FACULTEIT GENEESKUNDE EN GEZONDHEIDSWETENSCHAPPEN

# PSYCHOFARMACA BIJ ZWANGERSCHAP

Gilbert Lemmens, Universitaire Dienst Psychiatrie

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## DATA?

- Geen RCT in ZW en borstvoeding
- Data:
  - case-report/case series, nu grote systematische reviews en meta-analysis (>100.000 exposure)
  - wisselende exposure (binnen klassen en tussen klassen)
  - retrospectieve bias, lange-termijn effecten?
  - niet-psychiatrische populaties
  - geen controle voor andere risicofactoren (socio-economisch, roken, andere medicatie, somatische ziekten, ….)
  - grotere waakzaamheid voor malformaties bij medicatiegebruik

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SEMINARS IN PERINATOLOGY 39 (2015) 508–511

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www.elsevier.com/locate/semperi

## Epidemiology of medications use in pregnancy

*Martina Ayad, MD, and Maged M. Costantine, MD**

pharmacotherapy.[4,5,8–13] For example, while less than 1% of pregnant women used an antidepressant in the late 1980s, it is estimated that almost 10% of pregnant women are currently prescribed psychotropic medicines, with antidepressants being the most common ones (7.5%). Moreover, 1.6% of pregnant women are using 2 or more different categories of psychotropic medications, most often a combination of an antidepressant and an anxiolytic.[8,11] Similarly, the use of

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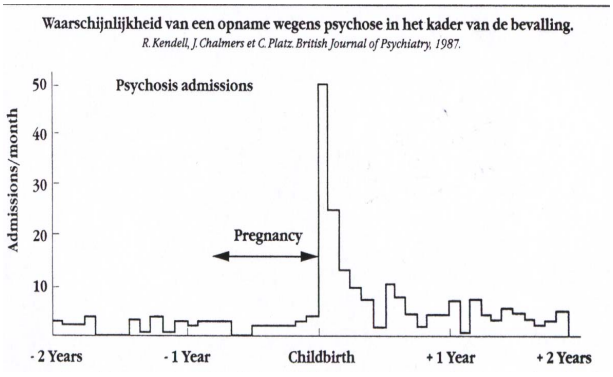
AD: 3% Europa vs 8 % VS



## PERINATALE PERIODE: GEEN BESCHERMING

- Depressie: ‘dezelfde’ prevalentie ZW vrouwen als niet-ZW vrouwen (cave onderdetectie ZW) (Pearlstein, 2015)
- Vaak ‘first lifetime episode’: 50% postpartum psychose; 40% OCD (Pawlby, 2009)
- 3X kans op recidief van depressieve episode tot 5j na bevalling wanneer antenatale depressie (Baker et al. Lancet, 2015)

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## PERINATALE PERIODE: GEEN BESCHERMING

Risk of Postpartum Relapse in Bipolar Disorder and Postpartum Psychosis: A Systematic Review and Meta-Analysis

Richard Wesseloo, M.D., Astrid M. Kamperman, Ph.D., Trine Munk-Olsen, Ph.D., Victor J.M. Pop, M.D., Ph.D., Steven A. Kushner, M.D., Ph.D., Veerle Bergink, M.D., Ph.D.

2016, AM J Psych: 37 studies/4023 patiënten

BP I en II

**FIGURE 3. Overall Postpartum Relapse Rate for Each Diagnostic Group in a Meta-Analysis of Risk of Postpartum Relapse in Bipolar Disorder and Postpartum Psychosis**

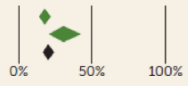
**A. Overall relapse[a] rate postpartum per diagnostic group**

| Diagnostic group | Relapse rate (%) | Lower limit | Upper limit | Total N |
|---|---|---|---|---|
| Bipolar disorder[b] | 37 | 29 | 45 | 5,105 |
| History of postpartum psychosis[c] | 31 | 22 | 42 | 595 |
| Overall | 35 | 29 | 41 | 5,700 |


$I^2$ for bipolar disorder=95%, $I^2$ for postpartum psychosis=78%, df=1, Q=0.71, p=0.400

**B. Overall severe relapse[d] rate postpartum per diagnostic group**

| Diagnostic group | Relapse rate (%) | Lower limit | Upper limit | Total N |
|---|---|---|---|---|
| Bipolar disorder[e] | 17 | 13 | 21 | 5,078 |
| History of postpartum psychosis[f] | 29 | 20 | 41 | 531 |
| Overall | 19 | 15 | 23 | 5,609 |




$I^2$ for bipolar disorder=82%, $I^2$ for postpartum psychosis=78%, df=1, Q=5.77, p=0.016

[a] Definitions of relapse: psychosis, mania or hypomania, depression (or a mixed episode), and/or psychiatric hospitalization.
[b] Studies, k=25; deliveries, N=5,105; patients, N=3,495.
[c] Studies, k=13; deliveries, N=595; patients, N=528.
[d] Definitions of severe relapse: psychosis, mania, mixed episode, and/or psychiatric hospitalization.
[e] Studies, k=24; deliveries, N=5,078; patients, N=3,468 .
[f] Studies, k=12; deliveries, N=531; patients, N=464.

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## ONBEHANDELD?

Perinatal mental health 3

Effects of perinatal mental disorders on the fetus and child

Alan Stein*, Rebecca M Pearson*, Sherryl H Goodman, Elizabeth Rapa, Atif Rahman, Meaghan McCallum, Louise M Howard, Carmine M Pariante

- Antenatale depressie:
  - Slechtere obstetrische outcome: miskraam, bloedingen, keizersnede, preterme bevalling
  - Minder borstvoeding (Yusuff, 2015)
  - Neonaat: slechte psychomotoriek, moeilijk temperament, slechtere slaap
  - Tragere taalontwikkeling, emotionele en gedragsstoornissen
  - Depressie op latere leeftijd

Best Practice & Research Clinical Obstetrics and Gynaecology xxx (2013) 1–12

Contents lists available at ScienceDirect

Best Practice & Research Clinical Obstetrics and Gynaecology

journal homepage: www.elsevier.com/locate/bpobgyn

The long-term psychiatric and medical prognosis of perinatal mental illness

Samantha Meltzer-Brody, MD, MPH, Associate Professor,

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## ONBEHANDELD?


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## STOP MEDICATIE?

Risk of Postpartum Relapse in Bipolar Disorder and Postpartum Psychosis: A Systematic Review and Meta-Analysis

Richard Wesseloo, M.D., Astrid M. Kamperman, Ph.D., Trine Munk-Olsen, Ph.D., Victor J.M. Pop, M.D., Ph.D., Steven A. Kushner, M.D., Ph.D., Veerle Bergink, M.D., Ph.D.

2016, AM J Psych

**FIGURE 4. Overall Postpartum Relapse Rates in Patients With Bipolar Disorder Stratified by Prophylactic Pharmacotherapy During Pregnancy[a]**

Prophylactic pharmacotherapy during pregnancy[b]

| | Relapse rate (%) | Lower limit | Upper limit | Total N[c] |
|---|---|---|---|---|
| Yes | 23 | 14 | 37 | 60 |
| No | 66 | 57 | 75 | 385 |


$I^2$ for yes=5%, $I^2$ for no=36%, df=1, Q=22.92, p<0.001

[a] Definitions of relapse: psychosis, mania or hypomania, depression (or a mixed episode), and/or psychiatric hospitalization.
[b] Medications included antipsychotics and mood stabilizers.
[c] Total N indicates the number of patients included in the analysis.

>lithium

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STOP MEDICATIE?

## Relapse of Major Depression During Pregnancy in Women Who Maintain or Discontinue Antidepressant Treatment

Lee S. Cohen, MD

**Context** Pregnancy has historically been described as a time of emotional well-

JAMA, February 1, 2006—Vol 295, No. 5

201 euthyme vrouwen behandeld met AD en VG van MDD

**Table 3.** Relapse of Major Depression During Pregnancy

JAMA, February 1, 2006—Vol 295, No. 5

| | | Medication Status | | | |
|---|---|---|---|---|---|
| Relapse Status | All Women | Maintained | Increased | Decreased | Discontinued |
| No relapse | 115 (57.2) | 61 (74.4) | 11 (55.0) | 22 (64.7) | 21 (32.3) |
| Relapse by trimester | | | | | |
| All | 86 (42.8) | 21 (25.6) | 9 (45.0) | 12 (35.3) | 44 (67.7) |
| First | 44 (51.2) | 11 (52.4) | 7 (77.8) | 5 (41.7) | 21 (47.7) |
| Second | 31 (36.0) | 9 (42.9) | 2 (22.2) | 3 (25.0) | 19 (43.2) |
| Third | 11 (12.8) | 1 (4.8) | 0 (0.0) | 4 (33.3) | 4 (9.1) |

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**Herval: 26% AD vs 68% stop AD**

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SEMINARS IN PERINATOLOGY 39 (2015) 512–519

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## Pharmacokinetics of drugs in pregnancy

*Maisa Feghali, MD[a,*], Raman Venkataramanan, PhD[b,c], and Steve Caritis, MD[a]*

- Absorptie ('first-pass metabolisme'), distributie (plasma eiwitten, volume), metabolisme eliminatie (nier, lever: plasmaconcentraties)
- Absorptie:
  - Verminderde maaglediging en gedaalde gastro-intestinale mobiliteit (progesteron): daling Cmax en langere tijd tot C max
  - Misselijk en braken
  - Gestegen vetmassa
- Distributie: Gestegen bloedvolume (40-50%), gedaalde plasma albuminebinding (> free drug)
- Metabolisme: Cytochroom P450 (oestrogenen en progesteron)
- Eliminatie: GFR stijgt tot 50% (daling lithium spiegel)

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Seminars in Perinatology 39 (2015) 512–519

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## Pharmacokinetics of drugs in pregnancy

Maisa Feghali, MD[a,*], Raman Venkataramanan, PhD[b,c], and Steve Caritis, MD[a]

↓ CYP1A2: ↑ clozapine/olanzapine

↑ CYP2D6/CYP3A4: ↓ risperidone/quetiapine/aripiprazole

**Table 2 – Pregnancy-induced enzyme-specific changes.**

| Enzyme (references) | Pregnancy-induced change | Potential substrates in obstetrics |
|---|---|---|
| CYP3A4[19,20,77,78] | Increased | Glyburide, nifedipine, and indinavir |
| CYP2D6[77,79] | Increased | Metoprolol, dextromethorphan, paroxetine, duloxetine, fluoxetine, and citalopram |
| CYP2C9[18,80] | Increased | Glyburide, NSAIDs, phenytoin, and fluoxetine |
| CYP2C19[18,80] | Decreased | Glyburide, citalopram, diazepam, omeprazole, pantoprazole, and propranolol |
| CYP1A2[17,23,77,81] | Decreased | Theophylline, clozapine, olanzapine, ondansetron, and cyclobenzaprine |
| UGT1A4[82–84] | Increased | Lamotrigine |
| UGT1A1/9[25] | Increased | Acetaminophen |
| NAT2[17,24,85] | Decreased | Caffeine |

