HHS Public Access

Author manuscript

Pharmacoepidemiol Drug Saf. Author manuscript; available in PMC 2024 August 01.

Published in final edited form as:

Pharmacoepidemiol Drug Saf. 2023 August ; 32(8): 855–862. doi:10.1002/pds.5619.

Maternal cyclobenzaprine exposure and risk of birth defects in the National Birth Defects Prevention Study (1997–2011) and Birth Defects Study to Evaluate Pregnancy exposureS (2014–2018)

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Abstract

Purpose: Cyclobenzaprine is a muscle relaxant indicated for acute pain. Little is known about cyclobenzaprine's safety during pregnancy. We explored the association between maternal cyclobenzaprine exposure and risk of birth defects among offspring.

Methods: We combined data from two large, multi-site, population-based case–control studies in the United States. Cases were identified from birth defects registries across 10 states; controls were liveborn infants without birth defects randomly selected from the same catchment areas. Participants reported cyclobenzaprine use during the month before conception through the third month of pregnancy ("periconception") via computer-assisted telephone interview. We used logistic regression to assess associations between periconceptional cyclobenzaprine exposure and

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AUTHOR CONTRIBUTIONS

Sarah C. Fisher designed the study, analyzed the data, and wrote the manuscript. Meredith M. Howley, Emmy L. Tran, Elizabeth C. Ailes, Eleni A. Papadopoulos, Wendy N. Nembhard, and Marilyn L. Browne contributed to the study design and interpretation of results. All authors reviewed and approved the final manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DISCLAIMER

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

selected structural birth defects. We calculated crude odds ratios (OR) with corresponding 95% confidence intervals (CI).

Results: Our study included 33 615 cases and 13 110 controls. Overall, 51 case (0.15%) and 9 control (0.07%) participants reported periconceptional cyclobenzaprine use. We observed increased risk for all seven defects with ≥3 exposed cases: cleft palate (OR = 4.79, 95% CI 1.71–13.44), cleft lip (OR = 2.50, 95% CI 0.89–7.02), anorectal atresia/stenosis (OR = 6.91, 95% CI 1.67, 28.65), d-transposition of the great arteries (OR = 6.97, 95% CI 2.17–22.36), coarctation of the aorta (OR = 5.58, 95% CI 1.88–16.58), pulmonary valve stenosis (OR = 4.55, 95% CI 1.10–18.87), and secundum atrial septal defect (OR = 3.08, 95% CI 0.83–11.45).

Conclusions: Even in our large sample, cyclobenzaprine use was rare. Our estimates are unadjusted and imprecise so should be interpreted cautiously. These hypothesis-generating results warrant confirmation and further research to explore possible mechanisms.

Plain Language Summary

Cyclobenzaprine is a commonly prescribed muscle relaxant among adults, but there is very little published research on the safety of its use in human pregnancies. We used data from two large US case–control studies to explore whether cyclobenzaprine use during pregnancy increases the risk of having a baby with a birth defect. In a telephone interview, study participants reported whether they used cyclobenzaprine during the month before conception through the first trimester of pregnancy. We calculated estimates for the association between cyclobenzaprine use and seven specific birth defects. We observed increased risk of all seven birth defects among cyclobenzaprine-exposed pregnancies, relative to unexposed pregnancies. Our results are based on a small number of exposed cases and should be interpreted cautiously. We cannot entirely rule out other risk factors that might explain the associations we observed. These results may help generate hypotheses for future research to confirm our findings and explore biologic mechanisms.

Keywords

BD-STEPS; birth defects; cyclobenzaprine; muscle relaxants; NBDPS; pregnancy

1 | INTRODUCTION

Cyclobenzaprine (e.g., Flexeril®, Amrix®) is a skeletal muscle relaxant indicated for the treatment of acute pain episodes associated with muscle spasms and/or musculoskeletal pain, particularly low back or neck pain. A recent study estimated that more than half of prescription fills in the United States for skeletal muscle relaxants were for cyclobenzaprine, with treatment prevalence of ~38 per 1000 adults.[1] Other uses may include the treatment of fibromyalgia and migraine/chronic headache, which are both about twice as likely to affect women as men.[2,3] Thus, the reproductive safety of their treatment is particularly relevant. Research on cyclobenzaprine use in pregnancy is sparse, however, with only a few published case reports.[4,5] Our comprehensive literature review did not identify any population-based epidemiologic studies of cyclobenzaprine exposure in early pregnancy.

