The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

GSK Medicine: Bupropion and Paroxetine
Study No.: EPIP083 **(Preliminary report)**
Title: EPIDEMIOLOGY STUDY: Preliminary Report on Bupropion in Pregnancy and the Occurrence of Cardiovascular and Major Congenital Malformation.
Rationale: The study was undertaken because of a possible signal for cardiovascular defects, in particular those involving ventricular outflow tracts, observed in the GSK Bupropion Pregnancy Registry of uncontrolled spontaneous reports from health-care providers. The secondary analysis, which was carried out at the request of the FDA following presentation of the bupropion data, was conducted to investigate the risk of major congenital malformations for other antidepressants, including paroxetine.
Objectives: The primary objectives were to: 1) estimate the prevalence at birth among infants born to women dispensed bupropion in the first trimester of pregnancy for congenital malformation collectively, and for cardiovascular defects in particular; and 2) in a nested case-control analyses, to assess the impact of risk factors including maternal body mass index, smoking, and parity on odds ratios between dispensing of bupropion in the first trimester and congenital malformation. A secondary objective was to assess the association between dispensing of individual antidepressants (other than just bupropion), in the first trimester of pregnancy and congenital malformations (both all congenital malformations and specifically, cardiovascular malformations).
Indication: Depression/ Smoking cessation (Bupropion) Major depressive disorder/Obsessive-compulsive disorder/Panic disorder/Social anxiety disorder/Generalized anxiety disorder/Post-traumatic stress disorder/Premenstrual dysphoric disorder (Paroxetine)
Study Investigators/Centers: Research conducted by Ingenix, A UnitedHealth Group Company.
Research Methods:
Data Source: This study was carried out within 2 Ingenix databases that contain insurance information from UnitedHealthcare, a large national managed care population: the Ingenix Research Database (RDB) and the Ingenix LabRx data. The RDB extends farther back in time, and can be validated through abstraction of medical records. The RDB contains medical and pharmacy claims data from 27 UnitedHealthcare affiliated health plans, located in the Northeast, Southeast, Midwest, and Western United States. LabRx covers a membership for a shorter time primarily from the Western United States, and when this work was undertaken, did not permit medical record abstraction.
Study Design: A retrospective cohort study, supplemented by a nested case-control study. A retrospective cohort study of major congenital malformation was conducted, with a focus on cardiovascular defects, among infants born to women dispensed bupropion in their first trimester of pregnancy. Infants born to the following two groups of women served as comparators: 1) women dispensed bupropion before or after the first trimester of pregnancy, but before delivery; and 2) women dispensed antidepressants other than bupropion during the first trimester. This study was conducted in both the RDB and LabRx databases. Secondary cohort analysis: In addition to the analysis of bupropion described above, two additional post-hoc analyses were conducted: 1) an additional analysis of overall congenital and cardiovascular malformations in infants born to first trimester recipients of bupropion was performed *excluding* cases where the mother was prescribed another antidepressant or a known teratogen during the first trimester; 2) similar to the bupropion analyses, analyses of other individual antidepressants were undertaken, both with or without concurrent first trimester exposure to other antidepressants or teratogenic drugs. Comparison cohorts consisted of recipients of first-trimester dispensings of all antidepressants other than the specific one of interest. Known teratogens were identified a priori and consisted of the following: aminoglycoside antibiotics, ACE inhibitors, androgens, anticholinergic drugs, busulfan*, carbamazepine*, cyclophosphamide*, danazol, diethylstilbestrol, etretinate*, fluconazole, indomethacin, isotretinoin*, lithium, methimazole, methotrexate*, misoprostol, oral corticosteroids, paramethadione*, penicillamine, phenytoin*, propylthiouracil, tetracycline, thalidomide*, trimethadoin*, valproic acid* and warfarin (*cardiovascular teratogens). A nested case-control study was also conducted in which infants with confirmed congenital malformation following review of abstracted medical records from the RDB study cohorts were selected as cases, and a randomly selected sample of infants without evidence of malformation served as controls. Cases and controls were matched by geographic region of health plan, calendar year, and quarter of birth; and subsequently compared with respect to drug exposure.

Study Population: All women dispensed bupropion or other antidepressants and who had a live born delivery in the RDB between January 1995 and December 2002, or in LabRx between May 2000 and June 2003 were identified. The subset of women aged 12-49 years as of their delivery date was selected. Cohort membership in the RDB database was further restricted to members within health plans where medical record abstraction could be conducted. To ensure that the populations selected from the two databases were mutually exclusive, subjects were excluded from LabRx if they were already included in RDB during the time period that the 2 databases overlapped (May 2000-Dec 2002). In the event that a woman was identified more than once during the study period due to subsequent pregnancies, all other deliveries were assessed for exposure to the study drugs. Deliveries were excluded if the mother did not have continuous health plan enrollment for one year before the delivery date.

Study Treatment Exposures, Outcomes:

Cohort study: For each infant delivery, sequences of diagnoses and procedures in the medical claims data were examined to estimate a window of time when conception probably occurred. The first trimester was defined as occurring from the earliest possible conception date through 12 weeks following the latest possible conception date. All deliveries with a dispensing of bupropion during the first trimester (or any dispensing prior to the start of the first trimester where the number of days dispensed extended into the first trimester) were counted as being part of the cohort of bupropion recipients during the first trimester, regardless of the dispensing of other antidepressants that occurred during or outside of the first trimester. Other pregnancies were classified into the two comparison cohorts consisting of: 1) women dispensed bupropion either before (i.e., greater than one month before the estimated earliest conception date) or after the first trimester of pregnancy, but before delivery; and 2) women dispensed antidepressants other than bupropion during the first trimester (or any other antidepressant dispensing prior to the start of the first trimester where the number of days dispensed extended into the first trimester). Pregnancies for which infants were not identified in enrollment records to be enrolled in the health plan, were excluded.

