

Use of topiramate in pregnancy and oral clefts

Andrea V Margulis, Martha M Werler, Suzanne Gilboa,
Murray A Mittleman, Robert J Glynn, Allen A Mitchell,
Sonia Hernández-Díaz, National Birth Defects Prevention Study

ICPE - August 15, 2011

Disclosure

- The Pharmacoepidemiology Program at Harvard School of Public Health received training grants from Pfizer, Novartis, and Asisa.
- The Slone Epidemiology Center receives support for unrelated research from McNeil Consumer Healthcare.
- Some authors have consulted for pharmaceutical companies, including some that manufacture anti-epileptic drugs.
- Dr. Mitchell's retirement fund owns stock in Johnson & Johnson.
- The findings and conclusions of this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Funding

Funding for the studies came from:

- Cooperative Agreement no. U50/CCU113247 with the Centers for Disease Control and Prevention to the SEC through the Massachusetts Department of Public Health
- Cooperative agreements under program announcement No. 02081 from the Centers for Disease Control and Prevention to the centers participating in the National Birth Defects Prevention Study
- Grant RO1 HD 046595 from the Eunice Kennedy Shriver National Institute of Child Health and Human Development

Topiramate

- A “new” antiepileptic drug 1996
- Migraine prevention 2004
- Available as a generic 2006
- Off-label uses
 - weight loss
- Proposed new indication
(combined with phentermine)
 - weight loss 2010

Topiramate

Animal studies:

- Craniofacial defects (mice) and other structural variations (rats)

Topiramate

Human studies:

Increased risk of cleft lip with or without cleft palate among infants exposed to topiramate monotherapy in the first trimester

- UK Epilepsy and Pregnancy Register
 - 2 cases among 70 exposed (>10 times the background risk)
- North American Antiepileptic Drug Pregnancy Registry
 - 4 cases among 321 exposed (10 times the background risk)
- Denmark Birth Registry Data
 - 1 case among 108 exposed (>5 times the background risk)

