Comparative Effectiveness Review
Number 236

Maternal, Fetal, and Child Outcomes of Mental Health Treatments in Women: A Systematic Review of Perinatal Pharmacologic Interventions

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None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

The information in this report is intended to help healthcare decision makers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of healthcare services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of healthcare in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new healthcare technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see https://effectivehealthcare.ahrq.gov/about/epc/evidence-synthesis.

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the healthcare system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the website (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input.

If you have comments on this systematic review, they may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov.

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Key Informants

In designing the study questions, the EPC consulted several Key Informants who represent the end-users of research. The EPC sought the Key Informant input on the priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest.

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Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

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Peer Reviewers

Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report do not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential nonfinancial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

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Maternal, Fetal, and Child Outcomes of Mental Health Treatments in Women: A Systematic Review of Perinatal Pharmacologic Interventions

Background. Untreated maternal mental health disorders can have devastating sequelae for the mother and child. For women who are currently or planning to become pregnant or are breastfeeding, a critical question is whether the benefits of treating psychiatric illness with pharmacologic interventions outweigh the harms for mother and child.

Methods. We conducted a systematic review to assess the benefits and harms of pharmacologic interventions compared with placebo, no treatment, or other pharmacologic interventions for pregnant and postpartum women with mental health disorders. We searched four databases and other sources for evidence available from inception through June 5, 2020 and surveilled the literature through March 2, 2021; dually screened the results; and analyzed eligible studies. We included studies of pregnant, postpartum, or reproductive-age women with a new or preexisting diagnosis of a mental health disorder treated with pharmacotherapy; we excluded psychotherapy. Eligible comparators included women with the disorder but no pharmacotherapy or women who discontinued the pharmacotherapy before pregnancy.

Results. A total of 164 studies (168 articles) met eligibility criteria. Brexanolone for depression onset in the third trimester or in the postpartum period probably improves depressive symptoms at 30 days (least square mean difference in the Hamilton Rating Scale for Depression, -2.6; p=0.02; N=209) when compared with placebo. Sertraline for postpartum depression may improve response (calculated relative risk [RR], 2.24; 95% confidence interval [CI], 0.95 to 5.24; N=36), remission (calculated RR, 2.51; 95% CI, 0.94 to 6.70; N=36), and depressive symptoms (p-values ranging from 0.01 to 0.05) when compared with placebo. Discontinuing use of mood stabilizers during pregnancy may increase recurrence (adjusted hazard ratio [AHR], 2.2; 95% CI, 1.2 to 4.2; N=89) and reduce time to recurrence of mood disorders (2 vs. 28 weeks, AHR, 12.1; 95% CI, 1.6 to 91; N=26) for bipolar disorder when compared with continued use. Brexanolone for depression onset in the third trimester or in the postpartum period may increase the risk of sedation or somnolence, leading to dose interruption or reduction when compared with placebo (5% vs. 0%). More than 95 percent of studies reporting on harms were observational in design and unable to fully account for confounding. These studies suggested some associations between benzodiazepine exposure before conception and ectopic pregnancy; between specific antidepressants during pregnancy and adverse maternal outcomes such as postpartum hemorrhage, preeclampsia, and spontaneous abortion, and child outcomes such as respiratory issues, low Apgar scores, persistent pulmonary hypertension of the newborn, depression in children, and autism spectrum disorder; between quetiapine or olanzapine and gestational diabetes; and between benzodiazepine and neonatal intensive care admissions. Causality cannot be inferred from these studies. We found insufficient evidence on benefits and harms from comparative effectiveness studies, with one exception: one study suggested a higher risk of overall congenital anomalies (adjusted RR [ARR], 1.85; 95% CI, 1.23 to 2.78; N=2,608) and cardiac anomalies (ARR, 2.25; 95% CI, 1.17 to 4.34; N=2,608) for lithium compared with lamotrigine during first-

trimester exposure.

Conclusions. 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. The limited evidence available is consistent with some benefit, and some studies suggested increased adverse events. However, because these studies could not rule out underlying disease severity as the cause of the association, the causal link between the exposure and adverse events is unclear. Patients and clinicians need to make an informed, collaborative decision on treatment choices.

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Evidence Summary

Main Points

- 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.
- First-trimester exposure to lithium is more likely to be associated with overall congenital and cardiac anomalies than first trimester exposure to lamotrigine, which can inform the decision to switch a medication in a successfully treated individual.
- We did not find eligible evidence on congenital anomalies for triazolam, alprazolam, valproate, carbamazepine, clonazepam, and topiramate, although evidence is available from studies of other populations ineligible for this review.
- 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.

Background and Purpose

Untreated mental health disorders in perinatal (pregnant and postpartum, including breastfeeding) women can have devasting sequelae. Pregnancy-associated suicide kills more women than hemorrhage or preeclampsia. Depressive symptoms are associated with reduced safety for the child, increased harsh punishment, impaired development of infant emotional regulation and attachment, and greater risk of psychiatric disease in the child. Treatment choices for mental health disorders include pharmacotherapy, psychotherapy, and other approaches (e.g., yoga, mindfulness, self-care, nutritional or herbal supplements). For women who are currently or planning to become pregnant, a critical question is whether the benefits for mother and fetus of treating psychiatric illness with pharmacologic interventions outweigh the harms; a systematic review will help clarify the balance of benefits and harms.

Methods

We employed methods consistent with those outlined in the Agency for Healthcare Quality and Research Evidence-based Practice Center Program Methods Guidance (https://effectivehealthcare.ahrq.gov/topics/cer-methods-guide/overview), and we describe these in the full report. Our searches covered publication dates in PubMed®, the Cochrane Library, Embase®, and PsycINFO® from inception through June 5, 2020. We surveilled key journals and PubMed through March 2, 2021.

Results

A total of 164 studies (168 articles) met eligibility criteria. Most studies were observational in design and had high risk of bias; they cannot fully address confounding. The associations

between psychotropic medications and outcomes reported in observational studies cannot be inferred to be causal and varied by exposure and outcome.

Key Question (KQ) 1: Benefits of Pharmacologic Treatments Versus No Treatment or Placebo for Pregnant and Postpartum Women With Anxiety, Depression, Bipolar Disorder, or Schizophrenia. Substantial evidence exists on the effectiveness of medications in the general population, but evidence in pregnant and postpartum women is sparse (9 randomized controlled trials [RCTs] and 10 observational studies). When evidence was available, we found low to moderate strength of evidence of benefit. Specifically, for depression, three RCTs offered evidence that brexanolone for depression onset in the third trimester or postpartum is associated with improved depressive symptoms shortly after infusion (60 hours) and at 30 days after treatment (moderate strength of evidence); two RCTs reported that sertraline in the postpartum period achieves response, remission, and improvements in depressive symptoms (low strength of evidence). For bipolar disorders, two cohort studies found that discontinuing mood stabilizers during pregnancy may increase recurrence and reduce time to recurrence (low strength of evidence).

KQ 2: Comparative Benefits of Pharmacologic Treatments for Pregnant and Postpartum Women With Anxiety, Depression, Bipolar Disorder, or Schizophrenia. For depression and bipolar disorder, we found insufficient evidence to judge the comparative effectiveness of a very limited number of outcomes and interventions from one RCT and four observational studies of exposure during pregnancy. For anxiety and schizophrenia, we found no evidence on comparative effectiveness.

KQ 3: Harms of Pharmacologic Treatments Versus No Treatment or Placebo for Pregnant and Postpartum Women With Mental Health Disorders. We found 5 RCTs and 70 observational studies. As a result, most studies could not assert a causal relationship between exposure and resultant harms. We found low strength of evidence for several outcomes. Regarding maternal harms, benzodiazepine before conception may be associated with an increased risk of ectopic pregnancy. During pregnancy, exposure to several antidepressants may be associated with a higher risk of postpartum hemorrhage; serotonin-norepinephrine reuptake inhibitor (SNRIs) and tricyclic antidepressants may be associated with an increased risk of preeclampsia; SNRIs may be associated with spontaneous abortion; and quetiapine and olanzapine may be associated with an increased risk of gestational diabetes. For depression onset in the third trimester or within 4 weeks of birth, brexanolone may be associated with the risk of sedation or somnolence leading to dose interruption or reduction. For child adverse outcomes, we found an association between benzodiazepine and neonatal intensive care unit admissions; between selective serotonin reuptake inhibitors and respiratory issues, low Apgar scores, persistent pulmonary hypertension of the newborn, and depression in children; and between citalopram and autism spectrum disorder. Signals of harms that we identified above may be partially or wholly attributable to residual confounding. Importantly, we found insufficient evidence on congenital anomalies and cardiac defects from studies included our review. We note, however, that we did not find eligible evidence on congenital anomalies for triazolam, alprazolam, valproate, carbamazepine, clonazepam, and topiramate, although evidence is available from studies of other populations ineligible for this review.

KQ 4: Comparative Harms of Pharmacologic Treatments for Pregnant and Postpartum Women With Mental Health Disorders. We found 1 RCT and 55 observational studies; 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 and cardiac anomalies may be greater than the association between first trimester exposure to lamotrigine and the same outcomes (low strength of evidence) during pregnancy, which can inform the decision to switch a medication in a successfully treated individual. The evidence is insufficient for all other comparisons and outcomes.

Limitations

We identified few randomized controlled RCTs of pharmacotherapy for mental health disorders during pregnancy or lactation; therefore we relied on observational studies for the bulk of this review. A significant constraint to interpreting the evidence is the widespread risk of confounding. Underlying mental health disorders result in the use of psychotropic medications. Underlying mental health disorders may also result in some of the harms investigated in this review regardless of exposure to medications. Studies varied greatly in the extent to which they were able to address underlying severity of mental health disorders. The majority were unable to address confounding, often because of a lack of the necessary variables in registry datasets. A small subset of studies attempted various approaches to address confounding (e.g., propensity score adjustment, stratification by number of disorders). In many instances, controls for confounding reduced the effect size and, in some instances, reversed the direction of effect. Most studies were unable to identify dose and duration of exposure. For the benefits question (KQ 1), eligible studies had comparator arms of women with the same disorder as in the treatment arm. For the harms question (KQ 3), however, we were more inclusive and included studies with comparator arms comprising women with prior exposure to the drug, even if the disorder status was not specified. As a result, our KQ 1 evidence base controls for underlying severity as a confounder better than the KQ 3 evidence base.

We elected to restrict the evidence to women with mental health disorders 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 the exposure and the outcome. Also, this criterion resulted in the exclusion of studies reporting on relevant outcomes for exposures to the intervention for other clinical conditions. Studies of multiple drug exposures presented results for each exposure but did not always present results separately for the women with multiple drug exposures. In these studies with overlapping arms, we were not able to attribute the effect of the intervention to a single drug. As a result, we excluded these studies. The exclusion of studies with overlapping arms also restricted the comprehensiveness of our review. These limitations of the evidence and of our review criteria mean that the signals of harms that we identified above may be partially or wholly attributable to residual confounding. We may also have missed eligible studies because of our restriction to English language studies.

Implications and Conclusions

The central decisional dilemma facing pregnant and postpartum women with mental health disorders and their healthcare providers is how to balance benefits and harms of psychotropic drugs for both themselves and their children. One such critical trade-off is whether improved symptoms in the mother outweigh the harms from potential congenital anomalies in the fetus. Given long-standing restrictions on including pregnant and lactating women in clinical trials, few clinical trials have evaluated the effectiveness of pharmacotherapy. By contrast, evidence is voluminous but of low quality on the harms of pharmacotherapy. Our findings indicate the need for clear communication to patients on four primary points: (1) evidence exists that medication

works in the general populations; (2) few studies have measured effectiveness in pregnant women; (3) the limited evidence available is consistent with some benefit; and (4) some studies suggested some increased adverse events, many of which are rare or transient. However, because these studies could not rule out the severity of the underlying mental health disorder as the cause of the association, the causal link between the exposure and adverse events is unclear. The patient and her provider are uniquely qualified to determine whether the mother's medical need for treatment exceeds any potential harms.

Introduction

Background

Untreated mental health disorders among perinatal women (i.e., women who are pregnant or postpartum through 1 year, including those who are breastfeeding) can have devasting sequelae. Pregnancy-associated suicide kills more women than hemorrhage or preeclampsia.[1] In addition to the negative effects on women's health and well-being, depressive symptoms are associated with adverse parenting practices such as reduced use of safety (such as always using car seats) and child development practices (such as limiting television or video watching) and increased use of harsh punishment.[2] In addition, postpartum depression is associated with reduced maternal sensitivity,[3] which may adversely affect development of infant emotional regulation and attachment.[4, 5] Insecure attachment, in turn, increases the risk of psychiatric disease in the child.[3, 6]

According to Census Bureau data, 86 percent of women in the United States will give birth at least once by age 44.[7] The risk of a psychiatric illness during the period immediately before pregnancy, during pregnancy, and through 12 months postpartum is substantial. A nationally representative survey of 14,019 women in the 2001-2002 National Epidemiologic Survey on Alcohol and Related Conditions compared the prevalence of mental health disorders in past-year pregnant women (pregnant at the time of the survey or pregnant in the prior 12 months) and nonpregnant women of childbearing age. The survey found that 25.3 percent of women pregnant in the past year reported any mental health or substance use disorder or combination of disorders.[8]

However, pregnancy does not appear to be associated with a higher or lower prevalence of mental health disorders in general. Differences in the prevalence for specific mental health disorders between nonpregnant women of childbearing age and past-year pregnant women all lie within the margin of error; major depressive disorder: 8.1 percent versus 8.4 percent, adjusted odds ratio (AOR), 1.24, (95% confidence interval [CI], 0.94 to 1.64), bipolar disorder: 2.3 percent versus 2.8 percent, AOR, 1.09, (95% CI, 0.70 to 1.70), anxiety disorders: 14.9 percent versus 13.0 percent, AOR, 0.99, (95% CI, 0.68 to 1.43) and any psychotic disorder (including schizophrenia): 0.3 percent versus 0.4 percent, AOR, 1.50, (95% CI, 0.54 to 4.18).[8]

Among mental health disorders in the perinatal period and the first year postpartum, depression (major depressive disorder and other depressive disorders) is the most common form, although depression and anxiety often coexist. In women with postpartum depression, for example, 66 percent have been reported to have a comorbid anxiety disorder diagnosis.[9]

In addition to understanding how to manage prevalent psychiatric illness, healthcare providers also need to consider how best to manage new-onset mental health disorders during the perinatal period. The incidence of these disorders may be difficult to quantify accurately because most women with a psychiatric condition do not receive mental healthcare, regardless of pregnancy status: many women have few encounters with the healthcare system prior to their pregnancy.

The National Epidemiologic Survey did find significantly higher odds of depression among postpartum women when compared with nonpregnant women. However, some uncertainty persists as to whether higher rates of postpartum depression reflect poor identification during pregnancy rather than new onset of the disorder in the postpartum period[10] and whether the differences in prevalence of depression between past-year pregnant women and nonpregnant women might be overstated.[11]

A recent Danish study of perinatal women found no differences between pregnancy and postpartum in first-time psychiatric episodes treated at outpatient facilities. It did, however, report a significant increase in first-time psychiatric episodes treated at inpatient facilities shortly following childbirth when compared with during pregnancy, suggesting a potentially different etiology for severe mental health disorders. The authors suggested that childbirth could serve as a "potent and highly significant trigger" of severe psychiatric episodes.[12]

Treatment Strategies

Treatment choices for mental health disorders include pharmacotherapy, psychotherapy, and other approaches (e.g., yoga, mindfulness, self-care, nutritional or herbal supplements). The likelihood of perinatal exposure to psychotropic drugs for mental health disorders is increasing, but no clear and comprehensive summary of their effects exists. Among women of childbearing age, use of prescription antidepressants in the 30 days before the National Health and Nutrition Examination Survey has increased markedly over the past 30 years, from 2.3 percent (1988 through 1994) to 14.8 percent (2007 through 2010).[13] Regarding exposure during pregnancy specifically, more recent data (2006 through 2011) on women with private insurance indicate a rate of exposure of 10.1 percent to psychotropic medications during pregnancy.[14] Rates of exposure during pregnancy vary by drug: Medicaid claims data from 2000 through 2007 show that 8.1 percent of women were exposed to an antidepressant during pregnancy.[15] From 2001 through 2007, use of second-generation antipsychotics by pregnant women more than doubled, from 0.3 percent to 0.8 percent;[16] use of antiepileptic drugs increased from 1.57 percent of deliveries to 2.19 percent.[17] Rates of exposure to psychotropic drugs may continue to rise as newer, more targeted therapies are approved: one recently approved drug, brexanolone, targets postpartum depression specifically.[18, 19]

Treatment strategies need to account for the balance between benefits and harms. Food and Drug Administration (FDA) offers information on potential harms through warning language in prescription labeling and boxed warnings. FDA offers cautionary language in prescription labeling sections that are specific to pregnancy, lactation, and males and females with reproductive potential.[20] Additionally, FDA may offer its most prominent warning in the form of a boxed warning. Boxed warnings are issued when the risk of adverse reactions is "so serious in proportion to the potential benefit"[21, p. 11] that the risks must be considered when deciding to use the drug. Through 2014, FDA also used to apply letter categories to drugs to indicate toxicity but has discontinued their use because of concerns about misinterpretation and oversimplification.[22]

Clinical and Policy Context

For women who are currently or planning to be pregnant, a critical question is whether the benefits for mother and fetus of treating psychiatric illness with pharmacologic interventions outweigh the harms. Similarly, a key decision for breastfeeding women is whether the harms of infants' medication exposure via breastmilk outweighs either harms to women of not being treated with pharmacotherapy[4, 5, 23, 24] or harms to mother and infant of not breastfeeding.[25]

In addressing these decisional dilemmas, clinical practice guidelines on the use of psychotropic medications during three stages of the perinatal period (before pregnancy, during pregnancy, and during lactation) must address multiple clinical scenarios. Specifically, guidance is needed at each stage on treatments for new diagnoses and whether to continue, add to, or switch psychotropic medications for preexisting diagnoses.[26, 27] These guidelines need to address

the high rate of unplanned pregnancies[28] and the consequent need for a change in medication management or reassurance to women in early stages of pregnancy.

The evidence base has two important constraints in providing support for clinical practice guidelines: (1) lack of trial data, which leads to reliance on observational data, and (2) heterogeneity of the included conditions, medications, and comparators.

Trial evidence on psychotropic medications (for any indication) in pregnant or breastfeeding women is "historically lacking."[29] Concerns about maternal and fetal safety, ethics, and the logistics of trial design serve as constraints,[30] leaving patients and clinicians with a dearth of information to make therapeutic decisions. To address this gap, a recent report to Congress advocates for inclusion of pregnant and lactating women in clinical trials.[31] At the same time, high-quality safety data are also limited.[32] Absent high-quality evidence, clinical recommendations may vary on key decisions—such as whether to continue antidepressants in the preconception, pregnancy, and breastfeeding phases and what agent to use[33]—or fall back on expert opinion.[34, 35]

The heterogeneity of included populations and pharmacologic interventions further complicates interpretation of the evidence. Some medications are prescribed across numerous conditions; coexisting mental health conditions are common. Complexity and severity of mental health conditions, baseline symptom control, and health status also require consideration. For example, dosage for a second-generation antipsychotic in hard-to-treat major depression is much lower than dosage used to treat a primary bipolar disorder; the balance of benefits and harms would differ as a result. Underlying variations in population characteristics and medication dosing might explain important differences in harms. The number and diversity of interventions also introduce complexity. A woman's decision to pursue pharmacologic or psychological therapy may turn on socioeconomic factors such as locally available psychotherapists, insurance coverage, transportation, paid time off from work to attend therapy, and access to childcare. These social determinants of health may confound observed associations between use of pharmacologic therapy and clinical outcomes.

Three recent reviews have reported on guidelines for treating depression, bipolar disorder, and schizophrenia in perinatal women;[26, 33, 36] there is no clear consensus on what best practices are. Table 1 summarizes areas where multiple guidelines agree, disagree, or indicate uncertainty. Areas of concordance are not always based on evidence: they may be based on clinical judgment. They do not necessarily represent consensus in the field because not all guidelines may comment on a topic. Notably, recommendations regarding the same drug class (e.g., antipsychotics or antidepressants) varied by mental health condition. Guidelines also varied in whether the recommendation was issued for a specific drug or drug class. Other areas of uncertainty include treatment options (starting, continuing, switching, or stopping medications) for breastfeeding women or symptomatic women.

Purpose and Scope of the Systematic Review

Inconsistencies and uncertainties in the management of maternal mental health disorders point to the need for a systematic review to help clarify the balance of benefits and harms from psychotropic drugs for these disorders. Guideline developers will benefit from a systematic review that addresses both benefits and harms of psychotropic drugs so that they can address net benefit. A systematic review of the harms of psychotropic drugs that accounts for underlying severity and disorders but also addresses drug class effects can help resolve inconsistencies in

recommendations. Finally, guideline developers will benefit from a synthesis of the evidence on the consequences of stopping or switching drugs.

The Agency for Healthcare Research and Quality and its partners, the American College of Obstetricians and Gynecologists and the American Psychiatric Association, will use this review to inform vital questions of safe management of psychotropic drugs in the perinatal period, considering both benefits (Key Questions [KQs] 1 and 2) and harms (KQs 3 and 4). Specifically, in pregnant or breastfeeding women with an anxiety, depressive, or bipolar disorder or schizophrenia, KQ 1 will consider the benefits of pharmacotherapy compared with placebo or no treatment, while KQ 2 will evaluate the comparative benefits of pharmacologic interventions. In women with any mental health condition during the preconception, pregnancy, or postpartum phase, KQ 3 will focus on maternal and fetal/child harms of pharmacotherapy compared with placebo or no treatment, while KQ 4 will evaluate the comparative harms of pharmacologic interventions. A Contextual Question asks about the harms of not treating a disorder or stopping or switching medications.

This review, as framed, does not span all eligible interventions. Notably, the review does not address the efficacy of nonpharmacologic interventions (e.g., psychological interventions vs. usual care, wait-list, or no treatment). Although this exclusion limits the scope of the review, it reduces the heterogeneity of the included populations: the efficacy population for psychotherapy-only interventions may have lower severity of psychiatric illness. The review also specifies eligible populations as those with a mental health condition; as a result, it excludes studies of negative controls.

Table 1. Concordance* and uncertainty in clinical practice guidelines

Perinatal Period	Depression[33]	Bipolar Disorder[37]	Schizophrenia[26]
Preconception	Concordance • Psychotherapy as initial treatment, antidepressants as initial therapy in severe cases	Concordance • Potential teratogenic effects for lithium, sodium valproate, and carbamazepine	Concordance • Inform patients and partners of the risk and benefits of antipsychotic treatment in pregnancy, especially risks for teratogenicity and malformations in pregnancy • Prescribe 5 mg folate per day 3 months before conception and throughout pregnancy

Perinatal Period	Depression[33]	Bipolar Disorder[37]	Schizophrenia[26]
During pregnancy	Concordance • Four guidelines advise continuation of antidepressants, five do not make a recommendation • Avoid paroxetine because of the risk of congenital cardiac malformations in the newborn Uncertainty • Switching: three guidelines discourage switching, and one promotes switching away from unfavorable medications (paroxetine and fluoxetine) • Optimal treatment for patients with current symptoms despite antidepressant use	Concordance • Consider the balance between risk and benefits in deciding whether to continue treatment • Medication is warranted for symptoms or when relapse is of concern • Consider lithium for women with severe bipolar disorder • Antipsychotics are safer than mood stabilizers • Antidepressants are relatively safe but carry potential neonatal side effects Uncertainty • Discontinuing or reducing lithium dose just before delivery to avoid lithium toxicity in the infant (one guideline only) • Safety of typical vs. atypical antipsychotics • Safety of lamotrigine vs. other drugs Specific antidepressant recommendations within and across drug classes	Concordance • Use antipsychotics that allow control of schizophrenia symptoms and are not contraindicated • If clinically tolerable, avoid introducing an antipsychotic drug until the second or third trimester due to teratogenic risk • Consider the lowest necessary dosage of haloperidol for treatment • Other first-generation antipsychotic should not be initiated in pregnancy • Among second-generation antipsychotics, olanzapine, risperidone, and quetiapine may be considered as treatment, but they all carry risks • Clozapine should not be used in pregnancy • Other second-generation antipsychotic should not be initiated in pregnancy • Do not stop medications without clear safety reasons
During breastfeeding	Concordance • For new episodes, start with psychotherapy as initial treatment and consider antidepressants for severe cases • Continue antidepressants to avoid relapse • Sertraline preferred due to its favorable profile during lactation • Two guidelines also recommend citalopram • Avoid fluoxetine due to its long half-life and presence in breastmilk	Concordance • Reintroduce lithium after delivery • Breastfeeding is not recommended with lithium due to a risk of toxicity for the baby Uncertainty • Lithium dose at reintroduction • Safety of breastfeeding with anticonvulsant mood stabilizers, including sodium valproate, carbamazepine, and lamotrigine, and second-generation antipsychotics • Safety of breastfeeding with antidepressants	Uncertainty • Benefits and harms of specific antipsychotics during breastfeeding

*Concordance indicates that at least two guidelines made similar recommendations and no guidelines disagreed.

Methods

Below we describe the approach used in this systematic review, list the Key Questions (KQs), and describe the analytic framework. We also outline briefly the study selection criteria, data sources and searches, data extraction and risk of bias, data synthesis and analysis, and grading of the strength of the body of evidence. Additional details can be found in Appendix A.

Review Approach

The methods for this systematic review followed the Agency for Healthcare Research and Quality's (AHRQ's) *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* (available at https://effectivehealthcare.ahrq.gov/topics/cer-methods-guide/overview). This systematic review also reports in accordance with the Preferred Items for Reporting in Systematic Reviews and Meta-Analyses.[38]

The topic of this report was developed by AHRQ in consultation with the American College of Obstetricians and Gynecologists and the American Psychiatric Association. A panel of Key Informants gave feedback on the initial proposed KQs; these KQs were posted on AHRQ's Effective Health Care (EHC) website for public comment in July 2018 for 3 weeks and revised in response to comments. We then drafted a protocol for the systematic review and recruited a panel of technical experts to provide high-level content and methodological expertise throughout the development of the review. The final protocol is posted on the EHC website at https://effectivehealthcare.ahrq.gov/products/mental-health-pregnancy/protocol. The PROSPERO registration is CRD42019124057.

Key Questions

The following KQs and Contextual Question (CQ) guided our systematic review.

KQ 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?

KQ 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?

KQ 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?

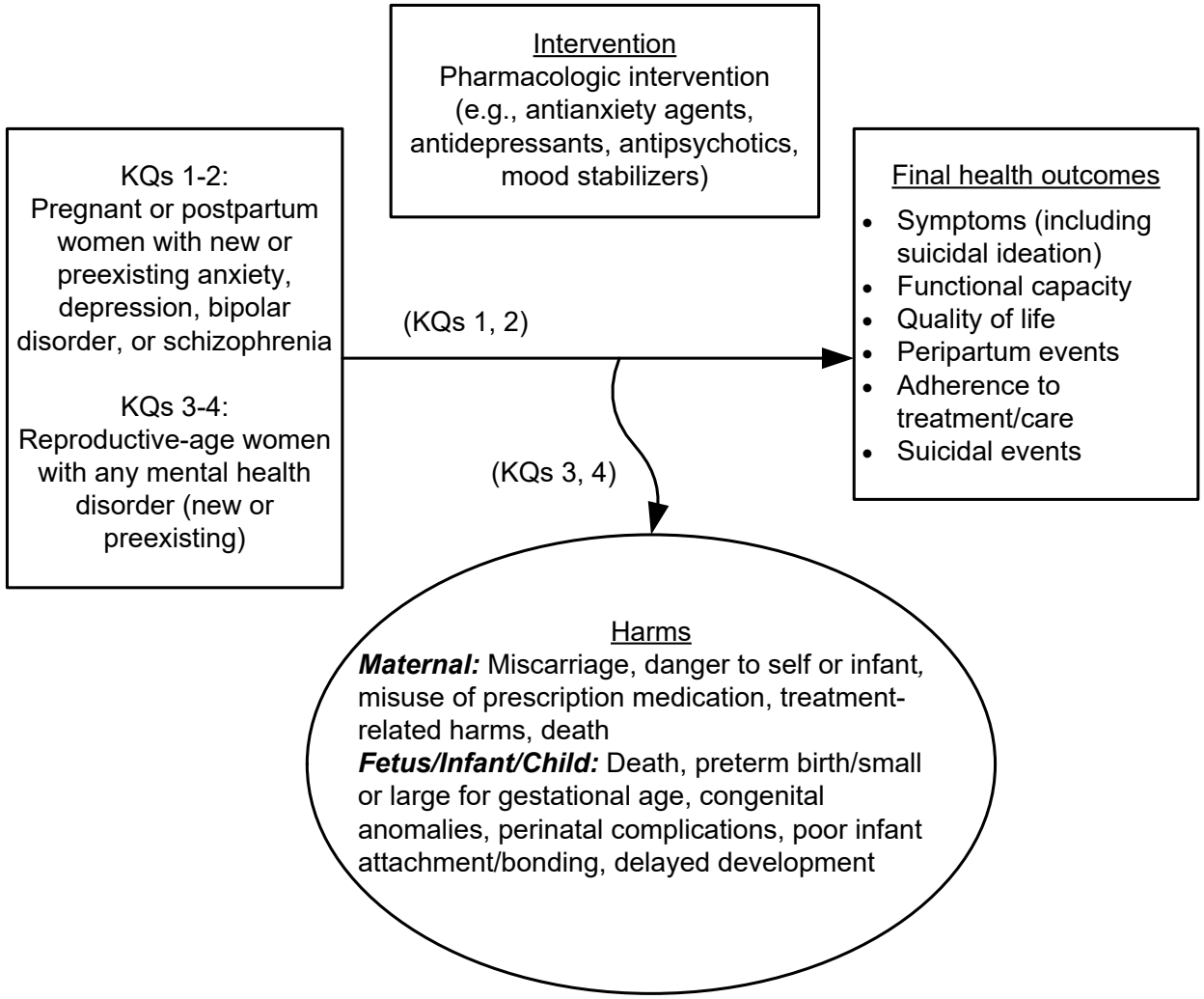
KQ 4. Among reproductive-age women with any mental health disorder, what are the *comparative maternal and fetal harms* of pharmacologic interventions for a mental health disorder during preconception, pregnancy, and postpartum?

CQ 1. Among women who are preconceptional, pregnant, or postpartum, within a given disorder, what are the harms of *not* treating the disorder, stopping a pharmacologic treatment, or switching medications?

Analytic Framework

The analytic framework in Figure 1 illustrates the KQs.

Figure 1. Analytic framework



KQ = Key Question.

Study Selection

Eligible studies met the following criteria: (1) included pregnant, postpartum, or reproductive-age women receiving a pharmacologic intervention for a mental health disorder; (2) included an eligible study design (i.e., randomized controlled trials [RCTs], controlled clinical trials (assignment without randomization), case-control studies, and cohort studies with comparison arms); and (3) were published in English. For KQ 1 and KQ 2, studies met the following additional criteria: (1) included pregnant or postpartum women with a new or preexisting diagnosis of anxiety, depression, bipolar disorder, or schizophrenia; (2) examined an outcome that measured maternal benefit; and (3) had a followup period that ranged from conception up to 1 year postpartum. For KQ 2 and KQ 4, studies also had to meet the following criteria: (1) included women who were of reproductive age (15-44 years old during preconception [≤12 weeks before pregnancy], pregnant, or postpartum [through 1 year]) with any mental health disorder; (2) included an eligible comparison arm; and (3) examined an eligible outcome of maternal or fetal/infant/child harm. For KQ 1 and KQ 3, eligible comparators included placebo or no treatment. For KQ 2 and KQ 4, eligible comparators included active pharmacotherapy.

In applying the criterion of "new or preexisting diagnosis" we did not restrict eligibility to studies with a clinical diagnosis. Many studies reported outcomes based on prescription refills, which used clinician judgment that the underlying disorder would benefit from a pharmacologic intervention as a proxy for diagnosis. We excluded analysis of negative controls (women without a mental health disorder). We also excluded comparisons with nonpharmacologic interventions.

Appendix A lists detailed inclusion and exclusion criteria, organized by population, intervention, comparator, outcome, timing, setting, and study design. In brief, eligible interventions include antipsychotics, selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, other antidepressants, mood stabilizers, antianxiety agents, and other medications for mental health disorders. We excluded psychotherapy.

Data Sources and Searches

We conducted focused searches of PubMed, the Cochrane Library, Embase, and PsycINFO from inception to December 11, 2018, and updated searches on June 4 and 5, 2020. We also searched relevant systematic reviews and gray literature. We surveilled key journals and PubMed through March 2, 2021.

Data Extraction and Risk-of-Bias Assessment

For each included study, one investigator extracted information about design, population, intervention, and outcomes, and a second investigator reviewed the information for completeness and accuracy. The criteria set forth by AHRQ's *Methods Guide for Comparative Effectiveness Reviews* guided our assessment of methodological risk of bias. Two independent investigators assessed the risk of bias of each study, using predefined criteria established in the Risk Of Bias In Non-Randomized Studies - of Interventions (ROBINS-I)[39] tool for observational studies and the Cochrane RCT[40] tool for RCTs. We rated outcomes as low, moderate, or high risk of bias for each study.

Data Synthesis and Analysis

For KQs 2 and 4, we grouped studies by exposure rather than underlying disorder for two reasons: first, many studies did not describe the specific underlying disorder, and second, some outcomes may be relevant across disorder categories. We synthesized all data qualitatively. When studies provided adjusted effect sizes, we used these data to interpret the evidence. When studies did not provide adjusted effect sizes, we calculated relative risks, odds ratios, and risk differences. Additionally, when at least three independent and similar studies were available, random-effects models using the inverse-variance weighted method of DerSimonian and Laird were used to estimate pooled effects for relative risks and risk differences for categorical outcomes and standardized and weighted mean differences for continuous outcomes. All quantitative analyses were conducted using Comprehensive Meta-Analysis (Version 3.3) software.[41] We did not exclude high risk-of-bias studies. We planned to conduct quantitative sensitivity analyses with and without high risk-of-bias studies when the volume of studies on a given outcome permitted such analyses.

Grading the Strength of the Body of Evidence

We graded the strength of evidence based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group guidance[42] and guidance established for the Evidence-based Practice Center Program.[43] Developed to grade the overall strength of a body of evidence, this approach incorporates five key domains: risk of bias (includes study design and aggregate quality), consistency, directness, precision of the evidence, and reporting bias. This approach requires looking beyond statistical significance alone. It requires considering whether studies are consistent and of high quality and outcomes are direct and clinically relevant. It emphasizes the adequacy of the sample size to rule out spurious associations and results that are not clinically relevant.

The domains listed above are reflected in an overall rating regarding the strength of the evidence of high, moderate, low, or insufficient.

- A high strength of evidence reflects high confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
- 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.
- 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.
- 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; be inconsistent, indirect, or imprecise; or be biased in reporting). When high risk-of-bias studies are likely to alter the judgment, we offer a strength-of-evidence grade that relies on the better quality evidence. When the signals from the evidence base are conflicting and we cannot attribute the differences to risk of bias alone, we assigned the grade as insufficient.

- We also note evidence bases where we found no eligible evidence based on our inclusion and exclusion criteria; evidence may be available from studies of other populations ineligible for this review.

Evidence bases consisting of RCTs begin with an overall rating of high; downgrading any domain (study limitations, precision, consistency, directness, and reporting bias) results in lower ratings. Evidence bases consisting of observational studies begin with a rating of low. They may be downgraded for the domains listed above. They may also be upgraded on three domains: dose-response association, plausible confounding that would decrease the observed effect, and strength of association (magnitude of effect).

In Chapter 3, we focus on evidence with high, moderate, or low strength of evidence and summarize insufficient evidence only for bodies of evidence for which we were unable to arrive at a conclusion despite multiple studies on a topic. Insufficient ratings from single studies with imprecise results (i.e., small sample sizes, few events, and very wide confidence intervals; adequately sized samples with wide confidence intervals that do not permit an inference of benefit, harm, or absence of benefit or harm) are described in detail in Appendix B.

Results

In this chapter, we present the yield from literature searches first, followed by a brief description of the characteristics of included studies. The remainder of the chapter presents results organized by Key Question (KQ) and then by evidence grade. Within each KQ section, we first present an overview followed by detailed results. The detailed results for KQ 1 and KQ 3 present evidence separately for disorder first (anxiety, depression, bipolar disorder, and lastly schizophrenia) and then by intervention. The detailed results for KQ 2 and KQ 4 are not specific to disorder groups but also present results for interventions in the same order as in KQs 1 and 3 for consistency; that is, we present results for drugs used for anxiety, depression, bipolar disorder, and then schizophrenia.

For each KQ, first we present results for outcomes graded as moderate or low. Second, we discuss outcomes rated as insufficient for which two or more studies provided evidence. Outcomes for which we found a single study with imprecise results are not discussed in detail. Third, we summarize outcomes and interventions for which we found no eligible evidence based on our review parameters. Summary tables in this chapter list populations; interventions; comparators; outcomes; study details; references; and factors that affect the strength of evidence, the strength of evidence grade, and the direction of effect. We do not provide ratings for directness: we selected outcomes a priori that are directly relevant to the KQ.

Details on results of literature searches, included studies, detailed results for all outcomes, meta-analyses, and excluded studies can be found in Appendix B. Appendix C lists references used in the appendixes.

Literature Searches and Study Characteristics

The electronic search, gray literature, and reference mining identified 31,846 citations. After title and abstract screening, 1,812 studies were retrieved for full-text review. A total of 164 studies (168 articles) met eligibility criteria. Surveillance through March 2, 2021 did not identify additional eligible studies. Thirty-three studies were not included in the data synthesis because they reported only unadjusted effectiveness data.[44-76]

A total of 131 studies (135 articles) were included in the analyses (see Appendix B). The evidence base predominantly comprises observational studies with high risk of bias, focusing on pregnant women (rather than postpartum women). About a third were set in the United States; another third were set in Canada and Denmark. More than three-quarters do not appear to be funded by industry (Table 2).

Description of Included Evidence

Table 2. Key characteristics for included studies

Study Characteristics	Subcharacteristics	Number of Studies (Articles)	Percent
Study quality	Low risk-of-bias studies	4	3.0
	Some concerns for risk-of-bias studies	44	33.6
	Some concerns/high risk-of-bias studies*	6	4.6
	High risk-of-bias studies	77 (81)	58.8
Population characteristics: Pregnant or postpartum	Pregnant	119 (122)	90.8
	Postpartum	11 (12)	8.4
	Pregnant and postpartum	1	0.8

Study Characteristics	Subcharacteristics	Number of Studies (Articles)	Percent
Population characteristics: Race	Majority white (>50%)	42 (44)	32.1
	Majority nonwhite (>50%)	7	5.3
	Not reported	82 (84)	62.6
Design	RCTs	10 (11)	7.6
	Observational	121 (124)	92.4
Comparator**	Active comparator	60 (62)	45.8
	Placebo or no treatment comparator	86 (88)	65.6
Geographic setting	United States	48 (50)	36.6
	United Kingdom	6	4.6
	Canada	26 (27)	19.8
	China	1	0.7
	Denmark	11 (12)	8.4
	Finland	3	2.3
	Australia	11	8.4
	Multiple countries	6	4.6
	Netherlands	1	0.7
	India	1	0.7
	Israel	1	0.7
	Italy	2	2.3
	Japan	1	0.7
	Norway	3	2.3
	Spain	1	0.7
	Sweden	7	5.3
	Taiwan	1	0.7
	Turkey	1	0.7
Funding	Industry	14 (16)	10.7
	No industry	93 (95)	71.0
	No funding source can be ascertained	22	16.8
	Unfunded	2	1.5

*Some concerns for risk of bias for KQs 1/3, high risk of bias for KQs 2/4.
**Some studies had multiple comparator arms; Ns sum to more than 100 percent.

KQ = Key Question; RCT = randomized controlled trial.

KQ 1: *Benefits of Pharmacologic Treatments Versus No Treatment or Placebo* for Pregnant and Postpartum Women With Anxiety, Depression, Bipolar Disorder, or Schizophrenia

Overview

- Nineteen studies reported on maternal benefits.
- For depression and bipolar disorder, the evidence was sparse, whereas for anxiety and schizophrenia, evidence was insufficient or unavailable.
- For depression, the strongest evidence is for a drug targeting postpartum depression, brexanolone. Three randomized controlled trials (RCTs) suggested moderate strength of evidence that brexanolone is associated with improved depressive symptoms shortly after infusion (60 hours) and at 30 days after treatment.

- For depression also, low strength of evidence from two RCTs supports the use of sertraline for postpartum depression to achieve response, remission, and improvements in symptoms of depression and anxiety.
- For depression, single small studies with few events results provided insufficient evidence on benefits for fluoxetine or paroxetine.
- For bipolar disorders, low strength of evidence from two cohort studies supports the continuation of mood stabilizers during pregnancy to prevent recurrence.
- For anxiety, we found one study reporting one outcome (response) on hydroxyzine only; the evidence was rated as insufficient.
- For schizophrenia, we found no eligible studies. Evidence may be available from studies of other populations ineligible for this review

Detailed Results

Table 3 provides an overview of the findings on benefits of pharmacotherapy in the perinatal period. Appendix B includes detailed tables on all outcomes. Nineteen studies reported on maternal benefit. We found very limited evidence supporting benefits among pregnant women for depression, anxiety, and bipolar disorder and none at all for schizophrenia.

Table 3. Summary of evidence for maternal benefit for treatment versus no treatment for mental health disorders in pregnancy and postpartum

Disorder	Exposure	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	-	-	-	-	-	-	-	-	-	-	-	-
	Hydroxyzine	-	I	-	-	-	-	-	-	-	-	-	-
	All other anxiolytics	-	-	-	-	-	-	-	-	-	-	-	-
	Sedatives*	-	-	-	-	-	-	-	-	-	-	-	-
Depression	SSRIs (unspecified)	-	-	-	-	-	-	-	I	-	-	-	-
	Fluoxetine	I	-	-	-	-	-	-	-	-	-	-	-
	Paroxetine	I	I	I	-	-	-	-	-	-	-	-	-
	Sertraline	L	L	L	-	-	I	-	-	-	-	-	-
	Brexanolone	M	-	-	-	-	I	-	-	-	-	-	-
Bipolar disorder	Mood stabilizers (unspecified)	-	-	-	L	-	-	-	-	-	-	-	-
	Lamotrigine	-	-	-	L	-	-	-	-	-	-	-	-
Schizophrenia	All antipsychotics	-	-	-	-	-	-	-	-	-	-	-	-

I: Insufficient for all measures for the outcome domain; **M**: Moderate evidence of benefit for at least one measure for the outcome domain; **L**: Low evidence of benefit for at least one measure for the outcome domain; -: No eligible evidence.
*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.
SSRI = selective serotonin reuptake inhibitor.

The remainder of this section describes the evidence of benefit, insufficient evidence, and no evidence in greater detail.

Evidence of Benefit: Brexanolone for Postpartum Depression

Overview

- Three small RCTs, enrolling women with depression onset in the third trimester or within 4 weeks of birth, demonstrated benefit for brexanolone to reduce depressive symptoms compared with placebo at 60 hours and 30 days after infusion, providing moderate evidence of benefit that brexanolone improves symptoms.

Detailed Synthesis

Three RCTs (rated low risk of bias) reported on the efficacy for brexanolone versus placebo for depression symptoms with onset in the third trimester of pregnancy or within 4 weeks of birth.[18, 77] The prespecified primary outcome of the RCTs was change from baseline to 60 hours in the 17-Item Hamilton Rating Scale for Depression (HAM-D) score. Brexanolone was administered as a 60-hour continuous infusion with a peak dose of either 60 μg/kg per hour or 90 μg/kg per h. The BRX60 schedule was administered at 30 μg/kg per hour (0–4 hours), 60 μg/kg per hour (4–56 hours), and 30 μg/kg per hour (56–60 hours). The BRX90 schedule was administered at 30 μg/kg per hour (0–4 hours), 60 μg/kg per hour (4–24 hours), 90 μg/kg per hour (24–52 hours), 60 μg/kg per hour (52–56 hours), and 30 μg/kg per hour (56–60 hours).

The first study[18] was a phase 2 clinical trial enrolling a total of 21 women from four hospitals in the United States, randomized to placebo (N=11) versus BRX90 (N=10). The second and third trials were reported together in a single publication.[77] Women were recruited at 30 centers in the United States. Among the latter two trials, one was a three-arm trial of placebo, BRX60, or BRX90 (N=138 randomized, 122 treated), and the second was a two-arm trial comparing BRX90 with placebo (N=108 randomized, 104 treated). The second publication included an integrated analysis that pooled participants treated with BRX 90 (N=102) versus placebo (N=107).

In the integrated analysis, BRX90 infusion reduced HAM-D scores more than placebo at 60 hours (least square [LS] mean difference, standard error [SE] -4.1, 0.9, $p<0.001$) and at 30 days (LS mean difference, SE -2.6, 1.1, $p=0.02$). Whereas BRX significantly reduced HAM-D scores, results were mixed for other depression measures. BRX90 reduced Montgomery-Åsberg Depression Rating Scale (MADRS) and Edinburgh Postnatal Depression Scale (EPDS) scores at 30 days in the phase 2 clinical trial, but in the phase 3 trials, only BRX60 differed from placebo. At 30 days post-treatment, there was no difference in Patient Health Questionnaire, 9 item (PHQ-9) or Generalized Anxiety Disorder 7-item (GAD-7) scores in any of the treatment groups. The phase 2 trial evaluated maternal function and found no difference at day 30. The authors note that the trials were powered to observe differences in HAM-D scores; the results were underpowered for other outcomes. Whether the specific focus of the instruments (depression only vs. depression and anxiety) and mode of data collection (clinical interview vs. self-report) may have influenced the magnitude of outcomes is unclear.

We rated the strength of evidence as moderate across all depression symptom outcomes (Table 4). We based this judgment on findings from three small RCTs with statistically significant results and consistent findings for HAM-D and statistically nonsignificant but largely consistent findings for other measures of depression. We also note that the magnitude of benefit declined between the 60-hour measurement and the 30-day measurement of HAM-D; the mean effect for brexanolone was stable, but the placebo group improved from 60 hours to 30 days.

Table 4. Strength of evidence for maternal benefit for brexanolone versus placebo for depression

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women with postpartum depression	Brexanolone 90 vs. placebo, integrated analysis	Symptom response: Change in HAM-D score from baseline to 60 hours	Placebo: -12.8 BRX90: -17.0	SD not reported by RCT, results cannot be pooled LS mean difference (SE) BRX 90 vs. placebo: -4.1 (0.9), p<0.001	3 RCTs, N=209[18, 77]	Low study limitations, precise (statistically significant results suggestive of benefit), consistent	Moderate across all symptom outcome measures
Women with postpartum depression	Brexanolone 90 vs. placebo, integrated analysis	Symptom response: Change in HAM-D score from baseline to 30 days	Placebo: -14.3 BRX90: -16.9	SD not reported by RCT, results cannot be pooled LS mean difference (SE) BRX 90 vs. placebo: -2.6 (1.1), p=0.02	3 RCTs, N=209[18, 77]	Low study limitations, consistent, precise (statistically significant results suggestive of benefit)	Moderate across all symptom outcome measures

BRX = brexanolone for postpartum depression; HAM-D = Hamilton Depression Rating; LS = least square; N = number; RCT = randomized controlled trial; SD = standard deviation; SE = standard error; vs. = versus.

Evidence of Benefit: Sertraline for Postpartum Depression

Overview

- Two RCTs compared sertraline with placebo for postpartum depression.
- For response, two RCTs comparing sertraline with placebo support a low strength of evidence that sertraline improves response rate.
- For remission, similarly, two RCTs comparing sertraline with placebo support a low strength of evidence that sertraline improves remission rates relative to placebo; the evidence for sertraline plus psychotherapy versus psychotherapy alone is insufficient.
- For depression onset between 0 and 1 month postpartum, the evidence from one RCT suggested greater improvement in depression severity with sertraline compared with placebo (low strength of evidence).
- For reduction in anxiety associated with perinatal depression, one low risk-of-bias study provided a low strength of evidence that sertraline produces a greater benefit severity than placebo.

Detailed Results

For response, two RCTs provided evidence of response for sertraline versus placebo (Table 5);[78, 79] one low risk-of-bias study with a small sample and a mean dose of 100 mg reported a statistically significant benefit for depression that onsets within 1 to 3 months postpartum.[78] A more restrictive definition of postpartum depression with onset up to 1 month postpartum from the same study also reported statistically significant differences favoring sertraline.[78] Calculated

relative risks suggest imprecise results with wide confidence intervals (CIs), few events, and small numbers of participants, but a large effect size. A second study, a high risk-of-bias study (because of high attrition) with a median dose of 150 mg, found no difference in response rates.[79]

Table 5. Strength of evidence for maternal benefit of sertraline versus no treatment for depression

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women with depression onset 0-3 months pp[78] or women with depression onset 0-12 months pp[79]	Sertraline vs. placebo	Response at 6 weeks in ITT group (≥50% reduction in HAM-D-19 symptoms and CGI-I score of "much improved" or "very much improved")[78] or response at 12 weeks (≥50% reduction in HAM-D-17 symptoms)	10/17 (59%) vs. 5/19 (26%),[78] NR[79]	AOR=NR, p=0.05; calculated RR: 2.24 (95% CI, 0.95 to 5.24); ARD: 326/1,000 (11 to 1116 more);[78] no difference between two arms, p=0.054[79]	2 RCTs, N=145[78, 79]	High study limitations (one high risk-of-bias study[79] imprecise (few events, small N, wide CIs), inconsistent; large effect for low risk-of-bias study	Low that response rate at 6 weeks is greater with sertraline
Women with depression onset 0-3 months pp[78] or women with depression onset 0-12 months pp[79]	Sertraline vs. placebo	Remission at 6 weeks in ITT group (meeting response above and with HAM-D-19 score ≤7)[78] or remission at 12 weeks (HAM-D-17 ≤7)[79]	9/17 (53%) vs. 4/19 (23%);[78] NR[79]	AOR=NR, p=0.05 calculated RR: 2.51 (95% CI, 0.94 to 6.70), ARD: 320/1,000 (4 to 619 more);[78] no difference between two arms, p=0.372[79]	2 RCTs, N=145[78, 79]	High study limitations (one high risk-of-bias study[79] imprecise (few events, small N, wide CIs), inconsistent; large effect for low risk-of-bias study	Low that remission rate at 6 weeks is greater with sertraline
Women with depression onset 0-1 month pp	Sertraline vs. placebo	Decrease in HAM-D-19 scores at 6 weeks	Sertraline: baseline HAM-D-19 NR, final NR Placebo: baseline HAM-D NR, final NR	Regression coefficient 1.18 favoring sertraline group, p=0.01[78]	1 RCT, N=27[78]	Low study limitations, statistical significance with small sample size, consistency unknown	Low that reduction in depressive severity is greater with sertraline
Women with depression onset 0-1 month pp	Sertraline vs. placebo	Decrease in EPDS scores at 6 weeks	Sertraline: baseline EPDS NR, final NR Placebo: baseline EPDS NR, final NR	Regression coefficient 0.91 favoring sertraline group, p=0.04[78]	1 RCT, N=27[78]	Low study limitations, statistical significance with small sample size, consistency unknown	Low that reduction in depressive severity is greater with sertraline
Women with depression onset 0-1 month pp	Sertraline vs. placebo	Decrease in HAM-A at 6 weeks	Sertraline: baseline HAM-A NR, final NR Placebo: baseline HAM-A NR, final NR	Regression coefficient 1.19 favoring sertraline group, p=0.03[78]	1 RCT, N=27[78]	Low study limitations, imprecise (small N), consistency unknown	Low that reduction in anxiety severity is greater with sertraline

ARD = absolute risk difference; AOR = adjusted odds ratio; CGI-I = Clinical Global Impression-Improvement; CI = confidence interval; EPDS = Edinburgh Postnatal Depression Scale; HAM-A = Hamilton Anxiety Rating Scale; HAM-D-17 = Hamilton

Depression Rating scale, 17-item version; HAM-D-19 = Hamilton Depression Rating scale, 19-item version; ITT = intention to treat; N = number; NR = not reported; pp = postpartum; RCT = randomized controlled trial; RR = relative risk; vs. = versus.

For remission, which was measured in the same two RCTs, evidence indicated that sertraline improves remission rates in one low risk-of-bias study whether onset is defined as 0 to 3 months postpartum or 0 to 1 month postpartum.[78] As with the results on response, calculated relative risks suggest imprecise results with wide CIs, few events, and small numbers of participants, but a large effect size. A high risk-of-bias study did not find any statistically significant improvement.[79] As with the results on response, we graded the strength of evidence as low for benefit for sertraline compared with placebo.

One low risk-of-bias RCT provided low strength of evidence of benefit that sertraline produces a greater reduction in depressive severity (rated separately for the EPDS and the HAM-D) when onset is between birth and 1 month when compared with placebo.[78] For reduction in anxiety associated with perinatal depression, one low risk-of-bias RCT provided a low grade of evidence that sertraline produces a greater benefit than placebo for those with onset within 1 month of delivery.[78]

Evidence of Benefit: Antipsychotics for Bipolar Disorder

Overview

- Evidence from two single small cohorts of women with bipolar disorder on recurrence and time to recurrence suggested benefit for treatment with mood stabilizers compared with discontinuation of treatment (low for benefit).

Detailed Synthesis

Two publications reported on mood stabilizers (Table 6);[80, 81] of these, one reported on mood stabilizers as a class,[80] and one focused on lamotrigine.[81] One was rated high risk of bias,[81] and the other as having some risk-of-bias concerns.[80] Both were nonrandomized observational cohort studies. These publications drew from two cohorts from the United States (one from Massachusetts[80] and one from Georgia[81]). Publications compared pregnant women who were exposed to mood stabilizers with women with mood disorders who discontinued the use of mood stabilizers.[80, 81] Although the studies are small (and one is high risk of bias[81]), they reported substantially higher risks of recurrence or shorter time to recurrence for discontinuation of medications, suggesting low strength of evidence of benefit with mood stabilizers. We graded the evidence as low for benefit, after upgrading the evidence for time to recurrence, based on a large effect size.

Insufficient Evidence

- We assigned insufficient grades to functional capacity (measured by the Postpartum Adjustment Questionnaire for sertraline and the Barkin Index of Maternal Function for brexanolone) and delivery mode for all reported interventions.
- We found no evidence of benefit for fluoxetine and paroxetine for any reported outcome.
- Insufficient grades were assigned based on study limitations, bias, consistency, and precision. The evidence for these outcomes comprised single studies for which we could not infer consistency of the evidence base. Additionally, some effects were imprecise (i.e., the results relied on small sample sizes, few events, or had wide CIs suggestive of

both benefits and harms) and had high study limitations (see Appendix B for further details).

Table 6. Strength of evidence for maternal benefit of mood stabilizers versus no treatment for bipolar disorder

Population	Intervention and Comparator	Outcome	Incidence by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Bipolar disorder	Women with bipolar disorder who discontinued mood stabilizers vs. women exposed to mood stabilizers in pregnancy	Recurrence of bipolar disorder	53/62 (85.5%) vs. 10/27 (37%)[80]	AHR for treatment discontinuation vs. exposure to mood stabilizers: 2.2 (95% CI, 1.2 to 4.2)[80] ARD: 268/1,000 (95% CI, 56 more to 486 more)	1 cohort, n=89[80]	Moderate study limitations, imprecise (few events); consistency unknown	Low (favoring treatment with mood stabilizers)
Bipolar disorder	Women with bipolar disorder who discontinued mood stabilizers vs. women exposed to lamotrigine in pregnancy	Time-to-25%-recurrence of bipolar disorder	16/16 (100%) vs. 3/10 (30%)[81]	2 vs, 28 weeks, AHR for discontinuation vs. exposure to lamotrigine: 12.1 (95% CI, 1.6 to 91.7)[81]; ARD: 687/1,000 (95% CI, 135 more to 700 more)	1 cohort, n=26[81]	High study limitations (high risk of bias[81]) imprecise (few events, small N, wide CIs); consistency unknown; very large effect size	Low (favoring treatment with lamotrigine)

ARD = absolute risk difference; AHR = adjusted hazard ratio; CI = confidence interval; n = number; vs. = versus.

No Evidence in Populations of Interest (Pregnant Women With Mental Health Disorders)

- For schizophrenia treatments, we found no evidence on benefits for any outcomes.
- For anxiety treatments, we found no evidence on symptoms, remission, relapse, functional outcomes, quality of life, delivery mode, breastfeeding, weight change, adherence to treatment, or suicidal ideation or events.
- For depression treatment, we found no evidence on relapse, functional outcomes, quality of life, breastfeeding, weight change, adherence to treatment, or suicidal ideation or events.
- For bipolar disorder. we found no evidence on symptoms, response, remission, functional capacity, quality of life, delivery mode, breastfeeding, weight change, adherence to treatment, or suicidal ideation or events.

KQ 2: *Comparative Benefits* of Pharmacologic Treatments for Pregnant and Postpartum Women With Anxiety, Depression, Bipolar Disorder, or Schizophrenia

Overview

- Five studies (7 articles) reported on comparative benefits.
- For depression and bipolar disorder, we found insufficient evidence to judge the comparative effectiveness of a very limited number of outcomes and interventions.
- For anxiety and schizophrenia, we found no evidence on comparative effectiveness for anxiety or schizophrenia.

Detailed Results

Table 7 provides an overview of the findings on comparative benefits of pharmacotherapy in the perinatal period. Appendix B includes detailed tables on all outcomes. The evidence on comparative benefits was sparse. Five studies (7 articles) reported on comparative benefits. The limited evidence that we identified was rated as insufficient.

Table 7. Summary of evidence from comparative effectiveness studies for maternal benefits of pharmacologic treatments for mental health disorders in pregnancy or postpartum

Disorder	Intervention	Comparator	Symptoms	Response	Mood Episodes	Psychiatric Admission	Remission	Relapse	Suicidal Ideation	Functional Capacity	Quality of Life	Delivery Mode	Breastfeeding	Weight Change	Adherence to Treatment and Care	Suicidal Events
Anxiety	All anxiolytics	NA	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Sedatives*	NA	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Depression	Fluoxetine	TCA	-	-	-	-	-	-	-	-	-	I	-	-	-	-
	Sertraline	Nortriptyline	-	I	I	-	I	-	-	I	-	-	-	-	-	-
Bipolar disorder	Lamotrigine	Lithium	-	-	-	I	-	-	-	-	-	-	-	-	-	-
	Olanzapine	Lithium	-	-	I	-	-	-	-	-	-	-	-	-	-	-
	Sodium valproate	Lithium plus sodium valproate	-	-	-	-	-	I	-	-	-	-	-	-	-	-
	Lithium	Lithium plus sodium valproate	-	-	-	-	-	I	-	-	-	-	-	-	-	-
	Lithium	Paroxetine	-	-	I	-	-	-	-	-	-	-	-	-	-	-
Schizophrenia	All antipsychotics	NA	-	-	-	-	-	-	-	-	-	-	-	-	-	-

I: Insufficient for all measures for the outcome domain; No eligible evidence.
*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.
NA = not applicable; TCA = tricyclic antidepressant.

Evidence of Benefit

For interventions for which evidence was available (fluoxetine vs. tricyclic antidepressants [TCAs], sertraline vs. nortriptyline, lamotrigine vs. lithium, olanzapine vs. lithium, and lithium vs. paroxetine, Table 7), no drug was judged as having greater benefit than a comparison drug for any evaluated disorder.

Insufficient Evidence

Overview

- We assigned insufficient grades to several outcomes (response, mood disorders, psychiatric admissions, remission, functional status, and mode of delivery) listed in Table 7. Insufficient grades were assigned based on study limitations, bias, consistency, and precision. The evidence for these outcomes comprised single studies for which we could not infer consistency of the evidence base. Additionally, some were imprecise (i.e., the results relied on small sample sizes, few events, or had wide CIs suggestive of both benefits and harms) and had high study limitations.

No Evidence in Populations of Interest (Pregnant Women With Mental Health Disorders)

Overview

- For anxiety and schizophrenia treatments, we found no evidence on comparative benefits for any outcomes in pregnant and postpartum women.
- For depression treatment, we found no evidence on symptoms, psychiatric admission, relapse, suicidal ideation, quality of life, breastfeeding, weight change, adherence to treatment and care, or suicidal events.
- For bipolar disorder treatment, we also found no evidence on symptoms, response, remission, relapse, suicidal ideation, functional capacity, delivery mode, quality of life, breastfeeding, weight change, adherence to treatment and care, or suicidal events.

KQ 3: *Harms of Pharmacologic Treatments Versus No Treatment or Placebo* for Pregnant and Postpartum Women With Mental Health Disorders

Overview

- Seventy-five studies (77 articles) reported on harms; 70 studies were observational and could not assert a causal relationship between exposure and the outcome. Harms in the results below include any eligible adverse event; the events may not be a direct result of the exposure.
- Most studies reporting on adverse outcomes characterized the population by exposure to the drug (rather than by the presence of a disorder). These studies generally included women with current or past depression, anxiety, or any mental health disorder as untreated controls. The findings on adverse outcomes are therefore not specific to a disorder.