The primary outcome under study was congenital malformation among live born infants, with a focus on cardiovascular defects. Congenital malformation was classified according to organ system and diagnosis. In the RDB cohorts, for infants whose medical claims data identified evidence of congenital malformation, medical records were abstracted to verify the diagnosis. By comparing the confirmed outcomes to the insurance claims records in the RDB, an algorithm was developed based on the claims data alone that could identify malformation with acceptable predictive value. This claims-based algorithm was applied to the LabRx claims data to define cases.

Medical and prescription claims data were used to characterize the mothers according to comorbid conditions, measures of health care utilization, and other concomitant prescription dispensings.

Nested case-control study: all infants with congenital malformations confirmed following review of abstracted medical records were selected as cases. A random sample of infants without evidence of malformation was selected as controls. Data on covariates were obtained from both the claims data and review of maternal medical records.

Data Analysis Methods:

Data from each database were analyzed separately. For the cohort study, the prevalence of infants with congenital malformation was assessed within each of the three comparator cohorts. Crude odds ratios were calculated as well as odds ratios which adjusted for relevant covariates through multivariate logistic regression. . Confidence intervals (CI) were calculated using exact binomial methods. No attempt was made to adjust the CI for multiple estimates and no significance testing was performed.

A second set of analyses was also performed to assess the risk of congenital/cardiovascular malformation for specific antidepressants relative to all other antidepressant exposures. Two approaches were used in calculating prevalence and odds ratios of all congenital malformations and cardiovascular malformations by specific antidepressant dispensed during the first trimester. In the first approach, calculations were performed according to “mutually exclusive” or “ever use” categories of antidepressants, indicating whether the antidepressant of interest was dispensed in the first trimester alone, or concomitantly with other antidepressants, respectively . In the second, the analyses additionally either included or excluded women who had been dispensed an *a-priori* defined known teratogen during the first trimester.

For the nested case-control study: cases and controls were compared with respect to drug exposure, with adjustment for covariates conducted using conditional logistic regression.

Study Results:

Primary cohort and nested case-control analyses:

In the primary cohort analysis of the RDB database, the adjusted estimates for the relative prevalence of congenital/cardiovascular malformations among the offspring of bupropion recipients during the first trimester compared with the offspring of recipients of other antidepressants during the first trimester were 1.29 (95% CI 0.74-2.24) for congenital malformations overall, and 1.72 (95% CI 0.82-3.64) for cardiovascular malformations alone. The RDB

nested case-control analysis provided results of a similar magnitude and direction (adjusted odds ratios bupropion first trimester vs. other antidepressants first trimester: 1.21, 95% CI 0.47-3.13 for all congenital malformations; and 1.52, 95% CI 0.34-6.71 for cardiovascular malformations). The corresponding cohort analysis in the LabRx database resulted in higher adjusted odds ratios than that in the RDB (1.61, 95% CI 0.97-2.66 for congenital malformations; and 2.07, 95% CI 0.91-4.69 for cardiovascular malformations), despite lower prevalences of both overall congenital malformations and cardiovascular defects among infants born to the two cohorts of women dispensed either bupropion or other antidepressants during the first trimester. None of these odds ratios had a confidence interval that excluded 1.

Secondary cohort analyses:
Upon secondary analysis to exclude other first trimester antidepressant and known teratogen use, the adjusted odds ratios for bupropion compared to other antidepressant exposures decreased to 0.99 (95% CI 0.42-2.30) for congenital malformations and decreased to 0.64 (95% CI 0.15-2.66) for cardiovascular malformations (i.e., when bupropion was the only antidepressant dispensed during the first trimester and in the absence of exposure to known teratogenic drugs). No specific pattern of cardiac defects among infants born to recipients of bupropion during the first trimester was observed.

The secondary cohort analysis for paroxetine showed that the adjusted odds ratios for first trimester dispensing of paroxetine as compared to first trimester dispensing of all other antidepressant drugs in the RDB database was 1.84 (95% CI 1.16-2.91) for congenital malformations collectively. After excluding from the analysis other concurrent antidepressant exposures during the first trimester, the adjusted odds ratio for paroxetine increased slightly to 2.01 (95% CI 1.25-3.25), and was 1.97 (95% CI 1.21-3.20) upon exclusion of concomitant first trimester teratogenic drug exposures. Excluding both concomitant other antidepressant and teratogen use in the first trimester resulted in an adjusted odds ratio of 2.20 (95% CI 1.34-3.63), with a prevalence of congenital malformations as a whole following first trimester paroxetine exposure of approximately 4% (43.6 per 1000).

