Maternal, Fetal, and Child Outcomes of Mental Health Treatments in Women: A Meta-Analysis of Pharmacotherapy

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Objective: The authors systematically reviewed evidence on pharmacotherapy for perinatal mental health disorders.

Methods: The authors searched for studies of pregnant, postpartum, or reproductive-age women with mental health disorders treated with pharmacotherapy in MEDLINE, EMBASE, PsycINFO, the Cochrane Library, and trial registries from database inception through June 5, 2020 and surveilled literature through March 2, 2021. Outcomes included symptoms; functional capacity; quality of life; suicidal events; death; and maternal, fetal, infant, or child adverse events.

Results: 164 studies were included. Regarding benefits, brexanolone for third-trimester or postpartum depression onset may be associated with improved depressive symptoms at 30 days when compared with placebo. Sertraline for postpartum depression may be associated with improved response, remission, and depressive symptoms when compared with placebo. Discontinuing mood stabilizers during pregnancy may be associated with

increased recurrence of mood episodes for bipolar disorder. Regarding adverse events, most studies were observational and unable to fully account for confounding. Evidence on congenital and cardiac anomalies for treatment compared with no treatment was inconclusive. Brexanolone for depression onset in the third trimester or the postpartum period may be associated with risk of sedation or somnolence, leading to dose interruption or reduction when compared with placebo.

Conclusions: Evidence from few studies supports the use of pharmacotherapy for perinatal mental health disorders. Although many studies report on adverse events, they could not rule out underlying disease severity as the cause of the association between exposures and adverse events. Patients and clinicians need to make informed, collaborative decisions on treatment choices.

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Untreated mental health disorders in perinatal (pregnant and postpartum, including breastfeeding) women can have devasting sequelae. Pregnancy-associated suicide kills more women than either hemorrhage or preeclampsia (1). Depressive symptoms are associated with reduced child safety, increased harsh punishment, impaired development of infant emotional regulation and attachment, and greater risk of child psychiatric disease (2–6). Some psychotropic medications that can improve outcomes may be accompanied by potential adverse events specific to pregnancy, lactation, and males and females with reproductive potential, as laid out in FDA prescription labels (7). For women who are pregnant or planning pregnancy, a critical question for women and their clinical providers is whether the potential maternal and fetal benefits of treating psychiatric illness with pharmacologic interventions

HIGHLIGHTS

- Few studies have been conducted in pregnant and postpartum women on the benefits of pharmacotherapy; many studies report on harms but are of low quality

- Brexanolone probably improves depressive symptoms; it may increase the risk of sedation or somnolence, leading to dose interruption or reduction. Sertraline may improve response, remission, and depression and anxiety symptoms. Mood stabilizers may reduce recurrence and increase time to recurrence

- Although associations may exist between psychotropic medications and adverse events, causality cannot be inferred. The paucity of evidence does not mean that pharmacotherapy is not beneficial, nor that harms do not exist; rather, it underscores the absence of high-quality research

outweigh the potential harms. This challenging benefit-harm tradeoff is further complicated by the potential for underlying mental health disorders to serve as confounders. Underlying mental health disorders result in the use of psychotropic medications. Underlying mental health disorders may also result in harms regardless of exposure to medications. Uncertainty in the management of maternal mental health disorders (8–10) points to the need for a systematic review to help clarify the balance of benefits and harms from psychotropic drugs for these disorders.

METHODS

This review followed an a priori protocol (11) and adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (12) statement. None of the authors reported financial conflicts of interest.

Scope of the Review
Figure 1 shows the key questions (KQs) guiding the review. Detailed methods (searches, list of excluded studies, approach to risk of bias, grading, and synthesis), evidence tables, results (including detailed results for all outcomes rated as insufficient), and meta-analyses are available in the full evidence report at https://doi.org/10.23970/AHRQEPCCER236.

Data Sources and Searches
PubMed, the Cochrane Library, PsycInfo, and EMBASE were searched for English language articles published from database inception through June 5, 2020. ClinicalTrials.gov, Cochrane Register of Controlled Trials, and the World Health Organization International Clinical Trials Registry Platform were also searched. Additionally, reference lists of pertinent articles and studies suggested by reviewers were searched. Ongoing surveillance of article alerts and targeted journal searches through March 2, 2021 identified no major studies published since the last search.

Inclusion and Exclusion Criteria
For benefits (KQ 1 and KQ 2), pregnant or postpartum women were included; for harms (KQ 3 and KQ 4), pregnant, postpartum, or reproductive-age women were included. Because benefits are disorder-specific but harms may not be, the review's population inclusion criteria were more inclusive for harms questions than benefits questions. An anxiety, depression, bipolar disorder, or schizophrenia diagnosis was required for benefits questions but not for harms questions. All U.S. Food and Drug Administration (FDA)-approved drugs for mental health disorders and off-label drugs used for mental health disorders were eligible. Outcomes included maternal benefits (symptoms, functional capacity, quality of life, delivery mode, breastfeeding, weight change, change in suicidal events); maternal harms (miscarriage, abruption, preterm labor/preterm birth, preeclampsia, gestational hypertensive disorders, gestational diabetes mellitus); and fetal, infant, or child harms (preterm birth, small or large for gestational age, congenital anomalies, Apgar score, withdrawal, respiratory distress, neonatal intensive care unit time, persistent pulmonary hypertension, delayed development, child mental health disorders, and death). Given limited trial evidence, all designs with a comparison arm were eligible (randomized controlled trials [RCTs], nonrandomized clinical trials, cohorts with comparisons, and case-controls). However, because of the lack of controls for potential confounding in observational studies, the review cataloged all evidence but focused synthesis on more robust evidence. Specifically, for benefits/harms (KQ 1 and KQ 3, comparing treatment with no treatment), the

FIGURE 1. Key questions: Maternal, fetal, and child outcomes of mental health treatments in women

1. Among pregnant and postpartum women, what is the effectiveness of pharmacologic interventions on maternal outcomes
    a. Among those with a new or preexisting anxiety disorder?
    b. Among those with a new or preexisting depressive disorder?
    c. Among those with a new or preexisting bipolar disorder?
    d. Among those with new or preexisting schizophrenia?
2. Among pregnant and postpartum women, what is the comparative effectiveness of pharmacologic interventions on maternal outcomes
    a. Among those with a new or preexisting anxiety disorder?
    b. Among those with a new or preexisting depressive disorder?
    c. Among those with a new or preexisting bipolar disorder?
    d. Among those with new or preexisting schizophrenia?
3. Among reproductive-age women with any mental health disorder, what are the maternal and fetal harms associated with pharmacologic interventions for a mental health disorder during preconception, pregnancy, and postpartum?
4. Among reproductive-age women with any mental health disorder, what are the comparative maternal and fetal harms of pharmacologic interventions for a mental health disorder during preconception, pregnancy, and postpartum?

synthesis was limited to studies controlling for confounding. For comparative benefits/harms (KQ 2 and KQ 4), the synthesis included studies that did not attempt to control for confounding, but these studies were downgraded for risk of bias.

Study Selection

Two investigators independently reviewed titles, abstracts, and full-text articles using prespecified inclusion criteria (Table S1 in the online supplement); conflicts were resolved by discussion or by a third reviewer. The Supplement also includes a complete list of all excluded studies along with reasons for exclusion.

Data Extraction and Quality Assessment

For each included study, one reviewer abstracted relevant study characteristics and outcomes into a structured form. A second reviewer checked all data for completeness and accuracy. Two senior reviewers independently assessed each study's methodological quality using predefined criteria using the ROBINS-I (13) tool for observational studies and the Cochrane ROB 2.0 (14) tool for RCTs; a third senior reviewer helped resolve conflicts.

Data Synthesis and Analysis

Data were synthesized in tabular and narrative formats. When at least three similar studies were available, a quantitative synthesis was performed using random effects models with the DerSimonian and Laird inverse-variance weighted method in Comprehensive Meta-Analysis (Version 3.3) software (15) to generate pooled estimates of the absolute risk difference (ARD) and the RR (16).

The strength of evidence (SOE) was assessed through the Grading of Recommendations Assessment, Development and Evaluation working group guidance (17), and guidance established for the Evidence-based Practice Center Program (18). Based on the assessment of study limitations, directness, consistency, precision, and reporting bias for each intervention comparison and major outcome of interest, evidence grades were assigned as high, moderate, low, or insufficient. Two senior reviewers independently developed initial SOE assessments for each relevant outcome and comparison across the KQs and resolved disagreements through discussion.

RESULTS

A total of 164 studies (168 articles) met eligibility criteria. Figure S1 in the online supplement depicts the article flowchart. The results below focus on primarily on evidence offering at least a low level of certainty. However, all results, including those with insufficient certainty to arrive at conclusions are described in Tables S2–S109 in the online supplement and in the full report (https://doi.org/10.23970/AHRQEPCCER236). Key results are presented below in order of certainty.

Effectiveness of Perinatal Pharmacotherapy

Evidence on benefits of pharmacotherapy in pregnant and postpartum women is sparse (9 RCTs and 10 observational studies).

When evidence was available, the benefit of pharmacotherapy for depression and bipolar disorder was graded as having low to moderate strength. Table 1 maps all the evidence on benefits for perinatal pharmacotherapy.

Specifically, for depression, moderate SOE from three RCTs suggests that postpartum brexanolone for depression onset in the third trimester or postpartum is associated with improved depressive symptoms shortly after infusion (60 h) (least square [LS] mean difference in the Hamilton Rating Scale for Depression [HAM-D], −4.1, standard error [SE] 0.9, $p < 0.001$) and at 30 days after treatment (LS mean difference, SE −2.6, 1.1, $p = 0.02$) (30,31). Brexanolone results were mixed for other depression measures.

Two RCTs provide low SOE suggesting that compared with placebo, sertraline for postpartum depression may improve response (Table 2) (RR, 4.00; 95% CI, 0.98 to 16.31; $N = 36$), remission (RR, 4.22; 95% CI, 0.98 to 18.12; $N = 36$), and depressive and anxiety symptoms (regression coefficients range from 0.91 to 1.18, p-values range from 0.01 to 0.05) (24,25).