PLOS | MEDICINE

RESEARCH ARTICLE

## Pregnancy-Associated Changes in Pharmacokinetics: A Systematic Review

Gali Pariente[1], Tom Leibson[1], Alexandra Carls[1], Thomasin Adams-Webber[2], Shinya Ito[1,3,4,5]*, Gideon Koren[6]

**Table 7. Antidepressant/anxiolytic drugs: consistent/single studies of pregnancy associated pharmacokinetic changes (percent calculated as pregnant/nonpregnant values).**

| Drug [Reference] | Number of Studies | Total Number of Women (Nonpregnant/Pregnant) | Average Quality | Distribution Parameters | Exposure Parameters | Elimination Parameters | Trimester |
|---|---|---|---|---|---|---|---|
| Citalopram [69,70] | 2 | 16/16 | 15 | NR | **$C_{trough}$ 59%[&]** | NR | 3rd |
| Fluoxetine [71] | 1 | 11/8 | 16 | NR | **$C_{trough}$ 39%** | NR | 3rd |
| Paroxetine [72] | 1 | 12/12 | 11 | NR | **Lower concentrations[β]** | NR | 3rd |
| Venlafaxine [73]) | 1 | 7/7 | 16 | NR | **Concentrations 87%** | NR | 3rd |
| Clorazepate [74] | 1 | 7/7 | 17 | NR | **$C_{max}$ 51%** | **Cl 209%, $t_{1/2}$ 50%** | 3rd |
| Midazolam [75,76] | 2 | 23/21 | 18 | **$V_d$ 112%[&], free fraction 163%[&]** | **$C_{max}$ 68%[&], AUC 53%[&]**, AUC 62%[&] | **Cl 184% (159%–210%), $t_{1/2}$ 87%** (79%–96%) | 3rd |

Significant results are marked in bold.
[&]Parameter not reported in all studies.
[β]Numbers were not provided.
NR, not reported.

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Clin Pharmacol Ther. 2018 Mar;103(3):477-484. doi: 10.1002/cpt.770. Epub 2017 Sep 19.

**Treatment With Antipsychotics in Pregnancy: Changes in Drug Disposition.**

Westin AA[1], Brekke M[2], Molden E[2,3], Skogvoll E[4,5], Castberg I[6], Spigset O[1,7].

Serum concentrations in the **third trimester** were **significantly lower** than baseline for

quetiapine (-76%; confidence interval (CI), -83%, -66%; P < 0.001)

aripiprazole (-52%; CI, -62%, -39%; P < 0.001),

BUT, not for olanzapine (-9%; CI, -28%, +14%; P = 0.40).

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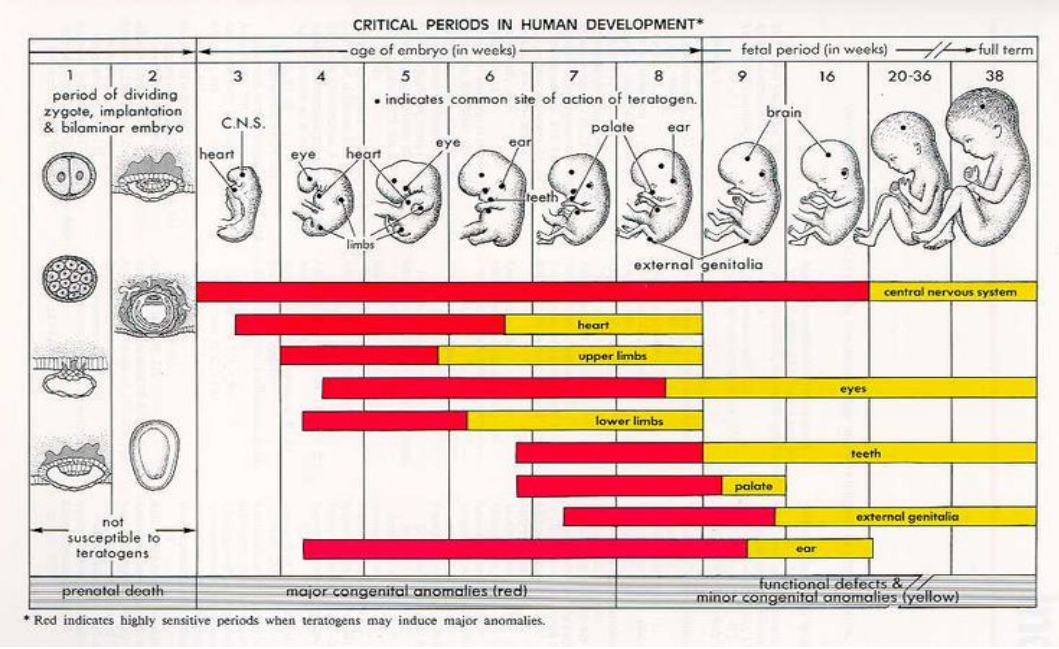
## FOETALE ONTWIKKELING

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## SAMENGEVAT

- Toenemende informatie over psychofarmaca en ZW
- Zwangerschap houdt risico in voor psychiatrische stoornissen (nieuwe aandoeningen/herval)
- Psychiatrische stoornissen hebben impact op moeder en ontwikkeling van het kind
- Medicatiestop: meer kans op herval
- Farmacokinetiek verloopt anders tijdens ZW
- Congenitale malformaties gaan samen met foetale ontwikkeling

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## VRAGEN BIJ BEHANDELING MET PSYCHOFARMACA

- Zijn psychofarmaca geassocieerd met verhoogd risico op malformaties?
- Wat zijn lange-termijn effecten van gebruik psychofarmaca?
- Wat zijn de implicatie van stoppen van psychofarmaca?

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# ANTIDEPRESSIVA

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FOCUS ON WOMEN'S MENTAL HEALTH
META-ANALYSIS



**Antidepressant Exposure During Pregnancy and Congenital Malformations: Is There an Association? A Systematic Review and Meta-Analysis of the Best Evidence**

*Sophie Grigoriadis, MD, PhD, FRCPC; Emily H. VonderPorten, MPH; Lana Mamisashvili, MSW; Michael Roerecke, PhD; Jürgen Rehm, PhD; Cindy-Lee Dennis, PhD; Gideon Koren, MD, FRCPC, FACMT; Meir Steiner, MD, PhD, FRCPC; Patricia Mousmanis, MD, CCFP, FCFP; Amy Cheung, MD, MSc, FRCPC; and Lori E. Ross, PhD*

*J Clin Psychiatry 2013;74(4):e293–e308*

CAVE < RR=2.0 klinische relevant

RR van 1.4 betekent absolute risico van 7/1000 ipv 5/1000

**'Vroegere studies'**

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**SUMMARY OF RESULTS AND IMPORTANT CONSIDERATIONS**

**Results**

***Any antidepressant medication exposure***

Significantly associated with:

- Cardiovascular malformations (RR = 1.36)
- Septal heart defects (atrial septal defects and ventral septal defects) (RR = 1.40)

Not significantly associated with:

- Congenital malformations (RR = 0.93)
- Major malformations (RR = 1.07)
  *Significant when all studies included (RR = 1.09), but RR similar to the nonsignificant RR of higher quality studies only*
- Ventral septal defects (RR = 1.54)
  *Able to be analyzed only for exposure to any antidepressant*

***Paroxetine exposure***

Significantly associated with:

- Cardiovascular malformations (RR = 1.43)

Not significantly associated with:

- Congenital malformations (RR = 1.03)
- Major malformations (RR = 1.11)
- Septal heart defects (RR = 0.97)

***Fluoxetine exposure***

Not significantly associated with:

- Congenital malformations (RR = 1.10)
- Major malformations (RR = 1.20)
  *Significant when all studies included (RR = 1.25), but RR similar to the nonsignificant RR of higher quality studies only*
- Cardiovascular malformations (RR = 1.17)
- Septal heart defects (RR = 1.18)

# Selective serotonin reuptake inhibitors and venlafaxine in early pregnancy and risk of birth defects: population based cohort study and sibling design

Kari Furu,[1] Helle Kieler,[2] Bengt Haglund,[2] Anders Engeland,[1 3] Randi Selmer,[1] Olof Stephansson,[2 4] Unnur Anna Valdimarsdottir,[5 6] Helga Zoega,[5] Miia Artama,[7 8] Mika Gissler,[9 10] Heli Malm,[11 12] Mette Nørgaard[13]

the bmj | *BMJ* 2015;350:h1798 | doi: 10.1136/bmj.h1798

**Table 2 | Exposure to antidepressants during first trimester**

| Substance (ATC code) | No (%) of infants |
|---|---|
| Any SSRI* (N06AB or N06AX16) | 36 772 (1.60) |
| Fluoxetine (N06AB03) | 6250 (0.27) |
| Citalopram (N06AB04) | 11 193 (0.48) |
| Paroxetine (N06AB05) | 2879 (0.12) |
| Sertraline (N06AB06) | 7245 (0.31) |
| Fluvoxamine (N06AB08) | 255 (0.01) |
| Escitalopram (N06AB10) | 3950 (0.17) |
| Venlafaxine (N06AX16) | 2763 (0.12) |
| Mixed† | 2237 (0.10) |
| Other antidepressants‡ | 7188 (0.31) |

Congenitale malformatie: **3.7%** SSRI en Venlafaxine vs **3.2%** unexposed

Cardiale geboortedefect: **1.5%** SSRI en Venlafaxine vs **1.2%** unexposed

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| Drug | No with birth defects (per 1000): Exposed group | Unexposed group | Crude odds ratio (95% CI) | Adjusted* odds ratio (95% CI) |
|---|---|---|---|---|
| Any SSRI | 1357 (36.9) | 71 374 (31.5) | 1.18 (1.12 to 1.24) | 1.13 (1.06 to 1.20) |
| Fluoxetine | 255 (40.8) | | 1.31 (1.15 to 1.48) | 1.25 (1.10 to 1.42) |
| Citalopram | 446 (39.9) | | 1.28 (1.16 to 1.40) | 1.19 (1.07 to 1.31) |
| Paroxetine | 116 (40.3) | | 1.29 (1.07 to 1.56) | 1.16 (0.95 to 1.41) |
| Sertraline | 248 (34.2) | | 1.09 (0.96 to 1.24) | 1.06 (0.93 to 1.22) |
| Fluvoxamine | 9 (35.3) | | 1.13 (0.58 to 2.19) | 0.77 (0.38 to 1.56) |
| Escitalopram | 107 (27.1) | | 0.86 (0.71 to 1.04) | 0.89 (0.73 to 1.10) |
| Venlafaxine | 95 (34.4) | | 1.10 (0.89 to 1.34) | 1.06 (0.86 to 1.32) |