For cardiovascular malformations, the adjusted odds ratio for first trimester dispensing of paroxetine compared to other antidepressant exposures was 2.26 (95% CI 1.17-4.33). Reductions in this odds ratio for paroxetine were observed following removal from the analysis of mothers concomitantly exposed in the first trimester to other antidepressants (adjusted odds ratio 2.00, 95% CI 0.99-4.03), or to drugs known to have teratogenic effects on the cardiovascular system (adjusted odds ratio 2.14, 95% CI 1.09-4.20), or to both other antidepressants and known cardiovascular teratogens (adjusted odds ratio 2.08, 95% CI 1.03-4.23). The prevalence of cardiovascular malformations following first trimester paroxetine exposure and no concurrent first trimester use of other antidepressants or cardiovascular teratogens is approximately 2% (18.7 per 1000). Of the cardiovascular malformations reported in infants whose mothers were dispensed paroxetine in the first trimester, the majority were ventricular septal defects.

Of the remaining antidepressants, there were malformations reported in infants exposed to seven of these as the only antidepressant dispensed during the first trimester (amitriptyline, citalopram, fluoxetine, nefazodone, sertraline, trazodone, and venlafaxine), and two as “ever use” (imipramine and nortriptyline). The adjusted odds ratios for these nine antidepressants ranged from 0.47-2.21 for overall malformations and 0.37-2.02 for cardiovascular malformations; none had CI’s that excluded 1. The other nine antidepressants, each with 26 or fewer exposures, had no malformations reported.

Demographics/Baseline Characteristics

RDB	**Bupropion-First Trimester**	**Other Antidepressant-First Trimester**	**Bupropion-Outside First Trimester**
Total infants, N	463	3241	519
Maternal age at delivery			
12-19 years, %	1.5	1.5	0.6
20-24 years, %	7.6	8.6	8.3
25-29 years, %	24.2	26.3	30.1
30-34 years, %	36.5	35.8	35.6
35-39 years, %	20.3	21.3	21.8
40-49 years, %	9.9	6.4	3.7
Infant sex			
Female, %	44.1	48.2	49.5

Male, %	55.9	51.8	50.5
LabRx	**Bupropion-First Trimester**	**Other Antidepressant-First Trimester**	**Bupropion-Outside First Trimester**
Total infants, N	766	4508	674
Maternal age at delivery			
12-19 years, %	0.5	1.8	2.4
20-24 years, %	7.7	8.9	7.3
25-29 years, %	24.4	26.6	27.3
30-34 years, %	37.9	36.1	39.6
35-39 years, %	25.8	21.7	19.6
40-49 years, %	3.7	5.0	3.9
Infant sex			
Female, %	41.5	42.1	46.1
Male, %	46.7	45.7	42.6
Not reported, %	11.7	12.2	11.3

Primary Outcomes

Cohort Study Results using RDB

Odds ratio (OR) for prevalence (Prev) of congenital malformation, cohort analysis, RDB

	n	**Total**	**Prev per 1000**	**OR**	
				Crude (95% CI)	**Adjusted* (95% CI)**
Bupropion-First Trimester	16	463	34.6		
Comparator:					
Other Antidepressant-First Trimester	81	3241	25.0	1.40 (0.81, 2.41)	1.29 (0.74, 2.24)
Bupropion-Outside First Trimester	8	519	15.4	2.29 (0.97, 5.41)	2.07 (0.87, 4.95)

Prevalence per 1,000 live born infants

* Adjusted for age, calendar year of delivery, dispensing of lithium, dispensing of carbamazepine, diagnosis of pre-eclampsia or eclampsia, and infant sex.

Prevalence of infants with congenital malformation, per 1000 live born infants (95% confidence interval [CI]), RDB

	Bupropion-First Trimester		**Other Antidepressant-First Trimester**		**Bupropion-Outside First Trimester**	
Total infants, N	463		3241		519	
Category of malformation	**n**	**Prev per 1000 (95% CI)**	**n**	**Prev per 1000 (95% CI)**	**n**	**Prev per 1000 (95% CI)**
Total	16	34.6 (19.9, 55.5)	81	25.0 (19.9, 31.0)	8	15.4 (6.7, 30.1)
Cardiovascular	9	19.4 (8.9, 36.6)	36	11.1 (7.8, 15.3)	4	7.7 (2.1, 19.6)
Central Nervous System	0		8	2.5 (1.1, 4.9)	0	
Chromosomal	1	2.2 (0.1, 12.0)	1	0.3 (0.0, 1.7)	0	
Ear	0		0		0	
Eye	1	2.2 (0.1, 12.0)	0		0	
Fetal Alcohol Syndrome	0		0		0	
Gastrointestinal	2	4.3 (0.5, 15.5)	8	2.5 (1.1, 4.9)	2	3.9 (0.5, 13.9)
Genitourinary	2	4.3 (0.5, 15.5)	21	6.5 (4.0, 9.9)	1	1.9 (0.0, 10.7)
Musculoskeletal	2	4.3 (0.5, 15.5)	6	1.9 (0.7, 4.0)	1	1.9 (0.0, 10.7)
Orofacial	1	2.2 (0.1, 12.0)	6	1.9 (0.7, 4.0)	0	
Respiratory	0		1	0.3 (0.0, 1.7)	0	

OR for cardiovascular malformation, cohort analysis, RDB

	n	**Total**	**Prev per 1000**	**OR**	
				Crude (95% CI)	**Adjusted* (95% CI)**
Bupropion-First Trimester	9	463	19.4		
Comparator:					

Other Antidepressant-First Trimester	36	3241	11.1	1.76 (0.84, 3.69)	1.72 (0.82, 3.64)
Bupropion-Outside First Trimester	4	519	7.7	2.55 (0.78, 8.33)	2.55 (0.77, 8.47)
Prevalence per 1,000 live born infants * Adjusted for age, calendar year of delivery, dispensing of lithium, dispensing of carbamazepine, diagnosis of pre-eclampsia or eclampsia, and infant sex.					

