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GSK Medicine: Bupropion and Paroxetine
Study No.: EPIP083 (Final report)
Title: EPIDEMIOLOGY STUDY: Final Report on Bupropion and Other Antidepressants, including Paroxetine, in Pregnancy and the Occurrence of Cardiovascular and Major Congenital Malformations
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 final report is based on updated analysis which expanded the calendar time period of the original study. 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. Additional analyses were subsequently performed for paroxetine and are reported in the CTR under paroxetine (EPI40404).
Objectives: The primary objective was to estimate the prevalence at birth among infants born to women dispensed bupropion in the first trimester of pregnancy for congenital malformations collectively, and for cardiovascular defects in particular. 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: Major depressive disorder / 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 I3 Drug Safety (formerly Ingenix), A UnitedHealth Group Company.
Research Methods:
Data Source: The study was carried out within the I3 Drug Safety database using data from the Ingenix Research Data Mart (RDM), containing insurance information from United HealthCare. The RDM contains medical and pharmacy claims data from United HealthCare affiliated health plans and large employer groups, located in the Northeast, South/Southeast, Midwest, and Western United States.
Study Design: A retrospective cohort study. The primary analysis was a retrospective cohort study of major congenital malformations, 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 the RDM database. Secondary cohort analysis: In addition to the analysis of bupropion described above, two additional post-hoc retrospective cohort analyses were conducted: 1) an additional analysis of overall congenital and cardiovascular malformations in infants born to first trimester recipients of bupropion was performed <i>excluding</i> 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 <i>a priori</i> 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).
Study Population: All women dispensed bupropion or other antidepressants and who had a live born delivery in the RDM between January 1995 and September 2004 were identified. The subset of women aged 12-49 years as of their delivery date was selected. Cohort membership was further restricted to members within health plans where medical record abstraction could be conducted. 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:

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 malformations among live born infants, with a focus on cardiovascular defects. Congenital malformations were classified according to organ system and diagnosis. Medical records were abstracted to verify the diagnosis for infants whose medical claims data identified evidence of congenital malformations. 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.

Data Analysis Methods:

For the primary cohort analysis, the prevalence of infants with congenital malformations 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. An additional set of analyses, the secondary cohort analyses, was also performed to assess the risk of congenital/cardiovascular malformations 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 "any 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.

Study Results:

Results of the primary cohort :

In the primary cohort analysis of the RDM 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 0.95 (95% CI 0.62-1.45) for congenital malformations overall, and 0.97 (95% CI 0.52-1.80) for cardiovascular malformations alone. None of these odds ratios had a confidence interval that excluded 1.

Updated results of the secondary cohort analyses (5956 infants born through September 2004):

Upon secondary analysis to exclude other first trimester antidepressant and known teratogen use, the adjusted odds ratios for bupropion compared to other antidepressant exposures was 0.77 (95% CI 0.42-1.41) for congenital malformations and decreased to 0.48 (95% CI 0.17-1.34) 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 RDM database was 1.75 (95% CI 1.19-2.59) for congenital malformations collectively. After excluding from the analysis other concurrent antidepressant exposures during the first trimester, the adjusted odds ratio for paroxetine was 1.75 (95% CI 1.15-2.66), and was 1.77 (95% CI 1.17-2.68) 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 1.83 (95% CI 1.18-2.84), with a prevalence of congenital malformations as a whole following first trimester paroxetine exposure of approximately 4% (37.7 per 1000).

For cardiovascular malformations, the adjusted odds ratio for first trimester dispensing of paroxetine compared to other antidepressant exposures was 1.78 (95% CI 1.01-3.15). 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 1.46, 95% CI 0.77-2.78), or to drugs known to have teratogenic effects on the cardiovascular system (adjusted odds ratio 1.74, 95% CI 0.97-3.10), or to both other antidepressants and known cardiovascular teratogens (adjusted odds ratio 1.54, 95% CI 0.81-2.93). The prevalence of cardiovascular malformations following first trimester paroxetine exposure and no concurrent first trimester use of other antidepressants or cardiovascular teratogens was approximately 2% (14.7 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 eight of these as the only antidepressant dispensed during the first trimester (amitriptyline, citalopram, escitalopram, fluoxetine, nefazodone, sertraline, trazodone, and venlafaxine), and three as "any use" (clomipramine, imipramine and nortriptyline). The adjusted odds ratios for these eleven antidepressants ranged from 0.52-7.65 for overall malformations and 0.43-17.95 for cardiovascular malformations; none had CI's that excluded 1 with the exception of clomipramine for cardiovascular malformations. The other ten antidepressants, each with 36 or fewer exposures, had no malformations reported.