For bipolar disorders, two cohort studies provide low SOE that discontinuing mood stabilizers during pregnancy may be associated with increased recurrence when compared with continuing mood stabilizers (AHR, 2.2; 95% CI, 1.2 to 4.2; $N = 89$) (32) and time-to-25%-recurrence of mood episodes when compared with continuing lamotrigine (2 vs. 28 weeks, AHR, 12.1; 95% CI, 1.6 to 91; $N = 26$) (33).

No evidence was available for schizophrenia. Evidence did not permit conclusions for any drug for anxiety disorder, nor for fluoxetine or paroxetine for depression.

Comparative Effectiveness of Perinatal Pharmacotherapy

One RCT and 10 observational studies of exposure provided insufficient evidence to judge the comparative effectiveness of a limited number of outcomes and interventions for depression and bipolar disorder (Table 1). For anxiety and schizophrenia, no eligible evidence on comparative effectiveness was found.

Harms of Perinatal Pharmacotherapy

Five RCTs and 70 observational studies were included. The authors judged the certainty of evidence to draw conclusions to be insufficient or low in all instances (Table 3), primarily because of lack of control for confounding. Table 2 indicates small absolute risk differences for all adverse events. Key outcomes—specifically, evidence from RCTs, for an association observed for more than one drug, or for serious adverse events—graded as low SOE are described below, as is evidence for congenital and cardiac anomalies (graded insufficient).

TABLE 1. Summary of evidence for maternal benefit for treatment versus placebo, no treatment, or active comparators for mental health disorders in pregnancy and postpartum

Disorder	Exposure	Comparator	Symptoms	Response	Remission	Relapse	Suicidal ideation	Functional capacity	Quality of life	Delivery mode	Breastfeeding	Weight change	Adherence to treatment and care	Suicidal events
Anxiety	Benzodiazepine	Placebo, no treatment, or active treatment	-	-	-	-	-	-	-	-	-	-	-	-
	Hydroxyzine	Placebo, no treatment, or active treatment (19)	-	I	-	-	-	-	-	-	-	-	-	-
	All other anxiolytics	Placebo, no treatment, or active treatment	-	-	-	-	-	-	-	-	-	-	-	-
	Sedatives[a]	Placebo, no treatment, or active treatment	-	-	-	-	-	-	-	-	-	-	-	-
Depression	SSRIs (unspecified)	Placebo, no treatment, or active treatment (20)	-	-	-	-	-	-	-	I	-	-	-	-
	Fluoxetine	Placebo, no treatment, or active treatment other than TCA (21)	I	-	-	-	-	-	-	-	-	-	-	-
	Fluoxetine	TCA (22)	-	-	-	-	-	-	-	I	-	-	-	-
	Paroxetine	Placebo, no treatment, or active treatment (23)	I	I	I	-	-	-	-	-	-	-	-	-
	Sertraline	Placebo, no treatment, or active treatment other than nortriptyline (24, 25, 26, 27)	L	L	L	-	-	I	-	-	-	-	-	-
	Sertraline	Nortriptyline (28, 29)	I	I	I	-	-	I	-	-	-	-	-	-
	Brexanolone	Placebo, no treatment, or active treatment (30, 31)	M	-	-	-	-	I	-	-	-	-	-	-
Bipolar disorder	Mood stabilizers (unspecified)	Placebo, no treatment, or active treatment (32)	-	-	-	L	-	-	-	-	-	-	-	-
	Lamotrigine	Placebo, no treatment, or active treatment other than lithium (33)	-	-	-	L	-	-	-	-	-	-	-	-
	Lamotrigine	Lithium[b] (34)	-	-	-	-	-	-	-	-	-	-	-	-
	Olanzapine	Lithium (35)	I	-	-	-	-	-	-	-	-	-	-	-
	Lithium	Lithium plus sodium valproate (36)	-	-	-	I	-	-	-	-	-	-	-	-
	Sodium valproate	Lithium plus sodium valproate (36)	-	-	-	-	-	I	-	-	-	-	-	-
	Lithium	Paroxetine (35)	I	-	-	-	-	-	-	-	-	-	-	-
Schizophrenia	All antipsychotics	Placebo, no treatment, or active treatment	-	-	-	-	-	-	-	-	-	-	-	-

Note: I: Insufficient evidence for conclusions on the outcome, that is, an insufficient rating indicates that the evidence does not permit estimation of an effect because multiple domain ratings indicate weakness in the evidence base (i.e., the evidence base may comprise studies with limitations such as uncontrolled or poorly controlled confounding or high and differential attrition; be inconsistent, indirect, or imprecise; or be biased in reporting); M: Moderate evidence of benefit for at least one measure for the outcome domain, that is, a moderate rating implies moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate; L: Low evidence of benefit for at least one measure for the outcome domain, that is, a low rating implies low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate.; -: No eligible evidence.

Abbreviations: SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

[a] Sedative hypnotics may be prescribed for sleep disturbances that occur during any mental health disorder as well as in the presence of no diagnosable mental health disorder; they may also be used, at times, off label as an anti-anxiety alternative.

[b] No prespecified outcomes were evaluated but one study reported on psychiatric admissions; the evidence was insufficient to judge the effectiveness of lamotrigine versus lithium.

TABLE 2. Detailed results for key outcomes rated low strength of evidence

Population	Outcome[a]	Exposure	Comparator	Incidence	N	Results	ARD per 1000 women[b] (95% CI)	NNTB/NNTH[c] (95% CI)	Key considerations
Women with postpartum depression	Response	Sertraline	Placebo	10/17 (59%) versus 5/19 (26%)	36	RR in low risk-of-bias study: 2.24 (95% CI, 0.95 to 5.24) (24) no difference between two arms in high risk-of-bias study, p = 0.054 (25)	326 (11 to 1116)	NNTB:4 (1 to 91)	RCT evidence, small sample, imprecise results
Women with postpartum depression	Remission	Sertraline	Placebo	9/17 (53%) versus 4/19 (21%)	36	RR: 2.52 (95% CI, 0.94 to 6.70); (24) no difference between two arms in high risk-of-bias study, p = 0.372 (25)	320 (4 to 619)	NNTB:4 (2 to 250)	RCT evidence, small sample, imprecise results
Women with bipolar disorder	Recurrence from discontinuation	Discontinued mood stabilizers	Continued mood stabilizers	53/62 (85.5%) versus.10/27 (37%)	89	AHR: 2.2 (95% CI, 1.2 to 4.2) (32)	268 (56 to 486)	NNTH: 4 (3 to 18)	Observational evidence, small sample, imprecise results
Women with bipolar disorder	Time-to-25%-recurrence from discontinuation	Discontinued mood stabilizers	Continued lamotrigine	16/16 (100%) versus 3/10 (30%)	26	AHR: 12.1 (95% CI, 1.6 to 91.7) (33)	687 (135 to 700)	NNTH: 2 (2 to 8)	Observational evidence, study has limitations, small sample, imprecise results
Women with at least one anxiety diagnosis in the year before conception	Ectopic pregnancy	Benzodiazepine exposure 90 days before conception	No benzodiazepine exposure before conception	249/9188 (2.71%) versus 1730/81,291 (2.13%)	90,479	ARR: 1.33 (95% CI, 1.17 to 1.51) (37)	7 (4 to 11)	NNTH: 143 (91 to 250)	Observational evidence, potential for residual confounding

TABLE 2, *continued*

Population	Outcome[a]	Exposure	Comparator	Incidence	N	Results	ARD per 1000 women[b] (95% CI)	NNTB/NNTH[c] (95% CI)	Key considerations
Women with mood or anxiety disorder	Postpartum hemorrhage	Exposed to SSRIs during delivery	Unexposed to SSRIs during delivery	503/12,710 (3.96%) versus 1896/69,044 (2.75%)	81,754	ARR, 1.47 (95% CI, 1.33 to 1.62) (38)	13 (9 to 17)	NNTH: 77 (59 to 112)	Observational evidence, potential for residual confounding
Women with mood or anxiety disorder	Postpartum hemorrhage	Exposed to SNRIs during delivery	Unexposed to SNRIs during delivery	35/702 (5.0%) versus 1896/69,044 (2.75%)	69,746	ARR, 1.90 (1.37 to 2.63) (38)	25 (10 to 45)	NNTH: 40 (23 to 100)	Observational evidence, potential for residual confounding
SNRI exposure or depression diagnosis, through second trimester	Preeclampsia	SNRIs exposure through second trimester	Unexposed depressed	107/1216 (9%) versus 3215/59,219 (5%) (39); 23/408 (5.6%) versus 1569/65,392 (2.4%) (40)	65,800	ARR, 1.52 (95% CI, 1.25 to 1.83) (39); ARR, 1.59 (95% CI, 1.26 to 3.03) (40)	14 (6 to 49)	NNTH: 72 (21 to 167)	Observational evidence, potential for residual confounding
Women with depression	Preeclampsia	Exposed to TCAs in pregnancy	Unexposed to TCAs in pregnancy	47/441 (10.7%) versus 3215//59,219 (5.4%) (39); 14/146 (9.59%) versus 1569/65,392 (2.40%) (40)	65,538	ARR, 1.62 (95% CI, 1.23 to 2.12) (39); ARR, 3.23 (95% CI, 1.87 to 5.59) (40)	54 (21 to 110)	NNTH: 19 (10 to 48)	Observational evidence, potential for residual confounding
Women prescribed second-generation antipsychotic	Gestational diabetes	Quetiapine continued in pregnancy	Quetiapine discontinued in pregnancy	110/1543 (7.1%) versus 122/2990 (4.1%)	4533	ARR, 1.28 (95% CI, 1.01 to 1.62) (41)	11 (<1 to 25)	NNTH: 88 (40 to 2439)	Observational evidence, potential for residual confounding
Women prescribed second-generation antipsychotic	Gestational diabetes	Olanzapine continued in pregnancy	Olanzapine discontinued in pregnancy	46/384 (12.0%) versus 49/1041 (4.7%)	1425	ARR, 1.61 (95% CI, 1.13 to 2.29) (41)	29 (6 to 61)	NNTH: 35 (17 to 167)	Observational evidence, potential for residual confounding
Pregnant women with depression or anxiety	Spontaneous abortion	Benzodiazepine exposure in first trimester (42) or within the first 19 weeks (43) versus untreated or a history of mood disorders or anxiety during pregnancy	Unmedicated mental illness	386/2384 (16%) versus 442/3647 (12%) (42); 198 cases/570 controls versus 3221 cases/15 382 controls (43)	6031	ARR, 1.6 (95% CI, 1.3 to 1.9) (42); AOR: 2.85 (95% CI, 1.72 to 4.72) (43)	73 (36 to 109)	NNTH: 14 (10 to 28)	Observational evidence, potential for residual confounding