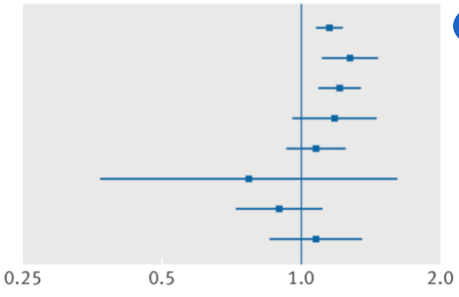


**Fig 1 | Selective serotonin reuptake inhibitors (SSRIs) or venlafaxine in early pregnancy and risk of birth defects. *Adjusted for maternal age, year of birth, birth order, smoking, maternal diabetes, country, and use of other prescribed drugs (antiepileptics (ATC code N03), anxiolytics and hypnotics (N05B and N05C), and angiotensin converting enzyme inhibitors (C09))**

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Selective serotonin reuptake inhibitors and venlafaxine in early pregnancy and risk of birth defects: population based cohort study and sibling design

Kari Furu,[1] Helle Kieler,[2] Bengt Haglund,[2] Anders Engeland,[1 3] Randi Selmer,[1] Olof Stephansson,[2 4] Unnur Anna Valdimarsdottir,[5 6] Helga Zoega,[5] Miia Artama,[7 8] Mika Gissler,[9 10] Heli Malm,[11 12] Mette Nørgaard[13]

the bmj | *BMJ* 2015;350:h1798 | doi: 10.1136/bmj.h1798

**Table 3 | Selective serotonin reuptake inhibitors or venlafaxine in early pregnancy and birth defects. Odds ratios in unmatched and sibling controlled analyses**

| | Full cohort analyses | | Sibling controlled analyses | | | | | |
|---|---|---|---|---|---|---|---|---|
| Type of birth defect | Crude odds ratio (95% CI) (n=2 303 647) | Adjusted* odds ratio (95% CI) (n=2 145 050) | No of families | No of infants | No exposed | No with birth defects | Crude odds ratio (95% CI) | Adjusted* odds ratio (95% CI) |
| Any | 1.18 (1.12 to 1.24) | 1.13 (1.05 to 1.20) | 895 | 2288 | 980 | 923 | 1.04 (0.91 to 1.19) | 1.06 (0.91 to 1.24) |
| Any cardiac | 1.30 (1.20 to 1.42) | 1.15 (1.05 to 1.26) | 378 | 991 | 422 | 386 | 0.94 (0.76 to 1.16) | 0.92 (0.72 to 1.17) |
| Right ventricular outflow tract obstruction | 1.66 (1.32 to 2.10) | 1.48 (1.15 to 1.89) | 42 | 115 | 48 | 42 | 0.96 (0.51 to 1.81) | 0.56 (0.21 to 1.49) |

*Adjusted for maternal age, year of birth, birth order, smoking, maternal diabetes, country, and use of other prescribed drugs (antiepileptics (ATC code N03), anxiolytics and hypnotics (N05B and N05C), and angiotensin converting enzyme inhibitors (C09))

.....familial related factors or other lifestyle related factors not adjusted.....

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Original Investigation

Antidepressant Use Late in Pregnancy and Risk of Persistent Pulmonary Hypertension of the Newborn

Krista F. Huybrechts, MS, PhD; Brian T. Bateman, MD, MSc; Kristin Palmsten, ScD; Rishi J. Desai, PhD; Elisabetta Patorno, MD, DrPH; Chandrasekar Gopalakrishnan, MD, MPH; Raisa Levin, MS; Helen Mogun, MS; Sonia Hernandez-Diaz, MD, DrPH

*JAMA*. 2015;313(21):2142-2151. doi:10.1001/jama.2015.5605

**Table 2. Absolute Risk of Persistent Pulmonary Hypertension of the Newborn Among Infants of Women With and Without Antidepressant Exposure During Pregnancy by Class**

| | Cohort of Women With Pregnancies | | | | | |
|---|---|---|---|---|---|---|
| | Overall | | | Depression Restricted | | |
| Exposure Groups | Unexposed | SSRI | Non-SSRI | Unexposed | SSRI | Non-SSRI |
| Total No. of Women | 3 660 380 | 102 179 | 26 771 | 657 515 | 65 316 | 16 283 |
| PPHN, No. | 7630 | 322 | 78 | 1635 | 221 | 56 |
| Risk per 10 000 (95% CI) | 20.8 (20.4-21.3) | 31.5 (28.3-35.2) | 29.1 (23.3-36.4) | 24.9 (23.7-26.1) | 33.8 (29.7-38.6) | 34.4 (26.5-44.7) |

Abbreviations: PPHN, persistent pulmonary hypertension of the newborn; SSRI, selective serotonin reuptake inhibitor.

**Unadjusted OR** for PPHN: **1.51** (95% CI, 1.35-1.69) for **SSRIs** and **1.40** (95% CI, 1.12-1.75) for **non-SSRIs**

**Adjusted OR: 1.12** (95% CI, 0.95-1.31) for **SSRIs** and **1.01** (95% CI, 0.76-1.35) for **non- SSRIs**.

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Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/psychires

Antidepressant use during pregnancy and risk of postpartum hemorrhage: A systematic review and meta-analysis

Hai-yin Jiang [a,1], Lian-lian Xu [b,1], Yu-cuan Li [a], Min Deng [a], Chun-ting Peng [a], Bing Ruai

Postpartum bloedingen: 1.32

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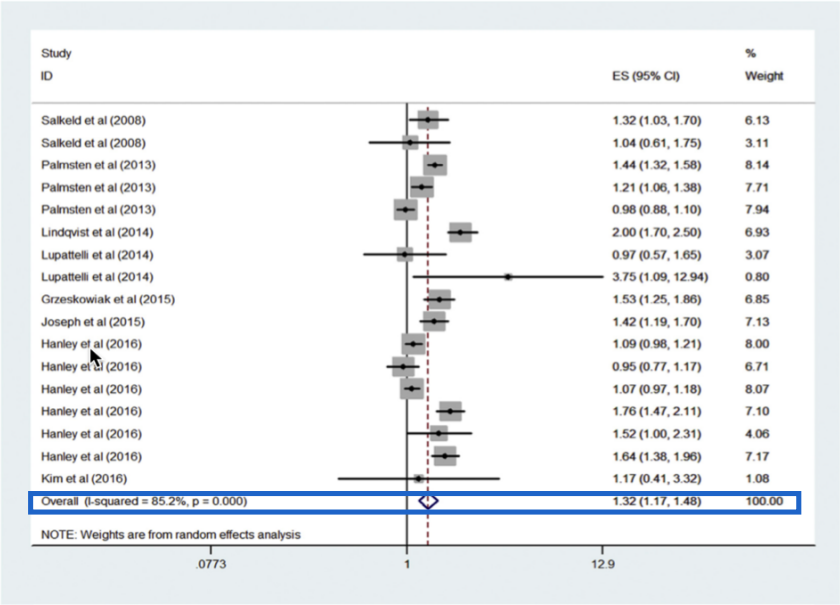


**Fig. 2.** Relative risk of postpartum haemorrhage in antidepressant users during pregnancy.

## Associations of Maternal Antidepressant Use During the First Trimester of Pregnancy With Preterm Birth, Small for Gestational Age, Autism Spectrum Disorder, and Attention-Deficit/Hyperactivity Disorder in Offspring

Ayesha C. Sujan, MA; Martin E. Rickert, PhD; A. Sara Öberg, MD, PhD; Patrick D. Quinn, PhD; Sonia Hernández-Díaz, MD, PhD; Catarina Almqvist, MD, PhD; Paul Lichtenstein, PhD; Henrik Larsson, PhD; Brian M. D'Onofrio, PhD

JAMA. 2017;317(15):1553-1562. doi:10.1001/jama.2017.3413

**Table 2. Baseline, Adjusted, and Sibling Comparison Associations Between Maternal Self-Reported First-Trimester Antidepressant Use and Birth and Neurodevelopmental Outcomes**

| | Model[a] | | |
|---|---|---|---|
| | Baseline[b] | Adjusted[c] | Sibling Comparison[d] |
| Any antidepressant | | | |
| Preterm birth, OR (95% CI) | 1.47 (1.40-1.55) | 1.35 (1.28-1.42) | 1.34 (1.18-1.52) |
| Small for gestational age, OR (95% CI) | 1.15 (1.06-1.25) | 1.12 (1.03-1.22) | 1.01 (0.81-1.25) |
| Autism spectrum disorder, HR (95% CI) | 2.02 (1.80-2.26) | 1.64 (1.46-1.83) | 0.83 (0.62-1.13) |
| Attention-deficit/hyperactivity disorder, HR (95% CI) | 2.21 (2.04-2.39) | 1.58 (1.46-1.71) | 0.99 (0.79-1.25) |
| SSRIs | | | |
| Preterm birth, OR (95% CI) | 1.38 (1.30-1.46) | 1.27 (1.20-1.35) | 1.33 (1.16-1.53) |
| Small for gestational age, OR (95% CI) | 1.11 (1.01-1.21) | 1.09 (0.99-1.20) | 0.88 (0.70-1.12) |
| Autism spectrum disorder, HR (95% CI) | 2.04 (1.80-2.32) | 1.66 (1.46-1.89) | 0.81 (0.58-1.14) |
| Attention-deficit/hyperactivity disorder, HR (95% CI) | 2.25 (2.06-2.46) | 1.60 (1.47-1.75) | 0.94 (0.73-1.22) |

Abbreviations: HR, hazard ratio; OR, odds ratio; SSRI, selective serotonin … country of birth, age at childbearing, highest level of completed education,

**Preterm**: 6.98% exposed vs 4.78% unexposed,
**Small gestational age**: 2.54% exposed vs 2.19% unexposed
**ASS** (15y): 5.28% exposed vs 2.14% unexposed,
**ADHD** (15y): 12.63% exposed vs 5.46% unexposed

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## Associations of Maternal Antidepressant Use During the First Trimester of Pregnancy With Preterm Birth, Small for Gestational Age, Autism Spectrum Disorder, and Attention-Deficit/Hyperactivity Disorder in Offspring

Ayesha C. Sujan, MA; Martin E. Rickert, PhD; A. Sara Öberg, MD, PhD; Patrick D. Quinn, PhD; Sonia Hernández-Díaz, MD, PhD; Catarina Almqvist, MD, PhD; Paul Lichtenstein, PhD; Henrik Larsson, PhD; Brian M. D'Onofrio, PhD