Demographics/Baseline Characteristics using RDM (January 1995 through September 2004)

	Bupropion First Trimester	Other Antidepressant First Trimester	Bupropion Outside First Trimester
Total number of infants, N	1213	4743	1049
Maternal age at delivery			
12-19 years, n%	19 (1.6)	78 (1.6)	9 (0.9)
20-24 years, n%	80 (6.6)	458 (9.7)	93 (8.9)
25-29 years, n%	304 (25.1)	1346 (28.4)	318 (30.3)
30-34 years, n%	467 (38.5)	1648 (34.7)	391 (37.3)
35-39 years, n%	260 (21.4)	974 (20.5)	198 (18.9)
40-49 years, n%	83 (6.8)	239 (5.0)	40 (3.8)
Infant sex			
Females	568 (46.8)	2286 (48.2)	499 (47.6)

Males	645 (53.2)	2457 (51.8)	550 (52.4)				
Outcomes using RDM (January 1995 through September 2004)							
Odds ratio (OR) for prevalence of congenital malformations							
	No. of infants	No. of cases	Prevalence per 1000	Crude OR (95% CI)	Adjusted OR ^a (95% CI)		
Bupropion (First Trimester)	1213	28	23.1				
Comparator							
Other Antidepressant (First Trimester)	4743	110	23.2	0.99 (0.65, 1.51)	0.95 (0.62, 1.45)		
Bupropion (Outside First Trimester)	1049	23	21.9	1.05 (0.60, 1.83)	1.00 (0.57, 1.73)		
^a Odds ratios adjusted for maternal age category, geographic region of the health plan, infant sex, diagnoses of bipolar disorder, eclampsia within one year before delivery, dispensings of lithium, phenytoin, fluconazole within one year before delivery through the end of the first trimester, and number of physician visits within 10 to 12 months before delivery.							
Prevalence of infants with congenital malformations confirmed through medical record abstraction by organ system category							
	Bupropion First Trimester (1213 infants)		Other Antidepressant First Trimester (4743 infants)		Bupropion Outside First Trimester (1049 infants)		
	n	Prevalence per 1000 (95% CI)	n	Prevalence per 1000 (95% CI)	n	Prevalence per 1000 (95% CI)	
Total number of cases, N ^b	28	23.1 (16.0, 33.2)	110	23.2 (19.3, 27.9)	23	21.9 (14.7, 32.7)	
Category of malformation							
Cardiovascular	13	10.7 (6.3, 18.3)	51	10.8 (8.2, 14.1)	10	9.5 (5.2, 17.5)	
Central Nervous System	0		8	1.7 (0.9, 3.3)	0		
Ear	0		0		0		
Eye	1	0.8 (0, 4.6)	0		1	1.0 (0, 5.3)	
Fetal Alcohol Syndrome	0		0		0		
Gastrointestinal	4	3.3 (0.9, 8.4)	11	2.3 (1.3, 4.2)	4	3.8 (1.0, 9.7)	
Genitourinary	6	5.0 (2.3, 10.7)	31	6.5 (4.6, 9.3)	4	3.8 (0.1, 10.0)	
Musculoskeletal	3	2.5 (0.5, 7.2)	7	1.5 (0.7, 3.0)	5	4.8 (2.0, 11.1)	
Orofacial	3	2.5 (0.5, 7.2)	7	1.5 (0.7, 3.0)	0		
Respiratory	0		1	0.2 (0, 1.2)	0		
^b Infants may be counted in multiple malformation categories							
OR for prevalence of cardiovascular malformations							
	No. of infants	No. of cases	Prevalence per 1000	Crude OR (95% CI)	Adjusted OR ^c (95% CI)		
Bupropion (First Trimester)	1213	13	10.7				
Comparator							
Other Antidepressant (First Trimester)	4743	51	10.8	1.00 (0.54, 1.84)	0.97 (0.52, 1.80)		
Bupropion (Outside First Trimester)	1049	10	9.5	1.13 (0.49, 2.58)	1.07 (0.48, 2.40)		
^c Odds ratios adjusted for maternal age category, geographic region of the health plan, infant sex, diagnoses of bipolar disorder, eclampsia within one year before delivery, dispensings of lithium, phenytoin, fluconazole within one year before delivery through the end of the first trimester, and number of physician visits within 10 to 12 months before delivery.							
Distribution of cardiovascular malformations by diagnosis following medical record abstraction							
Diagnosis	Bupropion First Trimester (1213 infants)		Other Antidepressant First Trimester (4743 infants)		Bupropion Outside First Trimester (1049 infants)		Total
Total number of cases, N	13		51		10		74
Aortic stenosis, bicuspid aortic valve	1		0		0		1
Atrial septal defect	0		5		0		5
Atrial septal defect, aneurysm of the	1		0		0		1