(Continues)

TABLE 2, *continued*

Population	Outcome[a]	Exposure	Comparator	Incidence	Results	N	ARD per 1000 women[b] (95% CI)	NNTB/NNTH[c] (95% CI)	Key considerations
Women with SNRI exposure or depression diagnosis in past 4 years	Spontaneous abortion	SNRI exposure in 1st trimester	Unexposed with depression diagnosis in past 4 years	20/90 (22%) versus 720/7034 (10%); results corrected for induced abortions: 20/137 (15%) versus 720/8877 (8.1%)	ARR, 2.1 (95% CI, 1.4 to 3.0); corrected for induced abortions ARR, 1.7 (95% CI, 1.2 to 2.6) (44)	9014	62 (16 to 130)	NNTH: 17 (8 to 63)	Observational evidence, potential for residual confounding
Women with a mental health disorder	NICU admission	Benzodiazepine exposure during pregnancy	Unexposed to benzodiazepine during pregnancy	32/144 (22.2%) versus 125/649 (19.3%)	AOR, 2.02 (95% CI, 1.11 to 3.66) (45)	793	133 (17 to 274)	NNTH: 8 (4 to 59)	Observational evidence, potential for residual confounding, benzodiazepine exposure may result in NICU admission by policy
Women exposed to SSRIs or unexposed with a psychiatric diagnosis	Apgar score <7 at 5 min	Exposed to SSRIs during pregnancy	Exposed to SSRIs before pregnancy or unexposed with a psychiatric diagnosis	28/2664 (1.1%) versus 31/5141 (0.6%) (46); 376/15,729 (2.4%) versus 113/9652 (1.2%) (47)	Adjusted prevalence ratio: 1.69 (95% CI, 1.02 to 2.79) (46) AOR, 1.68 (95% CI, 1.34 to 2.12) (47)	25,381	8 (4 to 13)	NNTH: 125 (77 to 250)	Observational evidence, potential for residual confounding, transient outcome
Women with depression	Persistent pulmonary hypertension of the newborn	Exposed to SSRIs during pregnancy	Unexposed to SSRIs during pregnancy	94/54,281 (0.2%) versus 669/567,118 (0.1%) (48)	Adjusted OR, 1.28 (95% CI, 1.01 to 1.70) (48) AOR, when not restricted to full-term or by outcome (persistent pulmonary hypertension rather than primary persistent pulmonary hypertension): 1.08 (95% CI, 0.92 to 1.27) (48)	621,399	1 (<1 to 1)	NNTH: 3031 (1220 to 11.112)	Observational evidence, potential for residual confounding

TABLE 2, *continued*

Population	Outcome[a]	Exposure	Comparator	Incidence	N	Results	ARD per 1000 women[b] (95% CI)	NNTB/ NNTH[c] (95% CI)	Key considerations
Women with a mental health disorder	Childhood depression	Exposed to SSRIs during pregnancy	Unexposed to SSRIs during pregnancy	60/15,729 (0.4%) versus 30/9651 (0.3%)	25,380	AHR, 1.78 (95% CI, 1.12 to 2.82) (49)	2 (0 to 6)	NNTH: 414 (178 to 2703)	Observational evidence, potential for residual confounding
Women with a mental health disorder	Autism spectrum disorder without intellectual disabilities	Exposed to citalopram during pregnancy	Unexposed to any antidepressants during pregnancy	46/1064 (4.3%) versus 291/ 12,325 (2.4%)	13,389	AOR, 1.75 (95% CI, 1.25 to 2.45) (50)	17 (6 to 32)	NNTH: 59 (32 to 167)	Observational evidence, potential for residual confounding

Abbreviations: AOR, adjusted odds ratio; ARD, absolute risk difference; ARR, adjusted relative risk; CI, confidence interval; NICU, neonatal intensive care unit; NNTB, number needed to treat for an additional beneficial outcome; NNTH, number needed to treat for an additional harmful outcome; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

[a] Key outcomes were selected from evidence bases rated as at least low strength of evidence.

[b] The ARD was calculated based on adjusted effect sizes when available. When multiple studies were available on harms, cohort studies with the highest effect size to present the outer bound for harms were selected.

[c] When multiple studies were available on harms, the NNTB and NNTH were based on the results reported for the ARD. NNTB and NNTH and their upper and lower confidence intervals are rounded up to the next whole number.

TABLE 3. Summary of evidence for harms from pharmacotherapy versus no treatment for mental health disorders in pregnancy or postpartum

Condition	Exposure	Maternal harms									Fetal and neonatal harms												Infant and child harms					
		Infertility	Preeclampsia	Spontaneous abortion	Abruption	Postpartum hemorrhage	Gestational hypertensive disorders	Glucose intolerance	Gestational diabetes mellitus	Reduced milk production/undesired weaning	Perinatal death	Preterm birth	Small for gestational age	Large for gestational age	Birthweight	Major congenital anomalies	Cardiac anomalies	Apgar score	Withdrawal	Respiratory distress	Neonatal intensive care unit time	Persistent pulmonary hypertension	Poor infant attachment/bonding	Delayed social, emotional, and cognitive development	Autism spectrum disorder	ADHD	Anxiety	Depression
Depression or anxiety	Benzodiazepine[a] (37, 42, 43, 45, 51)	-	I	L	-	-	-	-	-	-	I	-	-	-	I	-	-	I	-	I	L	-	-	-	-	-	-	-
Depression or anxiety	Diazepam[b] (51)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	I	-	-	-	-	-	-	-	-	-	-	-	-
Depression or anxiety	Temazepam[b] (51)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	I	-	-	-	-	-	-	-	-	-	-	-	-
Depression or anxiety	Zopiclone[b] (51)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	I	-	-	-	-	-	-	-	-	-	-	-	-
Mental health disorders	Zolpidem[b] (52)	-	I	-	-	-	I	-	-	-	-	I	-	-	-	-	-	I	-	I	I	-	-	-	-	-	-	-
Mental health disorders	Hydroxyzine	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Anxiety	Other anxiolytics	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Depression and/or anxiety and/or other mental health disorders	SSRIs (unspecified) (20, 38-40, 42, 44, 46-49, 53-74)	-	I	I	-	L	I	-	I	-	I	I	I	-	I	I	I	L	-	L	I	L	-	I	I	I	I	L
Depression and/or anxiety and/or other mental health disorders	Citalopram (38, 39, 50, 53, 55, 74)	-	I	-	-	L	-	-	I	-	-	-	-	-	-	I	I	-	-	-	-	-	-	-	L	-	-	-
Depression, mood, or anxiety disorder	Escitalopram (38, 39, 55, 59)	-	I	-	-	L	-	-	-	-	-	-	-	-	-	I	I	-	-	-	-	-	-	-	-	-	-	-
Depression, mood, or anxiety disorder	Fluoxetine (38, 39, 50, 53, 55, 58, 59, 74, 75)	-	I	-	-	L	-	-	I	-	-	-	-	-	-	I	I	-	-	-	-	-	-	-	I	-	-	-
Depression, mood, or anxiety disorder	Fluvoxamine (53)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	I	-	-	-	-	-	-	-	-	-	-	-	-
Depression, anxiety, or other mental health disorders	Paroxetine (23, 38, 39, 50, 53, 55, 57, 58, 59, 74, 75)	-	I	-	-	L	-	-	I	-	-	-	-	-	-	I	I	-	-	-	-	-	-	-	I	-	-	-
Depression and/or anxiety and/or other mental health disorders	Sertraline (25, 27, 38, 39, 50, 53, 54, 55, 58, 59, 74, 75)	-	I	-	-	L	-	-	I	-	-	-	-	-	-	I	I	-	-	-	-	-	-	-	I	-	-	-
Mood or anxiety disorders or prescribed medication	Trazodone (38, 39)	-	I	-	-	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Depression, mood, or anxiety disorder	SNRIs (unspecified) (40, 44, 58) (38, 53, 59) (39)	-	L	L	-	L	-	-	-	-	-	-	-	-	-	I	I	-	-	-	-	-	-	-	-	-	-	-
Prescribed medication***	Duloxetine (39, 75, 76)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	I	-	-	-	-	-	-	-	I	-	-	-
Depression, mood, or anxiety disorder	Venlafaxine (50, 67, 74) (38, 39, 53, 59, 75)	-	L	-	-	L	I	-	I	-	-	-	I	-	-	-	I	-	-	-	-	-	-	-	I	-	-	-
Depression and/or anxiety and/or other mental health disorders	TCAs (unspecified) (39, 40, 42, 44, 53, 55, 57, 58, 67)	-	L	I	-	-	-	-	-	-	I	-	I	-	-	I	I	-	-	-	-	-	-	-	-	-	-	-

(Continues)

Maternal Harm
Postpartum Hemorrhage
Regarding postpartum hemorrhage, results from one propensity score–adjusted study suggested an association between exposure to several antidepressants and postpartum hemorrhage that may vary by timing (38). Current exposure (at the time of delivery) is associated with postpartum hemorrhage for selective serotonin reuptake inhibitors (SSRIs) as a class, citalopram, escitalopram, sertraline, serotonin-norepinephrine reuptake inhibitors (SNRIs) as a class, and venlafaxine. Recent exposure (up to 1 month before delivery) is also associated with an increased risk of postpartum hemorrhage for SSRIs as a class, paroxetine, and sertraline (low SOE of harms). For bupropion, however, the association is with past exposure (supply of drug 1 to 5 months before delivery). Previous studies suggested that SSRIs in particular can reduce platelet function and result in bleeding because the drugs inhibit serotonin