Distribution of cardiovascular defects by diagnosis following medical record abstraction, RDB

	Bupropion-First Trimester (463 infants)	**Other Antidepressant-First Trimester (3241 infants)**	**Bupropion-Outside First Trimester (519 infants)**	**Total**
Atrial septal defect		4		4
Atrial septal defect, aneurysm of the fossa ovalis, bicuspid aortic valve, and mild right ventricle enlargement	1			1
Coarctation of the aorta	1	1		2
Coarctation of the aorta and bicuspid aortic valve		1		1
Patent ductus arteriosus		3		3
Pulmonary artery sling		1		1
Pulmonary stenosis	1	1	3	5
Pulmonary stenosis, aortic stenosis, tricuspid insufficiency, and mitral insufficiency		1		1
Tetralogy of Fallot		1		1
Transposition of the great arteries, and pulmonary stenosis		1		1
Tricuspid insufficiency		1		1
Ventricular septal defect	6	18	1	25
Ventricular septal defect and atrial septal defect		2		2
Ventricular septal defect, atrial septal defect, and pulmonary stenosis		1		1
Total	9	36	4	49

Cohort Study Results using LabRx

OR for congenital malformation, cohort analysis, LabRx

	n	**Total**	**Prev per 1000**	**OR**	
				Crude (95% CI)	**Adjusted* (95% CI)**
Bupropion-First Trimester	20	766	26.1		
Comparator:					
Other Antidepressant-First Trimester	74	4508	16.4	1.61 (0.97, 2.65)	1.61 (0.97, 2.66)
Bupropion-Outside First Trimester	14	674	20.8	1.26 (0.63, 2.53)	1.23 (0.61, 2.46)
Prevalence per 1,000 live born infants * Adjusted for age, calendar year of delivery, dispensing of lithium, dispensing of carbamazepine, diagnosis of pre-eclampsia or eclampsia, and infant sex.					

Prevalence of infants with congenital malformation, per 1000 live born infants (95% confidence interval [CI]), LabRx

	Bupropion-First Trimester		**Other Antidepressant-First Trimester**		**Bupropion-Outside First Trimester**	
Total infants, N	766		4508		674	
Category of malformation	**n**	**Prev per 1000 (95% CI)**	**n**	**Prev per 1000 (95% CI)**	**n**	**Prev per 1000 (95% CI)**
Total	20	26.1 (16.0, 40.0)	74	16.4 (12.9, 20.6)	14	20.8 (11.0, 34.6)

Cardiovascular	8	10.4 (4.5, 20.5)	23	5.1 (3.2, 7.6)	7	10.4 (4.2, 21.3)
Central Nervous System	0		0		0	
Chromosomal	2	2.6 (0.3, 9.4)	7	1.6 (0.6, 3.2)	3	4.5 (0.9, 13.0)
Ear	1	1.3 (0.0, 7.3)	1	0.2 (0.0, 1.2)	0	
Eye	1	1.3 (0.0, 7.3)	0		0	
Fetal Alcohol Syndrome	0		0		0	
Gastrointestinal	2	2.6 (0.3, 9.4)	12	2.7 (1.4, 4.6)	1	1.5 (0.0, 8.2)
Genitourinary	8	10.4 (4.5, 20.5)	17	3.8 (2.2, 6.0)	1	1.5 (0.0, 8.2)
Musculoskeletal	2	2.6 (0.3, 9.4)	7	1.6 (0.6, 3.2)	1	1.5 (0.0, 8.2)
Orofacial	2	2.6 (0.3, 9.4)	8	1.8 (0.8, 3.5)	0	
Respiratory	0		0		1	1.5 (0.0, 8.2)

OR for cardiovascular malformation, cohort analysis, LabRx

	n	**Total**	**Prev per 1000**	**OR**	
				Crude (95% CI)	**Adjusted* (95% CI)**
Bupropion-First Trimester	8	766	10.4		
Comparator:					
Other Antidepressant-First Trimester	23	4508	5.1	2.06 (0.92, 4.61)	2.07 (0.91, 4.69)
Bupropion-Outside First Trimester	7	674	10.4	1.01 (0.36, 2.79)	1.03 (0.37, 2.87)

Prevalence per 1,000 live born infants

* Adjusted for age, calendar year of delivery, dispensing of lithium, dispensing of carbamazepine, diagnosis of pre-eclampsia or eclampsia, and infant sex.

Distribution of cardiovascular defects by World Health Organization's Ninth Revision, International Classification of Diseases (ICD-9) diagnosis code in the medical claims data, LabRx

	Bupropion-First Trimester (766 infants)	**Other Antidepressant-First Trimester (4508 infants)**	**Bupropion-Outside First Trimester (674 infants)**	**Total**
Endocardial cushion defect (ICD-9 745.60, .61, .69)	1			1
Hypoplastic left heart syndrome (ICD-9 746.7)		1		1
Pulmonary artery anomalies (ICD-9 747.3)		2	1	3
Pulmonary valve atresia and stenosis (ICD-9 746.01, 746.02)	1	5	1	7
Tetralogy of Fallot (ICD-9 745.2)		1		1
Ventricular septal defect (ICD-9 745.4)	5	8	4	17
Ventricular septal defect (ICD-9 745.4); Tetralogy of Fallot (ICD-9 745.2); Coarctation of aorta (ICD-9 747.1)		1		1
Ventricular septal defect (ICD-9 745.4); Aortic valve stenosis (ICD-9 746.3); Coarctation of aorta (ICD-9 747.1)		1		1
Ventricular septal defect (ICD-9 745.4); Endocardial cushion defect (ICD-9 745.60, .61, .69)	1	1		2
Ventricular septal defect (ICD-9 745.4); Endocardial cushion defect (ICD-9 745.60, .61, .69); Coarctation of aorta (ICD-9 747.1)		1		1
Ventricular septal defect (ICD-9 745.4); Pulmonary artery anomalies (ICD-9 747.3)		1		1