fossa ovalis, bicuspid aortic valve, and mild right ventricle enlargement					
Atrial septal defect, aortic stenosis	0	1	0	1	
Atrial septal defect, pulmonary stenosis	1	0	1	2	
Coarctation of the aorta	1	2	0	3	
Coarctation of the aorta and bicuspid aortic valve	0	1	0	1	
Hypoplastic left heart syndrome	0	1	0	1	
Hypoplastic left heart, coarctation of the aorta	1	0	0	1	
Patent ductus arteriosus	0	4	0	4	
Pulmonary artery sling	0	1	0	1	
Pulmonary stenosis	1	3	4	8	
Pulmonary stenosis, aortic stenosis, tricuspid insufficiency, and mitral insufficiency	0	1	0	1	
Tetralogy of Fallot	0	2	0	2	
Transposition of the great arteries, and pulmonary stenosis	0	1	0	1	
Tricuspid insufficiency	0	1	0	1	
Ventricular septal defect	6	25	5	36	
Ventricular septal defect and atrial septal defect	0	2	0	2	
Ventricular septal defect, atrial septal defect, and pulmonary stenosis	0	1	0	1	
Ventricular septal defect, coarctation of the aorta, tricuspid and mitral valve regurgitation	1	0	0	1	
Prevalence of all congenital malformations and cardiovascular malformations according to the number of bupropion dispensings during the estimated first trimester					
No. of bupropion dispensings^d	No. of infants	No. of malformation cases	Prevalence per 1000	No. of cardiovascular cases	Prevalence per 1000
Total	1213	28	23.1	13	10.7
1	624	15	24.0	8	12.8
2	308	8	26.0	2	6.5
3 or more	281	5	17.8	3	10.7
^d Bupropion dispensings before pregnancy that overlapped into the estimated first trimester are counted in the first trimester window.					
OR for all congenital malformations stratified by maternal dispensing of teratogenic drugs^e					
	No. of infants	No. of cases	Prevalence per 1000	Crude OR (95% CI)	Adjusted OR^f (95% CI)
No teratogen dispensing					
Bupropion (First Trimester)	1024	24	23.4		
Comparator					
Other Antidepressant (First Trimester)	4068	96	23.6	0.99 (0.63, 1.56)	0.95 (0.60, 1.50)
Bupropion (Outside First Trimester)	908	19	21.0	1.12 (0.61, 2.06)	1.08 (0.58, 1.99)
Teratogen dispensing					
Bupropion (First Trimester)	189	4	21.2		
Comparator					
Other Antidepressant (First Trimester)	675	14	20.7	0.98 (0.32, 3.02)	0.90 (0.27, 2.97)
Bupropion (Outside First Trimester)	141	4	28.4	0.67 (0.17, 2.69)	0.94 (0.19, 4.65)
^e Maternal teratogenic drug dispensing within a year before delivery through the end of the estimated first trimester.					
^f Odds ratios adjusted for maternal age category, geographic region of the health plan, infant sex, diagnoses of bipolar					