We can make some inferences about cyclobenzaprine based on knowledge of tricyclic antidepressant (TCA) (e.g., amitriptyline, imipramine) use in pregnancy, as they are

structurally related. TCAs have been shown to readily cross the placenta[6,7] and, given their structural similarities, it is reasonable to assume that cyclobenzaprine does as well. A study of Swedish registry data reported increased risk of septal heart defects associated with TCA use in early pregnancy.[8] However, another study using Medicaid data did not replicate this finding.[9] An analysis of the Quebec Pregnancy Cohort observed a more than doubling of the risk of "eye, ear, face, and neck defects" (as a single outcome group) and "digestive defects" associated with TCA use among pregnant people with depression, although the number of exposed cases contributing to these estimates is unclear.[10] That study observed null associations between TCA use and birth defects in other organ systems. Like cyclobenzaprine, TCA use is also relatively rare among pregnant people, thus research on its association with birth defects is also limited.

The National Birth Defects Prevention Study (NBDPS) and Birth Defects Study to Evaluate Pregnancy exposureS (BD-STEPS) are among the largest studies of birth defects in the United States, with detailed information on self-reported medication use during pregnancy. We used these data sources to describe periconceptional cyclobenzaprine use (during the month before conception through the third gestational month) among pregnant people in the United States and assess associations between periconceptional cyclobenzaprine use and birth defects among offspring. Given the lack of human data about the safety of cyclobenzaprine use during pregnancy, we designed our study to be exploratory, serving as a first step toward generating hypotheses that future studies can test further.

2 | METHODS

2.1 | Study population

We combined data from two multi-site, population-based, case–control studies of birth defects in the United States: the NBDPS and BD-STEPS. Detailed study methods have been published elsewhere.[11,12] Briefly, NBDPS included cases and controls with delivery dates between October 1997 and December 2011 from study sites in 10 US states (Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, Utah) and BD-STEPS includes cases and controls with delivery dates between January 2014 and August 2015 and July 2016 and December 2018 from a subset of 7 of the NBDPS study sites (Arkansas, California, Georgia, Iowa, Massachusetts, New York, North Carolina). Pregnancy exposure data were collected via computer-assisted telephone interview in English or Spanish between 6 weeks and 2 years post-estimated delivery date (EDD); mean time to interview was 336 days post-EDD for cases and 266 days post-EDD for controls. Respondents self-reported information on medication use during pregnancy, as well as demographic, behavioral, medical history, and socioeconomic characteristics. Individuals were eligible to participate once if they were not incarcerated, could speak English or Spanish, and had legal custodial rights to their child. BD-STEPS participants were at least 15 years old at the time of delivery; NBDPS participants could be any age. Each study site and the Centers for Disease Control and Prevention received institutional review board approval for both studies and obtained informed consent.

2.2 | Outcome ascertainment

Cases were actively ascertained from population-based birth defect registries in participating study sites. NBDPS included more than 30 types of major structural birth defects; BD-STEPS included 17 of the NBDPS-eligible defects.[11,12] In both studies, cases were reviewed for eligibility and classification by trained clinical geneticists and pediatric cardiologists. Cases were classified as isolated (only one major birth defect, birth defects only in one organ system, or all birth defects resulting from a single primary defect), multiple (two or more unrelated major birth defects in at least two different organ systems), or complex (a pattern of embryologically related birth defects, such as Pentalogy of Cantrell).[13] Cases with cardiac birth defects were further classified according to the number and complexity of heart defects present.[14] Cases with known chromosomal abnormalities or single gene disorders were excluded. For analyses of hypospadias, we excluded female controls. Congenital cataracts, oral clefts, ventricular septal defects, and pulmonary valve stenosis were not actively ascertained by all sites in all study years, so analyses of these defects only included controls from the study sites and/or years in which cases were included.

With some variation across sites, cases could be liveborn, stillborn at 20 weeks gestation or later, or elective terminations at any gestational age.[11,12] Controls were liveborn infants without major birth defects randomly selected from hospital birth records or birth certificates from the same catchment areas as cases.