*JAMA*. 2017;317(15):1553-1562. doi:10.1001/jama.2017.3413

**Table 2. Baseline, Adjusted, and Sibling Comparison Associations Between Maternal Self-Reported First-Trimester Antidepressant Use and Birth and Neurodevelopmental Outcomes**

| | Model[a] | | |
|---|---|---|---|
| | Baseline[b] | Adjusted[c] | Sibling Comparison[d] |
| Any antidepressant | | | |
| Preterm birth, OR (95% CI) | 1.47 (1.40-1.55) | 1.35 (1.28-1.42) | 1.34 (1.18-1.52) |
| Small for gestational age, OR (95% CI) | 1.15 (1.06-1.25) | 1.12 (1.03-1.22) | 1.01 (0.81-1.25) |
| Autism spectrum disorder, HR (95% CI) | 2.02 (1.80-2.26) | 1.64 (1.46-1.83) | 0.83 (0.62-1.13) |
| Attention-deficit/hyperactivity disorder, HR (95% CI) | 2.21 (2.04-2.39) | 1.58 (1.46-1.71) | 0.99 (0.79-1.25) |
| SSRIs | | | |
| Preterm birth, OR (95% CI) | 1.38 (1.30-1.46) | 1.27 (1.20-1.35) | 1.33 (1.16-1.53) |
| Small for gestational age, OR (95% CI) | 1.11 (1.01-1.21) | 1.09 (0.99-1.20) | 0.88 (0.70-1.12) |
| Autism spectrum disorder, HR (95% CI) | 2.04 (1.80-2.32) | 1.66 (1.46-1.89) | 0.81 (0.58-1.14) |
| Attention-deficit/hyperactivity disorder, HR (95% CI) | 2.25 (2.06-2.46) | 1.60 (1.47-1.75) | 0.94 (0.73-1.22) |

Abbreviations: HR, hazard ratio; OR, odds ratio; SSRI, selective serotonin country of birth, age at childbearing, highest level of completed education,

Enkel kleine associatie met preterme bevalling (<37w)

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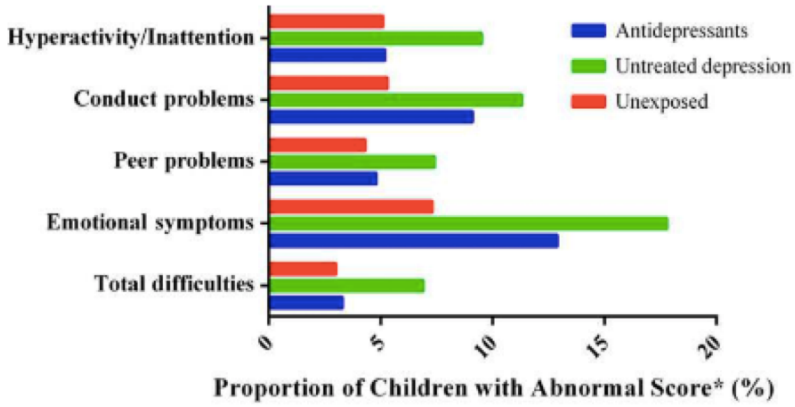
## Prenatal antidepressant exposure and child behavioural outcomes at 7 years of age: a study within the Danish National Birth Cohort

2015

LE Grzeskowiak,[a,b] JL Morrison,[c] TB Henriksen,[d] BH Bech,[e] C Obel,[d,f] J Olsen,[e] LH Pedersen[g]



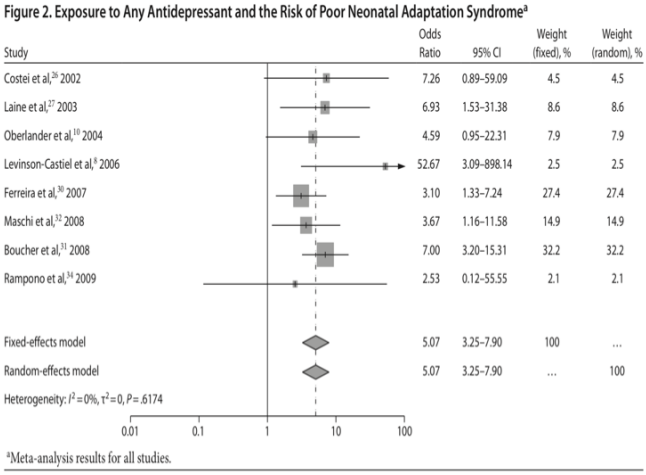

*Behavioural problems defined as scores above the 90th percentile on the parent-report version of the Strengths and Difficulties Questionnaire (SDQ)

Tot 30% in literatuur

**The Effect of Prenatal Antidepressant Exposure on Neonatal Adaptation: A Systematic Review and Meta-Analysis**

*Sophie Grigoriadis, MD, PhD, FRCPC; Emily H. VonderPorten, MPH; Lana Mamisashvili, MSW; Allison Eady, BA; George Tomlinson, PhD; Cindy-Lee Dennis, PhD; Gideon Koren, MD, FRCPC, FACMT; Meir Steiner, MD, PhD, FRCPC; Patricia Mousmanis, MD, CCFP, FCFP; Amy Cheung, MD, MSc, FRCPC; and Lori E. Ross, PhD*

Figure 2. Exposure to Any Antidepressant and the Risk of Poor Neonatal Adaptation Syndrome[a]




[a]Meta-analysis results for all studies.

Poor Neonatal adaptation syndrome (PNAS) OR= 5.07; 95% CI, 3.25–7.90; *P* < .0001)

Respiratory distress (OR = 2.20; 95% CI, 1.81–2.66; *P* < .0001)

tremors (OR = 7.89; 95% CI, 3.33–18.73; *P* < .0001)

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Clinical and Practical **Psychopharmacology**

**The Safety of Duloxetine During Pregnancy and Lactation**

*Chittaranjan Andrade, MD*

1. The use of duloxetine during pregnancy is associated with an increase in the risk of spontaneous abortion. One study[17] suggested an absolute risk of 18%, and another[18] suggested a trebled relative risk.
2. Two small studies[16,17] with a pooled sample of 441 cases found that, after duloxetine exposure during pregnancy, the risk of major fetal malformations was similar to that in the general population (2%–3%).
3. There are 2 case reports[20,21] describing PNAS after late-pregnancy exposure to duloxetine. There are also 3 case reports[14,22,23] describing a normal and uneventful perinatal course. The magnitude of the risk of PNAS with duloxetine is not known.
4. There are no data on the risk of other adverse outcomes such as preterm birth, low birth weight, persistent pulmonary hypertension of the newborn, neurodevelopmental delays, and neurobehavioral syndromes.
5. Infant exposure to duloxetine in breast milk is < 1% of the maternal weight-adjusted dose.
6. In general, from the very limited data available on the subject and with the exception of the increased risk of spontaneous abortion, there does not seem to be a signal that the use of duloxetine during pregnancy or lactation increases the risk of adverse outcomes.

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European Neuropsychopharmacology (2016) 26, 126-135

ELSEVIER www.elsevier.com/locate/euroneuro

## Mirtazapine in pregnancy and lactation - A systematic review

Mirte Smit[a], Koert M. Dolman[a], A. Honig[b,*]

- no increase in the incidence of major malformations in 334 cases exposed to mirtazapine

- low absolute and relative infant doses after exposure to mirtazapine ranging from undetectably low to 2.86%.

- No adverse effects on behavioural development were reported

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## ANTIDEPRESSIVA

SSRI
- Sertraline, citalopram, escitalopram: geen malformaties, geen miskramen, geen hypertensie, wel postpartum bloedingen
- Fluoxetine en paroxetine: malformaties? (3-7 meer/1000) en postpartum bloedingen, geen miskraam, geen hypertensie

SNRI:
- Venlafaxine: geen malformaties, miskraam?, wel hypertensie (9% vs 5%), wel preeclampsie (6% vs 2%), wel postpartum bloeding, wel preterme bevalling
- Duloxetine: geen malformaties, wel miskraam

Andere
- Mirtazapine: geen malformaties, geen miskraam, geen preeclampsie, preterme bevalling?
- Trazodone: geen malformaties, geen hypertensiie
- TCA (amitriptyline) geen malformaties (cave clomipramine), wel miskraam, wel preeclampsie, wel postpartumbloeding

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SAMENGEVAT: ANTIDEPRESSIVA

- Geen belangrijke aanwijzingen voor congenitale malformaties
- 'Klein' risico op preterme bevalling, postpartum bloeding, PPH
- risico op neonataal adaptatiesyndroom
- Geen belangrijke aanwijzingen voor negatieve lange-termijn effecten op het kind
- >SSRI (**sertraline,** citalopram**,..**) en venlafaxine, maar ook duloxetine, mirtazapine, TCA (amitriptyline),…

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# ANTIPSYCHOTICA

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## Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis

Stefan Leucht, Andrea Cipriani, Loukia Spineli, Dimitris Mavridis, Deniz Örey, Franziska Richter, Myrto Samara, Corrado Barbui, Rolf R Engel, John R Geddes, Werner Kissling, Marko Paul Stapf, Bettina Lässig, Georgia Salanti, John M Davis

Summary

Background The question of which antipsychotic drug should be preferred for the treatment of schizophrenia is

**Prolactine spiegels <25ng/ML**

…..,menstruatieproblemen,……

FGA 26-78% (Haddad & Wick, 2004)
SGA tot 48% (Bargiota, 2013)

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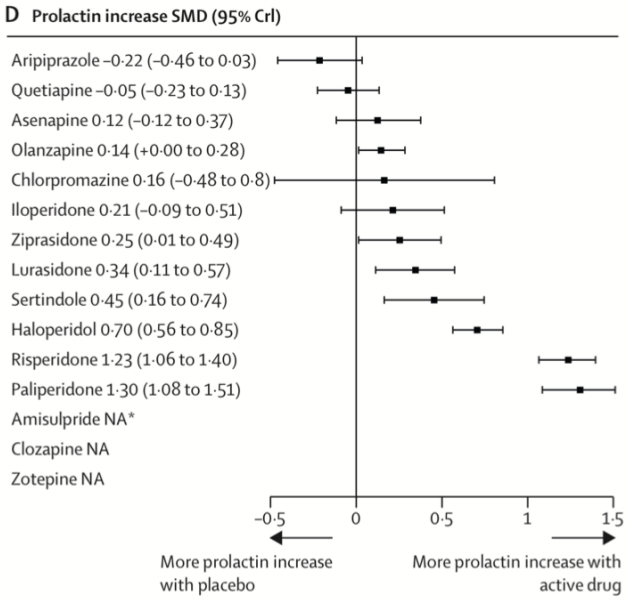