disorder, eclampsia within one year before delivery, and number of physician visits within 10 to 12 months before delivery.					
OR for all congenital malformations stratified by maternal dispensing of teratogenic drugs or antidepressants^g					
	No. of infants	No. of cases	Prevalence per 1000	Crude OR (95% CI)	Adjusted ORⁱ (95% CI)
Neither teratogen nor antidepressant dispensing^h					
Bupropion (First Trimester)	591	10	16.9		
Comparator					
Other Antidepressant (First Trimester)	4068	96	23.6	0.71 (0.37, 1.37)	0.69 (0.36, 1.34)
Bupropion (Outside First Trimester)	666	16	24.0	0.70 (0.31, 1.55)	0.68 (0.31, 1.52)
Teratogen or antidepressant dispensing^h					
Bupropion (First Trimester)	622	18	28.9		
Comparator					
Other Antidepressant (First Trimester)	675	14	20.7	1.38 (0.68, 2.80)	1.50 (0.72, 3.13)
Bupropion (Outside First Trimester)	383	7	18.3	1.55 (0.64, 3.73)	1.52 (0.61, 3.77)
^g Maternal teratogenic drug or antidepressant dispensing within a year before delivery through the end of the estimated first trimester.					
^h Only the bupropion cohorts were further stratified according to dispensing of another antidepressant.					
ⁱ Odds ratios adjusted for maternal age category, geographic region of the health plan, infant sex, diagnoses of bipolar disorder, eclampsia within one year before delivery, and number of physician visits within 10 to 12 months before delivery.					
OR for all cardiovascular malformations stratified by maternal dispensing of teratogenic drugs^j					
	No. of infants	No. of cases	Prevalence per 1000	Crude OR (95% CI)	Adjusted OR^k (95% CI)
No teratogen dispensing					
Bupropion (First Trimester)	1200	11	9.2		
Comparator					
Other Antidepressant (First Trimester)	4708	50	10.6	0.86 (0.45, 1.66)	0.83 (0.43, 1.60)
Bupropion (Outside First Trimester)	1036	9	8.7	1.06 (0.44, 2.56)	1.02 (0.42, 2.49)
Teratogen dispensing					
Bupropion (First Trimester)	13	2	153.8		
Comparator					
Other Antidepressant (First Trimester)	35	1	28.6	6.52 (0.54, 79.50)	
Bupropion (Outside First Trimester)	13	1	76.9	1.21 (0.12, 12.10)	
^j Maternal dispensing of a teratogenic drug thought or suspected to affect the cardiovascular system within a year before delivery through the end of the estimated first trimester.					
^k Odds ratios adjusted for maternal age category, geographic region of the health plan, infant sex, diagnoses of bipolar disorder, eclampsia within one year before delivery, dispensing of fluconazole within one year before delivery through the end of the first trimester, and number of physician visits within 10 to 12 months before delivery.					
OR for all cardiovascular malformations stratified by maternal dispensing of teratogenic drugs or antidepressants^l					
	No. of infants	No. of cases	Prevalence per 1000	Crude OR (95% CI)	Adjusted ORⁿ (95% CI)
Neither teratogen nor antidepressant dispensing^m					
Bupropion (First Trimester)	673	4	5.9		
Comparator					
Other Antidepressant (First Trimester)	4708	50	10.6	0.56 (0.20, 1.55)	0.54 (0.19, 1.51)
Bupropion (Outside First Trimester)	750	8	10.7	0.56 (0.17, 1.86)	0.56 (0.17, 1.88)
Teratogen or antidepressant dispensing^m					
Bupropion (First Trimester)	540	9	16.7		
Comparator					