UK: Hunt et al. Neurology 2008; 71:272

NA: Hernandez-Diaz et al. BDRA 2010:408

Denmark: Molgaard-Nielsen et al; JAMA 2011; 305:1996

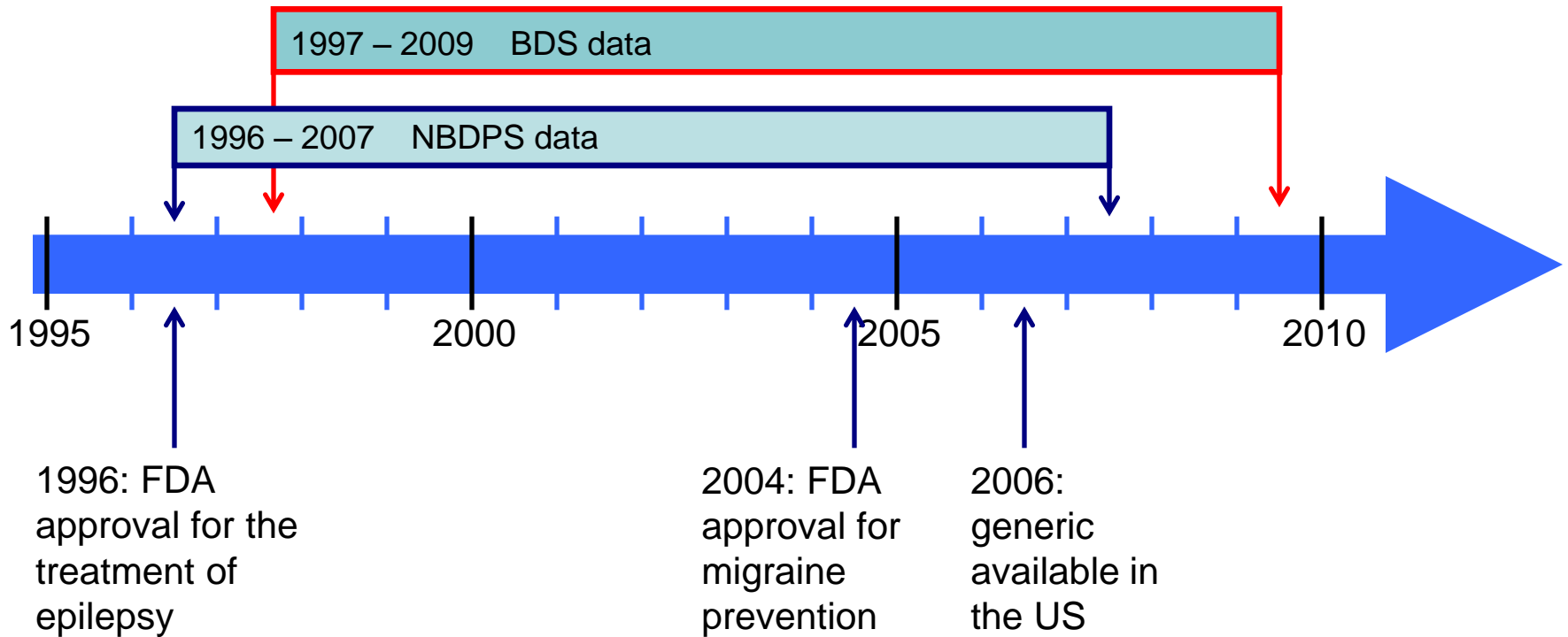
Objective

To assess the association between topiramate use in pregnancy and oral clefts

Data sources

- Two North American birth defects surveillance programs:
 - Boston University Slone Epidemiology Center
Birth Defects Study (BDS)
 - Centers for Disease Control and Prevention
National Birth Defects Prevention Study (NBDPS)
- Identification of cases and controls
 - Expert review of medical records
- Computer assisted telephone interview

Timeline



Exposure and outcomes

Exposure

- Topiramate use as monotherapy in first trimester
 - Dose (in BDS only)

Outcomes (cases)

- Major congenital malformations (MCM)
- Cleft lip with or without cleft palate (CL/P)
- Cleft palate (no exposed cases in either data set)

Infants with chromosomal abnormalities or single-gene conditions were not eligible

Non-malformed infants as controls

Statistical methods: Study-specific analyses

BDS and NBDPS separately

Conditional exact logistic regression matched on

- Year of birth
- Region of birth

Statistical methods: Pooled analyses

Conditional exact logistic regression matched on

- Year of birth
- Region of birth
- Study (BDS or NBDPS)

Additional factors considered as confounders:

family history of oral clefts and other malformations, maternal age, race/ethnicity, pre-pregnancy body mass index, smoking, alcohol consumption, folic acid supplementation, diabetes, and epilepsy

Malformations overall and CL/P

	BDS N = 17,607		NBDPS N = 31,827	
	Total	Topiramate	Total	Topiramate
Controls	6,986	2	8,494	4
MCM	10,621	5	23,333	10
CL/P	785	3	2,283	4

Slone Birth Defects Study

	No AED	Topiramate	Adjusted OR	(95% CI)
Controls	6,933	2	Reference	
MCM	10,503	5	1.22	(0.19 -13.01)
CL/P	778	3	10.13	(1.09 -129.21)

OR: odds ratio. CI: confidence interval. AED: antiepileptic drug

Slone Birth Defects Study

- Daily dose topiramate monotherapy

Subjects	Dose (mg)
Control #1	100
Control #2	100
CL/P Case #1	25
CL/P Case #2	100
CL/P Case #3	Not reported

NBDPS

	No AED	Topiramate	Adjusted OR	(95% CI)
Controls	8,434	4	Reference	
MCM	23,102	10	0.92	(0.26 - 4.06)
CL/P	2,256	4	3.63	(0.66 - 20.00)