- Interventions for which we found evidence of an association between exposure during pregnancy and adverse events for one or more outcome included benzodiazepines, SSRIs (unspecified), fluoxetine, citalopram, escitalopram, paroxetine, sertraline, SNRIs (unspecified), venlafaxine, bupropion, brexanolone, quetiapine, and olanzapine. In all instances, the strength of evidence on the harms from these drugs was rated low. The magnitude of the association varied by outcome.
- The evidence on harms was not consistent within or across interventions. For example, the association between exposure to the drug and postpartum hemorrhage varied by intervention and by timing of exposure within each intervention.
- Interventions for which we found insufficient evidence to judge the strength of association between exposure during pregnancy and adverse events included the sedative-hypnotics temazepam, zopiclone, and zolpidem; the antidepressants fluvoxamine, trazodone, duloxetine, clomipramine, amitriptyline/nortriptyline, and mirtazapine; mood stabilizers as a class, lamotrigine, valproate, topiramate, carbamazepine, oxcarbazepine, lithium; second-generation antipsychotics and first-generation antipsychotics, respectively, as a class; and the second-generation antipsychotics aripiprazole, ziprasidone, and risperidone.
- Maternal outcomes for which we found low strength of evidence of harms for one or more medications for exposure during pregnancy included ectopic pregnancy, preeclampsia, spontaneous abortion, postpartum hemorrhage, and gestational diabetes. The evidence on harms was not consistent within or across outcomes. The most consistent evidence of harm is for postpartum hemorrhage. For other outcomes, harms were detected for a subset of evaluated exposures.
- Child outcomes for which we found low strength of evidence of harms for one or more medications for exposure during pregnancy included neonatal intensive care unit (NICU) admission, respiratory issues, low Apgar scores, primary persistent pulmonary hypertension of the newborn, and depression in the child. These outcomes vary in severity. More serious outcomes such as persistent pulmonary hypertension of the newborn are very rare.
- Outcomes for which we found insufficient evidence included abruption, gestational hypertension; perinatal death, preterm birth; major congenital anomalies; cardiac defects; small for gestational age; large for gestational age; birthweight; delayed social, emotional, and cognitive development; attention-deficit/hyperactivity disorder (ADHD); and anxiety in children for all reported exposures.
- Outcomes for which we found no eligible evidence, based on our review parameters, for any interventions included infertility, glucose intolerance, reduced milk production or unwanted weaning, and withdrawal symptoms in the newborn. Evidence may be available from studies of other populations ineligible for this review.
- We did not find eligible evidence on congenital anomalies for triazolam, alprazolam, valproate, carbamazepine, clonazepam, and topiramate compared with no treatment or placebo, although evidence is available from studies of other populations ineligible for this review.

Detailed Results

Table 8 provides an overview of the findings on harms of pharmacotherapy in the perinatal period. Appendix B includes detailed tables on all outcomes. Seventy-five studies (77 articles)

reported on harms. The remainder of this section describes the evidence of maternal harm; evidence of fetal, neonatal, infant, or child harm; insufficient evidence of maternal harm; insufficient evidence of fetal, neonatal, infant, or child harm; and no evidence in greater detail.

Evidence of Maternal Harm

Overview

- The evidence on maternal harms from treatments for mental health disorders generally comes from single-study bodies of evidence with moderate limitations and precise results (i.e., sample size, event rate, and CIs permit inference of benefit, harm, or absence of benefit or harm).
- When compared with unexposed women with at least one anxiety diagnosis in the year before conception, evidence from one study suggested benzodiazepine exposure *90 days before conception* may be associated with an increased risk of ectopic pregnancy (low strength of evidence of harms).
- The evidence suggested potential associations between exposures to specific psychotropic medications (detailed below) *during pregnancy* and postpartum hemorrhage, preeclampsia, spontaneous abortion, and gestational diabetes.
    - When compared with unexposed women with depression or anxiety, evidence from one study suggests that exposure during pregnancy to selective serotonin reuptake inhibitors (SSRIs) as a class, citalopram, escitalopram, fluoxetine, paroxetine, sertraline, serotonin-norepinephrine reuptake inhibitors (SNRIs) as a class, venlafaxine, and bupropion may be associated with an increased risk of postpartum hemorrhage (low strength of evidence of harms). The association may vary by timing of exposure. Studies report associations between current (SSRIs and SNRIs), recent exposure (SSRIs), and past exposure (bupropion) and postpartum hemorrhage.
    - When compared with unexposed women with depression, evidence from two studies each suggested that SNRIs and TCAs exposure during pregnancy may be associated with an increased risk of preeclampsia (low strength of evidence).
    - When compared with women who discontinued quetiapine and olanzapine during pregnancy, evidence from one study suggested that continued use of quetiapine or olanzapine may be associated with an increased risk of gestational diabetes (low strength of evidence).
    - When compared with women with a depression diagnosis in the 4 years preceding pregnancy but not exposed to any antidepressant in the first trimester, evidence from one cohort suggested that SNRI exposure in the first trimester was associated with a higher risk of spontaneous abortion (low strength of evidence). When compared with unexposed women with a history of mood or anxiety disorders, evidence from two studies suggested that benzodiazepine exposure early during pregnancy may be associated with an increased risk of spontaneous abortion when compared with no exposure to benzodiazepines (low strength of evidence of harms).
- When compared with unexposed women with depression, evidence from the Food and Drug Administration (FDA) label for brexanolone exposure for depression onset *in the third trimester or within 4 weeks of birth* compared with placebo suggested sedation or loss of consciousness led to dose interruption or reduction in some patients during the infusion (low strength of evidence of harms).

Table 8. Summary of evidence for harms from pharmacologic treatments versus no treatment for mental health disorders in pregnancy or postpartum

Condition	Exposure	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	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	-	I	L	-	-	-	-	-	-	I	-	-	-	I	-	-	I	-	I	L	-	-	-	-	-	-	
Depression or anxiety	Diazepam*	-	-	-	-	-	-	-	-	-	-	-	-	-	-	I	-	-	-	-	-	-	-	-	-	-	-	-
Depression or anxiety	Temazepam*	-	-	-	-	-	-	-	-	-	-	-	-	-	-	I	-	-	-	-	-	-	-	-	-	-	-	-
Depression or anxiety	Zopiclone*	-	-	-	-	-	-	-	-	-	-	-	-	-	-	I	-	-	-	-	-	-	-	-	-	-	-	-
Mental health disorders	Zolpidem*	-	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)	-	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	-	I	-	-	L	-	-	I	-	-	-	-	-	-	I	I	-	-	-	-	-	-	-	L	-	-	-
Depression, mood, or anxiety disorder	Escitalopram	-	I	-	-	L	-	-	-	-	-	-	-	-	-	I	I	-	-	-	-	-	-	-	-	-	-	-
Depression, mood, or anxiety disorder	Fluoxetine	-	I	-	-	L	-	-	I	-	-	-	-	-	-	I	I	-	-	-	-	-	-	-	I	-	-	-
Depression, mood, or anxiety disorder	Fluvoxamine	-	-	-	-	-	-	-	-	-	-	-	-	-	-	I	-	-	-	-	-	-	-	-	-	-	-	-
Depression, anxiety, or other mental health disorders	Paroxetine	-	I	-	-	L	-	-	I	-	-	-	-	-	-	I	I	-	-	-	-	-	-	-	I	-	-	-

Condition	Intervention	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	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 and/or anxiety and/or other mental health disorders	Sertraline	-	I	-	-	L	-	-	I	-	-	-	-	-	-	I	I	-	-	-	-	-	-	-	I	-	-	-
Mood or anxiety disorders or prescribed medication***	Trazodone	-	I	-	-	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Depression, mood, or anxiety disorder	SNRIs (unspecified)	-	L	L	-	L	-	-	-	-	-	-	-	-	-	I	I	-	-	-	-	-	-	-	-	-	-	-
Prescribed medication***	Duloxetine	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	I	-	-	-	-	-	-	-	I	-	-	-
Depression, mood, or anxiety disorder	Venlafaxine	-	L	-	-	L	I	-	I	-	-	-	I	-	-	-	I	-	-	-	-	-	-	-	I	-	-	-
Depression and/or anxiety and/or other mental health disorders	TCAs (unspecified)	-	L	I	-	-	-	-	-	-	I	-	I	-	-	I	I	-	-	-	-	-	-	-	-	-	-	-
Mental health disorders	Clomipramine	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	I	-	-	-
Mental health disorders	Amitriptyline	-	-	-	-	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Mental health disorders	Amitriptyline or nortriptyline	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	I	-	-	-
Postpartum depression	Brexanolone**	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Depression, mood, or anxiety disorder	Bupropion	-	I	-	-	L	-	-	I	-	-	-	-	-	-	-	I	-	-	-	-	-	-	-	-	-	-	-
Depression, mood, or anxiety disorder	Mirtazapine	-	-	-	-	I	-	-	-	-	-	I	-	-	I	-	-	-	-	-	I	-	-	-	I	-	-	-
Bipolar disorder	Mood stabilizers	-	I	-	I	-	-	-	-	-	-	I	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Bipolar disorder	Lamotrigine	-	I	-	I	-	-	-	I	-	-	I	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Bipolar disorder	Valproate	-	I	-	I	-	-	-	-	-	-	I	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Condition	Intervention	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	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
Bipolar disorder	Topiramate	-	I	-	I	-	-	-	-	-	-	I	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Bipolar disorder	Carbamazepine	-	I	-	I	-	-	-	-	-	-	I	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Bipolar disorder	Oxcarbazepine	-	I	-	I	-	-	-	-	-	-	I	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Bipolar or mood disorder	Lithium	-	I	-	I	-	-	-	I	-	-	I	I	-	-	-	-	-	-	-	-	-	-	I	-	-	-	-
Mental health disorders or schizophrenia, bipolar disorder, or psychosis	Second-generation antipsychotics (unspecified)	-	-	-	-	-	-	-	I	-	-	I	I	I	I	I	I	-	-	-	-	-	-	-	-	-	-	-
Schizophrenia, bipolar disorder, or psychosis or prescribed medication***	First-generation antipsychotics (unspecified)	-	-	-	-	-	-	-	-	-	-	I	I	I	I	I	I	-	-	-	-	-	-	-	-	-	-	-
Prescribed medication***	Aripiprazole	-	-	-	-	-	-	-	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Mental health disorders*** or prescribed medication	Ziprasidone	-	-	-	-	-	-	-	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Prescribed medication***	Quetiapine	-	-	-	-	-	-	-	L	-	-	-	-	-	-	I	-	-	-	-	-	-	-	-	-	-	-	-
Prescribed medication***	Risperidone	-	-	-	-	-	-	-	I	-	-	-	-	-	-	I	I	-	-	-	-	-	-	-	-	-	-	-
Prescribed medication***	Olanzapine	-	-	-	-	-	-	-	L	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

*: Used as a sedative-hypnotic to address sleep difficulty, not targeted at underlying mental health disorder.
**: Although we found no evidence of harms for brexanolone for a priori outcomes, we rated the evidence on dose interruption or reduction due to somnolence or sedation as low.
***: Underlying mental health indication and exposure to medications are generally not specified; study populations are based on cohorts with prescriptions.
I: Insufficient for all measures for the outcome domain; **L**: Low evidence of harm for at least one measure for the outcome domain; -: No eligible evidence.
ADHD = attention-deficit/hyperactivity disorder; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

Detailed Synthesis

Table 9 provides an overview of the findings on maternal harms of pharmacotherapy in the perinatal period. Appendix B includes detailed tables on all outcomes. We describe results for six publications (7 studies) for harms below (Table 9).

The evidence for brexanolone came from three RCTs and is rated as low for harms. The evidence on other harms from treatments for mental health disorders, with one exception (two SNRI studies reported on preeclampsia), derives from single-study bodies of evidence with moderate limitations and precise results (studies large enough to detect a difference [or no difference] in effect estimates). The relative paucity of evidence for these harms led us to rate the strength of evidence as low. Although the potential for maternal harm may exist, we have low confidence that future studies will support this association.

Specifically, the identified harms include *ectopic pregnancy* for benzodiazepine exposure before conception; *postpartum hemorrhage* for SSRIs overall, citalopram, escitalopram, paroxetine, sertraline, SNRIs overall, venlafaxine, and bupropion; *preeclampsia* for SNRIs overall and TCAs overall; *gestational diabetes* for quetiapine olanzapine; and *spontaneous abortion* for SNRIs and benzodiazepine for exposure during pregnancy; and *somnolence or sedation leading to dose interruption or reduction* for brexanolone for late-pregnancy or postpartum depression.

Ectopic Pregnancy for Benzodiazepines

Evidence from one study[82] 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 strength of evidence of harms). Risk factors for ectopic pregnancy include previous ectopic pregnancy, history of pelvic infection, infertility, cigarette smoking and age older than 35 years.[83] To the extent that such risk factors are associated with an indication for treatment with benzodiazepines, 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 as a result.[82] The absolute risk difference is 7 more cases per 1,000 (95% CI, 4 to 11).

Postpartum Hemorrhage for SSRIs, Citalopram, Escitalopram, Sertraline, SNRIs, and Venlafaxine

Regarding postpartum hemorrhage, results from one propensity-score adjusted study suggested that an association between exposure to several antidepressants and postpartum hemorrhage that may vary by timing.[84] Current exposure (at the time of delivery) is associated with postpartum hemorrhage for SSRIs as a class, citalopram, escitalopram, sertraline, 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 strength of evidence of harms). For bupropion, however, the association is with past exposure to bupropion (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 reuptake into platelets.[85] In a sample with a prevalence of 2.75 percent in the unexposed arm, the absolute risk difference for SSRIs is 13 more cases per 1,000 (95% CI, 9 more to 16 more); for SNRIs, the risk is 25 more per 1,000 (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; the authors suggested more research to confirm the findings.[84] The risk of residual confounding also remains: the study was not able to control for confounding factors of inadequate diet, the use of tobacco, and severity of disorder.

Table 9. Strength of evidence from effectiveness studies for harm to the mother (intervention versus placebo or no treatment)

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Pregnant women with at least one anxiety diagnosis in the year before conception	Benzodiaz-epine exposure 90 days before conception vs. no benzodiaz-epine exposure before conception	Ectopic pregnancy	249/9,188 (2.71%) vs. 1,730/81,291 (2.13%)[82]	ARR: 1.33 (95% CI, 1.17 to 1.51)[82]	1 cohort, N=90,479[82]	Moderate study limitations, precise, consistency unknown	Low for harms with benzodiaz-epine
Mood or anxiety disorder	Current SSRI exposure (exposure during delivery) vs. unexposed with mood or anxiety disorder	Postpartum hemorrhage	503/12,710 (3.96%) vs. 1,896/69,044 (2.75%)[84]	ARR, 1.47 (95% CI, 1.33 to 1.62) [84]	1 cohort, n=81,754[84]	Moderate study limitations, precise, consistency unknown	Low for harms for current exposure with SSRIs
Mood or anxiety disorder	Recent SSRI exposure (within 1 month before delivery) vs. unexposed with mood or anxiety disorder	Postpartum hemorrhage	196/6,096 (3.2%) vs. 1,896/69,044 (2.75%)[84]	ARR, 1.19 (95% CI, 1.03 to 1.38)[84]	1 cohort, n= 75,140[84]	Moderate study limitations, precise, consistency unknown	Low for harms for recent exposure with SSRIs
Pregnant women with mood or anxiety disorder[84]	Current citalopram use vs. no treatment	Postpartum hemorrhage	36/891 (4%) vs. 1,896/69,044 (2.75%)	ARR, 1.48 (95% CI, 1.07 to 2.04)	1 cohort, N=69,935[84]	Moderate study limitations, precise, consistency unknown	Low for harms with citalopram

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Mood or anxiety disorder	Current escitalopram exposure vs. unexposed with mood or anxiety disorder	Postpartum hemorrhage	43/1,022 (4.21%) vs. 1,896/69,044 (2.75%)[84]	ARR, 1.56 (95% CI, 1.16 to 2.09)[84]	1 cohort, n=70,006[84]	Moderate study limitations, precise, consistency unknown	Low for harms with escitalopram
Women with diagnosis code for mood or anxiety disorder 1-5 months before delivery	Paroxetine current (at delivery) or unexposed	Postpartum hemorrhage billing diagnosis	77/2,055 (3.75%) vs. 1,896/69,044 (2.75%)	ARR, 1.39 (95% CI, 1.09 to 1.71)	1 cohort, N= 71,099[84]	Moderate study limitations, precise, consistency unknown	Low for harms with paroxetine
Women with diagnosis code for mood or anxiety disorder 1-5 months before delivery	Sertraline current (at delivery) or unexposed	Postpartum hemorrhage billing diagnosis	162/4,526 (3.58%) vs. 1,896/69,044 (2.75%)	ARR, 1.31 (95% CI, 1.12 to 1.54)	1 cohort, N= 73,570[84]	Moderate study limitations, precise, consistency unknown	Low for harms with sertraline
Women with diagnosis code for mood or anxiety disorder 1-5 months before delivery	Sertraline recent (<1 month before delivery) or unexposed	Postpartum hemorrhage billing diagnosis	78/2,226 (3.50%) vs. 1,896/69,044 (2.75%)	ARR, 1.27 (95% CI, 1.01 to 1.59)	1 cohort, N= 71,270[84]	Moderate study limitations, precise, consistency unknown	Low for harms with sertraline
Pregnant women with mood or anxiety disorders	SNRI exposure at time of delivery vs. unexposed	Postpartum hemorrhage	35/702 (5.0%) vs. 1,896/69,044 (2.75%)[84]	ARR, 1.90 (1.37 to 2.63)	1 cohort, N=69,746[84]	Moderate study limitations, precise; consistency unknown	Low for harms with SNRIs
Pregnant women with mood or anxiety disorders	Venlafaxine exposure at time of delivery vs. unexposed	Postpartum hemorrhage	46/763 (6.0%) vs. 1,896/69,044 (2.75%)[84]	ARR, 2.24 (1.69 to 2.97)	1 cohort, N=69,807[84]	Moderate study limitations, precise; consistency unknown	Low for harms with venlafaxine
Mood disorder or anxiety or bupropion-exposed women	Past bupropion exposure in pregnancy vs. bupropion unexposed women with mood disorder or anxiety	Postpartum hemorrhage	61/1712 (3.6%) vs. 1,896/69,044 (2.75%)[84]	ARR, 1.32 (95% CI, 1.02 to 1.69)[84]	1 cohort, n=70,206[84]	Moderate study limitations, precise, consistency unknown	Low for harms of bupropion

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Pregnant women: SNRI exposure or depression diagnosis, through second trimester	SNRI exposure through second trimester vs. unexposed	Preeclampsia	107/1,216 (9%) vs. 3,215/59,219 (5%)[86]; 23/408 (5.6%) vs. 1,569/65,392 (2.4%)[87]	ARR, 1.52 (95% CI, 1.25 to 1.83)[86]; ARR, 1.59 (95% CI, 1.26 to 3.03)[87]	2 cohorts, N=126,235[86, 87]	Moderate study limitations, precise; consistent	Low for harms with SNRIs
Depressed women	TCA exposure in pregnancy vs. unexposed women with depression in pregnancy	Preeclampsia	47/441 (10.7%) vs, 3,215//59,219 (5.4%)[86]; 14/146 (9.59%) vs. 1,569/65,392 (2.40%)[87]	ARR, 1.62 (95% CI, 1.23 to 2.12)[86]; ARR, 3.23 (95% CI, 1.87 to 5.59)[87]	2 cohorts, n=125,198[86, 87]	Moderate study limitations, precise, consistent	Low for harms of TCA
Women prescribed a second-generation antipsychotic	Quetiapine continued vs. quetiapine discontinued	Gestational diabetes	110/1,543 (7.1%) vs. 122/2,990 (4.1%)[88]	ARR, 1.28 (95% CI, 1.01 to 1.62)[88]	1 cohort, n=10,379[88]	Moderate study limitations, precise, consistency unknown	Low for harms of continued quetiapine
Women prescribed an second-generation antipsychotic	Olanzapine continued vs. olanzapine discontinued	Gestational diabetes	46/384 (12.0%) vs. 49/1,041 (4.7%)[88]	ARR, 1.61 (95% CI, 1.13 to 2.29)[88]	1 cohort, n=10,379[88]	Moderate study limitations, precise, consistency unknown	Low for harms of continued quetiapine
Pregnant women: SNRI exposure or depression diagnosis in past 4 years	SNRI exposure in 1st trimester vs. unexposed to any antidepressant	Spontaneous abortion	20/90 (22%) vs. 720/7,034 (10%);[89] results corrected for induced abortions: 20/137 (15%) vs. 720/8,877 (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)[89]	1 cohort, n=7,134, corrected for induced abortion, n=9,014[89]	Moderate study limitations, precise; consistency unknown	Low for harms with SNRIs
Pregnant women with depression or anxiety	Benzodiaz-epine exposure in first trimester[90] or within the first 19 weeks[91] vs. untreated or a history of mood disorders or anxiety during pregnancy	Spontaneous abortion	386/2,384 (16%) vs. 442/3,647 (12%)[90] 198 cases/570 controls vs. 3,221 cases/15,382 controls[91]	ARR, 1.6 (95% CI, 1.3 to 1.9)[90] AOR: 2.85 (95% CI, 1.72 to 4.72)[91]	1 cohort, 1 case-control study, N=21,983[90, 91]	Moderate study limitations (high risk of bias[90]) precise, consistent	Low for harms with benzodiaz-epine

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women with postpartum depression	Brexanolone vs. placebo	Dose interruption or reduction in some patients during the infusion due to sedation or somnolence	Treatment arm: 5% Placebo: 0 (from FDA prescribing information[92])	Data not reported by study, pooled RR not calculable	3 RCTs, N=209[18, 77]	Low study limitations, precision and consistency unknown	Low for harms with exposure to brexanolone
	Brexanolone vs. placebo	Loss of consciousness	BRX60: 5%; BRX90: 3%; Placebo: 0% (from FDA prescribing information[92])	Data not reported by study, cannot be pooled	3 RCTs, N=209[18, 77]	Low study limitations, precision and consistency unknown	
	Brexanolone vs. placebo	Somnolence	BRX60: 7/38 (18.4%) BRX90: 8/102 (7.8%) Placebo: 5/107 (4.7%)	Pooled RR, 2.00, 95% CI, 0.78 to 5.16, I^2=0%	3 RCTs, N=209[18, 77]	Low study limitations, inconsistent, imprecise (wide CIs, few events)	

ARR = adjusted risk ratio; BRX = brexanolone; CI = confidence interval; FDA = Food and Drug Administration; N = number; RCT = randomized controlled trial; RR = relative risk; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant; vs. = versus.

Preeclampsia for SNRIs and TCAs

Two studies[86, 87] offered low strength of evidence, suggesting increased risk of preeclampsia for women exposed to non-SSRI drugs, specifically SNRIs (adjusted risk ratios [ARRs] range from 1.52 to 1.59) and TCAs (ARRs range from 1.62 to 3.23); absolute risk differences range from 14 more cases per 1,000 to 54 cases per 1,000. Risk factors for preeclampsia include maternal antiphospholipid antibody syndrome, family history, nulliparity, donor egg pregnancy, diabetes, obesity, and preexisting hypertension. These factors may cause placental hypoxia and ischemia. However, it is also possible that antidepressants increase serotonin and norepinephrine levels and therefore lead to preeclampsia.[87] Because both serotonin and norepinephrine are vasoconstrictors, to the extent that placental ischemia[93] contributes to the pathophysiology of preeclampsia, SNRIs could affect preeclampsia risk. It is unclear why the results are not consistent across exposures: one possible explanation is residual confounding due to inadequately controlled depression severity or other comorbid conditions. It is also plausible that underlying characteristics associated with therapeutic response to SNRIs or TCAs are risk factors for preeclampsia.

Gestational Diabetes for Quetiapine or Olanzapine

For gestational diabetes mellitus (GDM), low strength of evidence from one cohort study[88] suggested that continuing use (as reflected in two or more prescription dispensings) during the first half of pregnancy of quetiapine (absolute risk difference: 11 per 1,000, 95% CI, 0 to 25) or olanzapine (absolute risk difference: 29 per 1,000, 95% CI, 6 to 61) may be associated with an increased risk of developing GDM compared with women discontinuing these respective 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.[94] FDA notes the risk of metabolic side effects from second-generation antipsychotics in prescription labels for these drugs.[95, 96] 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 analyses involved a generalized linear model and propensity-score stratification to obtain risks of developing GDM with adjustment for confounders.

Spontaneous Abortion and SNRIs

Associations between pharmacologic treatment and spontaneous abortion may be confounded by the severity of the underlying mental health disorder. In a systematic review, exposure to psychological stress was associated with an increased risk of miscarriage (odds ratio [OR], 1.42; 95% CI, 1.19 to 1.70).[97] Proposed mechanisms include dysregulation of the hypothalamic pituitary adrenal axis and early pregnancy immune function.[98] To the extent that women experiencing greater psychological stress would be more likely to be treated pharmacologically, confounding by indication by underlying observed associations.

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 strength of evidence).[89] Analyses controlling for induced abortion showed a slightly attenuated but still statistically significant difference (absolute risk difference: 62 per 1,000, 95% CI, 16 to 130). Although we rated this outcome as low strength of evidence for potential harms, we note that 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 medication 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 that is unaccounted for in the analysis.

Spontaneous Abortion and Benzodiazepines

Evidence from two studies[90, 91] suggested an increased risk of spontaneous abortion with benzodiazepine exposure 90 days before conception when compared with untreated or a history of mood disorders or anxiety (graded low strength of evidence of harms). 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.[82] The absolute risk difference is 73 per 1,000 (95% CI, 36 to 109).

Dose Interruption or Reduction Due to Somnolence or Sedation for Brexanolone

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. In the prescribing instructions, the manufacturer reports higher rates of dizziness, loss of consciousness, and somnolence with brexanolone compared with placebo. Results could not be pooled for loss of consciousness from the individual studies. Rates of loss of consciousness did not appear to increase with dose intensity: 5 percent of women randomized to BRX60 versus 3 percent for BRX90 experienced loss of consciousness.

Evidence of Fetal, Infant, or Child Harm

Overview

- The evidence on fetal, infant, or child harms from treatments for mental health disorders comes from bodies of evidence with moderate or high study limitations and precise results. Low strength-of-evidence grades from bodies of evidence with high limitations had precise results but also other factors beyond statistical significance alone (such as large effects or plausible confounding [i.e., one could infer that in the absence of confounding, the effect would be larger]) that contributed to moving the grade from insufficient to low.
- The evidence on fetal, infant, or child harms from treatments for mental health disorders comes from bodies of evidence with moderate or high study limitations but effects that did not cross the null. However, beyond statistical significance alone, other factors (such as large sample size or plausible confounding [i.e., the effect is larger when confounding is addressed]) contributed to moving the grade from insufficient to low.
- Among women with a history of mental health disorders, evidence from one study suggested that benzodiazepine exposure during pregnancy may be associated with an increased risk of NICU admission when compared with no exposure; hospital protocols may explain this association (low strength of evidence of harms).
- Among women with a history of mental health disorders or among women previously exposed to SSRIs, evidence from three studies suggested that exposure to SSRIs during pregnancy may be associated with increased risk of respiratory issues in the newborn (low strength of evidence); evidence from two studies suggested that exposure to SSRIs in pregnancy may be associated with an increased risk of low Apgar scores when compared with no exposure (low strength of evidence).
- When compared with women with untreated depression during pregnancy, evidence from one cohort suggested that exposure to SSRIs in pregnancy may be associated with an increased risk of primary persistent pulmonary hypertension of the newborn (without cardiac malformation or lung hypoplasia in full-term deliveries) (low strength of evidence); the absolute risk increase is small (33 more cases per 100,000 persons).
- Among women with a psychiatric diagnosis, evidence from one cohort indicated that an increased risk of childhood depression was observed among women exposed to SSRIs when compared women with no treatment; the study did not control for depression severity, and the direction of effect is unclear (low strength of evidence).
- When compared with unexposed women with a known mental health disorder, evidence from one cohort suggested that citalopram exposure in pregnant women may be associated with a higher risk of autism spectrum disorder in their children; residual confounding could potentially explain this effect (low strength of evidence).

Detailed Synthesis

Table 10 provides an overview of the findings on harms to the fetus, infant, or child of pharmacotherapy in the perinatal period. Appendix B includes detailed tables on all outcomes. We describe results from five publications on harms below (Table 10).

Table 10. Strength of evidence from effectiveness studies for harm to the fetus, infant, or child (intervention versus placebo or no treatment)

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Pregnant women with a mental health disorder[99]	Benzodiaze-pine exposure during pregnancy vs. unexposed to benzodiaze-pine use during pregnancy	NICU admission	32/144 (22.2%) vs. 125/649 (19.3%)	AOR, 2.02 (95% CI, 1.11 to 3.66)	1 cohort, N=793[99]	Moderate study limitations, precise, consistency unknown	Low for harms of benzodiaze-pine
History of SSRI exposure	SSRI exposure in pregnancy vs. women who discontinued SSRIs	Intrauterine hypoxia and birth asphyxia	94/2,664 (3.5%) vs. 124/5,141 (2.4%)[100]	Adjusted prevalence ratio in all women: 1.39 (95% CI, 1.07 to 1.81) Adjusted prevalence ratio in women with vaginal deliveries in the third trimester: 1.70 (95% CI, 1.23 to 2.33)	1 cohort, n= 7,805[100]	High study limitations (high risk-of-bias study)[100] precise, consistency unknown	Low for harms with SSRIs
History of mental health disorder or depression or SSRI-exposed women	SSRI exposure in pregnancy vs. unexposed women with depression or mental health disorder	Respiratory conditions (respiratory conditions of newborns other than intrauterine hypoxia and birth asphyxia,[100] undefined breathing problems,[101] respiratory distress[102])	Ranges from 4.3% to 4.9% in the treatment arm and 3.1% to 3.2 in the control arm[100, 101]; NR in one study[102]	All three[100-102] studies reported increased risk. Adjusted prevalence ratios and AOR, range from 1.37 to 1.4[100, 101]	3 cohort studies,[100-102] n>33,186 (N=NR in one study[102])	High study limitations (2 of 3 are high risk-of-bias studies,[100, 101] precise, wide CIs), consistent	Low for harms with SSRIs
Exposed to SSRIs during pregnancy, before pregnancy, or unexposed with a psychiatric diagnosis	Exposed to SSRIs during pregnancy vs. before pregnancy or unexposed with a psychiatric diagnosis	Low Apgar score (<7 at 5 min)	28/2,664 (1.1%) vs. 31/5141 (0.6%)[100] 376/15,729 (2.4%) vs. 113/9,652 (1.2%)[101]	Adjusted prevalence ratio: 1.69 (95% CI, 1.02 to 2.79)[100] AOR, 1.68 (95% CI, 1.34 to 2.12)[101]	2 cohorts, n=33,186[100, 101]	High study limitations (all risk-of-bias studies[100, 101]), precise, consistent	Low for harms with SSRIs

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Depressed	Exposed to SSRIs during pregnancy vs. unexposed during pregnancy	Primary persistent pulmonary hyperten-sion (without cardiac malforma-tion or hypoplasia in full-term deliveries)	94/54,281 (0.2%) vs. 669/567,118 (0.1%)[103]	Adjusted OR, 1.28 (95% CI, 1.01 to 1.70)[103] 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)[103]	1 cohort, n=621,399[103]	Moderate study limitations precise, consistency unknown, adjusting for confounding increased the odds	Low for harms with SSRIs
Exposed to SSRIs during pregnancy or unexposed with a psychiatric diagnosis	Exposed to SSRIs during pregnancy vs. unexposed with a psychiatric diagnosis	Depression	60/15,729 (0.4%) vs. 30/9,651 (0.3%)	AHR, 1.78 (95% CI, 1.12 to 2.82) p=0.015	1 cohort, n=25,380[104]	Moderate study limitations, precise, consistency unknown	Low for harms with SSRIs
Pregnant with or without a known psychiatric condition	Maternal exposure to citalopram vs. no maternal exposure to any antidepressant but with a known psychiatric condition	Autism spectrum disorder without intellectual disabilities among offspring	46/1064 (4.3%) vs. 291/12325 (2.4%)	AOR, 1.75 (95% CI, 1.25 to 2.45)	1 cohort, n=13,389[105]	Moderate study limitations, precise, consistency unknown	Low for harms with citalopram

AHR = adjusted hazard ratio; AOR = adjusted odds ratio; CI = confidence interval; N/n = number; NICU = neonatal intensive care unit; NR = not reported; OR = odds ratio; SSRI = selective serotonin reuptake inhibitor; vs. = versus.

The identified harms include *NICU admissions* for benzodiazepine; *respiratory issues, low Apgar scores, persistent pulmonary hypertension of the newborn,* and *depression in children* for SSRIs overall; and *autism spectrum disorder* for citalopram. The relative paucity of evidence for these harms led us to rate the strength of evidence as low. Although the potential for harm to the child may exist, we have low confidence that future studies will support this association.

The evidence on fetal, infant, or child harms from treatments for mental health disorders comes from bodies of evidence with moderate or high limitations and precise results. Bodies of evidence with high limitations and precise results were not automatically upgraded from insufficient to low strength of evidence: they had factors beyond adequate sample size/events and narrow CIs alone (such as large effect size) that resulted in the low strength-of-evidence grade.

NICU Admission and Benzodiazapines

Regarding fetal harms, the evidence suggested that benzodiazepine exposure during pregnancy may be associated with an increased risk of NICU admission when compared with no exposure to benzodiazepines among women with a history of psychiatric disorders (absolute risk difference: 133/1,000, 95% CI, 17 to 274) (low strength of evidence).[99] The authors noted several differences between the comparison arms and the results adjusted for these confounders, but residual confounding cannot be ruled out. Also the study did not comment on dose or frequency.

NICU admission may be confounded by provider knowledge of antenatal exposure to psychotropic medications and hospital protocols. Until recently, neonatal abstinence syndrome due to prenatal exposure to opiates or benzodiazepines was typically treated in the NICU.

Respiratory Issues and SSRIs

Three studies reporting on respiratory distress and SSRIs used different measures; their results could not be pooled. One reported on respiratory conditions of newborns other than intrauterine hypoxia and birth asphyxia (International Statistical Classification of Diseases and Related Health Problems [ICD-9] code of other respiratory conditions),[100] undefined breathing problems,[101] and respiratory distress (ICD-9 codes of 769, 770.6, and 770.8[102]). The two studies that did specify that the ICD-9 codes included very heterogeneous outcomes, ranging from benign self-limiting conditions such as transient tachypnea of the newborn to more serious outcomes such as respiratory arrest of the newborn. Although we rated the outcome as low strength of evidence for harm, in the absence of more details on the proportion and differences between study arms for more serious outcomes, the clinical implications of this finding are unclear.

One study reported higher rates of intrauterine hypoxia and birth asphyxia.[100] The study used the ICD-9 code of 768. One concern is whether the higher rate in the exposed arm may be attributable to the greater number of Caesarean sections in the exposed arm and the higher use of the ICD-9 code of 768.3 for fetal distress during labor for nonreassuring fetal testing. Analyses from the same study in a population of women with vaginal deliveries found a statistically significant difference in the third trimester only. Notably, the incidence of intrauterine hypoxia and birth asphyxia in the exposed arm (3.5%) is much higher than the incidence of low Apgar scores (<7 at 5 minutes) in the same study (1.1%). It is unclear under what circumstances an infant would meet criteria for intrauterine hypoxia and birth asphyxia with a 5-minute Apgar ≥7, so the clinical significance of this finding is unclear.

Low Apgar Score and SSRIs

Although both studies reporting on low Apgar scores and exposure to SSRIs are rated as high risk of bias, the direction is consistent.[100, 101] The inter-rater reliability and consistency of scoring within individuals can vary; of note, the prevalence of 5-minute Apgar <7 in the control group was 1.2 percent in one study and 0.6 percent in the other, suggesting differences in the study population or the local standards for assignment of scores. The absolute risk difference from the study with the larger effect size is 8 per 1,000 (95% CI, 4 more to 13 more). The Apgar score does not predict long-term neurological outcomes[106] and was developed to determine the immediate need for resuscitation. Although we have rated the strength of evidence as low rather than insufficient, based on consistency, the clinical implications are unclear. Also, given the high risk of bias, it is possible that both studies are consistently biased.

Persistent Pulmonary Hypertension of the Newborn and SSRIs

For the study reporting an association between persistent pulmonary hypertension of the newborn and SSRIs, as with other observational cohorts, residual confounding and the potential for misclassification may exist. Risk factors, such as smoking, obesity, and Caesarean section, are all more prevalent in populations of psychiatric patients.[107] However, adjustments for potential sources of confounding (restricting the sample to full-term births[107] and restricting the outcome to those without cardiac anomalies or hypoplasia) resulted in higher odds than unrestricted results when compared with no exposure.[103] Notably, the baseline risk (0.1% in the unexposed arm) and absolute risk increase are very low (33 more cases per 100,000 persons, 95% CI, 1 to 83 more cases); in the analyses adjusting for potential sources of confounding, the risks are 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 strength of evidence).

Depression in Children and SSRIs

A single large national Finnish registry cohort study provides low strength of evidence that offspring of mothers with psychiatric illness exposed to SSRIs during pregnancy were more likely to have had a diagnosis of depression by age 15 than mothers with psychiatric illness (nearly all of which were affective disorders) who were not exposed to SSRIs during pregnancy.[104, 108] Of note, the absolute incidence of a depression diagnosis was less than 0.4 percent in each group (absolute risk difference: 2/1,000, 95% CI, 0 to 6 more). Further, there was no control for depressive severity (although the study controlled for previous diagnoses related to suicidal behavior). If depressed mothers receiving SSRIs were more severely depressed than depressed mothers not receiving SSRIs, the increased risk of depression in the offspring of those who received SSRIs may reflect a greater congenital risk of developing depression independent of any exposure.

Autism Spectrum Disorder and Citalopram

Results from one study suggested an increased risk of autism spectrum disorder in pregnant women exposed to citalopram (absolute risk difference: 17 per 1,000, 95% CI, 6 to 32) (low strength of evidence). Residual confounding could explain these results: the study found a stronger effect for autism spectrum disorder without intellectual disabilities (adjusted odds ratio [AOR], 1.75; 95% CI, 1.25 to 2.45), which the study notes is more likely to be heritable.[105] The study also notes that 95 percent of women who took antidepressants during pregnancy did not have a child with autism, and if no pregnant women took antidepressants, only 2 percent of autism cases in this population would be prevented.[105]

Insufficient Evidence of Maternal Harms

Overview

- Insufficient grades were assigned based on study limitations, bias, consistency, and precision. Some bodies of evidence comprised single studies for which we could not infer consistency of the evidence base. Additionally, the reported associations were imprecise (i.e., the results relied on small sample sizes, few events, or had wide CIs suggestive of both benefits and harms), were inconsistent, or had high study limitations.
- We found insufficient evidence to judge the risk of abruption and gestational hypertension in pregnancy for all reported exposures.

- We found insufficient evidence to judge the risk of preeclampsia for all reported exposures other than SNRIs and TCAs during pregnancy. Exposures during pregnancy with insufficient evidence include benzodiazepine, zolpidem, SSRIs (unspecified), citalopram, escitalopram, fluoxetine, paroxetine, sertraline, trazodone, bupropion, and mood stabilizers (as a class and separately for lamotrigine, valproate, topiramate, carbamazepine, oxcarbazepine, and lithium).
- We found insufficient evidence to judge overall adverse events or dizziness from using brexanolone for depression onset in the third trimester or within 4 weeks of delivery but note that FDA requires a boxed warning for excessive sedation or sudden loss of consciousness during infusion.
- We found insufficient evidence to judge the risk of spontaneous abortion for SSRIs and benzodiazepine.
- We found insufficient evidence to judge the risk of postpartum hemorrhage for trazodone, TCAs, and mirtazapine.

Detailed Synthesis

We found single studies with imprecise results, often from high risk-of-bias studies for most outcomes, including evidence from single studies of different exposures on gestational hypertension (see Appendix B for further details). For a subset of outcomes and interventions, we identified multiple studies but graded the evidence as insufficient. We describe these results in greater detail below for **preeclampsia** for SSRIs, **spontaneous abortion** for SSRIs and TCAs, and brexanolone for any **adverse events** including **dizziness** (Table 11).

Preeclampsia and SSRIs

Two studies[86, 87] with some risk-of-bias concerns reported inconsistent and imprecise results (CIs for the estimate of effect span both appreciable benefit and appreciable harm) and inclusive of both appreciable benefits and appreciable harms, resulting in the evidence being graded as insufficient.

Spontaneous Abortion and SSRIs or TCAs

Two publications reported on spontaneous abortion when comparing SSRI or TCA exposure in pregnancy with no exposure. One, rated as having a high risk of bias, suggested an association between SSRI or TCA exposure and spontaneous abortion.[90] The second, rated as having some risk-of-bias concerns, reported imprecise results with wide CIs suggestive of both benefits and harms for both exposures. In accounting for study limitations, we rated the evidence base as insufficient.[89]

Adverse Events and Brexanolone

Three RCTs (rated low risk of bias) reported on the harms of brexanolone versus placebo for depression symptoms with onset in the third trimester of pregnancy or within 4 weeks of birth.[18, 77] Brexanolone was administered as a 60-hour continuous infusion with a peak dose of either 60 μg/kg per hour or 90 μg/kg per hour. The study reported similar rates of any adverse events during infusion in the brexanolone and placebo groups and a higher rate of dizziness in the brexanolone arm versus the placebo arm. The pooled results for any adverse events and dizziness are imprecise and inconsistent and were graded as insufficient.

Table 11. Insufficient strength of evidence from effectiveness studies for harm to the mother (intervention versus placebo or no treatment)

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Depressed women	SSRI exposure during pregnancy vs. unexposed women with depression	Preeclampsia	303/5215 (5.8%) vs. 222/4,661 (4.8%)[86]; 105/3,169 (3.3%) vs. 1,569/65,392 (2.4%)[87]	ARR, 1.21 (95% CI, 1.02 to 1.45)[86] but bias corrected RR=0.9; ARR, 1.22 (95% CI, 0.97 to 1.54[87]); severe preeclampsia: ARR, 1.03 (95% CI, 0.81 to 1.18)	2 cohorts, n=78,437[86, 87]	Moderate study limitations (both have some risk-of-bias concerns), imprecise (wide CIs), inconsistent	Insufficient
Depressed or TCA-exposed women	TCA exposure in pregnancy vs. unexposed women with depression	Spontaneous abortion	20/112 (17.9%) vs. 720/7,034 (10.2%)[89] NR in second[90]	ARR, 1.5, (95% CI, 0.96 to 2.2)[89] and 1.3 (99% CI, 1.1 to 1.5)[90]	2 cohorts, n=7,146 in one cohort,[89] NR in second[90]	Moderate study limitations (one high risk-of-bias study[90]), imprecise, consistent	Insufficient
Depressed women	SSRI exposure in pregnancy vs. unexposed women with depression	Spontaneous abortion	93/938 (9.9%) vs. 720/8,877 (8.1%)[89] 1,539/10,312 (14.9) vs. 442/3647 (12.1%)[90]	ARR, 1.2, (95% CI, 0.94 to 1.5)[89] and 1.4 (99% CI, 1.2 to 1.7)[90]	2 cohorts, n=23,774[89, 90]	Moderate study limitations (one high risk-of-bias study,[90]) imprecise, consistent	Insufficient
Women with postpartum depression	Brexanolone vs. placebo	Any adverse event	Placebo: 54/107 BRX60: 19/38 BRX90: 51/102	Pooled RR, 0.93 (95% CI, 0.72 to 1.21), I^2=1.5% Placebo: 50.5% BRX60: 50.0% BRX90: 50.0%	3 RCTs, N=209[18, 77]	Low study limitations, inconsistent, imprecise (wide CIs)	Insufficient
Women with postpartum depression	Brexanolone vs. placebo	Dizziness	Placebo: 8/107 BRX60: 6/38 BRX90: 13/102	Pooled RR, 1.56 (95% CI, 0.52 to 4.66), I^2=31.3% Placebo: 7.5% BRX60: 15.8 BRX90: 12.7%	3 RCTs, N=209[18, 77]	Low study limitations, inconsistent, imprecise (wide CIs)	Insufficient

ARR = adjusted risk ratio; BRX = brexanolone for postpartum depression; CI = confidence interval; n = number; NR = not reported; = RR = relative risk; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant; vs. = versus.

Insufficient Evidence of Fetal, Infant, or Child Harms

Overview

- Insufficient grades were assigned based on study limitations, bias, consistency, and precision. Some bodies of evidence comprised single studies for which we could not infer consistency of the evidence base. Additionally, the reported associations were imprecise (i.e., the results relied on small sample sizes, few events, or had CIs suggestive of both benefits and harms), were inconsistent, or had high study limitations.

- We found insufficient evidence for perinatal death, preterm birth; major congenital anomalies; cardiac defects; small for gestational age; large for gestational age; birthweight; neonatal convulsions; extended hospital stay; delayed social, emotional, and cognitive development; ADHD; and anxiety in children for all reported exposures.
- We found insufficient evidence to judge the risk of autism spectrum disorder for all reported exposures other than citalopram. Exposures during pregnancy with insufficient evidence include SSRIs (unspecified), fluoxetine, paroxetine, sertraline, venlafaxine, duloxetine, clomipramine, amitriptyline/nortriptyline, and mirtazapine.
  Although diazepam, temazepam, and paroxetine include language suggesting risks of major congenital anomalies, we found insufficient evidence from eligible studies for our population of interest; evidence is available from studies of other populations ineligible for this review.

Detailed Synthesis

We found single studies with imprecise results, often from high risk-of-bias studies for most outcomes, including evidence from single studies of different exposures on perinatal death, large for gestational age, ADHD, and anxiety (see Appendix B for further details). For a subset of outcomes and interventions, we identified multiple studies but graded the evidence as insufficient. We describe these results in greater detail below. Specifically, we found multiple publications providing evidence for one or more intervention for *preterm birth, neonatal convulsions, small for gestational age, birthweight, major congenital anomalies, cardiac defects, NICU admissions, extended hospital stay, infant and child development and behavior***,** and **autism spectrum disord***er* (Table 12).

Preterm Birth and SSRIs

Six studies reported inconsistent results on the associations between preterm birth (all defined as <37 weeks) and SSRIs.[101, 102, 109-112] The results could not be pooled because of variations in reported outcomes. One study reported statistically significant benefit;[101] a second reported statistically significant harms.[111] The other studies reported relative risks, odds, or incidences, with wide CIs suggestive of both benefits and harms. Four of the six studies did not account for severity of psychiatric illness.[102, 109, 110] The studies that accounted for this variable in found no statistically significant differences between the groups.[102, 112] Inconsistency, imprecision, and high study limitations for most studies led to a rating of insufficient.

Neonatal Convulsions and SSRIs

Regarding neonatal convulsions, two studies[100, 102] provided consistent but imprecise evidence on the risks of neonatal convulsions associated with exposure to SSRIs. Only one study provided rates, but the numbers suggest a very small baseline risk (0.1% in the unexposed arm) and a small absolute risk difference (2 in 1,000).

Table 12. Insufficient strength of evidence from effectiveness studies for harm to the fetus, infant, or child (intervention versus placebo or no treatment)

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Depressed, psychiatric disorders, or discontinued SSRIs during pregnancy exposed to SSRIs	SSRI exposure during pregnancy vs. no exposure (exposure prior to pregnancy or depressed or with psychiatric disorder)	Preterm birth	741/15,729 (4.7%) vs. 515/9,652; (5.3%)[101] 17/192 (8.8%) vs. 415/5,710 (7.3%);[110] 55/221 (24.9%) vs. 185/1,566 (11.8%);[111] 3/37 (8.11%) vs. 3/19 (15.79%)[112] N=NR for two publications[102, 109]	Overall 5 of 6 studies do not report increased risks with SSRIs. Prevalence, AOR, ARRs range from 0.84[101] to 2.68[111] with CIs spanning the null in 2 of 4 studies null (one study reported higher odds in the SSRI group,[111] the other reported lower odds in the SSRI group[101]; difference in incidence: 0.007 (95% CI, -0.018 to 0.034);[102] NR, p = 0.948[112]	6 cohorts; N>33,666 N= NR in one study[102])[101, 109-112]	High study limitations (5 high risk-of-bias studies[101, 109-112]), mostly consistent, imprecise (wide CIs in some studies)	Insufficient
Exposed to SSRIs during pregnancy or unexposed with previous exposure or depressed	Exposed to SSRIs during pregnancy vs. unexposed depressed or exposed before but not during pregnancy	Neonatal convulsions	9/2,664 (0.3%) vs. 7/5,141 (0.1%);[100] NR in one study[102]	Adjusted prevalence ratio: 2.28 (95% CI, 0.87 to 5.97)[100] Difference in incidence: 0.00077 (95% CI, -0.001 to 0.0036) p-value 0.3[102]	2 cohort studies, n>7,805 (N NR in one study[102])[100, 102]	High study limitations (1 of 2 studies are high risk of bias[100]) imprecise, consistent	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
History of mental health disorder or depression or SSRI-exposed women	SSRI exposure in pregnancy vs. unexposed women with depression or mental health disorder	Small for gestational age	Varies across studies from 2.5% to 17.4% in the treatment arm, and 2.5% to 14.7% in the control arm[100-102, 110, 113]	Five[100-102, 111, 113] of 6 studies report nonsignificant results (adjusted prevalence ratios, ARR, AOR, difference in incidence) with CIs spanning the null; one study reported AOR of 1.68 (95% CI, 1.03 to 2.74);[110] ARR varies by trimester of exposure from 0.7 to 1.4, 95% CI spans the null[113]	5 cohort studies,1 case-control, n varies by trimester, n=43,185[100-102, 110, 111, 113]	High study limitations (4 of 6 high risk-of-bias studies[100, 101, 110, 111]), imprecise (wide CIs), mostly consistent	Insufficient
Use of antidepressants before or during pregnancy or psychiatric illness	SSRI exposure during pregnancy vs. SSRI exposure just before but not during pregnancy or psychiatric illness with no exposure	Low birth weight	42/221 (19.0%) vs. 150/1,566 (9.6%);[111] NR in one study;[109] 4/36 (11.11%) vs. 3/19 (15.79%)[112]	Adjusted prevalence ratio: 1.1 (95% CI, 0.9 to 1.3)[109] AOR, 2.26 (95% CI, 1.31 to 3.91) NR, p=0.613[112]	3 cohorts, N>1,842,[111, 112] N=NR in one study[109]	High study limitations (high risk of bias[109, 111, 112]), imprecise (wide CIs), inconsistent	Insufficient
History of depression or anxiety or current or past SSRI-exposed women	Exposed to SSRIs in pregnancy vs. unexposed women with history of depression, anxiety or prior exposure	Major congenital anomalies	279/2,327 (12.0%) vs. 1,650/14,847 (11.1%)[114]; 204/7,683 (2.7%) vs, 380/13,432 (2.8%);[115] 208/4,183 (5.0%) vs. 36/806 (4.5%)[116]	Adjusted prevalence ratio: 1.07 (95% CI, 0.93 to 1.22);[114] AOR, 0.93 (95% CI, 0.78 to 1.11);[115] adjusted effect NR in one study, p=0.9[116]	3 cohorts, n=43,299[114-116]	High study limitations (all risk-of-bias studies),[114-116] imprecise (wide CIs), consistent	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Pregnant women with diagnosis of depression only[115] or depression and or anxiety, or exposed to antidepressants[114]	Maternal exposure to citalopram vs. no exposure anxiety and/or depression	Major congenital anomalies	NR/1946 vs. 666/23,833 (2.8%) in one study,[115] NR in second[114]	AOR, 1.36 (95% CI, 1.08 to 1.73)[114]; OR, 0.97 (95% CI, 0.71 to 1.31)[115]	2 cohort studies; n>25,779[115, 116]	High study limitations (high risk of bias[114, 115]), imprecise (CIs suggestive of both benefits and harms in one study[115]), inconsistent	Insufficient
Pregnant women: Cohort 1: depression and/or anxiety diagnosis and exposure to antidepressants in the year before pregnancy; Cohort 2: depression diagnosis from the year before conception through the first trimester	Fluoxetine exposure in the first trimester vs. unexposed	Major congenital anomalies	NR/191 vs. 1,650/14,847 (11.1%)[114]; 241/3,189 (7.6%) vs. 380/13,432 (2.8%)[115]	AOR, 0.80 (95% CI, 0.49 to 1.31);[114] AOR, 0.85 (95% CI, 0.66 to 1.09)[115]	2 cohorts: N= 15,038;[114] N=27,022[115]	High study limitations (both high risk of bias), imprecise (wide CIs); consistent	Insufficient
Women with depression or anxiety in the year before pregnancy	Paroxetine in 1st trimester vs. not exposed in 1st trimester	Major congenital anomalies	168/1,132 (14.8%) vs. 1,650/14,847 (11.1%)[114] Paroxetine exposed: 37 cases, 375 controls No antidepressant: 94 cases, 1134 controls[117] 36/1,200 (3.0%) vs. 380/13,432 (2.8%)[115]	Results not pooled because two publications[114, 117] potentially draw from the same population AOR, 1.24 (95% CI, 0.99 to 1.55; 99% CI, 0.79 to 1.66)[114] AOR, 1.27 (95% CI, 0.78 to 2.06)[117] AOR 1.01 (95% CI, 0.71 to 1.44)[115]	2 cohorts,[114, 115] 1 case-control,[117] N≥33,119 (N from two studies;[114, 115] third study may be a subset of one study[117]	High study limitations (two high risk-of-bias studies[114, 115]), imprecise, consistent	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women with depression or anxiety in the year before pregnancy	Sertraline in 1st trimester vs. not exposed in 1st trimester	Major congenital anomalies	NR/365 vs. 1650/14,847 (11.1%)[114] 45/366 (12.31099%) vs.1,651/14,868 (11.1%) from one study with potentially overlapping participants[118]) 25/757 (3.3%) vs. 380/13,432 (2.8%)[115]	Results not pooled because two publications[114, 118] potentially draw from the same population AOR, 1.09 (95% CI, 0.80 to 1.50)[114] (ARR, 1.11 (95%CI 0.81 to 1.52) from potentially overlapping citation[118] AOR, 1.17 (95% CI, 0.78 to 1.77)[115]	2 cohorts, N>32,676[114] (potential overlap of participants in two publications[114, 118])	High study limitations (two high risk-of- bias studies[114, 115]), consistent	Insufficient
History of depression, depression or anxiety or mental health disorder or TCA-exposed women	TCA exposure during the first trimester) vs. unexposed with history of depression, anxiety, or mental health disorder	Major congenital anomalies	51/382 (13.4%) vs. 1,650/14,847 (11.1%)[114]; 74/2,428 (3.0%) vs. 380/13,432 (2.8%)[115]; NR in other study[117]	Results not pooled because two publications[114, 117] potentially draw from the same population AOR, 1.16 (95% CI, 0.86 to 1.56)[114] AOR, 1.02 (95% CI, 0.79 to 1.32)[115] AOR, 0.78 (95% CI, 0.30 to 2.02)[117]	1 case-control,[117] 2 cohorts, n≥31,089[115, 119] N from two studies;[114, 115] (potential overlap of participants in the publications)	High study limitations (two high risk-of-bias studies),[114, 117] imprecise (wide CIs), consistent	Insufficient
Women with a psychiatric condition or women with schizophrenia, bipolar disorder, or psychosis	Second-generation antipsychotic exposure in first trimester vs. unexposed to second-generation antipsychotic	Major congenital anomalies	209/3,995 (5.2%) vs, 471/11,606 (4.1%)[120] 3/214 (1.4%) vs. 1/89 (1.1%)[121]	AOR, 1.16 (95% CI, 0.99 to 1.35)[120] AOR, 0.69 (95% CI, 0.06 to 8.09)[121]	2 cohorts, n=15,904[120, 121]	Moderate study limitations (one high risk-of-bias study[121] precise, inconsistent	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Pregnant women with diagnosis of depression only[115] or depression and or anxiety, or exposed to antidepressants[114, 122]	Maternal exposure to citalopram vs. no exposure or unexposed to SSRIs in early pregnancy	Cardiac congenital anomalies	NR in two studies;[114, 115] 50 cases/39 controls vs. 149 cases/125 controls[122]	Pooled OR, 1.09 (95% CI, 0.82 to 1.46), I^2: 0% AOR, 1.15 (95% CI, 0.69 to 1.92)[114] AOR, 1.02 (95% CI, 0.61 to 1.70)[115] AOR, 1.11 (95% CI, 0.68 to 1.83)[122]	2 cohort studies, 1 case control, N>363[122] N NR in two studies[114, 115]	High study limitations (high risk of bias[114, 115]), imprecision (wide CIs), consistent	Insufficient
Depression or antidepressant exposed women	Escitalopram exposure during early pregnancy vs. unexposed women with depression or unexposed to SSRIs in early pregnancy	Cardiac anomalies	3/333 (0.9%) vs. 112/13,432 (0.83%);[115] 43 cases/35 controls vs. 149 cases/125 controls[122]	AOR, 1.09 (95% CI (0.34 to 3.50)[115] AOR, 1.16 (0.69 to 1.97)[122]	1 cohort, n=13,765,[115] 1 case-control, n=352[122]	Serious study limitations (high risk of bias[115]), imprecision (wide CIs spanning the null), consistency unknown	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women with depression or anxiety in the year prior to pregnancy	Sertraline in 1st trimester vs. unexposed	Cardiac anomaly	NR in one study: NR/365 vs. NR/14,847[114] (results from publication with overlapping data: 10/366) (2.7%) vs. 344/14,868 (2.3%)[118]); 9/757 (1.0%) vs. NR/13,432;[115] 93/11,126 (0.8%) vs. 1,479/180,564 (0.8%)[123] 156 cases/129 controls vs. 149 cases /125 controls[122]	Pooled AOR, 1.08 (95% CI, 0.91 to 1.28), I^2: 0% AOR, 1.14 (95% CI, 0.60 to 2.15)[114] (Results from one publication potentially overlapping data with study[114] included in meta-analysis is also consistent, with ARR, 1.16 (95% CI, 0.62 to 2.19)[118] AOR, 1.39 (95% CI, 0.70 to 2.74)[115] Propensity score AOR, 1.09 (95% CI, 0.88 to 1.34, p=0.051)[123] AOR, 0.97 (95% CI, 0.69 to 1.37)	3 cohorts, 1 case-control, 5 publications,[114, 115, 118, 122, 123] N>250,577 (potential overlap in two publications[114, 118])	High risk of bias (3 studies,[114, 115, 118, 123]), imprecise (wide CIs), consistent	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women with depression or anxiety in the year prior to pregnancy or exposure to antidepressants outside of early pregnancy	Paroxetine in first trimester vs. unexposed	Cardiac anomalies	NR/1132 vs. NR/14,847[114] 17/1200 (1.4%) vs. 112/13,432 (0.8%[115] 93/11,126 vs. NR/180,564[123] 69 cases/43 controls vs. 149 cases/125 controls[122]	Pooled AOR, 1.26, 95% CI, 0. 96 to 1.65, I^2: 58%; high heterogeneity potentially explained by clinical (differences in the definition of cardiac anomaly) and statistical heterogeneity (differences in direction of effect) AOR, 1.45 (95% CI, 1.12-1.88; 99% CI, 0.87 to 2.03)[114] AOR, 1.67 (95% CI, 1.00 to 2.80, p=0.051)[115] Propensity score AOR, 0.94 (95% CI, 0.73 to 1.21)[123] AOR, 1.27 (95% CI, 0.8 to 2)[122]	3 cohorts, 1 case-control, N=222,505	High study limitations (3 studies[114, 115, 123]), imprecision (wide CIs), inconsistent	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women with depression or anxiety in the year before pregnancy	Sertraline in 1st trimester vs. unexposed	Cardiac anomalies	NR in one study: NR/365 vs. NR/14,847[114] (results from publication with overlapping data: 10/366 (2.7%) vs. 344/14,868 (2.3%)[118]); 9/757 (1.0%) vs. NR/13,432;[115] 93/11,126 (0.8%) vs. 1,479/180,564 (0.8%)[123]	Pooled AOR, 1.12 (95% CI, 0.92 to 1.35), I^2: 0%, AOR, 1.14 (95% CI, 0.60 to 2.15)[114] Results from one publication potentially overlapping data with study[114] included in meta-analysis is also consistent, with ARR, 1.16 (95% CI, 0.62 to 2.19)[118]	3 cohorts, 4 publications,[114, 115, 118, 123] N>250,018 (potential overlap in two publications[114, 118])	High risk of bias (all studies), imprecise (wide CIs), consistent	Insufficient
Depressed or exposed to SSRIs in pregnancy	Exposed to SSRIs vs. unexposed to SSRIs during pregnancy with depression or unexposed to SSRIs in early pregnancy	Cardiac anomalies	68/7683 (0.9%) vs. 112/13,432 (0.8%);[115] NR in second study;[123] 466 cases/341 controls vs. 149 cases/125 controls[122]	Pooled OR, 1.07 (95% CI, 0.97 to 1.20), I^2: 0% AOR, 1.06 (95% CI, 0.93 to 1.22)[123] AOR, 1.04 (95% CI, 0.76 to 1.41)[115] AOR, 1.14 (95% CI, 0.87 to 1.51)[122]	2 cohorts 1 case control,[115, 122, 123] N>22,196 (N=NR in one study[123])	High study limitations (2 high risk-of-bias studies[115, 123]) imprecise (wide CIs), consistent	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Pregnant women: cohort 1: depression and/or anxiety diagnosis and exposure to antidepressants in the 12 months before pregnancy. Cohort 2: depression diagnosis from the year before conception through the first trimester Cohort 3: timing of depression dx NR	Fluoxetine exposure in the first trimester vs. unexposed	Cardiac anomalies	NR/191 vs. NR/14,847;[114] 66/3,189 (2.1%) vs. 112/13,432 (0.8%)[115] 84/8,664 (1.0%) vs. 1,497/180,564 (0.8%)[123]	Pooled OR, 0.94, (95% CI, 0.65 to 1.37), I^2: 41.9% AOR, 0.42 (95% CI, 0.10 to 1.73)[114] AOR, 0.79 (95% CI, 0.49 to 1.26)[115] Propensity-score AOR, 1.14 (95% CI, 0.90 to 1.44)[123]	3 cohorts: N=15,038[114], N=16,621[115] N=189,228[123]	High study limitations (all high risk-of-bias studies), imprecise (wide CIs), inconsistent	Insufficient
Women with depression or anxiety before pregnancy or exposure to antidepressants outside of early pregnancy or duloxetine in the first trimester vs. discontinuation of duloxetine before the first trimester	Venlafaxine;[114] SNRI; exposure in the first trimester vs. unexposed;[122, 123] Duloxetine, exposure in the first trimester[124]	Cardiac anomalies	SNRI:69/ 1,497 (4.6%) vs. 1,497/ 180,564 (0.8%);[123] 59 cases/27 controls vs. 149 cases/125 controls[122] Venlafaxine: NR/738 vs. NR/14,847;[114] 47 cases/21 controls vs. 149 cases/125 controls[122] Duloxetine: 59/2,532 (2.33%) vs. 43/2,456 (1.75%)[124]	SNRI Propensity score AOR, 1.20 (0.91 to 1.57)[123] AOR, 1.14 (95% CI, 0.44 to 3.01)[122] Venlafaxine AOR, 0.80 (0.47 to 1.38)[114] AOR, 1.91 (95% CI, 1.05 to 3.45) SNRIs[122] Duloxetine ARR, 1.41 (95% CI, 0.92 to 2.17)[124]	3 cohorts, 1 case control: N=202,994[114, 122-124]	High study limitations (high risk of bias [114] [123]), imprecise (wide CIs), inconsistent	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
History of depression or anxiety or TCA-exposed women	TCA in first trimester vs. unexposed women with history of depression	Cardiac anomalies	20/2,428 (0.82%) vs. 112/13,432 (0.83%);[115] NR in other studies[114, 123]	Pooled AOR, 0.86 (95% CI, 0.65 to 1.13), I^2: 0%[114, 115, 123]	3 cohorts, n>15,860 (N=NR in two studies)[114, 115, 123]	High study limitations (all risk-of-bias studies),[114, 115, 123] imprecise (wide CIs), consistent	Insufficient
Depressed or bupropion-exposed women	Bupropion exposure in pregnancy vs. unexposed women with depression or unexposed in early pregnancy	Cardiac anomalies	NR;[123] 57 cases/45 controls vs.149 cases/125 controls[122]	AOR, 0.92 (95% CI, 0.69 to 1.22);[123] AOR, 1.06 (0.66 to 1.71)[122]	1 cohort,1 case-control, n NR in cohort[123] N in case-control=376[122]	Serious study limitations (high risk of bias[123]) imprecise (wide CIs spanning the null), consistency unknown	Insufficient
Exposed to SSRIs during pregnancy or unexposed with a psychiatric diagnosis	Exposed to SSRIs during pregnancy vs. unexposed with a psychiatric diagnosis	NICU	2,405/ 15,729 (15.3%) vs. 1,160/9,652 (12.0%);[101] 7/33 (21.21%) vs. 5/19 (26.32%)[112]	Adjusted OR, 1.24 (95% CI, 1.14 to 1.35);[101] NR, p=0.816[112]	2 cohorts, n=25,433[101, 112]	High study limitations (high risk of bias[101, 112]) precise, inconsistent	Insufficient
Exposed to SSRIs during pregnancy or unexposed depressed or with a psychiatric illness	Exposed to SSRIs during pregnancy vs. unexposed depressed during pregnancy or with a psychiatric illness	Extended hospital stay (>3 days for vaginal birth,[102] >7 days[101])	1315/15,729 (8.4%) vs. 821/9,652 (8.5%);[101] 20/221 (9.0%) vs. 75/1,566 (4.8%);[111] NR in one study[102]	Inconsistent results spanning benefits, harms, and no effect AOR, 0.89 (95% CI, 0.8 to 0.99);[101] AOR, 1.93 (95% CI, 1.11 to 3.36)[111] Difference in incidence: 0.035 (95% CI, -0.005 to 0.072), p-value 0.08[102]	3 cohort studies, n>27,168 N=NR in one study[101, 102, 111]	High study limitations (2 of 3 studies are high risk of bias[101, 111]) imprecise, inconsistent	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Depressed or anxious or exposed to SSRIs in pregnancy	Exposed to SSRIs vs. unexposed during pregnancy with depression or anxiety	Infant and child behavior and development	Varies by measure (measures include CBCL [including subscales], Behaviour Rating Inventory of Executive Function—Preschool version (BRIEF-P), Snijders-Oomen Niet-verbale intelligentie Test-Revisie (SON-R 2 1/2-7), NEPSY-II, NICU network neurobehavioral (NNNS [including subscales])—Attention scores, MDI, PDI, BRS	Results vary by specific outcome, but the majority of outcomes are not statistically significant; exceptions include 1 subscale measure for CBCL and NEPSY-II, and 3 of 13 NNNS subscale measures; studies with significant findings did not adjust for multiple comparisons	4 cohorts, N=4,410[125-128]	High study limitations (3 of 4 are high risk of bias,[125-127] imprecise, consistency unknown (single measures of outcomes not repeated in multiple studies)	Insufficient
Pregnant women: Any lifetime depression or anxiety diagnosis	Fluoxetine during pregnancy vs. unexposed women	Autism spectrum disorder	8/327 (2.1%) vs. 282/14,805 (1.9%);[129] 16/453 (3.5%) vs. 353/12,325 (2.9%)[105]	By 7- or 8-year followup ARR, 1.08 (0 95% CI, .53 to 2.21);[129] 4-year or more followup: AOR, 1.42 (95% CI, 0.84 to 2.39)[105]	2 cohorts: N=15,132;[129] N=12,778[105] (potential overlap of participants in the publications)	Moderate study limitations, imprecise (wide CIs); consistent	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women with current or past mental health disorder	Paroxetine vs. unexposed to antidepressants during pregnancy	Autism spectrum disorder	5/264 (1.9%) vs. 353/12,325 (2.9%)[105] 3/108 (2.8%) vs. 282/14,805 (1.9%)[129]	ARR, 0.61 (95% CI, 0.25 to 1.49)[105] ARR, 1.21 (95% CI, 0.38 to 3.8)[129] Results adjusting for the number of mental health disorders show attenuating risks of autism spectrum disorder ≥1 mental health disorder: ARR, 1.36 (95% CI, 0.51 to 3.64)[129] ≥2 mental health disorders: ARR, 1.02 (95% CI, 0.38 to 2.78)[129] ≥3 mental health disorders: ARR, 0.74 (95% CI, 0.27 to 2.04)[129]	2 cohorts, N>35,218[105, 129] (potential overlap of participants in the publications)	Moderate study limitations, imprecise (wide CIs), consistency unknown (potential overlap of participants)	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women with current or past mental health disorder	Sertraline vs. unexposed to antidepressants during pregnancy	Autism spectrum disorder	31/912 (3.4%) vs. 353/12,325 (2.9%)[105] 16/672 (2.4%) vs. 282/14,805 (1.9%)[129]	AOR, 1.45 (95% CI, 0.98 to 2.16)[105] ARR, 1.17, (95% CI, 0.99 to 2.32)[129] Results adjusting for the number of mental health disorders show attenuating risks of autism spectrum disorder ≥1 mental health disorder: ARR, 1.32 (95% CI, 0.86 to 2.24)[129] ≥2 mental health disorders: ARR, 0.99 (95% CI, 0.63 to 1.55)[129] ≥3 mental health disorders: ARR, 0.71 (95% CI, 0.43 to 1.17)[129]	2 cohorts, N>15,47728,714[105, 129] (potential overlap of participants in the publications)	Moderate study limitations, imprecise (wide CIs), some consistency	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Pregnant women: Any lifetime depression or anxiety diagnosis	Venlafaxine during pregnancy vs. unexposed women	Autism spectrum disorder	4/195 (2.1%) vs. 282/14,805 (1.9%);[129] 11/213 (5.1%) vs. 353/12,325 (2.9%)[105]	By 7- or 8-year followup ARR, 0.74 (0.32 to 1.72);[129] 4-year or more followup: AOR, 1.81 (0.89 to 3.71)[105] ≥1 mental health disorder: ARR, 1.36 (95% CI, 0.61 to 3.04)[129] ≥2 mental health disorders: ARR, 1.01 (95% CI, 0.44 to 2.29)[129] ≥3 mental health disorders: ARR, 0.74 (95% CI, 0.32 to 1.72)[129]	2 cohorts: N=27,538 [105, 129]	Moderate study limitations, imprecise (wide CIs); inconsistent	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Mental health disorder or clomipramine-exposed women	Clomipramine vs. unexposed women with history of psychiatric disorder	Autism spectrum disorder	16/235 (6.8%) vs. 353/12,325 (2.9%);[105] NR in second study[129]	AOR, 1.76 (95% CI, 1.01 to 3.05)[105]; ARR, 3.36, 95% CI, 1.39 to 8.13, results not statistically significant when corrected for multiple testing ≥1 mental health disorder: ARR, 3.36 (95% CI, 1.39 to 8.13)[129] ≥2 mental health disorders: ARR, 2.53 (95% CI, 1.02 to 6.22)[129] ≥3 mental health disorders: ARR, 1.88 (95% CI, 0.7 to 4.73)[129]	2 cohorts, n=36,936[105, 129] (potential overlap of participants in the publications)	Moderate study limitations, imprecise, consistent	Insufficient