Other Antidepressant (First Trimester)	35	1	28.6	0.58 (0.07, 4.70)	1.69 (0.11, 24.90)
Bupropion (Outside First Trimester)	299	2	6.7	2.48 (0.53, 11.50)	2.12 (0.44, 10.20)
^l Maternal dispensing of a teratogenic drug thought or suspected to affect the cardiovascular system within a year before delivery through the end of the estimated first trimester. ^m Only the bupropion cohorts were further stratified according to dispensing of another antidepressant. ⁿ Odds ratios adjusted for maternal age category, geographic region of the health plan, infant sex, diagnoses of bipolar disorder, eclampsia within one year before delivery, dispensing of fluconazole within one year before delivery through the end of the first trimester, and number of physician visits within 10 to 12 months before delivery.					
Risk of congenital/cardiac malformations for specific antidepressants relative to all other antidepressant exposures using RDM (January 1995 through September 2004)					
OR for all congenital malformations according to mutually exclusive categories of specific antidepressants dispensed during the first trimester					
Antidepressant	No. of infants	No. of cases	Prevalence per 1000	Crude OR ^o (95% CI)	Adjusted OR ^{op} (95% CI)
Amitriptyline	214	6	28.0	1.22 (0.53, 2.81)	1.23 (0.53, 2.85)
Amitriptyline / Chlordiazepoxide	4	0	0	0	0
Bupropion	718	14	19.5	0.82 (0.47, 1.43)	0.78 (0.44, 1.37)
Citalopram	363	7	19.3	0.82 (0.38, 1.76)	0.88 (0.41, 1.91)
Clomipramine	6	0	0	0	0
Desipramine	9	0	0	0	0
Doxepin	22	0	0	0	0
Escitalopram	83	3	36.1	1.61 (0.51, 5.09)	1.56 (0.48, 5.05)
Fluoxetine	1301	28	21.5	0.91 (0.60, 1.38)	0.95 (0.62, 1.45)
Fluvoxamine	22	0	0	0	0
Imipramine	36	0	0	0	0
Mirtazapine	12	0	0	0	0
Nefazodone	57	1	17.5	0.75 (0.10, 5.46)	0.74 (0.10, 5.41)
Nortriptyline	82	0	0	0	0
Paroxetine	815	29	35.6	1.71 (1.13, 2.59)	1.75 (1.15, 2.66)
Protriptyline	5	0	0	0	0
Sertraline	945	17	18.0	0.74 (0.44, 1.24)	0.76 (0.45, 1.28)
Trazodone	69	3	43.5	1.93 (0.60, 6.23)	1.90 (0.58, 6.21)
Venlafaxine	250	4	16.0	0.67 (0.25, 1.84)	0.57 (0.20, 1.58)
More than one type of antidepressant	943	26	27.6	1.24 (0.80, 1.91)	1.21 (0.78, 1.87)
OR for all congenital malformations according to any use of specific antidepressants during the first trimester					
Antidepressant	No. of infants	No. of cases	Prevalence per 1000	Crude OR ^o (95% CI)	Adjusted OR ^{op} (95% CI)
Amitriptyline	298	8	26.9	1.17 (0.57, 2.42)	1.15 (0.55, 2.38)
Amitriptyline / Chlordiazepoxide	6	0	0	0	0
Amitriptyline / Perphenazine	2	0	0	0	0
Bupropion	1213	28	23.1	0.99 (0.65, 1.51)	0.94 (0.62, 1.44)
Citalopram	511	12	23.5	1.02 (0.56, 1.85)	1.09 (0.60, 2.00)
Clomipramine	9	1	111.1	5.30 (0.66, 42.70)	7.65 (0.92, 64.03)
Desipramine	14	0	0	0	0
Doxepin	26	0	0	0	0
Escitalopram	152	5	32.9	1.46 (0.59, 3.59)	1.45 (0.58, 3.63)
Fluoxetine	1633	38	23.3	1.01 (0.69, 1.47)	1.03 (0.70, 1.51)
Fluvoxamine	36	0	0	0	0
Imipramine	50	2	40.0	1.76 (0.42, 7.34)	1.88 (0.45, 7.89)
Mirtazapine	35	0	0	0	0
Nefazodone	83	1	12.1	0.51 (0.07, 3.69)	0.52 (0.07, 3.77)