Arch Womens Ment Health (2013) 16:149–157
DOI 10.1007/s00737-013-0330-6

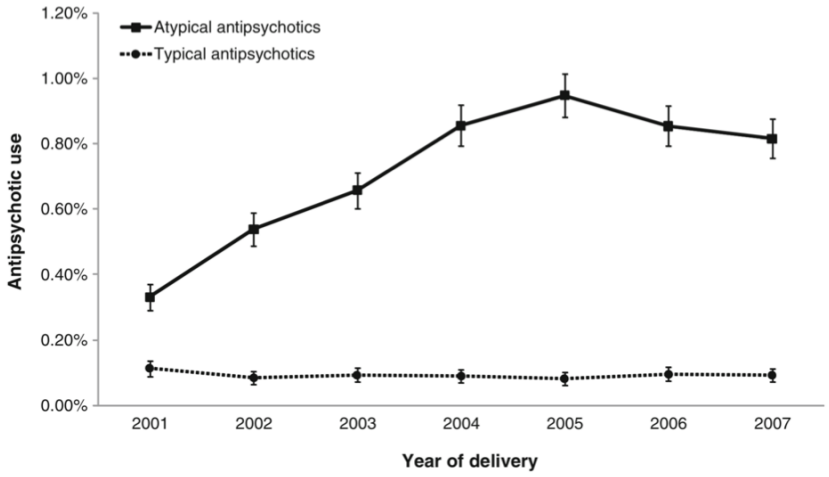
ORIGINAL ARTICLE

## Prevalence and trends in the use of antipsychotic medications during pregnancy in the U.S., 2001–2007: a population-based study of 585,615 deliveries

Sengwee Toh · Qian Li · T. Craig Cheetham · William O. Cooper ·



**Fig. 1** The prevalence of antipsychotic use from 60 days before pregnancy through delivery by year of delivery, the Medication Exposure in Pregnancy Risk Evaluation Program, 2001–2007. The proportion in a given year was calculated using the number of deliveries exposed to atypical (or typical) antipsychotics in that year as the numerator and the total number of deliveries in that year as the denominator. *Bars* represent the 95 % confidence intervals



Arch Womens Ment Health (2013) 16:149–157
DOI 10.1007/s00737-013-0330-6

ORIGINAL ARTICLE

**Prevalence and trends in the use of antipsychotic medications during pregnancy in the U.S., 2001–2007: a population-based study of 585,615 deliveries**

Sengwee Toh · Qian Li · T. Craig Cheetham · William O. Cooper ·

FDA:

depression (51 %), bipolar disorder (37 %) and schizophrenia (27 %)
>>> haloperidol and >chlorpromazine

SGA:

Depression (63 %) bipolar disorder (43 %) and schizophrenia (13 %)
quetiapine (42 %), olanzapine (32 %) and risperidone (23 %).

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## Congenital anomalies and antipsychotics (as a group) - *Coughlin et al, 2015*[1]

Meta-analysis of 13 cohort studies (6,289 exposed, 1.6 million un-exposed)

| Outcome | Odds ratio | Comments |
|---|---|---|
| Major congenital anomalies | 2.12 (CI: 1.25-3.57) | No difference between FGAs and SGAs |
| Heart defects | 2.09 (CI: 1.50–2.91) | |
| Preterm birth | 1.86 (CI:1.45-2.39) | No difference between FGAs and SGAs |
| Small for gestational age | 2.44 (CI:1.22-4.86) | No difference between FGAs and SGAs |
| Miscarriage | No association | - |
| Still birth | No association | - |

[1]Obstetrics and Gynecology, Vol 125; 1224-1235

| Confounder adjusted for | How many of the 13 studies adjusted |
|---|---|
| Smoking | 5 |
| Substance misuse | 1 for alcohol, 0 for drugs |
| Obesity | 2 |
| Diabetes | Not mentioned ! |
| Low socioeconomic status | 0 |
| Concomitant medication | 20 % used anti-epileptics<br>Antidepressant use frequent (details not stated) |
| Indication | 0 |

## Reproductive Safety of Second-Generation Antipsychotics: Current Data From the Massachusetts General Hospital National Pregnancy Registry for Atypical Antipsychotics

Lee S. Cohen, M.D., Adele C. Viguera, M.D., M.P.H., Kathryn A. McInerney, Sc.M., Marlene P. Freeman, M.D., Alexandra Z. Sosinsky, B.S., Danna Moustafa, B.S., Samantha P. Marfurt, B.S., Molly A. Kwiatkowski, B.A., Shannon K. Murphy, B.A., Adriann M. Farrell, M.A., David Chitayat, M.D., Sonia Hernández-Díaz, M.P.H., Dr.P.H.

*Am J Psychiatry 2016; 173:263–270; doi: 10.1176/appi.ajp.2015.15040506*

**TABLE 2. Odds Ratio of a Major Malformation Comparing Exposure Status With Second-Generation Antipsychotic (N=303)**

| Group | N | Prevalence | 95% CI | Odds Ratio | 95% CI |
|---|---|---|---|---|---|
| First-trimester exposure to second-generation antipsychotic (N=214) | 3 | 1.4 | 0.29–4.04 | 1.25 | 0.13–12.19 |
| Unexposed to second-generation antipsychotic (N=89) | 1 | 1.1 | 0.0–6.10 | Reference | Reference |

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JAMA Psychiatry | Original Investigation

## Antipsychotic Use in Pregnancy and the Risk for Congenital Malformations

Krista F. Huybrechts, MS, PhD; Sonia Hernández-Díaz, MD, DrPH; Elisabetta Patorno, MD, DrPH; Rishi J. Desai, PhD; Helen Mogun, MS; Sara Z. Dejene, BS; Jacqueline M. Cohen, PhD; Alice Panchaud, PhD; Lee Cohen, MD; Brian T. Bateman, MD, MSc

JAMA Psychiatry. 2016;73(9):938-946. doi:10.1001/jamapsychiatry.2016.1520
Published online August 17, 2016.

Table 3. Absolute Risk for Congenital Malformations in Women With and Without AP Exposure

| | | Any Malformation | | Cardiac Malformation | |
|---|---|---|---|---|---|
| Exposure Group | Total No. | No. of Events | Risk per 1000 Population (95% CI) | No. of Events | Risk per 1000 Population (95% CI) |
| Unexposed | 1 331 910 | 43 494 | 32.7 (32.4-33.0) | 15 405 | 11.6 (11.4-11.7) |
| Typical AP | 733 | 28 | 38.2 (26.6-54.7) | [a] | 13.6 (7.4-24.9) |
| Atypical AP | 9258 | 412 | 44.5 (40.5-48.9) | 150 | 16.2 (13.8-19.0) |
| Aripiprazole | 1756 | 75 | 42.7 (34.2-53.2) | 27 | 15.4 (10.6-22.3) |
| Olanzapine | 1394 | 59 | 42.3 (33.0-54.2) | 20 | 14.3 (9.3-22.1) |
| Quetiapine | 4221 | 182 | 43.1 (37.4-49.7) | 70 | 16.6 (13.1-20.9) |
| Risperidone | 1566 | 80 | 51.1 (41.2-63.1) | 29 | 18.5 (12.9-26.5) |
| Ziprasidone | 697 | 26 | 37.3 (25.6-54.1) | [a] | 12.9 (6.8-24.4) |

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JAMA Psychiatry | Original Investigation

Antipsychotic Use in Pregnancy and the Risk for Congenital Malformations

Krista F. Huybrechts, MS, PhD; Sonia Hernández-Díaz, MD, DrPH; Elisabetta Patorno, MD, DrPH; Rishi J. Desai, PhD; Helen Mogun, MS; Sara Z. Dejene, BS; Jacqueline M. Cohen, PhD; Alice Panchaud, PhD; Lee Cohen, MD; Brian T. Bateman, MD, MSc

JAMA Psychiatry. 2016;73(9):938-946. doi:10.1001/jamapsychiatry.2016.1520
Published online August 17, 2016.

Figure 1. Relative Risk (RR) for Congenital Malformations in Infants According to Maternal Exposure to Antipsychotics (APs)

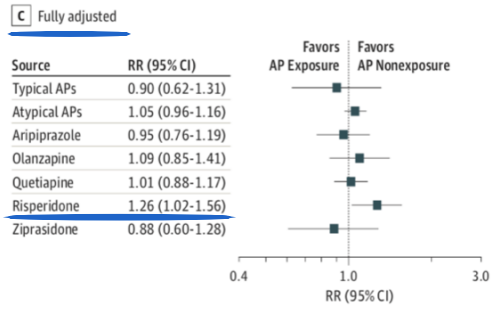
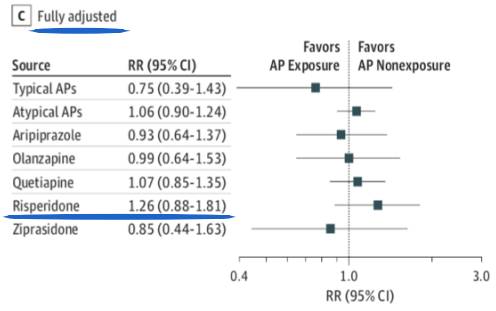



Figure 2. Relative Risk (RR) for Cardiac Malformations in Infants According to Maternal Exposure to Antipsychotics (APs)

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## Antipsychotic drug use in pregnancy: high dimensional, propensity matched, population based cohort study

Simone N Vigod,[1,2,3] Tara Gomes,[2] Andrew S Wilton,[2] Valerie H Taylor,[1,3] Joel G Ray[2,4]

the bmj | BMJ 2015;350:h2298 | doi: 10.1136/bmj.h2298

**Table 2 | Main maternal medical and perinatal outcomes in a cohort of 41 523 women who were categorised by whether they were prescribed an antipsychotic drug during pregnancy (n=1209) or not (n=40 314). Of these, 1021 antipsychotic drug users were matched 1:1 with 1021 non-users by means of a high dimensional propensity score (HDPS) algorithm**