2.3 | Cyclobenzaprine exposure

Neither the NBDPS nor BD-STEPS included a specific interview question on cyclobenzaprine use. In general, respondents could report medications used to treat any of the maternal health conditions specifically queried (diabetes, hypertension, seizures, respiratory illness, infections, febrile illness, injuries, and “other illnesses that we haven’t already talked about”). NBDPS participants were also asked, “did you take any medications, remedies, or treatments that we haven’t already talked about?” BD-STEPS included similar questions but included more specific conditions that might indicate cyclobenzaprine use, such as migraines and autoimmune disease, as well as a line of questioning specifically about medications used for treating pain.

Participants self-reported periconceptional cyclobenzaprine use. In both the NBPDS and BD-STEPS, respondents reported start and stop dates or duration of use and frequency. In BD-STEPS, respondents also reported the indication for use and dose. For analysis, we calculated a dichotomous exposure variable for any versus no cyclobenzaprine exposure during the periconceptional period. NBDPS participants reported exposures before and after the periconceptional period, as well; participants who reported cyclobenzaprine use only outside of the periconceptional period were considered unexposed ($n = 51$).

2.4 | Statistical analysis

Because the number of controls who reported cyclobenzaprine use was prohibitively small ($n = 9$), we assessed descriptive characteristics of all cyclobenzaprine users. We evaluated the distribution of potential confounding factors by exposure status and assessed patterns of timing of use by pregnancy month. We used logistic regression to estimate the risk of

individual birth defects associated with periconceptional cyclobenzaprine use. To account for sparse data bias, we used Firth's penalized likelihood when calculating odds ratios (OR) and 95% confidence intervals (CIs). Firth's penalized likelihood approach does not assume symmetry of the CI around the coefficient estimate and has been shown to produce finite confidence intervals achieving 95% coverage, despite small cell sizes.[15,16] We identified potential covariates for adjusted ORs a priori, based on a directed acyclic graph (DAG): maternal age at delivery, race/ethnicity, pre-pregnancy body mass index, pregestational diabetes, periconceptional cigarette smoking, periconceptional opioid use, periconceptional non-steroidal antiinflammatory drug (NSAID) use, and study site. However, given the rarity of cyclobenzaprine exposure in our dataset we were ultimately unable to truly adjust for confounding in our logistic models, so we present unadjusted ORs. As a sensitivity analysis, we stratified by study to assess whether our results might be an artifact of slight differences in methodology between NBDPS and BD-STEPS.

3 | RESULTS

Our study included 33 615 cases and 13 110 controls. Overall, 0.07% of controls (n = 9) and 0.15% of cases (n = 51) reported periconceptional cyclobenzaprine use. Of those who reported specific month(s) of use (n = 58), most people (n = 36) reported initiating cyclobenzaprine use before pregnancy; otherwise, there was not a clear pattern to the self-reported timing of use (Table 1). About half of respondents reported short-term cyclobenzaprine use in only one periconceptional month (n = 28, 48.3%) and about one third reported longer-term cyclobenzaprine use (i.e., in at least 3 periconceptional months; n = 20, 34.5%). Only 38% (n = 23) of participants who reported cyclobenzaprine use also reported an indication. Of those who reported longer-term cyclobenzaprine use, five reported an indication: chronic pain, injury, migraine, fibromyalgia, and sleep aid. Among the 28 participants who reported cyclobenzaprine in only 1 month, 11 reported an indication: injury (n = 7) and pain (n = 4) (data not shown). Cyclobenzaprine use was associated with older maternal age, non-Hispanic White race/ethnicity, higher educational attainment, use of other pain medication, cigarette smoking, and alcohol use (Table 2).

There were 27 specific birth defects represented among the 51 unique cyclobenzaprine-exposed cases in our dataset (Table 3). Of these, there were at least three exposed cases for seven defects: anorectal atresia, d-transposition of the great arteries (d-TGA), coarctation of the aorta, pulmonary valve stenosis, secundum atrial septal defect (ASD), cleft palate only, and cleft lip with or without cleft palate. All ORs were elevated, ranging from 2.50 (95% CI 0.89, 7.02) for cleft lip to 6.97 (95% CI 2.17, 22.36) for d-TGA, but imprecise (Table 4).