Nortriptyline	113	1	8.9	0.37 (0.05, 2.68)	0.37 (0.05, 2.69)
Paroxetine	1020	36	35.3	1.74 (1.18, 2.55)	1.75 (1.19, 2.59)
Protriptyline	5	0	0	0	0
Sertraline	1205	22	18.3	0.74 (0.47, 1.18)	0.76 (0.48, 1.21)
Trazodone	224	6	26.8	1.17 (0.51, 2.68)	1.10 (0.47, 2.56)
Trimipramine	1	0	0	0	0
Venlafaxine	396	8	20.2	0.86 (0.42, 1.77)	0.77 (0.37, 1.60)
OR for cardiovascular malformations according to mutually exclusive categories of specific antidepressants dispensed during the first trimester					
Antidepressant	No. of infants	No. of cases	Prevalence per 1000	Crude OR^o (95% CI)	Adjusted OR^{op} (95% CI)
Amitriptyline	214	3	14.0	1.32 (0.41, 4.25)	1.42 (0.44, 4.60)
Amitriptyline / Chlordiazepoxide	4	0	0	0	0
Bupropion	718	5	7.0	0.62 (0.25, 1.54)	0.59 (0.24, 1.48)
Citalopram	363	5	13.8	1.31 (0.52, 3.28)	1.35 (0.53, 3.42)
Clomipramine	6	0	0	0	0
Desipramine	9	0	0	0	0
Doxepin	22	0	0	0	0
Escitalopram	83	2	24.1	2.34 (0.57, 9.55)	2.09 (0.50, 8.78)
Fluoxetine	1301	16	12.3	1.19 (0.68, 2.11)	1.31 (0.73, 2.32)
Fluvoxamine	22	0	0	0	0
Imipramine	36	0	0	0	0
Mirtazapine	12	0	0	0	0
Nefazodone	57	0	0	0	0
Nortriptyline	82	0	0	0	0
Paroxetine	815	12	14.7	1.47 (0.78, 2.75)	1.46 (0.77, 2.78)
Protriptyline	5	0	0	0	0
Sertraline	945	5	5.3	0.45 (0.18, 1.11)	0.43 (0.17, 1.09)
Trazodone	69	1	14.5	1.36 (0.19, 9.93)	1.18 (0.16, 8.76)
Venlafaxine	250	3	12.0	1.12 (0.35, 3.60)	1.00 (0.31, 3.26)
More than one type of antidepressant	943	12	12.7	1.23 (0.66, 2.31)	1.22 (0.65, 2.31)
OR for cardiovascular malformations according to any use of specific antidepressants during the first trimester					
Antidepressant	No. of infants	No. of cases	Prevalence per 1000	Crude OR^o (95% CI)	Adjusted OR^{op} (95% CI)
Amitriptyline	298	3	10.1	0.93 (0.29, 2.99)	0.95 (0.29, 3.07)
Amitriptyline / Chlordiazepoxide	6	0	0	0	0
Amitriptyline / Perphenazine	2	0	0	0	0
Bupropion	1213	13	10.7	1.00 (0.54, 1.84)	0.95 (0.51, 1.77)
Citalopram	511	8	15.7	1.53 (0.73, 3.23)	1.57 (0.74, 3.34)
Clomipramine	9	1	111.1	11.70 (1.44, 94.60)	17.95 (2.08, 154.67)
Desipramine	14	0	0	0	0
Doxepin	26	0	0	0	0
Escitalopram	152	2	13.2	1.25 (0.30, 5.10)	1.21 (0.29, 5.03)
Fluoxetine	1633	21	12.9	1.30 (0.77, 2.19)	1.41 (0.83, 2.39)
Fluvoxamine	36	0	0	0	0
Imipramine	50	0	0	0	0
Mirtazapine	35	0	0	0	0
Nefazodone	83	0	0	0	0
Nortriptyline	113	0	0	0	0
Paroxetine	1020	17	16.7	1.76 (1.01, 3.08)	1.78 (1.01, 3.15)

Protriptyline	5	0	0	0	0
Sertraline	1205	7	5.8	0.48 (0.22, 1.06)	0.46 (0.21, 1.03)
Trazodone	224	3	13.4	1.27 (0.40, 4.06)	1.21 (0.37, 3.92)
Trimipramine	1	0	0	0	0
Venlafaxine	396	4	10.1	0.93 (0.34, 2.58)	0.87 (0.31, 2.42)

^o Reference group for the odds ratio calculation of each antidepressant category consists of all of the other antidepressant categories shown in the table.

^p Odds ratios adjusted for maternal age category, geographic region of the health plan, infant sex, diagnosis of bipolar disorder, eclampsia within one year before delivery, dispensings of lithium, phenytoin, fluconazole within one year before delivery through the end of the first trimester, and number of physician visits within 10 to 12 months before delivery.

OR for all congenital malformations according to mutually exclusive categories of specific antidepressants dispensed during the first trimester, excluding women with teratogenic drug dispensings^q