OR: odds ratio. CI: confidence interval. AED: antiepileptic drug

Pooled data

	No AED	Topiramate	Adjusted OR	(95% CI)
Controls	15,367	6	Reference	
MCM	33,605	15	1.01	(0.37 - 3.22)
CL/P	3,034	7	5.36	(1.49 - 20.07)

OR: odds ratio. CI: confidence interval. AED: antiepileptic drug

Pooled Data

Control of confounding: Range of adjusted ORs:

- Major congenital malformations 0.91 to 1.03
- CL/P 4.66 to 5.92

Limitations

- Small numbers of exposed subjects
- Unable to conduct full dose-response analysis
- Limited control of confounding
 - Cannot rule out role of epilepsy

Strengths

- Data on over 50,000 subjects from the two largest birth defects surveillance systems in the US
- Malformations are confirmed through review of medical records
- Detailed data on drug exposure as reported by the user
- Restricted to monotherapy to avoid confounding by concomitant use of other AEDs
- Recall bias unlikely: No association with MCM overall

Conclusions

- The risk of major congenital malformations overall does not seem to be increased among infants exposed to topiramate in monotherapy in the first trimester of pregnancy

Discussion

- However, the risk of CL/P was increased among infants exposed to topiramate monotherapy at the 25-100 mg dose range during the first trimester of pregnancy
- Two large databases show consistent results
- Consistent with other studies that were also limited by small numbers
- If pooled results represent “truth”, the risk of CL/P would increase from around 0.7 per 1,000 births to 2.5 per 1,000 births (compared to baseline risk of 20-30/1,000 for any major malformation)

Thank you

Project coordinators, medical record reviewers,
interviewers, research assistants and programmers

Participating institutions and local doctors

Mothers who were interviewed for the study

Extra slides

Participant characteristics

	Slone Birth Defects Study		National Birth Defects Prevention Study	
	Non-malformed infants N = 6,986	Infants with CL/P N = 785	Non-malformed infants N = 8,494	Infants with CL/P N = 2,283
Maternal age in years, mean (SD)	29.3 (5.9)	28.5 (6.1)	27.3 (6.1)	27.0 (6.1)
Maternal race/ethnicity, N (%)				
Non-Hispanic White	4,920 (70.4%)	507 (64.6%)	4,958 (58.4%)	1,370 (60.0%)
Non-Hispanic Black	538 (7.7%)	65 (8.3%)	935 (11.0%)	137 (6.0%)
Hispanic	997 (14.3%)	124 (15.8%)	1,918 (22.6%)	604 (26.5%)
Family history of oral clefts, N (%)				
First-degree relative with CL/P or CP	31 (0.4%)	56 (7.1%)	25 (0.3%)	158 (6.9%)
Second/third-degree relative with CL/P or CP	77 (1.1%)	45 (5.7%)	23 (0.3%)	159 (7.0%)
Diabetes, N (%)	365 (5.2%)	67 (8.5%)	627 (7.4%)	221 (9.7%)
Folic acid supplementation, N (%)	6,090 (87.2%)	640 (81.5%)	6,282 (74.0%)	1,654 (72.4%)
Smoked in first trimester, N (%)	1,150 (16.5%)	174 (22.2%)	1,350 (15.9%)	494 (21.6%)
Alcohol in first trimester, N (%)	2,756 (39.5%)	257 (32.7%)	3,087 (36.3%)	850 (37.2%)
Male sex, N (%)	3,450 (49.4%)	509 (64.8%)	4,314 (50.8%)	1,503 (65.8%)
Birth length in cm, mean (SD)	51.6 (3.5)	51.2 (3.7)	48.9 (6.7)	49.4 (4.7)
Birth weight in grams, mean (SD)	3,400 (565.1)	3,280 (617.5)	3,350 (557.1)	3,176 (726.0)