Four of the 7 birth defects analyzed were included in both NBDPS and BD-STEPS; however, there were not enough exposed cases to conduct a meaningful comparison of associations in NBDPS to associations in BD-STEPS. The only defect with enough exposed BD-STEPS cases to calculate an OR was cleft lip with or without cleft palate (n = 4; OR 3.14, 95% CI 0.78, 12.61), but there were only two exposed cases in NBDPS. The associations with the remaining three defects (cleft palate, d-TGA, coarctation of the aorta) were driven by NBDPS cases (Table S1).

4 | DISCUSSION

Our exploratory analysis adds population-based evidence of the possible association between periconceptional cyclobenzaprine use and risk of birth defects to the scant literature on this topic. Using two large case–control studies, the NBDPS and BD-STEPS, we observed elevated odds ratios for three non-cardiac birth defects (cleft palate, cleft lip with and without cleft palate, and anorectal atresia/stenosis) and four cardiac defects (d-TGA, coarctation of the aorta, pulmonary valve stenosis, and secundum ASD). However, cyclobenzaprine use was extremely rare, so even in our large study there were not enough exposed cases to calculate ORs for most types of birth defects included.

We were unable to find other population-based studies of cyclobenzaprine use in human pregnancies. The US Food and Drug Administration product labels for Flexeril and Amrix refer to experimental animal studies in which exposure up to 20 times the recommended human dose did not result in fetal malformations.[17,18] There is one published case report of birth defects following periconceptional cyclobenzaprine exposure, including imperforate oropharynx and vertebral and auricular anomalies.[5] We observed elevated ORs for orofacial clefts in our study, but no cases with this distinct pattern of defects.

TCAs are structurally similar to cyclobenzaprine, and there is some evidence for an association between amitriptyline and imipramine and birth defects, but not necessarily the same defects that we observed in our study. Encephalocele and omphalocele may be associated with TCA use,[19,20] but we did not observe any cyclobenzaprine-exposed cases in our study. Observational studies of TCA use and birth defects have produced inconsistent evidence. Three individual studies assessed associations between TCAs and a wide range of birth defects, with different results: increased risk of “digestive system” defects,[10] limb defects,[21] and cardiac defects, specifically ventricular septal defects (VSDs) “and/or” ASDs,[8] but null associations for all other defects examined. Others have reported null findings for any birth defects[22] and cardiac defects.[9] Limb reduction defects were included in NBPDS and BD-STEPS (transverse only), but we only enrolled one exposed case of transverse limb deficiency. Our results may overlap with the other associations identified in the TCA literature, but it is impossible to directly compare because case groups were lumped together (i.e., oral clefts and anorectal atresia with other “digestive defects”[10] and ASD with VSD[8]) and results for specific defects were not reported.

We observed increased ORs for several types of birth defects, across different organ systems. There is, however, some biologic plausibility for these findings. Cyclobenzaprine may have serotonergic effects, and serotonin is an important neurotransmitter involved in multiple aspects of embryogenesis. Serotonin is particularly involved in cardiac and craniofacial development, which could explain the associations with CHDs and oral clefts that we observed in our study.[23,24] Furthermore, serotonin is involved in laterality signaling, the interruption of which is associated with malformations in a variety of organ systems, including orofacial clefts and anorectal atresia.[25] Heterotaxy, a more typical laterality defect, was included in NBDPS but not BD-STEPS; we did not observe any cyclobenzaprine-exposed heterotaxy case in this study. Thus it remains possible that at least some of the

associations we observed are due to chance. All our estimates are based on <10 exposed people and have wide confidence intervals, so should be interpreted cautiously.

The pattern of cyclobenzaprine use that we observed among participants was somewhat unexpected. More than a third of exposed subjects reported cyclobenzaprine use at least once in at least three separate periconceptional months. This is in contrast with cyclobenzaprine's typically recommended short-term use (2–3 weeks maximum) for acute muscle pain,[17,18] generally stemming from an injury. Although available data on indication for use is limited in our study, we speculate that these users may represent those using cyclobenzaprine for chronic and/or recurring conditions. Three of the five long-term cyclobenzaprine users in our study who reported indication reported uses for migraine, fibromyalgia, and sleep aid, whereas none of the short-term users did. Longer-term and/or repeated episodic use is an important factor to consider in future studies of cyclobenzaprine safety in pregnancy.