Antidepressant	No. of infants	No. of cases	Prevalence per 1000	Crude OR ^r (95% CI)	Adjusted OR ^{rs} (95% CI)
Amitriptyline	175	3	17.1	0.71 (0.22, 2.27)	0.68 (0.21, 2.19)
Amitriptyline / Chlordiazepoxide	4	0	0	0	0
Bupropion	624	12	19.2	0.79 (0.43, 1.44)	0.77 (0.42, 1.41)
Citalopram	302	7	23.2	0.98 (0.45, 2.12)	1.05 (0.48, 2.28)
Clomipramine	6	0	0	0	0
Desipramine	8	0	0	0	0
Doxepin	16	0	0	0	0
Escitalopram	72	3	41.7	1.84 (0.58, 5.83)	1.59 (0.49, 5.16)
Fluoxetine	1118	23	20.6	0.84 (0.53, 1.33)	0.87 (0.55, 1.38)
Fluvoxamine	17	0	0	0	0
Imipramine	27	0	0	0	0
Mirtazapine	6	0	0	0	0
Nefazodone	47	1	21.3	0.90 (0.12, 6.58)	0.91 (0.12, 6.71)
Nortriptyline	72	0	0	0	0
Paroxetine	717	27	37.7	1.81 (1.17, 2.79)	1.83 (1.18, 2.84)
Protriptyline	4	0	0	0	0
Sertraline	843	16	19.0	0.77 (0.45, 1.31)	0.80 (0.47, 1.36)
Trazodone	57	2	35.1	1.51 (0.36, 6.28)	1.61 (0.39, 6.74)
Venlafaxine	204	3	14.7	0.61 (0.19, 1.93)	0.57 (0.18, 1.83)
More than one type of antidepressant	773	23	29.8	1.33 (0.84, 2.12)	1.28 (0.81, 2.04)

OR for all congenital malformations according to any use of specific antidepressants during the first trimester, excluding women with teratogenic drug dispensings^q

Antidepressant	No. of infants	No. of cases	Prevalence per 1000	Crude OR ^r (95% CI)	Adjusted OR ^{rs} (95% CI)
Amitriptyline	240	5	20.8	0.88 (0.35, 2.16)	0.84 (0.34, 2.08)
Amitriptyline / Chlordiazepoxide	5	0	0	0	0
Amitriptyline / Perphenazine	2	0	0	0	0
Bupropion	1024	24	23.4	0.99 (0.63, 1.56)	0.95 (0.60, 1.49)
Citalopram	417	12	28.8	1.25 (0.69, 2.30)	1.31 (0.71, 2.40)
Clomipramine	8	0	0	0	0
Desipramine	12	0	0	0	0
Doxepin	18	0	0	0	0
Escitalopram	129	5	38.8	1.71 (0.69, 4.23)	1.53 (0.61, 3.85)
Fluoxetine	1404	31	22.1	0.91 (0.60, 1.38)	0.94 (0.62, 1.43)
Fluvoxamine	29	0	0	0	0
Imipramine	39	2	51.3	2.26 (0.54, 9.49)	2.21 (0.52, 9.37)
Mirtazapine	24	0	0	0	0

Nefazodone	70	1	14.3	0.60 (0.08, 4.33)	0.61 (0.08, 4.48)
Nortriptyline	100	1	10.0	0.41 (0.06, 2.99)	0.38 (0.05, 2.74)
Paroxetine	880	32	36.4	1.77 (1.18, 2.67)	1.77 (1.17, 2.68)
Protriptyline	4	0	0	0	0
Sertraline	1066	21	19.7	0.80 (0.50, 1.28)	0.81 (0.50, 1.31)
Trazodone	178	5	28.1	1.21 (0.49, 2.99)	1.19 (0.48, 2.97)
Trimipramine	1	0	0	0	0
Venlafaxine	326	7	21.5	0.90 (0.42, 1.95)	0.84 (0.61, 3.85)

^q Maternal teratogenic drug dispensing within a year before delivery through the end of the estimated first trimester.

^r Reference group for the odds ratio calculation of each antidepressant category consists of all of the other antidepressant categories shown in the table.

^s Odds ratios adjusted for maternal age category, geographic region of the health plan, infant sex, diagnosis of bipolar disorder, eclampsia within one year before delivery, and number of physician visits within 10 to 12 months before delivery.

OR for cardiovascular malformations according to mutually exclusive categories of specific antidepressants dispensed during the first trimester, excluding women with dispensings of teratogenic drugs affecting the cardiovascular system[†]