Ventricular septal defect (ICD-9 745.4); Pulmonary valve atresia and stenosis (ICD-9 746.01, 746.02)			1	1
Ventricular septal defect (ICD-9 745.4); Pulmonary valve atresia and stenosis (ICD-9 746.01, 746.02); Pulmonary artery anomalies (ICD-9 747.3)		1		1
Total	8	23	7	38

Nested Case-Control Study Results

OR for congenital malformation, case-control analysis, RDB

	Cases	**Controls**	**OR**	
			Crude* (95% CI)	**Adjusted** (95% CI)**
Bupropion-First Trimester	16	13		
Comparator:				
Other Antidepressant-First Trimester	81	76	1.19 (0.54, 2.64)	1.21 (0.47, 3.13)
Bupropion-Outside First Trimester	8	16	3.04 (0.87, 10.64)	4.03 (0.92, 17.54)

* Adjusted for geographic region and calendar quarter/year of birth.

** Adjusted for geographic region, calendar quarter/year of birth, dispensing of lithium, dispensing of carbamazepine, diagnosis of pre-eclampsia or eclampsia, infant sex, parity, depression or anxiety during pregnancy, and smoking before or during pregnancy

OR for cardiovascular malformation, case-control analysis, RDB

	Cases	**Controls**	**OR**	
			Crude* (95% CI)	**Adjusted** (95% CI)**
Bupropion-First Trimester	9	6		
Comparator:				
Other Antidepressant-First Trimester	36	35	1.49 (0.48, 4.61)	1.52 (0.34, 6.71)
Bupropion-Outside First Trimester	4	8	4.29 (0.64, 28.57)	4.35 (0.33, 55.56)

* Adjusted for geographic region and calendar quarter/year of birth.

** Adjusted for geographic region, calendar quarter/year of birth, dispensing of lithium, dispensing of carbamazepine, diagnosis of pre-eclampsia or eclampsia, infant sex, parity, depression or anxiety during pregnancy, and smoking before or during pregnancy

Secondary Cohort Analysis

Risk of congenital/cardiac malformation for specific antidepressants relative to all other antidepressant exposures

OR for congenital malformation according to mutually exclusive categories of specific antidepressants dispensed during the first trimester, cohort analysis, RDB

Antidepressant	**n**	**Total**	**Prev per 1000**	**OR***	
				Crude (95% CI)	**Adjusted** (95% CI)**
Amitriptyline	3	171	17.5	0.67 (0.21, 2.13)	0.73 (0.23, 2.34)
Amitriptyline / Chlordiazepoxide	0	3	0	0	0
Bupropion	8	284	28.2	1.11 (0.53, 2.32)	1.14 (0.54, 2.39)
Citalopram	7	218	32.1	1.28 (0.59, 2.80)	1.16 (0.52, 2.59)
Clomipramine	0	3	0	0	0
Desipramine	0	6	0	0	0
Doxepin	0	19	0	0	0
Fluoxetine	22	963	22.8	0.85 (0.53, 1.38)	0.86 (0.53, 1.41)
Fluvoxamine	0	17	0	0	0
Imipramine	0	29	0	0	0
Mirtazapine	0	9	0	0	0
Nefazodone	1	51	19.6	0.76 (0.10, 5.54)	0.73 (0.10, 5.42)
Nortriptyline	0	69	0	0	0
Paroxetine	24	591	40.6	1.81 (1.13, 2.91)	2.01 (1.25, 3.25)
Protriptyline	0	4	0	0	0
Sertraline	8	568	14.1	0.50 (0.24, 1.04)	0.50 (0.24, 1.04)