Given the small number of exposed cases, all our OR estimates were unadjusted. Thus, our estimates are at least somewhat biased by uncontrolled confounding. Everyone who reported cyclobenzaprine use in our study also reported using other medications during their pregnancy, including antidepressant/antianxiety medications and often multiple types of over-the-counter and prescription pain medications. Use of opioid analgesics, acetaminophen, and NSAIDS were notably more prevalent among cyclobenzaprine users in our study. Although acetaminophen is not thought to be associated with birth defects, opioids and NSAIDS may be.[26,27] Cyclobenzaprine use was also associated with cigarette smoking and alcohol consumption in our study. Cigarette smoking, in particular, has been shown to be associated with oral clefts[28] and potentially with certain congenital heart defects.[29–31] The association between alcohol and the birth defects in our study is less clear,[32–34] but it is a known teratogen[35] and could play a role in biasing our observed estimates. Our study was exploratory and future studies are needed to consider the role of these and other potential confounders.

Misclassification bias is another possible explanation for the increased odds of several specific defects across different organ systems that we observed. While we expect there to be little to no outcome misclassification, given the active surveillance methods and detailed clinical review and classification protocols, exposure misclassification is more likely. Cyclobenzaprine use was self-reported in our study, up to 2 years after the estimated date of delivery, and thus is subject to recall error. Given the generally short-term nature of cyclobenzaprine use and the long period of recall, we also expect at least some misclassification of exposure timing. Given differences in the NBDPS and BD-STEPS questions about pain medication use, it is possible that exposure misclassification varies by study. Cyclobenzaprine use was more prevalent among BD-STEPS participants (0.31% of controls and 0.33% of cases) than NBDPS participants (0.04% among controls and 0.14% among cases), with the largest differences in prevalence observed among controls. If NBDPS controls were more likely to underreport cyclobenzaprine use, this could bias our results away from the null.

Finally, our analysis is limited by incomplete data on indication for use and dose, making it impossible to control for the severity of the underlying disease as a contributing factor to birth defect risk. Indication is available for some NBDPS subjects if they reported cyclobenzaprine use related to an injury or if they made a specific comment during the interview, but dose was not collected for any NBDPS subjects. Indication and dose are collected in the BD-STEPS interview, but BD-STEPS participants only made up 11 of our 60 cyclobenzaprine-exposed participants, and not all 11 provided complete answers to questions about dose and indication. Thus, our evaluation of underlying disease in relation to our results is strictly descriptive.

The NBDPS and BD-STEPS are among the largest population-based studies of birth defects, enabling us to explore for the first time in humans associations between this very rare exposure and specific birth defects. We report a signal of potential teratogenicity that could inform further exploration. Although some of our reported odds ratios are relatively high, the absolute risk remains low. The strongest association we observed was for d-TGA (OR 6.97); a causal factor of this magnitude would increase the absolute risk of d-TGA from 2.9/10000 to 20.4/10000 among exposed pregnancies.[36] This equates to an increase from ~1 affected infant per year to 5 affected infants per year, out of the 2515 cyclobenzaprine-exposed births we would expect to see per year in the United States.[37] As the only epidemiologic study of periconceptional cyclobenzaprine use and specific birth defects, our results are exploratory and hypothesis-generating, and should be interpreted within this context. Additional research could help confirm our current findings, identify possible mechanisms, and evaluate clinical implications. Future studies, including experimental studies, should consider taking into account the variety of indications for which pregnant people use cyclobenzaprine, including those that involve longer-term use.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

We thank the participating families, scientists, and staff from the NBDPS and BD-STEPS sites. Portions of this analysis were presented as a poster at the 62nd Annual Meeting of the Society for Birth Defects Research and Prevention. Portions of the data analysis were replicated prior to submission per the replication policy of the NBDPS; we thank Jada Scott for replicating the analysis.