AOR = adjusted odds ratio; ARR = adjusted risk ratio; BRIEF-P = Behaviour Rating Inventory of Executive Function—Preschool version; BRS = Behavioral Rating Scale; CBCL = childhood behavior checklist; CI = confidence interval; dx = diagnosis; MDI = Mental Development Index; N = number; NEPSY-II = Developmental NEuroPSYchological Assessment-II; NICU = neonatal intensive care unit; NNNS = NICU Network Neurobehavioral Scale subscale measures; NR = not reported; OR = odds ratio; PDI = Provisional Diagnostic Instrument; SON-R = Snijders-Oomen Niet-verbale intelligentie Test-Revisie; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant; vs. = versus.

Small for Gestational Age and SSRIs

Six studies reported on the association between small for gestational age and SSRI exposure.[100-102, 110, 111, 113] The results could not be pooled because of differences in reported outcomes. Five of six studies reported results with wide CIs suggestive of both benefits and harms. The only study that controlled for severity of psychiatric illness reported no statistically significant difference between the groups. Wide CIs indicated the potential for both appreciable benefit and appreciable harm. This imprecision, coupled with high study limitations for most studies, led to a rating of insufficient.

Low Birthweight and SSRIs

Although two studies[109, 111] provided consistent evidence of an increased association between low birth weight and SSRI exposure, both had limitations. Neither controlled for severity of maternal illness. A third study reported no statistically significant differences.[112]

Congenital Anomalies and Pharmacologic Interventions

Prescription labeling from FDA suggests potential fetal concerns for several psychotropic drugs. These include paroxetine, temazepam, triazolam, alprazolam, diazepam, valproate, carbamazepine, and topiramate for congenital anomalies and clonazepam for increased risk of hypothermia, hypotonia, respiratory depression, difficulty feeding, and withdrawal. We did not find eligible evidence on congenital anomalies for triazolam, alprazolam, valproate, carbamazepine, and topiramate, although evidence is available from studies of other populations ineligible for this review. This broader evidence formed the basis of the FDA warning language. For paroxetine, the concern was based on increased reports of cardiac malformation at the time of the labeling. For temazepam and diazepam, the concerns were based on increased reports of congenital anomalies.

Regarding major congenital anomalies, 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 (any type).[114-118, 121, 130, 131] Figure 2 displays results for all reported exposures in a forest plot (the results are not pooled because of potential overlap of participants across studies for some interventions). The results almost always span the null with CIs suggesting benefits and harms (with the exception of one study each on citalopram[114] and second-generation antipsychotics[120]), with adjusted odds ratios on both sides on 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.

Regarding findings specific to temazepam and diazepam , our review identified a single eligible study with serious limitations arising from residual confounding and potential selection bias. The study reported AORs of 0.99 (95% CI, 0.61 to 1.61) for diazepam and 1.04 (95% CI, 0.47 to 2.32) for temazepam.[131] FDA found that "an increased risk of congenital anomalies associated with the use of diazepam and chlordiazepoxide during the first trimester of pregnancy has been suggested in several studies,"[132] but the studies are not cited.

Regarding cardiac anomalies, eight studies evaluated associations with cardiac anomalies[114, 115, 118, 122, 123, 133-135] and used different criteria to identify affected infants. Studies using the Medicaid Analytic eXtract cohort[123, 133] required either (1) ICD-9 diagnosis for a specific

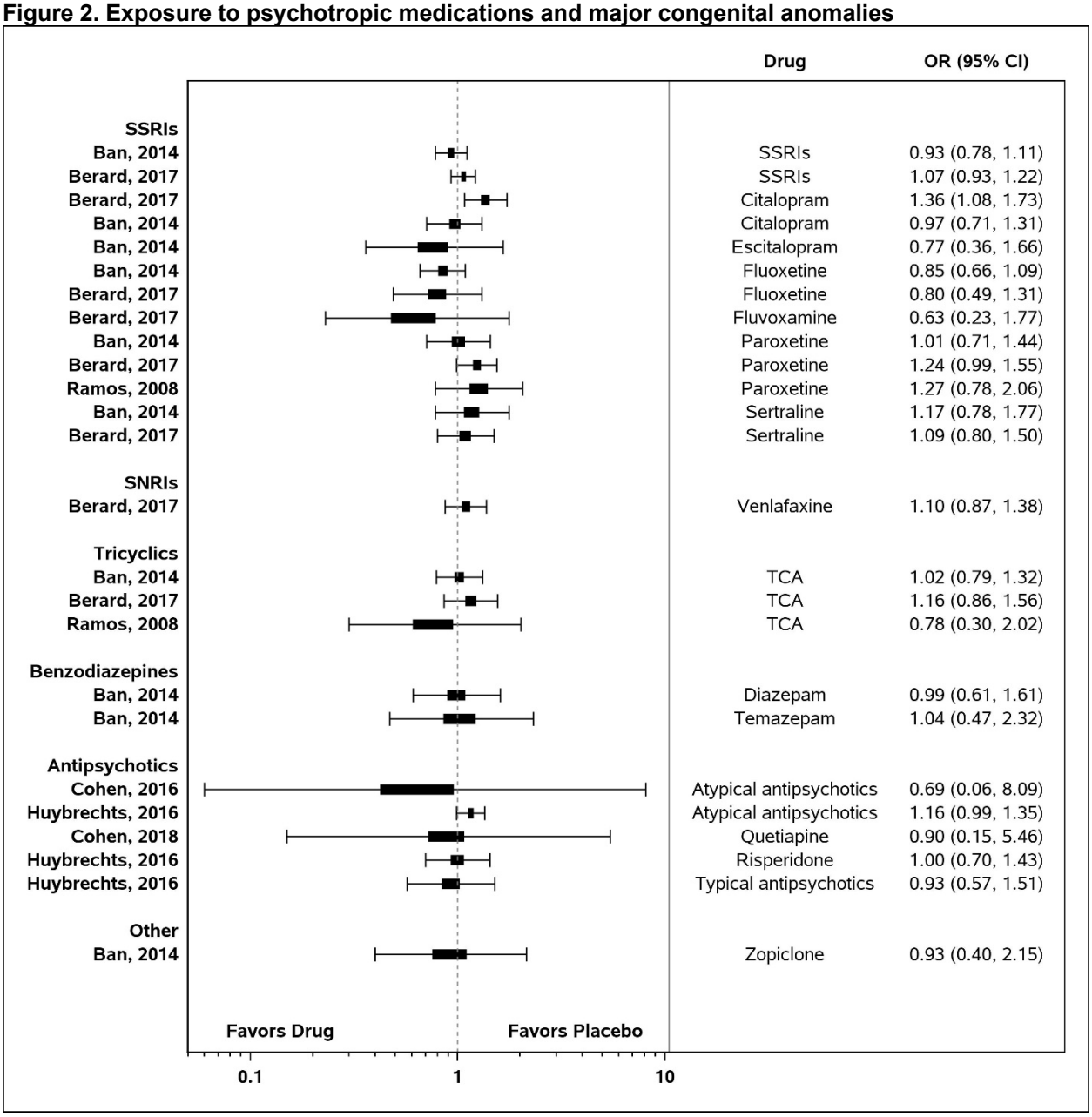
malformation on more than one date, (2) a diagnosis on one date and a relevant procedure code, or (3) a diagnosis on only one date with an infant death before 90 days. For infants born preterm, these studies excluded isolated cardiac anomalies associated with prematurity (745.5, atrial septal defect, 747.0, patent ductus arteriosus, 746.02, pulmonary-valve stenosis, and 747.3 anomalies of the pulmonary artery). A single U.K. study[115] used European Surveillance of Congenital Anomalies (EUROCAT) criteria, which similarly exclude Q21.11, patent, or persistent foramen ovale, if gestational age at birth is <37 weeks. In contrast, studies from the Quebec Pregnancy Cohort[114, 118, 134] used diagnosis codes from hospitalizations in Quebec to identify cardiac anomalies using ICD-9 codes 745-746 or ICD-10 codes Q20-Q22, with no exclusion for atrial septal defect (ICD-9: 745.5, ICD-10: Q21.1) for preterm infants. The National Birth Defects Prevention Study[122] relied on a classification of heart defects developed for the study.[136] Lastly, a 1983 study[135] used information from the Swedish Registry of Congenital Malformations and from special child cardiology clinics to identify six infants with heart defects; no further details were provided. Given that atrial septal defects are part of preterm infant physiology, the clinical validity of studies that do not exclude these cases is unclear.

Regarding findings specific to paroxetine (previously labeled Category X drug for cardiac defects), although we found no evidence supporting an association between exposure to psychotropic agents and cardiac defects, one study reported an association between paroxetine exposure and atrial or ventricular septal defects.[114] A second study, focusing on ventricular septal defects, found no association with paroxetine exposure, raising the possibility that differences in findings could be attributable to how outcomes were defined.[123] The clinical validity of an association with atrial septal defects is unclear. Beyond differences in outcome measurement, differences between studies in design and controls for confounding could potentially explain variations in results. The study that adjusted for numerous potential confounders through propensity score adjustment found no differences in ventricular septal defects.[123]

NICU Admission and SSRIs

Regarding fetal harms, evidence from two studies provided inconsistent evidence on SSRI exposure during pregnancy and NICU admissions.[101, 112] One study—adjusting for sex, birth period, maternal age at delivery, place of residence, marital status, parity, smoking, socioeconomic status, purchase of anxiolytics, sedative-hypnotics, or antiepileptic drugs, prepregnancy diabetes, and other chronic diseases, but not severity of mental health disorder—reported significantly increased risk.[101] The second study accounted for severity of the disorder and for smoking and found no difference.[112] In addition to inconsistent adjustment for severity, as noted previously, NICU admission may be confounded by provider knowledge of antenatal exposure to psychotropic medications and hospital protocols.

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.

Extended Hospital Stay and SSRIs

Three studies reported inconsistent results (one suggested benefit,[101] the second no statistically significant difference,[102] and the third suggested harm[111]) from exposure to SSRIs. The study reporting no statistically significant differences controlled for maternal illness severity; the other two did not. The inconsistencies, coupled with high study limitations, led to a strength-of-evidence grade of insufficient.

Infant and Child Behavior and Development and SSRIs

Four studies[125-128] reported on numerous scales and subscale measures of infant and child development and behavior associated with exposure to SSRIs. These results could not be pooled because of heterogeneity, but the majority of outcomes reported results that were not statistically significant.

Autism Spectrum Disorder and Fluoxetine, Paroxetine, Sertraline, Venlafaxine, or Clomipramine

Two studies,[129] N=12,778[105] with a potential overlap in participants, did not consistently find associations between exposure to fluoxetine, paroxetine, sertraline, venlafaxine, or clomipramine and autism spectrum disorder. When one study controlled for number of mental health disorders, the effect always attenuated, suggesting that severity of psychiatric illness was a strong confounder of the observed effect.

No Evidence in Populations of Interest (Pregnant Women With Mental Health Disorders)

Overview

- For outcomes prioritized for this review, we found no eligible studies that provided evidence about infertility, abruption, glucose intolerance, reduced milk production or unwanted weaning, and withdrawal symptoms in the newborn.
- For interventions in our populations of interest, we found no eligible studies that provided evidence of fetal harms on several drugs with FDA pregnancy-related boxed warnings (valproate) or language suggesting fetal harm (alprazolam, valproate, carbamazepine, topiramate, clonazepam , triazolam, asenapine, brexpiprazole, chlordiazepoxide, clorazepate, fluphenazine, hydroxyzine, imipramine, and lorazepam). Evidence may be available from studies of other populations ineligible for this review (such as among pregnant or women without mental health disorders who were exposed to these drugs).
- We did not find eligible studies that provided evidence of the harms reported in warnings for amitriptyline and lithium, although we found insufficient evidence on other reported harms (autism spectrum disorder for amitriptyline; preeclampsia, placental abruption, preterm birth, and small-for-gestational-age for valproate, carbamazepine, topiramate; and preeclampsia, placental abruption, preterm birth, small-for-gestational-age, and child IQ for lithium).

Detailed Synthesis

We found no evidence of fetal harms for several drugs that had FDA pregnancy-related boxed warnings (valproate [for women without epilepsy]) or language suggesting fetal or neonatal harm in the past (alprazolam, valproate [for women with epilepsy], carbamazepine , topiramate, clonazepam, triazolam, amitriptyline, asenapine, brexpiprazole, chlordiazepoxide, clorazepate, fluphenazine, hydroxyzine, imipramine, lithium, and lorazepam).

Valproate has an FDA boxed warning related to pregnancy in women without epilepsy. This drug can cause serious birth defects, including neural tube defects, decreased IQ, and neurodevelopmental disorders. Triazolam is contraindicated in pregnant women because of the risk of congenital anomalies. Hydroxyzine does not have a boxed warning, but the prescription language notes that it is contraindicated for early pregnancy. Risks from other drugs (alprazolam,

carbamazepine, clonazepam, diazepam, and topiramate) per FDA include congenital anomalies (alprazolam, carbamazepine), oral clefts (topiramate), small for gestational age (topiramate), and perinatal complications (clonazepam).

Per FDA prescribing information, other fetal risks include extrapyramidal and/or withdrawal symptoms following delivery (asenapine, brexpiprazole, and fluphenazine) and congenital anomalies (chlordiazepoxide, clorazepate, imipramine, and lorazepam).

The warning label for lithium notes that although early voluntary reporting suggested an increase in cardiovascular anomalies, subsequent studies suggested a small increased risk.

KQ 4: *Comparative Harms* of Pharmacologic Treatments for Pregnant and Postpartum Women With Mental Health Disorders

Overview

- Fifty-six studies (57 articles) reported on comparative adverse outcomes; 55 studies were observational and could not assert a causal relationship between exposure and resultant harms.
- As with the evidence on adverse outcomes of exposure versus no exposure, the studies reporting on comparative harms characterized the population by exposure to the drug (rather than by the presence of a disorder). The findings on adverse events are therefore not specific to a disorder.
- The strength of evidence on the adverse outcomes from these drugs was rated low primarily due to study limitations.
- We found evidence of two comparative adverse outcomes for lithium versus lamotrigine during pregnancy. Results from one study suggested that first trimester exposure to lithium may be more likely to be associated with overall congenital anomalies and cardiac anomalies than first trimester exposure to lamotrigine (low strength of evidence), a finding that can inform the decision to switch a medication in a successfully treated individual.
- We found evidence on one or more outcome for 108 comparisons; we found insufficient evidence on 107 of these comparisons, primarily due to study limitations arising from the lack of adjustment for confounding. Most comparisons had single-study bodies of evidence; consistency could not be ascertained.
- Interventions for which we found no eligible studies in our population of interest providing comparative evidence of adverse outcomes include anxiolytics, hypnotic sedatives, and brexanolone; evidence may be available from studies of other populations ineligible for this review.
- Maternal outcomes for which we found insufficient evidence include preeclampsia, spontaneous abortion, postpartum hemorrhage, gestational hypertensive disorders, and GDM.
- Child outcomes for which we found insufficient evidence include perinatal death; preterm birth; small for gestational age; large for gestational age; birthweight; low Apgar; withdrawal symptoms; respiratory distress; NICU time; delayed social, emotional, and cognitive development; autism spectrum disorder; and ADHD.

- Outcomes for which we found no evidence include infertility, abruption, glucose intolerance, and reduced milk production/undesired weaning for women; we also found no evidence for persistent pulmonary hypertension of the newborn, poor infant attachment/bonding, anxiety in children, and depression in children.

Detailed Results

Table 13 provides an overview of the findings on harms of pharmacotherapy in the perinatal period. Appendix B includes detailed tables on all outcomes. Fifty-six studies (57 articles) reported on comparative harms. Although several studies drew from large databases, the vast majority of graded evidence was insufficient owing to failure to control for confounding. The remainder of this section describes in greater detail the evidence for comparative maternal harm; comparative fetal, neonatal, infant, or child harm; insufficient evidence of comparative maternal harm; insufficient evidence of fetal, neonatal, infant, or child harm; and no evidence.

Evidence of Maternal Harm

We did not find sufficient evidence to support a judgment of maternal harms from studies comparing pharmacotherapy in pregnancy or postpartum.

Evidence of Fetal, Infant, or Child Harms

Overview

- The evidence on fetal, infant, or child harms from treatments for mental health disorders comes from bodies of evidence with high limitations and precise results (i.e., sample size, event rate, and confidence intervals permit inference of benefit, harm, or absence of benefit or harm). Precise results came from bodies of evidence with high limitations but effects that did not cross the null. However, beyond statistical significance alone, other factors contributed to moving the grade from insufficient to low.
- Evidence from one cohort study suggested that exposure to lithium during pregnancy may be more likely to be associated with overall congenital anomalies and cardiac anomalies than exposure to lamotrigine, which can inform the decision to switch a medication in a successfully treated individual.

Table 13. Summary of evidence from comparative effectiveness studies for harm of pharmacologic treatments for mental health disorders in pregnancy or postpartum

Exposure	Comparator	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	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
Anxiolytics	Any other comparator	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Sedative hypnotics	Any other comparator	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
SSRIs	SSRIs plus mirtazapine	-	-	-	-	-	-	-	-	-	-	|	-	-	|	-	-	-	-	-	|	-	-	-	-	-	-	-
SSRIs	SNRIs	-	|	|	-	-	|	-	|	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	|	|	|	-	-
SSRIs	TCAs	-	|	|	-	-	-	-	-	-	-	|	|	-	|	|	-	|	-	-	|	-	-	-	-	|	|	-	-
SSRIs	MAOIs	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	|	|	-	-
Citalopram	Bupropion	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	|	-	-	-	-	-	-	-	-	-	-	-	-	-
Citalopram	Duloxetine	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	|	-	-	-	-	-	-	-	-	-	-	-	-	-
Citalopram	Escitalopram	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	|	-	-	-	-	-	-	-	-	-	-	-	-	-
Citalopram	Fluvoxamine	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	|	-	-	-	-
Citalopram	Fluoxetine	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	|	-	-	-	-	-	-	-	-	|	-	-	-	-
Citalopram	Paroxetine	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	|	-	-	-	-	-	-	-	-	|	-	-	-	-
Citalopram	Sertraline	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	|	-	-	-	-	-	-	-	-	|	-	-	-	-

Exposure	Comparator	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	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
Citalopram	Venlafaxine	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	I	-	-	-	-	-	-	-	-	-	-	-
Escitalopram	Bupropion	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	I	-	-	-	-	-	-	-	-	-	-	-
Escitalopram	Duloxetine	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	I	-	-	-	-	-	-	-	-	-	-	-
Escitalopram	Paroxetine	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	I	-	-	-	-	-	-	-	-	-	-	-
Escitalopram	Sertraline	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	I	-	-	-	-	-	-	-	-	-	-	-
Fluoxetine	Bupropion	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	I	-	-	-	-	-	-	-	-	-	-	-
Fluoxetine	Duloxetine	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	I	-	-	-	-	-	-	-	-	-	-	-
Fluoxetine	Escitalopram	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	I	-	-	-	-	-	-	-	-	-	-	-
Fluoxetine	Sertraline	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	I	-	-	-	-	-	-	-	-	-	-	-
Fluoxetine	Venlafaxine	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	I	-	-	-	-	-	-	-	-	-	-	-
Fluoxetine	Citalopram or escitalopram	-	-	I	-	-	-	-	-	-	I	-	-	-	I	I	I	-	-	-	-	-	-	-	-	-	-	-
Fluoxetine	Escitalopram or fluvoxamine	-	-	I	-	-	-	-	-	-	I	-	-	-	I	I	-	-	-	-	-	-	-	-	-	I	-	-

Exposure	Comparator	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	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
Paroxetine	Duloxetine	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	|	-	-	-	-	-	-	-	-	-	-	-
Paroxetine	Fluoxetine	-	|	|	-	-	-	-	-	-	|	-	-	-	|	|	|	-	-	-	-	-	-	-	-	-	-	-
Paroxetine	Venlafaxine	-	-	|	-	-	-	-	-	-	-	-	-	-	-	-	|	-	-	-	-	-	-	-	-	-	-	-
Paroxetine	Citalopram or escitalopram	-	-	|	-	-	-	-	-	-	-	-	-	-	|	|	-	-	-	-	-	-	-	-	-	-	-	-
Paroxetine	Sertraline	-	-	|	-	-	-	-	-	-	-	-	-	-	|	|	|	-	-	-	-	-	-	-	-	|	-	-	-
Paroxetine	SNRIs	-	-	-	-	-	-	-	-	-	|	-	-	-	|	|	-	-	-	-	-	-	-	-	-	-	-	-
Paroxetine	Other SSRI comparators	-	-	-	-	-	-	-	-	-	-	-	|	|	|	|	|	-	|	-	-	-	-	-	-	-	-	-	-
Paroxetine	TCAs	-	-	-	-	-	-	-	-	-	-	-	-	-	-	|	-	-	-	-	-	-	-	-	-	-	-	-	-
Fluoxetine	SNRIs	-	-	|	-	-	-	-	-	-	|	-	-	-	|	|	-	-	-	-	-	-	-	-	-	-	-	-
Fluoxetine	TCAs	-	-	-	-	-	-	-	-	-	-	-	-	-	|	|	-	-	-	-	-	-	-	|	-	-	-	-
Fluvoxamine	Citalopram or escitalopram	-	-	|	-	-	-	-	-	-	|	-	-	-	|	|	-	-	-	-	-	-	-	-	|	-	-	-
Fluvoxamine	Fluoxetine	-	-	|	-	-	-	-	-	-	|	-	-	-	|	|	-	-	-	-	-	-	-	-	|	-	-	-
Fluvoxamine	Paroxetine	-	-	|	-	-	-	-	-	-	|	-	-	-	|	|	-	-	-	-	-	-	-	-	|	-	-	-
Fluvoxamine	Sertraline	-	-	|	-	-	-	-	-	-	|	-	-	-	|	|	-	-	-	-	-	-	-	-	|	-	-	-

Exposure	Comparator	Infertility	Preeclampsia	Spontaneous Abortion	Abruption	Postpartum Hemorrhage	Gestational Hypertensive Disorders	Glucose Intolerance	Gestational Diabetes Mellitus	Reduced Milk Production/Undesired ...	Perinatal Death	Preterm Birth	Small For Gestational Age	Large For Gestational Age	Birthweight	Major Congenital Anomalies	Cardiac Anomalies	Apgar	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
Fluvoxamine	Venlafaxine or desvenlafaxine	-	-	|	-	-	-	-	-	-	|	-	-	-	|	|	-	-	-	-	-	-	-	-	-	-	-	-
Sertraline	Citalopram or escitalopram	-	-	|	-	-	-	-	-	-	|	-	-	-	|	|	|	-	-	-	-	-	-	-	-	-	-	-
Sertraline	Duloxetine	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	|	-	-	-	-	-	-	-	-	-	-	-
Sertraline	Escitalopram or fluvoxamine	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	|	-	-	-
Sertraline	Fluoxetine	-	-	|	-	-	-	-	-	-	|	-	-	-	|	|	-	-	-	-	-	-	-	|	-	-	-
Sertraline	Nonsertraline SSRIs	-	-	-	-	-	-	-	-	-	-	-	-	-	-	|	-	-	-	-	-	-	-	-	-	-	-	-
Sertraline	Venlafaxine or desvenlafaxine	-	-	-	-	-	-	-	-	-	|	-	-	-	|	|	-	-	-	-	-	-	-	-	-	-	-	-
Sertraline	Bupropion	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	|	-	-	-	-	-	-	-	-	-	-	-
Sertraline	Nortriptyline	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Duloxetine	SSRIs	-	|	-	-	|	-	-	-	-	-	|	|	-	-	-	|	-	-	-	-	-	-	-	-	-	-	-
Duloxetine	Venlafaxine	-	|	-	-	|	-	-	-	-	-	|	|	-	-	-	|	-	-	-	-	-	-	-	-	-	-	-
Venlafaxine	SSRIs	-	-	|	-	-	-	-	-	-	-	|	|	-	|	|	-	-	-	-	-	-	-	-	-	-	-	-
Venlafaxine	Bupropion	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	|	-	-	-	-	-	-	-	-	-	-	-
Venlafaxine	Escitalopram	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	|	-	-	-	-	-	-	-	-	-	-	-

Exposure	Comparator	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	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
Venlafaxine	Sertraline	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	|	-	-	-	-	-	-	-	-	-	-	-
SNRIs	MAOIs	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	|	|	-	-
SNRIs	TCAs	-	|	|	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
MAOIs	TCAs	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	|	|	-	-
Venlafaxine	TCAs	-	-	-	-	-	-	-	-	-	-	-	|	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Bupropion	Duloxetine	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	|	-	-	-	-	-	-	-	-	-	-	-
Bupropion	Paroxetine	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	|	-	-	-	-	-	-	-	-	-	-	-
Bupropion	Sertraline	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	|	-	-	-	-	-	-	-	-	-	-	-
Brexanolone	Any other comparator	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Exposure	Comparator	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	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
Mirtazapine	SSRIs	-	-	I	-	-	-	-	-	-	I	I	-	-	I	I	-	-	-	-	I	-	-	-	-	-	-	-
Mirtazapine	SSRIs plus mirtazapine	-	-	-	-	-	-	-	-	-	-	I	-	-	I	-	-	-	-	-	I	-	-	-	-	-	-	-
Lithium	Lamotrigine	-	-	-	-	-	-	-	I	-	-	-	-	-	-	L	L	-	-	-	-	-	-	-	-	-	-	-
Haloperidol	Olanzapine	-	-	-	-	-	-	-	-	-	-	I	-	-	I	-	-	I	-	I	I	-	-	-	-	-	-	-
Haloperidol	Quetiapine	-	-	-	-	-	-	-	-	-	-	I	-	-	I	-	-	I	-	I	I	-	-	-	-	-	-	-
Haloperidol	Risperidone	-	-	-	-	-	-	-	-	-	-	I	-	-	I	-	-	I	-	I	I	-	-	-	-	-	-	-
Aripiprazole	Risperidone	-	-	-	-	-	-	-	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Clozapine	Aripiprazole	-	-	-	-	-	-	-	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Clozapine	Risperidone	-	-	-	-	-	-	-	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Olanzapine	Aripiprazole	-	-	-	-	-	-	-	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Olanzapine	Clozapine	-	-	-	-	-	-	-	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Olanzapine	Quetiapine	-	-	-	-	-	-	-	I	-	-	I	-	-	I	-	-	-	-	I	I	-	-	-	-	-	-	-
Olanzapine	Risperidone	-	-	-	-	-	-	-	I	-	-	I	-	-	I	-	-	-	-	I	I	-	-	-	-	-	-	-
Quetiapine	Clozapine	-	-	-	-	-	-	-	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Quetiapine	Aripiprazole	-	-	-	-	-	-	-	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Exposure	Comparator	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	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
Quetiapine	Risperidone	-	-	-	-	-	-	-	I	-	-	I	-	-	I	-	-	-	-	I	I	-	-	-	-	-	-	-
First generation antipsychotics	Second generation antipsychotics	-	-	-	-	-	-	-	-	-	-	-	I	I	I	-	-	-	-	-	-	-	-	I	-	-	-	-
Olanzapine	Lithium	-	-	-	-	-	-	-	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Olanzapine	Lamotrigine	-	-	-	-	-	-	-	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Quetiapine	Lithium	-	-	-	-	-	-	-	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Quetiapine	Lamotrigine	-	-	-	-	-	-	-	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Aripiprazole	Lithium	-	-	-	-	-	-	-	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Aripiprazole	Lamotrigine	-	-	-	-	-	-	-	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Clozapine	Lithium	-	-	-	-	-	-	-	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Clozapine	Lamotrigine	-	-	-	-	-	-	-	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Risperidone	Lithium	-	-	-	-	-	-	-	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Risperidone	Lamotrigine	-	-	-	-	-	-	-	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

I: Insufficient for all measures for the outcome domain; **L**: Low evidence of harm for at least one measure for the outcome domain; -: No eligible evidence.
ADHD = attention-deficit/hyperactivity disorder; MAOI = monoamine oxidase inhibitor; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

Detailed Synthesis

Table 14 provides an overview of the findings on harms to the fetus, infant, or child of pharmacotherapy in the perinatal period. Appendix B includes detailed tables on all outcomes. We describe results from one high risk-of-bias publication that yielded evidence of harm below.

Table 14. Strength of evidence from effectiveness studies for harm to the fetus, infant, or child (intervention versus placebo or no treatment)

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Lithium- or lamotrigine-exposed women	Lithium vs. lamotrigine exposure in first-trimester pregnancy	Fetal cardiac anomalies	16/663 (2.4%) vs. 27/1,945 (1.4%)[133]	ARR, 2.25 (95% CI, 1.17 to 4.34)	1 cohort; n=2,608[133]	High study limitations (high risk of bias),[133] precise, large effect size, consistency unknown	Low for greater harms with lithium than lamotrigine
Lithium- or lamotrigine-exposed women	Lithium vs. lamotrigine exposure in first-trimester pregnancy	Overall congenital anomalies	38/663 (5.7%) vs. 76/1,945 (3.9%)[133]	ARR, 1.85 (95% CI, 1.23 to 2.78)	1 cohort; n=2,608[133]	High study limitations (high risk of bias),[133] precise, large effect size, consistency unknown	Low for greater harms with lithium than lamotrigine

ARR = adjusted risk ratio; CI = confidence interval; n = number; vs. = versus.

The evidence on fetal, infant, or child harms from treatments for mental health disorders comes from bodies of evidence with high limitations and precise results. Precise results from bodies of evidence with high limitations had factors beyond statistical significance alone that resulted in the low strength-of-evidence grade. Specifically, the identified harms include **congenital anomalies** and **cardiac anomalies** favoring lithium over lamotrigine, which can inform the decision to switch a medication in a successfully treated individual.[133] Although the study was rated high risk of bias because of the restriction to live births and the resulting potential for selection bias, we upgraded the evidence from insufficient to low for lithium versus lamotrigine because of the large effect size and note the relatively small number of events in the lithium arm.

Insufficient Evidence of Maternal Harms

Overview

- Insufficient grades were assigned based study limitations, bias, consistency, and precision. Some bodies of evidence comprised single studies for which we could not infer consistency of the evidence base. Additionally, the reported associations were imprecise (i.e., the results relied on small sample sizes, few events, or had wide CIs suggestive of both benefits and harms) and had high study limitations.

- The evidence is insufficient for comparative evidence on maternal harms for mental health disorders; the evidence comes from bodies of evidence with high limitations and imprecise results.
- Evidence from two cohort studies was insufficient to judge the strength of association between preeclampsia and exposure to SSRIs versus SNRIs during pregnancy.
- Evidence from two cohort studies was insufficient to judge the strength of association between gestational hypertension and exposure to SSRIs versus SNRIs during pregnancy.
- Evidence from two cohort studies was insufficient to judge the strength of association between spontaneous abortion and exposure to SSRIs versus venlafaxine during pregnancy.

Detailed Synthesis

Table 15 provides an overview of the findings on maternal harms from use of pharmacotherapy in the perinatal period. Appendix B includes detailed tables on all outcomes. We describe results from two publications on harms below.

We found single studies with imprecise results, often from high risk-of-bias studies for most outcomes (see Appendix B for further details). For three outcomes, we identified multiple studies but graded the evidence as insufficient. We describe these results in greater detail below.

Preeclampsia for SSRIs Versus SNRIs

Two high risk-of-bias studies[87, 137] reported results that suggest lower relative risks for **preeclampsia** with SSRIs compared with SNRIs (one was imprecise with a very small number of events). Neither study presented adjusted results for this comparison. With no controls for confounders, we rated the strength-of-evidence grade as insufficient.

Gestational Hypertension for SSRIs Versus SNRIs

Two high risk-of-bias studies[137, 138] reported results that suggest lower relative risks for **gestational hypertension** with SSRIs compared with SNRIs. Both were imprecise with a very small number of events. Neither study presented adjusted results for this comparison. With no controls for confounders, we rated the strength-of-evidence grade as insufficient.

Spontaneous Abortion for SSRIs Versus Venlafaxine

Two studies[139, 140] (one high risk-of-bias study[139]) reported no significant differences in spontaneous abortion associated with SSRIs compared with venlafaxine. One attempted to control for potential confounding.[140] Both were imprecise with wide CIs spanning both appreciable benefit and appreciable harm; as a result, we could not conclude equivalence and graded the evidence as insufficient.

Table 15. Insufficient strength of evidence from comparative effectiveness studies for harm to the mother

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Pregnant women who used SSRIs or SNRIs during pregnancy or who had depression	SSRI vs. SNRI	Preeclampsia	23/408 (5.6%) vs. 105/3,169 (3.3%)[87] Continued AD use ≥20 weeks of gestation: 4/157 (2.5%) vs. 2/21 (9.5%)[137]	RR, 0.59 (95% CI, 0.38 to 0.91)[87] RR, 0.27 (95% CI, 0.052 to 1.37)[137]	2 cohorts; n=3,577 in one cohort,[87] n=252 in second[137]	High study limitations (high risk of bias[87, 137]), imprecise (few events), consistent	Insufficient
Pregnant women who used SSRIs or SNRIs during pregnancy	SSRI vs. SNRI	Gestational hypertension	Continued AD use ≥20 weeks of gestation: 11/157 (7.0%) vs 3/21 (14.6%)[137] 2/23 (8.3%) vs. 23/60 (39.1%)[138]	RR, 0.49 (95% CI, 0.15 to 1.62)[137] RR, 0.24. (95% CI, 0.06 to 0.89)[138]	2 cohorts, n=335[137, 138]	High study limitations (high risk of bias[137, 138]), imprecise (wide CIs), consistent	Insufficient
Pregnant women with depression, pregnant women who used SSRIs or venlafaxine during pregnancy	Venlafaxine vs. SSRI, first trimester exposure[139]	Spontaneous abortion	18/150 (12%) vs. 16/150 (10.7%)[139] 46/281 (16.37%) vs. 144/843 (17.1%)[140]	RR, 1.1 (95% CI, 0.60 to 2.12) [139] AOR, 1.0 (95% CI, 0.67 to 1.53)	2 cohorts, n=1424[139, 140]	Moderate study limitations (high risk of bias[139]) imprecise (wide CIs), consistent	Insufficient

AD = antidepressant; AOR = adjusted odds ratio; CI = confidence interval; RR = relative risk; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; n = number; vs. = versus.

Insufficient Evidence of Fetal, Infant, or Child Harms

Overview

- Insufficient grades were assigned based on study limitations, bias, consistency, and precision. Some bodies of evidence comprised single studies for which we could not infer consistency of the evidence base. Additionally, the reported associations were imprecise (i.e., the results relied on small sample sizes, few events, or had wide CIs suggestive of both benefits and harms) and had high study limitations.
- We found insufficient evidence to judge the comparative fetal, infant, or child harms of psychiatric medications during pregnancy or the postpartum period given evidence with high limitations and imprecise results.
- Evidence from three cohort studies provided insufficient evidence to judge the strength of association between anomalies and exposure to SSRIs versus TCAs during pregnancy.

- Evidence from two cohort studies provided insufficient evidence to judge the strength of association between preterm births, and birthweight and exposure to SSRIs versus TCAs during pregnancy.
- Evidence from two cohort studies provided insufficient evidence to judge the strength of association between autism spectrum disorder and different SSRIs during pregnancy.
- Evidence from two cohort studies provided insufficient evidence to judge the strength of association between preterm births and birthweight and exposure to mirtazapine versus SSRIs during pregnancy.
- Evidence from two cohort studies provided insufficient evidence to judge the strength of association between small for gestational age and birthweight and exposure to venlafaxine versus SSRIs during pregnancy.

Detailed Synthesis

We found single studies with imprecise results, often from high risk-of-bias studies for most outcomes (see Appendix B for further details). For some outcomes, we identified multiple studies but graded the evidence as insufficient. Specifically, we found insufficient evidence on **congenital anomalies, preterm births, small for gestational age, birthweight,** and **autism spectrum disorder** (Table 16).

Table 16. Strength of evidence for harms outcomes: SSRIs versus SNRIs

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Exposed to SSRIs in the first trimester vs. exposed to TCAs in the first trimester (full-term infants)	SSRIs vs. TCAs	Preterm birth	166/1,768 (9.4%) vs. 42/381 (11.0%)[141] 3/42 (7.1%) vs. 6/37 (16.2%)[142]	RR, 0.85 (95% CI, 0.62 to 1.17)[141] RR: 2.27 (95% CI, 0.61 to 8.44)[142]	2 cohort study, N=2,228[141, 142]	High study limitations (high risk of bias[141, 142]), imprecise (wide CIs), inconsistent	Insufficient
Women exposed to therapeutic agents during pregnancy	Mirtazapine exposure during pregnancy vs. SSRI exposure during pregnancy	Preterm delivery	31/279 (11.1%) vs. 32/302 (10.6%)[143] 1/16 (6.25%) vs. 3/40 (7.50%)[112]	OR, 1.06 (95% CI (0.63 to 1.78);[143] the OR did not change after adjusting for concomitant drug treatment RR, 0.83 (95% CI, 0.09 to 7.43)[112]	2 cohorts, n=637[112, 143]	High study limitations (high risk of bias[112, 143]), imprecise, consistent	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Exposed to SSRIs in the first trimester vs. exposed to TCAs in the first trimester (full-term infants)	SSRIs vs. TCAs	Malformations (one or more malformations, major congenital malformations, minor malformations)	Ranges from 3.7% to 13.4% in the SSRI arm vs. 3.4% to 12.0% in the TCA arm[113]	RRs range from 1.08 to 1.45, all CIs cross the null[141, 144, 145]	3 cohort studies, N=5,651[141, 144, 145]	High study limitations (high risk of bias[141, 144, 145]), imprecise (wide CIs), consistent	Insufficient
Pregnant women with a psychiatric disorder (second trimester) or exposed to venlafaxine or SSRIs (during pregnancy)	Venlafaxine vs. SSRI during first or second trimester	SGA (<10th percentile)	5/17 (29.4%) vs. 24/155 (15.5%)[113] 12/133 (9.02%) vs. 55/438 (12.6%)[140]	RR, 1.90, 95% CI, 0.83 to 4.33[113] AOR, 0.714 (95% CI, 0.353 to 1.35)	2 cohorts, n=772[113, 140]	Moderate study limitations (high risk of bias,[113]) imprecise (wide CIs), inconsistent	Insufficient
Exposed to SSRIs vs. exposed to TCAs	SSRIs vs. TCAs	Birthweight (birthweight ≤2,500 g or total birthweight[144] or undefined[142])	19/185 (10.3%) vs. 21/209 (10.0%), mean difference: -80 g[144]; 1/42 (2.4%) vs. 2/37 (5.4%)	RR, 1.02 (95% CI, 0.57 to 1.84); CIs for mean difference span the null[144]; RR, 2.27 (95% CI, 0.21 to 2.40)[142]	2 cohort study, N=473[142, 144]	High study limitations (high risk of bias[142, 144]), imprecise, consistent	Insufficient
Women exposed to therapeutic agents during pregnancy	Mirtazapine exposure during pregnancy vs. SSRI exposure during pregnancy	Birth weight (grams)	39 (IQR 38-40) vs. 39 (IQR 38-40)[143] 3251.25 gm (SD: 502.27, n=16 vs. 3,153.17 gm (SD: 435.17), n=40[112]	No difference between groups;[143] mean difference, 98.08 (95% CI, -165.60 to 361.76)[112] The OR did not change after adjusting for concomitant drug treatment[143]	2 cohorts, n=652[112, 143]	High study limitations (high risk of bias[112, 143]), imprecise (wide CIs), consistent	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women exposed to antidepressants in second/third trimester of pregnancy	Paroxetine vs. sertraline	Autism spectrum disorder	Paroxetine: 11/744 (1.5%) vs. sertraline: 1/292 (0.34%)[146] Paroxetine: 7/871 (0.8%) vs. sertraline: 9/1576 (0.57%)[146]	RR, 4.3 (95% CI, 0.56 to 33.3)[146] RR, 1.41 (95% CI, 0.53 to 3.77)[147]	2 cohorts, N= 3,483[146, 147]	High study limitations (high risk of bias[146, 147]), imprecise (wide CIs), consistent	Insufficient
Pregnant women taking fluoxetine or sertraline	Sertraline monotherapy vs. fluoxetine monotherapy	Autism spectrum disorder	9/1,576 (0.6%) vs. 18/160 (11%)[147] 1/292 (0.3%) vs. 5/171 (2.9%)[146]	RR, 0.05 (95% CI, 0.02 to 0.11)[147] RR, 0.12 (95% CI, 0.01 to 0.99)[146]	2 cohorts; n=1,736 in one cohort,[147] n=463 in one cohort[146]	High study limitations (high risk of bias)[147] precise, consistent	Insufficient
Pregnant women taking fluoxetine, fluvoxamine or escitalopram	Fluoxetine monotherapy vs. fluvoxamine or escitalopram monotherapy;[147] fluoxetine monotherapy vs. fluvoxamine[146]	Autism spectrum disorder	18/160 (11%) vs. 1/1047 (0.09%)[147] 5/171 (2.9%) vs. 1/35 (2.9%)[146]	RR, 117.79, (95% CI, 15.83 to 876.27) RR, 1.02 (95% CI, 0.12 to 8.49)	2 cohorts; n=1.207 in one cohort,[147] n=206 in one cohort[146]	High study limitations (high risk of bias[146, 147]), imprecise (wide CIs), consistent	Insufficient
Pregnant women taking paroxetine or fluoxetine	Paroxetine monotherapy vs. fluoxetine monotherapy	Autism spectrum disorder	11/744 (1.5%) vs. 5/171 (2.9%)[146] 7/871 (0.6%) vs. 18/160 (11%)[147]	RR, 0.51 (95% CI, 0.18 to 1.44)[146] RR, 0.07 (95% CI, 0.03 to 0.17)[147]	2 cohorts, n=915 in one cohort[146], n=1,031 in one cohort[147]	High study limitations (high risk of bias[148]), imprecise (few events), consistent	Insufficient
Pregnant women taking fluoxetine or sertraline	Sertraline monotherapy vs. fluoxetine monotherapy	Autism spectrum disorder	9/1576 (0.6%) vs. 18/160 (11%)[147] 1/292 (0.3%) vs. 5/171 (2.9%)[146]	RR, 0.05 (95% CI, 0.02 to 0.11)[147] RR, 0.12 (95 % CI, 0.01 to 0.99)[146]	2 cohorts; n=1,736 in one cohort,[147] n=463 in one cohort[146]	High study limitations (high risk of bias, potential inaccuracy in data[147, 148] precise, consistent	Insufficient
Pregnant women in second or third trimester[146] or during pregnancy[147] exposed to citalopram or fluoxetine	Maternal exposure to citalopram vs. maternal exposure to fluoxetine	Autism spectrum disorder	5/421 (1.2%) vs. 5/171 (2.9%);[146] 14/1751 (0.8%) vs. 18/160 (11.3%)[147]	RR, 0.41 (95% CI, 0.11 to 1.4);[146] RR, 7.1 (95% CI, 0.036 to 0.14)[147]	2 cohorts, N=2,503[146, 147]	High study limitations (high risk of bias[146, 147]), imprecise, inconsistent	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Pregnant women in second or third trimester[146] or during pregnancy[147] exposed to citalopram or paroxetine	Maternal exposure to citalopram vs. maternal exposure to paroxetine	Autism spectrum disorder	5/421 (1.2%) vs. 11/744 (1.5%);[146] 14/1,751 (0.8%) vs. 7/871 (0.8%)[147]	RR, 0.80 (95% CI, 0.28 to 2.3);[146] RR, 0.99 (95% CI, 0.4 to 2.5)[147]	2 cohorts, N=3,787[146, 147]	High study limitations (high risk of bias[147]), imprecise, consistent	Insufficient
Pregnant women in second or third trimester[146] or during pregnancy[147] exposed to citalopram or sertraline	Maternal exposure to citalopram vs. maternal exposure to sertraline	Autism spectrum disorder	5/421(1.2%) vs. 1/292 (0.34%);[146] 14/1,751 (0.8%) vs. 9/1,576 (0.57%)[147]	RR, 3.5 (95% CI, 0.41 to 29.5);[146] RR, 1.4 (95% CI, 0.61 to 3.2)[147]	2 cohorts, N=4,040[146, 147]	High study limitations (high risk of bias[146, 147]), imprecise, consistent	Insufficient

AD = antidepressant; CI = confidence interval; IQR = interquartile range; N/n = number; RR = relative risk; SD = standard deviation; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant; vs. = versus.

Congenital Anomalies for SSRIs Versus TCAs

Three studies[141, 144, 145] reported results that suggest higher relative risks for anomalies with SSRIs compared with TCAs, with wide CIs suggestive of both benefits and harms. No study presented adjusted relative risks, leading to high study limitations and an insufficient grade.

Preterm Births for SSRIs Versus TCAs

Two studies[141, 142] reported inconsistent results for preterm births for SSRIs compared with TCAs, with wide CIs suggestive of both benefits and harms. No study presented adjusted relative risks, leading to high study limitations and an insufficient grade.

Preterm Births for Mirtazapine Versus SSRIs

Two studies[141, 142] reported inconsistent results for preterm births for mirtazapine compared with SSRIs, with wide CIs suggestive of both benefits and harms. No study presented adjusted relative risks, leading to high study limitations and an insufficient grade.

Small for Gestational Age for Venlafaxine Versus SSRIs

Two studies[113, 140]reported inconsistent results for the risks of small for gestational age with venlafaxine versus SSRIs, with wide CIs suggestive of both benefits and harms. One study reported higher but nonsignificant risks for unadjusted results for venlafaxine,[113] and a second reported lower but adjusted odds risks for venlafaxine. Inconsistency and imprecision from wide CIs in studies with small samples and events resulted in an insufficient grade.

Birthweight for SSRIs Versus TCAs

Two studies[142, 144] reported results that suggest higher relative risks for low birthweight with SSRIs compared with TCAs, with wide CIs suggestive of both benefits and harms. No study presented adjusted relative risks, leading to high study limitations and an insufficient grade.

Birthweight for Mirtazapine Versus SSRIs

Two studies[112, 143] reported no significant differences in birthweight with mirtazapine versus SSRIs, with wide CIs suggestive of both benefits and harms. No study presented adjusted relative risks, leading to high study limitations and an insufficient grade.

Autism Spectrum Disorder for Head-to-Head SSRI Comparisons

Two studies[146, 147] reported results on autism spectrum disorder for paroxetine versus sertraline; sertraline versus fluoxetine; fluoxetine monotherapy versus fluvoxamine or escitalopram; paroxetine versus fluoxetine, sertraline versus fluoxetine, citalopram versus fluoxetine, citalopram versus paroxetine, and citalopram versus sertraline. No study presented adjusted relative risks, leading to high study limitations and an insufficient grade.

No Evidence in Populations of Interest (Pregnant Women With Mental Health Disorders)

Overview

- We found no evidence on active treatment in comparison with anxiolytics, hypnotic sedatives, and brexanolone.
- We found no evidence on maternal harms of infertility, abruption, glucose intolerance, and reduced milk production or undesired weaning.
- We also found no evidence on child harms of persistent pulmonary hypertension, poor infant attachment/bonding, anxiety in children, and depression.

Discussion

Findings in Relation to the Decisional Dilemma

The central decisional dilemma facing pregnant and postpartum women with mental health disorders and their healthcare providers is how to balance benefits and harms of psychotropic drugs for themselves and their children. One such critical trade-off is whether improved symptoms in the mother outweigh the harms from potential congenital anomalies in the fetus. The available evidence from studies of pregnant or postpartum women with mental health disorders does little to clarify these issues. Despite the high reported prevalence for any mental health disorders among pregnant women (25.3% in the United States in 2001 to 2002[8]), the evidence is very sparse on the benefits of treatment, mostly reflecting how little controlled, high-quality research this particular area has received. Indeed, only 10 randomized controlled trials involving psychotropic medication for any mental health disorder were eligible for this review. This limited evidence base reflects decades of exclusion of pregnant and lactating women from clinical trials.[29] In contrast, evidence on harms of treatment is voluminous but of low quality primarily because of the inability to control for confounding.

Regarding benefits of treatment (Key Question [KQ] 1), 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. For symptom response, for example, we found signals of benefits for symptom response for sertraline and brexanolone: for both drugs, we found evidence bases with two or more randomized controlled trials (RCTs). For fluoxetine and paroxetine, one small RCT apiece with imprecise results was not sufficient to arrive at a conclusion. For all other drugs, we found no eligible studies; evidence may be available from studies of other populations ineligible for this review.

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 pharmacologic agents for anxiety, depression, bipolar disorder, and schizophrenia. For example, an evidence-based treatment review on pharmacotherapy for generalized anxiety disorder, published in 2018, summarized findings from RCTs with adults across classes of treatment options.[149] The authors concluded that evidence of efficacious treatment options include selective serotonin reuptake inhibitors (SSRIs) (paroxetine and escitalopram), serotonin-norepinephrine reuptake inhibitors (SNRIs) (venlafaxine and duloxetine), benzodiazepines, and tricyclic antidepressants (TCAs).

In adults with major depressive disorder, multiple systematic evidence reviews have demonstrated the efficacy of all classes of antidepressants, including second-generation antidepressants (SSRIs, serotonin modulators, SNRIs, bupropion, and mirtazapine) and TCAs compared with placebo.[150-152] There is not a clear consensus on whether there are sex differences in antidepressant efficacy, likely due to variability in methodology and few specific investigations addressing this question.[153] Some studies have shown that men experience a better therapeutic response to TCAs than women, while others show that women respond better to SSRI treatment than men.

A recent systematic review on treatments for bipolar disorder, published in 2018, found modest evidence of benefit for several drugs.[154] This review synthesized evidence from 108 studies for 28 drugs. The review found that lithium, asenapine, cariprazine, olanzapine, quetiapine, risperidone, and ziprasidone may modestly improve acute mania symptoms in adults with bipolar I disorder when compared with placebo. Although eligible studies included men and

women, the review did not find sufficient evidence to be able to ascertain effects specific to women but noted that the prevalence is similar in men and women.