Antidepressant	No. of infants	No. of cases	Prevalence per 1000	Crude OR ^u (95% CI)	Adjusted OR ^{uv} (95% CI)
Amitriptyline	214	3	14.0	1.38 (0.43, 4.44)	1.40 (0.43, 4.54)
Amitriptyline / Chlordiazepoxide	4	0	0	0	0
Bupropion	714	4	5.6	0.51 (0.18, 1.40)	0.48 (0.17, 1.34)
Citalopram	362	5	13.8	1.37 (0.55, 3.44)	1.40 (0.56, 3.55)
Clomipramine	6	0	0	0	0
Desipramine	8	0	0	0	0
Doxepin	22	0	0	0	0
Escitalopram	83	2	24.1	2.44 (0.60, 9.98)	2.04 (0.48, 8.61)
Fluoxetine	1292	15	11.6	1.16 (0.65, 2.09)	1.26 (0.70, 2.28)
Fluvoxamine	22	0	0	0	0
Imipramine	36	0	0	0	0
Mirtazapine	11	0	0	0	0
Nefazodone	56	0	0	0	0
Nortriptyline	82	0	0	0	0
Paroxetine	814	12	14.7	1.54 (0.82, 2.91)	1.54 (0.81, 2.93)
Protriptyline	5	0	0	0	0
Sertraline	937	5	5.3	0.47 (0.19, 1.18)	0.48 (0.19, 1.19)
Trazodone	67	1	14.9	1.46 (0.20, 10.70)	1.31 (0.18, 9.70)
Venlafaxine	244	3	12.3	1.20 (0.37, 3.86)	1.12 (0.34, 3.61)
More than one type of antidepressant	929	11	11.8	1.18 (0.61, 2.28)	1.17 (0.60, 2.26)

OR for cardiovascular malformations according to any use of specific antidepressants during the first trimester, excluding women with dispensings of teratogenic drugs affecting the cardiovascular system[†]

Antidepressant	No. of infants	No. of cases	Prevalence per 1000	Crude OR ^u (95% CI)	Adjusted OR ^{uv} (95% CI)
Amitriptyline	296	3	10.1	0.98 (0.30, 3.14)	0.97 (0.30, 3.13)
Amitriptyline / Chlordiazepoxide	6	0	0	0	0
Amitriptyline / Perphenazine	2	0	0	0	0
Bupropion	1200	11	9.2	0.86 (0.45, 1.66)	0.82 (0.42, 1.58)
Citalopram	509	8	15.7	1.61 (0.76, 3.41)	1.61 (0.76, 3.42)
Clomipramine	9	1	111.1	12.2 (1.50, 98.70)	18.60 (2.16, 161.00)
Desipramine	13	0	0	0	0
Doxepin	26	0	0	0	0
Escitalopram	151	2	13.2	1.31 (0.32, 5.36)	1.20 (0.29, 4.97)

Fluoxetine	1620	19	11.7	1.20 (0.70, 2.07)	1.30 (0.75, 2.26)
Fluvoxamine	35	0	0	0	0
Imipramine	50	0	0	0	0
Mirtazapine	33	0	0	0	0
Nefazodone	82	0	0	0	0
Nortriptyline	113	0	0	0	0
Paroxetine	1014	16	15.8	1.73 (0.97, 3.07)	1.74 (0.97, 3.10)
Protriptyline	5	0	0	0	0
Sertraline	1193	7	5.9	0.51 (0.23, 1.12)	0.51 (0.23, 1.12)
Trazodone	219	3	13.7	1.36 (0.42, 4.34)	1.32 (0.41, 4.26)
Trimipramine	1	0	0	0	0
Venlafaxine	389	4	10.3	0.99 (0.36, 2.75)	0.94 (0.34, 2.61)

[†] Maternal teratogenic drug dispensing within a year before delivery through the end of the estimated first trimester.

[‡] Reference group for the odds ratio calculation of each antidepressant category consists of all of the other antidepressant categories shown in the table.

[§] Odds ratios adjusted for maternal age category, geographic region of the health plan, infant sex, diagnoses of bipolar disorder, eclampsia within one year before delivery, dispensing of fluconazole within one year before delivery through the end of the first trimester, and number of physician visits within 10 to 12 months before delivery.

Limitations: Limitations of this study include:

- 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
- There are potential differences in clinical characteristics across cohorts which may have resulted in residual confounding.

See publication below for further details

Conclusion: See publication below

Additional analyses from the "Paroxetine in the First Trimester and the Prevalence of Congenital Malformations" epidemiology study (EPI40404) are reported in the paroxetine section of the CTR.

Publications:

Cole JA, Modell JG, Haight BR, Cosmatos IS, Stoler JM, Walker AM. Bupropion in pregnancy and the prevalence of congenital malformations. *Pharmacoepidemiology and Drug Safety* 2007;16(5):474-484

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