CL/P: cleft lip with or without cleft palate – CP: cleft palate

Participant characteristics

	Birth Defects Study			National Birth Defects Prevention Study		
	Non-malformed infants N = 6,986	Infants with CL/P N = 785	Adjusted OR (95% CI)	Non-malformed infants N = 8,494	Infants with CL/P N = 2,283	Adjusted OR (95% CI)
Maternal age in years, mean (SD)	29.3 (5.9)	28.5 (6.1)	0.98 (0.97 - 0.99)	27.3 (6.1)	27.0 (6.1)	0.99 (0.99 – 1.00)
Prepregnancy BMI in kg/m², N (%)						
18.5 or less	207 (3.0%)	38 (4.8%)	1.77 (1.2 - 2.59)	439 (5.2%)	150 (6.6%)	1.33 (1.09 - 1.62)
(18.5;25]	3,966 (56.8%)	379 (48.3%)	reference	4,180 (49.2%)	1,069 (46.8%)	reference
(25; 30]	1,565 (22.4%)	173 (22.0%)	1.18 (0.97 - 1.44)	2,033 (23.9%)	504 (22.1%)	0.95 (0.85 - 1.08)
(30; 35]	566 (8.1%)	75 (9.6%)	1.35 (1.03 - 1.78)	912 (10.7%)	255 (11.2%)	1.08 (0.92 - 1.26)
Over 35	327(4.7%)	52 (6.6%)	1.57 (1.13 - 2.18)	564 (6.6%)	182 (8.0%)	1.22 (1.02 - 1.47)
Maternal race/ethnicity, N (%)						
Non-Hispanic White	4,920 (70.4%)	507 (64.6%)	reference	4,958 (58.4%)	1,370 (60.0%)	reference
Non-Hispanic Black	538 (7.7%)	65 (8.3%)	0.80 (0.60 - 1.07)	935 (11.0%)	137 (6.0%)	0.50 (0.41 - 0.61)
Hispanic	997 (14.3%)	124 (15.8%)	1.27 (1.01 - 1.59)	1,918 (22.6%)	604 (26.5%)	0.97 (0.85 - 1.11)
Asian/Pacific Islander	386 (5.5%)	71 (9.0%)	1.47 (1.11 - 1.96)	200 (2.4%)	49 (2.1%)	0.84 (0.61 - 1.15)
Native American/Alaskan Native	NA	NA	NA	40 (0.5%)	18 (0.8%)	1.52 (0.87 - 2.68)
Other	139 (2.0%)	15 (1.9%)	1.13 (0.64 - 1.99)	368 (4.3%)	91 (4.0%)	0.83 (0.65 - 1.06)
Maternal education, N (%)						
Less than 13 years	1,936 (27.7%)	287 (36.6%)	reference	3,446 (40.6%)	1,106 (48.4%)	reference
13 – 15 years	1,636 (23.4%)	195 (24.8%)	0.79 (0.65 - 0.97)	2,260 (26.6%)	583 (25.5%)	0.82 (0.73 - 0.92)
Over 16 years	3,411 (48.8%)	303 (38.6%)	0.59 (0.49 - 0.71)	2,637 (31.0%)	573 (25.1%)	0.71 (0.63 - 0.8)