Regarding schizophrenia, numerous guidelines consistently recommend antipsychotic medication for maintenance of remission following a first episode of schizophrenia and clozapine for treatment resistance.[155] Some evidence suggested better response among women than men.[156]

In the absence of evidence comparing benefits from pharmacotherapy in pregnant or postpartum women with general populations, the results from general populations 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.[157, 158]

When evidence from studies of pregnant and postpartum women was available, we found low to moderate strength of evidence of benefit. Specifically, for depression, we found moderate strength of evidence that brexanolone is associated with improved depressive symptoms shortly after infusion (60 hours) and at 30 days after treatment. Moreover, the substantial reduction in symptoms in the placebo group illustrates the importance of restorative sleep and material support for management of postpartum depression symptoms. However, the mode of delivery of the drug (infusion), requirements for healthcare personnel to be present for the duration of the infusion, and cost may serve as barriers to widespread use of brexanolone. We found low strength of evidence from two RCTs that sertraline achieves response, remission, and improvements in symptoms of depression and anxiety. For bipolar disorders, we found low strength of evidence from two cohort studies that discontinuing mood stabilizers increases recurrence and reduces time to recurrence. Other than one small study for hydroxyzine, we found no information on the efficacy of anxiolytics or sedative-hypnotics during the perinatal period and nothing on the efficacy of antipsychotics.

Regarding harms of treatment (KQ 3), we restricted the review to studies comparing women receiving psychotropic drugs with women with a mental health disorder who were not receiving psychotropic drugs. This requirement narrowed the pool of eligible evidence to studies that made some attempt to control for this possible source of underlying confounding, but the risk of residual confounding in this literature is substantial: no observational study could completely control for severity of psychiatric illness that could have predicted both exposure and outcome. Fewer than a quarter of studies across the review considered dose of exposure.[18, 77-79, 81, 118, 128, 133, 143, 159-177] This limited information on dose of exposure further complicates the extent to which inferences can be drawn between the stated exposure and the outcome. Nonetheless, within this pool of evidence, we found some signals of harms for a limited set of exposures; all were rated as low strength of evidence. Our low confidence that future results will confirm these findings stems from multiple considerations: limited precision for rare outcomes, high study limitations primarily from an inability to address confounding fully, and concerns about exposure and outcome measurement. We note that our findings pertain to the population eligible for our review; evidence on the harms of these drugs in broader populations (such as nonpregnant populations and populations without mental health disorders) will also be relevant for clinical practice. These evidence bases may form the basis, for example, for the Food and Drug Administration (FDA) warnings on some psychotropic drugs.

Specifically, for maternal harms, we found evidence that several antidepressants are associated with increased risk of postpartum hemorrhage; SNRIs and TCAs may be associated with an increased risk of preeclampsia; and quetiapine or olanzapine may be associated with an

increased risk of gestational diabetes. For child harms, we found an association between benzodiazepine and neonatal intensive care unit admissions; between SSRIs and respiratory issues, low Apgar scores, persistent pulmonary hypertension of the newborn, and depression in children; and between citalopram and autism spectrum disorder, although the studies were not able to fully control for confounding. Importantly, we found insufficient evidence on congenital anomalies and cardiac defects for most comparisons, although we did find some evidence of increased cardiac defects for paroxetine.

These findings need to be interpreted in the context of low absolute risks for several outcomes. For example, recent systematic reviews also found an increased risk of persistent pulmonary hypertension with SSRIs and SNRIs but noted the very high numbers of patients needed to harm, ranging from 286 to 1,000.[178, 179] Similarly, the study reporting higher rates of postpartum hemorrhage notes low absolute risk differences, with a number needed to harm ranging from 80 to 100.[84]

The findings are consistent with other prior work on this topic. A 2009 report came to the same conclusions;[180] unfortunately, our review indicates that the state of the science has not advanced substantially. This narrow evidence base is not limited to mental health disorders; a 2018 report to Congress detailed deficiencies in the evidence base and outlined strategies to improve the quantity, quality, and timeliness of research on safety and efficacy of therapeutic products used by pregnant women and lactating women.[31]

The findings on comparative benefits (KQ 2) and harms (KQ 4) were very sparse. Results on numerous comparisons yielded insufficient evidence to judge comparative benefits or harms, with one exception: results from one study suggested that exposure to lithium may be more likely to be associated with overall congenital anomalies and cardiac anomalies than exposure to lamotrigine. As with the results on comparative efficacy, the paucity or absence of evidence in this population cannot be interpreted as lack of benefit. Systematic reviews in nonpregnant populations suggested that different classes of antidepressants may be similar in benefits.[151] Systematic reviews on benefits of medications for these disorders in the general population offer some insights on comparative effectiveness. Regarding anxiety, one review[149] reported studies evaluating the benefits of paroxetine and other SSRIs. In one study, no difference in response or remission was found in relation to sertraline,[181] and in a second, no difference was found in relation to escitalopram.[182] Based on a recent meta-analysis, benzodiazepines were found to be more effective than SSRIs and SNRIs,[183] and a Cochrane review found that benzodiazepines were more effective than azapirones.[184]

Regarding comparative effectiveness for depression, multiple comparative reviews have shown no clear benefit of one antidepressant versus any other for pharmacologic treatment of depression, although medications do differ by measures such as adherence and tolerability.[150, 151, 185] The types of antidepressants involved both direct and indirect comparisons of second-generation antidepressants (SSRIs, serotonin modulators, SNRIs, bupropion, and mirtazapine) and TCAs compared with each other in adults with major depressive disorder.

Regarding comparative effectiveness of treatments for bipolar disorder, one review found low strength of evidence that olanzapine and divalproex/valproate are not different in their effect on acute mania.[154] The review authors also found that lithium improved acute mania better than topiramate (low strength of evidence). The review found insufficient evidence for all other drug comparisons with active controls.

Reviews have found that antipsychotics are similar in function, quality of life, and mortality.[186, 187] One report also noted that core illness symptoms improved more with

olanzapine and risperidone than asenapine, quetiapine, and ziprasidone and with paliperidone than lurasidone.[186] The review generally found insufficient evidence of differences in benefits by sex.

Our review findings do support some currently existing clinical guidelines. For example, our findings support clinical guidelines[26, 33, 36, 188, 189] suggesting the need to consider the balance between risk and benefits in deciding whether to continue treatment and the use of medications for symptoms or when relapse is of concern. Our review is also consistent with current guidelines suggesting that antidepressants are relatively safe but may carry potential neonatal side effects. Guidelines have not yet offered recommendations for brexanolone and express uncertainty regarding lamotrigine: our findings may contribute to filling these gaps.

Some guidelines are silent on whether to continue exposure to medications during pregnancy.[33] Our review of the contextual evidence on this question (harms of *not* treating the disorder, stopping a pharmacologic treatment, or switching medications) offers some clarity for the use of mood stabilizers for bipolar disorder and continued uncertainty for the use of antidepressants for depression. Two studies of women with bipolar disorder supported continued use of mood stabilizers to reduce recurrence and increase time to recurrence.[80, 81] A third study noted a higher rate of relapse among postpartum women who switched from lithium to sodium valproate to breastfeed (4/7) than among women who stayed on lithium (1/9); however, small numbers limit our ability to make conclusions.[190] The evidence for depression is mixed. Three studies compared evaluated outcomes for those discontinuing medications with those continuing medications through pregnancy. One study of Medicaid claims data from 28,493 women found higher odds of relapse with *continuation* (odds ratio, 2.0; 95% confidence interval [CI], 1.8 to 2.2) (authors note that this result could be explained by systematic biases but could not rule out the possibility that antidepressant medications are less effective in pregnancy).[191] A second study of 778 women from 137 obstetrical practices and hospital-based clinics found an adjusted hazard ratio of 0.88 (95% CI, 0.51 to 1.5) of onset of a major depressive episode in pregnancy and after delivery.[188] A third study of 201 women, drawing from three centers with specific expertise in treating psychiatric illness, found an increased risk of relapse with *discontinuation* (hazard ratio, 5.0; 95% CI, 2.8 to 9.1).[169] Potential explanation for these differences may lie in the severity of disorders in each population, difference in the type of care offered to the patient populations, or the limitations of claims data to fully capture the context around the decision to discontinue medications.[188, 191, 192] One study of duloxetine, prescribed primarily for depression and anxiety, did not report a difference between duloxetine continuers and duloxetine discontinuers for the risk of any congenital malformations (adjusted relative risk, 1.09; 95% CI. 0.84 to 1.42) or cardiovascular anomalies (adjusted relative risk, 1.41; 95% CI, 0.92 to 2.17).[124]

Some guidelines note uncertainty about how to treat new-onset psychiatric illness during the perinatal period and the implications of treatment during lactation.[26, 36] We did not identify any studies of treatment for new-onset disorders or for lactating women.

Strengths and Limitations

As noted above, a significant constraint to interpreting the evidence is the lack of data from RCTs and the widespread risk of confounding in observational studies. Underlying mental health disorders result in the use of psychotropic medications. They may also result in some of the harms investigated in this review regardless of exposure to medications. One strength of our review is that we required, for the effectiveness questions (KQs 1 and 3), that studies include comparison groups defined by exposure to a mental health disorder; however, it is likely that

illness severity is correlated with pharmacologic treatment, confounding observed associations. We also required that studies made some attempt to adjust for confounding; this helped manage the scope and heterogeneity of the review but resulted in some limitations. Studies varied greatly in the extent to which they were able to address underlying severity of psychiatric illness. The majority were unable to address confounding adequately because they could not control for severity of psychiatric illness. A subset of studies attempted measures at addressing confounding such as multivariate regression with propensity score adjustment and stratification by number of disorders. In most instances, controls for confounding reduced the effect size and, in some instances, reversed the direction of effect.

For the benefits question (KQ 1), eligible studies had comparator arms of women with the same disorder as in the treatment arm. For the harms question (KQ 3), however, we were more inclusive and included studies with comparator arms comprising women with prior exposure to the drug, even if the disorder status was not specified. As a result, our KQ 1 evidence base controls for underlying severity as a confounder better than the KQ 3 evidence base.

We elected to restrict the evidence to women with mental health disorders 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 the exposure and the outcome. Also, this criterion resulted in the exclusion of studies reporting on relevant outcomes for exposures to the intervention for other clinical conditions. Studies of multiple drug exposures presented results for each exposure but did not always present results separately for the women with multiple drug exposures. In these studies with overlapping arms, we were not able to attribute the effect of the intervention to a single drug. As a result, we excluded these studies. The exclusion of studies with overlapping arms also restricted the comprehensiveness of our review. These limitations of the evidence and of our review mean that the signals of harms that we identified above may be partially or wholly attributable to residual confounding. A further consequence of our inclusion criteria is that we did not find eligible evidence on harms of some psychotropic drugs compared with no treatment for which FDA has issued warnings, such valproate, alprazolam, carbamazepine, topiramate, clonazepam, and triazolam. These evidence bases may draw on literature outside the parameters of our review, such as single-arm studies or cohorts of women exposed to psychotropic drugs, but either not pregnant or not with a mental health disorder.

Another limitation of the evidence pertains to common data sources and resultant issues with measurement of exposures and comparators. Rare outcomes and harms are difficult to identify prospectively; the use of registries for prospectively collected data obviates that problem but creates several others. Healthcare utilization databases studies often defined exposure as having a prescription. Some studies conducted sensitivity analyses with more than one prescription. Although this approach offers a proxy for adherence, it cannot fully address the concern that prescriptions, particularly during pregnancy, may not wholly represent exposure to the drug. Few studies reported dose or duration of exposure. Registry studies that attempted to address confounding generally defined the comparison arm as unexposed to the drug in pregnancy but with a mental health disorder. In some cases, the mental health disorder was further defined as depression or anxiety; in other cases, any history of mental health disorders allowed women to qualify for the comparison arm. Such broad inclusions for psychiatric history and duration of the lookback period allow for greater precision from amassing large sample sizes in the comparison arm but also increase the risk of unmeasured confounding. Another concern relates to the absence of information on participation in psychotherapy or other psychological interventions in

the unexposed arm. The likely impact of poorly defined exposures and comparators further serves to weaken our confidence in the findings.

We may also have missed eligible studies because of our restriction to English language studies.

Applicability

The results from this review are generally applicable to populations of pregnant women with the same mental health condition as women included in the individual studies that comprise the body of evidence for each drug-treatment outcome. However, the criteria used to identify specific mental health conditions differed across studies and few studies controlled for baseline clinical severity. Therefore, we cannot comment on the additional effect, if any, of particular symptoms of a condition and whether the severity of the condition in the study populations would be similar to that in other similarly diagnosed patient populations. Criteria used to identify specific conditions differed across studies, and few studies controlled for baseline clinical severity.

Often studies determined receipt of pharmacotherapy through pharmacy and medical records of prescriptions filled. Some of these studies included women as receiving treatment with as few as one filled prescription, resulting in findings being limited to any possible exposure versus none. Other studies included a larger number of prescriptions to be filled, resulting in greater confidence that exposure occurred and continued over time. However, determining a specific level of exposure is further limited by adherence not being measured in studies. Also, some drugs are reported by class and the results may not extrapolate to all of the individual drugs in the class.

Most studies were conducted in majority-white populations and may not generalize to other races or ethnicities. Similarly, access to care may differ in U.S. versus non-U.S. cohorts, resulting in differences in outcomes between the populations that cannot be measured. Few studies reported on concurrent or recent psychological or behavioral treatment so that benefits of treatment cannot differentiate between efficacy and augmentation.

Implications for Clinical Practice, Education, Research, or Health Policy

Implications for Clinical Practice and Education

Pregnant women often seek information outside of the clinical context on psychotropic medications; information shared on popular internet message boards may be inaccurate, contradictory, or judgmental.[193] Clinicians and health communicators can use the findings from our review as an evidence-based source to inform and educate patients.

Although our results do not substantially add to the evidence base on benefits, we did not find any evidence that benefit would be different (or similar) in pregnant populations. We found some evidence of associations with maternal and child harms but note that these may be explained by residual confounding, rather than by either exposure to the drug. 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[106]) or very rare (as in the case of persistent pulmonary hypertension or postpartum hemorrhage). The absolute risks of these harms should be included when considering the balance of benefits and harms. Table 17

summarizes the absolute risks for some of the outcomes evaluated in this report. 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, clinicians should consider the possible adverse effects of pharmacologic treatments in contrast with the known adverse effects of untreated psychiatric illness (rather than when the patient is without any mental health disorders and not in need of treatment). The severity of the patient's mental health disorder should be carefully considered. Depending on the severity of the mental health disorder, maternal and fetal risks of foregoing treatment may change significantly.

Given these complexities, a shared decision-making framework is essential for clinical decision making. Shared decision making includes at least two experts: the patient, who is an expert on her life experience and preferences, and the provider, who is an expert in clinical care.[194, 195] The provider's role is to elicit the patient's personal values and preferences and risk tolerance and share relevant clinical knowledge to inform the decision-making process. During patient counseling, the clinician should inform the patient about the limitations of current research on the topic of pharmacologic treatments for pregnant or postpartum women with mental health disorders. To provide informed consent to initiate or to forgo treatment, patients need to understand that the evidence base is limited and insufficient to provide a strong recommendation. Under these circumstances, a patient's values and preferences and her unique clinical circumstances become even more important in the decision-making process.

Warfarin provides an example of how important it is to consider the severity of maternal disease when making decisions about pharmacologic treatments during pregnancy. Warfarin is a well-known teratogen, and use is generally avoided during pregnancy. However, in those women at exceptionally high risk of thromboembolic events, such as those with mechanical heart valves, warfarin is the most effective anticoagulant, and this maternal risk reduction may outweigh the fetal risks in certain patients. As is the case with psychiatric illness, the balance of benefits and risks shifts significantly depending on the severity of maternal disease, and patients' individual values and preferences must inform such complex decision making.

These complex decisions require shared decision-making tools that clinicians and patients can use to jointly make informed decisions.

Table 17. Absolute risk differences for key outcomes

Population	Outcome*	Exposure	Comparator	N	ARD per 1000 Women	95% Lower CI	95% Upper CI	Key Considerations
Women with postpartum depression	Response	Sertraline	Placebo	36	326	11	1116	RCT evidence, small sample, imprecise results
Women with postpartum depression	Remission	Sertraline	Placebo	36	320	4	619	RCT evidence, small sample, imprecise results
Women with bipolar disorder	Recurrence from discontinuation	Discontinued mood stabilizers	Continued mood stabilizers	89	268	56	486	Observational evidence, small sample, imprecise results
Women with bipolar disorder	Time-to-25%-recurrence from discontinuation	Discontinued mood stabilizers	Continued lamotrigine	26	687	135	700	Observational evidence, study has limitations, small sample, imprecise results

Population	Outcome*	Exposure	Comparator	N	ARD per 100 Women	95% Lower CI	95% Upper CI	Key Considerations
Women with at least one anxiety diagnosis in the year before conception	Ectopic pregnancy	Benzodiaz-epine exposure 90 days before conception	No benzodiaz-epine exposure before conception	90479	7	4	11	Observational evidence, potential for residual confounding
Women with mood or anxiety disorder	Postpartum hemorrhage	Exposed to SSRIs during delivery	Unexposed to SSRIs during delivery	81754	13	9	17	Observational evidence, potential for residual confounding
Women with mood or anxiety disorder	Postpartum hemorrhage	Exposed to SNRIs during delivery	Unexposed to SNRIs during delivery	69746	25	10	45	Observational evidence, potential for residual confounding
SNRI exposure or depression diagnosis, through second trimester	Preeclampsia	SNRIs exposure through second trimester	Unexposed depressed	65800	14	6	49	Observational evidence, potential for residual confounding
Women with depression	Preeclampsia	Exposed to TCAs in pregnancy	Unexposed to TCAs in pregnancy	65538	54	21	110	Observational evidence, potential for residual confounding
Women prescribed second-generation antipsychotic	Gestational diabetes	Quetiapine continued in pregnancy	Quetiapine discontinued in pregnancy	4533	11	<1	25	Observational evidence, potential for residual confounding
Women prescribed second-generation antipsychotic	Gestational diabetes	Olanzapine continued in pregnancy	Olanzapine discontinued in pregnancy	1425	29	6	61	Observational evidence, potential for residual confounding
Women with depression or anxiety	Spontaneous abortion	Benzodiaz-epine exposure in 1st trimester	Unmedicated mental illness	6031	73	36	109	Observational evidence, potential for residual confounding
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	9014	62	16	130	Observational evidence, potential for residual confounding
Women with a mental health disorder	NICU admission	Benzodiaz-epine exposure during pregnancy	Unexposed to benzodiaz-epine during pregnancy	793	133	17	274	Observational evidence, potential for residual confounding, benzodiazepine exposure may result in NICU admission by policy

Population	Outcome*	Exposure	Comparator	N	ARD per 100 Women	95% Lower CI	95% Upper CI	Key Considerations
Women exposed to SSRIs or unexposed with a psychiatric diagnosis	Apgar score	Exposed to SSRIs during pregnancy	Exposed to SSRIs before pregnancy or unexposed with a psychiatric diagnosis	25,381	8	4	13	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	621, 399	<1	<1	<1	Observational evidence, potential for residual confounding
Women with a mental health disorder	Childhood depression	Exposed to SSRIs during pregnancy	Unexposed to SSRIs during pregnancy	25,380	2	<1	6	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	13,389	17	6	32	Observational evidence, potential for residual confounding

ARD = absolute risk difference; CI = confidence interval; NICU = neonatal intensive care unit; RCT = randomized controlled trial; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

* Outcomes selected from evidence bases rated as low or moderate strength of evidence The ARD was calculated based on adjusted effect sizes when available. When multiple studies were available on harms, we selected cohort studies with the highest effect size to present the outer bound for harms.

Implications for Research

The paucity of definitive evidence on this topic offers a vast expanse of new opportunities. Clinical trials offer the greatest rigor, but feasibility and ethics have constrained their use. There is an emerging consensus that routine exclusion of pregnant and lactating women from clinical trials has harmful consequences, forcing patients and providers to make clinical decisions in the absence of evidence. Even when providers infer efficacy for pregnant women from studies of nonpregnant populations, little information is available on dose adjustment that may be needed given the physiological changes during pregnancy.[196] 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.[31] It will be essential to leverage this consensus to conduct clinical trials evaluating the efficacy and effectiveness of pharmacologic[196] mental health treatments in perinatal women. In addition, future observational studies should address confounding adequately. 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. Additionally, clinical practice and protocols for women with known

exposure to psychotropic medication may result in harms being more likely to be detected or suspected than among women without known psychotropic exposure.

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.[197] 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.

Implications for Health Policy

The complexity of the clinical considerations calls for greater involvement of mental health professionals in treatment decisions (rather than primary care or obstetrics alone). Adequate specialist care may be lacking in rural and other underserved areas. Telemedicine may help provide access to care where it might otherwise be inaccessible. At the same time, coverage of mental health services, including both pharmacologic and nonpharmacologic treatment, is essential, with particular attention to ongoing coverage in the postpartum period. Medicaid provides insurance for nearly 50 percent of pregnancies in the United States, but coverage ends at 60 days postpartum, and in many states, a large proportion of women lose coverage at that time.[198] Continued coverage is necessary to treat maternal mental health problems beyond the first 60 days after delivery.

Conclusions

The central decisional dilemma facing pregnant and postpartum women with mental health disorders and their provider is how to balance benefits and harms of psychotropic drugs for both themselves and their children. One such critical trade-off is whether improved symptoms in the mother outweigh the harms from potential congenital anomalies in the fetus. The evidence is very sparse on the benefits of pharmacotherapy. By contrast, evidence on harms of pharmacotherapy is voluminous but of low quality. Our findings indicate the need for clear communication to patients on four primary points: evidence exists that medications work in general populations; few studies have measured effectiveness in pregnant women; the limited evidence available is consistent with some benefit; and some studies suggested some potential risks, many of which are transient or rare. The patient and her provider are uniquely qualified to determine whether the mother's medical need for treatment exceeds any potential harms.

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Abbreviations and Acronyms

AD = antidepressants
ADD = attention deficit disorder
ADHD = attention-deficit/hyperactivity disorder
AEDs = anti-epileptic drugs
AHR = adjusted hazard ratio
AHRQ = Agency for Healthcare Research and Quality
AOR = adjusted odds ratio
ARR = adjusted risk ratio
ASD = autism spectrum disorder
ASEX = Arizona Sexual Experience Scale
BDI = Beck Depression Inventory
BDI-II = Beck Depression Inventory-II;
BRIEF-P = Behaviour Rating Inventory of Executive Function - Preschool version
BRS = Behavioral Rating Scale
BRX = brexanolone for postpartum depression
CBCL = childhood behavior checklist
CBT = cognitive behavioral therapy
CGI = Clinical Global Impression
CGI-I = Clinical Global Impression- Improvement
CGI-S = Clinical Global Impression-Severity of Illness
CI = confidence interval
dx = diagnosis
EHC = Effective Health Care
EPDS = Edinburgh Postnatal Depression Scale
FDA = Food and Drug Administration
GAD-7 = Generalized Anxiety Disorder 7-item
GAS = general adaptation syndrome
GRADE = Grading of Recommendations Assessment, Development and Evaluation
HAM-A = Hamilton Anxiety Rating Scale
HAM-D = Hamilton Depression Rating
HAM-D-17= Hamilton Depression Rating scale, 17-item version
HAM-D-19= Hamilton Depression Rating scale, 19-item version
HRSD = Hamilton Rating Scale for Depression
IDAS-GD = Inventory of Depression and Anxiety Symptoms, General Depression scale
IDS-SR = Inventory of Depression Symptoms – SR
INFANIB = Infant Neurological International Battery
IQR = interquartile ratio

ITT = intention to treat
KQ = Key Question
LGA = large for gestational age
LMP = last menstrual period
LS = least square
MADRS = Montgomery-Åsberg Depression Rating Scale
MAOI = Monoamine oxidase inhibitors
MDI = Mental Development Index
N/n = number
NA = not applicable
NEPSY-II = Developmental NEuroPSYchological Assessment-II
NICU = neonatal intensive care unit
NNNS = NICU Network Neurobehavioral Scale
NR = not reported
NS = not significant
OR = odds ratio
PDI = Provisional Diagnostic Instrument
PHQ9 = Patient Health Questionnaire, 9 item
pp = postpartum
PPH = persistent pulmonary hypertension
PPAQ = Postpartum Adjustment Questionnaire
QPC = Quebec Pregnancy/Children Cohort
RCT = randomized controlled trial
RD = risk difference
ROB = risk of bias
RR = relative risk
RRR = relative risk ratio
SD = standard deviation
SE = standard error
SON-R 2 1/2-7 = Snijders-Oomen Niet-verbale intelligentie Test-Revisie
SNRI = serotonin-norepinephrine reuptake inhibitor
SPQ = Social Problems Questionnaire
SSRI = selective serotonin reuptake inhibitor
TCA = tricyclic antidepressant
vs. = versus

Appendix A. Detailed Methods

Details of Data Sources and Searches

We conducted focused searches of PubMed, the Cochrane Library, Embase, and PsycINFO from inception to June 5, 2020. The inception date varied by database. PubMed has some citations from the 1940s, but indexing starts reliably in 1950. Cochrane Database of Systematic Reviews records start from 1995. Cochrane Central Register of Controlled Trials is not a standard bibliographic database, rather a collection of records harvested primarily from other databases; therefore, it has no inception (start) date. For Embase, the inception date is 1947. For PsycINFO, the inception date is 1887. Medical subject headings were used as search terms when available and keywords when appropriate, focusing on terms to describe relevant populations, interventions, outcomes, and study designs. Targeted searches for unpublished literature were conducted by searching ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform. The search strategy was developed by an experienced librarian with inputs from the study investigators. The search strategy was also peer reviewed by an independent experienced librarian. To supplement electronic searches, we reviewed the reference lists of pertinent systematic reviews published in 2013 or later to ensure the search strategy captured all relevant studies. A *Federal Register* notice (FRN) was posted between December 10, 2019 and January 9, 2020, as well as a request for supplemental evidence and data between December 16, 2019 and January 10, 2020. We updated the literature search during the public posting period of the draft report on June 4 to 5, 2020.

Study Selection

Table A-1 lists inclusion and exclusion criteria.

Table A-1. Inclusion/exclusion criteria

PICOTS	Inclusion	Exclusion
Population	KQs 1, 2: Women who are pregnant or postpartum with new or preexisting diagnosis of anxiety, depression, bipolar disorder, or schizophrenia • Anxiety disorders include *Diagnostic and Statistical Manual* (DSM) 5 and DSM-IV diagnoses (including generalized anxiety disorder, panic disorder, social anxiety disorder [social phobia], obsessive compulsive disorder [OCD], and posttraumatic stress disorder [PTSD]) • Depressive disorders include major depressive disorder KQs 3, 4: Reproductive-aged women (15-44 years old during preconception [≤12 weeks before pregnancy], pregnancy, and postpartum [through 1 year]) with any mental health disorder (new or preexisting)	KQs 1, 2: Studies of women with disorders other than anxiety (including PTSD and OCD), depression, bipolar disorder, and schizophrenia KQs 3, 4: <90% of sample are women reproductive age (15-44) KQs 1-4: Studies with 100% substance use disorders

PICOTS	Inclusion	Exclusion
Intervention[a]	Pharmacologic interventions for a mental health disorder including: • Antipsychotics (haloperidol, chlorpromazine, aripiprazole, quetiapine, olanzapine, risperidone, clozapine, lurasidone, paliperidone, fluphenazine, perphenazine, iloperidone, asenapine, brexpiprazole, and ziprasidone) • Selective serotonin reuptake inhibitors (SSRIs) and serotonin modulators (citalopram, escitalopram, fluoxetine, fluvoxamine, nefazodone, paroxetine, sertraline, trazodone, vilazodone, and vortioxetine) • Serotonin and norepinephrine reuptake inhibitors (SNRIs) (venlafaxine, desvenlafaxine, milnacipran, and duloxetine) • Tricyclic antidepressants (amitriptyline, amoxapine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, and trimipramine) • Other antidepressants (bupropion, mirtazapine) • Mood stabilizers (lithium and anticonvulsants [valproate, carbamazepine, oxcarbazepine, topiramate, and lamotrigine]) • Antianxiety agent (benzodiazepines [alprazolam, clobazam, clonazepam, clorazepate, clonidine, chlordiazepoxide, diazepam, lorazepam, temazepam, and triazolam] and buspirone) • Other medications for a mental health disorder (brexanolone, gabapentin, zolpidem, eszopiclone, zaleplon, ramelteon, diphenhydramine, lisdexamfetamine, and hydroxyzine)	All other interventions, including psychotherapy
Comparator	KQs 1, 3: Placebo or no treatment KQs 2, 4: Other pharmacologic interventions (studies of any psychotherapy, combined pharmacotherapy and psychotherapy are eligible if they report a pharmacologic comparison arm)	KQs 1, 3: Active comparators, no comparators KQs 2, 4: • Studies of treatments other than pharmacologic interventions or psychotherapy (e.g., yoga, mindfulness, self-care, nutritional or herbal supplements) • No comparators • Placebo or no treatment comparators

PICOTS	Inclusion	Exclusion
Outcomes[b]	KQs 1, 2: Effectiveness • Final health outcomes (maternal benefits) • Symptoms (response/remission/relapse, suicidal ideation) • Functional capacity[b] • Quality of life[b] • Peripartum events (delivery mode, breastfeeding, weight change) • Adherence to treatment/care/discontinuation • Suicidal events KQs 3, 4: Harms • Maternal harms ○ Harms specific to pregnancy and breastfeeding (infertility, miscarriage, abruption, preterm labor/preterm birth, preeclampsia, gestational hypertensive disorders, glucose intolerance/gestational diabetes mellitus, reduced milk production in breastfeeding/undesired weaning) ○ Danger to self or infant ○ Misuse of prescription medication ○ Serious adverse events related to treatment ○ Death • Fetal/infant/child harms ○ Preterm birth/small for gestational age or large for gestational age ○ Congenital anomalies ○ Perinatal complications (low APGAR, withdrawal, respiratory distress, neonatal intensive care unit time, persistent pulmonary hypertension) ○ Poor infant attachment/bonding[b] ○ Delayed social, emotional, and cognitive development[b] ○ Death	All other outcomes
Time frame	Followup KQs 1, 2: From conception up to 1 year postpartum for maternal outcomes KQs 3, 4: All	Followup • KQs 1, 2: more than 12 weeks preconception for maternal preconception outcomes, more than 1 year for maternal postpartum outcomes • KQs 3, 4: None
Settings	Clinical setting All settings	Clinical setting None

PICOTS	Inclusion	Exclusion
Study design[c]	Randomized controlled trials (RCTs), controlled clinical trials (CCTs), case-control studies, cohort studies with comparison arms Reference lists of relevant systematic reviews published in 2013 or later are used to ensure our search strategies captured all relevant studies.	All other designs and studies using included designs that do not meet the sample size criterion
Language	Studies published in English	Studies published in languages other than English

[a] Strength of evidence (SOE) grades were focused on outcomes above prioritized by the Technical Expert Panel (TEP).

[b] Outcomes were limited to validated measures.

[c] KQs 1 and 3 analyses were limited to studies that control for confounding.

CCT = case-controlled trial; DSM = *Diagnostic and Statistical Manual*; KQ = Key Question; OCD = obsessive compulsive disorder; PICOTS = population, interventions, comparisons, outcomes, timing, and setting; PTSD = posttraumatic stress disorder; RCT = randomized controlled trial; SNRI = serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; SOE = strength of evidence; TEP = Technical Expert Panel.

We imported all citations identified through searches and other sources into EndNote v.X9. Independent reviewers screened the titles and abstracts of all citations using the inclusion and exclusion criteria using Abstrackr. Studies included by either reviewer were retrieved for full-text screening. Independent reviewers then screened the full-text version of eligible references. Discrepancies between the reviewers were resolved through discussions and consensus or consultation with a third reviewer. Excluded studies are listed in the Results Appendix.

Data Abstraction

We developed and pilot tested a standardized data extraction form to extract study characteristics (author, study design, inclusion and exclusion criteria, patient characteristics, interventions, comparisons, outcomes, settings, and related items for assessing study quality and applicability). Trained reviewers abstracted the relevant data from each included article into the evidence tables; a second member of the team reviewed all data abstractions for completeness and accuracy.

Assessment of Methodological Risk of Bias of Individual Studies

The criteria set forth by the Agency for Healthcare Research and Quality's *Methods Guide for Comparative Effectiveness Reviews* guided our assessment of methodological risk of bias. To assess the risk of bias (i.e., internal validity), we used the ROBINS-I[1] tool for observational studies and the Cochrane RCT[2] tool for RCTs. For both observational studies and RCTs, risk-of-bias assessment included questions to assess selection bias, confounding, performance bias, detection bias, and attrition bias; concepts covered include those about adequacy of randomization (for RCTs only), similarity of groups at baseline, masking, attrition, whether intention-to-treat analysis was used, method of handling dropouts and missing data, validity and reliability of outcome measures, and treatment fidelity.[3]

Two independent reviewers assigned risk-of-bias ratings for each study with disagreements resolved by discussion and consensus. Reviewers assigned a rating of low risk of bias (study met all criteria), some concerns (study met some criteria), high risk of bias (methodological

shortcomings leading to high risk of bias in one or more categories), or unclear risk of bias (methods not reported clearly).

We did not assess the risk of bias or strength of evidence for studies eligible for the contextual question.

Data Synthesis

Planned Analyses

We summarized all included studies in narrative form and in summary tables that tabulate the important features of the study populations, design, intervention, comparison, outcomes, setting (including geographic location), and results.

If we found three or more studies with low levels of heterogeneity (similar populations, interventions, comparators, outcomes), we considered meta-analysis. To determine whether quantitative analyses were appropriate for bodies of evidence that contained three or more similar studies, we assessed the clinical and methodological heterogeneity of the studies under consideration following established guidance.[3, 4] For all analyses, we used random effects models to estimate pooled or comparative effects; unlike a fixed-effects model, this approach allowed for the likelihood that the true population effect may vary from study to study.

We calculated standardized differences (relative risks or standardized mean differences) for outcomes; when we graded the strength-of-evidence (SOE) grade as higher than insufficient, we also presented absolute differences in effect, when possible, in the detailed results to aid with interpretation of results.

We assessed statistical heterogeneity in effects between studies included in meta-analyses by calculating the chi-square statistic and the I^2 statistic (the proportion of variation in study estimates due to heterogeneity). The importance of the observed value of I^2 depends on the magnitude and direction of effects and on the SOE for heterogeneity (e.g., p-value from the chi-square test or a confidence interval for I^2).

When possible, for each intervention/comparator grouping, we present findings clustered by perinatal status and disorder. We also note special characteristics of the sample required for study inclusions.

Addressing Confounding

As noted in the main report, one significant methodological limitation of the nonrandomized controlled trial (non-RCT) evidence base is confounding. All observational studies are subject to confounding by indication—that is, the extent to which exposure to maternal mental health morbidity influences both exposure to the medication and outcomes. To address this limitation, some studies have compared women receiving pharmacotherapy with women who have the same mental health disorder but who are not receiving treatment.[5] However, this approach does not address confounding arising from disease severity, in that women who are receiving pharmacologic treatment may be likely to have more severe underlying disease than women who forgo pharmacologic therapy. Others trying to address residual confounding with high-dimensional propensity scores have found that full adjustment leads to many associations being no longer statistically significant.[6, 7] In analyzing the evidence, we accounted for the manner of adjustment for confounding.

Study designs most likely to report on harms associated with maternal use of psychotropic medications include case-control studies, pregnancy registry studies, observational cohort studies, and secondary analyses of administrative databases. Each of these study designs has strengths and limitations. Case-control studies allow assessment of associations with rare outcomes, such as congenital anomalies; however, both recall bias and selection of an appropriate control population are concerns. Pregnancy registry studies facilitate postmarketing surveillance of new medications but may be limited by selection bias. Observational cohort studies, particularly large birth cohorts such as the Norwegian Mother and Child Cohort Study[8] and the Danish National Birth Cohort,[9] capture sufficiently large samples to assess relatively rare outcomes with prospective assessment of exposure, but they cannot fully address confounding. Large administrative databases[10, 11] allow assessment of rare outcomes such as congenital anomalies but have problems in identifying pregnancies, misclassifying exposures, specifying outcomes and covariates, and addressing confounding.[11]

To address these limitations, we limited analysis of results of KQs 1 and 3 (benefits and harms of interventions compared with no treatment, usual care, or placebo) to studies that adjusted for confounding through matching, regression, or propensity score adjustments and provided these adjusted results for the comparison of interest (e.g., active intervention vs. no treatment for women with a diagnosis). We did not calculate indirect comparisons from studies that present adjusted results for comparisons outside the remit of this review. For example, several studies presented adjusted results for women with a drug exposure versus women with no drug exposure and no disorders and, separately, adjusted results comparing women with a disorder but no drug exposure versus women with no drug exposure and no disorder. Calculated indirect comparisons for women with a drug exposure versus women with a disorder but no drug exposure would be at risk of violating assumptions about transitivity and would likely have residual confounding.[12]

For KQs 2 and 4 (benefits and harms from head-to-head comparisons of interventions), we included studies that did not provide adjusted results that addressed confounding, but we marked down the evidence base for high potential for risk of bias. We excluded studies that did not present mutually exclusive arms: in studies with overlapping cases in exposure arms, the association between the intervention and the outcome cannot be established. We also required clarity on the interventions for both arms. We did not synthesize results from studies comparing an active intervention with "other antidepressants," polytherapy, or co-exposure to other drugs with no further elaboration. In these instances, because we could not discern the nature of the exposure, we could not interpret the clinical significance of differences in outcomes between the arms.

Sensitivity Analyses

When relevant (the evidence included both studies with high risk of bias and without high risk of bias), we conducted qualitative or quantitative sensitivity analyses to gauge the difference in conclusions upon including and excluding high risk-of-bias studies. For bodies of evidence with meta-analyses, we reported effect sizes with and without high risk-of-bias studies.

Grading the Strength of Evidence

We graded the SOE based on the Grading of Recommendations Assessment, Development and Evaluation (short GRADE) working group guidance[13] and guidance established for the Evidence-based Practice Center Program.[14] Developed to grade the overall strength of a body of

evidence, this approach incorporates five key domains: risk of bias (includes study design and aggregate quality), consistency, directness, precision of the evidence, and reporting bias. This approach requires looking beyond statistical significance alone, even when studies are consistent and of high quality and outcomes are direct and clinically relevant. It emphasizes the adequacy of the sample size to rule out spurious associations and results that are not clinically relevant. It also considers other optional domains that may be relevant to increasing the SOE for some scenarios, such as a dose-response association, plausible confounding that would decrease the observed effect, and strength of association (magnitude of effect). We depart from GRADE guidance and follow EPC-specific guidance on the starting grade for observational studies and the rating of the consistency domain for single-study bodies of evidence. We rate bodies of evidence from observational studies as moderate if no other reasons arise to downgrade the evidence. We downgrade single-study bodies of evidence for unknown consistency.

Table 2 describes the grades of evidence that could be assigned. Grades reflect the strength of the body of evidence to answer KQs on the comparative effectiveness, efficacy, and harms of the interventions included in this review. Two reviewers assessed each domain for each key outcome with differences resolved by consensus. Because these are direct outcomes, the evidence was not downgraded for indirectness; the SOE tables do not explicitly grade for directness as a result.

Table A-2. Definitions of the grades of overall SOE[14]

Grade	Definition
High	High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	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.
Low	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.
Insufficient	Evidence either is unavailable or does not permit estimation of an effect.

SOE = strength of evidence.

For bodies of evidence for which we could conduct sensitivity analyses, we based the final SOE grade on the evidence base without high risk-of-bias studies. We appended a footnote to SOE tables to indicate when sensitivity analyses changed the SOE grade.

Assessing Applicability

We assessed the applicability of individual studies and the applicability of a body of evidence following guidance from the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.[15] For individual studies, we examined conditions that may limit applicability based on the PICOTS (population, interventions, comparisons, outcomes, timing, and setting) structure. Some factors identified that may limit the applicability of evidence include the following: perinatal status, severity and type of disorder, comorbid conditions, history of previous depressive episodes or depression treatment, or setting (primary care vs. specialty care). We indicated perinatal status and type of disorder in the analysis and otherwise call out characteristics of the study populations that might limit applicability.

Peer Review and Public Commentary

Experts in the treatment of mental health conditions in perinatal populations were invited to provide external peer review of the draft systematic review that was entitled “Maternal and Fetal Effects of Mental Health Treatments in Pregnant and Breastfeeding Women: A Systematic

Review of Pharmacological Interventions." AHRQ staff and an Associate Editor reviewed the draft systematic review before it went out for peer review. The EPC Associate Editors are leaders in their respective fields and are actively involved as directors or leaders at their EPCs. Their role is to assess adherence to established methodology and guidelines for EPC-based research. We revised the report in response to AHRQ staff, the Associate Editor, peer reviewer, and public comments.

Search Strategy

Mental Health Treatment in Pregnant Women Published Literature Searches

PubMed

12-9-2018

Search	Query	Items Found	Notes
#1	Search ("Anxiety Disorders"[Mesh] OR anxiety[tiab] OR "Bipolar Disorder"[Mesh] OR bipolar[tiab] OR "Depressive Disorder"[MeSH] OR "Depressive Disorder, Major"[Mesh] OR Depression[Mesh] OR depress*[tiab] OR depression[tiab] OR depressive[tiab] OR depressed[tiab] OR "Dysthymic Disorder"[Mesh] OR dysthymia[tiab] OR dysthymic[tiab] OR "Feeding and Eating Disorders"[Mesh] OR anorexia[tiab] OR anorexic[tiab] OR "binge eating"[tiab] OR bulimic[tiab] OR bulimia[tiab] OR GAD OR "Psychotic Disorders"[Mesh] OR "psychotic disorder"[tiab] OR "psychotic disorders"[tiab] OR psychosis[tiab] OR psychoses[tiab] OR (mental[Tiab] AND (health[Tiab] OR illness[Tiab] OR disorders[Tiab])) OR "Mental Health"[Mesh] OR "Mental Disorders"[Mesh] OR "Obsessive-Compulsive Disorder"[Mesh] OR "Obsessive-Compulsive Disorder"[tiab] OR OCD[tiab] OR "panic disorder" OR "Persistent Depressive Disorder"[tiab] OR phobia*[tiab] OR phobic[tiab] OR psychotic*[tiab] OR "Stress Disorders, Post-Traumatic"[Mesh] OR "post-traumatic stress disorder"[All Fields] OR "post-traumatic stress disorders"[All Fields] OR "posttraumatic stress disorder"[All Fields] OR "posttraumatic stress disorders"[All Fields] OR (disorder* AND "post-traumatic"[tiab]) OR "Stress Disorders, Traumatic"[Mesh:NOEXP] OR PTSD[tiab] OR "Schizophrenia"[Mesh] OR schizophren*[tiab] OR "stress disorder"[All Fields])	1656505	
#2	Search (alprazolam OR "Anti-Anxiety Agents"[Mesh] OR "Anti-Anxiety Agents"[Pharmacological Action] OR anti-anxiety OR antianxiety OR "Amitriptyline"[Mesh] OR amitriptyline OR "Amoxapine"[Mesh] OR amoxapine OR Anticonvulsants[Mesh] OR Anticonvulsants[Pharmacological Action] OR anticonvulsant OR anticonvulsants OR "Antidepressive Agents"[MeSH] OR "Antidepressive Agents, Second-Generation"[MeSH] OR anti-depress* OR antidepressant* OR antidepressive* OR "antidepressive agent" OR "antidepressive agents" OR "antidepressive drug" OR "antidepressive drugs" OR "Antipsychotic Agents"[Mesh] OR antipsychotic* OR anxiolytic* OR "Aripiprazole"[Mesh] OR aripiprazole OR "Asenapine"[Supplementary Concept] OR Asenapine OR benzodiazepine* OR brexanolone OR brexpiprazole OR Bupropion[MeSH] OR Bupropion OR "Buspirone"[Mesh] OR Buspirone OR "Carbamazepine"[Mesh] OR Carbamazepine OR Cariprazine OR "Chlorpromazine"[Mesh] OR Chlorpromazine OR Citalopram[MeSH] OR citalopram OR "clobazam" [Supplementary Concept] OR clobazam OR "Clomipramine"[Mesh] OR Clomipramine OR "Clonazepam"[Mesh] OR Clonazepam OR "Clonidine"[Mesh] OR Clonidine OR "Clorazepate Dipotassium"[Mesh] OR Clorazepate OR "Chlordiazepoxide"[Mesh] OR Chlordiazepoxide OR "Clozapine"[Mesh] OR clozapine)	447815	

Search	Query	Items Found	Notes
#3	Search ("Desipramine"[Mesh] OR Desipramine OR "Desvenlafaxine Succinate"[Mesh] OR Desvenlafaxine OR "Diazepam"[Mesh] OR Diazepam OR "Diphenhydramine"[Mesh] OR Diphenhydramine OR "Doxepin"[Mesh] OR doxepin OR "Duloxetine Hydrochloride"[Mesh] OR duloxetine OR escitalopram OR "Eszopiclone"[Mesh] OR eszopiclone OR Fluoxetine[MeSH] OR fluoxetine OR "Fluphenazine"[Mesh] OR fluphenazine OR Fluvoxamine[MeSH] OR fluvoxamine OR "gabapentin"[Supplementary Concept] OR gabapentin OR "Haloperidol"[Mesh] OR Haloperidol OR "Hydroxyzine"[Mesh] OR Hydroxyzine OR "iloperidone"[Supplementary Concept] OR iloperidone OR "Imipramine"[Mesh] OR imipramine OR "lamotrigine"[Supplementary Concept] OR lamotrigine OR "Levomilnacipran"[Mesh] OR Levomilnacipran OR "Lisdexamfetamine Dimesylate "[Mesh] OR "Lithium Carbonate"[Mesh] OR lithium OR "Lorazepam"[Mesh] OR lorazepam OR "Lurasidone Hydrochloride"[Mesh] OR lurasidone OR "milnacipran"[Supplementary Concept])	160740	
#4	Search (milnacipran OR "Maprotiline"[Mesh] OR Maprotiline OR mirtazapine[Supplementary Concept] OR mirtazapine OR "nefazodone"[Supplementary Concept] OR nefazodone OR "norepinephrine reuptake inhibitor" OR "norepinephrine reuptake inhibitors" OR "Nortriptyline"[Mesh] OR nortriptyline OR "olanzapine"[Supplementary Concept] OR olanzapine OR "oxcarbazepine"[Supplementary Concept] OR oxcarbazepine OR "Paliperidone Palmitate"[Mesh] OR Paliperidone OR Paroxetine[MeSH] OR paroxetine OR "Perphenazine"[Mesh] OR perphenazine OR "Protriptyline"[Mesh] OR protriptyline OR "Quetiapine Fumarate"[Mesh] OR quetiapine OR "ramelteon" [Supplementary Concept] OR ramelteon OR "Risperidone"[Mesh] OR risperidone OR "selective serotonin reuptake inhibitor" OR "selective serotonin reuptake inhibitors" OR "Serotonin Uptake Inhibitors"[MeSH] OR "serotonin norepinephrine reuptake inhibitor"[All Fields] OR "serotonin norepinephrine reuptake inhibitors"[All Fields] OR Sertraline[MeSH] OR sertraline OR SNRI* OR SSRI OR SSRIs)	70738	
#5	Search ("Temazepam"[Mesh] OR Temazepam "Thioridazine"[Mesh] OR Thioridazine OR "Thiothixene"[Mesh] OR Thiothixene OR "topiramate"[Supplementary Concept] OR topiramate OR Trazodone[Mesh] OR trazodone OR "Triazolam"[Mesh] OR triazolam OR "Trifluoperazine"[Mesh] OR Trifluoperazine OR "Trimipramine"[Mesh] OR Trimipramine OR "Valproic Acid"[Mesh] OR valproate OR "Venlafaxine Hydrochloride"[Mesh] OR venlafaxine OR "Vilazodone Hydrochloride"[Mesh] OR vilazodone OR "vortioxetine"[Supplementary Concept] OR vortioxetine OR "zaleplon"[Supplementary Concept] OR zaleplon OR "ziprasidone"[Supplementary Concept] OR ziprasidone OR "zolpidem"[Supplementary Concept] OR zolpidem)	42558	
#6	Search (#2 or #3 or #4 or #5)	534672	
#7	Search (#1 and #6)	184651	
#8	Search ("Pregnant Women"[Mesh] OR Pregnancy[Mesh] OR preconception[tiab] OR pregnant[tiab] OR pregnancy[tiab] OR prenatal[tiab] OR "post-partum"[tiab] OR postpartum[tiab] OR postnatal[tiab] OR perinatal[tiab] OR antenatal[tiab] OR "Maternal Health Services"[Mesh] OR "maternal health"[tiab] OR "Infant Nutritional Physiological Phenomena"[Mesh] OR "Breast Feeding"[Mesh] OR "breast feeding"[tiab] OR breastfeed*[tiab] OR (breast[tiab] AND fed[tiab]) OR breastfed[tiab] OR "Pregnancy Complications"[All Fields] OR "Maternal Welfare"[All Fields] OR gestation*[tiab] OR maternal*[tiab] OR "Pregnancy Outcome"[Mesh])	1220300	
#9	Search (#7 and #8)	6083	
#10	Search (#7 and #8) Filters: English	5540	
#11	Search ((#10 AND Humans[Mesh:noexp]) OR (#10 NOT Animals[Mesh:noexp]))	4340	

Search	Query	Items Found	Notes
#12	Search (accident* OR "Adverse Effects" OR "adverse effect" or "adverse event" OR "adverse events" OR "adverse outcome" OR "adverse outcomes" OR "adverse reaction" OR "adverse reactions" OR "chemically induced" OR complication* OR death* OR "Drug Allergies" OR "Drug Dependency" OR "drug effects" OR "Drug Sensitivity" OR harm* OR harms OR "Long Term Adverse Effects"[Mesh] OR "manic episode" OR overdos* OR "Patient Safety" OR poisoning OR self damage* OR self injur* OR self inflict* OR "Self-Injurious Behavior"[Mesh] OR "Side Effect" OR "side effects" OR Suicide OR suicidal* OR toxicity)	7964680	
#13	Search ("Abortion, Spontaneous"[Mesh] OR "Abruptio Placentae"[Mesh] OR abruption*[tiab] OR "Apgar Score"[Mesh] OR "Birth Weight/chemically induced"[Mesh] OR "Birth Weight/drug effects"[Mesh] OR "Child Development Disorders, Pervasive/chemically induced"[Mesh] OR "Child Development/drug effects"[Mesh] OR "Craniofacial Abnormalities/chemically induced"[Mesh] OR "Congenital Abnormalities"[Mesh] OR "congenital abnormality"[tiab] OR "congenital abnormalities"[tiab] OR death[tiab] OR "delayed development"[ALL FIELDS] OR "Glucose Intolerance"[Mesh] OR "glucose intolerance"[tiab] OR "Infant, Extremely Premature/growth and development"[Mesh] OR (infant* AND (attachment* OR bonding)) OR "Infertility, Female"[Mesh] OR “Infantile Respiratory Distress Syndrome”[tiab] OR infertility[tiab] OR ("Intellectual Disability"[Mesh] AND child*[tw]) OR "Low APGAR"[tiab] OR miscarry[tiab] OR miscarriage*[tiab] OR Mortality[Mesh] OR mortality[tiab] OR "Neonatal Abstinence Syndrome"[Mesh] OR “Neonatal Respiratory Distress Syndrome”[tiab] OR "Obstetric Labor, Premature"[Mesh] OR "Persistent Fetal Circulation Syndrome"[Mesh] OR "Persistent Pulmonary Hypertension of Newborn"[tiab] OR "Pre-Eclampsia"[Mesh] OR preeclampsia[tiab] OR pre-eclampsia[tiab] OR "Premature Birth"[Mesh] OR "premature birth"[tiab] OR "preterm birth" OR "pre-term birth"[tiab] OR "Prenatal Exposure Delayed Effects"[Mesh] OR "Prescription Drug Misuse"[Mesh] OR ("Prescription Drug"[tiab] AND misuse[tiab]) OR "preterm labor"[tiab] OR "pre-term labor"[tiab] OR "Postpartum Hemorrhage"[Mesh] OR "Respiratory Distress Syndrome, Newborn"[Mesh] OR "Uterine Inertia/chemically induced"[Mesh])	2154910	Now with all harms terms mentioned in PICOs table
#14	Search (#12 or #13)	8795543	
#15	Search ("Drug Therapy"[Mesh] OR "drug therapy"[Subheading] OR drug*[tiab] OR pharmacotherap*[tiab] OR pharmacologic*[tiab] OR medicine*[tiab] OR medication*[tiab])	4349451	
#16	Search (#14 and #15 and #8 and #1)	11864	
#17	Search (#14 and #15 and #8 and #1) Filters: English	10679	
#18	Search ((#17 AND Humans[Mesh:noexp]) OR (#17 NOT Animals[Mesh:noexp]))	8952	
#19	Search ((#10 AND Humans[Mesh:noexp]) OR (#10 NOT Animals[Mesh:noexp])) Filters: Case Reports	550	
#20	Search ((#10 AND Humans[Mesh:noexp]) OR (#10 NOT Animals[Mesh:noexp])) Filters: Case Reports; Editorial	615	
#21	Search (#11 NOT (#19 or #20))	3725	Benefits results
#22	Search ((#17 AND Humans[Mesh:noexp]) OR (#17 NOT Animals[Mesh:noexp])) Filters: Case Reports	902	
#23	Search ((#17 AND Humans[Mesh:noexp]) OR (#17 NOT Animals[Mesh:noexp])) Filters: Case Reports; Editorial	1005	
#24	Search (#18 NOT (#22 OR #23))	7947	Harms results
#25	Search (#21 and #24)	2384	Overlap of benefits and harms results

Search	Query	Items Found	Notes
#26	Search (#21 not #25)	1341	Unique benefits results not in harms results
#27	Search (#24 not #25)	5563	Unique harms results not in benefits results
#28	Search (#25 or #26 or #27)	9288	Total number for PubMed

PubMed

6-4-2020

Search Number	Query	Filters	Results
1	"Anxiety Disorders"[Mesh] OR anxiety[tiab] OR "Bipolar Disorder"[Mesh] OR bipolar[tiab] OR "Depressive Disorder"[MeSH] OR "Depressive Disorder, Major"[Mesh] OR Depression[Mesh] OR depress*[tiab] OR depression[tiab] OR depressive[tiab] OR depressed[tiab] OR "Dysthymic Disorder"[Mesh] OR dysthymia[tiab] OR dysthymic[tiab] OR "Feeding AND Eating Disorders"[Mesh] OR anorexia[tiab] OR anorexic[tiab] OR "binge eating"[tiab] OR bulimic[tiab] OR bulimia[tiab] OR GAD OR "Psychotic Disorders"[Mesh] OR "psychotic disorder"[tiab] OR "psychotic disorders"[tiab] OR psychosis[tiab] OR psychoses[tiab] OR (mental[Tiab] AND (health[Tiab] OR illness[Tiab] OR disorders[Tiab])) OR "Mental Health"[Mesh] OR "Mental Disorders"[Mesh] OR "Obsessive-Compulsive Disorder"[Mesh] OR "Obsessive-Compulsive Disorder"[tiab] OR OCD[tiab] OR "panic disorder" OR "Persistent Depressive Disorder"[tiab] OR phobia*[tiab] OR phobic[tiab] OR psychotic*[tiab] OR "Stress Disorders, Post-Traumatic"[Mesh] OR "post-traumatic stress disorder"[All Fields] OR "post-traumatic stress disorders"[All Fields] OR "posttraumatic stress disorder"[All Fields] OR "posttraumatic stress disorders"[All Fields] OR (disorder* AND "post-traumatic"[tiab]) OR "Stress Disorders, Traumatic"[Mesh:NOEXP] OR PTSD[tiab] OR "Schizophrenia"[Mesh] OR schizophren*[tiab] OR "stress disorder"[All Fields]		1,791,649
2	alprazolam OR "Anti-Anxiety Agents"[Mesh] OR "Anti-Anxiety Agents"[Pharmacological Action] OR anti-anxiety OR antianxiety OR "Amitriptyline"[Mesh] OR amitriptyline OR "Amoxapine"[Mesh] OR amoxapine OR Anticonvulsants[Mesh] OR Anticonvulsants[Pharmacological Action] OR anticonvulsant OR anticonvulsants OR "Antidepressive Agents"[MeSH] OR "Antidepressive Agents, Second-Generation"[MeSH] OR anti-depress* OR antidepressant* OR antidepressive* OR "antidepressive agent" OR "antidepressive agents" OR "antidepressive drug" OR "antidepressive drugs" OR "Antipsychotic Agents"[Mesh] OR antipsychotic* OR anxiolytic* OR "Aripiprazole"[Mesh] OR aripiprazole OR "Asenapine"[Supplementary Concept] OR Asenapine OR benzodiazepine* OR brexanolone OR brexpiprazole OR Bupropion[MeSH] OR Bupropion OR "Buspirone"[Mesh] OR Buspirone OR "Carbamazepine"[Mesh] OR Carbamazepine OR Cariprazine OR "Chlorpromazine"[Mesh] OR Chlorpromazine OR Citalopram[MeSH] OR citalopram OR "clobazam" [Supplementary Concept] OR clobazam OR "Clomipramine"[Mesh] OR Clomipramine OR "Clonazepam"[Mesh] OR Clonazepam OR "Clonidine"[Mesh] OR Clonidine OR "Clorazepate Dipotassium"[Mesh] OR Clorazepate OR "Chlordiazepoxide"[Mesh] OR Chlordiazepoxide OR "Clozapine"[Mesh] OR clozapine		505,728
3	"Desipramine"[Mesh] OR Desipramine OR "Desvenlafaxine Succinate"[Mesh] OR Desvenlafaxine OR "Diazepam"[Mesh] OR Diazepam OR "Diphenhydramine"[Mesh] OR Diphenhydramine OR "Doxepin"[Mesh] OR doxepin OR "Duloxetine Hydrochloride"[Mesh] OR duloxetine OR escitalopram OR "Eszopiclone"[Mesh] OR eszopiclone OR Fluoxetine[MeSH] OR fluoxetine OR "Fluphenazine"[Mesh] OR fluphenazine OR Fluvoxamine[MeSH] OR fluvoxamine OR "gabapentin"[Supplementary Concept] OR gabapentin OR "Haloperidol"[Mesh] OR Haloperidol OR "Hydroxyzine"[Mesh] OR Hydroxyzine OR "iloperidone"[Supplementary Concept] OR iloperidone OR "Imipramine"[Mesh] OR imipramine OR "lamotrigine"[Supplementary Concept] OR lamotrigine OR "Levomilnacipran"[Mesh] OR Levomilnacipran OR "Lisdexamfetamine Dimesylate "[Mesh] OR "Lithium Carbonate"[Mesh] OR lithium OR "Lorazepam"[Mesh] OR lorazepam OR "Lurasidone Hydrochloride"[Mesh] OR lurasidone OR "milnacipran"[Supplementary Concept]		170,275

Search Number	Query	Filters	Results
4	milnacipran OR "Maprotiline"[Mesh] OR Maprotiline OR mirtazapine[Supplementary Concept] OR mirtazapine OR "nefazodone"[Supplementary Concept] OR nefazodone OR "norepinephrine reuptake inhibitor" OR "norepinephrine reuptake inhibitors" OR "Nortriptyline"[Mesh] OR nortriptyline OR "olanzapine"[Supplementary Concept] OR olanzapine OR "oxcarbazepine"[Supplementary Concept] OR oxcarbazepine OR "Paliperidone Palmitate"[Mesh] OR Paliperidone OR Paroxetine[MeSH] OR paroxetine OR "Perphenazine"[Mesh] OR perphenazine OR "Protriptyline"[Mesh] OR protriptyline OR "Quetiapine Fumarate"[Mesh] OR quetiapine OR "ramelteon" [Supplementary Concept] OR ramelteon OR "Risperidone"[Mesh] OR risperidone OR "selective serotonin reuptake inhibitor" OR "selective serotonin reuptake inhibitors" OR "Serotonin Uptake Inhibitors"[MeSH] OR "serotonin norepinephrine reuptake inhibitor"[All Fields] OR "serotonin norepinephrine reuptake inhibitors"[All Fields] OR Sertraline[MeSH] OR sertraline OR SNRI* OR SSRI OR SSRIs		74,815
5	"Temazepam"[Mesh] OR Temazepam "Thioridazine"[Mesh] OR Thioridazine OR "Thiothixene"[Mesh] OR Thiothixene OR "topiramate"[Supplementary Concept] OR topiramate OR Trazodone[Mesh] OR trazodone OR "Triazolam"[Mesh] OR triazolam OR "Trifluoperazine"[Mesh] OR Trifluoperazine OR "Trimipramine"[Mesh] OR Trimipramine OR "Valproic Acid"[Mesh] OR valproate OR "Venlafaxine Hydrochloride"[Mesh] OR venlafaxine OR "Vilazodone Hydrochloride"[Mesh] OR vilazodone OR "vortioxetine"[Supplementary Concept] OR vortioxetine OR "zaleplon"[Supplementary Concept] OR zaleplon OR "ziprasidone"[Supplementary Concept] OR ziprasidone OR "zolpidem"[Supplementary Concept] OR zolpidem		44,808
6	#2 OR #3 OR #4 OR #5		585,792
7	#1 AND #6		199,331
8	"Pregnant Women"[Mesh] OR Pregnancy[Mesh] OR preconception[tiab] OR pregnant[tiab] OR pregnancy[tiab] OR prenatal[tiab] OR "post-partum"[tiab] OR postpartum[tiab] OR postnatal[tiab] OR perinatal[tiab] OR antenatal[tiab] OR "Maternal Health Services"[Mesh] OR "maternal health"[tiab] OR "Infant Nutritional Physiological Phenomena"[Mesh] OR "Breast Feeding"[Mesh] OR "breast feeding"[tiab] OR breastfeed*[tiab] OR (breast[tiab] AND fed[tiab]) OR breastfed[tiab] OR "Pregnancy Complications"[All Fields] OR "Maternal Welfare"[All Fields] OR gestation*[tiab] OR maternal*[tiab] OR "Pregnancy Outcome"[Mesh]		1,296,988
9	#7 AND #8		6,782
10	#7 AND #8	English	6,208
11	(#10 AND Humans[Mesh:noexp]) OR (#10 NOT Animals[Mesh:noexp])		4,843
12	accident* OR "Adverse Effects" OR "adverse effect" OR "adverse event" OR "adverse events" OR "adverse outcome" OR "adverse outcomes" OR "adverse reaction" OR "adverse reactions" OR "chemically induced" OR complication* OR death* OR "Drug Allergies" OR "Drug Dependency" OR "drug effects" OR "Drug Sensitivity" OR harm* OR harms OR "Long Term Adverse Effects"[Mesh] OR "manic episode" OR overdos* OR "Patient Safety" OR poisoning OR self damage* OR self injur* OR self inflict* OR "Self-Injurious Behavior"[Mesh] OR "Side Effect" OR "side effects" OR Suicide OR suicidal* OR toxicity		8,665,883