| | Unmatched cohort | | Matched cohort | | |
|---|---|---|---|---|---|
| Outcome and use of antipsychotic medication | No (%) with outcome | Relative risk (95% CI) | No (%) with outcome | Relative risk (95% CI) | Adjusted relative risk (95% CI)* |
| **Main maternal medical outcomes** | | | | | |
| Gestational diabetes: | | | | | |
| Non-users | 2497 (6.2) | 1.00 (referent) | 62 (6.1) | 1.00 (referent) | 1.00 (referent) |
| Antipsychotic users | 93 (7.7) | 1.24 (1.01 to 1.53) | 71 (7.0) | 1.15 (0.82 to 1.61) | 1.10 (0.77 to 1.57) |
| Hypertensive disorders of pregnancy: | | | | | |
| Non-users | 1409 (3.5) | 1.00 (referent) | 42 (4.1) | 1.00 (referent) | 1.00 (referent) |
| Antipsychotic users | 63 (5.2) | 1.49 (1.16 to 1.92) | 48 (4.7) | 1.14 (0.76 to 1.73) | 1.12 (0.70 to 1.78) |
| Venous thromboembolism: | | | | | |
| Non-users | 4264(1.1) | 1.00 (referent) | 13 (1.3) | 1.00 (referent) | 1.00 (referent) |
| Antipsychotic users | 12 (1.0) | 0.95 (0.53 to 1.68) | 12 (1.2) | 0.92 (0.42 to 2.02) | 0.95 (0.40 to 2.27) |
| **Main perinatal outcomes** | | | | | |
| Preterm birth (<37 weeks gestation): | | | | | |
| Non-users | 4158 (10.3) | 1.00 (referent) | 146 (14.3) | 1.00 (referent) | 1.00 (referent) |
| Antipsychotic users | 179 (14.8) | 1.51 (1.29 to 1.78) | 148 (14.5) | 1.01 (0.81 to 1.27) | 0.99 (0.78 to 1.26) |
| Small for gestational age (birth weight <3rd centile): | | | | | |
| Non-users | 2081 (5.2) | 1.00 (referent) | 51 (5.1) | 1.00 (referent) | 1.00 (referent) |
| Antipsychotic users | 74 (6.2) | 1.20 (0.95 to 1.53) | 62 (6.1) | 1.22 (0.84 to 1.77) | 1.21 (0.81 to 1.82) |
| Large for gestational age (birth weight >97th centile): | | | | | |
| Non-users | 1029 (2.6) | 1.00 (referent) | 23 (2.3) | 1.00 (referent) | 1.00 (referent) |
| Antipsychotic users | 44 (3.7) | 1.44 (1.06 to 1.96) | 36 (3.6) | 1.64 (0.96 to 2.78) | 1.26 (0.69 to 2.29) |

*Adjusted for a prescribed selective serotonin reuptake inhibitor (SSRI), non-SSRI, mood stabiliser, or benzodiazepine during the index pregnancy.

Geen hoger risico:
- zwangerschapdiabetes
- Hypertensie
- Tromboembolisme
- Preterm bevalling
- Laag en hoog geboortegewicht

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Psychopharmacology (2013) 228:577–584
DOI 10.1007/s00213-013-3060-6

ORIGINAL INVESTIGATION

## Effects of prenatal exposure to atypical antipsychotics on postnatal development and growth of infants: a case-controlled, prospective study

Mei Peng · Keming Gao · Yiling Ding · Jianjun Ou · Joseph R. Calabrese · Renrong Wu · Jingping Zhao

**Table 2** Dosages and antipsychotics were used by mothers with schizophrenia throughout pregnancy

| Antipsychotics | Minimum dosage (mg) | Maximum dosage (mg) | Mean (mg) | SD (mg) |
|---|---|---|---|---|
| Clozapine ($n$=33) | 75.00 | 450.00 | 178.03 | 70.37 |
| Risperidone ($n$=16) | 1.00 | 4.00 | 2.06 | 0.85 |
| Sulpiride ($n$=13) | 300.00 | 600.00 | 461.54 | 76.79 |
| Olanzapine ($n$=8) | 5.0 | 10.00 | 7.81 | 2.48 |
| Quetiapine ($n$=6) | 400.00 | 600.00 | 550.00 | 83.67 |

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**Table 4** The proportion of infants with delayed development defined as below 85 standard scores of the Bayley-III in infants who have fetal exposure to antipsychotic versus those in the control group

| Variables | Exposed group ($n$=76) | Comparison group ($n$=76) | Test statistics | $P$ value |
|---|---|---|---|---|
| Cognitive scale | | | | |
| 2 months of age | 14 (18.4) | 5 (6.6) | 4.872 | 0.048 |
| 6 months of age | 9 (11.8) | 5 (6.6) | 1.259 | 0.401 |
| 12 months of age | 8 (10.5) | 6 (7.9) | 0.315 | 0.780 |
| Language scale | | | | |
| 2 months of age | 12 (15.8) | 10 (13.2) | 0.213 | 0.818 |
| 6 months of age | 10 (13.2) | 9 (11.8) | 0.060 | 1.000 |
| 12 months of age | 10 (13.2) | 9 (11.8) | 0.060 | 1.000 |
| Motor scale | | | | |
| 2 months of age | 15 (19.7) | 5 (6.6) | 5.612 | 0.029 |
| 6 months of age | 9 (11.8) | 5 (6.6) | 1.259 | 0.401 |
| 12 months of age | 8 (10.5) | 5 (6.6) | 0.757 | 0.564 |
| Social–emotional scale | | | | |
| 2 months of age | 17 (22.4) | 7 (9.2) | 4.948 | 0.044 |
| 6 months of age | 15 (19.7) | 8 (10.5) | 2.510 | 0.174 |
| 12 months of age | 12 (15.8) | 6 (7.9) | 2.269 | 0.209 |
| Adaptive behavior scale | | | | |
| 2 months of age | 24 (31.6) | 8 (10.5) | 10.133 | 0.002 |
| 6 months of age | 13 (17.1) | 6 (7.9) | 2.947 | 0.140 |
| 12 months of age | 10 (13.2) | 5 (6.6) | 1.921 | 0.185 |

Data were expressed as no. (percent)

Geen verschil apgar en geboortegewicht

## SAMENGEVAT: ANTIPSYCHOTICA

- Geen aanwijzingen dat antipsychotica (**olanzapine, haloperidol**,…) majeur teratogeen (met uitzondering van risperidone?)
- ??? preterme bevalling, zwangerschapsdiabetes
- Poor neonatal adaptation syndroom (15-27%)
- Geen aanwijzingen voor lange-termijn effecten op psychomotore ontwikkeling (cave clozapine)

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# LITHIUM

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Associatie met Ebstein anomalie: x400?

**Rechter ventrikel outflow defect**:
Lithium: **0.6%**
Unexposed: **0.18%**

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Lithium Use in Pregnancy and the Risk of Cardiac Malformations

Elisabetta Patorno, M.D., Dr.P.H., Krista F. Huybrechts, Ph.D., Brian T. Bateman, M.D., Jacqueline M. Cohen, Ph.D., Rishi J. Desai, Ph.D., Helen Mogun, M.S., Lee S. Cohen, M.D., and Sonia Hernandez-Diaz, M.D., Dr.P.H.

N Engl J Med 2017;376:2245-54.

Table 2. Absolute and Relative Risk of Cardiac, Noncardiac, and Overall Malformations among Infants Exposed to Lithium during the First Trimester as Compared with Lamotrigine-Exposed or Unexposed Infants.*

| Variable | No Exposure to Lithium or Lamotrigine | Exposure to Lamotrigine | Exposure to Lithium |
|---|---|---|---|
| No. of pregnancies | 1,322,955 | 1945 | 663 |
| Cardiac malformations | | | |
| Events | 15,251 | 27 | 16 |
| Prevalence per 100 births | 1.15 | 1.39 | 2.41 |
| Unadjusted risk ratio (95% CI) | Reference | 1.20 (0.83–1.75) | 2.09 (1.29–3.40) |
| Propensity-score–adjusted risk ratio (95% CI) | Reference | 0.89 (0.61–1.30) | 1.65 (1.02–2.68) |
| Unadjusted risk ratio (95% CI) | — | Reference | 1.74 (0.94–3.21) |
| Propensity-score–adjusted risk ratio (95% CI) | — | Reference | 2.25 (1.17–4.34) |
| Noncardiac malformations | | | |
| Events | 27,816 | 49 | 22 |
| Prevalence per 100 births | 2.10 | 2.52 | 3.32 |
| Unadjusted risk ratio (95% CI) | Reference | 1.20 (0.91–1.58) | 1.58 (1.05–2.38) |
| Propensity-score–adjusted risk ratio (95% CI) | Reference | 0.90 (0.68–1.18) | 1.22 (0.81–1.84) |
| Unadjusted risk ratio (95% CI) | — | Reference | 1.32 (0.80–2.16) |
| Propensity-score–adjusted risk ratio (95% CI) | — | Reference | 1.63 (0.96–2.78) |
| Overall malformations | | | |
| Events | 43,067 | 76 | 38 |
| Prevalence per 100 births | 3.26 | 3.91 | 5.73 |
| Unadjusted risk ratio (95% CI) | Reference | 1.20 (0.96–1.50) | 1.76 (1.29–2.40) |
| Propensity-score–adjusted risk ratio (95% CI) | Reference | 0.90 (0.72–1.12) | 1.37 (1.01–1.87) |
| Unadjusted risk ratio (95% CI) | — | Reference | 1.47 (1.00–2.14) |
| Propensity-score–adjusted risk ratio (95% CI) | — | Reference | 1.85 (1.23–2.78) |

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**Dosis effect!: <600; 600-900, >900**

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Lithium Use in Pregnancy and the Risk of Cardiac Malformations

Elisabetta Patorno, M.D., Dr.P.H., Krista F. Huybrechts, Ph.D., Brian T. Bateman, M.D., Jacqueline M. Cohen, Ph.D., Rishi J. Desai, Ph.D., Helen Mogun, M.S., Lee S. Cohen, M.D., and Sonia Hernandez-Diaz, M.D., Dr.P.H.

N Engl J Med 2017;376:2245-54.

| Exposure Group | No. of Pregnancies | No. of Events | Prevalence per 100 Births | Propensity-Score-Adjusted Risk Ratio (95% CI) |
|---|---|---|---|---|
| No exposure | 1,322,955 | 15,251 | 1.15 | Reference |
| Exposure to lithium | | | | |
| ≤600 mg/day | 305 | <11 | 1.64 | 1.11 (0.46–2.64) |
| 601–900 mg/day | 235 | <11 | 2.13 | 1.60 (0.67–3.80) |
| >900 mg/day | 123 | <11 | 4.88 | 3.22 (1.47–7.02) |
| Exposure to lamotrigine | | | | |
| ≤100 mg/day | 904 | <11 | 1.11 | 0.70 (0.38–1.30) |
| 101–200 mg/day | 620 | <11 | 1.61 | 1.00 (0.54–1.86) |
| >200 mg/day | 421 | <11 | 1.66 | 1.02 (0.49–2.13) |

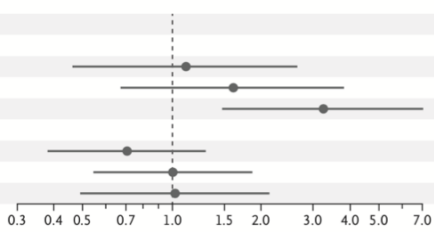


Figure 2. Absolute and Relative Risk of Cardiac Malformations among Lithium-Exposed and Lamotrigine-Exposed Infants as Compared with Unexposed Infants, Stratified According to the Mother's Dose of the Drug.