FUNDING INFORMATION

This project was supported through Centers for Disease Control and Prevention (CDC) cooperative agreements under PA #96043, PA #02081, FOA #DD09-001, FOA #DD13-003, and NOFO #DD18-001 to the Centers for Birth Defects Research and Prevention participating in the National Birth Defects Prevention Study (NBDPS) and/or the Birth Defects Study To Evaluate Pregnancy exposureS (BD-STEPS) and the New York Center for Birth Defects Research and Prevention U01 DD001227.

DATA AVAILABILITY STATEMENT

The study questionnaires and process for accessing the data used in this study is described at https://www.cdc.gov/ncbddd/birthdefects/nbdps-public-access-procedures.html. The code book may be made available upon request.

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Key Points

- Cyclobenzaprine is one of the most commonly prescribed muscle relaxants for adults in the United States
- Ours is the first population-based epidemiologic study of the association between cyclobenzaprine use during pregnancy and birth defects
- We observed increased odds of select cardiac and non-cardiac birth defects associated with cyclobenzaprine use
- Our exploratory study is based on a small number of exposed cases and warrants further research to validate and better understand our results

TABLE 1

Patterns of self-reported cyclobenzaprine exposure, by gestational month, NBDPS (1997–2011) and BD-STEPS (2014–2018).

	Exposed gestational month[a]			
n[b]	Prel	P1	P2	P3
9	■	■	■	■
7	■	■	■	
7	■	■		
13	■			
8		■		
9				■

Note: Shaded boxes indicate exposed months.

Abbreviations: BD-STEPS, Birth Defects Study to Evaluate Pregnancy exposureS; NBDPS, National Birth Defects Prevention Study; P1, 0–30 days post-conception; P2, 31–60 days post-conception; P3, 61–90 days postconception; Pre1, 30–1 days before conception.

[a]One participant reported use in Pre1 but did not respond for P1–P3, another participant reported periconceptional use but did not report specific dates.

[b]Due to small cell sizes, cases and controls are combined; 3 distinct patterns reported by <5 participants each are not presented.

TABLE 2

Maternal characteristics by self-reported periconceptional[a] cyclobenzaprine use, National Birth Defects Prevention Study (1997–2011) and Birth Defects Study to Evaluate Pregnancy exposures (2014–2018).

Characteristic	Cyclobenzaprine use *N* (%) (*n* = 60)	No cyclobenzaprine use *N* (%) (*n* = 46 665)
Case	51 (85.0)	33 564 (71.9)
Maternal age at delivery		
<20 years	1 (1.7)	4602 (9.9)
20–24 years	12 (20.0)	10 720 (23.0)
25–29 years	19 (31.7)	12 605 (27.0)
30–34 years	16 (26.7)	11 669 (25.0)
≥35 years	12 (20.0)	7069 (15.2)
missing	*0 (0)*	*0 (0)*
Maternal race/ethnicity		
Non-Hispanic White	43 (71.7)	27 019 (57.9)
Non-Hispanic Black	6 (10.0)	4865 (10.4)
Hispanic	9 (15.0)	11 586 (24.8)
Other	2 (3.3)	3170 (6.8)
missing	*0 (0)*	*25 (0.1)*
Maternal prepregnancy body mass index (kg/m^2)		
Underweight (<18.5)	3 (5.0)	2335 (5.0)
Healthy weight (18.5–24.9)	31 (51.7)	22 696 (48.6)
Overweight (25.0–29.9)	11 (18.3)	10 246 (22.0)
Obese (≥30.0)	14 (23.3)	8951 (19.2)
missing	*1 (1.7)*	*2437 (5.2)*
Maternal education level		
<High school	5 (8.3)	7694 (16.5)
High school/GED	11 (18.3)	11 241 (24.1)
Some college	21 (35.0)	12 230 (26.2)
≥ Bachelor degree	21 (35.0)	14 022 (30.1)
missing	*2 (3.3)*	*1478 (3.2)*
Pregestational diabetes (type 1 or 2)	2 (3.3)	998 (2.1)
missing	*0 (0)*	*333 (0.7)*
Other perimnceptional[a] pain medications[b]		
Acetaminophen	43 (71.7)	25 495 (54.6)
missing	*3 (5.0)*	*2182 (4.7)*
NSAIDs	34 (56.7)	13 897 (29.8)
missing	*0 (0)*	*1306 (2.8)*
Opioids	28 (46.7)	1129 (2.4)
missing	*0 (0)*	*780 (1.7)*
Periconceptional[a] cigarette smoking	24 (40.0)	8666 (18.6)
missing	*1 (1.7)*	*1308 (2.8)*