Search Number	Query	Filters	Results
13	"Abortion, Spontaneous"[Mesh] OR "Abruptio Placentae"[Mesh] OR abruption*[tiab] OR "Apgar Score"[Mesh] OR "Birth Weight/chemically induced"[Mesh] OR "Birth Weight/drug effects"[Mesh] OR "Child Development Disorders, Pervasive/chemically induced"[Mesh] OR "Child Development/drug effects"[Mesh] OR "Craniofacial Abnormalities/chemically induced"[Mesh] OR "Congenital Abnormalities"[Mesh] OR "congenital abnormality"[tiab] OR "congenital abnormalities"[tiab] OR death[tiab] OR "delayed development"[ALL FIELDS] OR "Glucose Intolerance"[Mesh] OR "glucose intolerance"[tiab] OR "Infant, Extremely Premature/growth AND development"[Mesh] OR (infant* AND (attachment* OR bonding)) OR "Infertility, Female"[Mesh] OR “Infantile Respiratory Distress Syndrome”[tiab] OR infertility[tiab] OR ("Intellectual Disability"[Mesh] AND child*[tw]) OR "Low APGAR"[tiab] OR miscarry[tiab] OR miscarriage*[tiab] OR Mortality[Mesh] OR mortality[tiab] OR "Neonatal Abstinence Syndrome"[Mesh] OR “Neonatal Respiratory Distress Syndrome”[tiab] OR "Obstetric Labor, Premature"[Mesh] OR "Persistent Fetal Circulation Syndrome"[Mesh] OR "Persistent Pulmonary Hypertension of Newborn"[tiab] OR "Pre-Eclampsia"[Mesh] OR preeclampsia[tiab] OR pre-eclampsia[tiab] OR "Premature Birth"[Mesh] OR "premature birth"[tiab] OR "preterm birth" OR "pre-term birth"[tiab] OR "Prenatal Exposure Delayed Effects"[Mesh] OR "Prescription Drug Misuse"[Mesh] OR ("Prescription Drug"[tiab] AND misuse[tiab]) OR "preterm labor"[tiab] OR "pre-term labor"[tiab] OR "Postpartum Hemorrhage"[Mesh] OR "Respiratory Distress Syndrome, Newborn"[Mesh] OR "Uterine Inertia/chemically induced"[Mesh]		2,345,644
14	#12 OR #13		9,559,975
15	"Drug Therapy"[Mesh] OR "drug therapy"[Subheading] OR drug*[tiab] OR pharmacotherap*[tiab] OR pharmacologic*[tiab] OR medicine*[tiab] OR medication*[tiab]		4,692,865
16	#14 AND #15 AND #8 AND #1		13,011
17	#14 AND #15 AND #8 AND #1	English	11,788
18	(#17 AND Humans[Mesh:noexp]) OR (#17 NOT Animals[Mesh:noexp])		9,848
19	(#10 AND Humans[Mesh:noexp]) OR (#10 NOT Animals[Mesh:noexp])	Case Reports	612
20	(#10 AND Humans[Mesh:noexp]) OR (#10 NOT Animals[Mesh:noexp])	Case Reports, Editorial	684
21	#11 NOT (#19 OR #20)		
22	(#17 AND Humans[Mesh:noexp]) OR (#17 NOT Animals[Mesh:noexp])	Case Reports	967
23	(#17 AND Humans[Mesh:noexp]) OR (#17 NOT Animals[Mesh:noexp])	Case Reports, Editorial	1,077
24	#18 NOT (#22 OR #23)		8,771
25	#21 AND ("2018/06/09"[Date - Publication] : "3000"[Date - Publication])		546
26	#24 AND ("2018/06/09"[Date - Publication] : "3000"[Date - Publication])		811
27	retraction[All Fields] OR “Retracted Publication”[pt] OR Duplicate Publication [pt] OR Erratum[All Fields]		116,824
28	#27 AND (#21 OR #24)		6

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12-10-2018

Search	Query	Results
#1	[mh "Anxiety Disorders"] OR anxiety:ti,ab OR [mh "Bipolar Disorder"] OR bipolar:ti,ab OR [mh "Depressive Disorder"] OR [mh "Depressive Disorder, Major"] OR [mh Depression] OR depress*:ti,ab OR depression:ti,ab OR depressive:ti,ab OR depressed:ti,ab OR [mh "Dysthymic Disorder"] OR dysthymia:ti,ab OR dysthymic:ti,ab OR [mh "Feeding and Eating Disorders"] OR anorexia:ti,ab OR anorexic:ti,ab OR "binge eating":ti,ab OR bulimic:ti,ab OR bulimia:ti,ab OR GAD OR [mh "Psychotic Disorders"] OR "psychotic disorder":ti,ab OR "psychotic disorders":ti,ab OR psychosis:ti,ab OR psychoses:ti,ab OR (mental:ti,ab AND (health:ti,ab OR illness:ti,ab OR disorders:ti,ab)) OR [mh "Mental Health"] OR [mh "Mental Disorders"] OR [mh "Obsessive-Compulsive Disorder"] OR "Obsessive-Compulsive Disorder":ti,ab OR OCD:ti,ab OR "panic disorder" OR "Persistent Depressive Disorder":ti,ab OR phobia*:ti,ab OR phobic:ti,ab OR psychotic*:ti,ab OR [mh "Stress Disorders, Post-Traumatic"] OR "post-traumatic stress disorder" OR "post-traumatic stress disorders" OR "posttraumatic stress disorder" OR "posttraumatic stress disorders" OR (disorder* AND "post-traumatic":ti,ab) OR [mh ^"Stress Disorders, Traumatic"] OR PTSD:ti,ab OR [mh "Schizophrenia"] OR schizophren*:ti,ab OR "stress disorder"	135850
#2	alprazolam OR [mh "Anti-Anxiety Agents"] OR anti-anxiety OR antianxiety OR [mh "Amitriptyline"] OR amitriptyline OR [mh "Amoxapine"] OR amoxapine OR [mh Anticonvulsants] OR anticonvulsant OR anticonvulsants OR [mh "Antidepressive Agents"] OR [mh "Antidepressive Agents, Second-Generation"] OR anti-depress* OR antidepressant* OR antidepressive* OR [mh "Antipsychotic Agents"] OR antipsychotic* OR anxiolytic* OR [mh "Aripiprazole"] OR aripiprazole OR Asenapine OR benzodiazepine* OR brexanolone OR brexpiprazole OR [mh Bupropion] OR Bupropion OR [mh "Buspirone"] OR Buspirone OR [mh "Carbamazepine"] OR Carbamazepine OR Cariprazine OR [mh "Chlorpromazine"] OR Chlorpromazine OR [mh Citalopram] OR citalopram OR clobazam OR [mh Clomipramine] OR Clomipramine OR [mh "Clonazepam"] OR Clonazepam OR [mh "Clonidine"] OR Clonidine OR [mh "Clorazepate Dipotassium"] OR Clorazepate OR [mh "Chlordiazepoxide"] OR Chlordiazepoxide OR [mh "Clozapine"] OR clozapine	41190
#3	[mh "Desipramine"] OR Desipramine OR [mh "Desvenlafaxine Succinate"] OR Desvenlafaxine OR [mh "Diazepam"] OR Diazepam OR [mh "Diphenhydramine"] OR Diphenhydramine OR [mh "Doxepin"] OR doxepin OR [mh "Duloxetine Hydrochloride"] OR duloxetine OR escitalopram OR [mh "Eszopiclone"] OR eszopiclone OR [mh Fluoxetine] OR fluoxetine OR [mh "Fluphenazine"] OR fluphenazine OR [mh Fluvoxamine] OR fluvoxamine OR gabapentin OR [mh "Haloperidol"] OR Haloperidol OR [mh "Hydroxyzine"] OR Hydroxyzine OR iloperidone OR [mh "Imipramine"] OR imipramine OR lamotrigine OR Levomilnacipran [mh "Lisdexamfetamine Dimesylate"] OR [mh "Lithium Carbonate"] OR lithium OR [mh "Lorazepam"] OR lorazepam OR [mh "Lurasidone Hydrochloride"] OR lurasidone OR Maprotiline	24642
#4	milnacipran OR mirtazapine OR nefazodone OR "norepinephrine reuptake inhibitor" OR "norepinephrine reuptake inhibitors" OR [mh "Nortriptyline"] OR nortriptyline OR olanzapine OR oxcarbazepine OR [mh "Paliperidone Palmitate"] OR Paliperidone OR [mh Paroxetine] OR paroxetine OR [mh "Perphenazine"] OR perphenazine OR [mh "Protriptyline"] OR protriptyline OR [mh "Quetiapine Fumarate"] OR quetiapine OR ramelteon OR [mh "Risperidone"] OR risperidone OR "selective serotonin reuptake inhibitor" OR "selective serotonin reuptake inhibitors" OR [mh "Serotonin Uptake Inhibitors"] OR "serotonin norepinephrine reuptake inhibitor":ti,ab,kw OR "serotonin norepinephrine reuptake inhibitors":ti,ab,kw OR [mh Sertraline] OR sertraline OR SNRI* OR SSRI*	15699
#5	[mh "Temazepam"] OR Temazepam OR Thioridazine OR Thiothixine OR topiramate OR [mh Trazodone] OR trazodone OR [mh "Triazolam"] OR triazolam OR Trifluoperazine OR [mh "Trimipramine"] OR Trimipramine OR [mh "Valproic Acid"] OR valproate OR [mh "Venlafaxine Hydrochloride"] OR venlafaxine OR [mh "Vilazodone Hydrochloride"] OR vilazodone OR Vistaril OR vortioxetine OR Vyvanse OR zaleplon OR ziprasidone OR zolpidem	8257
#6	(#2 or #3 or #4 or #5)	61747
#7	(#1 and #6)	35441

Search	Query	Results
#8	[mh "Pregnant Women"] OR [mh Pregnancy] OR preconception:ti,ab OR pregnant:ti,ab OR pregnancy:ti,ab OR prenatal:ti,ab OR "post-partum":ti,ab OR postpartum:ti,ab OR postnatal:ti,ab OR perinatal:ti,ab OR antenatal:ti,ab OR [mh "Maternal Health Services"] OR "maternal health":ti,ab OR [mh "Infant Nutritional Physiological Phenomena"] OR [mh "Breast Feeding"] OR "breast feeding":ti,ab OR breastfeed*:ti,ab OR (breast:ti,ab AND fed:ti,ab) OR breastfed:ti,ab OR "Pregnancy Complications":ti,ab,kw OR "Maternal Welfare":ti,ab,kw OR gestation*:ti,ab OR maternal*:ti,ab OR [mh "Pregnancy Outcome"]	51540
#9	(#7 and #8)	443
#10	(#9 AND [mh ^Humans]) OR (#9 NOT [mh ^Animals])	443
#11	[mh "Drug Therapy"] OR drug*:ti,ab OR pharmacotherap*:ti,ab OR pharmacologic*:ti,ab OR medicine*:ti,ab OR medication*:ti,ab	321669
#12	accident* OR "Adverse Effects" OR "adverse effect" or "adverse event" OR "adverse events" OR "adverse outcome" OR "adverse outcomes" OR "adverse reaction" OR "adverse reactions" OR "chemically induced" OR complication* OR death* OR "Drug Allergies" OR "Drug Dependency" OR "drug effects" OR "Drug Sensitivity" OR harm* OR harms OR [mh "Long Term Adverse Effects"] OR "manic episode" OR overdos* OR "Patient Safety" OR poisoning OR self damage* OR self injur* OR self inflict* OR [mh "Self-Injurious Behavior"] OR "Side Effect" OR "side effects" OR Suicide OR suicidal* OR toxicity	477736
#13	[mh "Abortion, Spontaneous"] OR [mh "Abruptio Placentae"] OR abruption*:ti,ab OR [mh "Apgar Score"] OR [mh "Birth Weight"/CI] OR [mh "Birth Weight"/DE] OR [mh "Child Development Disorders, Pervasive"/CI] OR [mh "Child Development"/DE] OR [mh "Craniofacial Abnormalities"/CI] OR [mh "Congenital Abnormalities"] OR "congenital abnormality":ti,ab OR "congenital abnormalities":ti,ab OR death:ti,ab OR "delayed development":ti,ab,kw OR [mh "Glucose Intolerance"] OR "glucose intolerance":ti,ab OR [mh "Infant, Extremely Premature"/GD] OR (infant* AND (attachment* OR bonding)) OR [mh "Infertility, Female"] OR "Infantile Respiratory Distress Syndrome":ti,ab OR infertility:ti,ab OR ([mh "Intellectual Disability"] AND child*:ti,ab,kw) OR "Low APGAR":ti,ab OR miscarry:ti,ab OR miscarriage*:ti,ab OR [mh Mortality] OR mortality:ti,ab OR [mh "Neonatal Abstinence Syndrome"] OR "Neonatal Respiratory Distress Syndrome":ti,ab OR [mh "Obstetric Labor, Premature"] OR [mh "Persistent Fetal Circulation Syndrome"] OR "Persistent Pulmonary Hypertension of Newborn":ti,ab OR [mh "Pre-Eclampsia"] OR preeclampsia:ti,ab OR "pre-eclampsia":ti,ab OR [mh "Premature Birth"] OR "premature birth":ti,ab OR "preterm birth":ti,ab OR "pre-term birth":ti,ab OR [mh "Prenatal Exposure Delayed Effects"] OR [mh "Prescription Drug Misuse"] OR ("Prescription Drug":ti,ab AND misuse:ti,ab) OR "preterm labor":ti,ab OR "pre-term labor":ti,ab OR [mh "Postpartum Hemorrhage"] OR [mh "Respiratory Distress Syndrome, Newborn"] OR [mh "Uterine Inertia"/CI]	102127
#14	#12 OR #13	507255
#15	#1 and #8 and #11 and #14	785
#16	(#15 AND [mh ^Humans]) OR (#15 NOT [mh ^Animals])	785
#17	editorial:pt OR case study:pt OR [mh "case reports"]	8739
#18	#10 not #17	441
#19	#16 not #17	779
#20	#19 not #18	548

Cochrane Library

6-5-2020

Search	Query	Results
#1	[mh "Anxiety Disorders"] OR anxiety:ti,ab OR [mh "Bipolar Disorder"] OR bipolar:ti,ab OR [mh "Depressive Disorder"] OR [mh "Depressive Disorder, Major"] OR [mh Depression] OR depress*:ti,ab OR depression:ti,ab OR depressive:ti,ab OR depressed:ti,ab OR [mh "Dysthymic Disorder"] OR dysthymia:ti,ab OR dysthymic:ti,ab OR [mh "Feeding AND Eating Disorders"] OR anorexia:ti,ab OR anorexic:ti,ab OR "binge eating":ti,ab OR bulimic:ti,ab OR bulimia:ti,ab OR GAD OR [mh "Psychotic Disorders"] OR "psychotic disorder":ti,ab OR "psychotic disorders":ti,ab OR psychosis:ti,ab OR psychoses:ti,ab OR (mental:ti,ab AND (health:ti,ab OR illness:ti,ab OR disorders:ti,ab)) OR [mh "Mental Health"] OR [mh "Mental Disorders"] OR [mh "Obsessive-Compulsive Disorder"] OR "Obsessive-Compulsive Disorder":ti,ab OR OCD:ti,ab OR "panic disorder" OR "Persistent Depressive Disorder":ti,ab OR phobia*:ti,ab OR phobic:ti,ab OR psychotic*:ti,ab OR [mh "Stress Disorders, Post-Traumatic"] OR "post-traumatic stress disorder" OR "post-traumatic stress disorders" OR "posttraumatic stress disorder" OR "posttraumatic stress disorders" OR (disorder* AND "post-traumatic":ti,ab) OR [mh ^"Stress Disorders, Traumatic"] OR PTSD:ti,ab OR [mh "Schizophrenia"] OR schizophren*:ti,ab OR "stress disorder"	175238
#2	alprazolam OR [mh "Anti-Anxiety Agents"] OR anti-anxiety OR antianxiety OR [mh "Amitriptyline"] OR amitriptyline OR [mh "Amoxapine"] OR amoxapine OR [mh Anticonvulsants] OR anticonvulsant OR anticonvulsants OR [mh "Antidepressive Agents"] OR [mh "Antidepressive Agents, Second-Generation"] OR anti-depress* OR antidepressant* OR antidepressive* OR [mh "Antipsychotic Agents"] OR antipsychotic* OR anxiolytic* OR [mh "Aripiprazole"] OR aripiprazole OR Asenapine OR benzodiazepine* OR brexanolone OR brexpiprazole OR [mh Bupropion] OR Bupropion OR [mh "Buspirone"] OR Buspirone OR [mh "Carbamazepine"] OR Carbamazepine OR Cariprazine OR [mh "Chlorpromazine"] OR Chlorpromazine OR [mh Citalopram] OR citalopram OR clobazam OR [mh Clomipramine] OR Clomipramine OR [mh "Clonazepam"] OR Clonazepam OR [mh "Clonidine"] OR Clonidine OR [mh "Clorazepate Dipotassium"] OR Clorazepate OR [mh "Chlordiazepoxide"] OR Chlordiazepoxide OR [mh "Clozapine"] OR clozapine	48106
#3	[mh "Desipramine"] OR Desipramine OR [mh "Desvenlafaxine Succinate"] OR Desvenlafaxine OR [mh "Diazepam"] OR Diazepam OR [mh "Diphenhydramine"] OR Diphenhydramine OR [mh "Doxepin"] OR doxepin OR [mh "Duloxetine Hydrochloride"] OR duloxetine OR escitalopram OR [mh "Eszopiclone"] OR eszopiclone OR [mh Fluoxetine] OR fluoxetine OR [mh "Fluphenazine"] OR fluphenazine OR [mh Fluvoxamine] OR fluvoxamine OR gabapentin OR [mh "Haloperidol"] OR Haloperidol OR [mh "Hydroxyzine"] OR Hydroxyzine OR iloperidone OR [mh "Imipramine"] OR imipramine OR lamotrigine OR Levomilnacipran [mh "Lisdexamfetamine Dimesylate"] OR [mh "Lithium Carbonate"] OR lithium OR [mh "Lorazepam"] OR lorazepam OR [mh "Lurasidone Hydrochloride"] OR lurasidone OR Maprotiline	27651
#4	milnacipran OR mirtazapine OR nefazodone OR "norepinephrine reuptake inhibitor" OR "norepinephrine reuptake inhibitors" OR [mh "Nortriptyline"] OR nortriptyline OR olanzapine OR oxcarbazepine OR [mh "Paliperidone Palmitate"] OR Paliperidone OR [mh Paroxetine] OR paroxetine OR [mh "Perphenazine"] OR perphenazine OR [mh "Protriptyline"] OR protriptyline OR [mh "Quetiapine Fumarate"] OR quetiapine OR ramelteon OR [mh "Risperidone"] OR risperidone OR "selective serotonin reuptake inhibitor" OR "selective serotonin reuptake inhibitors" OR [mh "Serotonin Uptake Inhibitors"] OR "serotonin norepinephrine reuptake inhibitor":ti,ab,kw OR "serotonin norepinephrine reuptake inhibitors":ti,ab,kw OR [mh Sertraline] OR sertraline OR SNRI* OR SSRI*	18539
#5	[mh "Temazepam"] OR Temazepam OR Thioridazine OR Thiothixine OR topiramate OR [mh Trazodone] OR trazodone OR [mh "Triazolam"] OR triazolam OR Trifluoperazine OR [mh "Trimipramine"] OR Trimipramine OR [mh "Valproic Acid"] OR valproate OR [mh "Venlafaxine Hydrochloride"] OR venlafaxine OR [mh "Vilazodone Hydrochloride"] OR vilazodone OR Vistaril OR vortioxetine OR Vyvanse OR zaleplon OR ziprasidone OR zolpidem	9442
#6	(#2 OR #3 OR #4 OR #5)	72329

Search	Query	Results
#7	(#1 AND #6)	42201
#8	[mh "Pregnant Women"] OR [mh Pregnancy] OR preconception:ti,ab OR pregnant:ti,ab OR pregnancy:ti,ab OR prenatal:ti,ab OR "post-partum":ti,ab OR postpartum:ti,ab OR postnatal:ti,ab OR perinatal:ti,ab OR antenatal:ti,ab OR [mh "Maternal Health Services"] OR "maternal health":ti,ab OR [mh "Infant Nutritional Physiological Phenomena"] OR [mh "Breast Feeding"] OR "breast feeding":ti,ab OR breastfeed*:ti,ab OR (breast:ti,ab AND fed:ti,ab) OR breastfed:ti,ab OR "Pregnancy Complications":ti,ab,kw OR "Maternal Welfare":ti,ab,kw OR gestation*:ti,ab OR maternal*:ti,ab OR [mh "Pregnancy Outcome"]	78260
#9	(#7 AND #8)	1127
#10	(#9 AND [mh ^Humans]) OR (#9 NOT [mh ^Animals])	1127
#11	[mh "Drug Therapy"] OR drug*:ti,ab OR pharmacotherap*:ti,ab OR pharmacologic*:ti,ab OR medicine*:ti,ab OR medication*:ti,ab	405459
#12	accident* OR "Adverse Effects" OR "adverse effect" OR "adverse event" OR "adverse events" OR "adverse outcome" OR "adverse outcomes" OR "adverse reaction" OR "adverse reactions" OR "chemically induced" OR complication* OR death* OR "Drug Allergies" OR "Drug Dependency" OR "drug effects" OR "Drug Sensitivity" OR harm* OR harms OR [mh "Long Term Adverse Effects"] OR "manic episode" OR overdos* OR "Patient Safety" OR poisoning OR self damage* OR self injur* OR self inflict* OR [mh "Self-Injurious Behavior"] OR "Side Effect" OR "side effects" OR Suicide OR suicidal* OR toxicity	590895
#13	[mh "Abortion, Spontaneous"] OR [mh "Abruptio Placentae"] OR abruption*:ti,ab OR [mh "Apgar Score"] OR [mh "Birth Weight"/CI] OR [mh "Birth Weight"/DE] OR [mh "Child Development Disorders, Pervasive"/CI] OR [mh "Child Development"/DE] OR [mh "Craniofacial Abnormalities"/CI] OR [mh "Congenital Abnormalities"] OR "congenital abnormality":ti,ab OR "congenital abnormalities":ti,ab OR death:ti,ab OR "delayed development":ti,ab,kw OR [mh "Glucose Intolerance"] OR "glucose intolerance":ti,ab OR [mh "Infant, Extremely Premature"/GD] OR (infant* AND (attachment* OR bonding)) OR [mh "Infertility, Female"] OR "Infantile Respiratory Distress Syndrome":ti,ab OR infertility:ti,ab OR ([mh "Intellectual Disability"] AND child*:ti,ab,kw) OR "Low APGAR":ti,ab OR miscarry:ti,ab OR miscarriage*:ti,ab OR [mh Mortality] OR mortality:ti,ab OR [mh "Neonatal Abstinence Syndrome"] OR "Neonatal Respiratory Distress Syndrome":ti,ab OR [mh "Obstetric Labor, Premature"] OR [mh "Persistent Fetal Circulation Syndrome"] OR "Persistent Pulmonary Hypertension of Newborn":ti,ab OR [mh "Pre-Eclampsia"] OR preeclampsia:ti,ab OR "pre-eclampsia":ti,ab OR [mh "Premature Birth"] OR "premature birth":ti,ab OR "preterm birth":ti,ab OR "pre-term birth":ti,ab OR [mh "Prenatal Exposure Delayed Effects"] OR [mh "Prescription Drug Misuse"] OR ("Prescription Drug":ti,ab AND misuse:ti,ab) OR "preterm labor":ti,ab OR "pre-term labor":ti,ab OR [mh "Postpartum Hemorrhage"] OR [mh "Respiratory Distress Syndrome, Newborn"] OR [mh "Uterine Inertia"/CI]	134167
#14	#12 OR #13	630035
#15	#1 AND #8 AND #11 AND #14	1673
#16	(#15 AND [mh ^Humans]) OR (#15 NOT [mh ^Animals])	1673
#17	editorial:pt OR case study:pt OR [mh "case reports"]	10833
#18	#10 not #17	1124
#19	#16 not #17	1666
#20	#19 not #18	1130

Embase

12-10-2018

No.	Query	Results
#1	'anxiety disorder'/exp/mj OR 'anxiety disorder' OR 'anxiety'/exp OR anxiety OR 'bipolar disorder'/exp/mj OR 'bipolar disorder' OR bipolar OR 'depression'/exp OR 'depression' OR depress* OR 'dysthymia' OR 'dysthymia'/exp OR dysthymia OR dysthymic OR 'eating disorder'/exp OR 'eating disorder' OR 'anorexia'/exp OR 'anorexia' OR 'anorexic'/exp OR anorexic OR 'binge eating'/exp OR 'binge eating' OR bulimic OR 'bulimia'/exp OR bulimia OR 'gad'/exp OR gad OR 'psychosis' OR 'psychotic disorder'/exp OR 'psychotic disorder' OR 'psychotic disorders'/exp OR 'psychotic disorders' OR 'psychosis'/exp OR psychosis OR 'psychoses'/exp OR psychoses OR (mental AND ('health'/exp OR health OR 'illness'/exp OR illness OR 'disorders'/exp OR disorders)) OR 'mental health'/exp OR 'mental health' OR 'mental disease'/exp OR 'mental disease' OR 'mental disorder'/exp OR 'mental disorder' OR 'mental disorders'/exp OR 'mental disorders' OR 'obsessive compulsive disorder'/exp OR 'obsessive compulsive disorder' OR 'obsessive-compulsive disorder'/exp OR 'obsessive-compulsive disorder' OR ocd OR 'panic disorder'/exp OR 'panic disorder' OR 'panic'/exp OR 'panic' OR 'persistent depressive disorder'/exp OR 'persistent depressive disorder' OR 'phobia'/exp OR 'phobia' OR phobia* OR phobic OR psychotic* OR 'post-traumatic stress disorder'/exp OR 'post-traumatic stress disorder' OR 'post-traumatic stress disorders' OR 'posttraumatic stress disorder'/exp OR 'posttraumatic stress disorder' OR 'posttraumatic stress disorders' OR (disorder* AND 'post-traumatic') OR 'acute stress disorder'/exp OR 'acute stress disorder' OR 'schizophrenia'/exp OR 'schizophrenia' OR schizophren* OR 'stress disorder' OR 'ptsd'/exp OR pts	2,834,461
#2	('anxiolytic agent'/exp OR 'anti anxiety' OR antianxiety OR 'amitriptyline'/exp OR amitriptyline OR 'amoxapine'/exp OR amoxapine OR 'anticonvulsive agent'/exp OR anticonvulsant OR anticonvulsants OR 'antidepressant agent'/exp) AND antidepressant* OR antidepressive* OR 'antidepressive agent' OR 'antidepressive agents' OR 'antidepressive drug' OR 'antidepressive drugs' OR 'neuroleptic agent'/exp OR antipsychotic* OR anxiolytic* OR 'aripiprazole'/exp OR aripiprazole OR 'asenapine'/exp OR asenapine OR benzodiazepine* OR 'brexanolone'/exp OR brexanolone OR 'brexpiprazole'/exp OR brexpiprazole OR 'amfebutamone'/exp OR bupropion OR 'buspirone'/exp OR buspirone OR 'carbamazepine'/exp OR carbamazepine OR 'cariprazine'/exp OR cariprazine OR 'chlorpromazine'/exp OR chlorpromazine OR 'citalopram'/exp OR citalopram OR 'clobazam'/exp OR clobazam OR clomipramine OR 'clonazepam'/exp OR clonazepam OR 'clonidine'/exp OR clonidine OR 'clorazepate'/exp OR clorazepate OR 'chlordiazepoxide'/exp OR chlordiazepoxide OR 'clozapine'/exp OR clozapine	560,87
#3	'desipramine'/exp OR desipramine OR 'desvenlafaxine'/exp OR desvenlafaxine OR 'diazepam'/exp OR diazepam OR 'diphenhydramine'/exp OR diphenhydramine OR 'doxepin'/exp OR doxepin OR 'duloxetine'/exp OR duloxetine OR 'escitalopram'/exp OR escitalopram OR 'eszopiclone'/exp OR eszopiclone OR 'fluoxetine'/exp OR fluoxetine OR 'fluphenazine'/exp OR fluphenazine OR 'fluvoxamine'/exp OR fluvoxamine OR 'gabapentin'/exp OR gabapentin OR 'haloperidol'/exp OR haloperidol OR 'hydroxyzine'/exp OR hydroxyzine OR 'iloperidone'/exp OR iloperidone OR 'imipramine'/exp OR imipramine OR 'lamotrigine'/exp OR lamotrigine OR levomilnacipran OR 'lisdexamfetamine'/exp OR 'lithium carbonate'/exp OR lithium OR 'lorazepam'/exp OR lorazepam OR 'lurasidone'/exp OR lurasidone OR maprotiline OR 'milnacipran'/exp OR milnacipran	361,628
#4	'mirtazapine'/exp OR mirtazapine OR 'nefazodone'/exp OR nefazodone OR 'noradrenalin uptake inhibitor'/exp OR 'norepinephrine reuptake inhibitors' OR 'nortriptyline'/exp OR nortriptyline OR 'olanzapine'/exp OR olanzapine OR 'oxcarbazepine'/exp OR oxcarbazepine OR 'paliperidone'/exp OR paliperidone OR 'paroxetine'/exp OR paroxetine OR 'perphenazine'/exp OR perphenazine OR 'protriptyline'/exp OR protriptyline OR 'quetiapine'/exp OR quetiapine OR 'ramelteon'/exp OR ramelteon OR 'risperidone'/exp OR risperidone OR 'serotonin uptake inhibitor'/exp OR 'selective serotonin reuptake inhibitor' OR 'selective serotonin reuptake inhibitors' OR 'serotonin noradrenalin reuptake inhibitor'/exp OR 'serotonin norepinephrine reuptake inhibitor' OR 'serotonin norepinephrine reuptake inhibitors' OR 'sertraline'/exp OR sertraline OR snri* OR ssri OR ssris	331,071
#5	'temazepam'/exp OR temazepam OR thioridazine OR thiothixene OR 'topiramate'/exp OR topiramate OR 'trazodone'/exp OR trazodone OR 'triazolam'/exp OR triazolam OR trifluoperazine OR 'trimipramine'/exp OR trimipramine OR 'valproic acid'/exp OR valproate OR 'venlafaxine'/exp OR venlafaxine OR 'vilazodone'/exp OR vilazodone OR vistaril OR 'vortioxetine'/exp OR vortioxetine OR 'zaleplon'/exp OR zaleplon OR 'ziprasidone'/exp OR ziprasidone OR 'zolpidem'/exp OR zolpidem	141,235
#6	#2 OR #3 OR #4 OR #5	851,104
#7	#1 AND #6	388,498

No.	Query	Results
#8	'pregnant woman'/exp OR 'pregnancy'/exp OR 'prepregnancy care'/exp OR preconception OR pregnant OR pregnancy OR prenatal OR 'post-partum' OR postpartum OR postnatal OR perinatal OR antenatal OR 'maternal health service'/exp OR 'maternal health' OR 'breast feeding'/exp OR 'breast feeding' OR breastfeed* OR (breast AND fed) OR breastfed OR 'pregnancy complication'/exp OR 'pregnancy complications' OR gestation* OR maternal* OR 'pregnancy outcome'/exp	1,483,983
#9	#7 AND #8	16,024
#10	#7 AND #8 AND [english]/lim	14,898
#11	#10 AND [humans]/lim OR (#10 NOT [animals]/lim)	12,536
#12	#11 AND ([medline]/lim OR [pubmed-not-medline]/lim)	8,123
#13	#11 NOT #12	4,413
#14	#13 AND ('case report'/de OR 'editorial'/it)	657
#15	#13 NOT #14	3,756
#16	'drug therapy'/exp OR 'drug therapy' OR drug* OR pharmacotherap* OR pharmacologic* OR medicine* OR medication*	16,864,660
#17	'accident'/exp OR accident* OR 'adverse event'/exp OR 'adverse effect' OR 'adverse event' OR 'adverse events' OR 'adverse outcome' OR 'adverse outcomes' OR 'adverse reaction' OR 'adverse reactions' OR 'chemically induced' OR complication* OR death* OR 'drug allergies' OR 'drug dependency' OR 'drug effects' OR 'drug sensitivity' OR 'harm reduction'/exp OR harm* OR harms OR 'adverse drug reaction'/exp OR 'manic episode' OR overdos* OR 'patient safety' OR poisoning OR (self AND damage*) OR (self AND injur*) OR (self AND inflict*) OR 'side effect' OR 'side effects' OR suicide OR suicidal* OR toxicity	6,755,371
#18	abruption OR 'apgar score'/exp OR 'birth weight'/exp OR ('chemically induced disorder'/exp AND child*) OR ('child development'/exp AND (dd_to:lnk OR dm_si:lnk)) OR 'congenital abnormalities etiology'/exp OR 'congenital abnormality' OR 'congenital abnormalities' OR 'craniofacial malformation'/exp OR 'death'/exp OR 'delayed development' OR 'dystocia'/exp OR 'extremely premature infant'/exp OR 'female infertility'/exp OR 'glucose intolerance'/exp OR 'glucose intolerance' OR (infant* AND (attachment* OR bonding)) OR 'infantile respiratory distress syndrome' OR (('intellectual impairment'/exp OR 'intellectual disability') AND child*) OR 'low apgar' OR miscarry OR miscarriage* OR 'mortality'/exp OR mortality OR 'neonatal abstinence syndrome'/exp OR 'neonatal respiratory distress syndrome'/exp OR 'neonatal respiratory distress syndrome' OR ('persistent pulmonary hypertension'/exp AND fetal) OR 'persistent pulmonary hypertension of newborn' OR 'preeclampsia'/exp OR preeclampsia OR 'pre eclampsia' OR 'premature labor'/exp OR 'prematurity'/exp OR 'premature birth' OR 'preterm birth' OR 'pre-term birth' OR 'preterm labor' OR 'pre-term labor' OR 'prenatal exposure'/exp OR 'prescription drug misuse'/exp OR ('prescription drug' AND misuse) OR 'postpartum hemorrhage'/exp OR 'solutio placentae'/exp OR 'spontaneous abortion'/exp	2,281,378
#19	#17 OR #18	7,768,027
#20	#1 AND #8 AND #16 AND #19	45,429
#21	#20 AND [english]/lim	42,503
#22	#21 AND [humans]/lim OR (#21 NOT [animals]/lim)	37,678
#23	#22 AND ([medline]/lim OR [pubmed-not-medline]/lim)	25,770
#24	#22 NOT #23	11,914
#25	#24 NOT #15	9,679
#26	#25 AND ('case report'/de OR 'editorial'/it)	1,676
#27	#25 NOT #26	8,003

Embase

6-4-2020

No.	Query	Results
#1	'anxiety disorder'/exp/mj OR 'anxiety disorder' OR 'anxiety'/exp OR anxiety OR 'bipolar disorder'/exp/mj OR 'bipolar disorder' OR bipolar OR 'depression'/exp OR 'depression' OR depress* OR 'dysthymia' OR 'dysthymia'/exp OR dysthymia OR dysthymic OR 'eating disorder'/exp OR 'eating disorder' OR 'anorexia'/exp OR 'anorexia' OR 'anorexic'/exp OR anorexic OR 'binge eating'/exp OR 'binge eating' OR bulimic OR 'bulimia'/exp OR bulimia OR 'gad'/exp OR gad OR 'psychosis' OR 'psychotic disorder'/exp OR 'psychotic disorder' OR 'psychotic disorders'/exp OR 'psychotic disorders' OR 'psychosis'/exp OR psychosis OR 'psychoses'/exp OR psychoses OR (mental AND ('health'/exp OR health OR 'illness'/exp OR illness OR 'disorders'/exp OR disorders)) OR 'mental health'/exp OR 'mental health' OR 'mental disease'/exp OR 'mental disease' OR 'mental disorder'/exp OR 'mental disorder' OR 'mental disorders'/exp OR 'mental disorders' OR 'obsessive compulsive disorder'/exp OR 'obsessive compulsive disorder' OR 'obsessive-compulsive disorder'/exp OR 'obsessive-compulsive disorder' OR ocd OR 'panic disorder'/exp OR 'panic disorder' OR 'panic'/exp OR 'panic' OR 'persistent depressive disorder'/exp OR 'persistent depressive disorder' OR 'phobia'/exp OR 'phobia' OR phobia* OR phobic OR psychotic* OR 'post-traumatic stress disorder'/exp OR 'post-traumatic stress disorder' OR 'post-traumatic stress disorders' OR 'posttraumatic stress disorder'/exp OR 'posttraumatic stress disorder' OR 'posttraumatic stress disorders' OR (disorder* AND 'post-traumatic') OR 'acute stress disorder'/exp OR 'acute stress disorder' OR 'schizophrenia'/exp OR 'schizophrenia' OR schizophren* OR 'stress disorder' OR 'ptsd'/exp OR ptsd	3,112,575
#2	('anxiolytic agent'/exp OR 'anti anxiety' OR antianxiety OR 'amitriptyline'/exp OR amitriptyline OR 'amoxapine'/exp OR amoxapine OR 'anticonvulsive agent'/exp OR anticonvulsant OR anticonvulsants OR 'antidepressant agent'/exp) AND antidepressant* OR antidepressive* OR 'antidepressive agent' OR 'antidepressive agents' OR 'antidepressive drug' OR 'antidepressive drugs' OR 'neuroleptic agent'/exp OR antipsychotic* OR anxiolytic* OR 'aripiprazole'/exp OR aripiprazole OR 'asenapine'/exp OR asenapine OR benzodiazepine* OR 'brexanolone'/exp OR brexanolone OR 'brexpiprazole'/exp OR brexpiprazole OR 'amfebutamone'/exp OR bupropion OR 'buspirone'/exp OR buspirone OR 'carbamazepine'/exp OR carbamazepine OR 'cariprazine'/exp OR cariprazine OR 'chlorpromazine'/exp OR chlorpromazine OR 'citalopram'/exp OR citalopram OR 'clobazam'/exp OR clobazam OR clomipramine OR 'clonazepam'/exp OR clonazepam OR 'clonidine'/exp OR clonidine OR 'clorazepate'/exp OR clorazepate OR 'chlordiazepoxide'/exp OR chlordiazepoxide OR 'clozapine'/exp OR clozapine	590,700
#3	'desipramine'/exp OR desipramine OR 'desvenlafaxine'/exp OR desvenlafaxine OR 'diazepam'/exp OR diazepam OR 'diphenhydramine'/exp OR diphenhydramine OR 'doxepin'/exp OR doxepin OR 'duloxetine'/exp OR duloxetine OR 'escitalopram'/exp OR escitalopram OR 'eszopiclone'/exp OR eszopiclone OR 'fluoxetine'/exp OR fluoxetine OR 'fluphenazine'/exp OR fluphenazine OR 'fluvoxamine'/exp OR fluvoxamine OR 'gabapentin'/exp OR gabapentin OR 'haloperidol'/exp OR haloperidol OR 'hydroxyzine'/exp OR hydroxyzine OR 'iloperidone'/exp OR iloperidone OR 'imipramine'/exp OR imipramine OR 'lamotrigine'/exp OR lamotrigine OR levomilnacipran OR 'lisdexamfetamine'/exp OR 'lithium carbonate'/exp OR lithium OR 'lorazepam'/exp OR lorazepam OR 'lurasidone'/exp OR lurasidone OR maprotiline OR 'milnacipran'/exp OR milnacipran	384,886
#4	'mirtazapine'/exp OR mirtazapine OR 'nefazodone'/exp OR nefazodone OR 'noradrenalin uptake inhibitor'/exp OR 'norepinephrine reuptake inhibitors' OR 'nortriptyline'/exp OR nortriptyline OR 'olanzapine'/exp OR olanzapine OR 'oxcarbazepine'/exp OR oxcarbazepine OR 'paliperidone'/exp OR paliperidone OR 'paroxetine'/exp OR paroxetine OR 'perphenazine'/exp OR perphenazine OR 'protriptyline'/exp OR protriptyline OR 'quetiapine'/exp OR quetiapine OR 'ramelteon'/exp OR ramelteon OR 'risperidone'/exp OR risperidone OR 'serotonin uptake inhibitor'/exp OR 'selective serotonin reuptake inhibitor' OR 'selective serotonin reuptake inhibitors' OR 'serotonin noradrenalin reuptake inhibitor'/exp OR 'serotonin norepinephrine reuptake inhibitor' OR 'serotonin norepinephrine reuptake inhibitors' OR 'sertraline'/exp OR sertraline OR snri* OR ssri OR ssris	365,931
#5	'temazepam'/exp OR temazepam OR thioridazine OR thiothixene OR 'topiramate'/exp OR topiramate OR 'trazodone'/exp OR trazodone OR 'triazolam'/exp OR triazolam OR trifluoperazine OR 'trimipramine'/exp OR trimipramine OR 'valproic acid'/exp OR valproate OR 'venlafaxine'/exp OR venlafaxine OR 'vilazodone'/exp OR vilazodone OR vistaril OR 'vortioxetine'/exp OR vortioxetine OR 'zaleplon'/exp OR zaleplon OR 'ziprasidone'/exp OR ziprasidone OR 'zolpidem'/exp OR zolpidem	149,136
#6	#2 OR #3 OR #4 OR #5	916,325
#7	#1 AND #6	417,309

No.	Query	Results
#8	'pregnant woman'/exp OR 'pregnancy'/exp OR 'prepregnancy care'/exp OR preconception OR pregnant OR pregnancy OR prenatal OR 'post-partum' OR postpartum OR postnatal OR perinatal OR antenatal OR 'maternal health service'/exp OR 'maternal health' OR 'breast feeding'/exp OR 'breast feeding' OR breastfeed* OR (breast AND fed) OR breastfed OR 'pregnancy complication'/exp OR 'pregnancy complications' OR gestation* OR maternal* OR 'pregnancy outcome'/exp	1,602,653
#9	#7 AND #8	17,798
#10	#7 AND #8 AND [english]/lim	16,630
#11	#10 AND [humans]/lim OR (#10 NOT [animals]/lim)	13,950
#12	#11 AND ([medline]/lim OR [pubmed-not-medline]/lim)	9,279
#13	#11 NOT #12	4,671
#14	#13 AND ('case report'/de OR 'editorial'/it)	711
#15	#13 NOT #14	3,960
#16	'drug therapy'/exp OR 'drug therapy' OR drug* OR pharmacotherap* OR pharmacologic* OR medicine* OR medication*	18,908,546
#17	'accident'/exp OR accident* OR 'adverse event'/exp OR 'adverse effect' OR 'adverse event' OR 'adverse events' OR 'adverse outcome' OR 'adverse outcomes' OR 'adverse reaction' OR 'adverse reactions' OR 'chemically induced' OR complication* OR death* OR 'drug allergies' OR 'drug dependency' OR 'drug effects' OR 'drug sensitivity' OR 'harm reduction'/exp OR harm* OR harms OR 'adverse drug reaction'/exp OR 'manic episode' OR overdos* OR 'patient safety' OR poisoning OR (self AND damage*) OR (self AND injur*) OR (self AND inflict*) OR 'side effect' OR 'side effects' OR suicide OR suicidal* OR toxicity	7,370,502
#18	abruption OR 'apgar score'/exp OR 'birth weight'/exp OR ('chemically induced disorder'/exp AND child*) OR ('child development'/exp AND (dd_to:lnk OR dm_si:lnk)) OR 'congenital abnormalities etiology'/exp OR 'congenital abnormality' OR 'congenital abnormalities' OR 'craniofacial malformation'/exp OR 'death'/exp OR 'delayed development' OR 'dystocia'/exp OR 'extremely premature infant'/exp OR 'female infertility'/exp OR 'glucose intolerance'/exp OR 'glucose intolerance' OR (infant* AND (attachment* OR bonding)) OR 'infantile respiratory distress syndrome' OR (('intellectual impairment'/exp OR 'intellectual disability') AND child*) OR 'low apgar' OR miscarry OR miscarriage* OR 'mortality'/exp OR mortality OR 'neonatal abstinence syndrome'/exp OR 'neonatal respiratory distress syndrome'/exp OR 'neonatal respiratory distress syndrome' OR ('persistent pulmonary hypertension'/exp AND fetal) OR 'persistent pulmonary hypertension of newborn' OR 'preeclampsia'/exp OR preeclampsia OR 'pre eclampsia' OR 'premature labor'/exp OR 'prematurity'/exp OR 'premature birth' OR 'preterm birth' OR 'pre-term birth' OR 'preterm labor' OR 'pre-term labor' OR 'prenatal exposure'/exp OR 'prescription drug misuse'/exp OR ('prescription drug' AND misuse) OR 'postpartum hemorrhage'/exp OR 'solutio placentae'/exp OR 'spontaneous abortion'/exp	2,533,578
#19	#17 OR #18	8,500,781
#20	#1 AND #8 AND #16 AND #19	51,856
#21	#20 AND [english]/lim	48,832
#22	#21 AND [humans]/lim OR (#21 NOT [animals]/lim)	43,352
#23	#22 AND ([medline]/lim OR [pubmed-not-medline]/lim)	30,464
#24	#22 NOT #23	12,888
#25	#24 NOT #15	10,537
#26	#25 AND ('case report'/de OR 'editorial'/it)	1,966
#27	#25 NOT #26	8,573
#28	(#15 OR #27) AND '(retraction of publication or retracted publication).pt'	0
#29	(#15 OR #27) AND erratum	6
#30	#15 AND [2018-2020]/py	544
#31	#27 AND [2018-2020]/py	1,721

PsycINFO
12-11-2018

#	Query	Limiters/ Expanders	Results
1	DE "Anxiety Disorders" OR DE "Acute Stress Disorder" OR DE "Death Anxiety" OR DE "Generalized Anxiety Disorder" OR DE "Obsessive Compulsive Disorder" OR DE "Panic Disorder" OR DE "Phobias" OR DE "Post-Traumatic Stress" OR DE "Posttraumatic Stress Disorder" OR DE "Separation Anxiety Disorder" OR anxiety OR DE "Bipolar Disorder" OR bipolar OR DE "Major Depression" OR DE "Anaclitic Depression" OR DE "Dysthymic Disorder" OR DE "Endogenous Depression" OR DE "Late Life Depression" OR DE "Postpartum Depression" OR DE "Reactive Depression" OR DE "Recurrent Depression" OR DE "Treatment Resistant Depression" OR dysthymia OR dysthymic OR DE "Feeding Disorders" OR DE "Eating Disorders" OR DE "Anorexia Nervosa" OR DE "Binge Eating Disorder" OR DE "Bulimia" OR DE "Hyperphagia" OR DE "Purging (Eating Disorders)" OR anorexia OR anorexic OR "binge eating" OR bulimic OR bulimia OR GAD OR DE "Acute Psychosis" OR DE "Psychosis" OR DE "Acute Psychosis" OR DE "Affective Psychosis" OR DE "Chronic Psychosis" OR DE "Experimental Psychosis" OR DE "Hallucinosis" OR DE "Paranoia (Psychosis)" OR DE "Postpartum Psychosis" OR DE "Reactive Psychosis" OR DE "Toxic Psychoses" OR "psychotic disorder" OR "psychotic disorders" OR psychosis OR psychoses OR (mental AND (health OR illness OR disorder*)) OR "Mental Health"[Mesh] OR DE "Mental Disorders" OR DE "Adjustment Disorders" OR DE "Affective Disorders" OR DE "Anxiety Disorders" OR DE "Chronic Mental Illness" OR DE "Dementia" OR DE "Dissociative Disorders" OR DE "Hysteria" OR DE "Mental Disorders due to General Medical Conditions" OR DE "Neurosis" OR DE "Personality Disorders" OR DE "Obsessive Compulsive Disorder" OR DE "Substance/Medication Induced Obsessive-Compulsive Disorder" OR "Obsessive-Compulsive Disorder" OR OCD OR DE "Panic Disorder" OR "panic disorder" OR "Persistent Depressive Disorder" OR phobia* OR phobic OR psychotic* OR DE "Post-Traumatic Stress" OR "post-traumatic stress disorder" OR "post-traumatic stress disorders" OR "posttraumatic stress disorder" OR "posttraumatic stress disorders" OR (disorder* AND "post-traumatic") OR PTSD OR DE "Schizophrenia" OR DE "Acute Schizophrenia" OR DE "Catatonic Schizophrenia" OR DE "Paranoid Schizophrenia" OR DE "Process Schizophrenia" OR DE "Schizophrenia (Disorganized Type)" OR DE "Schizophreniform Disorder" OR DE "Undifferentiated Schizophrenia" OR schizophren* OR "stress disorder" OR “stress disorders”		1,188,879
2	(alprazolam OR "Anti-Anxiety Agents" OR anti-anxiety OR antianxiety OR DE "Tranquilizing Drugs" OR DE "Amitriptyline" OR DE "Doxepin" OR DE "Haloperidol" OR DE "Minor Tranquilizers" OR DE "Neuroleptic Drugs" OR amitriptyline OR OR amoxapine OR DE "Anticonvulsive Drugs" OR anticonvulsant OR anticonvulsants OR DE "Antidepressant Drugs" OR "Antidepressive Agents, Second-Generation" OR anti-depress* OR antidepressant* OR antidepressive* OR "antidepressive agent" OR "antidepressive agents" OR "antidepressive drug" OR "antidepressive drugs" OR antipsychotic* OR anxiolytic* OR DE "Aripiprazole" OR aripiprazole OR Asenapine OR DE "Benzodiazepines" OR benzodiazepine* OR brexanolone OR brexpiprazole OR DE "Bupropion" OR Bupropion OR DE "Buspirone" OR Buspirone OR DE "Carbamazepine" OR Carbamazepine OR Cariprazine OR DE "Chlorpromazine" OR Chlorpromazine OR DE "Citalopram" OR citalopram OR clobazam OR clomipramine OR DE "Clonazepam" OR Clonazepam OR DE "Clonidine" OR Clonidine OR Clorazepate OR DE "Chlordiazepoxide" OR Chlordiazepoxide OR DE "Clozapine" OR clozapine	Search modes - Boolean/Phrase	123,726

#	Query	Limiters/ Expanders	Results
3	DE "Desipramine" OR Desipramine OR Desvenlafaxine OR DE "Diazepam" OR Diazepam OR DE "Diphenhydramine" OR Diphenhydramine OR DE "Doxepin" OR doxepin OR duloxetine OR escitalopram OR eszopiclone OR DE "Fluoxetine" OR fluoxetine OR DE "Fluphenazine" OR fluphenazine OR DE "Fluvoxamine" OR fluvoxamine OR DE "Gabapentin" OR gabapentin OR DE "Haloperidol" OR Haloperidol OR DE "Hydroxyzine" OR Hydroxyzine OR iloperidone OR DE "Imipramine" OR imipramine OR lamotrigine OR Levomilnacipran OR "Lisdexamfetamine Dimesylate" OR DE "Lithium" OR lithium OR DE "Lorazepam" OR lorazepam OR lurasidone OR Maprotiline OR milnacipran	Search modes - Boolean/Phrase	46,720
4	mirtazapine OR DE "Nefazodone" OR nefazodone OR DE "Neuroleptic Drugs" OR "norepinephrine reuptake inhibitor" OR "norepinephrine reuptake inhibitors" OR DE "Nortriptyline" OR nortriptyline OR DE "Olanzapine" OR olanzapine OR oxcarbazepine OR Paliperidone OR DE "Paroxetine" OR paroxetine OR DE "Perphenazine" OR perphenazine OR protriptyline OR Prozac OR DE "Quetiapine" OR quetiapine OR ramelteon OR DE "Risperidone" OR risperidone OR DE "Serotonin Reuptake Inhibitors" OR "selective serotonin reuptake inhibitor" OR "selective serotonin reuptake inhibitors" OR DE "Serotonin Norepinephrine Reuptake Inhibitors" OR "serotonin norepinephrine reuptake inhibitor" OR "serotonin norepinephrine reuptake inhibitors" OR DE "Sertraline" OR sertraline OR SNRI* OR SSRI OR SSRIs	Search modes - Boolean/Phrase	43,811
5	Temazepam OR Thioridazine OR Thiothixene OR Topiramate OR DE "Tranquilizing Drugs" OR DE "Trazodone" OR trazodone OR DE "Triazolam" OR triazolam OR Trifluoperazine OR Trimipramine OR DE "Valproic Acid" OR valproate OR DE "Venlafaxine" OR venlafaxine OR vilazodone OR Vistaril OR vortioxetine OR zaleplon OR ziprasidone OR zolpidem	Search modes - Boolean/Phrase	16,407
6	S2 or S3 or S4 or S5	Search modes - Boolean/Phrase	145,539
7	S1 and S6	Search modes - Boolean/Phrase	101,270
8	DE "Pregnancy" OR preconception[tiab] OR pregnant" OR pregnancy OR prenatal OR "post-partum" OR postpartum OR postnatal OR perinatal OR antenatal OR "Maternal Health Services" OR "maternal health" OR "Infant Nutritional Physiological Phenomena" OR "Breast Feeding"[Mesh] OR "breast feeding" OR breastfeed* OR (breast AND fed) OR breastfed OR "Maternal Welfare" OR gestation* OR maternal*	Search modes - Boolean/Phrase	97,482
9	S7 and S8	Search modes - Boolean/Phrase	1,827
10	S7 and S8	Limiters - English Search modes - Boolean/Phrase	1,773
11	S10	Limiters - Population Group: Human Search modes - Boolean/Phrase	1,328
12	S10	Limiters - Population Group: Animal Search modes - Boolean/Phrase	435
13	S10 not S12	Limiters - Population Group: Animal Search modes - Boolean/Phrase	0
14	S11 or S13	Search modes - Boolean/Phrase	1,328

#	Query	Limiters/ Expanders	Results
15	DE "Case Report"	Search modes - Boolean/Phrase	22,842
16	S14 not S15	Search modes - Boolean/Phrase	1,284
17	PZ editorial	Search modes - Boolean/Phrase	42,667
18	S16 NOT S17	Search modes - Boolean/Phrase	1,271
19	DE "Drug Therapy" OR "drug therapy" OR drug*[tiab] OR pharmacotherap*: ti,ab OR pharmacologic* OR medicine* OR medication*	Search modes - Boolean/Phrase	700,317
20	DE "Accidents" OR accident* OR "adverse effects" OR "adverse effect" or "adverse event" OR "adverse events" OR "adverse outcome" OR "adverse outcomes" OR "adverse reaction" OR "adverse reactions" OR "chemically induced" OR complication* OR DE "Death and Dying" OR death* OR DE "Drug Allergies" OR "Drug Allergies" OR DE "Drug Dependency" OR "Drug Dependency" OR "drug effects" OR DE "Drug Sensitivity" OR "Drug Sensitivity" OR DE "Harm Reduction" OR harm* OR harms OR "manic episode" OR overdos* OR DE "Patient Safety" OR "Patient Safety" OR poisoning OR DE "Self-Destructive Behavior" OR DE "Attempted Suicide" OR DE "Head Banging" OR DE "Self-Inflicted Wounds" OR DE "Self-Injurious Behavior" OR DE "Self-Mutilation" OR DE "Suicide" OR self damage* OR self injur* OR self inflict* OR "Self-Injurious Behavior" OR DE "Sequelae" OR DE "Side Effects (Drug)" OR "Side Effect" OR "side effects" OR Suicide OR suicidal* OR DE "Toxic Disorders" OR toxicity	Search modes - Boolean/Phrase	382,221
21	Abruption* OR DE "Agenesis" OR "Apgar Score" OR DE "Anencephaly" OR (DE "Birth Weight" AND chemical*) OR (DE "Birth Weight" AND chemical*) OR DE "Childhood Development" OR DE "Cleft Palate" OR DE "Congenital Disorders" OR "congenital abnormality" OR "congenital abnormalities" OR DE "Conjoined Twins" OR ("Craniofacial Abnormalities" AND chemical*) OR death OR DE "Death and Dying" OR DE "Delayed Development" OR DE "Delayed Speech" OR DE "Developmental Disabilities" OR DE "Down's Syndrome" OR "Drug Induced Congenital Disorders" OR DE "Failure to Thrive" OR "Glucose Intolerance" OR DE "Hemorrhage" OR DE "Hermaphroditism" OR (infant* AND (DE "Attachment Behavior" OR attachment* OR bonding)) OR "Infantile Respiratory Distress Syndrome" OR DE "Infertility" OR ("Intellectual Disability" AND child*) OR DE "Klinefelters Syndrome" OR DE "Language Delay" OR ((DE "Learning Disabilities" OR DE "Multiple Disabilities" OR DE "Reading Disabilities") AND child*) OR "Low APGAR" OR DE "Microcephaly" OR miscarry OR miscarriage* OR mortality OR "Neonatal Abstinence Syndrome" OR DE "Neonatal Disorders" OR "Neonatal Respiratory Distress Syndrome" OR "Persistent Fetal Circulation Syndrome" OR "Persistent Pulmonary Hypertension of Newborn" OR DE "Phenylketonuria" OR "Postpartum Hemorrhage" OR DE "Prader Willi Syndrome" OR DE "Preeclampsia" OR preeclampsia OR pre-eclampsia OR DE "Premature Birth" OR "premature birth" OR "Premature labor" OR "Prescription Drug Misuse" OR ("Prescription Drug" AND misuse) OR "preterm birth" OR "pre-term birth" OR "preterm labor" OR "pre-term labor" OR DE "Prenatal Exposure" OR ("Respiratory Distress Syndrome" AND newborn) OR DE "Spina Bifida" OR DE "Spontaneous Abortion" OR DE "Tay Sachs Disease" OR DE "Turners Syndrome" OR ("Uterine Inertia" AND chemical*)	Search modes - Boolean/Phrase	260,875
22	S20 or S21	Search modes - Boolean/Phrase	529,322
23	S1 and S8 and S19 and S22	Search modes - Boolean/Phrase	4,407
24	S23	Limiters - English Search modes - Boolean/Phrase	4,364

#	Query	Limiters/ Expanders	Results
25	S24	Limiters - Population Group: Human Search modes - Boolean/Phrase	3,999
26	S24	Limiters - Population Group: Animal Search modes - Boolean/Phrase	275
27	S24 not S26	Search modes - Boolean/Phrase	4,089
28	S25 or S27	Search modes - Boolean/Phrase	4,139
29	S28 NOT (DE "Case Report" OR PZ Editorial)	Search modes - Boolean/Phrase	4,067
30	S29 NOT S18	Search modes - Boolean/Phrase	3,393