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# Benzodiazepines en Z-drugs

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# Effects of Commonly Used Benzodiazepines on the Fetus, the Neonate, and the Nursing Infant

Mohammad Masud Iqbal, M.D., M.P.H.
Tanveer Sobhan, M.D., M.P.H.
Thad Ryals, M.D.

(*Psychiatric Services* 53:39–49, 2002)

- Withdrawal syndrome and
- Floppy infant syndrome
- Cleft palate: 6.3% vs 1.1% controls (Diazepam, Aarskog, Lancet 1975)

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***Table 1***

Classifications, dosages, and effects of benzodiazepines during pregnancy and lactation

| Drug | Half-life[a] | FDA pregnancy category[b] | Important active major metabolites and metabolic pathway | Approved daily dosage range[c] | Possible effects on fetus during pregnancy and on infant during lactation |
|---|---|---|---|---|---|
| Diazepam | Long | D | Desmethyldiazepam, 3 hydroxydiazepam, oxazepam<br>Metabolic pathway: oxidation | 4–40 mg | Pregnancy: Oral clefts, central nervous system anomalies, ocular hypertelorism, absence of both thumbs, dislocation of head of right radius, polycystic kidney, periauricular tags, cardiovascular anomalies, polydactyly, hemangioma, neonatal withdrawal syndrome, floppy infant syndrome, low birth weight and head circumference, mental retardation, decreased fetal movement, temporary loss of beat-to-beat variability on fetal heart tracings, jaundice, kernicterus<br>Lactation: Lethargy, sedation, weight loss |

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***Table 1***

Classifications, dosages, and effects of benzodiazepines during pregnancy and lactation

| Drug | Half-life[a] | FDA pregnancy category[b] | Important active major metabolites and metabolic pathway | Approved daily dosage range[c] | Possible effects on fetus during pregnancy and on infant during lactation |
|---|---|---|---|---|---|
| Clonazepam | Intermediate | C | None<br>Metabolic pathway: reduction | 1–6 mg | Pregnancy: Congenital heart disease, ventral septal defect, hip dislocation, uteropelvic junction obstruction, bilateral inguinal hernia, undescended testicle, paralytic ileus of the small bowel, cyanosis, lethargy, hypotonia, apnea<br>Lactation: Apnea, cyanosis, hypotonia, excessive periodic breathing, central nervous system depression |
| Lorazepam | Intermediate | D | None<br>Metabolic pathway: conjugation | .5–10 mg | Pregnancy: Anal atresia and neonatal withdrawal symptoms, such as low Apgar scores, depressed respiration, hypothermia, poor suckling, jaundice, sleep disturbances associated with intravenous use<br>Lactation: Effects unknown |
| Alprazolam | Short | D | Alpha hydroxyalprazolam<br>Metabolic pathway: oxidation | .75–4 mg (anxiety), 1.5–10 mg (panic) | Pregnancy: Cleft lip, inguinal hernia, hypospadias, cryptorchidism, tracheoesophageal fistula, patent ductus arteriosus, microcephaly, strabismus, congenital hip dislocation, fused lacrimal duct, Down's syndrome, cat's eye with Pierre Robin syndrome, pyloric stenosis, umbilical hernia, ankle inversion, lipomeningocele, neonatal withdrawal syndrome<br>Lactation: Neonatal withdrawal syndrome, mild drowsiness |

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PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2007; **16**: 1203–1210
Published online 26 September 2007 in Wiley InterScience (www.interscience.wiley.com) **DOI**: 10.1002/pds.1457

ORIGINAL REPORT

## Use of benzodiazepines and benzodiazepine receptor agonists during pregnancy: neonatal outcome and congenital malformations[1]

Birgitta Norstedt Wikner MD[1]*, Carl-Olav Stiller MD, PhD[1], Ulf Bergman MD, PhD[2], Charlotte Asker MD, PhD[1] and Bengt Källén MD, PhD[3]

Table 2. Some characteristics of infants after maternal use of BZD and/or HBRA

| Outcome | Early exposure | | | | Late exposure | | |
|---|---|---|---|---|---|---|---|
| | Number in population | Number exposed | OR | 95%CI | Number exposed | OR | 95%CI |
| Singleton births | | | | | | | |
| Preterm birth (<37 weeks) | 42875 | 161 | 1.48 | 1.26–1.75 | 50 | 2.57 | 1.92–3.43 |
| Low birth weight (<2500 g) | 27429 | 103 | 1.30 | 1.06–1.59 | 28 | 1.89 | 1.29–2.76 |
| Small for gestational age (SGA) | 18260 | 64 | 1.12 | 0.87–1.44 | 14 | 1.39 | 0.80–2.40 |
| Low Agar score (<7 at 5 minutes) | 11761 | 36 | 1.25 | 0.90–1.75 | 11 | 2.02 | 1.13–3.65 |
| Low Apgar score, term infants | 8815 | 22 | 1.09 | 0.72–1.67 | 8 | 2.20 | 1.11–4.39 |
| All infants | | | | | | | |
| Respiratory problems | 38638 | 108 | 1.19 | 0.98–1.45 | 41 | 2.21 | 1.62–3.02 |
| Neonatal jaundice | 31735 | 86 | 1.16 | 0.93–1.44 | 21 | 1.32 | 0.85–2.04 |
| Hypoglycaemia | 20770 | 77 | 1.37 | 1.09–1.72 | 20 | 1.50 | 0.96–2.35 |
| Neonatal convulsions | 1386 | 5 | 1.35 | 0.44–3.15* | 1 | — | |
| CNS problems | 4610 | 18 | 1.51 | 0.94–2.45 | 4 | 1.53 | 0.42–3.92* |

Odds ratios (OR) with 95% confidence intervals (95%CI), adjusted for year of birth, maternal age, parity, smoking and years of involuntary

MEER:
- preterme bevalling
- Laag geboortegewicht
- neonatale problemen

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Meer GI malformaties (cave 7 personen)

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2007; 16: 1203–1210
Published online 26 September 2007 in Wiley InterScience (www.interscience.wiley.com) DOI: 10.1002/pds.1457

ORIGINAL REPORT

## Use of benzodiazepines and benzodiazepine receptor agonists during pregnancy: neonatal outcome and congenital malformations†

Birgitta Norstedt Wikner MD[1]*, Carl-Olav Stiller MD, PhD[1], Ulf Bergman MD, PhD[2], Charlotte Asker MD, PhD[1] and Bengt Källén MD, PhD[3]



Table 4. Observed (Obs) and expected (Exp) numbers of some specific types of congenital malformations (sometimes associated with other malformations) after exposure in early pregnancy for BZD or HBRA

| Congenital malformation | Number among exposed infants | Number in population | Expected number | RR | 95%CI |
|---|---|---|---|---|---|
| Any CNS defect | 1 | 708 | 0.64 | 1.56 | 0.04–8.71 |
| Orofacial cleft | 2 | 2375 | 5.23 | 0.38 | 0.05–1.38 |
| Cardiovascular defect | 19* | 11257 | 25.96 | 0.73 | 0.46–1.19 |
| Oesophageal, anal, or small gut atresia | 7 | 1179 | 2.66 | 2.63 | 1.01–5.42 |
| Pylorostenosis | 7 | 693 | 1.84 | 3.80 | 1.53–7.84 |
| Hypospadias | 10 | 3163 | 6.51 | 1.52 | 0.73–2.79 |
| Severe kidney defect | 1 | 675 | 1.74 | 0.57 | 0.01–3.20 |
| Limb reduction defect | 2 | 673 | 1.45 | 1.38 | 0.17–4.98 |
| Body wall defect | 1 | 316 | 0.71 | 1.41 | 0.04–3.85 |

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# ANTI-EPILEPTICA

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JAMA Clinical Evidence Synopsis

## Maternal Use of Antiepileptic Agents During Pregnancy and Major Congenital Malformations in Children

Rebecca L. Bromley, PhD; Jennifer Weston, CPsychol; Anthony G. Marson, MB, ChB, MD

JAMA November 7, 2017 Volume 318, Number 17

Table. Absolute Rates and Risk Differences for Major Congenital Malformation Rates According to Antiepileptic Drug (AED) Therapy

| AED Comparison[a] | | | Drug 1 | | Drug 2 | | | |
|---|---|---|---|---|---|---|---|---|
| Drug 1 | Drug 2 | No. of Studies | No. of Children | No. of Malformations | No. of Children | No. of Malformations | Risk Ratio (95% CI)[b] | Absolute Risk Difference (95% CI)[b] |
| Carbamazepine | Valproate | 25 | 4549 | 167 | 2529 | 229 | 0.41 (0.34 to 0.50) | -0.05 (-0.07 to -0.04) |
| Carbamazepine | Levetiracetam | 3 | 3051 | 92 | 817 | 14 | 1.84 (1.03 to 3.29) | 0.01 (0 to 0.02) |
| Carbamazepine | Lamotrigine | 7 | 3385 | 108 | 4164 | 94 | 1.34 (1.01 to 1.76) | 0.01 (0 to 0.02) |
| Valproate | Gabapentin | 3 | 1814 | 149 | 190 | 2 | 6.21 (1.91 to 20.23) | 0.08 (0.05 to 0.11) |
| Valproate | Levetiracetam | 3 | 1814 | 149 | 817 | 14 | 5.82 (3.13 to 10.81) | 0.07 (0.05 to 0.09) |
| Valproate | Lamotrigine | 7 | 2021 | 174 | 4164 | 94 | 3.56 (2.77 to 4.58) | 0.06 (0.05 to 0.07) |
| Valproate | Topiramate | 3 | 1814 | 149 | 473 | 19 | 2.35 (1.40 to 3.95) | 0.05 (0.03 to 0.08) |
| Valproate | Oxcarbazepine | 4 | 676 | 74 | 238 | 5 | 3.71 (1.65 to 8.33) | 0.08 (0.04 to 0.11) |
| Valproate | Phenobarbital | 20 | 1137 | 128 | 626 | 38 | 1.59 (1.11 to 2.29) | 0.04 (0.01 to 0.08) |
| Valproate | Phenytoin | 21 | 2319 | 212 | 1137 | 55 | 2.00 (1.48 to 2.71) | 0.05 (0.03 to 0.08) |
| Gabapentin | Phenobarbital | 2 | 159 | 1 | 204 | 11 | 0.12 (0.02 to 0.96) | -0.05 (-0.08 to -0.01) |
| Levetiracetam | Phenobarbital | 2 | 513 | 12 | 204 | 11 | 0.43 (0.20 to 0.96) | -0.03 (-0.06 to 0.01) |
| Lamotrigine | Phenobarbital | 4 | 1959 | 44 | 282 | 17 | 0.32 (0.17 to 0.61) | -0.04 (-0.07 to -0.01) |
| Lamotrigine | Phenytoin | 5 | 4082 | 94 | 624 | 25 | 0.53 (0.34 to 0.84) | -0.02 (-0.04 to 0) |
| Levetiracetam[c] | Phenytoin[c] | 3 | 817 | 14 | 566 | 21 | 0.49 (0.26 to 0.92) | -0.02 (-0.04 to 0) |
| Levetiracetam | Topiramate | 3 | 817 | 14 | 473 | 19 | 0.50 (0.26 to 0.97) | -0.02 (-0.04 to 0) |
| Lamotrigine | Topiramate | 3 | 3975 | 93 | 473 | 19 | 0.56 (0.34 to 0.94) | -0.02 (-0.04 to 0) |

**Valproate**: the highest prevalence of major congenital malformation: 10.93% [95% CI, 8.91%-13.13%]; 235 of 2565 children).