TABLE 3. *continued*

Condition	Intervention	Maternal harms									Fetal and neonatal harms												Infant and child harms					
		Infertility	Preeclampsia	Spontaneous abortion	Abruption	Postpartum hemorrhage	Gestational hypertensive disorders	Glucose intolerance	Gestational diabetes mellitus	Reduced milk production/undesired weaning	Perinatal death	Preterm birth	Small for gestational age	Large for gestational age	Birthweight	Major congenital anomalies	Cardiac anomalies	Apgar score	Withdrawal	Respiratory distress	Neonatal intensive care unit time	Persistent pulmonary hypertension	Poor infant attachment/bonding	Delayed social, emotional, and cognitive development	Autism spectrum disorder	ADHD	Anxiety	Depression
Mental health disorders	Clomipramine (50, 75)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	I	-	-	-
Mental health disorders	Amitriptyline (38)	-	-	-	-	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Mental health disorders	Amitriptyline or nortriptyline (50, 75)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	I	-	-	-
Postpartum depression	Brexanolone[c] (30, 31)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Depression, mood, or anxiety disorder	Bupropion (38, 39, 58, 59, 74)	-	I	-	-	L	-	-	I	-	-	-	-	-	-	-	I	-	-	-	-	-	-	-	-	-	-	-
Depression, mood, or anxiety disorder	Mirtazapine (38, 39, 73, 75)	-	-	-	-	I	-	-	-	-	-	I	-	-	I	-	-	-	-	-	I	-	-	-	I	-	-	-
Bipolar disorder	Mood stabilizers[d] (77)	-	I	-	I	-	-	-	-	-	-	I	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Bipolar disorder	Lamotrigine[d] (77) (79)	-	I	-	I	-	-	I	-	-	-	I	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Bipolar disorder	Valproate[d] (77)	-	I	-	I	-	-	-	-	-	-	I	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Bipolar disorder	Topiramate[d] (77)	-	I	-	I	-	-	-	-	-	-	I	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Bipolar disorder	Carbamazepine[d] (77)	-	I	-	I	-	-	-	-	-	-	I	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Bipolar disorder	Oxcarbazepine[d] (77)	-	I	-	I	-	-	-	-	-	-	I	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Bipolar or mood disorder	Lithium (77-79)[d]	-	I	-	I	-	-	I	-	-	-	I	I	-	-	-	-	-	-	-	-	-	-	I	-	-	-	-
Mental health disorders or schizophrenia, bipolar disorder, or psychosis	Second-generation antipsychotics (unspecified) (80) (79, 81, 82, 83)	-	-	-	-	-	-	-	I	-	-	I	I	I	I	I	I	-	-	-	-	-	-	-	-	-	-	-

reuptake into platelets (85). In a sample with a prevalence of 2.75% in the unexposed arm, the ARD for SSRIs is 13 more cases per 1000 (95% CI, 9 more to 17 more); for SNRIs, the risk is 25 more per 1000 (95% CI, 10 more to 45 more). The mechanism of action for other antidepressants is not clear, and associations could potentially be attributable to chance (38). The risk of residual confounding also remains: the study was not able to control for confounding factors of inadequate diet, tobacco use, and disorder severity. Additionally, the study was not powered to examine the association between antidepressants and severe postpartum hemorrhage leading to blood transfusion, further morbidity, or mortality.

Preeclampsia
Low SOE from two studies (39,40) suggests increased risk of preeclampsia for women exposed to non-SSRI drugs, specifically SNRIs and TCAs; ARDs range from 14 more cases per 1000 to 54 cases per 1000. Risk factors for preeclampsia include maternal antiphospholipid antibody syndrome, family history, nulliparity, donor egg, diabetes, obesity, and preexisting hypertension. These factors may cause placental hypoxia and ischemia. However, antidepressants may increase serotonin and norepinephrine levels and therefore contribute to preeclampsia (40). Because both serotonin and norepinephrine are vasoconstrictors, SNRIs could affect preeclampsia risk through placental ischemia (86). Although both studies controlled for age, primiparity, multiple gestation, diabetes, proxies of depression severity (such as number of visits or claims), and general markers of comorbidity (such as healthcare and prescription use other than for depression), results are not consistent across exposures: these differences may be attributable to residual confounding because of inadequately controlled depression severity or another comorbid condition.

Gestational Diabetes
For gestational diabetes mellitus (GDM), low SOE from one cohort study (41) suggested that continuing use (as reflected in two or more dispensed prescriptions) during the first half of pregnancy of quetiapine (ARD, 11 per 1000;

TABLE 3. *continued*

Condition	Intervention	Maternal harms									Fetal and neonatal harms												Infant and child harms					
		Infertility	Preeclampsia	Spontaneous abortion	Abruption	Postpartum hemorrhage	Gestational hypertensive disorders	Glucose intolerance	Gestational diabetes mellitus	Reduced milk production/undesired weaning	Perinatal death	Preterm birth	Small for gestational age	Large for gestational age	Birthweight	Major congenital anomalies	Cardiac anomalies	Apgar score	Withdrawal	Respiratory distress	Neonatal intensive care unit time	Persistent pulmonary hypertension	Poor infant attachment/bonding	Delayed social, emotional, and cognitive development	Autism spectrum disorder	ADHD	Anxiety	Depression
Schizophrenia, bipolar disorder, or psychosis or prescribed medication[e]	First-generation antipsychotics (unspecified) (82, 83)	-	-	-	-	-	-	-	-	-	-	I	I	I	I	I	I	I	-	-	-	-	-	-	-	-	-	-
Prescribed medication[d]	Aripiprazole (41)	-	-	-	-	-	-	-	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Mental health disorders[d] or prescribed medication	Ziprasidone (41)	-	-	-	-	-	-	-	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Prescribed medication[d]	Quetiapine (41, 84)	-	-	-	-	-	-	-	L	-	-	-	-	-	-	I	-	-	-	-	-	-	-	-	-	-	-	-
Prescribed medication[d]	Risperidone (41, 82)	-	-	-	-	-	-	-	I	-	-	-	-	-	-	I	I	-	-	-	-	-	-	-	-	-	-	-
Prescribed medication[d]	Olanzapine (41)	-	-	-	-	-	-	-	L	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Note: I: Insufficient evidence for conclusions on the outcome, that is, an insufficient rating indicates that the evidence does not permit estimation of an effect because multiple domain ratings indicate weakness in the evidence base (i.e., the evidence base may comprise studies with limitations such as uncontrolled or poorly controlled confounding or high and differential attrition; be inconsistent, indirect, or imprecise; or be biased in reporting); L: Low evidence of benefit for at least one measure for the outcome domain, that is, a low rating implies low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate.; -: No eligible evidence.
Abbreviations: ADHD, attention-deficit/hyperactivity disorder; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.
[a]Included studies also reported a higher risk of ectopic pregnancy for benzodiazepine use when compared with no benzodiazepine exposure (graded low for harms).
[b]Used as a sedative-hypnotic to address sleep difficulty, not targeted at underlying mental health disorder.
[c]Although no evidence of harms for brexanolone was found for a priori outcomes, the evidence on dose interruption or reduction due to somnolence or sedation was graded as low.
[d]Data obtained by personal communication with authors after release of their publication (77).
[e]Underlying mental health indication and exposure to medications are generally not specified; study populations are based on cohorts with prescriptions.

95% CI, 0 to 25) or olanzapine (ARD, 29 per 1000; 95% CI, 6 to 61) may be associated with an increased risk of developing GDM compared with women discontinuing these medications before the start of pregnancy. Antipsychotics may result in changes in appetite and diet because of interactions with serotonergic, histaminergic, and dopaminergic neurotransmitter systems (87). FDA notes the risk of metabolic side effects from second-generation antipsychotics in prescription labels for these drugs (88,89). The other second-generation antipsychotics analyzed that showed no clear difference in risk were aripiprazole, ziprasidone, and risperidone. Women who continued antipsychotic treatment during pregnancy generally had higher comorbidity and longer baseline antipsychotic use. Of note, these studies used a generalized linear model and propensity score stratification to obtain risks of developing GDM with adjustment for confounders, such as demographic data, psychiatric diagnoses, comorbidity, other medication use, history of gestational diabetes, and the duration of antipsychotic treatment received during the 3 months before the last menstrual period.

Early Pregnancy Loss
Evidence from one study (37) suggested an increased risk of ectopic pregnancy with benzodiazepine exposure 90 days before conception when compared with no exposure before conception, among pregnant women with at least one anxiety disorder diagnosis in the year before conception (graded low SOE of harms). Risk factors for ectopic pregnancy include previous ectopic pregnancy, history of pelvic infection, infertility, cigarette smoking, and age older than 35 years (90). Confounding by indication may explain these results; however, one suggested mechanism of action could be through the central relaxation of smooth muscle and the direct effect on gamma-aminobutyric acid receptors in the fallopian tube, potentially resulting in a higher incidence of ectopic pregnancy (37). The ARD is 7 per 1000 (95% CI, 4 to 11).

One study suggested that SNRI exposure in the first trimester may be associated with a higher rate of spontaneous abortion when compared with no exposure (low SOE) (44). Analyses controlling for induced abortion showed a slightly attenuated but still statistically significant difference (ARD, 62 per 1000; 95% CI, 16 to 130). The

comparison group includes women with a depression diagnosis in the 4 years preceding pregnancy. Although the authors adjusted for use of teratogenic medication in the first trimester, number of prescription medications in 3 months before pregnancy, and number of mental health visits in 3 months before pregnancy, the two comparison groups likely had different baseline severity, which is unaccounted for in this analysis.

Evidence from two studies (42,43) suggested an increased risk of spontaneous abortion with benzodiazepine exposure 90 days before conception when compared with untreated women or women with a history of mood disorders or anxiety (graded low SOE of harms). To the extent that women experiencing greater psychological stress would be more likely to be treated pharmacologically, confounding by indication by underlying may explain the observed associations. Although residual confounding may explain these results, as with the results for ectopic pregnancy, the authors note that benzodiazepines cross the placental barrier easily and may accumulate in fetal issues (37). The ARD is 73 per 1000 (95% CI, 36 to 109).

Excessive Sedation or Loss of Consciousness
FDA includes a boxed warning on the prescribing information of excessive sedation or loss of consciousness in the active arm for brexanolone leading to dose interruption or reduction (5% vs. 0% for the placebo arm). In the prescribing instructions, the manufacturer reports higher rates of dizziness, loss of consciousness, and somnolence with brexanolone compared with placebo. The pooled RR for somnolence was 2.00 (95% CI, 0.78 to 5.16; Figure S2 in the online supplement) and the ARD was 0.05 (95% CI, −0.01 to 0.12). Results could not be pooled for loss of consciousness from the individual studies; they did not appear to increase with dose intensity: 5% of women randomized to brexanolone with a maximum dose of 60 μg/kg per hour versus 3% for brexanolone with a maximum dose of 90 μg/kg per hour experienced loss of consciousness.