PsycINFO
6-4-2020

#	Query	Limiters/ Expanders	Results
S1	DE "Anxiety Disorders" OR DE "Acute Stress Disorder" OR DE "Death Anxiety" OR DE "Generalized Anxiety Disorder" OR DE "Obsessive Compulsive Disorder" OR DE "Panic Disorder" OR DE "Phobias" OR DE "Post-Traumatic Stress" OR DE "Posttraumatic Stress Disorder" OR DE "Separation Anxiety Disorder" OR anxiety OR DE "Bipolar Disorder" OR bipolar OR DE "Major Depression" OR DE "Anaclitic Depression" OR DE "Dysthymic Disorder" OR DE "Endogenous Depression" OR DE "Late Life Depression" OR DE "Postpartum Depression" OR DE "Reactive Depression" OR DE "Recurrent Depression" OR DE "Treatment Resistant Depression" OR dysthymia OR dysthymic OR DE "Feeding Disorders" OR DE "Eating Disorders" OR DE "Anorexia Nervosa" OR DE "Binge Eating Disorder" OR DE "Bulimia" OR DE "Hyperphagia" OR DE "Purging (Eating Disorders)" OR anorexia OR anorexic OR "binge eating" OR bulimic OR bulimia OR GAD OR DE "Acute Psychosis" OR DE "Psychosis" OR DE "Acute Psychosis" OR DE "Affective Psychosis" OR DE "Chronic Psychosis" OR DE "Experimental Psychosis" OR DE "Hallucinosis" OR DE "Paranoia (Psychosis)" OR DE "Postpartum Psychosis" OR DE "Reactive Psychosis" OR DE "Toxic Psychoses" OR "psychotic disorder" OR "psychotic disorders" OR psychosis OR psychoses OR (mental AND (health OR illness OR disorder*)) OR "Mental Health"[Mesh] OR DE "Mental Disorders" OR DE "Adjustment Disorders" OR DE "Affective Disorders" OR DE "Anxiety Disorders" OR DE "Chronic Mental Illness" OR DE "Dementia" OR DE "Dissociative Disorders" OR DE "Hysteria" OR DE "Mental Disorders due to General Medical Conditions" OR DE "Neurosis" OR DE "Personality Disorders" OR DE "Obsessive Compulsive Disorder" OR DE "Substance/Medication Induced Obsessive-Compulsive Disorder" OR "Obsessive-Compulsive Disorder" OR OCD OR DE "Panic Disorder" OR "panic disorder" OR "Persistent Depressive Disorder" OR phobia* OR phobic OR psychotic* OR DE "Post-Traumatic Stress" OR "post-traumatic stress disorder" OR "post-traumatic stress disorders" OR "posttraumatic stress disorder" OR "posttraumatic stress disorders" OR (disorder* AND "post-traumatic") OR PTSD OR DE "Schizophrenia" OR DE "Acute Schizophrenia" OR DE "Catatonic Schizophrenia" OR DE "Paranoid Schizophrenia" OR DE "Process Schizophrenia" OR DE "Schizophrenia (Disorganized Type)" OR DE "Schizophreniform Disorder" OR DE "Undifferentiated Schizophrenia" OR schizophren* OR "stress disorder" OR “stress disorders”		1,266,162
S2	(alprazolam OR "Anti-Anxiety Agents" OR anti-anxiety OR antianxiety OR DE "Tranquilizing Drugs" OR DE "Amitriptyline" OR DE "Doxepin" OR DE "Haloperidol" OR DE "Minor Tranquilizers" OR DE "Neuroleptic Drugs" OR amitriptyline OR OR amoxapine OR DE "Anticonvulsive Drugs" OR anticonvulsant OR anticonvulsants OR DE "Antidepressant Drugs" OR "Antidepressive Agents, Second-Generation" OR anti-depress* OR antidepressant* OR antidepressive* OR "antidepressive agent" OR "antidepressive agents" OR "antidepressive drug" OR "antidepressive drugs" OR antipsychotic* OR anxiolytic* OR DE "Aripiprazole" OR aripiprazole OR Asenapine OR DE "Benzodiazepines" OR benzodiazepine* OR brexanolone OR brexpiprazole OR DE "Bupropion" OR Bupropion OR DE "Buspirone" OR Buspirone OR DE "Carbamazepine" OR Carbamazepine OR Cariprazine OR DE "Chlorpromazine" OR Chlorpromazine OR DE "Citalopram" OR citalopram OR clobazam OR clomipramine OR DE "Clonazepam" OR Clonazepam OR DE "Clonidine" OR Clonidine OR Clorazepate OR DE "Chlordiazepoxide" OR Chlordiazepoxide OR DE "Clozapine" OR clozapine	Search modes - Boolean/Phrase	129,042

#	Query	Limiters/ Expanders	Results
S3	DE "Desipramine" OR Desipramine OR Desvenlafaxine OR DE "Diazepam" OR Diazepam OR DE "Diphenhydramine" OR Diphenhydramine OR DE "Doxepin" OR doxepin OR duloxetine OR escitalopram OR eszopiclone OR DE "Fluoxetine" OR fluoxetine OR DE "Fluphenazine" OR fluphenazine OR DE "Fluvoxamine" OR fluvoxamine OR DE "Gabapentin" OR gabapentin OR DE "Haloperidol" OR Haloperidol OR DE "Hydroxyzine" OR Hydroxyzine OR iloperidone OR DE "Imipramine" OR imipramine OR lamotrigine OR Levomilnacipran OR "Lisdexamfetamine Dimesylate" OR DE "Lithium" OR lithium OR DE "Lorazepam" OR lorazepam OR lurasidone OR Maprotiline OR milnacipran	Search modes - Boolean/Phrase	49,631
S4	mirtazapine OR DE "Nefazodone" OR nefazodone OR DE "Neuroleptic Drugs" OR "norepinephrine reuptake inhibitor" OR "norepinephrine reuptake inhibitors" OR DE "Nortriptyline" OR nortriptyline OR DE "Olanzapine" OR olanzapine OR oxcarbazepine OR Paliperidone OR DE "Paroxetine" OR paroxetine OR DE "Perphenazine" OR perphenazine OR protriptyline OR Prozac OR DE "Quetiapine" OR quetiapine OR ramelteon OR DE "Risperidone" OR risperidone OR DE "Serotonin Reuptake Inhibitors" OR "selective serotonin reuptake inhibitor" OR "selective serotonin reuptake inhibitors" OR DE "Serotonin Norepinephrine Reuptake Inhibitors" OR "serotonin norepinephrine reuptake inhibitor" OR "serotonin norepinephrine reuptake inhibitors" OR DE "Sertraline" OR sertraline OR SNRI* OR SSRI OR SSRIs	Search modes - Boolean/Phrase	47,743
S5	Temazepam OR Thioridazine OR Thiothixene OR Topiramate OR DE "Tranquilizing Drugs" OR DE "Trazodone" OR trazodone OR DE "Triazolam" OR triazolam OR Trifluoperazine OR Trimipramine OR DE "Valproic Acid" OR valproate OR DE "Venlafaxine" OR venlafaxine OR vilazodone OR Vistaril OR vortioxetine OR zaleplon OR ziprasidone OR zolpidem	Search modes - Boolean/Phrase	16,983
S6	S2 OR S3 OR S4 OR S5	Search modes - Boolean/Phrase	152,221
S7	S1 AND S6	Search modes - Boolean/Phrase	106,198
S8	DE "Pregnancy" OR preconception[tiab] OR pregnant" OR pregnancy OR prenatal OR "post-partum" OR postpartum OR postnatal OR perinatal OR antenatal OR "Maternal Health Services" OR "maternal health" OR "Infant Nutritional Physiological Phenomena" OR "Breast Feeding"[Mesh] OR "breast feeding" OR breastfeed* OR (breast AND fed) OR breastfed OR "Maternal Welfare" OR gestation* OR maternal*	Search modes - Boolean/Phrase	103,648
S9	S7 AND S8	Search modes - Boolean/Phrase	1,981
S10	S7 AND S8	Limiters - English Search modes - Boolean/Phrase	1,925
S11	S10	Limiters - Population Group: Human Search modes - Boolean/Phrase	1,436
S12	S10	Limiters - Population Group: Animal Search modes - Boolean/Phrase	479
S13	S10 not S12	Limiters - Population Group: Animal Search modes - Boolean/Phrase	0

#	Query	Limiters/ Expanders	Results
S14	S11 OR S13	Search modes - Boolean/Phrase	1,436
S15	DE "Case Report"	Search modes - Boolean/Phrase	22,945
S16	S14 not S15	Search modes - Boolean/Phrase	1,392
S17	PZ editorial	Search modes - Boolean/Phrase	44,005
S18	S16 NOT S17	Search modes - Boolean/Phrase	1,379
S19	DE "Drug Therapy" OR "drug therapy" OR drug*[tiab] OR pharmacotherap*: ti,ab OR pharmacologic* OR medicine* OR medication*	Search modes - Boolean/Phrase	766,776
S20	DE "Accidents" OR accident* OR "adverse effects" OR "adverse effect" OR "adverse event" OR "adverse events" OR "adverse outcome" OR "adverse outcomes" OR "adverse reaction" OR "adverse reactions" OR "chemically induced" OR complication* OR DE "Death AND Dying" OR death* OR DE "Drug Allergies" OR "Drug Allergies" OR DE "Drug Dependency" OR "Drug Dependency" OR "drug effects" OR DE "Drug Sensitivity" OR "Drug Sensitivity" OR DE "Harm Reduction" OR harm* OR harms OR "manic episode" OR overdos* OR DE "Patient Safety" OR "Patient Safety" OR poisoning OR DE "Self-Destructive Behavior" OR DE "Attempted Suicide" OR DE "Head Banging" OR DE "Self-Inflicted Wounds" OR DE "Self-Injurious Behavior" OR DE "Self-Mutilation" OR DE "Suicide" OR self damage* OR self injur* OR self inflict* OR "Self-Injurious Behavior" OR DE "Sequelae" OR DE "Side Effects (Drug)" OR "Side Effect" OR "side effects" OR Suicide OR suicidal* OR DE "Toxic Disorders" OR toxicity	Search modes - Boolean/Phrase	423,684
S21	Abruption* OR DE "Agenesis" OR "Apgar Score" OR DE "Anencephaly" OR (DE "Birth Weight" AND chemical*) OR (DE "Birth Weight" AND chemical*) OR DE "Childhood Development" OR DE "Cleft Palate" OR DE "Congenital Disorders" OR "congenital abnormality" OR "congenital abnormalities" OR DE "Conjoined Twins" OR ("Craniofacial Abnormalities" AND chemical*) OR death OR DE "Death AND Dying" OR DE "Delayed Development" OR DE "Delayed Speech" OR DE "Developmental Disabilities" OR DE "Down's Syndrome" OR "Drug Induced Congenital Disorders" OR DE "Failure to Thrive" OR "Glucose Intolerance" OR DE "Hemorrhage" OR DE "Hermaphroditism" OR (infant* AND (DE "Attachment Behavior" OR attachment* OR bonding)) OR "Infantile Respiratory Distress Syndrome" OR DE "Infertility" OR ("Intellectual Disability" AND child*) OR DE "Klinefelters Syndrome" OR DE "Language Delay" OR ((DE "Learning Disabilities" OR DE "Multiple Disabilities" OR DE "Reading Disabilities") AND child*) OR "Low APGAR" OR DE "Microcephaly" OR miscarry OR miscarriage* OR mortality OR "Neonatal Abstinence Syndrome" OR DE "Neonatal Disorders" OR "Neonatal Respiratory Distress Syndrome" OR "Persistent Fetal Circulation Syndrome" OR "Persistent Pulmonary Hypertension of Newborn" OR DE "Phenylketonuria" OR "Postpartum Hemorrhage" OR DE "Prader Willi Syndrome" OR DE "Preeclampsia" OR preeclampsia OR pre-eclampsia OR DE "Premature Birth" OR "premature birth" OR "Premature labor" OR "Prescription Drug Misuse" OR ("Prescription Drug" AND misuse) OR "preterm birth" OR "pre-term birth" OR "preterm labor" OR "pre-term labor" OR DE "Prenatal Exposure" OR ("Respiratory Distress Syndrome" AND newborn) OR DE "Spina Bifida" OR DE "Spontaneous Abortion" OR DE "Tay Sachs Disease" OR DE "Turners Syndrome" OR ("Uterine Inertia" AND chemical*)	Search modes - Boolean/Phrase	276,659
S22	S20 OR S21	Search modes - Boolean/Phrase	579,290
S23	S1 AND S8 AND S19 AND S22	Search modes - Boolean/Phrase	4,955

#	Query	Limiters/ Expanders	Results
S24	S23	Limiters - English Search modes - Boolean/Phrase	4,903
S25	S24	Limiters - Population Group: Human Search modes - Boolean/Phrase	4,467
S26	S24	Limiters - Population Group: Animal Search modes - Boolean/Phrase	319
S27	S24 not S26	Search modes - Boolean/Phrase	4,584
S28	S25 OR S27	Search modes - Boolean/Phrase	4,639
S29	S28 NOT (DE "Case Report" OR PZ Editorial)	Search modes - Boolean/Phrase	4,563
S30	S29 NOT S18	Search modes - Boolean/Phrase	3,827
S31		**Limiters - Published Date: 20180601-20200631** Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	264,781
S32	S18 AND S31	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	101
S33	S30 AND S31	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	416
S34	S18 OR S30	Limiters - Document Type: Erratum/Correction, Retraction Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	35

Gray Literature Searches for MHT in Pregnancy: ClinicalTrials.gov and WHO ICRTP Strategies

ClinicalTrials.gov results = **446**
WHO ICTRP results = **112**

ClinicalTrials.gov (12-14-2018)
BENEFITS
Condition box:
anxiety OR bipolar OR depress* OR dysthymi* OR "Eating Disorders" OR anorexi* OR "binge eating" OR bulimi* OR GAD OR "psychotic disorder" OR "psychotic disorders" OR psychosis OR psychoses OR "Mental Health" OR "Mental Disorders" OR "Obsessive-Compulsive Disorder" OR OCD OR "panic disorder" OR phobia* OR phobic OR psychotic* OR "post-traumatic stress disorder" OR "post-traumatic stress disorders" OR "posttraumatic stress disorder" OR "posttraumatic stress disorders" OR (disorder* AND "post-traumatic") OR PTSD OR schizophren* OR "stress disorder" OR "stress disorders"

Intervention box:
alprazolam OR anti-anxiety OR antianxiety OR amitriptyline OR amoxapine OR anticonvulsant* OR anti-depress* OR antidepressant* OR antidepressive* OR antipsychotic* OR anxiolytic* OR aripiprazole OR Asenapine OR benzodiazepine* OR brexanolone OR brexpiprazole OR Bupropion OR Buspirone OR Carbamazepine OR cariprazine OR Chlorpromazine OR citalopram OR clobazam OR clomipramine OR Clonazepam OR Clonidine OR Clorazepate OR Chlordiazepoxide OR clozapine OR Desipramine OR Desvenlafaxine OR Diazepam OR Diphenhydramine OR doxepin OR duloxetine OR escitalopram OR eszopiclone OR fluoxetine OR fluphenazine OR fluvoxamine OR gabapentin OR Haloperidol OR Hydroxyzine OR iloperidone OR imipramine OR lamotrigine OR levomilnacipran OR “lisdexamfetamine dimesylate” OR lithium OR lorazepam OR lurasidone OR Maprotiline OR milnacipran OR mirtazapine OR nefazodone OR "norepinephrine reuptake inhibitor" OR "norepinephrine reuptake inhibitors" OR nortriptyline OR olanzapine OR oxcarbazepine OR Paliperidone OR paroxetine OR perphenazine OR protriptyline OR quetiapine OR ramelteon OR risperidone OR "selective serotonin reuptake inhibitor" OR "selective serotonin reuptake inhibitors" OR "Serotonin Uptake Inhibitors" OR "serotonin norepinephrine reuptake inhibitor" OR "serotonin norepinephrine reuptake inhibitors" OR sertraline OR SNRI* OR SSRI OR SSRIs OR Temazepam OR thioridazine OR thiothixene OR topiramate OR trazodone OR triazolam OR trifluoperazine OR Trimipramine OR valproate OR venlafaxine OR vilazodone OR Vistaril OR vortioxetine OR zaleplon OR ziprasidone OR zolpidem

Population (Other Terms box):
Preconception OR pregnant OR pregnancy OR prenatal OR "post-partum" OR postpartum OR postnatal OR perinatal OR antenatal OR "maternal health" OR "Infant Nutritional Physiological Phenomena" OR "breast feeding" OR breastfeed* OR (breast AND fed) OR breastfed OR gestation* OR maternal*

Benefits/effectiveness KQs - Whole block: = 74 results, all imported
(Preconception OR pregnant OR pregnancy OR prenatal OR "post-partum" OR postpartum OR postnatal OR perinatal OR antenatal OR "maternal health" OR "Infant Nutritional Physiological

Phenomena" OR "breast feeding" OR breastfeed* OR breastfed or breast-fed OR gestation* OR maternal*) AND (anxiety OR bipolar OR depress* OR dysthymi* OR "Eating Disorders" OR anorexi* OR "binge eating" OR bulimi* OR GAD OR "psychotic disorder" OR "psychotic disorders" OR psychosis OR psychoses OR "Mental Health" OR "Mental Disorders" OR "Obsessive-Compulsive Disorder" OR OCD OR "panic disorder" OR phobia* OR phobic OR psychotic* OR "post-traumatic stress disorder" OR "post-traumatic stress disorders" OR "posttraumatic stress disorder" OR "posttraumatic stress disorders" OR (disorder* AND "post-traumatic") OR PTSD OR schizophren* OR "stress disorder" OR "stress disorders") [DISEASE] AND (alprazolam OR anti-anxiety OR antianxiety OR amitriptyline OR amoxapine OR anticonvulsant* OR anti-depress* OR antidepressant* OR antidepressive* OR antipsychotic* OR anxiolytic* OR aripiprazole OR Asenapine OR benzodiazepine* OR brexanolone OR brexpiprazole OR Bupropion OR Buspirone OR Carbamazepine OR cariprazine OR Chlorpromazine OR citalopram OR clobazam OR clomipramine OR Clonazepam OR Clonidine OR Clorazepate OR Chlordiazepoxide OR clozapine OR Desipramine OR Desvenlafaxine OR Diazepam OR Diphenhydramine OR doxepin OR duloxetine OR escitalopram OR eszopiclone OR fluoxetine OR fluphenazine OR fluvoxamine OR gabapentin OR Haloperidol OR Hydroxyzine OR iloperidone OR imipramine OR lamotrigine OR levomilnacipran OR “lisdexamfetamine dimesylate” OR lithium OR lorazepam OR lurasidone OR Maprotiline OR milnacipran OR mirtazapine OR nefazodone OR "norepinephrine reuptake inhibitor" OR "norepinephrine reuptake inhibitors" OR nortriptyline OR olanzapine OR oxcarbazepine OR Paliperidone OR paroxetine OR perphenazine OR protriptyline OR quetiapine OR ramelteon OR risperidone OR "selective serotonin reuptake inhibitor" OR "selective serotonin reuptake inhibitors" OR "Serotonin Uptake Inhibitors" OR "serotonin norepinephrine reuptake inhibitor" OR "serotonin norepinephrine reuptake inhibitors" OR sertraline OR SNRI* OR SSRI OR SSRIs OR Temazepam OR thioridazine OR thiothixene OR topiramate OR trazodone OR triazolam OR trifluoperazine OR Trimipramine OR valproate OR venlafaxine OR vilazodone OR Vistaril OR vortioxetine OR zaleplon OR ziprasidone OR zolpidem) [TREATMENT]

HARMS
445 found, 372 imported and the rest were duplicates with the benefits search above.

Use condition terms from above
Guide to below search: Did not use treatment terms, as including them did not net any results
Instead used population string AND concatenated harms string AND condition terms with [DISEASE] qualifier
(Preconception OR pregnant OR pregnancy OR prenatal OR "post-partum" OR postpartum OR postnatal OR perinatal OR antenatal OR "maternal health" OR "Infant Nutritional Physiological Phenomena" OR "breast feeding" OR breastfeed* OR breast AND fed OR breastfed OR gestation* OR maternal*) AND (accident* OR "adverse effect" OR "Adverse Effects" OR "adverse event" OR "adverse events" OR "adverse outcome" OR "adverse outcomes" OR "adverse reaction" OR "adverse reactions" OR "chemically induced" OR complication* OR death* OR "Drug Allergies" OR "Drug Dependency" OR "drug effects" OR "Drug Sensitivity" OR harm* OR harms OR "manic episode" OR overdos* OR "Patient Safety" OR poisoning OR self damage* OR self injur* OR self inflict* OR "Self-Injurious Behavior" OR "Side Effect" OR "side effects" OR Suicide OR suicidal* OR toxicity OR "Abruptio Placentae" OR abruption* OR

"Apgar Score" OR (("Birth Weight" OR "Craniofacial Abnormalities" OR "Extremely Premature" OR "Uterine Inertia") AND ("chemically induced" OR "drug effects" OR "growth and development")) OR "Child Development" OR "Congenital Abnormalities" OR "congenital abnormality" OR "congenital abnormalities" OR (infant* AND (attachment* OR bonding)) OR "Infantile Respiratory Distress Syndrome" OR "delayed development" OR "Glucose Intolerance" OR (Infertility AND female) OR ("Intellectual Disability" AND child*) OR "Low APGAR" OR miscarry OR miscarriage* OR Mortality OR "Neonatal Abstinence Syndrome" OR "Neonatal Respiratory Distress Syndrome" OR "Persistent Fetal Circulation Syndrome" OR "Persistent Pulmonary Hypertension of Newborn" OR "Postpartum Hemorrhage" OR "Pre-Eclampsia" OR preeclampsia OR pre-eclampsia OR "premature birth" OR "Prenatal Exposure Delayed Effects" OR "Prescription Drug Misuse" OR ("Prescription Drug" AND misuse) OR "preterm birth" OR "pre-term birth" OR "preterm labor" OR "pre-term labor" OR ("Respiratory Distress Syndrome" AND newborn) OR "spontaneous abortion") AND (anxiety OR bipolar OR depress* OR dysthymi* OR "Eating Disorders" OR anorexi* OR "binge eating" OR bulimi* OR GAD OR "psychotic disorder" OR "psychotic disorders" OR psychosis OR psychoses OR "Mental Health" OR "Mental Disorders" OR "Obsessive-Compulsive Disorder" OR OCD OR "panic disorder" OR phobia* OR phobic OR psychotic* OR "post-traumatic stress disorder" OR "post-traumatic stress disorders" OR "posttraumatic stress disorder" OR "posttraumatic stress disorders" OR disorder* AND "post-traumatic" OR PTSD OR schizophren* OR "stress disorder" OR "stress disorders") [DISEASE]

WHO ICTRP searches (Advanced Search) 12-17-2018
Benefits
256 maximum character limit per search box.
Recruitment status: ALL and no other limits selected.
(7 searches; same condition and Title (population) search terms as listed below for all searches, but split into 7 queries in order to capture all pharmacotherapy terms used in the ClinicalTrials.gov search)
Title box (used for population)
Preconception OR pregnant OR pregnancy OR prenatal OR "post-partum" OR postpartum OR postnatal OR perinatal OR antenatal OR "maternal health" OR "breast feeding" OR breastfeed* OR (breast AND fed) OR breastfed OR gestation* OR maternal*

Condition box:
Anxiety OR anxio* OR bipolar OR depress* OR anorexi* OR binge OR bulimi* OR psycho* OR “Mental Disorder” OR "Obsessive-Compulsive" OR OCD OR panic OR phobi* OR "post-traumatic” OR posttraumatic stress disorder" OR PTSD OR schizophren* OR stress

Intervention boxes:
Search 1 - 9 results, 9 imported
alprazolam OR anti-anxiety OR antianxiety OR amitriptyline OR amoxapine OR anticonvulsant* OR anti-depress* OR antidepressant* OR antidepressive* OR antipsychotic* OR anxiolytic* OR aripiprazole OR Asenapine OR benzodiazepine* OR brexanolone
Search 2 – 7 results, 5 imported

brexpiprazole OR Bupropion OR Buspirone OR Carbamazepine OR cariprazine OR Chlorpromazine OR citalopram OR clobazam OR clomipramine OR Clonazepam OR Clonidine OR Clorazepate OR Chlordiazepoxide OR clozapine
Search 3 – 102 results, 92 imported
Desipramine OR Desvenlafaxine OR Diazepam OR Diphenhydramine OR doxepin OR duloxetine OR escitalopram OR eszopiclone OR fluoxetine OR fluphenazine OR fluvoxamine OR gabapentin OR Haloperidol OR Hydroxyzine OR iloperidone
Search 4 – 5 results, 2 imported
imipramine OR lamotrigine OR levomilnacipran OR "lisdexamfetamine dimesylate" OR lithium OR lorazepam OR lurasidone OR Maprotiline OR milnacipran OR mirtazapine OR nefazodone OR "norepinephrine reuptake inhibitor"
Search 5 – 6 results, 1 imported
"norepinephrine reuptake inhibitors" OR nortriptyline OR olanzapine OR oxcarbazepine OR Paliperidone OR paroxetine OR perphenazine OR protriptyline OR quetiapine OR ramelteon OR risperidone
Search 6 – 11 results, 3 imported
"selective serotonin reuptake inhibitor" OR "selective serotonin reuptake inhibitors" OR "Serotonin Uptake Inhibitors" OR "serotonin norepinephrine reuptake inhibitor" OR "serotonin norepinephrine reuptake inhibitors" OR sertraline OR SNRI* OR SSRI
Search 7 – 104 results, 0 imported
SSRIs OR Temazepam OR thioridazine OR thiothixene OR topiramate OR trazodone OR triazolam OR trifluoperazine OR Trimipramine OR valproate OR venlafaxine OR vilazodone OR Vistaril OR vortioxetine OR zaleplon OR ziprasidone OR zolpidem

Harms searches (12-18-2018)
Advanced Search
256 maximum character limit per search box.
Recruitment status: ALL and no other limits selected.
Various searches broken up into shorter chunks of harms terms to keep title box 256 char or less
Title box (used for population):
Format for this search box:
(Preconception OR pregnant OR pregnancy OR prenatal OR "post-partum" OR postpartum OR postnatal OR perinatal OR antenatal OR "maternal health") AND (partial harms terms from below)
Search 1 – 0 results
(Preconception OR pregnant OR pregnancy OR prenatal OR "post-partum" OR postpartum OR postnatal OR perinatal OR antenatal OR "maternal health") AND (accident* OR "adverse effect" OR "Adverse Effects" OR "adverse event" OR "adverse events")
Search 2 - 0 results
(Preconception OR pregnant OR pregnancy OR prenatal OR "post-partum" OR postpartum OR postnatal OR perinatal OR antenatal OR "maternal health") AND ("adverse outcome" OR "adverse outcomes" OR "adverse reaction" OR "adverse reactions" OR "chemically induced")
Search 3 - 0 results

(Preconception OR pregnant OR pregnancy OR prenatal OR "post-partum" OR postpartum OR postnatal OR perinatal OR antenatal OR "maternal health") AND (complication* OR death* OR "Drug Allergies" OR "Drug Dependency" OR "drug effects" OR "Drug Sensitivity")
Search 4 – 10 results, 0 imported (duplicates to **other gray literature search results)**
(Preconception OR pregnant OR pregnancy OR prenatal OR "post-partum" OR postpartum OR postnatal OR perinatal OR antenatal OR "maternal health") AND (harm* OR harms OR "manic episode" OR overdos* OR "Patient Safety" OR poisoning OR self damage*)
Search 5 - 0 results
(Preconception OR pregnant OR pregnancy OR prenatal OR "post-partum" OR postpartum OR postnatal OR perinatal OR antenatal OR "maternal health") AND (self injur* OR self inflict* OR "Self-Injurious Behavior" OR "Side Effect" OR "side effects" OR Suicide)
Search 6 - 0 results
(Preconception OR pregnant OR pregnancy OR prenatal OR "post-partum" OR postpartum OR postnatal OR perinatal OR antenatal OR "maternal health") AND (suicidal* OR toxicity OR "Abruptio Placentae" OR abruption* OR "Apgar Score")
Search 7 - 0 results
(Preconception OR pregnant OR pregnancy OR prenatal OR "post-partum" OR postpartum OR postnatal OR perinatal OR antenatal OR "maternal health") AND (("Birth Weight" OR "Craniofacial Abnormalities" OR "Extremely Premature" OR "Uterine Inertia") AND ("chemically induced" OR "drug effects" OR "growth and development"))
Search 8 - 0 results
(Preconception OR pregnant OR pregnancy OR prenatal OR "post-partum" OR postpartum OR postnatal OR perinatal OR antenatal OR "maternal health") AND ("Child Development" OR "Congenital Abnormalities" OR "congenital abnormality" OR "congenital abnormalities")
Search 9 - 0 results
(Preconception OR pregnant OR pregnancy OR prenatal OR "post-partum" OR postpartum OR postnatal OR perinatal OR antenatal OR "maternal health") AND ((infant* AND (attachment* OR bonding)) OR "Infantile Respiratory Distress Syndrome" OR "delayed development")
Search 10 - 0 results
(Preconception OR pregnant OR pregnancy OR prenatal OR "post-partum" OR postpartum OR postnatal OR perinatal OR antenatal OR "maternal health") AND ("Glucose Intolerance" OR (Infertility AND female) OR ("Intellectual Disability" AND child*) OR "Low APGAR")
Search 11 -1 result, 0 imported (duplicate to **other gray literature search results)**
(Preconception OR pregnant OR pregnancy OR prenatal OR "post-partum" OR postpartum OR postnatal OR perinatal OR antenatal OR "maternal health") AND (miscarry OR miscarriage* OR Mortality OR "Neonatal Abstinence Syndrome" OR "Neonatal Respiratory Distress Syndrome")
Search 12 - 0 results
(Preconception OR pregnant OR pregnancy OR prenatal OR "post-partum" OR postpartum OR postnatal OR perinatal OR antenatal OR "maternal health") AND ("Persistent Fetal Circulation Syndrome" OR "Persistent Pulmonary Hypertension of Newborn")
Search 13 – 1 result, 0 imported (duplicate to other gray literature search results)
(Preconception OR pregnant OR pregnancy OR prenatal OR "post-partum" OR postpartum OR postnatal OR perinatal OR antenatal OR "maternal health") AND ("Postpartum Hemorrhage" OR "Pre-Eclampsia" OR preeclampsia OR pre-eclampsia OR "premature birth")
Search 14 - 0 results

(Preconception OR pregnant OR pregnancy OR prenatal OR "post-partum" OR postpartum OR postnatal OR perinatal OR antenatal OR "maternal health") AND ("Prenatal Exposure Delayed Effects" OR "Prescription Drug Misuse" OR ("Prescription Drug" AND misuse))
Search 15 - 0 results
(Preconception OR pregnant OR pregnancy OR prenatal OR "post-partum" OR postpartum OR postnatal OR perinatal OR antenatal OR "maternal health") AND ("preterm birth" OR "pre-term birth" OR "preterm labor" OR "pre-term labor")
Search 16 - 0 results
(Preconception OR pregnant OR pregnancy OR prenatal OR "post-partum" OR postpartum OR postnatal OR perinatal OR antenatal OR "maternal health") AND (("Respiratory Distress Syndrome" AND newborn) OR "spontaneous abortion")

Condition box:

Anxiety OR anxio* OR bipolar OR depress* OR anorexi* OR binge OR bulimi* OR psycho* OR “Mental Disorder” OR "Obsessive-Compulsive" OR OCD OR panic OR phobi* OR "post-traumatic” OR posttraumatic stress disorder" OR PTSD OR schizophren* OR stress

Intervention box:

Generic drug therapy string:
drug* OR pharmacotherap* OR pharmacologic* OR medicine* OR medication*

Gray Literature Searches for MHT in Pregnancy: ClinicalTrials.gov

ClinicalTrials.gov results = **290**

ClinicalTrials.gov (12-14-2018)
BENEFITS
Condition box:

anxiety OR bipolar OR depress* OR dysthymi* OR "Eating Disorders" OR anorexi* OR "binge eating" OR bulimi* OR GAD OR "psychotic disorder" OR "psychotic disorders" OR psychosis OR psychoses OR "Mental Health" OR "Mental Disorders" OR "Obsessive-Compulsive Disorder" OR OCD OR "panic disorder" OR phobia* OR phobic OR psychotic* OR "post-traumatic stress disorder" OR "post-traumatic stress disorders" OR "posttraumatic stress disorder" OR "posttraumatic stress disorders" OR (disorder* AND "post-traumatic") OR PTSD OR schizophren* OR "stress disorder" OR "stress disorders"

Intervention box:

alprazolam OR anti-anxiety OR antianxiety OR amitriptyline OR amoxapine OR anticonvulsant* OR anti-depress* OR antidepressant* OR antidepressive* OR antipsychotic* OR anxiolytic* OR aripiprazole OR Asenapine OR benzodiazepine* OR brexanolone OR brexpiprazole OR Bupropion OR Buspirone OR Carbamazepine OR cariprazine OR Chlorpromazine OR citalopram OR clobazam OR clomipramine OR Clonazepam OR Clonidine OR Clorazepate OR Chlordiazepoxide OR clozapine OR Desipramine OR Desvenlafaxine OR Diazepam OR Diphenhydramine OR doxepin OR duloxetine OR escitalopram OR eszopiclone OR fluoxetine OR fluphenazine OR fluvoxamine OR gabapentin OR Haloperidol OR Hydroxyzine OR iloperidone OR imipramine OR lamotrigine OR levomilnacipran OR “lisdexamfetamine dimesylate” OR lithium OR lorazepam OR lurasidone OR Maprotiline OR milnacipran OR mirtazapine OR nefazodone OR "norepinephrine reuptake inhibitor" OR "norepinephrine reuptake inhibitors" OR nortriptyline OR olanzapine OR oxcarbazepine OR Paliperidone OR

paroxetine OR perphenazine OR protriptyline OR quetiapine OR ramelteon OR risperidone OR "selective serotonin reuptake inhibitor" OR "selective serotonin reuptake inhibitors" OR "Serotonin Uptake Inhibitors" OR "serotonin norepinephrine reuptake inhibitor" OR "serotonin norepinephrine reuptake inhibitors" OR sertraline OR SNRI* OR SSRI OR SSRIs OR Temazepam OR thioridazine OR thiothixene OR topiramate OR trazodone OR triazolam OR trifluoperazine OR Trimipramine OR valproate OR venlafaxine OR vilazodone OR Vistaril OR vortioxetine OR zaleplon OR ziprasidone OR zolpidem

Population (Other Terms box):
Preconception OR pregnant OR pregnancy OR prenatal OR "post-partum" OR postpartum OR postnatal OR perinatal OR antenatal OR "maternal health" OR "Infant Nutritional Physiological Phenomena" OR "breast feeding" OR breastfeed* OR (breast AND fed) OR breastfed OR gestation* OR maternal*

Benefits/effectiveness KQs - Whole block: = 26 results, 26 imported
(Preconception OR pregnant OR pregnancy OR prenatal OR "post-partum" OR postpartum OR postnatal OR perinatal OR antenatal OR "maternal health" OR "Infant Nutritional Physiological Phenomena" OR "breast feeding" OR breastfeed* OR (breast AND fed) OR breastfed OR gestation* OR maternal*) AND AREA[ConditionSearch] (anxiety OR bipolar OR depress* OR dysthymi* OR "Eating Disorders" OR anorexi* OR "binge eating" OR bulimi* OR GAD OR "psychotic disorder" OR "psychotic disorders" OR psychosis OR psychoses OR "Mental Health" OR "Mental Disorders" OR "Obsessive-Compulsive Disorder" OR OCD OR "panic disorder" OR phobia* OR phobic OR psychotic* OR "post-traumatic stress disorder" OR "post-traumatic stress disorders" OR "posttraumatic stress disorder" OR "posttraumatic stress disorders" OR (disorder* AND "post-traumatic") OR PTSD OR schizophren* OR "stress disorder" OR "stress disorders") AND AREA[InterventionSearch] (alprazolam OR anti-anxiety OR antianxiety OR amitriptyline OR amoxapine OR anticonvulsant* OR anti-depress* OR antidepressant* OR antidepressive* OR antipsychotic* OR anxiolytic* OR aripiprazole OR Asenapine OR benzodiazepine* OR brexanolone OR brexpiprazole OR Bupropion OR Buspirone OR Carbamazepine OR cariprazine OR Chlorpromazine OR citalopram OR clobazam OR clomipramine OR Clonazepam OR Clonidine OR Clorazepate OR Chlordiazepoxide OR clozapine OR Desipramine OR Desvenlafaxine OR Diazepam OR Diphenhydramine OR doxepin OR duloxetine OR escitalopram OR eszopiclone OR fluoxetine OR fluphenazine OR fluvoxamine OR gabapentin OR Haloperidol OR Hydroxyzine OR iloperidone OR imipramine OR lamotrigine OR levomilnacipran OR “lisdexamfetamine dimesylate” OR lithium OR lorazepam OR lurasidone OR Maprotiline OR milnacipran OR mirtazapine OR nefazodone OR "norepinephrine reuptake inhibitor" OR "norepinephrine reuptake inhibitors" OR nortriptyline OR olanzapine OR oxcarbazepine OR Paliperidone OR paroxetine OR perphenazine OR protriptyline OR quetiapine OR ramelteon OR risperidone OR "selective serotonin reuptake inhibitor" OR "selective serotonin reuptake inhibitors" OR "Serotonin Uptake Inhibitors" OR "serotonin norepinephrine reuptake inhibitor" OR "serotonin norepinephrine reuptake inhibitors" OR sertraline OR SNRI* OR SSRI OR SSRIs OR Temazepam OR thioridazine OR thiothixene OR topiramate OR trazodone OR triazolam OR trifluoperazine OR Trimipramine OR valproate OR venlafaxine OR vilazodone OR Vistaril OR vortioxetine OR zaleplon OR ziprasidone OR zolpidem) AND AREA[LastUpdatePostDate] EXPAND[Term] RANGE[06/14/2018, 06/05/2020]

HARMS
290 found, 264 imported and the rest were duplicates with the benefits search above.

Use condition terms from above
Guide to below search: Did not use treatment terms, as including them did not net any results
Instead used population string AND concatenated harms string AND condition terms with [DISEASE] qualifier
(Preconception OR pregnant OR pregnancy OR prenatal OR "post-partum" OR postpartum OR postnatal OR perinatal OR antenatal OR "maternal health" OR "Infant Nutritional Physiological Phenomena" OR "breast feeding" OR breastfeed* OR breast AND fed OR breastfed OR gestation* OR maternal*) AND (accident* OR "adverse effect" OR "Adverse Effects" OR "adverse event" OR "adverse events" OR "adverse outcome" OR "adverse outcomes" OR "adverse reaction" OR "adverse reactions" OR "chemically induced" OR complication* OR death* OR "Drug Allergies" OR "Drug Dependency" OR "drug effects" OR "Drug Sensitivity" OR harm* OR harms OR "manic episode" OR overdos* OR "Patient Safety" OR poisoning OR self damage* OR self injur* OR self inflict* OR "Self-Injurious Behavior" OR "Side Effect" OR "side effects" OR Suicide OR suicidal* OR toxicity OR "Abruptio Placentae" OR abruption* OR "Apgar Score" OR (("Birth Weight" OR "Craniofacial Abnormalities" OR "Extremely Premature" OR "Uterine Inertia") AND ("chemically induced" OR "drug effects" OR "growth and development")) OR "Child Development" OR "Congenital Abnormalities" OR "congenital abnormality" OR "congenital abnormalities" OR (infant* AND (attachment* OR bonding)) OR "Infantile Respiratory Distress Syndrome" OR "delayed development" OR "Glucose Intolerance" OR (Infertility AND female) OR ("Intellectual Disability" AND child*) OR "Low APGAR" OR miscarry OR miscarriage* OR Mortality OR "Neonatal Abstinence Syndrome" OR "Neonatal Respiratory Distress Syndrome" OR "Persistent Fetal Circulation Syndrome" OR "Persistent Pulmonary Hypertension of Newborn" OR "Postpartum Hemorrhage" OR "Pre-Eclampsia" OR preeclampsia OR pre-eclampsia OR "premature birth" OR "Prenatal Exposure Delayed Effects" OR "Prescription Drug Misuse" OR ("Prescription Drug" AND misuse) OR "preterm birth" OR "pre-term birth" OR "preterm labor" OR "pre-term labor" OR ("Respiratory Distress Syndrome" AND newborn) OR "spontaneous abortion") AND (anxiety OR bipolar OR depress* OR dysthymi* OR "Eating Disorders" OR anorexi* OR "binge eating" OR bulimi* OR GAD OR "psychotic disorder" OR "psychotic disorders" OR psychosis OR psychoses OR "Mental Health" OR "Mental Disorders" OR "Obsessive-Compulsive Disorder" OR OCD OR "panic disorder" OR phobia* OR phobic OR psychotic* OR "post-traumatic stress disorder" OR "post-traumatic stress disorders" OR "posttraumatic stress disorder" OR "posttraumatic stress disorders" OR disorder* AND "post-traumatic" OR PTSD OR schizophren* OR "stress disorder" OR "stress disorders") [DISEASE]

Appendix B. Results

Results of Literature Searches

The electronic search, gray literature, and reference mining identified 31,846 citations. After title and abstract screening, 1,812 studies were retrieved for full-text review. A total of 164 studies (168 articles) met eligibility criteria. Thirty-three studies were not included in the data synthesis due to only reporting unadjusted effectiveness data. A total of 131 studies (135 articles) were included in the analyses (Figure B-1).

Description of Included Studies

For KQ 1, we identified 9 trials and 10 observational studies. Four studies were assessed as having low risk of bias, 8 studies were assessed as having some concerns for bias, and 7 studies were assessed as having high risk of bias.[16-34]

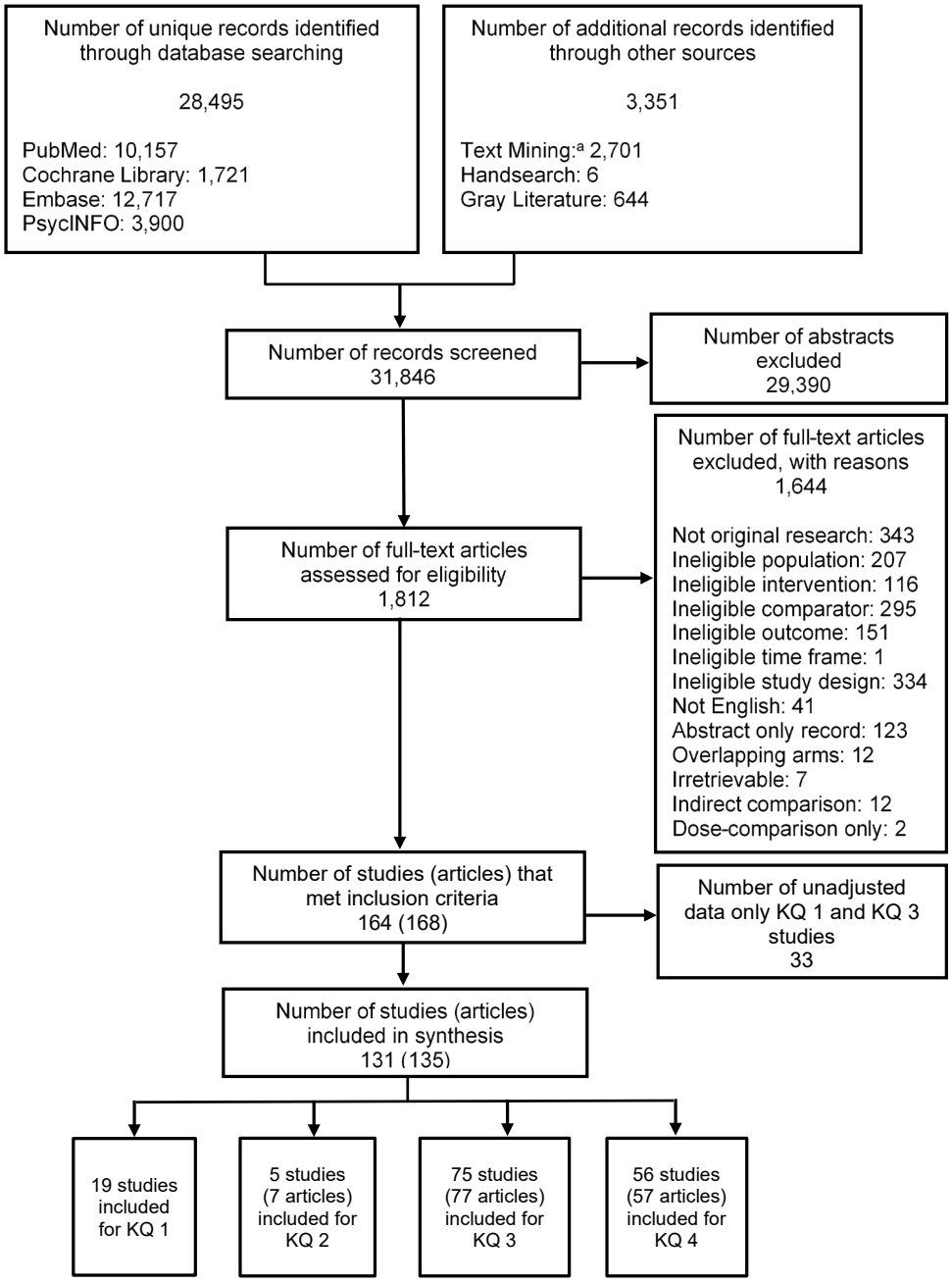
For KQ 2, we identified one trial (2 articles) and four observational studies (5 articles). One study was assessed as having some concerns for risk of bias and four studies (6 articles) were assessed as having high risk of bias.[35-41]

For KQ 3, we identified 5 trials and 70 observational studies (72 articles). Three studies were assessed as having low risk of bias, 32 studies were assessed as having some concerns for bias, 35 studies (37 articles) were assessed as having high risk of bias, and 5 studies were rated as having some concerns/high risk of bias.[6-9, 16, 17, 19, 23, 25, 27, 31, 33, 42-106]

For KQ 4, we identified one trial (2 articles) and 55 observational studies. Seven studies were assessed as having some concerns for bias, 44 studies (45 articles) were assessed as having high risk of bias, and 5 studies were assessed as having some concerns/high risk of bias.[35, 36, 42, 45, 53, 55, 64, 70, 81, 83-85, 87, 95-98, 107-146]

An overview of the pharmacologic interventions that were examined are provided in Table B-1. All of the included studies were published in English. Additional details of the risk of bias assessments are downloadable on SRDR.

Figure B-1. Article flow diagram



Note: The sum of the number of studies per KQ exceeds the total number of studies because some studies were applicable to multiple KQs.

[a] As part of a methods project, an independent search was undertaken, using text-mining software to identify additional relevant keywords and MeSH search terms. This search was also independently peer reviewed. Duplicate citations were removed prior to screening.

KQ = Key Question

Table B-1. Pharmacologic interventions for included studies

Pharmacologic Intervention	Number of Studies	Percent
Amitriptyline	2[56, 74]	1.5
Antipsychotics (Second-generation)	7[44, 50, 62, 85, 97, 119, 125]	5.3
Antipsychotics (First-generation)	4[62, 85, 119, 125]	3.1
Antipsychotics associated with increased risk of T2DM (Quetiapine [high-dose], Olanzapine, Risperidone, or Clozapine)	1[97]	0.8
Anxiolytics	4[30, 46, 71, 79]	3.1
Aripiprazole	2[90, 97]	1.5
Benzodiazepine	2	1.5
Brexanolone	2[17, 19]	1.5
Bupropion	6[7, 74, 104, 106, 141]	4.6
Carbamazepine	1[96]	0.8
Citalopram	9[51, 57, 72, 74, 75, 104, 111, 117, 141]	6.9
Citalopram or Escitalopram	3[107, 111, 141]	2.3
Clomipramine	2[51, 56]	1.5
Clozapine	1[97]	0.8
Duloxetine	4[56, 75, 98, 141]	3.1
Escitalopram	5[72, 74, 75, 106, 141]	3.8
Escitalopram or Fluvoxamine	1[117]	0.8
Fluoxetine	18[7, 29, 39, 40, 51, 56, 57, 72, 74, 75, 81, 104, 106, 107, 111, 117, 134, 136, 141]	13.7
Fluvoxamine	3[57, 107, 111]	2.3
Haloperidol	1[127]	0.8
Lamotrigine	6[24, 37, 38, 96, 97, 108]	4.6
Lithium	6[37, 38, 41, 47, 97, 108]	4.6
Mirtazapine	6[56, 74, 75, 95, 116]	4.6
Mood Stabilizers	2[26, 96]	1.5
MAOIs	2[53, 114]	1.5
Nortriptyline	2[35, 36, 56]	1.5
Olanzapine	3[90, 97, 127]	2.3
Oxcarbazepine	1[96]	0.8
Paroxetine	20[7, 25, 38, 51, 56, 57, 72, 74, 75, 81, 87, 93, 104, 106, 107, 111, 117, 122, 131, 141]	15.3
Quetiapine	4[43, 90, 97, 127]	3.0
Risperidone	4[62, 90, 97, 127]	3.0
Sertraline	19[7, 16, 21-23, 35, 36, 51, 56, 57, 70, 72, 74, 75, 104, 106, 107, 111, 117, 141]	14.5
SNRIs	19[7, 51, 53, 56, 57, 64, 74, 75, 81, 83, 98, 104, 106, 107, 110, 112, 114, 124, 140]	14.5
Sodium Valproate	2[41, 96]	1.5
SSRIs	47[6-9, 27, 53, 54, 57-61, 63, 64, 66, 69, 70, 72, 74-76, 79-84, 87, 88, 91, 93, 95, 104, 106, 110, 112, 114, 116, 123, 124, 126, 131, 133, 135]	35.9
Nonsertraline SSRIs	1[70]	0.8
TCA	18[7, 39, 40, 53, 57, 64, 72, 75, 79, 81, 83, 93, 110, 114, 123, 126, 133, 134, 136]	13.7
Topiramate	1[96]	0.8
Trazadone	2[74, 75]	1.5
Venlafaxine	6[83, 98, 122, 135, 141, 144]	4.6
Venlafaxine or desvenlafaxine	1[107]	0.8
Ziprasidone	1[90]	0.8
Zolpidem	1[92]	0.8

Pharmacologic Intervention	Number of Studies	Percent
Zopiclone	1[71]	0.8
Pharmacologic Combinations	9[41, 45, 72, 95, 115, 120, 129, 132, 141]	6.9
Nonspecific/Undefined Pharmacologic Interventions	68[6, 7, 9, 18, 20, 28, 31, 32, 33 Schaffer, 34, 42, 45, 48, 49, 51-58, 60, 64, 65, 67, 68, 70, 73, 75, 77-79, 83, 84, 86, 87, 89, 93, 94, 96, 97, 99, 101, 102, 104-107, 109-114, 117-119, 121, 123, 128, 130, 137, 138, 142, 143, 145, 146]	51.9

Detailed Results

Key Question 1: Among pregnant and postpartum women, what is the effectiveness of **pharmacologic** interventions on maternal outcomes among those with a new or preexisting anxiety disorder, depressive disorder, bipolar disorder, or schizophrenia?

Anxiety: Anti-Anxiety Medications

Overview

- The evidence is insufficient to judge maternal benefits from anxiolytics following delivery.

Detailed Results

One randomized controlled trial (RCT), rated high risk of bias, reported on the maternal benefits of anxiolytics in 1967.[30] The trial included 51 postpartum women with anxiety in one hospital site in the United States. Women were given either hydroxyzine or placebo for anxiety over a period of 3 days following delivery.

This trial used an unvalidated tool to measure "a series of behavioral responses"[30] and did not present data on variance by arm. We judged the evidence to be insufficient due to bias, potential imprecision, and lack of information on consistency (Table B-2).

Table B-2. Strength of evidence for effectiveness: Anxiolytics versus no treatment

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Postpartum women with anxiety	Hydroxyzine vs. placebo for 3 days following delivery	Maternal behavioral response	Average "response rating": 7.24 vs. 3.25[30]	Effect not calculable (variance NR)	1 RCT, N=51[30]	High study limitations (high risk of bias[30]), likely imprecise (small Ns), consistency unknown	Insufficient

KQ = Key Question; N = number; NR = not reported; RCT = randomized controlled trial; vs. = versus.

Depression: Selective Serotonin Reuptake Inhibitors (SSRIs)

Overview

- The evidence is insufficient to judge the risk of benefits of SSRIs during pregnancy as a drug class for mode of delivery.
- Included studies did not report on other maternal benefits.

Detailed Results

One publication with some risk-of-bias concerns reported on mode of delivery, specifically, incidence of Cesarean section (C-section), among depressed women with and without SSRI

exposure during pregnancy.[27] The evidence is insufficient to judge the effect of SSRI exposure (Table B-3).

Table B-3. Strength of evidence for effectiveness: SSRIs versus no treatment

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Depressed women	SSRI exposure in pregnancy vs. unexposed women with depression	Cesarean section	NR	Difference in incidence: -0.009 (95% CI, -0.05 to 0.036), p-value=0.69[27]	1 cohort, n=NR[27]	Moderate study limitations[27] imprecise, consistency unknown	Insufficient

CI = confidence interval; N = number; NR = not reported; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant; vs. = versus.

Depression: Fluoxetine

Overview

- The evidence is insufficient to judge the risk of benefits of fluoxetine for postpartum depression.
- No other maternal benefits were evaluated.

Detailed Results

One RCT of women in an urban health district in the United Kingdom reported on a fluoxetine benefit outcome.[29] The RCT examined the effect of fluoxetine versus placebo exposure on depression outcomes during the postpartum period.[29] Both arms also received one session of CBT in one fluoxetine/placebo comparison and six sessions in a second; the dose of fluoxetine was not specified.[29] The study risk of bias was rated as some concerns. Hamilton depression scores improved in all groups, but results were not superior in the fluoxetine arm in either the one-session or six-session CBT co-intervention comparisons (Table B-4).

Table B-4. Strength of evidence for effectiveness outcomes: Fluoxetine versus no treatment

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Postpartum women: Fluoxetine exposure or depression diagnosis 12 weeks after delivery	Fluoxetine exposure for 3 months vs. placebo. Both arms also received CBT (1 or 6 sessions)	Hamilton Depression score	Intent-to-treat findings: 1 Session of CBT: 4.4 (2.4 to 7.4) vs. 8.1 (6.1 to 10.7); calculated mean difference: -3.7 (95% CI, -8.8 to 1.4) 6 sessions of CBT: 5.1 (2.6 to 9.2) vs. 4.9 (3.0 to 8.9); calculated mean difference: 0.2 (95% CI, -10.0 to 10.4)[29]	ARR	1 cohort: N=87[29]	Moderate study limitations, seriously imprecise (small sample size, CIs spanning the null), consistency unknown	Insufficient

ARR = adjusted risk ratio; CBT = cognitive behavioral therapy; CI = confidence interval; N = number; vs. = versus.

Depression: Paroxetine

Overview

- The evidence is insufficient to rate the strength of evidence for the likelihood of response, remission, or symptoms for women with postpartum onset of depression compared with women on placebo.

Detailed Results

A single publication reported on women with onset of depressive symptoms at 0 to 3 months postpartum, randomized to paroxetine versus placebo with the primary outcome of change in depressive symptoms indexed by HAM-D-17 at 8 weeks after treatment initiation.[25] Enrollment of 120 women was planned, but only 70 women were recruited. Women in the active arm received one capsule (10 mg of immediate release paroxetine) daily for the first and second week with increases up to 40 mg if participants did not experience sufficient improvement. There was no change in HAM-D-17 score between the two groups. More women allocated to paroxetine were more likely to achieve remission, indexed by HAM-D-17 ≤8 (adjusted odds ratio [AOR], 3.5; 95% CI, 1.1 to 11.5); however, only 31 of 70 women completed the 8-week followup (Table B-5).

Depression: Sertraline

Overview

- The evidence for sertraline for postpartum depression was mixed and varied by outcome.
- For response, two studies comparing sertraline with placebo only showed that sertraline improves response rate (low strength of evidence); the evidence for sertraline plus psychotherapy versus psychotherapy alone is insufficient.
- For remission, similarly, two studies comparing sertraline with placebo only showed that sertraline improves remission rates relative to placebo (low strength of evidence); the evidence for sertraline plus psychotherapy versus psychotherapy alone is insufficient.
- For reduction in depression severity, when onset of depression occurred after the first month postpartum, the evidence was insufficient for sertraline with placebo only and for sertraline plus psychotherapy versus psychotherapy alone.
- For reduction in depression severity, when onset of depression occurred, between 0 and 1 month postpartum, the evidence from one study suggested greater improvement with sertraline compared with placebo.
- For reduction in anxiety among women with depression, one low risk-of-bias study reported that sertraline produces a greater reduction in severity than placebo (low strength of evidence).
- Evidence addressing differences in postpartum adjustment was insufficient.

Table B-5. Strength of evidence for effectiveness: Paroxetine versus no treatment

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women with depression onset 0-3 months postpartum	Paroxetine vs. placebo	Response: CGI-I score = 1 or 2	Paroxetine: 15/35 Placebo: 11/35	AOR, 1.04 (0.33-3.26), p=0.94	1 RCT, N=70[25]	High study limitations (high risk of bias[25]), serious imprecision (wide CIs, small sample size), consistency unknown	Insufficient
Women with depression onset 0-3 months postpartum	Paroxetine vs. placebo	Remission: HAM-D-17 total score ≤8	Paroxetine: 13/35 Placebo: 5/35	AOR, 3.5 (1.1-11.5), p=0.04	1 RCT, N=70[25]	High study limitations (high risk of bias[25]), imprecision (small sample size), consistency unknown	Insufficient
Women with depression onset 0-3 months postpartum	Paroxetine vs. placebo	Symptoms: IDS-SR symptom score	Paroxetine: baseline 38.6, final 14.0 Placebo: baseline 42.8, final 22.6	Group effect: -4.98 (p=0.019), but group x time NS	1 RCT, N=70[25]	High study limitations (high risk of bias[25]), imprecision (small sample size), consistency unknown	Insufficient
Women with depression onset 0-3 months postpartum	Paroxetine vs. placebo	Symptoms: HAM-D-17 score	Paroxetine: baseline 23.6, final 8.6 Placebo: baseline 24.7, final 13.3	Group effect: -1.62 (p=0.22)	1 RCT, N=70[25]	High study limitations (high risk of bias[25]), serious imprecision (wide CIs, small sample size), consistency unknown	Insufficient
Women with depression onset 0-3 months postpartum	Paroxetine vs. placebo	Symptoms: CGI-S symptom score	Paroxetine: baseline 4.2, final 1.8 Placebo: baseline 4.5, final 3.1	Group effect: -0.48 (p=0.047)	1 RCT, N=70[25]	High study limitations (high risk of bias[25]), imprecision (small sample size), consistency unknown	Insufficient

AOR = adjusted odds ratio; CGI-I = Clinical Global Impression-Improvement; CGI-S = Clinical Global Impression-Severity of Illness; CI = confidence interval; HAM-D-17= Hamilton Depression Rating scale, 17-item version; IDS-SR = Inventory of Depression Symptoms – SR; N = number; NS = not significant; RCT = randomized controlled trial; vs. = versus.