Characteristic	Cyclobenzaprine use *N* (%) (*n* = 60)	No cyclobenzaprine use *N* (%) (*n* = 46 665)
Periconceptional[a] alcohol use	28 (46.7)	16 929 (36.3)
missing	*1 (1.7)*	*1469 (3.2)*
Periconceptional[c] prenatal vitamin use	33 (55.0)	24 765 (53.1)
missing	*1 (1.7)*	*714 (1.5)*

Abbreviations: GED, General Educational Development test; NSAIDs, nonsteroidal anti-inflammatory drugs.

[a]Defined as 1 month before conception through the third gestational month.

[b]Not mutually exclusive categories.

[c]Defined as 1 month before and after conception.

TABLE 3

Number of cases[a] by defect type and by cyclobenzaprine exposure status, National Birth Defects Prevention Study (1997–2011) and Birth Defects Study to Evaluate Pregnancy exposures (2014–2018).

Outcome	Exposed	Unexposed
Controls	9	13 101
All cases	51	33 564
Non-cardiac birth defects		
Amniotic band sequence/limb-body wall complex[b]	1	343
Anencephaly[b]	2	660
Spina bifida	2	1456
Dandy-Walker malformation[b]	1	186
Cleft palate[c]	6	1848
Cleft lip, with or without cleft palate[c]	6	3548
Anorectal atresia or stenosis[b]	3	1090
Hypospadias[d]	1	2606
Transverse limb deficiency	1	787
Craniosynostosis[b]	2	1624
Diaphragmatic hernia	1	1016
Gastroschisis	2	1661
Cardiac birth defects		
Truncus arteriosus	1	160
Interrupted aortic arch, type B[b]	1	49
Tetralogy of Fallot	1	1403
D-transposition of the great arteries	4	889
Double outlet right ventricle	1	123
Conoventricular ventricular septal defect[e]	1	116
Hypoplastic left heart syndrome	2	776
Coarctation of the aorta	5	1355
Aortic stenosis[b]	1	523
Pulmonary atresia	2	309
Pulmonary valve stenosis[f]	3	1588
Tricuspid atresia	1	194
Ebstein anomaly[b]	1	182
Perimembranous ventricular septal defect[e]	2	1466
Secundum atrial septal defect[b]	4	3140

[a] Case counts are not mutually exclusive, so will not sum to the total number of unique individuals included in this study.

[b] $n = 5$ exposed controls, 11 824 unexposed controls (NBDPS only).

[c] *n* = 9 exposed controls, 12 964 unexposed controls (NBDPS and BD-STEPS).

[d] *n* = 0 exposed controls, 6024 unexposed controls (NBDPS only).

[e] *n* = 2 exposed controls, 6819 unexposed controls (NBDPS only).

[f] *n* = 5 exposed controls, 11 351 unexposed controls (NBDPS only).

TABLE 4

Association between periconceptional cyclobenzaprine use and select birth defects, National Birth Defects Prevention Study (1997–2011) and Birth Defects Study to Evaluate Pregnancy exposureS (2014–2018).

Birth defect	Exposed	Unexposed	OR (95% CI)
Controls	9	13 101	1.00
Cleft palate	6	1848	4.79 (1.71, 13.44)
Cleft lip, with or without cleft palate	6	3548	2.50 (0.89, 7.02)
Anorectal atresia or stenosis	3	1090	6.91 (1.67, 28.65)
D-transposition of the great arteries	4	889	6.97 (2.17, 22.36)
Coarctation of the aorta	5	1355	5.58 (1.88, 16.58)
Pulmonary valve stenosis	3	1588	4.55 (1.10, 18.87)
Secundum atrial septal defect	4	3140	3.08 (0.83, 11.45)

Abbreviations: CI, confidence interval; OR, odds ratio.