Fetal, Infant, or Child Harms
Persistent Pulmonary Hypertension of the Newborn
For the study reporting an association between persistent pulmonary hypertension of the newborn and SSRIs, like with other observational cohorts, residual confounding and the potential for misclassification may exist. Risk factors like smoking, obesity, and Caesarean section are all more prevalent in populations of psychiatric patients (91). However, adjustments for potential sources of confounding (restricting the sample to full-term births (91) and restricting the outcome to those without cardiac anomalies or hypoplasia) resulted in higher odds (odds ratio [OR], 1.28; 95% CI, 1.01 to 1.64) than results without these adjustments (OR, 1.10; 95% CI, 0.94 to 1.29) when compared

with no exposure (48). Notably, the baseline risk (0.1% in the unexposed arm) and the ARD (33 more cases per 100,000 persons, 95% CI, 1 to 83 more cases) are very low; in the analyses adjusting for potential sources of confounding, the ARD is lower still at 9 more cases per 100,000 (95% CI ranges from 9 fewer cases to 32 more cases). These results suggest that although the exposure may be associated with a higher risk of a potentially serious complication, the absolute risk of harm is very low (low SOE).
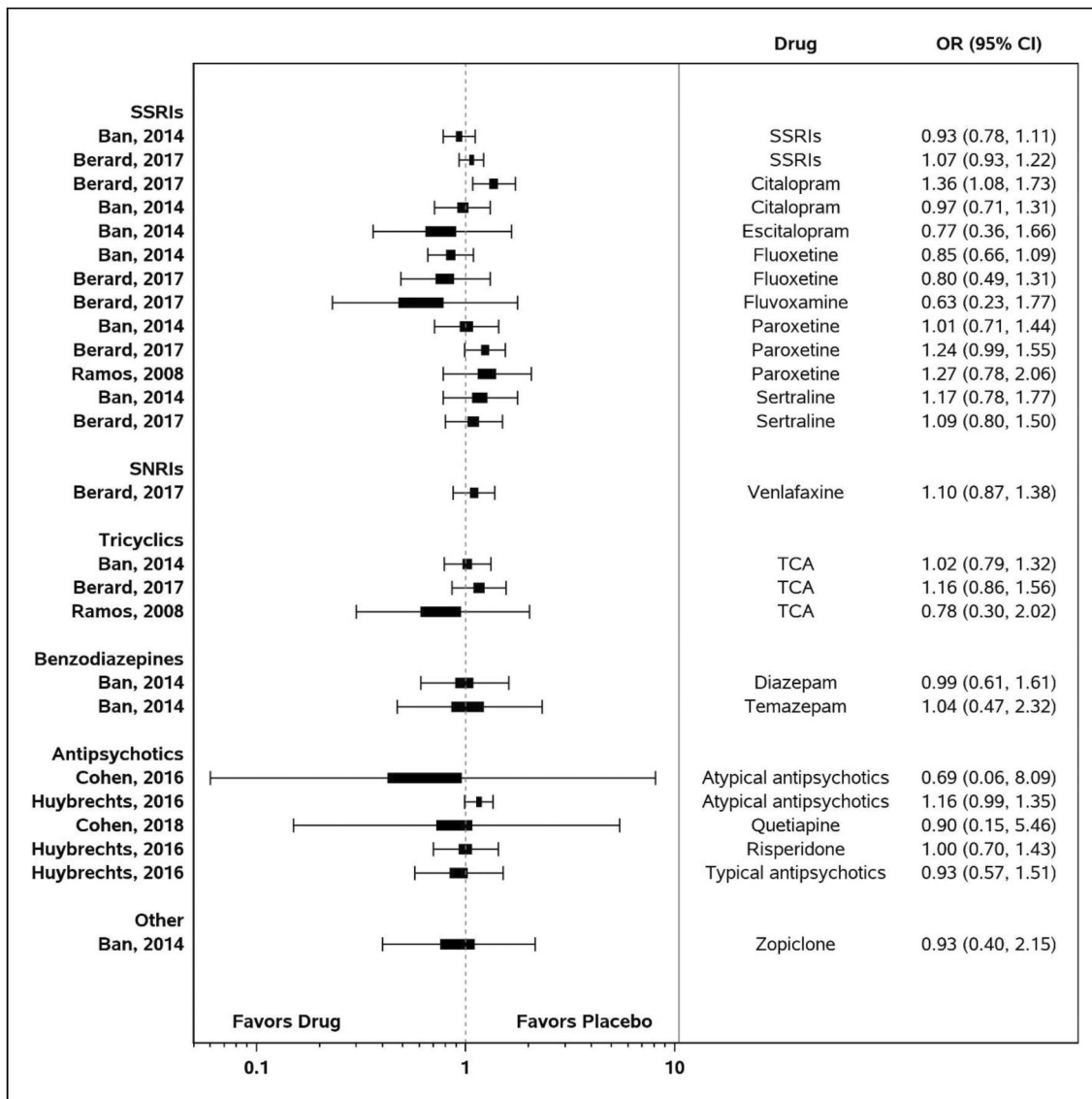
Congenital Anomalies
FDA prescription labeling suggests potential concerns for congenital anomalies for several psychotropic drugs, including paroxetine, temazepam, triazolam, alprazolam, diazepam, valproate, carbamazepine, and topiramate. The evidence was insufficient to judge the risks of congenital anomalies (Figure 2) and cardiac defects from studies included in our review. Figure 2 displays results for all studies reporting on major congenital malformations as an outcome in a forest plot (the results are not pooled because of potential overlap of participants across studies for some interventions). Figure 2 does not include studies reporting on subsets of major congenital malformations, such as cardiac malformations: these results are described after the synthesis on all major congenital malformations.

Regarding major congenital anomalies overall, eight studies evaluated associations between various exposures (diazepam, temazepam, zopiclone, SSRIs as a class, citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, SNRIs as a class, TCAs as a class, quetiapine, risperidone, second-generation antipsychotics, and first-generation antipsychotics) and major congenital anomalies (51-57,81,84). Except for one study each on citalopram (53) and second-generation antipsychotics (82), ORs span from 0.69 to 1.36, with wide CIs spanning the null. For both citalopram and second-generation antipsychotics, the evidence base comprised two studies with conflicting results. Inconsistency was one factor in downgrading the evidence base overall; another was the potential study limitations of the evidence base. No eligible evidence was available on congenital anomalies for triazolam, alprazolam, valproate, carbamazepine, clonazepam, and topiramate, although evidence is available from studies of other populations ineligible for this review.

Regarding cardiac anomalies specifically, eight studies evaluated associations (53–55,58,59,92–94) and used different criteria to identify affected infants. Odds risks from meta-analyses for SSRIs, citalopram, fluoxetine, paroxetine, sertraline, and TCAs ranged from 0.86 to 1.26, with wide CIs spanning the null. Studies used varying definitions that did not consistently exclude cardiac anomalies associated with prematurity. Beyond differences

FIGURE 2. Exposure to psychotropic medications and major congenital anomalies. CI, confidence interval; OR, odds ratio; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant

	Drug	OR (95% CI)
SSRIs		
Ban, 2014	SSRIs	0.93 (0.78, 1.11)
Berard, 2017	SSRIs	1.07 (0.93, 1.22)
Berard, 2017	Citalopram	1.36 (1.08, 1.73)
Ban, 2014	Citalopram	0.97 (0.71, 1.31)
Ban, 2014	Escitalopram	0.77 (0.36, 1.66)
Ban, 2014	Fluoxetine	0.85 (0.66, 1.09)
Berard, 2017	Fluoxetine	0.80 (0.49, 1.31)
Berard, 2017	Fluvoxamine	0.63 (0.23, 1.77)
Ban, 2014	Paroxetine	1.01 (0.71, 1.44)
Berard, 2017	Paroxetine	1.24 (0.99, 1.55)
Ramos, 2008	Paroxetine	1.27 (0.78, 2.06)
Ban, 2014	Sertraline	1.17 (0.78, 1.77)
Berard, 2017	Sertraline	1.09 (0.80, 1.50)
SNRIs		
Berard, 2017	Venlafaxine	1.10 (0.87, 1.38)
Tricyclics		
Ban, 2014	TCA	1.02 (0.79, 1.32)
Berard, 2017	TCA	1.16 (0.86, 1.56)
Ramos, 2008	TCA	0.78 (0.30, 2.02)
Benzodiazepines		
Ban, 2014	Diazepam	0.99 (0.61, 1.61)
Ban, 2014	Temazepam	1.04 (0.47, 2.32)
Antipsychotics		
Cohen, 2016	Atypical antipsychotics	0.69 (0.06, 8.09)
Huybrechts, 2016	Atypical antipsychotics	1.16 (0.99, 1.35)
Cohen, 2018	Quetiapine	0.90 (0.15, 5.46)
Huybrechts, 2016	Risperidone	1.00 (0.70, 1.43)
Huybrechts, 2016	Typical antipsychotics	0.93 (0.57, 1.51)
Other		
Ban, 2014	Zopiclone	0.93 (0.40, 2.15)

CI = confidence interval; OR = odds ratio; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

in outcome measurement, differences between studies in design and controls for confounding could potentially explain variations in results.

Comparative Harms of Perinatal Pharmacotherapy

One RCT and 55 observational studies were identified, limiting causal inference regarding exposures and resultant harms. Evidence from one study suggested that the association between first trimester exposure to lithium and overall congenital anomalies (adjusted RR, 1.85; 95% CI, 1.23 to 2.78) and cardiac anomalies (adjusted RR, 2.25; 95% CI, 1.17 to 4.34) may be greater than the association between first trimester exposure to lamotrigine and the same

outcomes (low SOE). This evidence could support a decision to transition from lithium to lamotrigine when clinically appropriate. The evidence is insufficient for all other comparisons and outcomes.