Trazodone	3	59	50.8	2.07 (0.64, 6.73)	2.21 (0.65, 7.51)
Venlafaxine	3	154	19.5	0.75 (0.23, 2.39)	0.69 (0.22, 2.24)
More than one type of antidepressant	16	486	32.9	1.35 (0.78, 2.34)	1.23 (0.70, 2.14)
Prevalence per 1,000 live born infants * Reference group for OR calculations is all other antidepressants. ** Adjusted for age, calendar year of delivery, dispensing of lithium, dispensing of carbamazepine, diagnosis of pre-eclampsia or eclampsia, and infant sex.					
OR for congenital malformation according to ever use of specific antidepressants during the first trimester, cohort analysis, RDB					
Antidepressant	**n**	**Total**	**Prev per 1000**	**OR***	
				Crude (95% CI)	**Adjusted** (95% CI)**
Amitriptyline	4	233	17.2	0.65 (0.24, 1.78)	0.68 (0.25, 1.89)
Amitriptyline / Chlordiazepoxide	0	5	0	0	0
Amitriptyline / Perphenazine	0	1	0	0	0
Bupropion	15	463	32.4	1.32 (0.76, 2.32)	1.23 (0.70, 2.17)
Citalopram	10	298	33.6	1.36 (0.70, 2.64)	1.23 (0.62, 2.45)
Clomipramine	0	5	0	0	0
Desipramine	0	10	0	0	0
Doxepin	0	22	0	0	0
Fluoxetine	31	1178	26.3	1.04 (0.67, 1.61)	1.03 (0.67, 1.60)
Fluvoxamine	0	26	0	0	0
Imipramine	2	42	47.6	1.92 (0.46, 8.06)	1.97 (0.46, 8.40)
Mirtazapine	0	23	0	0	0
Nefazodone	1	75	13.3	0.51 (0.07, 3.70)	0.49 (0.07, 3.58)
Nortriptyline	1	87	11.5	0.44 (0.06, 3.16)	0.47 (0.06, 3.41)
Paroxetine	27	704	38.4	1.72 (1.09, 2.71)	1.84 (1.16, 2.91)
Protriptyline	0	4	0	0	0
Sertraline	12	705	17.0	0.61 (0.33, 1.12)	0.58 (0.31, 1.08)
Trazodone	3	154	19.5	0.75 (0.23, 2.39)	0.70 (0.21, 2.30)
Trimipramine	0	1	0	0	0
Venlafaxine	6	215	27.9	1.10 (0.47, 2.54)	1.05 (0.45, 2.45)
Prevalence per 1,000 live born infants * Reference group for OR calculations is all other antidepressants. ** Adjusted for age, calendar year of delivery, dispensing of lithium, dispensing of carbamazepine, diagnosis of pre-eclampsia or eclampsia, and infant sex.					
OR for cardiovascular malformation according to mutually exclusive categories of specific antidepressants dispensed during the first trimester, cohort analysis, RDB					
Antidepressant	**n**	**Total**	**Prev per 1000**	**OR***	
				Crude (95% CI)	**Adjusted** (95% CI)**
Amitriptyline	1	171	5.8	0.49 (0.07, 3.57)	0.55 (0.08, 4.08)
Amitriptyline / Chlordiazepoxide	0	3	0	0	0
Bupropion	3	284	10.6	0.90 (0.28, 2.94)	0.90 (0.28, 2.97)
Citalopram	5	218	22.9	2.13 (0.83, 5.47)	2.02 (0.76, 5.36)
Clomipramine	0	3	0	0	0
Desipramine	0	6	0	0	0
Doxepin	0	19	0	0	0
Fluoxetine	13	963	13.5	1.24 (0.64, 2.38)	1.26 (0.65, 2.45)
Fluvoxamine	0	17	0	0	0
Imipramine	0	29	0	0	0
Mirtazapine	0	9	0	0	0
Nefazodone	0	51	0	0	0

Nortriptyline	0	69	0	0	0
Paroxetine	11	591	18.6	1.83 (0.92, 3.64)	2.00 (0.99, 4.03)
Protriptyline	0	4	0	0	0
Sertraline	0	568	0	0	0
Trazodone	1	59	16.9	1.48 (0.20, 10.93)	1.31 (0.17, 10.43)
Venlafaxine	2	154	13.0	1.13 (0.27, 4.70)	1.07 (0.25, 4.52)
More than one type of antidepressant	7	486	14.4	1.29 (0.57, 2.92)	1.24 (0.54, 2.84)
Prevalence per 1,000 live born infants * Reference group for OR calculations is all other antidepressants. ** Adjusted for age, calendar year of delivery, dispensing of lithium, dispensing of carbamazepine, diagnosis of pre-eclampsia or eclampsia, and infant sex.					
OR for cardiovascular malformation according to ever use of specific antidepressants during the first trimester, cohort analysis, RDB					
Antidepressant	**n**	**Total**	**Prev per 1000**	**OR***	
				Crude (95% CI)	**Adjusted** (95% CI)**
Amitriptyline	1	233	4.3	0.35 (0.05, 2.57)	0.37 (0.05, 2.73)
Amitriptyline / Chlordiazepoxide	0	5	0	0	0
Amitriptyline / Perphenazine	0	1	0	0	0
Bupropion	8	463	17.3	1.61 (0.74, 3.49)	1.58 (0.72, 3.46)
Citalopram	6	298	20.1	1.87 (0.78, 4.47)	1.74 (0.70, 4.31)
Clomipramine	0	5	0	0	0
Desipramine	0	10	0	0	0
Doxepin	0	22	0	0	0
Fluoxetine	17	1178	14.4	1.41 (0.76, 2.61)	1.45 (0.78, 2.70)
Fluvoxamine	0	26	0	0	0
Imipramine	0	42	0	0	0
Mirtazapine	0	23	0	0	0
Nefazodone	0	75	0	0	0
Nortriptyline	0	87	0	0	0
Paroxetine	14	704	19.9	2.08 (1.09, 3.96)	2.26 (1.17, 4.33)
Protriptyline	0	4	0	0	0
Sertraline	1	705	1.4	0.10 (0.01, 0.73)	0.09 (0.01, 0.67)
Trazodone	1	154	6.5	0.55 (0.08, 3.99)	0.51 (0.07, 3.91)
Trimipramine	0	1	0	0	0
Venlafaxine	3	215	14.0	1.22 (0.37, 3.98)	1.18 (0.36, 3.86)
Prevalence per 1,000 live born infants * Reference group for OR calculations is all other antidepressants. ** Adjusted for age, calendar year of delivery, dispensing of lithium, dispensing of carbamazepine, diagnosis of pre-eclampsia or eclampsia, and infant sex.					
OR for congenital malformation according to mutually exclusive categories of specific antidepressants dispensed during the first trimester, excluding women with teratogenic drug dispensings, cohort analysis, RDB					
Antidepressant	**n**	**Total**	**Prev per 1000**	**OR***	
				Crude (95% CI)	**Adjusted** (95% CI)**
Amitriptyline	1	146	6.8	0.26 (0.04, 1.85)	0.27 (0.04, 1.96)
Amitriptyline / Chlordiazepoxide	0	3	0	0	0
Bupropion	6	248	24.2	0.95 (0.41, 2.20)	0.99 (0.42, 2.30)
Citalopram	7	188	37.2	1.53 (0.70, 3.37)	1.39 (0.62, 3.11)
Clomipramine	0	3	0	0	0
Desipramine	0	5	0	0	0
Doxepin	0	14	0	0	0
Fluoxetine	18	820	22.0	0.82 (0.48, 1.40)	0.82 (0.48, 1.39)