Detailed Results

Four publications compared the benefits of sertraline with no sertraline treatment; these study designs compared sertraline with placebo (Table B-6)[16, 22] or compared sertraline plus a psychotherapy (cognitive behavioral therapy[21] or brief dynamic psychotherapy[23]) with that respective psychotherapy alone. All four studies were RCTs.[16, 21-23] Two studies were high risk of bias[16, 21] and two had low risk of bias.[22, 23]

The four trials addressed postpartum depression (onset varied between 2 months and 12 months following delivery).[16, 21-23] One study looked at two intervals: onset within 3 months of delivery (the primary outcome, which is consistent with how DSM-5 defines the postpartum specifier), and onset within the more strict DSM-IV definition of 1 month postpartum.[22] Three studies allowed doses ranging from 50 mg to 200 mg,[16, 21, 22] while the other allowed doses ranging from 25 mg to 100 mg.[23]

Table B-6. Strength of evidence for effectiveness: Sertraline versus no treatment

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women with depression onset 0-3 months postpartum[22] or women with depression onset 0-12 months postpartum[16]	Sertraline vs. placebo	Response at 6 weeks in ITT group (≥50% reduction in HAM-D-19 symptoms and CGI-I score of "much improved" or "very much improved")[22] or response at 12 weeks (≥50% reduction in HAM-D-17 symptoms)	10/17 (59%) vs. 5/19 (26%),[22] NR[16]	AOR, = NR, p=0.05 calculated RR: 2.24 (95% CI, 0.95 to 5.24);[22] no difference between two arms, p=0.054[16]	2 RCTs, N=145[16, 22]	Moderate study limitations (one high risk-of-bias study)[16] imprecise (few events, small N, wide CIs), inconsistent; large effect for low risk of bias study	Low that response at 6 weeks is greater with sertraline
Women with depression onset 0-2 months postpartum	Sertraline plus brief dynamic psychotherapy vs. placebo	Response at 8 weeks (>50% reduction in MADRS or EPDS score)	14/20 (70%) vs. 11/20 (55%)[23]	RR = NR, between groups p-value=0.33[23]	1 RCT, N=40[23]	Low risk of bias[23]), seriously imprecise (few events, likely CIs span the null), consistency unknown	Insufficient
Women with depression onset 0-3 months postpartum[22] or women with depression onset 0-12 months postpartum[16]	Sertraline vs. placebo	Remission at 6 weeks in ITT group (meeting response above and with HAM-D-19 score ≤7)[22] or remission at 12 weeks (HAMD-17 ≤7)[16]	9/17 (53%) vs. 4/19 (23%);[22] NR[16]	AOR = NR, p=0.05 calculated RR: 2.51 (95% CI, 0.94 to 6.70);[22] no difference between two arms, p=0.372[16]	2 RCTs, N=145[16, 22]	Moderate study limitations (one high risk-of-bias study[16] imprecise (few events), inconsistent; large effect for low risk of bias study	Low that remission at 6 weeks is greater with sertraline

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women with depression onset 0-2 months postpartum	Sertraline plus brief dynamic psychotherapy vs. placebo	Remission at 8 weeks (final score of <10 on MADRS or <7 on EPDS)	13/20 (65%) vs. 10/20 (50%)[23]	RR = NR, between groups p-value p=0.34[23]	1 RCT, N=40[23]	Low risk of bias,[23] likely imprecise (few events, CIs likely span the null), consistency unknown	
Women with depression onset 0-3 months postpartum[22] or women with depression onset 0-12 months postpartum[16]	Sertraline vs. placebo	Decrease in HAM-D-19 scores at 6 weeks	Sertraline: baseline HAM-D-19 20.6, final NR Placebo: baseline HAM-D 23.2, final NR	Regression coefficient 0.6 favoring sertraline group, p=0.15[22]	1 RCT, N=36[22]	High study limitations (one high risk-of-bias stud)y[16] imprecise (few events), consistency unknown	Insufficient across all measures of change in symptom severity
		Decrease in EPDS scores at 6 weeks	Sertraline: baseline EPDS 18.8, final NR Placebo: baseline EPDS 20.8, final NR	Regression coefficient 0.25 favoring sertraline group, p=0.51[22]	1 RCT, N=36[22]		
		Decrease in depressive severity at 12 weeks (HAM-D-17)	NR[16]	No difference between two arms, p=NR[16]	1 RCT, N=109[16]		
		Decrease in depressive severity at 12 weeks (BDI)	NR[16]	No difference between two arms, p=NR[16]	1 RCT, N=109[16]		
		Decrease in depressive severity at 12 weeks (IDAS-GD)	NR[16]	No difference between two arms, p=NR[16]	1 RCT, N=109[16]		
		CGI-S at 12 weeks	NR[16]	No difference between two arms, p=NR[16]	1 RCT, N=109[16]		
Women with depression onset 0-12 months postpartum	Sertraline vs. placebo	CGI-I at 12 weeks	NR[16]	No difference between two arms, p=NR[16]	1 RCT, N=109[16]	High study limitations (high risk of bias[16]), likely imprecise, consistency unknown	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women with depression onset between 2 and 8 months postpartum	Sertraline plus CBT vs. CBT	Decrease in BDI-II at 24 weeks	Sertraline plus CBT: -14.54 CBT: -16.2[21]	Between-group mean difference: 1.6 favoring CBT group, p=NS[21]	1 RCT, N=30[21]	High study limitations (high risk of bias[21]) seriously imprecise (small sample size, CIs likely span the null), consistency unknown	Insufficient
Women with depression onset 0-1 month postpartum	Sertraline vs. placebo	Decrease in HAM-D-19 scores at 6 weeks	Sertraline: baseline HAM-D-19 NR, final NR Placebo: baseline HAM-D NR, final NR	Regression coefficient 1.18 favoring sertraline group, p=0.01[22]	1 RCT, N=27[22]	Low study limitations, imprecise (small sample size), consistency unknown	Low that reduction in depressive severity is greater with sertraline
Women with depression onset 0-1 month postpartum	Sertraline vs. placebo	Decrease in EPDS scores at 6 weeks	Sertraline: baseline EPDS NR, final NR Placebo: baseline EPDS NR, final NR	Regression coefficient 0.91 favoring sertraline group, p=0.04[22]	1 RCT, N=27[22]	Low study limitations, imprecise (small sample size), consistency unknown	Low that reduction in depressive severity is greater with sertraline
Women with depression onset 0-3 months postpartum	Sertraline vs. placebo	Decrease in HAM-A at 6 weeks	Sertraline: baseline HAM-A 21.3, final NR Placebo: baseline HAM-A 24.5, final NR	Regression coefficient 0.92 favoring sertraline group, p=0.08[22]	1 RCT, N=36[22]	Low study limitations, imprecise (small sample size), consistency unknown	Insufficient
Women with depression onset 0-1 month postpartum	Sertraline vs. placebo	Decrease in HAM-A at 6 weeks	Sertraline: baseline HAM-A NR, final NR Placebo: baseline HAM-A NR, final NR	Regression coefficient 1.19 favoring sertraline group, p=0.03[22]	1 RCT, N=27[22]	Low study limitations, imprecise (few events),con-sistency unknown	Low that reduction in anxiety severity is greater with sertraline
Women with depression onset 0-12 months postpartum	Sertraline vs. placebo	PPAQ at 12 weeks	NR[16]	No difference between two arms, p=NR[16]	1 RCT, N=109[16]	High study limitations (high risk of bias[16]), likely imprecise, consistency unknown	Insufficient

AOR = adjusted odds ratio; BDI = Beck Depression Inventory; BDI-II = Beck Depression Inventory-II; CBT = cognitive behavioral therapy; CGI-S = Clinical Global Impression-Severity of Illness; CGI-I = Clinical Global Impression- Improvement; CI = confidence interval; EPDS = Edinburgh Postnatal Depression Scale; HAM-A = Hamilton Anxiety Rating Scale; HAM-D-17= Hamilton Depression Rating scale, 17-item version; HAM-D-19= Hamilton Depression Rating scale, 19-item version; IDA-

GD = Inventory of Depression and Anxiety Symptoms, General Depression scale; ITT = intention to treat; NR = not reported; NS = not significant; PPAQ = Postpartum Adjustment Questionnaire; RCT = randomized controlled trial; vs. = versus.

The evidence for sertraline was mixed and varied by outcome. For response, two studies provided evidence of response for sertraline versus placebo;[16, 22] a third study provided evidence from a comparison of sertraline plus psychotherapy versus psychotherapy alone. Because of the clinical heterogeneity in comparators, we did not pool results. The evidence from the two studies of sertraline versus placebo only offers low strength of evidence of benefit: one low risk-of-bias study with a small sample and a mean dose of 100 mg reported a statistically significant benefit for depression with onset within 1 or 3 months postpartum, respectively.[22] A more restrictive definition of postpartum depression with onset up to 1 month postpartum from the same study also reported statistically significant differences favoring sertraline.[22] Calculated relative risks suggest imprecise results with wide CIs, few events, and small numbers of participants, but a large effect size. A second study, a high risk-of-bias study with a median dose of 150 mg, found no difference in response rates.[16]

A low risk-of-bias study comparing sertraline (mean dose between 65 and 70 mg) plus brief dynamic psychotherapy with brief dynamic psychotherapy alone showed a benefit in the same direction, which does not reach statistical significance.[23] In this trial, the control group was an active treatment, brief dynamic psychotherapy, which would raise the response rate in the control group and make significance harder to demonstrate.[23]

For remission, which involves the same three studies, there is evidence that sertraline improves remission rates in one low risk-of-bias study whether onset is defined as 0 to 3 months postpartum or 0 to 1 month postpartum.[22] A high risk-of-bias study did not report any statistically significant improvement.[16] As with the results on remission, we graded the strength of evidence as low for benefit for sertraline compared with placebo. A low risk-of-bias study comparing sertraline plus brief dynamic psychotherapy with brief dynamic psychotherapy alone did not report any statistically significant differences.[23]

For reduction in depressive severity, two studies provided evidence on change in symptom response for sertraline versus placebo;[16, 22] a third study provided evidence from a comparison of sertraline plus CBT versus CBT alone. As with the results on response and remission, because of the clinical heterogeneity in comparators, we did not pool results.

Two trials with onset of depression between 0 to 3 and 0 to 12 months compared sertraline with placebo only. These trials (1 low risk of bias and 1 high risk of bias) did not demonstrate differences in any of a range of outcomes measuring differences in symptoms (HAM-D 19, EPDS, HAM-D 17, BDI, IDA-GD, CGI-S).[16, 22]

One low risk-of-bias study provided low strength of evidence of benefit that sertraline produces a greater reduction in depressive severity when onset is between birth and 1 month when compared with placebo.[22]

One high risk-of-bias study provided insufficient data to judge the strength of evidence for this outcome when comparing sertraline plus CBT with placebo plus CBT.[21] As with the trial on psychodynamic therapy, differences are likely to be harder to demonstrate.

For reduction in anxiety, one low risk-of-bias study reported that sertraline produces a greater reduction in anxiety severity than placebo (low strength of evidence).[22] For those with onset of postpartum depression within 3 months of delivery, the reduction favors sertraline but not to a statistically significant degree; for those with onset within 1 month of delivery, the statistically significant reduction favors sertraline despite the small sample size. Evidence addressing differences in postpartum adjustment was insufficient.[22]

Depression: Brexanolone

Overview

- Three small randomized controlled trials demonstrated benefit for brexanolone to reduce depressive symptoms compared with placebo at 60 hours and 30 days after infusion for depression onset in the third trimester of pregnancy or within 4 weeks of birth. These trials provided moderate evidence of benefit that brexanolone improves symptoms.
- The evidence is insufficient to judge the benefits of brexanolone for functional outcomes.

Detailed Results

Three RCTs (rated low risk of bias) reported on the efficacy for brexanolone versus placebo for depression symptoms with onset in the third trimester of pregnancy or within 4 weeks of birth.[17, 19] The prespecified primary outcome of the trials was change from baseline to 60 hours in the 17-Item Hamilton Rating Scale for Depression (HAM-D) score. Brexanolone was administered as a 60-hour continuous infusion with a peak dose of either 60 μg/kg per hour or 90 μg/kg per hour. The BRX60 schedule was administered at 30 μg/kg per hour (0–4 hours), 60 μg/kg per hour (4–56 hours), or 30 μg/kg per hour (56–60 hours). The BRX90 schedule was administered at 30 μg/kg per hour (0–4 hours), 60 μg/kg per hour (4–24 hours), 90 μg/kg per hour (24–52 hours), 60 μg/kg per hour (52–56 hours), or 30 μg/kg per hour (56–60 hours).

The first study[19] was a phase 2 clinical trial enrolling a total of 21 women from four hospitals in the United States, randomized to placebo (N=11) versus BRX90 (N=10). The second and third trials were reported together in a single publication.[17] Women were recruited at 30 centers in the United States. Two trials were conducted, including a three-arm trial of placebo, BRX60 or BRX90 (N=138 randomized, 122 treated), and a two-arm trial comparing BRX90 with placebo (N=108 randomized, 104 treated). The second publication included an integrated analysis that pooled participants treated with BRX 90 (N=102) versus placebo (N=107).

In the integrated analysis, BRX90 infusion reduced HAM-D scores more than placebo at 60 hours (least square [LS] mean difference, SE -4.1, 0.9, $p<0.001$) and at 30 days (LS mean difference, SE -2.6, 1.1, $p=0.02$). Whereas BRX reduced HAM-D scores, results were mixed for other depression measures. BRX90 reduced MADRS and EPDS scores at 30 days in the phase 2 clinical trial, but in the phase 3 trials, only BRX60 differed from placebo. At 30 days post-treatment, there was no difference in PHQ-9 or GAD-9 scores in any of the treatment groups. The phase 2 trial evaluated maternal function and found no difference at day 30. The authors note that the trials were powered to observe differences in HAM-D scores; the trials were underpowered for other outcomes. Whether the specific focus of the instruments used (depression only vs. depression and anxiety) and mode of data collection (clinical interview vs. self-report) may have influenced the magnitude of outcomes is unclear.

We rated the strength of evidence as moderate across all depression symptom outcomes (Table B-7). We based this judgment on findings from three small trials with precise and consistent findings for HAM-D and imprecise but largely consistent for other measures of depression. We also note that the magnitude of benefit declined between the 60-hour measurement and the 30-day measurement of HAM-D.

Table B-7. Strength of evidence for effectiveness outcomes for brexanolone versus placebo

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women with postpartum depression	Brexanolone 90 vs. placebo, integrated analysis	Symptom response: Change in HAM-D score from baseline to 60 hours	Placebo: -12.8 BRX90: -17.0	SD not reported by RCT, results cannot be pooled LS mean difference (SE) BRX 90 vs. placebo: -4.1 (0.9), p<.001	3 RCTs, N=209, BRX90=102, placebo-107[17]	Low study limitations, precise (statistically significant results suggestive of benefit), consistent	Moderate across all symptom outcome measures
Women with postpartum depression	Brexanolone 90 vs. placebo, integrated analysis	Symptom response: Change in HAM-D score from baseline to 30 days	Placebo: -14.3 BRX90: -16.9	SD not reported by RCT, results cannot be pooled LS mean difference (SE) BRX 90 vs. placebo: -2.6 (1.1), p=0.02	3 RCTs, N=209, BRX90=102, placebo-107[17]	Low study limitations, precise (statistically significant results suggestive of benefit), consistent	
Women with postpartum depression	Brexanolone 60 vs. 90 vs. placebo	Symptom response: change in EPDS score from baseline to 30 days	Study 1: Placebo: -5.3 BRX90: -13.5 Study 2: Placebo: -9.2 BRX60: -12.8 BRX90: -11.9 Study 3: Placebo: -11.2 BRX90: -10.8	SD not reported by RCT, results cannot be pooled Study1: p using mixed effects model: 0.024 LS mean difference (SE) Study 2: BRX60 vs. placebo, -3.7 (1.7), p=0.03 BRX90 vs. placebo, -1.8 (1.6), p=0.55 Study 3: BRX90 vs. placebo, 0.4 (1.2), p=0.72	RCT Study 1: N=21, BRX90=10, placebo-11[19] Study 2, N=122, placebo=43, BRX60=38, BRX90=41[17] Study 3, N=104, placebo=53, BRX90=51[17]	Low study limitations, seriously imprecise (nonsignificant results, underpowered), consistent	

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women with postpartum depression	Brexanolone 60 vs. 90 vs. placebo	Symptom response: change in MADRS score from baseline to 30 days	Study 1: Placebo: -11.3 BRX90: -26.2 Study 2: Placebo: -19.4 BRX60: -25.1 BRX90: -23.0 Study 3: Placebo: -20.5 BRX90: -20.5	SD not reported by RCT, results cannot be pooled Study 1: p using mixed effects model:.01 LS mean difference (SE) Study 2: BRX60 vs. placebo, -5.6 (2.8), p=.045. BRX90 vs. placebo, -3.6 (2.7), p=.19 Study 3: BRX90 vs. placebo, 0 (1.8), p=.98	RCT Study 1: N=21, BRX90=10, placebo-11[19] Study 2, N=122, placebo=43, BRX60=38, BRX90=41[17] Study 3, N=104, placebo=53, BRX90=51[17]	Low study limitations, seriously imprecise (nonsignificant results, underpowered), consistent	
Women with postpartum depression	Brexanolone 60 vs. 90 vs. placebo	Symptom response: change in PHQ9 score from baseline to 30 days	Study 1: Placebo: -8.3 BRX90: -11.0 Study 2: Placebo: -9.5 BRX60: -12.0 BRX90: -11.9 Study 3: Placebo: -8.3 BRX90: -11.0	SD not reported by RCT, results cannot be pooled Study 1: p using mixed-effects model:.47 LS mean difference (SE) Study 2: BRX60 vs. placebo, -2.5 (1.6), p=0.13 BRX90 vs. placebo, -2.4 (1.6), p=0.13 Study 3: BRX90 vs. placebo, -0.5 (1.1), p=0.69	RCT Study 1: N=21, BRX90=10, placebo-11[19] Study 2, N=122, placebo=43, BRX60=38, BRX90=41[17] Study 3, N=104, placebo=53, BRX90=51[17]	Low study limitations, seriously imprecise (nonsignificant results, underpowered), consistent	

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women with postpartum depression	Brexanolone 60 vs. 90 vs. placebo	Symptom response: change in GAD-7 score from baseline to 30 days	Study 1: Placebo: -8.1 BRX90: -8.7 Study 2: Placebo: -7.7 BRX60: -9.7 BRX90: -9.2 Study 3: Placebo: -9.9 BRX90: -10.2	SD not reported by RCT, results cannot be pooled Study 1: p using mixed-effects model: 0.47 LS mean difference (SE) Study 2: BRX60 vs. placebo, -2 (1.5), p=0.18 BRX90 vs. placebo, -1.5 (1.5), p=0.32 Study 3: BRX90 vs. placebo, -0.4 (1.1), p=0.78	RCT Study 1: N=21, BRX90=10, placebo-11[19] Study 2, N=122, placebo=43, BRX60=38, BRX90=41[17] Study 3, N=104, placebo=53, BRX90=51[17]	Low study limitations, seriously imprecise (nonsignificant results, underpowered), consistent	
Women with postpartum depression	Brexanolone 60 vs. placebo	Symptom response: change in Barkin Index of Maternal function	Placebo: 12.1 BRX90: 24.4	p=0.221	RCT N=21, BRX90=10, placebo-11[19]	Low study limitations, seriously imprecise (nonsignificant results, underpowered), consistency unknown	

BRX90 = brexanolone for postpartum depression; EPDS = Edinburgh Postnatal Depression Scale; GAD-7 = Generalized Anxiety Disorder 7-item; HAM-D = Hamilton Depression Rating; LS = least square; MADRS = Montgomery-Åsberg Depression Rating Scale; N = number; PHQ9 = Patient Health Questionnaire, 9 item; RCT = randomized controlled trial; SD = standard deviation; SE = standard error; vs. = versus.

Depression: Other Drugs

Overview

- No included publications reported on the benefits of citalopram, escitalopram, fluvoxamine, trazodone, serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), bupropion, or mirtazapine.

Bipolar Disorder: Mood Stabilizers

Overview

- Evidence from single small trials on recurrence and time to recurrence suggest benefit for treatment with mood stabilizers compared with discontinuation of treatment (low for benefit) during pregnancy.

Detailed Results

Two publications reported on mood stabilizers;[24, 26] of these, one reported on mood stabilizers as a class,[26] and one focused on lamotrigine.[24] For the study evaluating mood stabilizers as a class, participants were exposed to lithium (61.8%), anticonvulsants (36.0%; valproic acid, lamotrigine, carbamazepine, and gabapentin), and atypical antipsychotics (2.3%; olanzapine and quetiapine).[26] One was rated high risk of bias[24] and the other as having some risk-of-bias concerns.[26] Both were nonrandomized observational cohort studies. These publications drew from two cohorts from the United States (one from Massachusetts[26] and one from Georgia[24]). Publications compared pregnant women who were exposed to mood stabilizers with women with mood disorders who discontinued mood stabilizers.[24, 26]

Although the studies are small (and one is high risk of bias[24]), they reported substantially higher risks of recurrence or time to recurrence (time-to-25%-recurrence was 28.0 versus 2.0 weeks) for discontinuation of medications, suggesting low strength of evidence of benefit with mood stabilizers (Table B-8).

Table B-8. Strength of evidence for effectiveness: Mood stabilizers versus no treatment

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Bipolar disorder	Women with bipolar disorder who discontinued mood stabilizers vs. women exposed to mood stabilizers in pregnancy	Recurrence of bipolar disorder	53/62 (85.5%) vs.10/27 (37%) [26]	AHR for treatment discontinuation vs. exposure to mood stabilizers: 2.2 (95% CI, 1.2 to 4.2)[26]	1 cohort, N=89[26]	Moderate study limitations, imprecise (few events); consistency unknown	Low (favoring treatment with mood stabilizers)
Bipolar disorder	Women with bipolar disorder who discontinued mood stabilizers vs. women exposed to lamotrigine in pregnancy	Recurrence of bipolar disorder	16/16 (100%) vs 3/10 (30%). [24]	AHR for discontinuation vs. exposure to lamotrigine: 12.1 (95% CI, 1.6 to 91)[24]	1 cohort, n=26[24]	High study limitations (high risk of bias[24]) imprecise (few events, small N, wide CIs); consistency unknown; very large effect size	Low (favoring treatment with lamotrigine)

AHR = adjusted hazard ratio; CI = confidence interval; N = number; vs. = versus.

Schizophrenia: Antipsychotics

Overview

- No included publications reported on benefits of antipsychotic medications.

Pharmacologic Combinations

Overview

- No included publications reported on the benefits of pharmacologic combinations.

Nonspecific or Undefined Pharmacologic Interventions

Overview

- Seven publications reported on nonspecific or undefined pharmacologic interventions on maternal outcomes (C-section, deliberate self-harm, inpatient hospital stays, postnatal depression symptom severity, or relapse of major depression). Because the clinical utility is limited, we did not judge the risk of harms for maternal or child outcomes.

Detailed Results

Seven publications reported on nonspecific/undefined pharmacologic interventions.[18, 20, 28, 31, 32, 34] These publications drew from seven cohorts (1 from the Multinational Medication Use in Pregnancy Study,[18] 1 from the U.S. Medicaid Analytic eXtract,[20] 1 from MothertoBaby Antidepressants in Pregnancy Cohort,[32] 1 from a perinatal mental health unit based in Spain,[34] one based in Canada,[31] 1 based on a cohort in Australia,[33] and 1 based in the United States).[28] All were nonrandomized studies and were rated as having some risk of bias. Six of the publications focused on exposure during pregnancy,[20, 28, 31-34] and one focused on exposure during pregnancy and the postpartum period.[18] Five publications compared any antidepressant use to not exposed to antidepressants.[18, 20, 28, 31, 32] These five studies evaluated the outcomes of inpatient hospital stays, deliberate self-harm, postnatal depression symptom severity, relapse of major depression, and the likelihood of a C-section. Two studies evaluated the likelihood of a C-section: one study compared lithium plus antidepressants with not exposed to lithium plus antidepressants,[34] and one study compared antipsychotics use with not exposed to antipsychotics.[33] Because the interventions of these studies were not clearly defined, they are not evaluated any further given their limited clinical utility.

Key Question 2: Among pregnant and postpartum women, what is the comparative effectiveness of pharmacologic interventions on maternal outcomes among those with a new or preexisting anxiety disorder, depressive disorder, bipolar disorder, or schizophrenia?

Anxiety: Anti-Anxiety Medications

Overview

- No included publications reported on the comparative benefits of anxiolytics.

Depression: Fluoxetine Versus TCAs

Overview

- The evidence is insufficient to judge the comparative risk of harms from fluoxetine versus TCAs during pregnancy for any maternal outcomes (emergency C-section or

repeated C-section) or child outcomes (gestational age, birthweight, major congenital anomalies, or infant mental development).

Detailed Results

One high risk-of-bias publication from the Canadian Motherisk cohort reported on the comparative harms of fluoxetine versus TCAs as a class.[39] The publication reported on women who used one of the medications during the first trimester or longer.[39]

No significant differences were found in the risk of harms for maternal outcomes (emergency C-section or repeated C-section). The strength of evidence was rated as insufficient because of imprecision and potential risk of bias (Table B-9).

Table B-9. Strength of evidence for comparative effectiveness outcomes: Fluoxetine versus TCAs

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Pregnant women with depression	Fluoxetine vs. TCAs	Emergency C-section	4/42 (9.5%) vs. 5/43 (12%)[39]	RR, 0.82 (95% CI, 0.24 to 2.84)[39]	1 cohort, n=85[39]	High study limitations (high risk of bias[39]), seriously imprecise (few events, wide CIs), inconsistency unknown	Insufficient
Pregnant women with depression	Fluoxetine vs. TCAs	Repeated C-section	6/42 (14%) vs. 6/43 (14%)[39]	RR, 1.02 (95% CI, 0.36 to 2.92)[39]	1 cohort, n=85[39]	High study limitations (high risk of bias[39]), seriously imprecise (few events, wide CIs), inconsistency unknown	Insufficient

CI = confidence interval; n = number; RR = relative risk; TCA = tricyclic antidepressant; vs. = versus.

Depression: Sertraline Versus Nortriptyline

Overview

- One high risk-of-bias trial did not report any differences between sertraline and nortriptyline for postpartum depression for response; remission; time to response and remission; and general, sexual, or psychosocial functioning, but we rated the evidence as insufficient because of imprecision and potential bias.

Detailed Results

One RCT (rated high risk of bias) reported on the comparative effectiveness of sertraline versus nortriptyline for women with postpartum depression.[35, 36] Some women may also have had chronic depression: the study began including women with chronic depression after the trial started. Women were treated with a fixed dose strategy of 25 mg/day of sertraline or 10 mg/day of nortriptyline initially. The dose was escalated to 50 mg/day of sertraline or 25 mg/day of nortriptyline after 2 days and then gradually increased up to a maximum of 200 mg/day of sertraline and 150 mg/day nortriptyline if response or side effects did not prohibit further escalation. The study was rated high risk of bias because of high and differential attrition by 8 weeks (42% vs. 24%). The study was powered to detect differences in proportion greater than 32 percent, differences in time to remission of 28 percent, and differences in HRSD scores of less than -1.7 to more than 3.7 points and in GAS scores of less than -5.72 to more than 4.9 points.

The study was not powered to test for equivalence. The study did not report differences at 8 weeks or at other time points for response; remission; time to response and remission; and general, sexual, or psychosocial functioning. We graded the evidence as insufficient because of imprecision and potential for bias due to attrition (Table B-10).

Table B-10. Strength of evidence for comparative effectiveness outcomes: Sertraline versus nortriptyline

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women with postpartum depression (with or without chronic depression)	Sertraline vs. nortriptyline	Response at 8 weeks (50% reduction in HRSD)	31/55 (56.4%) vs. 37/54 (68.5%)[36]	RR, 0.94 (95% CI, 0.63 to 1.41)[36]	1 trial, N=108[36]	High study limitations (high risk of bias,[36]) imprecise (wide CIs), consistency unknown	Insufficient
Women with postpartum depression (with or without chronic depression)	Sertraline vs. nortriptyline	Time to response (50% reduction in HRSD)	NR	NR, p=.21	1 trial, N=95[36]	High study limitations (high risk of bias[36]) likely imprecise, consistency unknown	Insufficient
Women with postpartum depression (with or without chronic depression)	Sertraline vs. nortriptyline	Remission at 8 weeks (HRSD <7 at week 8)	25/55 (45.5%) vs. 26/54 (48.1%)[36]	RR, 0.82 (95% CI, 0.61 to 1.10)[36]	1 trial, N=108[36]	High study limitations (high risk of bias,[36]) imprecise (wide CIs), consistency unknown	Insufficient
Women with postpartum depression (with or without chronic depression)	Sertraline vs. nortriptyline	Time to remission at 8 weeks (HRSD <7 at week 8)	Median: 5 weeks vs. 5 weeks[36]	NR, p=0.82[36]	1 trial, N=95[36]	High study limitations (high risk of bias,[36]) imprecise (likely imprecise), consistency unknown	Insufficient
Women with postpartum depression (with or without chronic depression)	Sertraline vs. nortriptyline	Symptom scores (HRSD) at 8 weeks	NR	Effect size: 0.13 (95% CI, -0.26 to 0.55)[36]	1 trial, N=95[36]	High study limitations (high risk of bias[36]) imprecise (wide CIs), consistency unknown	Insufficient
Women with postpartum depression (with or without chronic depression)	Sertraline vs. nortriptyline	Symptom scores (CGI score of 0 or 1) at 8 weeks	32/36 (88.9%) vs. 44/47 (93.6%)[36]	RR, 0.95 (95% CI, 0.83 to 1.09)[36]	1 trial, N=83[36]	High study limitations (high risk of bias,[36]) imprecise (wide CIs), consistency unknown	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women with postpartum depression (with or without chronic depression)	Sertraline vs. nortriptyline	Global functioning (GAS) at 8 weeks	NR	Effect size 0.005 (95% CI, -0.44 to 0.38)[36]	1 trial, N=95[36]	High study limitations (high risk of bias[36]) imprecise (wide CIs), consistency unknown	Insufficient
Women with postpartum depression (with or without chronic depression)	Sertraline vs. nortriptyline	Social functioning (SPQ) at 8 weeks	NR	NR, p=0.33[36]	1 trial, N=83[36]	High study limitations (high risk of bias,[36]) imprecise (wide CIs), consistency unknown	Insufficient
Women with postpartum depression (with or without chronic depression)	Sertraline vs. nortriptyline	Arizona Sexual Experience Scale (ASEX)	NR	AOR, 2.35 (95% CI, 0.6 to 9.26)[35]	1 trial, N=70[35]	High study limitations (high risk of bias,[35]) imprecise (wide CIs), consistency unknown	Insufficient

ASEX = Arizona Sexual Experience Scale; AOR = adjusted odds ratio; CGI = Clinical Global Impression; CI = confidence interval; GAS = general adaptation syndrome; HRSD = Hamilton Rating Scale for Depression; N = number; NR = not reported; RR = relative risk; SPQ = Social Problems Questionnaire.

Depression: Other Drugs

Overview

- No included publications reported on the comparative benefits of other medications for depression, including brexanolone, bupropion, mirtazapine, MAOIs, SNRIs, or TCAs.

Bipolar Disorder: Lamotrigine Versus Lithium

Overview

- The evidence for lamotrigine versus lithium during pregnancy is insufficient to judge the comparative effectiveness of associated maternal benefits (specifically reduced postpartum psychiatric admissions).

Detailed Results

One publication, focusing on comparing lithium and lamotrigine[37] drew from a cohort from Denmark. The study was rated as high risk of bias. The publication focused on any exposure from preconception through postpartum.[37]

The evidence is insufficient to judge the associated maternal benefits (reduced postpartum psychiatric admissions) (Table B-11).

Table B-11. Strength of evidence for comparative effectiveness: Lamotrigine versus lithium

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women with bipolar disorder	Lamotrigine vs. lithium exposure during pregnancy	Postpartum psychiatric admission	4/55 (7.3%) vs. 9/59 (15.2%)[37]	OR, 0.83 (95% CI, 0.22 to 3.14)[37]	1 cohort, n=114[37]	High study limitations high risk of bias,[37] imprecise (wide CIs), consistency unknown	Insufficient

CI = confidence interval; n = number; OR = odds ratio; vs. = versus.

Bipolar Disorder: Olanzapine Versus Lithium

Overview

- The evidence for olanzapine versus lithium during pregnancy is insufficient to judge the comparative effectiveness of associated maternal benefits (specifically mood episodes).

Detailed Results

One publication, focusing on comparing olanzapine and lamotrigine,[38] drew from a cohort from Canada. The study was rated as high risk of bias. The publication focused on any exposure during pregnancy.[38]

The evidence is insufficient to judge the associated maternal benefits (postpartum mood episodes) (Table B-12).

Table B-12. Strength of evidence for comparative effectiveness: Olanzapine versus lithium

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women with bipolar disorder	Olanzapine vs. Lithium exposure during pregnancy	Postpartum mood episode	2/9 (22.2%) vs. 2/2 (100%)[38]	RR, 0.3 (95% CI, 0.09 to 0.98)[38]	1 cohort, n=25[38]	High study limitations, high risk of bias,[38] imprecise (few events, small N, wide CIs), consistency unknown	Insufficient

CI = confidence interval; n = number; RR = relative risk; vs = versus.

Bipolar Disorder: Lithium Versus Sodium Valproate

Overview

- The evidence for lithium versus sodium valproate postpartum is insufficient to judge the comparative effectiveness of associated maternal benefits (relapse).

Detailed Results

One high risk-of-bias publication, comparing lithium and sodium valproate,[41] drew from a mother-baby-unit in a hospital-based cohort from Australia. The publication focused on exposure during the postpartum period, but the duration of the period was not defined. Women were on

lithium, sodium valproate, or a combination on discharge. Relapse was defined as readmission to the mother-baby-unit or detailed as such in patient notes.

The evidence is insufficient to judge the associated maternal benefits (relapse) (Table B-13).

Table B-13. Strength of evidence for comparative effectiveness: Lithium versus sodium valproate

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women with bipolar disorder	Lithium vs. sodium valproate exposure postpartum	Relapse	13/34 (38.2%) vs. 14/30 (46.7%)[41]	RR, 0.82 (95% CI, 0.46 to 1.45)[41]	1 cohort, n=64[41]	High study limitations (high risk of bias,[41]) imprecise (few events, small Ns, wide CIs), consistency unknown	Insufficient

CI = confidence interval; n = number; RR = relative risk; vs = versus.

Bipolar Disorder: Lithium Versus Lithium Plus Sodium Valproate

Overview

- The evidence for lithium versus lithium plus sodium valproate postpartum is insufficient to judge the comparative effectiveness of associated maternal benefits (relapse).

Detailed Results

One high risk-of-bias publication, comparing lithium and lithium plus sodium valproate,[41] drew from a mother-baby-unit in a hospital-based cohort from Australia. The publication focused on exposure during the postpartum period, but the duration of the period was not defined. Women were on lithium, sodium valproate, or a combination on discharge. Relapse was defined as readmission to the mother-baby-unit or detailed as such in patient notes.

The evidence is insufficient to judge the associated maternal benefits (relapse) (Table B-14).

Table B-14. Strength of evidence for comparative effectiveness: Lithium versus lithium plus sodium valproate

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women with bipolar disorder	Lithium vs. lithium plus sodium valproate exposure postpartum	Relapse	13/34 (38.2%) vs. 1/3 (33.3%)[41]	RR, 1.15 (95% CI, 0.22 to 6.01)[41]	1 cohort, n=38[41]	High study limitations (high risk of bias,[41]) imprecise (few events, small Ns, wide CIs), consistency unknown	Insufficient

CI = confidence interval; n = number; RR = relative risk; vs = versus.

Bipolar Disorder: Sodium Valproate Versus Lithium Plus Sodium Valproate

Overview

- The evidence for sodium valproate versus lithium plus sodium valproate postpartum is insufficient to judge the comparative effectiveness of associated maternal benefits (relapse).

Detailed Results

One high risk-of-bias publication, comparing sodium valproate versus lithium plus sodium valproate,[41] drew from a mother-baby-unit in a hospital-based cohort from Australia. The publication focused on exposure during the postpartum period, but the duration of the period was not defined. Women were on lithium, sodium valproate, or a combination on discharge. Relapse was defined as readmission to the mother-baby-unit or detailed as such in patient notes.

The evidence is insufficient to judge the associated maternal benefits (relapse) (Table B-15).

Table B-15. Strength of evidence for comparative effectiveness: Sodium valproate versus lithium plus sodium valproate

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women with bipolar disorder	Sodium valproate vs. lithium plus sodium valproate exposure postpartum	Relapse	14/30 (46.7%) vs. 1/3 (33.3%)[41]	RR, 1.40 (95% CI, 0.27 to 7.26)[41]	1 cohort, n=33[41]	High study limitations (high risk of bias[41]) imprecise (few events, small Ns, wide CIs), consistency unknown	Insufficient

CI = confidence interval; n = number; RR = relative risk; vs = versus.

Bipolar Disorder: Lithium Versus Paroxetine

Overview

- The evidence for lithium versus paroxetine during pregnancy is insufficient to judge the comparative effectiveness of associated maternal benefits (specifically a mood episode).

Detailed Results

One publication, focusing on comparing lithium versus paroxetine,[38] drew from a cohort from Canada. The study was rated as high risk of bias. The publication focused on any exposure during pregnancy.[38]

The evidence is insufficient to judge the associated maternal benefits (postpartum mood episodes) (Table B-16).

Table B-16. Strength of evidence for comparative effectiveness: Lithium versus paroxetine

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women with bipolar disorder	Lithium vs. Paroxetine exposure during pregnancy	Postpartum mood episode	2/2 (100%) vs. 2/2 (100%)[38]	Not calculated	1 cohort, n=25[38]	High study limitations, high risk of bias,[38] imprecise, consistency unknown	Insufficient

n = number; vs. = versus.

Schizophrenia: Antipsychotics Versus Specific Active Comparators

Overview

- No included publications reported on the comparative benefits on antipsychotic medications.

Pharmacologic Combinations Versus Specific Active Comparators

Overview

- No included publications reported on the benefits of pharmacologic combinations.

Nonspecific or Undefined Pharmacologic Interventions Versus Specific Active Comparators

Overview

- No included publications reported on the benefits of nonspecific/undefined pharmacologic interventions.

Key Question 3: Among reproductive-aged 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?

Anti-Anxiety Medications

Overview

- Benzodiazepine exposure 90 days before conception may be associated with an increased risk of ectopic pregnancy when compared with no exposure to benzodiazepines among unexposed women having at least one anxiety diagnosis in the year before conception (low strength of evidence of harms).
- Benzodiazepine exposure early during pregnancy may be associated with an increased risk of spontaneous abortion when compared with no exposure to benzodiazepines among unexposed women with a history of mood or anxiety disorders (low strength of evidence of harms).

- Benzodiazepine exposure during pregnancy may be associated with an increased risk of neonatal intensive care unit (NICU) admission when compared with no exposure to benzodiazepines among women with a history of psychiatric disorders (low strength of evidence of harms).
- The evidence is insufficient to judge the risk of harms for maternal (spontaneous abortion, preeclampsia) or child outcomes (perinatal mortality, prematurity, birth weight, breathing difficulty, feeding difficulty, Apgar score, or major congenital anomalies).

Detailed Results

Five publications reported on maternal or fetal harms of anxiolytics, specifically on benzodiazepines and sedative-hypnotics (Table B-17).[46, 71, 79, 100, 103] Medications such as SSRIs, TCAs, and SNRIs that may also be prescribed for anxiety are described elsewhere in this review. All but one were cohort studies (1 was a case-control) and focused on exposure to anxiolytics immediately before or during pregnancy, with two studies exclusively focusing on first trimester exposure.[71, 79] The five studies drew from four cohorts of pregnant women (the Health improvement Network [THIN] based in the United Kingdom,[71, 79] the Quebec Pregnancy Cohort in Canada,[100] the MarketScan Research Databases,[103] and National Pregnancy Registry for Psychiatric Medications based in the United States[46]).

Every study reported on benzodiazepines as a class, although one trial specifically evaluated diazepam and temazepam.[71] Two studies[71, 79] compared pregnant women exposed to anxiolytics with untreated anxiety. One of those studies also compared women who continued benzodiazepine use during the first trimester to women who discontinue medication.[79] Three studies compared women with benzodiazepine exposure to those without exposure to benzodiazepine during pregnancy but with a history of psychiatric morbidity.[46, 100, 103]

One study was rated as having some concerns[46] and two were rated as high risk of bias.[71, 79]

Evidence from one study[103] suggests 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 strength of evidence of harms). Although residual confounding may explain these results, 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 as a result.[103] The absolute risk difference is 7 per 1,000 (95% CI, 4 to 11).

Evidence from two studies[79, 100] suggests an increased risk of spontaneous abortion with benzodiazepine exposure 90 days before conception when compared with untreated or a history of mood disorders or anxiety (graded low strength of evidence of harms). 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.[103] The absolute risk difference is 73 per 1,000 (95% CI, 36 to 109).

Table B-17. Strength of evidence for harms outcomes: Anxiolytics versus no treatment

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Pregnant women with least one anxiety diagnosis in the year before conception	Benzodiazepine exposure 90 days before conception vs. no benzodiazepine exposure before conception	Ectopic pregnancy	249/9,188 (2.71%) vs. 1,730/81,291 (2.13%)[103]	ARR: 1.33 (95% CI, 1.17 to 1.51)[103]	1 cohort, N=90,479[103]	Moderate study limitations, precise, consistency unknown	Low for harms with benzodiazepine
Pregnant women with depression or anxiety	Benzodiazepine exposure in first trimester vs. untreated depression or anxiety during pregnancy	Perinatal death	16/2,384 (0.7%) vs. 20/3,647 (0.5%)[79]	RRR, 1.4 (95% CI, 0.6 to 1.9)[79]	1 cohort, N=6,031[79]	High study limitations (high risk of bias[79]), imprecision (wide CIs spanning the null, few events), consistency unknown	Insufficient
Pregnant women with depression or anxiety	Benzodiazepine exposure in first trimester[79] or within the first 19 weeks[100] vs. untreated or a history of mood disorders or anxiety during pregnancy	Spontaneous abortion	386/2,384 (16%) vs. 442/3,647 (12%)[79] 198 cases/570 controls vs. 3,221 cases/15,382 controls[100]	RRR, 1.6 (95% CI, 1.3 to 1.9)[79] AOR: 2.85 (95% CI, 1.72 to 4.72)[100]	1 cohort, 1 case-control study, N=21,983[79, 100]	Moderate study limitations (high risk of bias[79]) precise, consistent	Low for harms with benzodiazepine
Pregnant women with depression or anxiety	Continuation of benzodiazepine through first trimester vs. discontinuation of benzodiazepine during first trimester	Perinatal death	6/611 (1%) vs. 19/2,717 (0.7%)[79]	RRR, 1.7 (95% CI, 0.5 to 6.0)[79]	1 cohort, N=3,328[79]	High study limitations (high risk of bias[79]) imprecision (wide CIs spanning the null, few events), consistency unknown	Insufficient
Pregnant women with depression or anxiety	Continuation of benzodiazepine through first trimester vs. discontinuation of benzodiazepine during first trimester	Spontaneous abortion	105/611 (17%) vs. 415/2,717 (15%)[79]	RRR, 1.5 (95% CI, 1.0 to 2.1)[79]	1 cohort, N=3,328[79]	High study limitations (high risk of bias[79]) precise, consistency unknown	Insufficient
Pregnant women with depression or anxiety	Diazepam use in first trimester vs. untreated depression or anxiety during pregnancy	Major congenital anomalies	31/1,159 (2.7%) vs. 518/19,193 (2.7%)[71]	AOR, 0.99 (95% CI, 0.61 to 1.61)[71]	1 cohort, N=20,352[71]	High study limitations (high risk of bias[71]) imprecision (wide CIs spanning the null), consistency unknown	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Pregnant women with depression or anxiety	Temazepam use in first trimester vs. untreated depression or anxiety during pregnancy	Major congenital anomalies	11/379 (2.9%) vs. 518/19,193 (2.7%)[71]	AOR, 1.04 (95% CI, 0.47 to 2.32)[71]	1 cohort, N=19,572[71]	High study limitations (high risk of bias[71]) imprecision (wide CIs spanning the null), consistency unknown	Insufficient
Pregnant women with a psychiatric disorder	Benzodiazepine exposure during pregnancy vs. unexposed to benzodiazepine use during pregnancy	Low birth weight	7/112 (6.3%) vs. 16/398 (4%)[46]	AOR, 2.33 (95% CI, 0.63 to 8.59)[46]	1 cohort, N=510[46]	Moderate study limitations, serious imprecision (wide CIs spanning the null, few events), consistency unknown	Insufficient
Pregnant women with a psychiatric disorder	Benzodiazepine exposure during pregnancy vs. unexposed to benzodiazepine use during pregnancy	High birth weight	11/112 (9.8%) vs. 47/398 (11.8%)[46]	AOR, 0.94 (95% CI, 0.38 to 2.3)[46]	1 cohort, N=510[46]	Moderate study limitations, serious imprecision (wide CIs spanning the null, few events), consistency unknown	Insufficient
Pregnant women with a psychiatric disorder	Benzodiazepine exposure during pregnancy vs. unexposed to benzodiazepine use during pregnancy	Breathing difficulty in neonate	20/96 (20.8%) vs. 78/387 (20.2%)[46]	AOR, 1.84 (95% CI, 0.87 to 3.93)[46]	1 cohort, N=483[46]	Moderate study limitations, serious imprecision (wide CIs spanning the null, few events), consistency unknown	Insufficient
Pregnant women with a psychiatric disorder	Benzodiazepine exposure during pregnancy vs. unexposed to benzodiazepine use during pregnancy	Feeding difficulties in neonate	21/96 (21.9%) vs. 78/387 (20.2%)[46]	AOR, 1.4 (95% CI, 0.65 to 3.04)[46]	1 cohort, N=483[46]	Moderate study limitations, serious imprecision (wide CIs spanning the null, few events), consistency unknown	Insufficient
Pregnant women with a psychiatric disorder	Benzodiazepine exposure during pregnancy vs. unexposed to benzodiazepine use during pregnancy	Low 5-minute Apgar scores[46]	6/108 (5.6%) vs. 12/378 (3.2%)[46]	AOR, 4.91 (95% CI, 0.69 to 34.96)[46]	1 cohort, N=486[46]	Moderate study limitations, serious imprecision (wide CIs spanning the null, few events), consistency unknown	Insufficient
Pregnant women with a psychiatric disorder	Benzodiazepine exposure during pregnancy vs. unexposed to benzodiazepine use during pregnancy	NICU admission	32/144 (22.2%) vs. 125/649 (19.3%)[46]	AOR, 2.02(95 % CI, 1.11 to 3.66)[46]	1 cohort, N=793[46]	Moderate study limitations, precise, consistency unknown	Low for harms of benzodiazepine

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Pregnant women with a psychiatric disorder	Benzodiazepine exposure during pregnancy vs. unexposed to benzodiazepine use during pregnancy	Prematurity	17/144 (11.8%) vs. 87/650 (13.4%)[46]	AOR, 1.31 (95% CI, 0.55 to 2.32)[46]	1 cohort, N=794[46]	Moderate study limitations, serious imprecision (wide CIs spanning the null, few events), consistency unknown	Insufficient
Pregnant women with a psychiatric disorder	Benzodiazepine exposure during pregnancy vs. unexposed to benzodiazepine use during pregnancy	Preeclampsia	30/144 (20.8%) vs. 118/650 (18.2%)[46]	AOR, 0.81 (95% CI, 0.43 to 1.52)[46]	1 cohort, N=794[46]	Moderate study limitations, serious imprecision (wide CIs spanning the null, few events), consistency unknown	Insufficient

AOR = adjusted odds ratio; CI = confidence interval; KQ = Key Question; N = number; NICU = neonatal intensive care unit; RRR = relative risk reduction; vs. = versus.

The evidence for anxiolytics is insufficient to draw conclusions on preeclampsia. Regarding fetal harms, the evidence suggests that benzodiazepine exposure during pregnancy may be associated with an increased risk of NICU admission when compared with no exposure to benzodiazepines among women with a history of psychiatric disorders.[46] The authors noted several differences between the comparison arms and the results adjusted for these confounders, but residual confounding cannot be ruled out. Additionally, NICU admission[147] may be confounded by provider knowledge of antenatal exposure to psychotropic medications and hospital protocols. Until recently, neonatal abstinence syndrome due to prenatal exposure to opiates or benzodiazepines was typically treated in the neonatal intensive care unit. In an analysis of discharges from 23 tertiary care pediatric hospitals between January 2013 and March 2016, 93 percent of infants receiving pharmacologic treatment and 72 percent of infants receiving nonpharmacologic treatment were admitted to the NICU.[147]

Hypnotic Sedatives

Overview

- The evidence on hypnotic sedatives (zolpidem and zopiclone) during pregnancy is insufficient to judge the risk of harms for maternal (hypertension/preeclampsia) or child outcomes (preterm delivery, major congenital anomalies, NICU admission, respiratory difficulties, lethargy, hypotonia, Apgar scores)

Detailed Results

Two publications reported on other medications.[71, 92]These publications drew from two cohorts (one from THIN[71] and one from a cohort based in the United States[92]). Both were nonrandomized studies and rated as high risk of bias.[71, 92]

Both publications focused on exposure during pregnancy. One compared zopiclone exposure to untreated depression or anxiety,[71] and one compared zolpidem exposure to untreated psychiatric illness.[92]

The evidence for other medications, is insufficient to judge the risk of maternal harms (preterm delivery, hypertension/preeclampsia) or child outcomes (major congenital anomalies, NICU admission, respiratory difficulties, lethargy, hypotonia, Apgar score) (Table B-18).

Table B-18. Strength of evidence for harms outcomes: Other medications versus no treatment

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women with psychiatric illness	Zolpidem exposure during pregnancy vs. unexposed to zolpidem during pregnancy	Hypertension/ Preeclampsia	3/45 (6.7%) vs. 4/45 (8.9%)[92]	NR, NS based on multivariate conditional logistic regression, p = 1.00[92]	1 cohort, n=90[92]	Imprecise, consistent, high risk of bias[92]	Insufficient
Women with psychiatric illness	Zolpidem exposure during pregnancy vs. unexposed to zolpidem during pregnancy	Preterm delivery	12/45 (26.7%) vs. 6/45 (13.3%)[92]	NR, NS based on multivariate conditional logistic regression, p <.18[92]	1 cohort, n=90[92]	Imprecise, consistent, high risk of bias[92]	Insufficient
Women with psychiatric illness	Zolpidem exposure during pregnancy vs. unexposed to zolpidem during pregnancy	Hypotonia	0/45 (0.0%) vs. 4/45 (8.9%)[92]	NR, NS based on multivariate conditional logistic regression, p <.13[92]	1 cohort, n=90[92]	Imprecise, consistent, high risk of bias[92]	Insufficient
Women with psychiatric illness	Zolpidem exposure during pregnancy vs. unexposed to zolpidem during pregnancy	Lethargy	1/45 (2.2%) vs. 4/45 (8.9%)[92]	NR, NS based on multivariate conditional logistic regression, p <.38[92]	1 cohort, n=90[92]	Imprecise, consistent, high risk of bias[92]	Insufficient
Women with psychiatric illness	Zolpidem exposure during pregnancy vs. unexposed to zolpidem during pregnancy	NICU admission	4/45 (8.9%) vs. 6/45 (13.3%)[92]	NR, NS based on multivariate conditional logistic regression, p <.76[92]	1 cohort, n=90[92]	Imprecise, consistent, high risk of bias[92]	Insufficient
Women with psychiatric illness	Zolpidem exposure during pregnancy vs. unexposed to zolpidem during pregnancy	Respiratory difficulty	10/45 (22.2%) vs. 14/45 (31.1%)[92]	NR, NS based on multivariate conditional logistic regression, p <.49[92]	1 cohort, n=90[92]	Imprecise, consistent, high risk of bias[92]	Insufficient
Women with psychiatric illness	Zolpidem exposure during pregnancy vs. unexposed to zolpidem during pregnancy	Apgar score at 1 minute	NR[92]	NR, NS based on multivariate conditional logistic regression, p <.14[92]	1 cohort, n=90[92]	Imprecise, consistent, high risk of bias[92]	Insufficient
Women with psychiatric illness	Zolpidem exposure during pregnancy vs. unexposed to zolpidem during pregnancy	Apgar score at 5 minutes	NR[92]	NR, NS based on multivariate conditional logistic regression, p <.10[92]	1 cohort, n=90[92]	Imprecise, consistent, high risk of bias[92]	Insufficient
Women with depression or anxiety	Zopiclone exposure during pregnancy vs. unexposed women with untreated depression or anxiety	Major congenital anomalies	10/406 (2.5%) vs. 518/19193 (2.7%)[71]	AOR: 0.93 (95% CI, (0.4 to 2.15)[71]	1 cohort; n=19599[71]	Imprecise, consistent, high risk of bias[71]	Insufficient

AOR = adjusted odds ratio; CI = confidence interval; N = number; NICU = neonatal intensive care unit; NR = not reported; NS = not sufficient; vs. = versus.

SSRIs as a Drug Class

Overview

- Exposure to SSRIs in pregnancy may be associated with an increased risk of low Apgar scores, respiratory distress, and primary persistent hypertension of the newborn (without cardiac anomaly or lung hypoplasia in full-term deliveries) compared with no treatment (low strength of evidence).
- Current or recent exposure (at or up to 1 month prior to delivery) may be associated with an increased risk of postpartum hemorrhage; the evidence for past exposure (1 to 5 months prior to delivery) or undefined exposure is insufficient.
- Exposure to SSRIs in pregnancy may be associated with an increased risk of depression in the child compared with no treatment (low strength of evidence).
- The evidence for SSRIs as a class during pregnancy is insufficient to judge the risk of harms for maternal (spontaneous abortion, gestational diabetes, hypertension, preeclampsia) or child outcomes (preterm birth, perinatal mortality, major congenital anomalies, cardiac anomalies, small for gestational age, low birth weight, birthweight, gestational age, neonatal convulsions, NICU admissions, extended hospital stay, feeding problems, jaundice, infant and child behavior and development, infant or child weight, autism spectrum disorder, attention-deficit/hyperactivity disorder, or anxiety).

Detailed Results

Thirty-two publications (31 studies)[6-9, 27, 54, 57-61, 63, 64, 66, 69, 70, 72, 74-76, 79-84, 88, 91, 93, 95, 104, 106] reported on harms associated with SSRI exposure in pregnancy compared with no exposure (Table B-19). Multiple publications reported on different outcomes from the same database (British Columba,[27, 81] Finland population register,[59, 63, 66] Lombardy healthcare utilization database,[54, 58] THIN,[72, 79] and the U.S. Medicaid Analytic eXtract[6, 7, 74, 75]) or potentially from the same population source (Danish Medical Birth Registry[91] and Danish National Birth Cohort;[9, 60] one or more databases from Quebec including the Quebec Pregnancy/Children Cohort, the public health plan administrator database [Regie I'assurance maladie du Quebec or RAMQ], the hospitalization database [Med-Echo], and the Quebec birth and death registries[57, 64, 70, 83, 93]). Other cohorts represented by single publications include the Generation R study,[61] the Lifestyle During Pregnancy Study,[69] the Norwegian Mother and Child Cohort Study (MoBa),[8] the Slone Epidemiology Center Birth Defects Study,[84] the Women's and Children's Health Network,[80] a Kaiser Permanente Washington cohort,[104] the National Birth Defects Prevention Study,[106] and unnamed cohorts.[76, 82, 88, 95]

Table B-19. Strength of evidence for harms: SSRIs versus no treatment

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Depressed women	SSRI exposure in pregnancy vs. unexposed women with depression	Spontaneous abortion	93/938 (9.9%) vs. 720/8,877 (8.1%)[64] 1,539/ 10,312 (14.9) vs. 442/3,647 (12.1%)[79]	ARR, 1.2 (95% CI, 0.94 to 1.5)[64] and 1.4 (99% CI, 1.2 to 1.7)[79]	2 cohorts; n=23,774[64, 79]	Moderate study limitations (one high risk of bias study,[79]) imprecise (wide CIs), consistent	Insufficient
Psychiatric disorder during pregnancy or exposed to SSRIs	SSRI exposure during pregnancy vs. unexposed women with a psychiatric during pregnancy	Bleeding during and after delivery	520/15,729 (3.3%) vs. 342/9,652 (3.5%)[66]	AOR, 0.83 (95% CI, 0.71 to 0.96)[66] AOR, for exposure in the first trimester: 0.82 (95% CI, 0.69 to 0.99) AOR, for exposure in the second and/or third trimesters: 0.84 (95% CI, 0.71 to 1.00)	1 cohort, n=104,841[66]	High study limitations (high risk of bias[66]), precise, consistency	Insufficient
Mood or anxiety disorder	Current SSRI exposure (exposure during delivery) vs. unexposed with mood or anxiety disorder	Postpartum hemorrhage	503/12,710 (3.96%) vs. 1,896/69,044 (2.75%)[74]	ARR, 1.47 (95% CI, 1.33 to 1.62)[74]	1 cohort, n=81,754[74]	Moderate study limitations, precise, consistency unknown	Low for harms for current exposure with SSRIs
Mood or anxiety disorder	Recent SSRI exposure (within 1 month before delivery) vs. unexposed with mood or anxiety disorder	Postpartum hemorrhage	196/6,096 (3.2%) vs. 1,896/ 69,044 (2.75%)[74]	ARR, 1.19 (95% CI, 1.03 to 1.38)[74]	1 cohort, n= 75,140[74]	Moderate study limitations, precise, consistency unknown	Low for harms for recent exposure with SSRIs
Mood or anxiety disorder	Past SSRI exposure (1 to 5 months before delivery) vs. unexposed with mood or anxiety disorder	Postpartum hemorrhage	264/10,416 (2.5%) vs. 1,896/ 69,044 (2.75%)[74]	ARR, 0.93 (95% CI, 0.82 to 1.06)[74]	1 cohort, n= 69,984[74]	Moderate study limitations, imprecision (wide CIs spanning the null), consistency unknown	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Depressed, psychiatric disorders, or discontinued SSRIs during pregnancy exposed to SSRIs	SSRI exposure during pregnancy vs. no exposure (exposure prior to pregnancy or depressed or with psychiatric disorder)	Preterm birth	741/15,729 (4.7%) vs. 515/9,652; (5.3%)[66] 17/192 (8.8%) vs. 415/5,710 (7.3%);[84] 55/221 (24.9%) vs. 185/1,566 (11.8%);[80] 3/37 (8.11%) vs. 3/19 (15.79%)[95] N=NR for two publications[27, 58]	Overall 5 of 6 studies do not report increased risks with SSRIs. Prevalence, AOR, ARRs range from 0.84[66] to 2.68[80] with CIs spanning the null in 2 of 4 studies null (one study reported higher odds in the SSRI group,[80] the other reported lower odds in the SSRI group[66]; difference in incidence: 0.007 (95% CI, -0.018 to 0.034);[27] NR, p=0.948[95]	6 cohorts; N>33,666 N=NR in one study[27])[58, 66, 80, 84, 95]	High study limitations (5 high risk-of-bias studies[58, 66, 80, 84, 95]), mostly consistent, imprecise (wide CIs in some studies)	Insufficient
Exposure to anti-depressants before pregnancy or exposed to SSRIs during pregnancy	SSRI exposure during pregnancy vs. exposure before but not during pregnancy	Gestational diabetes	126/1,403 (8.90%) vs. 90/1,211 (7.43%)[104]	RR (inverse probability of treatment weighted): 1.10 (95% CI, 0.84 to 1.45)[104]	1 cohort, n=2,614[104]	Moderate study limitations, imprecise (wide CIs), consistency unknown	Insufficient
Depressed women	SSRI exposure during pregnancy vs. unexposed women with depression	Preeclampsia	303/5215 (5.8%) vs. 222/4,661 (4.8%);[75] 105/3,169 (3.3%) vs. 1569/65,392 (2.4%)[81]	ARR, 1.21 (95% CI, 1.02 to 1.45)[75] but bias corrected RR=0.9; ARR, 1.22 (95% CI, 0.97 to 1.54[81]; severe preeclampsia: ARR, 1.03, 95% CI, 0.81 to 1.18	2 cohorts, n=78,437[75, 81]	Moderate study limitations (both have some risk-of-bias concerns), imprecise (wide CIs), inconsistent	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Psychiatric disorder or exposed to SSRIs	SSRI exposure during pregnancy vs. unexposed with psychiatric disorders	Hypertension	813/15,729 (5.2%) vs. 434/9,652 (4.5%)[66]	AOR, 1.1 (95% CI, 0.97 to 1.26)[66]	1 cohort, n=25,381[66]	High study limitations (high risk of bias[66]) imprecise (wide CIs spanning the null), consistency unknown	Insufficient
Depressed or anxious women	SSRI exposure in pregnancy vs. unexposed women with depression	Perinatal mortality	57/10312 (0.6%) vs. 20/3,647 (0.6%)[79]	ARR, 1.2 (99% CI, 0.6 to 2.3)[79]	1 cohort, n=13,959[79]	High study limitations (high study limitations[79]), imprecise (wide CIs), consistency unknown	Insufficient
History of psychiatric disorder or depression or SSRI-exposed women	SSRI exposure in pregnancy vs. unexposed women with depression or psychiatric disorder	Small for gestational age	Varies across studies from 2.5% to 17.4% in the treatment arm, and 2.5% to 14.7% in the control arm[27, 54, 66, 83, 84]	Five[27, 54, 66, 80, 83] of six studies report nonsignificant results (adjusted prevalence ratios, ARR, AOR, difference in incidence) with CIs spanning the null; one study reported AOR, of 1.68 (95% CI, 1.03 to 2.74)[84] ARR, varies by trimester of exposure from 0.7 to 1.4, 95% CI, spans the null[83]	5 cohort studies,1 case-control, n varies by trimester, n=43,185[27, 54, 66, 80, 83, 84]	High study limitations (4 of 6 high risk-of-bias studies[54, 66, 80, 84]), imprecise (wide CIs), mostly consistent	Insufficient
Use of antidepressants before or during pregnancy or psychiatric illness	SSRI exposure during pregnancy vs. SSRI exposure just before but not during pregnancy or psychiatric illness with no exposure	Low birth weight	42/221 (19.0%) vs. 150/1,566 (9.6%);[80] NR in one study;[58] 4/36 (11.11%) vs. 3/19 (15.79%)[95]	Adjusted prevalence ratio: 1.1 (95% CI, 0.9 to 1.3)[58] AOR, 2.26 (95% CI, 1.31 to 3.91) NR, p=0.613[95]	3 cohorts, N>1,842,[80, 95] N=NR in one study[58]	High study limitations (high risk of bias[58, 80, 95]), imprecise (wide CIs), inconsistent	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Exposed to SSRIs during pregnancy or depressed	SSRI exposure during pregnancy vs. untreated depressed	Birthweight	NR	Adjusted difference (g): 10 (95% CI, -43 to 70) p-value 0.72[27]	1 cohort, N=15,685[27]	Moderate study limitations, imprecise (wide CIs), consistency unknown	Insufficient
Exposed to SSRIs during pregnancy or depressed	SSRI exposure during pregnancy vs. untreated depressed	Gestational age	NR	Adjusted difference (weeks): -0.14 (95% CI, -0.34 to 0.06) p-value 0.18[27]	1 cohort, N=15,685[27]	Moderate study limitations, imprecise (wide CIs), consistency unknown	Insufficient
History of depression or anxiety or current or past SSRI-exposed women	Exposed to SSRIs in pregnancy vs. unexposed women with history of depression, anxiety or prior exposure	Major congenital anomalies	279/2,327 (12.0%) vs. 1,650/14,847 (11.1%)[57]; 204/7,683 (2.7%) vs. 380/13,432 (2.8%);[72] 208/4183 (5.0%) vs. 36/806 (4.5%)[91]	Adjusted prevalence ratio: 1.07 (95% CI, 0.93 to 1.22);[57] AOR, 0.93 (95% CI, 0.78 to 1.11);[72] adjusted effect NR in one study, p=0.9[91]	3 cohorts, n=43,299[57, 72, 91]	High study limitations (all risk of bias studies),[57, 72, 91] imprecise (wide CIs), consistent	Low for no harms with SSRIs
Psychiatric disorder with prescription prior to pregnancy	Exposed to SSRIs other than sertraline vs. unexposed to SSRIs during pregnancy with a psychiatric disorder	Major congenital anomalies	236/1,936 (12.0%) vs. 1,651/14,868 (11.1%)[70]	ARR, 1.08 (95% CI, 0.93 to 1.25)[70]	1 cohort, N=16,831[70]	High study limitations (high risk of bias[70]), imprecise (wide CIs), consistency unknown	Insufficient
Psychiatric disorder with prescription prior to pregnancy	Exposed to SSRIs other than paroxetine vs. unexposed to SSRIs during pregnancy with a psychiatric disorder	Major congenital anomalies	Not applicable for case-control	AOR, 1.19 (95% CI, 0.71 to 1.97)[93]	1 case-control, N NR[93]	Medium study limitations, imprecise (wide CIs), consistency unknown	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Depressed or exposed to SSRIs in pregnancy	Exposed to SSRIs vs. unexposed to SSRIs during pregnancy with depression or unexposed to SSRIs in early pregnancy	Cardiac anomalies	68/7683 (0.9%) vs. 112/13,432 (0.8%);[72] NR in second study;[7] 466 cases/341 controls vs. 149 cases/125 controls[106]	Pooled OR, 1.07 (95% CI, 0.96 to 1.20), I^2: 0% AOR, 1.06 (95% CI, 0.93 to 1.22)[7] AOR, 1.04 (95% CI, 0.76 to 1.41)[72] AOR, 1.14 (95% CI, 0.87 to 1.51)[106]	2 cohorts 1 case control, N>22,196 (N=NR in one study[7])[72, 106]	High study limitations (two high risk of bias studies[7, 72]) imprecise (wide CIs), consistent	Insufficient
Psychiatric disorder with prescription prior to pregnancy	Exposed to SSRIs other than sertraline vs. unexposed to SSRIs during pregnancy with a psychiatric disorder	Cardiac anomalies	51/1936 (2.6%) vs. 344/14,868 (2.3%)[70]	ARR, 1.08 (95% CI, 0.93 to 1.25)[70]	1 cohort, N=16,831[70]	High study limitations (high risk of bias[70]) imprecise (wide CIs spanning the null), consistency unknown	Insufficient
Exposed to SSRIs during pregnancy, before pregnancy, or unexposed with a psychiatric diagnosis	Exposed to SSRIs during pregnancy vs. before pregnancy or unexposed with a psychiatric diagnosis	Low Apgar score (<7 at 5 min)	28/2,664 (1.1%) vs. 31/5,141 (0.6%)[54] 376/15,729 (2.4%) vs. 113/9,652 (1.2%)[66]	Adjusted prevalence ratio: 1.69 (95% CI, 1.02 to 2.79)[54] AOR, 1.68 (95% CI, 1.34 to 2.12)[66]	2 cohorts, n=33,186[54, 66]	High study limitations (all risk-of-bias studies[54, 66]), precise, consistent	Low for harms with SSRIs
History of SSRI-exposure	SSRI exposure in pregnancy vs. women who discontinued SSRIs	Intrauterine hypoxia and birth asphyxia	94/2664 (3.5%) vs. 124/5141 (2.4%)[54]	Adjusted prevalence ratio in all women: 1.39 (95% CI, 1.07 to 1.81) Adjusted prevalence ratio in women with vaginal deliveries in the third trimester: 1.70 (95% CI, 1.23 to 2.33)[54]	1 cohort, n= 7805[54]	High study limitations (high risk-of-bias study[54] precise, consistency unknown	Low for harms with SSRIs