DISCUSSION

Despite the high reported prevalence for any mental health disorder among pregnant women (25.3% in the United States in 2001 to 2002 (95)), the evidence is very sparse on the benefits of pharmacotherapy, mostly reflecting how little controlled, high-quality research has been undertaken in this population. Available evidence of

benefit is limited in design (e.g., 2 cohort studies for bipolar disorder (32,33)), number and size of studies (e.g., 2 RCTs for sertraline response and remission, $N = 145$ (24,25)), and duration for outcome reporting (e.g., 30 days for brexanolone (30,31)). Regarding benefits of treatment, the absence of evidence on the efficacy of many psychotropic drugs in pregnancy or in the postpartum period should not be interpreted as an absence of their benefit. Substantial evidence exists on the efficacy of psychotropic medications across a broad spectrum of persons with mental health disorders. Systematic reviews in the general population have found evidence of benefit for several pharmacological agents for anxiety, depression, bipolar disorder, and schizophrenia (96–100), may be interpreted as applicable to pregnant and postpartum women. However, doses of medication may need to be adjusted to maintain comparable blood levels of medication given the physiological changes in blood volume and other pharmacokinetic considerations during pregnancy (101,102); specialist training may help attune clinical providers to these issues.

Regarding treatment harms, the review was restricted to studies comparing women receiving psychotropic drugs with women with a mental health disorder who were not receiving psychotropic drugs. Despite this requirement, no observational study could completely control for psychiatric illness severity that could have predicted both exposure and outcome. Fewer than one quarter of studies across the review considered dose of exposure, further complicating the extent to which inferences can be drawn between the stated exposure and the outcome. Furthermore, some harms are self-limiting (as in the case of Apgar scores, which assess immediate need for resuscitation and do not predict individual neonatal mortality or neurologic outcome (103)) or very rare (as in the case of persistent pulmonary hypertension). The consideration of the balance of benefits and harms should include a discussion of the absolute risks of these harms. Additionally, the risks of proceeding without treatment should be compared with the specific pharmacologic treatment being considered. Given the well-documented maternal and fetal risks of untreated maternal mental health disorders, shared and collaborative decision-making tailored to a patient's specific mental health diagnosis is essential for clinical decision making.

Finally, the findings on comparative benefits and harms were very sparse. The paucity of definitive evidence on this topic offers many new opportunities for research. Clinical trials offer the greatest rigor, but feasibility and ethics have constrained their use. Routine exclusion of pregnant and lactating women from clinical trials forces patients and providers to make clinical decisions in the absence of evidence. In 2018, the Task Force on Research Specific to Pregnant Women and Lactating Women issued recommendations to include pregnant and lactating women in scientific studies and remove regulatory barriers to participation in research (104). Pragmatic trial designs and collaborative care models that allow ongoing data collection may permit greater rigor while addressing confounding.

A large proportion of studies included in our review are observational and often draw from registries and prescription databases. The limitations posed by these data sources, particularly with regard to data collection on symptoms, can skew the overall evidence base to focus on harms rather than benefits. New efforts, such as the Outcome Measures Framework, supported by the Agency for Healthcare Research and Quality, can help categorize outcomes and harmonize data collection. A recent publication suggested a minimum set of outcome measures for depression in patient registries and clinical practice and provides guidance for implementation and data collection (105). Claims data will also continue to be important in identifying harms but will need to offer better evidence of severity of disorders, dosing, and duration of exposure to adequately control for confounding. Linked databases of maternal and child outcomes can also help to control for selection bias and confounding.

Limitations

Few pharmacotherapy RCTs for mental health disorders during pregnancy or lactation were identified; observational studies comprised the bulk of this review. A significant constraint to interpreting the evidence is the widespread risk of confounding. Common data sources such as registry studies did not have data on severity of psychiatric illness and as a result were unable to control for confounding adequately. In some instances, controls for confounding reduced the effect size and reversed the direction of effect.

The restriction of the evidence to women with mental health disorders served as a means of reducing the potential for confounding in the evidence base. However, this criterion excluded studies of well-conducted negative controls that might bolster the evidence on the association between exposure and outcome. Also, this criterion excluded studies reporting on relevant outcomes for pharmacotherapy exposures for other clinical conditions (e.g., epilepsy). Studies of multiple drug exposures presented results for each exposure but did not always present results separately for women with multiple drug exposures. In studies with overlapping arms, the association of the specific drug and the outcome could not be ascertained. As a result, these studies were excluded. The exclusion of studies with overlapping arms also restricted the comprehensiveness of the review. These limitations of the evidence and review criteria mean that the signals of harms identified may be partially or wholly attributable to residual confounding. Eligible studies were further limited by restriction to English language studies.

CONCLUSION

Evidence from few studies supports the use of pharmacotherapy for perinatal mental health disorders. Although many studies report on increased adverse events, they could not rule out underlying disease severity as the cause of the association between exposures and adverse events. Patients and clinicians need to make informed, collaborative decisions on treatment choices.

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REFERENCES

1. Palladino CL, Singh V, Campbell J, et al: Homicide and suicide during the perinatal period. Obstet Gynecol 2011; 118(5):1056–1063. https://doi.org/10.1097/AOG.0b013e31823294da
2. McLearn KT, Minkovitz CS, Strobino DM, et al: The timing of maternal depressive symptoms and mothers' parenting practices with young children: implications for pediatric practice. Pediatrics 2006; 118 (1):e174–e182. https://doi.org/10.1542/peds.2005-1551
3. Ashman SB, Dawson G: Maternal depression, infant psychobiological development, and risk for depression. Children of depressed parents: mechanisms of risk and implications for treatment. Washington: American Psychological Association; 2002. p. 37–58
4. Field T, Sandberg D, Garcia R, et al: Pregnancy problems, postpartum depression, and early mother–infant interactions. Dev Psychol 1985; 21 (6):1152–1156. https://doi.org/10.1037/0012-1649.21.6.1152
5. Burke L: The impact of maternal depression on familial relationships. Int Rev Psychiatr 2003; 15 (3):243–255. https://doi.org/10.1080/0954026031000136866
6. Beck CT: The effects of postpartum depression on maternal-infant interaction. Nurs Res. 1995;44 (5):298–305
7. Roca C: An evolution of labeling information for pregnant women: PLLR history and background. Silver Spring, MD: U. S. Food & Drug Administration; 2018. https://www.fda.gov/files/advisory%20committees/published/An-Evolution-of-Labeling-Information-for-Pregnant-Women--PLLR-History.pdf. Accessed Feb 18, 2020
8. Hasan A, Falkai P, Wobrock T, et al: World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for Biological treatment of schizophrenia Part 3: update 2015 management of special circumstances: depression, suicidality, substance use disorders and pregnancy and lactation. World J Biol Psychiatr 2015; 16 (3):142–170. https://doi.org/10.3109/15622975.2015.1009163
9. Molenaar NM, Kamperman AM, Boyce P, et al: Guidelines on treatment of perinatal depression with antidepressants: an international review. Aust N Z J Psychiatry 2018; 52 (4):320–327. https://doi.org/10.1177/0004867418762057
10. Parker GB, Graham RK, Tavella G: Is there consensus across international evidence-based guidelines for the management of bipolar disorder? Acta Psychiatr Scand 2017; 135 (6):515–526. https://doi.org/10.1111/acps.12717
11. Viswanathan M, Middleton J, Goulding A, et al: Maternal and fetal effects of mental health treatments in pregnant and breastfeeding women: a systematic review of pharmacological interventions. 2019. https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019124057

12. Moher D, Liberati A, Tetzlaff J, et al: Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009; 151 (4):264–269. https://doi.org/10.7326/0003-4819-151-4-200908180-00135

13. Sterne JA, Hernán MA, Reeves BC, et al: ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 2016; 355:i4919. https://doi.org/10.1136/bmj.i4919

14. Higgins JPT, Green S: Cochrane handbook for systematic reviews of interventions. Chichester, UK: John Wiley & Sons, Ltd; 2011

15. Borenstein M, Hedges L, Higgins J, et al: Comprehensive meta-analysis version 3. Englewood: Biostat; 2013

16. DerSimonian R, Laird N: Meta-analysis in clinical trials. Contr Clin Trials 1986; 7 (3):177–188. https://doi.org/10.1016/0197-2456(86)90046-2

17. Akl E, Mustafa R, Wiercioch N, GRADE Working Group. 1. Overview of the GRADE approach. In: Schunemann H, Brozek J, Guyatt G, Oxman A, editors. GRADE handbook. Geneva: World Health Organization; 2013

18. Berkman ND, Lohr KN, Ansari MT, et al: Grading the strength of a body of evidence when assessing health care interventions: an EPC update. J Clin Epidemiol. 2015; 68 (11):1312–1324. https://doi.org/10.1016/j.jclinepi.2014.11.023

19. Reisner JG: Hydroxyzine for controlling postpartum anxiety: a double-blind study. Nebr State Med J 1967; 52 (11): 498–499

20. Oberlander TF, Warburton W, Misri S, et al: Neonatal outcomes after prenatal exposure to selective serotonin reuptake inhibitor antidepressants and maternal depression using population-based linked health data. Arch Gen Psychiatry 2006; 63 (8):898–906. https://doi.org/10.1001/archpsyc.63.8.898

21. Appleby L, Warner R, Whitton A, et al: A controlled study of fluoxetine and cognitive-behavioural counselling in the treatment of postnatal depression. BMJ 1997; 314 (7085): 932–932

22. Koren G, Nulman I, Addis A: Outcome of children exposed in utero to fluoxetine: a critical review. Depress Anxiety. 1998; 8 (Suppl 1):27–31

23. Yonkers KA, Lin H, Howell HB, et al: Pharmacologic treatment of postpartum women with new-onset major depressive disorder. J. Clin. Psychiatry 2008; 69 (4):659–665

24. Hantsoo L, Ward-O'Brien D, Czarkowski KA, et al: A randomized, placebo-controlled, double-blind trial of sertraline for postpartum depression. Psychopharmacology 2014; 231 (5):939–948. https://doi.org/10.1007/s00213-013-3316-1

25. O'Hara MW, Pearlstein T, Stuart S, et al: A placebo controlled treatment trial of sertraline and interpersonal psychotherapy for postpartum depression. J Affect Disord 2019; 245:524–532. https://doi.org/10.1016/j.jad.2018.10.361

26. Milgrom J, Gemmill AW, Ericksen J, et al: Treatment of postnatal depression with cognitive behavioural therapy, sertraline and combination therapy: a randomised controlled trial. Aust N Z J Psychiatry 2015; 49 (3):236–245. https://doi.org/10.1177/0004867414565474

