWH)/Harvard Medical School (HMS)) research centers on studying the utilization and outcomes of psychotropic medications, with particular reference to vulnerable populations including pregnant women, using large administrative databases. She has extensive prior experience implementing advanced, novel epidemiologic and statistical approaches to account for confounding and other biases in the context of mental health research. Dr. Brian Bateman (Brigham and Women's Hospital /Massachusetts General Hospital, HMS) is a practicing obstetric anesthesiologist and has published extensively on the epidemiology of pregnancy complications and pharmacoepidemiology in pregnancy. He has worked as an advisor to the FDA and CDC and brings his experience directly caring for pregnant patients to the proposed work. Over the past few years, Drs. Hernandez-Diaz, Huybrechts and Bateman have successfully, cordially and productively collaborated on many studies evaluating the safety of medications during pregnancy using the MAX data. Selected publications related to the safety and effectiveness of antidepressants during pregnancy resulting from this collaboration are listed below.

1. Huybrechts KF, Hernandez-Diaz S, Patorno E, Desai RJ, Mogun H, Dejene SZ, Cohen JM, Panchaud A, Cohen L, Bateman BT. Antipsychotic Medication Use in Pregnancy and Risk of Congenital Malformations. (with editorial) JAMA Psychiatry 2016;73(9):938-46.
2. Huybrechts KF, Bateman BT, Palmsten K, Desai R, Patorno E, Gopalakrishnan C, Levin R, Mogun H, Hernández-Díaz S. Antidepressant Use Late in Pregnancy and Risk of Persistent Pulmonary Hypertension of the Newborn Among US Medicaid Beneficiaries. *JAMA*. 2015;313(21):2142-51.
3. Swanson SA, Hernandez-Diaz S, Palmsten K, Mogun H, Olfson M, Huybrechts K. Methodological Considerations in Assessing the Effectiveness of Antidepressant Medication Continuation during Pregnancy using Administrative Data. *Pharmacoepidemiol Drug Saf*. 2015. 24(9):934-42.
4. Huybrechts K, Palmsten K, Avorn J, Cohen LJ, Holmes LB, Franklin JM, Mogun H, Levin R, Kowal M, Setoguchi S, Hernández-Díaz S. Antidepressant Use in Pregnancy and the Risk of Cardiac Defects. *New England Journal of Medicine* 2014;370:2397-407.
5. Palmsten K, Huybrechts KF, Kowal MK, Mogun H, Hernández-Díaz S. Validity of maternal and infant outcomes within nationwide Medicaid data. *Pharmacoepidemiol Drug Saf* 2014; 23(6): 646-55

6. Huybrechts KF, Sanghani RS, Avorn J, Urato AC. Preterm birth and antidepressant medication use during pregnancy: A systematic review and meta-analysis. *PLoS One* 2014; 26;9(3):e92778.
7. Palmsten K, Huybrechts KF, Setoguchi S, Hernández-Díaz S. Antidepressant Use during Pregnancy and Risk for Preeclampsia in the U.S. Medicaid Population. *Epidemiology* 2013;24(5):682-691.
8. Palmsten K, Hernández-Díaz S, Huybrechts KF, Williams PL, Michels KB, Mogun L, Setoguchi S. Use of antidepressants near delivery and risk of postpartum hemorrhage: cohort study of low income women in the United States. *BMJ* 2013 21;347:f4877.
9. Huybrechts KF, Palmsten K, Mogun H, Kowal M, Avorn J, Setoguchi S, Hernández-Díaz S. National trends in antidepressant medication treatment among publicly insured pregnant women. *Gen Hosp Psychiatry* 2013; 35:265-71.
10. Palmsten K, Huybrechts KF, Mogun H, Kowal MK, Williams PL, Michels KB, Setoguchi S, Hernández-Díaz S. Harnessing the Medicaid Analytic eXtract (MAX) to Evaluate Medications in Pregnancy: Design Considerations. *PLoS One* 2013;8(6):e67405