Fluvoxamine	0	13	0	0	0
Imipramine	0	24	0	0	0
Mirtazapine	0	5	0	0	0
Nefazodone	1	41	24.4	0.96 (0.13, 7.07)	0.94 (0.13, 6.96)
Nortriptyline	0	62	0	0	0
Paroxetine	23	527	43.6	2.05 (1.25, 3.36)	2.20 (1.34, 3.63)
Protriptyline	0	3	0	0	0
Sertraline	7	507	13.8	0.49 (0.23, 1.08)	0.48 (0.22, 1.05)
Trazodone	2	49	40.8	1.65 (0.39, 6.92)	1.98 (0.47, 8.39)
Venlafaxine	2	129	15.5	0.60 (0.15, 2.45)	0.59 (0.14, 2.42)
More than one type of antidepressant	14	406	34.5	1.45 (0.81, 2.60)	1.42 (0.79, 2.55)
Prevalence per 1,000 live born infants * Reference group for OR calculations is all other antidepressants. ** Adjusted for age, calendar year of delivery, diagnosis of pre-eclampsia or eclampsia, and infant sex.					
OR for congenital malformation according to ever use of specific antidepressants during the first trimester, excluding women with teratogenic drug dispensings, cohort analysis, RDB					
Antidepressant	**n**	**Total**	**Prev per 1000**	**OR***	
				Crude (95% CI)	**Adjusted** (95% CI)**
Amitriptyline	2	194	10.3	0.39 (0.09, 1.58)	0.41 (0.10, 1.69)
Amitriptyline / Chlordiazepoxide	0	4	0	0	0
Amitriptyline / Perphenazine	0	1	0	0	0
Bupropion	11	395	27.8	1.12 (0.59, 2.13)	1.12 (0.59, 2.14)
Citalopram	10	250	40.0	1.69 (0.86, 3.31)	1.55 (0.77, 3.10)
Clomipramine	0	5	0	0	0
Desipramine	0	8	0	0	0
Doxepin	0	15	0	0	0
Fluoxetine	25	1005	24.9	0.97 (0.60, 1.57)	0.96 (0.59, 1.55)
Fluvoxamine	0	22	0	0	0
Imipramine	2	36	55.6	2.29 (0.54, 9.71)	2.21 (0.51, 9.55)
Mirtazapine	0	16	0	0	0
Nefazodone	1	63	15.9	0.62 (0.08, 4.49)	0.59 (0.08, 4.36)
Nortriptyline	1	78	12.8	0.49 (0.07, 3.59)	0.49 (0.07, 3.62)
Paroxetine	25	621	40.3	1.89 (1.17, 3.05)	1.97 (1.21, 3.20)
Protriptyline	0	3	0	0	0
Sertraline	11	624	17.6	0.64 (0.34, 1.22)	0.62 (0.33, 1.18)
Trazodone	2	124	16.1	0.62 (0.15, 2.55)	0.69 (0.17, 2.84)
Trimipramine	0	1	0	0	0
Venlafaxine	5	183	27.3	1.08 (0.43, 2.71)	1.08 (0.43, 2.71)
Prevalence per 1,000 live born infants * Reference group for OR calculations is all other antidepressants. ** Adjusted for age, calendar year of delivery, diagnosis of pre-eclampsia or eclampsia, and infant sex.					
OR for cardiovascular malformation according to mutually exclusive categories of specific antidepressants dispensed during the first trimester, excluding women with dispensings of teratogenic drugs affecting the cardiovascular system, cohort analysis, RDB					
Antidepressant	**n**	**Total**	**Prev per 1000**	**OR***	
				Crude (95% CI)	**Adjusted** (95% CI)**
Amitriptyline	1	171	5.8	0.52 (0.07, 3.82)	0.56 (0.08, 4.16)
Amitriptyline / Chlordiazepoxide	0	3	0	0	0
Bupropion	2	282	7.1	0.63 (0.15, 2.62)	0.64 (0.15, 2.66)
Citalopram	5	217	23.0	2.30 (0.89, 5.94)	2.22 (0.83, 5.95)
Clomipramine	0	3	0	0	0