27. Bloch M, Meiboom H, Lorberblatt M, et al: The effect of sertraline add-on to brief dynamic psychotherapy for the treatment of postpartum depression. J. Clin. Psychiatry 2012; 73 (2):235–241. https://doi.org/10.4088/JCP.11m07117

28. Wisner KL, Hanusa BH, Perel JM, et al: Postpartum depression. J Clin Psychopharmacol 2006; 26 (4):353–360. https://doi.org/10.1097/01.jcp.0000227706.56870.dd

29. Lanza di Scalea T, Hanusa BH, Wisner KL: Sexual function in postpartum women treated for depression. J. Clin. Psychiatry 2009; 70 (3):423–428

30. Meltzer-Brody S, Colquhoun H, Riesenberg R, et al: Brexanolone injection in post-partum depression: two multicentre, double-blind, randomised, placebo-controlled, phase 3 trials Lancet. 2018;392 (10152):1058–1070. https://doi.org/10.1016/s0140-6736(18)31551-4

31. Kanes S, Colquhoun H, Gunduz-Bruce H, et al: Brexanolone (SAGE-547 injection) in post-partum depression: a randomised controlled trial. Lancet 2017; 390 (10093):480–489. https://doi.org/10.1016/s0140-6736(17)31264-3

32. Viguera AC, Whitfield T, Baldessarini RJ, et al: Risk of recurrence in women with bipolar disorder during pregnancy: prospective study of mood stabilizer discontinuation. Am J Psychiatry 2007; 164 (12):1817–1824, quiz 923. https://doi.org/10.1176/appi.ajp.2007.06101639

33. Newport DJ, Stowe ZN, Viguera AC, et al: Lamotrigine in bipolar disorder: efficacy during pregnancy. Bipolar Disord 2008; 10 (3):432–436. https://doi.org/10.1111/j.1399-5618.2007.00565.x

34. Wesseloo R, Liu X, Clark CT, et al: Risk of postpartum episodes in women with bipolar disorder after lamotrigine or lithium use during pregnancy: a population-based cohort study. J Affect Disord 2017; 218:394–397. https://doi.org/10.1016/j.jad.2017.04.070

35. Sharma V, Smith A, Mazmanian D: Olanzapine in the prevention of postpartum psychosis and mood episodes in bipolar disorder. Bipolar Disord. 2006; 8 (4):400–444. https://doi.org/10.1111/j.1399-5618.2006.00335.x

36. Lebedevs T, Gan M, Teoh SWK, et al: Analysis of perinatal women attending a mother and baby unit taking sodium valproate or lithium with a diagnosis of bipolar affective disorder. Psychiatr Q 2020; 91:695. https://doi.org/10.1007/s11126-020-09729-2

37. Wall-Wieler E, Robakis TK, Lyell DJ, et al: Benzodiazepine use before conception and risk of ectopic pregnancy. Hum Reprod 2020; 35:1685. https://doi.org/10.1093/humrep/deaa082

38. Palmsten K, Hernandez-Diaz S, Huybrechts KF, et al: Use of antidepressants near delivery and risk of postpartum hemorrhage: cohort study of low income women in the United States. BMJ 2013; 347:f4877. https://doi.org/10.1136/bmj.f4877

39. Palmsten K, Huybrechts KF, Michels KB, et al: Antidepressant use and risk for preeclampsia. Epidemiology 2013;24 (5):682–691. https://doi.org/10.1097/EDE.0b013e31829e0aaa

40. Palmsten K, Setoguchi S, Margulis AV, et al: Elevated risk of preeclampsia in pregnant women with depression: depression or antidepressants? Am J Epidemiol 2012; 175 (10):988–997. https://doi.org/10.1093/aje/kwr394

41. Park Y, Hernandez-Diaz S, Bateman BT, et al: Continuation of atypical antipsychotic medication during early pregnancy and the risk of gestational diabetes. Am J Psychiatry 2018; 175 (6):564–574. https://doi.org/10.1176/appi.ajp.2018.17040393

42. Ban L, Tata LJ, West J, et al: Live and non-live pregnancy outcomes among women with depression and anxiety: a population-based study. PloS One 2012; 7 (8):e43462. https://doi.org/10.1371/journal.pone.0043462

43. Sheehy O, Zhao J-P, Bérard A: Association between incident exposure to benzodiazepines in early pregnancy and risk of spontaneous abortion. JAMA Psychiatry 2019; 76 (9):948–957. https://doi.org/10.1001/jamapsychiatry.2019.0963

44. Almeida ND, Basso O, Abrahamowicz M, et al: Risk of miscarriage in women receiving antidepressants in early pregnancy, correcting for induced abortions. Epidemiology 2016; 27 (4):538–546. https://doi.org/10.1097/ede.0000000000000484

45. Freeman MP, Góez-Mogollón L, McInerney KA, et al: Obstetrical and neonatal outcomes after benzodiazepine exposure during pregnancy: results from a prospective registry of women

with psychiatric disorders. Gen Hosp Psychiatr 2018; 53:73–79. https://doi.org/10.1016/j.genhosppsych.2018.05.010

46. Cantarutti A, Merlino L, Giaquinto C, et al: Use of antidepressant medication in pregnancy and adverse neonatal outcomes: a population-based investigation. Pharmacoepidemiol Drug Saf 2017; 26 (9):1100–1108. https://doi.org/10.1002/pds.4242

47. Malm H, Sourander A, Gissler M, et al: Pregnancy complications following prenatal exposure to SSRIs or maternal psychiatric disorders: results from population-based national register data. Am J Psychiatry 2015; 172 (12):1224–1232. https://doi.org/10.1176/appi.ajp.2015.14121575

48. Huybrechts KF, Bateman BT, Palmsten K, et al: Antidepressant use late in pregnancy and risk of persistent pulmonary hypertension of the newborn. J Am Med Assoc 2015; 313 (21):2142–2151. https://doi.org/10.1001/jama.2015.5605

49. Malm H, Brown AS, Gissler M, et al: Gestational exposure to selective serotonin reuptake inhibitors and offspring psychiatric disorders: a national register-based study. J Am Acad Child Adolesc Psychiatry 2016; 55 (5):359–366. https://doi.org/10.1016/j.jaac.2016.02.013

50. Rai D, Lee BK, Dalman C, et al: Antidepressants during pregnancy and autism in offspring: population based cohort study. BMJ 2017;358:j2811. https://doi.org/10.1136/bmj.j2811

51. Ban L, West J, Gibson JE, et al: First trimester exposure to anxiolytic and hypnotic drugs and the risks of major congenital anomalies: a United Kingdom population-based cohort study. PLoS One 2014; 9(6):e100996. https://doi.org/10.1371/journal.pone.0100996

52. Juric S, Newport DJ, Ritchie JC, et al: Zolpidem (Ambien) in pregnancy: placental passage and outcome. Arch Womens Ment Health 2009; 12 (6):441–446. https://doi.org/10.1007/s00737-009-0100-7

53. Bérard A, Zhao J-P, Sheehy O: Antidepressant use during pregnancy and the risk of major congenital malformations in a cohort of depressed pregnant women: an updated analysis of the Quebec Pregnancy Cohort. BMJ Open 2017;7 (1):e013372. https://doi.org/10.1136/bmjopen-2016-013372

54. Bérard A, Zhao J-P, Sheehy O. Sertraline use during pregnancy and the risk of major malformations. Am J Obstet Gynecol 2015; 212 (6):e1–e795. https://doi.org/10.1016/j.ajog.2015.01.034

55. Ban L, Gibson J, West J, et al: Maternal depression, antidepressant prescriptions, and congenital anomaly risk in offspring: a population-based cohort study. BJOG 2014; 121 (12):1471–81. https://doi.org/10.1111/1471-0528.12682

56. Jimenez-Solem E, Andersen JT, Petersen M, et al: Exposure to selective serotonin reuptake inhibitors and the risk of congenital malformations: a nationwide cohort study. BMJ Open 2012; 2 (3):e001148. https://doi.org/10.1136/bmjopen-2012-001148

57. Ramos É, St-André M, Rey É, et al: Duration of antidepressant use during pregnancy and risk of major congenital malformations. Br J Psychiatry 2008; 192 (5):344–350. https://doi.org/10.1192/bjp.bp.107.042523

58. Huybrechts KF, Palmsten K, Avorn J, et al: Antidepressant use in pregnancy and the risk of cardiac defects. N Engl J Med 2014; 370 (25):2397–2407. https://doi.org/10.1056/NEJMoa1312828

59. Anderson KN, Lind JN, Simeone RM, et al: Maternal use of specific antidepressant medications during early pregnancy and the risk of selected birth defects. JAMA Psychiatry 2020; 77:1246. https://doi.org/10.1001/jamapsychiatry.2020.2453

60. Lupattelli A, Wood M, Ystrom E, et al: Effect of time-dependent selective serotonin reuptake inhibitor antidepressants during pregnancy on behavioral, emotional, and social development in preschool-aged children. J Am Acad Child

Adolesc Psychiatry 2018; 57 (3):200–208. https://doi.org/10.1016/j.jaac.2017.12.010

61. Cantarutti A, Merlino L, Monzani E, et al: Is the risk of preterm birth and low birth weight affected by the use of antidepressant agents during pregnancy? A population-based investigation. PLoS One 2016; 11 (12):e0168115. https://doi.org/10.1371/journal.pone.0168115

62. Brown AS, Gyllenberg D, Malm H, et al: Association of selective serotonin reuptake inhibitor exposure during pregnancy with speech, scholastic, and motor disorders in offspring. JAMA Psychiatry 2016; 73 (11):1163–1170. https://doi.org/10.1001/jamapsychiatry.2016.2594

63. El Marroun H, White TJ, Fernandez G, et al: Prenatal exposure to selective serotonin reuptake inhibitors and non-verbal cognitive functioning in childhood. J Psychopharmacol 2017; 31 (3):346–355. https://doi.org/10.1177/0269881116665335

64. Eriksen H-LF, Kesmodel US, Pedersen LH, et al: No association between prenatal exposure to psychotropics and intelligence at age five. Acta Obstet Gynecol Scand 2015; 94 (5):501–507. https://doi.org/10.1111/aogs.12611