**Lamotrigine:** 2.31% major congenital malformations [95% CI, 1.87%-2.78%])

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PLOS ONE

RESEARCH ARTICLE

## Congenital Anomalies in Children of Mothers Taking Antiepileptic Drugs with and without Periconceptional High Dose Folic Acid Use: A Population-Based Cohort Study

Lu Bian[1], Kate M. Fleming[1], Pat Doyle[2], Liam Smeeth[2], Richard B. Hubbard[1], Linda Flaschi[3], Laila J. Tata[1]*

Table 2. Absolute risks (per 10,000 children) of major congenital anomalies in children according to their mothers' prescriptions of antiepileptic drugs in pregnancy*.

| | No AEDs in pregnancy | | AEDs in the 1st trimester | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Overall | | Monotherapy | | Polytherapy[a] | |
| | n = 257,153 | | n = 1,259 | | n = 1,032 | | n = 227 | |
| | n | n/10,000 | n | n/10,000 | n | n/10,000 | n | n/10,000 |
| Any major anomaly | 6,922 | 269 | 60 | 476 | 44 | 426 | 16 | 705 |
| Heart | 2,041 | 79 | 25 | 198 | 20 | 194 | 5 | 220 |
| Limb | 1,263 | 49 | 10 | 79 | 7 | 68 | 3 | 132 |
| Genital system | 1,023 | 40 | 11 | 87 | 7 | 68 | 4 | 176 |
| Nervous system | 367 | 14 | 4 | 32 | 3 | 29 | 1 | 44 |
| Other anomalies[b] | 2,872 | 112 | 17 | 135 | 14 | 136 | 4 | 176 |

*Results for 179 children born to women with AEDs only in the 2nd or 3rd trimester, of which 5 had major congenital anomalies, are presented in the text only;

[a] more than one type of antiepileptic drug was prescribed;

[b] All other major congenital anomalies not classified as heart, lim

AEDs = antiepileptic drugs

**>X2**

Hartafwijkingen, facial cleft, spina bifida

Table 4. Absolute risks (per 10,000 children) of major congenital anomalies in children according to type of antiepileptic drug in the 1st trimester of pregnancy.

| | Individual types of AEDs in the 1st trimester of pregnancy | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Carbamazepine | | Sodium valproate | | Other older AEDs[a] combined | | Lamotrigine | | Other newer AEDs[b] combined | |
| | n = 450 | | n = 291 | | n = 155 | | n = 389 | | n = 217 | |
| | n | n/10,000 | n | n/10,000 | n | n/10,000 | n | n/10,000 | n | n/10,000 |
| Any major anomaly | 19 | 422 | 20 | 687 | 11 | 710 | 20 | 514 | 8 | 369 |
| Heart | 8 | 178 | 6 | 206 | 5 | 323 | 9 | 231 | 2 | 92 |
| Limb | 2 | 44 | 5 | 172 | 1 | 65 | 4 | 103 | 0 | - |
| Genital system | 5 | 111 | 4 | 137 | 3 | 194 | 2 | 51 | 3 | 138 |
| Nervous system | 2 | 44 | 3 | 103 | 0 | - | 1 | 26 | 0 | - |
| Other anomalies[c] | 5 | 111 | 4 | 137 | 4 | 258 | 5 | 129 | 4 | 184 |

[a] phenytoin, clonazepam, clobazam, phenobarbital, ethosuximide, or primidone;

[b] gabapentin, levetiracetam, pregabalin, topiramate, vigabatrin, zonisamide, or lacosamide;

[c] All other major congenital anomalies not classified as heart, limb, genital system, or nervous system;

AEDs = antiepileptic drugs

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BMJ Open **Comparative safety of antiepileptic drugs for neurological development in children exposed during pregnancy and breast feeding: a systematic review and network meta-analysis**

Areti Angeliki Veroniki,[1] Patricia Rios,[1] Elise Cogo,[1] Sharon E Straus,[1,2]

**cognitive developmental delay**
valproate (OR=7.40, 95% credible interval (CrI) 3.00 to 18.46)

**developing autism:** **<12y**
oxcarbazepine (OR 13.51, CrI 1.28 to 221.40)
valproate (OR 17.29, 95% CrI 2.40 to 217.60)
lamotrigine (OR 8.88, CrI 1.28 to112.00)
lamotrigine+valproate (OR 132.70, CrI 7.41 to 3851.00)

**psychomotor developmental delay**
valproate (OR 4.16, CrI 2.04 to 8.75)
carbamazepine+phenobarbital+valproate (OR 19.12, CrI 1.49 to 337.50)

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*BMJ* 2017;358:j4426 doi: 10.1136/bmj.j4426 (Published 2017 September 22) 

NEWS

Check for updates

## Women still not being told about pregnancy risks of valproate

Jacqui Wise

Current advice is that valproate should not be used by female children and adolescents, women of childbearing potential, and pregnant women unless other treatments are ineffective or not tolerated. Women of childbearing potential must use effective contraception while taking the drug.

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## ALGEMENE PRINCIPES (OFF-LABEL VOORSCHRIJVEN)

- Rekeninghouden met
  - Mogelijke risico's van niet behandeling van psychiatrische stoornissen
  - Afwegen voordelen en nadelen
  - Risico op herval bij verandering of stop medicatie
  - Ernst van vorige episodes, respons op vroegere behandelingen, voorkeur van de vrouw

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## ALGEMENE PRINCIPES (OFF-LABEL VOORSCHRIJVEN)

- **Mogelijke ZW**:
  - bespreek ZW en vermijd onveilige medicatie (bv valproaat)
- **Als psychofarmaca en ZW wens**
  - Enkel stop psychofarmaca bij stabiliteit en laag risico op herval
  - Vermijdt stop psychofarmaca bij ernstige stoornis en groot risico op herval, evt switch naar meer veiligere medicatie te overwegen
- **Nieuwe psychiatrische stoornis bij ZW**
  - Vermijdt medicatie in eerste trimester behalve als voordelen groter dan nadelen
  - Als niet-medicamenteuze behandeling niet effectief of adequaat, psychofarmaca aan laagste dosis
- **Als psychofarmaca en ZW**
  - Vermijdt stop psychofarmaca bij ernstige stoornis en groot risico op herval
  - Overweeg continuering psychofarmaca ipv switch wegens risico op herval

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## ALGEMENE PRINCIPES (OFF-LABEL VOORSCHRIJVEN)

- Steeds informed consent
- Laagst mogelijke effectieve dosis
- Gebruik meest veilige medicatie
- Vermijdt polyfarmacie
- Pas dosissen aan tijdens ZW
- Overweeg doorverwijzing naar gespecialiseerde perinale GGZ/ monitoring van ZW
- Adequate foetale screening tijdens ZW
- Informeer verloskundige over gebruik van psychofarmaca
- Monitoring van de neonaat

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## NEUROLEPTICA (NICE)

- If a pregnant woman is stable on an antipsychotic and likely to relapse without medication, **advise her to continue**
- Advise pregnant women taking antipsychotic medication about diet and **monitor for excessive weight gain**
- week 24-28: **oral glucose tolerance test**
- **Do not offer depot antipsychotics** to a woman who is planning a pregnancy, pregnant or considering breastfeeding, unless she is responding well to a depot and has a previous history of non-adherence with oral medication.

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ANTI-EPILEPTICA (NICE)

- Foliumzuur 5mg/d
- Clearance of lamotrigine stijgt tijdens ZW en daalt postpartum

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LITHIUM (NICE)

- High resolutie echo op 6 en 18 weken
- Maandelijkse spiegelcontrole lithium (daling tgv gestegen waterV) en wekelijks vanaf week 36
- Stop lithium bij start arbeid en controleer bloedspiegel 12 uur na laatste inname
- Na bevalling. start pre ZW dosissen
- Neonatale goitre, hypotonie, lethargie en cardiale arithmieën zijn mogelijk

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**Postpartum psychose/manie**

TREATMENT IN PSYCHIATRY

Treatment of Psychosis and Mania in the Postpartum Period

Veerle Bergink, M.D., Ph.D., Karin M. Burgerhout, M.D., Katheljne M. Koorengevel, M.D., Ph.D., Astrid M. Kamperman, M.Sc., Ph.D., Witte J. Hoogendijk, M.D., Ph.D., Mijke P. Lambregtse-van den Berg, M.D., Ph.D., Steven A. Kushner, M.D., Ph.D.

Step 1. lorazepam at bedtime for 3 days.
Step 2. haloperidol at 2–6 mg/day of atypical antipsychotic
Step 3.After 2 weeks adjunctive lithium (plasma level: 0.8–1.2 mmol/L).
Step 4. after 12 weeks ECT

Maintenance Treatment
- antipsychotic monotherapy of lithium (0.6–0.8 mmol/L) until 9 months postpartum

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**98.4%: complete remission within the first three steps**

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This article addresses the Core Competency of *Practice-Based Learning and Improvement*

REVIEWS AND OVERVIEWS
Evidence-Based Psychiatric Treatment

Postpartum Psychosis: Madness, Mania, and Melancholia in Motherhood

Veerle Bergink, M.D., Ph.D., Natalie Rasgon, M.D., Ph.D., Katherine L. Wisner, M.D., M.S.

**For women with an isolated episode of postpartum psychosis (20-50%)**:
Initiate pharmacologic prophylaxis, preferably with **lithium, immediately after delivery** for relapse prevention.

**For women with bipolar disorder:**
consider continuation of **prophylactic lithium during pregnancy.**
prophylactic efficacy of lamotrigine, olanzapine, quetiapine, and risperidone are scarce.

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FACULTEIT GENEESKUNDE EN GEZONDHEIDSWETENSCHAPPEN

**Perinatale raadpleging Verloskunde: Dienst Psychiatrie, UZ Gent (09/332.43.95)**

Prof. dr. Gilbert Lemmens
Mevr. Rita Van Damme

**Moeder-baby eenheid, Karus, Campus Gent (09/222.58.94)**

Dr. Caroline Vogels
Heer Klaas Bauters

**Multidisciplinair overleg, Perinatale werkgroep**

Prof. dr. Gilbert Lemmens
Mevr. Rita Van Damme

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