Participant characteristics

	Birth Defects Study			National Birth Defects Prevention Study		
	Non-malformed infants N = 6,986	Infants with CL/P N = 785	Adjusted OR (95% CI)	Non-malformed infants N = 8,494	Infants with CL/P N = 2,283	Adjusted OR (95% CI)
First-degree relative with CL/P or CP	31 (0.4%)	56 (7.1%)	18.65 (11.32 - 30.71)	25 (0.3%)	158 (6.9%)	28.99 (18.91 - 44.44)
Second/third-degree relative with CL/P or CP	77 (1.1%)	45 (5.7%)	5.78 (3.81 - 8.77)	23 (0.3%)	159 (7.0%)	33.73 (21.65 - 52.54)
Any relative with non CL/P or CP	1,775 (25.4%)	176 (22.4%)	1.14 (0.94 - 1.37)	1,985 (23.4%)	590 (25.8%)	1.43 (1.28 - 1.59)
No family history of CM	5,103 (73.0%)	508 (64.7%)	reference	6,461 (76.1%)	1,376 (60.3%)	reference
Diabetes, N (%)	365 (5.2%)	67 (8.5%)	1.64 (1.23 - 2.19)	627 (7.4%)	221 (9.7%)	1.3 (1.11 - 1.53)
Folic acid supplementation, N (%)	6,090 (87.2%)	640 (81.5%)	0.7 (0.57 - 0.86)	6,282 (74.0%)	1,654 (72.4%)	0.97 (0.87 - 1.08)
Smoked in first trimester, N (%)	1,150 (16.5%)	174 (22.2%)	1.51 (1.25 - 1.84)	1,350 (15.9%)	494 (21.6%)	1.52 (1.35 - 1.71)
Alcohol in first trimester, N (%)	2,756 (39.5%)	257 (32.7%)	0.8 (0.68 - 0.94)	3,087 (36.3%)	850 (37.2%)	1.04 (0.95 - 1.15)
Gestational age at birth in weeks, mean (SD)	38.9 (2.0)	38.5 (2.5)	0.94 (0.91 - 0.97)	38.8 (14.1)	42.3 (63.5)	1.00 (1.00 - 1.00)
Male sex, N (%)	3,450 (49.4%)	509 (64.8%)	1.94 (1.65 - 2.27)	4,314 (50.8%)	1,503 (65.8%)	1.88 (1.70 - 2.07)
Birth length in cm, mean (SD)	51.6 (3.5)	51.2 (3.7)	0.98 (0.96 - 1.00)	48.9 (6.7)	49.4 (4.7)	1.00 (0.99 - 1.01)
Birth weight in grams, mean (SD)	3,400 (565.1)	3,280 (617.5)	1.00 (1.00 - 1.00)	3,350 (557.1)	3,176 (726.0)	1.00 (1.00 - 1.00)

CL/P: cleft lip with or without cleft palate – CP: cleft palate – OR: odds ratio – 95%CI: 95% confidence interval – BMI: body mass index – NA: category not available
 Note: Birth Defects Study: 423 subjects did not report their BMI, 9 subjects did not report race/ethnicity, 3 did not report years of education, 262 did not report on smoking status and 133 did not report on alcohol intake. National Birth Defects Prevention Study: 489 subjects did not report their BMI, 89 subjects did not report race/ethnicity, 172 did not report years of education, 144 did not report on smoking status, 182 did not report on alcohol intake and 15 did not report the offspring's sex.

Control of confounding

Matching on additional factors, major congenital malformations; pooled data.

	OR (95% CI)
Familiiy history of congenital malformations	0.91 (0.33 - 2.90)
Maternal age at conception	1.03 (0.37 - 3.32)
Prepregnancy BMI	1.02 (0.37 - 3.25)
Diabetes	1.02 (0.37 - 3.24)
Folic acid supplementation	1.02 (0.37 - 3.23)
Cigarette smoking	0.96 (0.35 - 3.06)
Alcohol consumption	0.99 (0.36 - 3.15)

BMI: body mass index

Control of confounding

Matching on additional factors, cleft lip with or without cleft palate; pooled data

	OR (95%CI)
Family history of CL/P	4.66 (1.13 - 18.52)
Self-reported race/ethnicity	4.79 (1.33 - 18.03)
Maternal age at conception	5.92 (1.60 - 22.62)
Prepregnancy BMI	5.46 (1.47 - 21.02)
Diabetes	5.36 (1.49 - 20.08)
Epilepsy	4.99 (1.17 - 22.26)
Folic acid supplementation	5.52 (1.53 - 20.59)
Cigarette smoking	4.98 (1.36 - 19.02)
Alcohol consumption	5.34 (1.49 - 19.87)

BMI: body mass index

Epilepsy

	Topiramate users	Epilepsy
BDS	7	2
NBDPS	14	3
Pooled data	21	5