Desipramine	0	5	0	0	0
Doxepin	0	19	0	0	0
Fluoxetine	12	955	12.6	1.22 (0.62, 2.41)	1.23 (0.62, 2.44)
Fluvoxamine	0	17	0	0	0
Imipramine	0	29	0	0	0
Mirtazapine	0	8	0	0	0
Nefazodone	0	50	0	0	0
Nortriptyline	0	69	0	0	0
Paroxetine	11	589	18.7	2.00 (0.99, 4.03)	2.08 (1.03, 4.23)
Protriptyline	0	4	0	0	0
Sertraline	0	563	0	0	0
Trazodone	1	58	17.2	1.61 (0.22, 11.90)	1.66 (0.22, 12.43)
Venlafaxine	2	150	13.3	1.24 (0.30, 5.18)	1.22 (0.29, 5.15)
More than one type of antidepressant	6	476	12.6	1.19 (0.50, 2.84)	1.19 (0.49, 2.86)
Prevalence per 1,000 live born infants * Reference group for OR calculations is all other antidepressants. ** Adjusted for age, calendar year of delivery, diagnosis of pre-eclampsia or eclampsia, and infant sex.					
OR for cardiovascular malformation according to ever use of specific antidepressants during the first trimester, excluding women with dispensings of teratogenic drugs affecting the cardiovascular system, cohort analysis, RDB					
Antidepressant	**n**	**Total**	**Prev per 1000**	**OR***	
				Crude (95% CI)	**Adjusted** (95% CI)**
Amitriptyline	1	232	4.3	0.38 (0.05, 2.76)	0.40 (0.05, 2.92)
Amitriptyline / Chlordiazepoxide	0	5	0	0	0
Amitriptyline / Perphenazine	0	1	0	0	0
Bupropion	6	454	13.2	1.25 (0.52, 3.00)	1.29 (0.54, 3.09)
Citalopram	6	296	20.3	2.03 (0.85, 4.88)	1.90 (0.76, 4.75)
Clomipramine	0	5	0	0	0
Desipramine	0	9	0	0	0
Doxepin	0	22	0	0	0
Fluoxetine	15	1166	12.9	1.29 (0.68, 2.46)	1.33 (0.70, 2.55)
Fluvoxamine	0	26	0	0	0
Imipramine	0	42	0	0	0
Mirtazapine	0	21	0	0	0
Nefazodone	0	74	0	0	0
Nortriptyline	0	87	0	0	0
Paroxetine	13	699	18.6	2.07 (1.06, 4.02)	2.14 (1.09, 4.20)
Protriptyline	0	4	0	0	0
Sertraline	1	697	1.4	0.11 (0.02, 0.79)	0.10 (0.01, 0.75)
Trazodone	1	150	6.7	0.60 (0.08, 4.39)	0.63 (0.09, 4.67)
Trimipramine	0	1	0	0	0
Venlafaxine	3	211	14.2	1.33 (0.41, 4.36)	1.31 (0.40, 4.32)
Prevalence per 1,000 live born infants * Reference group for OR calculations is all other antidepressants. ** Adjusted for age, calendar year of delivery, diagnosis of pre-eclampsia or eclampsia, and infant sex.					
Congenital Malformations In Infants Whose Mothers Were Dispensed Paroxetine During the 1st Trimester, RDB					
Non-Cardiovascular Malformations				**No. infants**	
Pyloric stenosis				2	
Agenesis of corpus callosum w/ left cerebellum hypoplasia				1	
Arthrogryposis multiplex congenita. The baby was premature and died.				1	
Bilateral hip dysplasia				1	
Cleft palate and hypospadias				1	

Congenital left hip subluxation	1
Congenital microcephaly	1
First degree hypospadias	1
Imperforate anus and posterior forchette fistula (rectal vaginal fistula)	1
Imperforate anus w/ perineal fistula, right renal agenesis and left sided Grade II hydronephrosis	1
Left unilateral complete cleft lip and cleft palate	1
Lipomyelomeningocele - skin appendage over thoracolumbar junction	1
Cardiovascular Malformations	**No. infants**
Ventricular septal defect (VSD)	2
Small muscular VSD	2 (1*)
Atrial septal defect (ASD) w/ bilateral pulmonary artery branch stenosis	1
Coarctation of the aorta	1*
Congenitally corrected transposition of the great arteries w/ mild - moderate pulmonary stenosis	1
High perimembranous VSD of moderate size	1*
Moderate anterior muscular VSD	1
Moderate midmuscular VSD	1
Small ASD, perimembranous VSD, possible mild valvar pulmonary stenosis	1
Small-Moderate patent ductus arteriosus; restrictive patent foramen ovale w/ left ventricular volume overload	1
Trabecular VSD	1
VSD w/ small ASD	1
* malformations associated with "ever-use" of paroxetine; all other malformations associated with "single use"	
Limitations: Limitations of this study include that there were no comparison cohorts of non-recipients of any antidepressant during the first trimester or of non-depressed women, there are uncertainties associated with both exposure and outcome measure, and there are potential differences in clinical characteristics across cohorts which may have resulted in residual confounding. Additionally, as this is a preliminary analysis, a major limitation of this study is the statistical instability of the estimates due to the relatively small numbers of cases reported.	
Conclusion: The results of this epidemiologic study do not show an increased risk of congenital malformations specifically associated with the use of bupropion in the first trimester of pregnancy compared with the use of other antidepressants. In this study, the use of paroxetine in the first trimester of pregnancy was associated with an increased risk of congenital malformations compared with the use of other antidepressants. A final analysis, which will contain data on additional confirmed cases from the Ingenix Research Database (RDB) from January 2003 through September 2004, will be subsequently reported.	
Publications: No publication	

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