65. Wisner KL, Bogen DL, Sit D, et al: Does fetal exposure to SSRIs or maternal depression impact infant growth? Am J Psychiatry 2013; 170 (5):485–493. https://doi.org/10.1176/appi.ajp.2012.11121873

66. Salisbury AL, Wisner KL, Pearlstein T, et al: Newborn neurobehavioral patterns are differentially related to prenatal maternal major depressive disorder and serotonin reuptake inhibitor treatment. Depress Anxiety 2011; 28 (11):1008–1019. https://doi.org/10.1002/da.20883

67. Ramos É, St-André M, Bérard A. Association between antidepressant use during pregnancy and infants born small for gestational age. Can J Psychiatry 2010; 55 (10):643–652

68. Toh S, Mitchell AA, Louik C, et al: Antidepressant use during pregnancy and the risk of preterm delivery and fetal growth restriction. J Clin Psychopharmacol 2009; 29 (6):555–560. https://doi.org/10.1097/JCP.0b013e3181bf344c

69. Casper RC, Fleisher BE, Lee-Ancajas JC, et al: Follow-up of children of depressed mothers exposed or not exposed to antidepressant drugs during pregnancy. J Pediatr 2003; 142 (4):402–408. https://doi.org/10.1067/mpd.2003.139

70. Grzeskowiak LE, Gilbert AL, Sørensen TIA, et al: Prenatal exposure to selective serotonin reuptake inhibitors and childhood overweight at 7 years of age. Ann Epidemiol 2013; 23 (11):681–687. https://doi.org/10.1016/j.annepidem.2013.08.005

71. Grzeskowiak L, Morrison J, Henriksen T, et al: Prenatal antidepressant exposure and child behavioural outcomes at 7 years of age: a study within the Danish National Birth Cohort. BJOG 2016; 123 (12):1919–1928. https://doi.org/10.1111/1471-0528.13611

72. Grzeskowiak LE, Gilbert AL, Morrison JL. Neonatal outcomes after late-gestation exposure to selective serotonin reuptake inhibitors. J Clin Psychopharmacol. 2012;32 (5):615–621. https://doi.org/10.1097/JCP.0b013e31826686bc

73. Güngör BB, Öztürk N, Atar AÖ, et al: Comparison of the groups treated with mirtazapine and selective serotonine reuptake inhibitors with respect to birth outcomes and severity of psychiatric disorder. Psychiatry Clin Psychopharmacol 2019; 29 (4):822–831. https://doi.org/10.1080/24750573.2019.1673936

74. Wartko PD, Weiss NS, Enquobahrie DA, et al: Antidepressant continuation in pregnancy and risk of gestational diabetes. Pharmacoepidemiol Drug Saf 2019; 28 (9):1194–1203. https://doi.org/10.1002/pds.4799

75. Viktorin A, Uher R, Reichenberg A, et al: Autism risk following antidepressant medication during pregnancy. Psychol Med 2017; 47 (16):2787–2796. https://doi.org/10.1017/s0033291717001301

76. Huybrechts KF, Bateman BT, Pawar A, et al: Maternal and fetal outcomes following exposure to duloxetine in pregnancy: cohort study. BMJ 2020; 368:m237 https://doi.org/10.1136/bmj.m237

77. Cohen JM, Huybrechts KF, Patorno E, et al: Anticonvulsant mood stabilizer and lithium use and risk of adverse pregnancy outcomes. J. Clin. Psychiatry 2019; 80(4). https://doi.org/10.4088/JCP.18m12572

78. Forsberg L, Adler M, Römer Ek I, et al: Maternal mood disorders and lithium exposure in utero were not associated with poor cognitive development during childhood. Acta Paediatr 2018; 107 (8):1379–1388. https://doi.org/10.1111/apa.14152

79. Galbally M, Frayne J, Watson SJ, et al: The association between gestational diabetes mellitus, antipsychotics and severe mental illness in pregnancy: a multicentre study. Aust N Z J Obstet Gynaecol 2020; 60 (1):63–69. https://doi.org/10.1111/ajo.12986

80. Panchaud A, Hernandez-Diaz S, Freeman MP, et al: Use of atypical antipsychotics in pregnancy and maternal gestational diabetes. J Psychiatr Res 2017; 95:84–90. https://doi.org/10.1016/j.jpsychires.2017.07.025

81. Cohen LS, Viguera AC, McInerney KA, et al: Reproductive safety of second-generation antipsychotics: current data from the Massachusetts general hospital national pregnancy registry for atypical antipsychotics. Am J Psychiatry 2016; 173 (3):263–270. https://doi.org/10.1176/appi.ajp.2015.15040506

82. Huybrechts KF, Hernández-Díaz S, Patorno E, et al: Antipsychotic use in pregnancy and the risk for congenital malformations. JAMA Psychiatry 2016; 73 (9):938–946. https://doi.org/10.1001/jamapsychiatry.2016.1520

83. Lin H-C, Chen I-J, Chen Y-H, et al: Maternal schizophrenia and pregnancy outcome: does the use of antipsychotics make a difference?. Schizophr Res 2010; 116 (1):55–60. https://doi.org/10.1016/j.schres.2009.10.011

84. Cohen LS, Góez-Mogollón L, Sosinsky AZ, et al: Risk of major malformations in infants following first-trimester exposure to quetiapine. Am J Psychiatry 2018; 175:1225. https://doi.org/10.1176/appi.ajp.2018.18010098

85. McCloskey DJ, Postolache TT, Vittone BJ, et al: Selective serotonin reuptake inhibitors: measurement of effect on platelet function. Transl Res 2008; 151 (3):168–172. https://doi.org/10.1016/j.trsl.2007.10.004

86. Qu H, Khalil RA: Vascular mechanisms and molecular targets in hypertensive pregnancy and preeclampsia. Am J Physiol Heart Circ Physiol 2020; 319: H661. https://doi.org/10.1152/ajpheart.00202.2020

87. Bak M, Fransen A, Janssen J, et al: Almost all antipsychotics result in weight gain: a meta-analysis. PLoS One 2014; 9 (4): e94112. https://doi.org/10.1371/journal.pone.0094112

88. Lilly USA: Highlights of prescribing information—Zyprexa. Reference ID: 3675779. Indianapolis, IN:Eli Lilly and Company; 2009. https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/020592s062021086s040021253s048lbl.pdf. Accessed May 20, 2020

89. AstraZeneca Pharmaceuticals LP. Seroquel medicaiton guide. Reference ID: 3397413. Wilmington: AstraZeneca Pharmaceuticals LP; 2013. https://www.fda.gov/files/drugs/published/Seroquel-Medication-Guide.pdf. Accessed May 20, 2020

90. American College of Obstetricians, Gynecologists' Committee on Practice B-G. ACOG practice Bulletin No. 193: tubal ectopic pregnancy. Obstet Gynecol 2018; 131 (3):e91–e103. https://doi.org/10.1097/AOG.0000000000002560

91. Steurer MA, Baer RJ, Oltman S, et al: Morbidity of persistent pulmonary hypertension of the newborn in the first year of life. J Pediatr 2019; 213:58–65. https://doi.org/10.1016/j.jpeds.2019.06.053

92. Patorno E, Huybrechts KF, Bateman BT, et al: Lithium use in pregnancy and the risk of cardiac malformations. N Engl J Med 2017; 376 (23):2245–2254. https://doi.org/10.1056/NEJMoa1612222

93. Bérard A, Ramos É, Rey É, et al: First trimester exposure to paroxetine and risk of cardiac malformations in infants: the importance of dosage. Birth Defect Res B 2007; 80 (1):18–27. https://doi.org/10.1002/bdrb.20099

94. Källén B, Tandberg A: Lithium and pregnancy. Acta Psychiatr Scand 1983; 68 (2):134–139

95. Vesga-López O, Blanco C, Keyes K, et al: Psychiatric disorders in pregnant and postpartum women in the United States. Arch Gen Psychiatry 2008; 65 (7):805–815. https://doi.org/10.1001/archpsyc.65.7.805

96. Strawn JR, Geracioti L, Rajdev N, et al: Pharmacotherapy for generalized anxiety disorder in adult and pediatric patients: an evidence-based treatment review. Expet Opin Pharmacother 2018; 19 (10):1057–1070. https://doi.org/10.1080/14656566.2018.1491966

97. Cipriani A, Furukawa TA, Salanti G, et al: Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. Lancet 2018; 391 (10128):1357–1366. https://doi.org/10.1016/S0140-6736(17)32802-7

98. Gartlehner G, Hansen RA, Morgan LC, et al: Comparative benefits and harms of second-generation antidepressants for treating major depressive disorder. Ann Intern Med 2011; 155 (11):772–785. https://doi.org/10.7326/0003-4819-155-11-201112060-00009

99. Gartlehner G, Wagner G, Matyas N, et al: Pharmacological and non-pharmacological treatments for major depressive disorder: review of systematic reviews. BMJ Open 2017; 7 (6): e014912. https://doi.org/10.1136/bmjopen-2016-014912

100. Butler M, Urosevic S, Desai P, et al: Treatment for bipolar disorder in adults: a systematic review. Rockville, MD: Comparative Effectiveness Review No. 208. (Prepared by the Minnesota Evidence-based Practice Center under Contract No. 290-2012-00016-I.); 2018

101. Seeman MV: Gender differences in the prescribing of antipsychotic drugs. Am J Psychiatry 2004; 161 (8):1324–1333. https://doi.org/10.1176/appi.ajp.161.8.1324

102. Westin AA, Brekke M, Molden E, et al: Treatment with antipsychotics in pregnancy: changes in drug disposition. Clin Pharmacol Ther 2018; 103 (3):477–484. https://doi.org/10.1002/cpt.770

103. American Academy of Pediatrics Committee on Fetus and Newborn, American College of Obstetricians and Gynecologists Committee on Obstetric Practice. The Apgar score. Pediatrics. 2015; 136

104. Byrne JJ, Saucedo AM, Spong CY. Task force on research specific to pregnant and lactating women. Semin Perinatol 2020; 44 (3):151226. https://doi.org/10.1016/j.semperi.2020.151226

105. Gliklich RE, Leavy MB, Cosgrove L, et al: Harmonized outcome measures for use in depression patient registries and clinical practice. Ann Intern Med 2020; 172:803. https://doi.org/10.7326/M19-3818