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
History of psychiatric disorder or depression or SSRI-exposed women	SSRI exposure in pregnancy vs. unexposed women with depression or psychiatric disorder	Respiratory conditions (respiratory conditions of newborns other than intrauterine hypoxia and birth asphyxia,[54] undefined breathing problems,[66] respiratory distress[27])	Ranges from 4.3% to 4.9% in the treatment arm and 3.1% to 3.2 in the control arm[54, 66]; NR in one study[27]	All three[27, 54, 66] studies reported increased risk. Adjusted prevalence ratios and AOR, range from 1.37 to 1.4[54, 66]	3 cohort studies, n>33,186 (N=NR in one study[27])[27, 54, 66]	High study limitations (2 of 3 are high risk-of-bias studies,[54, 66] precise, consistent	Low for harms with SSRIs
Exposed to SSRIs during pregnancy or unexposed with previous exposure or depressed	Exposed to SSRIs during pregnancy vs. unexposed depressed or exposed prior to but not during pregnancy	Neonatal convulsions	9/2,664 (0.3%) vs. 7/5,141 (0.1%);[54] NR in one study[27]	Adjusted prevalence ratio: 2.28 (95% CI, 0.87 to 5.97)[54] Difference in incidence: 0.00077 (95% CI, -0.001 to 0.0036) p-value 0.3[27]	2 cohort studies, n>7,805 (N=NR in one study[27])[27, 54]	High study limitations (1 of 2 studies is high risk of bias[54]) imprecise (wide CIs spanning the null), consistent	Insufficient
Exposed to SSRIs during pregnancy or unexposed with a psychiatric diagnosis	Exposed to SSRIs during pregnancy vs. unexposed with a psychiatric diagnosis	NICU	2,405/ 15,729 (15.3%) vs. 1,160/9,652 (12.0%);[66] 7/33 (21.21%) vs. 5/19 (26.32%)[95]	Adjusted OR, 1.24 (95% CI, 1.14 to 1.35);[66] NR, p=0.816[95]	2 cohorts, n=25,433[66, 95]	High study limitations (high risk of bias[66, 95]) precise, inconsistent	Insufficient
Exposed to SSRIs during pregnancy or unexposed depressed or with a psychiatric illness	Exposed to SSRIs during pregnancy vs. unexposed depressed during pregnancy or with a psychiatric illness	Extended hospital stay (>3 days for vaginal birth,[27] >7 days[66])	1,315/15,729 (8.4%) vs. 8,21/9,652 (8.5%);[66] 20/221 (9.0%) vs. 75/1,566 (4.8%);[80] NR in one study[27]	Inconsistent results spanning benefits, harms, and no effect AOR, 0.89 (95% CI, 0.8 to 0.99);[66] AOR, 1.93 (95% CI, 1.11 to 3.36) Difference in incidence: 0.035 (95% CI, -0.005 to 0.072), p-value 0.08[27]	3 cohort studies, n>27,168 (N= NR in one study[27])[66, 80]	High study limitations (2 of 3 studies are high risk of bias[66, 80]) imprecise, inconsistent	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Exposed to SSRIs during pregnancy or unexposed depressed	Exposed to SSRIs during pregnancy vs. unexposed depressed during pregnancy	Feeding problems	NR	Difference in incidence: 0.011 (95% CI, -0.009 to 0.03), p-value 0.28[27]	1 cohort, n NR[27]	Moderate study limitations, imprecise (CIs spanning the null), consistency unknown	Insufficient
Exposed to SSRIs during pregnancy or unexposed depressed	Exposed to SSRIs during pregnancy vs. unexposed depressed during pregnancy	Jaundice	NR	Difference Incidence: 0.01 (95% CI, -0.02 to 0.04), p-value 0.45[27]	1 cohort, n NR[27]	Moderate study limitations, imprecise (CIs spanning the null), consistency unknown	Insufficient
Depressed	Exposed to SSRIs during pregnancy vs. unexposed during pregnancy	Primary persistent pulmonary hypertension (without cardiac anomaly or hypoplasia in full-term deliveries)	94/54,281 (0.2%) vs. 669/567,118 (0.1%)[6]	Adjusted OR, 1.28 (95% CI, 1.01 to 1.70)[6] AOR, when not restricted to full-term or by outcome (primary persistent pulmonary hypertension rather than primary persistent pulmonary hypertension): 1.08 (95% CI, 0.92 to 1.27)[6]	1 cohort, n=621,399[6]	Moderate study limitations, precise, consistency unknown, adjusting for confounding increased the odds	Low for harms with SSRIs

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Depressed or anxious or exposed to SSRIs in pregnancy	Exposed to SSRIs vs. unexposed during pregnancy with depression or anxiety	Infant and child behavior and development	Varies by measure (measures include CBCL [including subscales], Behaviour Rating Inventory of Executive Function - Preschool version (BRIEF-P), Snijders-Oomen Niet-verbale intelligentie Test-Revisie (SON-R 2 1/2-7), NEPSY-II, NICU network neurobe-havioral (NNNS [including subscales]) - Attention scores, MDI, PDI, BRS)	Results vary by specific outcome, but the majority of outcomes are not statistically significant; exceptions include 1 subscale measure for CBCL, NEPSY-II, and 3 of 13 NNNS subscale measures; studies with significant findings did not adjust for multiple comparisons	4 cohorts, N=4,410[8, 61, 82, 88]	High study limitations (3 of 4 are high risk of bias[8, 61, 82]) imprecise, consistency unknown (single measures of outcomes not repeated in multiple studies)	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Depressed in pregnancy	Exposed to SSRIs vs. unexposed during pregnancy with depression	Infant weight at 52 weeks	NR	NR, p=0.6[76]	1 cohort, N=73[76]	High study limitations (high risk of bias[76]) likely imprecise, consistency unknown	Insufficient
Psychiatric illness in pregnancy or exposed to SSRIs	Exposed to SSRIs vs. unexposed during pregnancy with psychiatric illness and no psychotropic medication use	Child weight at 7 years	NR	Regression coefficient: 0.04, 95% CI, -0.19 to 0.26[9, 60]	1 cohort, N=617[9, 60]	High study limitations (high risk of bias[9, 60]likely precise, consistency unknown	Insufficient
Depression-related psychiatric disorder	Exposed to SSRIs during pregnancy vs. unexposed with a depression-related psychiatric disorder	Incidence of developmental disorders (speech/ language, motor, scholastic)	Rates range 0.4% to 1.6% in the treatment arm and 0.6% to 1.8% in the control arm[59]	AHR ranges from 0.88 to 1.3, all CIs cross the null; adjustments that resulted in greater risk of confounding by restricting to women with more than one prescription in the control arm increased the likelihood of disorders[59]	1 cohort, N=25,133[59]	Moderate study limitations, imprecise (wide CIs), consistency unknown	Insufficient
Exposed to SSRIs during pregnancy or unexposed with a psychiatric diagnosis	Exposed to SSRIs during pregnancy vs. unexposed with a psychiatric diagnosis	Autism spectrum disorder	88/15,729 (0.6%) vs. 79/9,651 (0.8%)[63]	AHR: 0.88 (95% CI, 0.65 to 1.2) p=0.428[63]	1 cohort, n=25,380[63]	Moderate study limitations, imprecise (wide CIs), consistency unknown	Insufficient
Exposed to SSRIs during pregnancy or unexposed with a psychiatric diagnosis	Exposed to SSRIs during pregnancy vs. unexposed with a psychiatric diagnosis	ADHD	160/15,729 (1.0%) vs. 137/9,651 (1.4%)[63]	AHR: 0.98 (95% CI, 0.77 to 1.24) p=0.847[63]	1 cohort, n=25,380[63]	Moderate study limitations, imprecise (wide CIs), consistency unknown	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Exposed to SSRIs during pregnancy or unexposed with a psychiatric diagnosis	Exposed to SSRIs during pregnancy vs. unexposed with a psychiatric diagnosis	Anxiety	65/ 15,729 (0.4%) vs. 39/9,651 (0.4%)[63]	AHR: 1.3 (95% CI, 0.84 to 2.01) p=0.234[63]	1 cohort, n=25,380[63]	Moderate study limitations, imprecise (wide CIs), consistency unknown	Insufficient
Exposed to SSRIs during pregnancy or unexposed with a psychiatric diagnosis	Exposed to SSRIs during pregnancy vs. unexposed with a psychiatric diagnosis	Depression	60/15,729 (0.4%) vs. 30/9,651 (0.3%)[63]	AHR: 1.78 (95% CI, 1.12 to 2.82) p=0.015[63]	1 cohort, n=25,380[63]	Moderate study limitations, precise, consistency unknown	Low for harms with SSRIs

ADHD = attention-deficit/hyperactivity disorder; AHR = adjusted hazard ratio; AOR = adjusted odds ratio; ARR = adjusted risk ratio; BRIEF-P = Behaviour Rating Inventory of Executive Function - Preschool version; BRS = Behavior Rating Scale; CBCL = childhood behavior checklist; CI = confidence interval; MDI = Mental Development Index; n/N = number; NEPSY-II = A Developmental NEuroPSYchological Assessment-II; NICU = neonatal intensive care unit; NNNS = NICU Network Neurobehavioral Scale; NR = not reported; OR = odds ratio; PDI = Psychomotor Development Index; RR = relative risk; SON-R 2 1/2-7 = Snijders-Oomen Niet-verbale intelligentie Test-Revisie; SSRI = selective serotonin reuptake inhibitor; vs. = versus.

All were nonrandomized studies. Nineteen were rated high risk of bias;[6-9, 45, 54, 57, 58, 60, 66, 69, 70, 72, 76, 79, 80, 82, 84, 88, 91, 95] others were rated as having some risk-of-bias concerns.

All publications focused on exposure during pregnancy. Publications compared pregnant women exposed to SSRIs with women with untreated depression,[7, 57, 64, 72, 75, 81] depression and anxiety,[79] mood or anxiety disorders,[74] history of a psychiatric disorder,[51, 83, 93, 95] or history of antidepressant exposure before the last menstrual period.[104] Studies specifying a history of disorders varied significantly in their definition and included depression only, depression or anxiety, or a history of psychiatric illness. The most inclusive specified the control arm as having a lifetime history of psychiatric illness but no drug exposure during pregnancy.[80, 83, 93] Among those specifying the control arm with respect to exposure during pregnancy, the allowable period of exposure also varied: no exposure in the past year to 20 weeks gestation,[81] no exposure in the trimester of interest,[79, 83] no exposure in an unspecified period of "late gestation,"[80] no exposure after the last menstrual period,[104] and a history of anxiety or depression but no supply of antidepressants in the 5 months before delivery in another.[74] These sources of clinical heterogeneity, coupled with statistical heterogeneity, precluded meta-analyses.

Consistent and precise evidence from two or more of three studies indicated a risk of harm with SSRIs for some neonatal outcomes, specifically, low Apgar score,[54, 66] and respiratory distress.[27, 54, 66] Two of these studies were rated as high risk of bias,[54, 66] leading to low confidence in the reported effects in these outcomes. Three studies reported on respiratory distress used different measures and could not be pooled. One reported on respiratory conditions of newborns other than intrauterine hypoxia and birth asphyxia (ICD-9 code of other respiratory conditions),[54] undefined breathing problems,[66] and respiratory distress (ICD-9 codes of 769, 770.6, and 770.8[27]). The two studies that do specify the ICD-9 codes include very heterogeneous outcomes, ranging from benign self-limiting conditions such as transient tachypnea of the newborn to more serious outcomes such as respiratory arrest of the newborn. Although we

graded the outcome as low strength of evidence for harm, in the absence of more details on the proportion and differences between study arms for more serious outcomes, the clinical implications of this finding are unclear.

One study reported higher rates of intrauterine hypoxia and birth asphyxia.[54] The study uses the ICD-9 code of 768. One concern is whether the higher rate in the exposed arm may be attributable to the greater number of c-sections in the exposed arm and the higher use of the ICD-9 code of 768.3 for fetal distress during labor for nonreassuring fetal testing. Analyses from the same study in a population of women with vaginal deliveries found a statistically significant difference in the third trimester only. Notably, the incidence of this outcome in the exposed arm (3.5%) is much lower than the incidence of low Apgar scores (<7 at 5 minutes) in the same study (1.1%), so the clinical significance of this finding is unclear.

Evidence from a single study suggests harms of postpartum hemorrhage with current or recent exposure to SSRIs (measured as having a prescription at or in the month prior to delivery) but not for past exposure (defined as having a prescription 1 to 5 months prior to delivery), when compared with no exposure to SSRIs among women with depression or anxiety.[74] The association between SSRI exposure and postpartum hemorrhage persisted in multiple sensitivity analyses. A second high risk-of-bias study found a protective association between SSRIs and bleeding during and after delivery.[66]

Evidence from a single study suggested harms of primary persistent pulmonary hypertension.[6] We graded the evidence as low for harms. The study reported higher odds (AOR, 1.28; 95% CI, 1.01 to 1.64) after restricting the cohort to term deliveries and redefining the outcome as primary persistent pulmonary hypertension (the absence of congenital cardiac anomalies and lung hypoplasia) than when the study included all deliveries and defined the outcome as all primary persistent pulmonary hypertension cases (AOR, 1.28; 95% CI, 1.01 to 1.64). We note, however, that risk factors, such as smoking, obesity, and C-section, are all more prevalent in populations of psychiatric patients.[148] Evidence from one study with high risk of bias suggested a greater risk of harms of depression in children who were exposed in utero to SSRIs.[63] As with other results, the risk of residual confounding cannot be ruled out.

The evidence for SSRIs as a class is insufficient to judge the risk of harms for maternal (spontaneous abortion, gestational diabetes, hypertension) or child outcomes (perinatal mortality, small for gestational age, birthweight, gestational age, neonatal convulsions, NICU admissions, extended hospital stay, feeding problems, jaundice, infant and child behavior and development, infant or child weight, autism spectrum disorder, attention-deficit hyperactivity disorder, or anxiety) (Table B-19). These bodies of evidence generally comprised one or two studies with nonsignificant results. One exception was for NICU studies: one of two studies, with high risk-of-bias reported higher rates of NICU admissions in the treatment group.[66] The study found higher odds ratios for unadjusted analyses than for unadjusted analyses; because residual confounding could potentially explain the association between SSRI exposure and the outcome, we rated the evidence as insufficient.

Multiple SSRI studies reported on some maternal (preeclampsia) and child (preterm birth, low birth weight, small for gestational age, outcomes, major congenital anomalies) outcomes. We were unable to pool most of these results because of the variations in outcome measures (with the exception of cardiac anomalies). Although studies consistently (or nearly consistently) reported no statistically significant effects and, in some cases, drew from large samples, the span of the CIs in these studies included appreciable benefit and appreciable harm. As a result, we could not infer that the results were equivalent. Additionally, many of the evidence bases solely

comprised or included high risk-of-bias studies, so we judge the strength of the evidence as insufficient for these outcomes. Three publications[7, 72, 106] (2 high risk of bias[7, 72]) reporting on cardiac anomalies were pooled, resulting in a finding of no increased risk from SSRIs as a drug class (1.07; 95% CI, 0.96 to 1.20; I^2, 0%; Figure B-2). The CIs were wide and spanned both appreciable benefit and appreciable harm; as a result, we could not conclude equivalence.

Three studies also reported numerous other birth defects. One found an increased risk of craniosynostosis (RR, 2.43; 95% CI, 1.44 to 4.11; 19 exposed cases) and musculoskeletal defects (RR, 1.28; 95% CI, 1.03 to 1.58; 104 exposed cases) with nonsertraline SSRIs.[70] A second found a decreased risk of genital system anomalies with SSRIs (AOR, 0.57; 95% CI, 0.35 to 0.92).[72] Neither study adjusted for multiple comparisons, and both were rated as high risk of bias. A third study with moderate study limitations that also did not adjust for multiple comparisons generally reported no difference in several other birth defects, including neural tube defects (AOR, 0.81; 95% CI, 0.48 to 1.36).[106] We also found insufficient evidence from a single study each on the harms of SSRIs other than sertraline[70] (major congenital anomalies and cardiac anomalies) and SSRIs other than paroxetine (major congenital anomalies)[93] when compared with no treatment.

SSRIs: Citalopram

Overview

- When compared with unexposed women with depression or anxiety, citalopram exposure at the time of delivery may be associated with a risk of postpartum hemorrhage (low strength of evidence of harms).
- When compared with unexposed women with a known psychiatric disorder, citalopram exposure in pregnant women may be associated with a higher risk of autism spectrum disorder in their children (low strength of evidence of harms).
- The evidence is insufficient to judge the risk of harms for maternal (gestational diabetes, preeclampsia, postpartum hemorrhage for recent or past exposure to citalopram during pregnancy) or child outcomes (congenital anomalies or cardiac anomalies).

Detailed Results

Six publications reported on either maternal or fetal harms of citalopram (Table B-20).[51, 57, 72, 74, 75, 104] All of these studies drew from large cohorts including THIN from the United Kingdom,[72] the Quebec Pregnancy/Children Cohort (QPC) in Canada,[57] the Stockholm Youth Cohort in Sweden,[51] a U.S. Kaiser Permanente Washington cohort,[104] the National Birth Defects Prevention Study,[106] and the Medicaid Analytic eXtract in the United States.[74, 75] Two studies were rated as high risk of bias;[57, 72] the rest had some risk-of-bias concerns.

The studies looked at a variety of outcomes; three focused on maternal harms, including gestational diabetes,[104] postpartum hemorrhage, and preeclampsia,[74, 75] and four evaluated fetal harms, specifically autism spectrum disorder and congenital anomalies.[51, 57, 72, 106] Regarding maternal harms, one study reported a higher risk of postpartum hemorrhage with current use (at delivery) of citalopram, but no difference with recent (up to 1 month before delivery) or past use (1 to 5 months before delivery) of citalopram when compared with pregnant women with a diagnosis of depression of anxiety.[74] Other studies did not find a difference in risk of gestational diabetes[104] or preeclampsia with citalopram.[75] Study results for fetal harms were conflicting. Two studies evaluated risk of major congenital anomalies with one study finding increased risk of major congenital anomalies with citalopram,[72] and another study found no change in risk with

major congenital anomalies.[72] Three studies found no increased risk of cardiac anomalies (pooled OR, 1.09; 95% CI, 0.82 to 1.46; I^2, 0%; Figure B-3).[57, 72, 106] The CIs were wide and spanned both appreciable benefit and appreciable harm; as a result, we could not conclude equivalence. One study also found no increased association with other anomalies, with the exception of a higher risk of craniosynostosis congenital anomalies, but the study had not conducted testing for multiple comparisons.[57] A third study with moderate study limitations that also did not adjust for multiple comparisons generally reported no difference in several other birth defects, including neural tube defects (AOR, 0.56; 95% CI, 0.18 to 1.76).[106] One study evaluated risk of autism spectrum disorder both with and without intellectual disabilities and found an increased risk with citalopram use[51] (Table B-20).

Table B-20. Strength of evidence for harms outcomes: citalopram versus no treatment

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Exposure to antidepressants before pregnancy or exposed to citalopram	Citalopram exposure during pregnancy vs. exposure before but not during pregnancy	Gestational diabetes	28/343 (8.16%) vs. 90/1211 (7.43%)	RR (inverse probability of treatment weighted): 0.82 (95% CI, 0.51 to 1.28)[104]	1 cohort, n=1,554[104]	Moderate study limitations, imprecise (wide CIs), consistency unknown	Insufficient
Pregnant women with depression[75]	Use of citalopram vs. no treatment	Preeclampsia	91/1680 (5.4%) vs. 3,215/59,219 (5.4%)[75]	RR, 1.01 (95% CI, 0.82 to 1.23)[75]	1 cohort, N=60,899[75]	Moderate study limitations, imprecision (wide CIs), consistency unknown	Insufficient
Pregnant women with mood or anxiety disorder[74]	Current citalopram use vs. no treatment	Postpartum hemorrhage	36/891 (4%) vs. 1,896/69,044 (2.7%)[74]	RR, 1.48 (95% CI, 1.07 to 2.04)[74]	1 cohort, N=69,935[74]	Moderate study limitations, precise, consistency unknown	Low for harms with citalopram
Pregnant women with mood or anxiety disorder[74]	Recent citalopram use (1-30 days before delivery) vs. no treatment	Postpartum hemorrhage	NR/830 vs. 1,896/69,044 (2.7%)[74]	RR, 0.7 (95% CI, 0.37 to 1.34)[74]	1 cohort, N=69,874[74]	Moderate study limitations, imprecision (wide CIs), consistency unknown	Insufficient
Pregnant women with mood or anxiety disorder[74]	Past citalopram use (1-5 months before delivery) vs. no treatment	Postpartum hemorrhage	17/830 (2%) vs. 1,896/69,044 (2.7%)[74]	RR, 0.76 (95% CI, 0.47 to 1.23)[74]	1 cohort, N=69,874[74]	Moderate study limitations, imprecision (wide CIs), consistency unknown	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Pregnant women with diagnosis of depression only[72] or depression and or anxiety, or exposed to antidepressants[57]	Maternal exposure to citalopram vs. no exposure anxiety and/or depression	Major congenital anomalies	52/1,946 (2.7%) vs. 666/23,833 (2.8%) in one study,[72] NR in second[57]	AOR, 1.36 (95% CI, 1.08 to 1.73)[57]; OR, 0.97 (95% CI, 0.71 to 1.31)[72]	2 cohort studies; n>25,779[57, 72]	High study limitations (high risk of bias[57, 72]), imprecision (CIs span null in one study[72]), inconsistent	Insufficient
Pregnant women with diagnosis of depression only[72] or depression and or anxiety, or exposed to antidepressants[57, 106]	Maternal exposure to citalopram vs. no exposure or unexposed to SSRIs in early pregnancy	Cardiac congenital anomalies	NR in two studies;[57, 72] 50 cases/39 controls vs. 149 cases/125 controls[106]	Pooled OR, 1.09 (95% CI, 0.82 to 1.46), I^2: 0% AOR, 1.15 (95% CI, 0.69 to 1.92)[57] AOR, 1.02 (95% CI, 0.61 to 1.70)[72] AOR, 1.11 (95% CI, 0.68 to 1.83)[106]	2 cohort studies, 1 case control, N>363[106] N NR in two studies[57, 72]	High study limitations (high risk of bias[57, 72]), imprecision (wide CIs), consistent	Insufficient
Pregnant with or without a known psychiatric condition	Maternal exposure to citalopram vs. no maternal exposure to any antidepressant but with a known psychiatric condition	Autism spectrum disorder among offspring	52/1,064 (4.9%) vs. 353/12,325 (2.9%)[51]	AOR, 1.65 (95% CI, 1.2 to 2.26)[51]	1 cohort study, n= 13,389[51]	Moderate study limitations, precise, consistency unknown	Low for harms with citalopram
Pregnant with or without a known psychiatric condition	Maternal exposure to citalopram vs. no maternal exposure to any antidepressant but with a known psychiatric condition	Autism spectrum disorder without intellectual disabilities among offspring	46/1,064 (4.3%) vs. 291/12,325 (2.4%)	AOR, 1.75 (95% CI, 1.25 to 2.45)	Cohort study 13,389[51]	Moderate study limitations, precise, consistency unknown	Low for harms with citalopram

AOR = adjusted odds ratio; CI = confidence interval; N = number; NR = not reported; RR = relative risk; vs. = versus.

SSRIs: Escitalopram

Overview

- When compared with unexposed women with depression or anxiety, escitalopram exposure *at the time of delivery* may be associated with a risk of postpartum hemorrhage (low strength of evidence of harms).
- The evidence of postpartum hemorrhage was judged to be insufficient if escitalopram exposure was prior to delivery (either 1 to 30 days or 1 to 5 months prior to delivery).
- The evidence is also insufficient to judge the risk of harms for exposure to escitalopram during pregnancy for other maternal (preeclampsia) or child outcomes (major congenital or heart anomalies).

Detailed Results

Four publications reported on escitalopram.[72, 74, 75, 106] These publications drew from three cohorts: two from the U.S. Medicaid Analytic eXtract,[74, 75] one from the U.K. THIN,[72] and one from the National Birth Defect Study.[106] All were nonrandomized studies. One was rated as high risk of bias;[72] the other two were rated as having some risk-of-bias concerns.[74, 75, 106]

All publications focused on exposure during pregnancy. Publications compared pregnant women exposed to escitalopram in the first trimester with women with untreated depression;[72] pregnant women with current (on the date of delivery), recent (1 to 30 days before delivery), or past (1 to 5 months before delivery) exposure to escitalopram with women with untreated mood or anxiety disorders;[74] pregnant women with escitalopram exposure in the second to third trimester with women with untreated depression;[75] and women exposed to escitalopram during early pregnancy to women not exposed during early pregnancy.[106]

When compared with unexposed women with depression or anxiety, escitalopram exposure at the time of delivery may be associated with a risk of postpartum hemorrhage (low strength of evidence of harms).[74] The results are insufficient to rate the harms of escitalopram on other maternal (recent exposure for postpartum hemorrhage or preeclampsia) or fetal outcomes (major congenital or heart anomalies) (Table B-21). One study with moderate study limitations that did not adjust for multiple comparisons reported no differences in several other birth defects, including neural tube defects (AOR, 1.14; 95% CI, 0.44 to 3.01).[106]

Table B-21. Strength of evidence for harms: Escitalopram versus no treatment

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Mood or anxiety disorder	Current escitalopram exposure vs. unexposed with mood or anxiety disorder	Postpartum hemorrhage	43/1,022 (4.21%) vs. 1,896/69,044 (2.75%)[74]	ARR, 1.56 (95% CI, 1.16 to 2.09)[74]	1 cohort, n=70,006[74]	Moderate study limitations, precise, consistency unknown	Low for harms with escitalopram
Mood or anxiety disorder	Recent escitalopram exposure (within 1 month before delivery) vs. unexposed with mood or anxiety disorder	Postpartum hemorrhage	14/520 (2.69%) vs. 1,896/69,044 (2.75%)[74]	ARR, 1.01 (95% CI, 0.61 to 1.7)[74]	1 cohort, n= 69,564[74]	Moderate study limitations, imprecision (wide CIs spanning the null), consistency unknown	Insufficient
Mood or anxiety disorder	Past escitalopram exposure (1 to 5 months before delivery) vs. unexposed with mood or anxiety disorder	Postpartum hemorrhage	24/940 (2.55%) vs. 1,896/69,044 (2.75%)[74]	ARR, 0.96 (95% CI, 0.64 to 1.42)[74]	1 cohort, n= 69,984[74]	Moderate study limitations, imprecision (wide CIs spanning the null), consistency unknown	Insufficient
Depression	Escitalopram exposure in 2nd-3rd trimester vs. unexposed women with depression	Preeclampsia	125/1,936 (6.46%) vs. 3,215/59,219 (5.43%)[75]	ARR, 1.14 (95% CI, 0.96 to 1.36)[75]	1 cohort, n=61,155[75]	Moderate study limitations, imprecision (wide CIs spanning the null), consistency unknown	Insufficient
Depression	Escitalopram exposure in first trimester vs. unexposed women with depression	Major congenital anomalies	7/333 (2.1%) vs. 380/13,432 (2.83%)[72]	AOR, 0.77 (95% CI, (0.36 to 1.66)[72]	1 cohort, n=13,765[72]	Serious study limitations (high risk of bias[72]), imprecision (wide CIs spanning the null), consistency unknown	Insufficient
Depression or anti-depressant exposed women	Escitalopram exposure during early pregnancy vs. unexposed women with depression or unexposed to SSRIs in early pregnancy	Cardiac anomalies	3/333 (0.9%) vs. 112/13,432 (0.83%)[72] 43 cases/35 controls vs. 149 cases/125 controls[106]	AOR, 1.09 (95% CI, (0.34 to 3.50)[72] AOR, 1.16 (0.69 to 1.97)[106]	1 cohort, n=13,765,[72] 1 case-control, n=352[106]	Serious study limitations (high risk of bias[72]), imprecision (wide CIs spanning the null), consistency unknown	Insufficient

AOR = adjusted odds ratio; ARR = adjusted risk ratio; CI = confidence interval; n = number; vs. = versus.

SSRIs: Fluoxetine

Overview

- When compared with unexposed women with mood or anxiety disorders, fluoxetine exposure at the time of delivery may be associated with a risk of postpartum hemorrhage (low strength of evidence of harms). The evidence of postpartum hemorrhage was judged to be insufficient if fluoxetine exposure was prior to delivery (either 1 to 30 days or 1 to 5 months prior to delivery).
- The evidence was judged as insufficient for exposure to fluoxetine during pregnancy for all other examined maternal outcomes (gestational diabetes or preeclampsia) and child outcomes (major congenital anomalies, cardiac anomalies, or autism spectrum disorder).

Detailed Results

Nine publications reported on the evidence for harms from fluoxetine (Table B-22).[7, 51, 56, 57, 72, 74, 75, 104, 106] All publications were nonrandomized studies and drew data from seven cohorts (3 studies from the U.S. Medicaid Analytic eXtract,[7, 74, 75] and 1 each from a U.S. Kaiser Permanente Washington cohort,[104] the U.S. National Birth Defects Prevention Study,[106] the Canadian QPC,[57] the United Kingdom's THIN,[72] the Swedish Stockholm youth cohort,[51] and a Swedish birth cohort).[56] Five studies' risk of bias was rated as some concerns;[51, 56, 75, 104, 106] the other three studies were rated as high.

Table B-22. Strength of evidence for harms: Fluoxetine versus no treatment

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women with an antidepressant prescription fill during the 6 months before pregnancy	Fluoxetine exposure before gestational diabetes screening (24-28 weeks gestation) or unexposed	Gestational diabetes	35/474 (7.17%) vs. 90/1211 (7.43%)[104]	ARR: 1.00 (0.66-1.52)[104]	1 cohort, N=1,685[104]	Moderate study limitations, imprecise (CIs span the null), consistency unknown	Insufficient
Pregnant women: Fluoxetine exposure gestational days 90 to 225 or depression diagnosis, LMP to gestational day 225	Fluoxetine exposure, 2nd to first half of 3rd trimester vs. unexposed	Preeclampsia	299/5,650 (5%) vs. 3,215/59,219 (5%)[75]	ARR, 0.97 (95% CI, 0.87 to 1.09)[75]	1 cohort: N=64,869[75]	Moderate study limitations, imprecise (CIs span the null), consistency unknown	Insufficient
Women with diagnosis code for mood or anxiety disorder 1-5 months prior to delivery	Fluoxetine current (at delivery) or unexposed	Postpartum hemorrhage billing diagnosis	Current: 137/3,322 (4.1%) Unexposed: 1,896/69,044 (2.8%)[74]	ARR, current vs. unexposed: 1.51 (95% CI, 1.27 to 1.79)[74]	1 cohort, N=72,366[74]	Moderate study limitations, precise, consistency unknown	Low for harms with fluoxetine

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women with diagnosis code for mood or anxiety disorder 1-5 months prior to delivery	Fluoxetine recent (≤1 month before delivery), or unexposed	Postpartum hemorrhage billing diagnosis	Recent: 50/1,628 (3.1%) Unexposed: 1,896/69,044 (2.8%)[74]	ARR, recent vs. unxexp: 1.14 (95% CI, 0.86 to 1.50)[74]	1 cohort, N=70,672[74]	Moderate study limitations, imprecision (wide CIs), consistency unknown	Insufficient
Women with diagnosis code for mood or anxiety disorder 1-5 months prior to delivery	Fluoxetine past (>1 to 5 months before delivery), or unexposed	Postpartum hemorrhage billing diagnosis	Past: 78/3,075 (2.5%) Unexposed: 1,896/69,044 (2.8%)[74]	ARR, past vs. unxexp: 0.93 (95% CI, 0.75 to 1.17)[74]	1 cohort, N=72,119[74]	Moderate study limitations, precision (wide CIs), consistency unknown	Insufficient
Pregnant women: Cohort 1: depression and/or anxiety diagnosis and exposure to antidepressants in the year before pregnancy; Cohort 2: depression diagnosis from the year before conception through the first trimester	Fluoxetine exposure in the first trimester vs. unexposed	Major congenital anomalies	NR/191 vs. 1,650/14,847 (11.1%)[57]; 241/3,189 (7.6%) vs. 380/13,432 (2.8%)[72]	AOR, 0.80 (95% CI, 0.49 to 1.31);[57] AOR, 0.85 (95% CI, 0.66 to 1.09)[72]	2 cohorts: N=15,038;[57] N=27,022[72]	High study limitations (both high risk of bias), imprecise (wide CIs); consistent	Insufficient
Women with depression or anxiety before pregnancy or exposure to antidepressants outside of early pregnancy	Fluoxetine exposure in the first trimester vs. unexposed	Cardiac anomalies	NR/191 vs. NR/14,847;[57] 66/3,189 (2.1%) vs. 112/13,432 (0.8%)[72] 84/8,664 (1.0%) vs. 1,497/180,564 (0.8%)[7] 125 cases/81 controls vs. 149 cases/125 controls[106]	Pooled OR, 1.06 (95% CI, 0.82 to 1.39), I^2: 35.9% AOR, 0.42 (95% CI, 0.10 to 1.73)[57] AOR, 0.79 (95% CI, 0.49 to 1.26)[72] Propensity score AOR, 1.14 (95% CI, 0.90 to 1.44)[7] AOR, 1.33 (95% CI, 0.91 to 1.95)[106]	3 cohorts, 1 case-control: N=15,038,[57] N=16,621,[72] N=189,228,[7] N=480[106]	High study limitations (all high risk-of-bias studies), imprecise (wide CIs), inconsistent	Insufficient
Pregnant women: Any lifetime depression or anxiety diagnosis	Fluoxetine during pregnancy vs. unexposed women	Autism spectrum disorder	8/327 (2.1%) vs. 282/14,805 (1.9%);[56] 16/453 (3.5%) vs. 353/12,325 (2.9%)[51]	By 7 or 8-year followup ARR, 1.08 (0.53 to 2.21);[56] 4 year or more followup: AOR, 1.42 (0.84 to 2.39)[51]	2 cohorts: N=15,132;[56] N=12,778[51] (potential overlap of participants in the publications)	Moderate study limitations, imprecise (wide CIs); consistent	Insufficient

AOR = adjusted odds ratio; ARR = adjusted risk ratio; CI = confidence interval; dx = diagnosis; LMP = last menstrual period; N = number; NR = not reported; vs. = versus.

Study cohorts consisted of pregnant women with depression or depression/anxiety, comparing women exposed to fluoxetine with those not exposed. The time period used to determine depression or depression/anxiety in the not exposed group differed across studies, including a period during pregnancy that was comparable to the fluoxetine exposure;[72, 74, 75] the 6 months before pregnancy;[104] exposed to antidepressants outside of early pregnancy;[106] the year prior to pregnancy;[57] any lifetime diagnosis;[51, 56] or, in one publication, the time period was not reported.[7]

The evidence for harms from fluoxetine was graded as low strength of evidence for increased risk of postpartum hemorrhage among women exposed at the time of delivery (RR=1.51), based on evidence from one large Medicaid cohort (N=72,366).[74] In this study, the risk of postpartum hemorrhage was not significantly different between the two groups if fluoxetine exposure was prior to delivery (either ≤1 month or >1 to 5 months) (insufficient strength of evidence).

The evidence was insufficient to judge any of the other studied outcomes. The outcomes include maternal outcomes (gestational diabetes or preeclampsia) and child adverse outcomes (major congenital anomalies, cardiac anomalies, or autism spectrum disorder) (Table B-19).

One publication reporting on gestational diabetes (N=1,685) did not find an increased risk (ARR, 1.00) and the CI surrounding the estimate is large (imprecise), precluding no difference. Similarly, preeclampsia, only reported in one publication, did not find an increased risk.[75] Based on a large cohort (N=64,869), the ARR is close to 1 (ARR=0.97), but the CI surrounding the estimate is large (imprecise), precluding concluding no difference. Two high risk-of-bias publications, reporting on the risk of major congenital anomalies related to exposure to fluoxetine during the first trimester, found no increased risk in either study, but similar to the preeclampsia finding, large confidence intervals preclude concluding no difference.[57, 72] Four high risk-of-bias publications reporting on cardiac anomalies were pooled, resulting in a finding of no increased risk from fluoxetine (OR, 1.06; 95% CI, 0.82 to 1.39, Figure B-4). The CIs were wide and spanned both appreciable benefit and appreciable harm; as a result, we could not conclude equivalence. One study with moderate study limitations that also did not adjust for multiple comparisons generally reported no difference in several other birth defects, including neural tube defects (AOR, 0.94; 95% CI, 0.46 to 1.93).[106] Lastly, two publications, with potential overlaps in the cohort, reporting on autism spectrum disorder results[51, 56] were consistent in reporting an increased association in the fluoxetine group, but the confidence intervals were large in both studies, resulting in the association not being significantly different from that of the not exposed group. When the referent group was restricted to women with more than one psychiatric diagnosis, the point estimate for relative risk moved from 1.18 (≥1 disorder, with CIs spanning the null) to 0.66 (≥3 disorders, also with CIs spanning the null).[56] This adjustment for confounding further suggests that the incidence of autism cannot be attributed to exposure to fluoxetine.

SSRIs: Fluvoxamine

Overview

- The evidence for fluvoxamine during pregnancy, when analyzed individually, is insufficient to judge the risk of harms for the child outcome (major congenital anomalies).

Detailed Results

One publication reported on fluvoxamine.[57] This study drew from one cohort (the Canadian QPC), which was a nonrandomized observational study and was rated as high risk of bias. This publication focused on exposure 12 months preconception or during pregnancy. The publication compared pregnant women exposed to fluvoxamine with women with untreated depression or anxiety.[57]

The evidence for fluvoxamine, when analyzed individually, is insufficient to judge the risk of harms for the child outcome (major congenital anomalies) (Table B-23). This study found no association between fluvoxamine use in pregnancy or preconception and the prevalence odds of major congenital anomalies. There was no study to which to compare findings, so the consistency of results is not known.

Table B-23. Strength of evidence for harms: Fluvoxamine versus no treatment

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Depression/ anxiety or fluvoxamine-exposed women	Fluvoxamine exposure in preconception or pregnancy vs. unexposed women with depression or anxiety	Major congenital anomalies	NR[57]	AOR, 0.63, 95% CI, (0.23 to 1.77)[57]	1 cohort, NR[57]	High study limitations (high risk of bias[57]), likely imprecise, consistency unknown	Insufficient

AOR = adjusted odds ratio; CI = confidence interval; NR = not reported.

SSRIs: Paroxetine

Overview

- When compared with unexposed women with depression or anxiety, paroxetine exposure within 1 month prior to delivery may be associated with a risk of postpartum hemorrhage (low strength of evidence of harms). The evidence of postpartum hemorrhage was judged to be insufficient if paroxetine exposure was at the time of delivery or 1 to 5 months prior to delivery.
- Paroxetine exposure in the first trimester is associated with a higher risk of atrial septal defect but not with other cardiac anomalies.
- The evidence is insufficient to judge the risk of harms for exposure to paroxetine for other maternal (discontinuation due to adverse events, preeclampsia, or gestational diabetes) or child outcomes ("harm to infant," major congenital anomalies, cardiac anomalies, or autism spectrum disorder).

Detailed Results

Eleven publications reported on harms of paroxetine (Table B-24).[7, 25, 51, 56, 57, 72, 74, 75, 93, 104, 106] Of these, four reported on maternal harms,[25, 74, 75, 104] and eight reported on fetal or infant harms.[7, 25, 51, 56, 57, 72, 93, 106] Four were rated high risk of bias.[7, 25, 57, 72] The rest had some risk-of-bias concerns.

Table B-24. Strength of evidence for harms outcomes: Paroxetine versus no treatment

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women with depression onset 0-3 months pp	Paroxetine vs. placebo	Discontin-uation due to adverse events	1/35 (2.86%) vs 4/35 (16%)[25]	No difference	RCT, N=70[25]	High study limitations (high risk of bias,[25] serious imprecision (few events, small sample size), consistency unknown	Insufficient
Women with history of anti-depressant use at least 6 months before pregnancy	Paroxetine vs. no anti-depressant fill	Gestational Diabetes	12/147 (8%) vs. 90/1,211 (7%)[104]	Weighted RR, 0.88 (95% CI,.49 to 1.60)[104]	1 cohort, N=1,358[104]	Moderate study limitations, imprecision (small sample size, wide CIs), consistency unknown	Insufficient
Women with a diagnosis code for depression between LMP and 225 gestational days	Paroxetine dispensed between 90 and 225 days of gestation vs. no antidepres-sant, LMP to 225 days of gestation	Preeclampsia billing code between 140 days of gestation and 30 days postpartum	183/3517 (5%) vs. 3,215/59,219 (5%)	ARR, paroxetine vs. unexposed: 0.99 (95% CI, 0.86 to 1.15)	1 cohort, N= 100,942[75]	Moderate study limitations, precision (wide CIs), consistency unknown	Insufficient
Women with diagnosis code for mood or anxiety disorder 1-5 months prior to delivery	Paroxetine current (at delivery) or unexposed	Postpartum hemorrhage billing diagnosis	77/2,055 (3.75%) vs. 1,896/69,044 (2.75%)[74]	ARR, Current vs. unexposed: 1.39 (95% CI, 1.09 to 1.71)[74]	1 cohort, N= 71,099[74]	Moderate study limitations, precise, consistency unknown	Low for harms with paroxetine
Women with diagnosis code for mood or anxiety disorder 1-5 months prior to delivery	Paroxetine recent (<1 month before delivery), or unexposed	Postpartum hemorrhage billing diagnosis	40/962 (4.16%) vs, 1,896/69,044 (2.75%)[74]	ARR, recent vs. unexposed: 1.52 (95% CI, 1.12-2.07) Past: 1.13 (95% CI, 0.85 to 1.49)[74]	1 cohort, N= 70,006[74]	Moderate study limitations, imprecision (wide CIs), consistency unknown	Insufficient
Women with diagnosis code for mood or anxiety disorder 1-5 months prior to delivery	Paroxetine past (>1 to 5 months before delivery), or unexposed	Postpartum hemorrhage billing diagnosis	49/1617 (3.03%) vs. 1,896/69,044 (2.75%)[74]	ARR, past vs. unexposed: 1.13 (95% CI, 0.85 to 1.49)[74]	1 cohort, N= 70,661[74]	Moderate study limitations, precision (wide CIs), consistency unknown	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women with depression or anxiety in the year prior to pregnancy	Paroxetine in 1st trimester vs. not exposed in 1st trimester	Major congenital anomalies	168/1,132 (14.8%) vs. 1,650/14,847 (11.1%)[57] Paroxetine-exposed: 37 cases, 375 controls No antidepres-sant: 94 cases, 1,134 controls[93] 36/1,200 (3.0%) vs. 380/13,432 (2.8%)[72]	Results not pooled because two publications[57, 93] potentially drew from the same population AOR, 1.24 (95% CI, 0.99 to 1.55; 99% CI, 0.79 to 1.66)[57] AOR, 1.27 (95% CI, 0.78 to 2.06)[93] AOR, 1.01 (95% CI, 0.71 to 1.44)[72]	2 cohorts,[57, 72] 1 case-control,[93] N≥33,119 (N from two studies);[57, 72] (study samples may overlap)	High study limitations (two high risk-of-bias studies[57, 72]), imprecise, consistent	Insufficient
Women with depression or anxiety in the year prior to pregnancy or exposure to anti-depressants outside of early pregnancy	Paroxetine in first trimester vs. unexposed	Cardiac anomalies	NR/1132 vs. NR/14,847[57] 17/1200 (1.4%) vs. 112/13,432 (0.8%[72] 93/11,126 vs. NR/180,564[7] 69 cases/43 controls vs. 149 cases/125 controls[106]	Pooled AOR, 1.26, 95% CI, 0.96 to 1.65, I^2: 59%; high heterogeneity potentially explained by clinical (differences in the definition of cardiac anomaly) and statistical heterogeneity (differences in direction of effect) AOR, 1.45 (95% CI, 1.12-1.88; 99% CI, 0.87 to 2.03)[57] AOR, 1.67 (95% CI, 1.00 to 2.80, p=0.051)[72] Propensity score AOR, 0.94 (95% CI, 0.73 to 1.21)[7] AOR, 1.27 (95% CI, 0.8 to 2)[106]	3 cohorts,[7, 57, 72] 1 case-control,[106] N=222,505	High study limitations (3 studies[7, 57, 72]), imprecision (wide CIs), inconsistent	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women with depression onset 0-3 months pp	Paroxetine vs. placebo	Harm to infant	0/35 vs. 0/35[25]	No difference[25]	RCT, N=70[25]	High study limitations (high risk of bias,[25] serious imprecision (no events, small sample size), consistency unknown	Insufficient
Women with current or past psychiatric disorder	Paroxetine vs. unexposed to anti-depressants during pregnancy	Autism spectrum disorder	5/264 (1.9%) vs. 353/12,325 (2.9%)[51] 3/108 (2.8%) vs. 282/14,805 (1.9%)[56]	ARR, 0.61 (95% CI, 0.25 to 1.49)[51] ARR, 1.21 (95% CI, 0.38 to 3.8)[56] Results adjusting for the number of psychiatric disorders show attenuating risks of autism spectrum disorder ≥1 psychiatric disorder: ARR, 1.36 (95% CI, 0.51 to 3.64)[56] ≥2 psychiatric disorders: ARR, 1.02 (0.38 to 2.78)[56] ≥3 psychiatric disorders: ARR, 0.74 (0.27 to 2.04)[56]	2 cohorts, N>35,218[51, 56] (potential overlap of participants in the publications)	Moderate study limitations, imprecise (wide CIs), consistency unknown (potential overlap of participants)	Insufficient
Women with current or past psychiatric disorder	Paroxetine vs. unexposed to anti-depressants during pregnancy	Autism spectrum disorder without intellectual disability	4/264 (1.5%) vs. NR/12,325 (2.4%)[51]	ARR, 0.60 (95% CI, 0.22 to 1.62)[51]	Stockholm Youth Cohort, N=16,667[51]	Moderate study limitations, imprecision (wide CIs), consistency unknown	Insufficient

AOR = adjusted odds ratio; ARR = adjusted risk ratio; CI = confidence interval; LMP = last menstrual period; N = number; NR = not reported; RCT = randomized controlled trial; vs. = versus.

Results were drawn from seven independent cohorts, including a small RCT;[25] a British population sample;[72] and cohorts from Sweden,[51, 56] Quebec,[57, 93] and the United States.[7, 74, 75, 104, 106] The two Swedish cohorts evaluated risk of autism spectrum disorder, and both included children residing in Stockholm County who were born in 2006 or 2007.[51, 56] The two Quebec studies evaluated congenital anomalies among births in Quebec from 1998 to 2002[93] and from 1998 to 2008.[57] The two publications from Quebec potentially drew participants from the same cohort, similarly, the Swedish publications may have drawn from the same cohort.

One randomized trial among postpartum women with onset of depression symptoms between 0 and 3 months postpartum compared paroxetine with placebo[25] and found no differences in discontinuation for maternal side effects or harm to the infant. The remaining publications were nonrandomized studies. Two publications reported on maternal harms of hemorrhage or preeclampsia using data from the U.S. Medicaid Analytic eXtract. The hemorrhage analysis[74] quantified the association between a diagnosis code for postpartum hemorrhage and dispensing of a supply of paroxetine that overlapped with the delivery date (current), within 1 month of delivery date (recent), of >1 to 5 months before delivery date (past), compared with a referent group of women with a depression or anxiety diagnosis within 1 to 5 months of delivery but no medical therapy. Current or recent, but not past, dispensing of paroxetine was associated with an increased risk of postpartum hemorrhage, with adjustment for multiple confounders. A second publication using the Medicaid Analytic eXtract sample among women with a depression diagnosis between the last menstrual period and 255 days of pregnancy found no association between paroxetine exposure and preeclampsia, adjusting for multiple confounders.[75] One study, a Kaiser Permanente Washington cohort,[104] reported no differences in the rate of gestational diabetes.

Three observational studies evaluated the association between paroxetine exposure in the first trimester compared with no antidepressant and the risk of major congenital anomalies[57, 72, 93] among women with depression or anxiety in the year prior to pregnancy. Two publications, likely drawing from the same population source from Quebec, found modest associations, but confidence intervals were wide;[57, 93] a U.K. THIN publication found no association.[72]

Four studies specifically quantified associations between first trimester paroxetine exposure and cardiac anomalies.[7, 57, 72, 106] In the Quebec and THIN cohorts, exposure was associated with cardiac anomalies, but in the propensity-score-adjusted Medicaid eXtract study and a National Birth Defects Prevention case-control, no association was found. The pooled adjusted OR was 1.26 (95% CI, 0.96 to 1.65, I^2, 59%; Figure B-5). These differences may reflect the diagnosis codes used to define cardiac anomalies: Whereas atrial septal defect/patent foramen ovale (ICD9 745.5, ICD10 Q21.1) was included in the definition of cardiac anomaly for the Quebec and U.K. cohorts, this code was excluded from the definition of cardiac anomalies in the Medicaid eXtract sample. The National Birth Defects Prevention Study relied on a classification of heart defects developed for the study.[149] The publication from the Quebec cohort reported a higher risk of ASD/VSD;[57] the Medicaid eXtract publication found no association with VSD.[7] There was no association between paroxetine exposure and any other class of birth defects in adjusted analyses in two studies;[57, 72] a third generally reported no significant differences but did not control for multiple comparisons.[106] Given differences in criteria used, it is unclear whether there is a clinically meaningful association between paroxetine exposure and cardiac anomalies.

Two publications from Swedish birth cohorts, with potential overlaps in the cohort, found no association between paroxetine exposure during pregnancy among women with a current or past psychiatric disorder and autism spectrum disorder in offspring.[51, 56] Moreover, when the referent

group was restricted to women with more than one psychiatric diagnosis, the point estimate for relative risk moved from 1.36 (≥1 disorder) to 0.74 (≥3 disorders).[56]

SSRIs: Sertraline

Overview

- One moderate risk-of-bias cohort study reported that sertraline use during pregnancy increases the risk of postpartum hemorrhage for exposure at the time of delivery or exposure 1 to 30 days prior to delivery (low strength of evidence). The evidence of postpartum hemorrhage was judged to be insufficient if sertraline exposure was 1 to 5 months prior to delivery.
- The evidence for the remaining maternal outcome comparisons (side effects, attrition, preeclampsia, gestational diabetes), as well as all of the fetal outcomes (major congenital anomalies, cardiac anomalies, or autism spectrum disorder), is insufficient for the risks of harm with sertraline use during pregnancy.

Detailed Results

Twelve publications reported on either maternal or fetal harms of sertraline (Table B-25).[7, 16, 23, 51, 56, 57, 70, 72, 74, 75, 104, 106] Two studies were RCTs.[16, 23] Of the remaining ten studies, three drew from the United States Medicaid Analytic Extract;[7, 74, 75] one from the United Kingdom's THI);[72] two from Canada's QPC, likely drawing on the same population;[57, 70] two from Sweden, one from the Stockholm Youth Cohort[51] and one from the Swedish National Registers;[56] one from Kaiser Permanente Washington,[104] and one from the U.S. National Birth Defects Prevention Study.[106] Five were rated high risk of bias,[7, 16, 57, 70, 72] six were rated some risk-of-bias concerns,[51, 56, 74, 75, 104, 106] and one was rated low risk of bias.[23]

Table B-25. Strength of evidence for harms: Sertraline versus no treatment

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women with depression onset 0-12 months postpartum	Sertraline vs. interpersonal psychotherapy	Overall attrition	16/56 (28.6%) vs. 9/53 (17.0%)[16]	No difference between two arms (p=0.119)[16]	RCT, n=109[16]	High study limitations (high risk of bias[16]), likely imprecise, consistency unknown	Insufficient
Women with depression onset 0-2 month postpartum	Sertraline plus brief dynamic psychotherapy vs. placebo	UKU Side Effects Rating Scale at 8 weeks postpartum	Mean change in UKU with sertraline = -8.4; without sertraline = -7.8	No difference between two arms (p=0.456)[23]	RCT, n=40[23]	Low risk of bias[23]) seriously imprecise (no statistical significance, small sample size), consistency unknown	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women with an antidepressant prescription filled during the 6 months before pregnancy	Sertraline continuation (1 or more refills of sertraline between last menstrual period and 20-24 weeks gestation) vs. sertraline discontinuation (no sertraline refill)	Gestational diabetes	52/462 (11.23%) vs. 90/1211 (7.43%)[104]	IPTW RR, 1.30 (95% CI, 0.63 to 1.81)[104]	Retrospective study within Kaiser Permanente Washington[104] N=1,673	Moderate study limitations, precise (wide CIs), consistency unknown	Insufficient
Women with a diagnosis code for depression between LMP and 225 gestational days	Sertraline dispensed between 90 and 225 days of gestation vs. no antidepressant, LMP to 225 days of gestation	Preeclampsia billing code between 140 days of gestation and 30 days postpartum	3,98/7,143 (5.6%) vs. 3,215/59,219 (5%)[75]	ARR, 1.03 (95% CI, 0.93 to 1.14)[75]	1 cohort, N= 66,362[75]	Moderate study limitations, precise (wide CIs), consistency unknown	Insufficient
Women with diagnosis code for mood or anxiety disorder 1-5 months prior to delivery	Sertraline current (at delivery), or unexposed	Postpartum hemorrhage billing diagnosis	162/4526 (3.6%) vs. 1,896/69,044 (2.7%)[74]	ARR, 1.31 (95% CI, 1.12 to 1.54)[74]	1 cohort, N=73,570[74]	Moderate study limitations, precise, consistency unknown	Low strength of evidence of increased risk of postpartum hemorrhage with current exposure to sertraline
Women with diagnosis code for mood or anxiety disorder 1-5 months prior to delivery	Sertraline recent (<1 month before delivery) or unexposed	Postpartum hemorrhage billing diagnosis	78/2,226 (3.5%) vs. 1,896/69,044 (2.7%)[74]	ARR, 1.27 (95% CI, 1.01 to 1.59)[74]	1 cohort, N=71,270[74]	Moderate study limitations, imprecise (wide CIs), consistency unknown	Low strength of evidence of increased risk of postpartum hemorrhage with recent exposure to sertraline
Women with diagnosis code for mood or anxiety disorder 1-5 months prior to delivery	Sertraline past (>1 to 5 months before delivery) vs. unexposed	Postpartum hemorrhage billing diagnosis	85/3,812 (2.2%) vs. 1,896/69,044 (2.7%)[74]	ARR, 0.82 (95% CI, 0.66 to 1.01)[74]	1 cohort, N=72,856[74]	Moderate study limitations, imprecise (wide CIs), consistency unknown	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women with depression or anxiety in the year prior to pregnancy	Sertraline in 1st trimester vs. not exposed in 1st trimester	Major congenital anomaly	NR/365 vs. 1,650/14,847 (11.1%)[57] 45/366 (12.30%) vs.1,651/ 14,868 (11.1%) from potentially overlapping citation[70]) 25/757 (3.3%) vs. 380/13,432 (2.8%)[72]	Results not pooled because two publications[57, 70] potentially draw from the same population AOR, 1.09 (95% CI, 0.80 to 1.50)[57] ARR, 1.11 (95% CI, 0.81 to 1.52) from potentially overlapping citation[70] AOR, 1.17 (95% CI, 0.78 to 1.77)[72]	2 cohorts, N>32,676[57] (potential overlap of participants in two publications[57, 70])	High study limitations (two high risk-of-bias studies[57, 72]), consistent	Insufficient
Women with depression or anxiety in the year prior to pregnancy	Sertraline in 1st trimester vs. unexposed	Cardiac anomaly	NR in one study: NR/365 vs. NR/14,847[57] (results from publication with overlapping data: 10/366) (2.7%) vs. 344/14,868 (2.3%)[70]); 9/757 (1.0%) vs. NR/13,432;[72] 93/11,126 (0.8%) vs. 1,479/180,564 (0.8%)[7] 156 cases/129 controls vs. 149 cases /125 controls[106]	Pooled AOR, 1.08 (95% CI, 0.91 to 1.28), I^2: 0% AOR, 1.14 (95% CI, 0.60 to 2.15)[57] (Results from one publication potentially overlapping data with study[57] included in meta-analysis is also consistent, with ARR, 1.16 (95% CI, 0.62 to 2.19)[70] AOR, 1.39 (95% CI, 0.70 to 2.74)[72] Propensity score AOR, 1.09 (95% CI, 0.88 to 1.34, p=0.051)[7] AOR, 0.97 (95% CI, 0.69 to 1.37)	3 cohorts, 1 case-control, 5 publications[7, 57, 70, 72, 106] N>250,577 (potential overlap in two publications[57, 70])	High risk of bias (3 studies,[7, 57, 70, 72]), imprecise (wide CIs), consistent	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women with current or past psychiatric disorder	Sertraline vs. unexposed to antidepressants during pregnancy	Autism spectrum disorder	31/912 (3.4%) vs. 353/12,325 (2.9%)[51] 16/672 (2.4%) vs. 282/14,805 (1.9%)[56]	AOR, 1.45 (95% CI, 0.98 to 2.16)[51] ARR, 1.17 (95% CI, 0.99 to 2.32);[56] results adjusting for the number of psychiatric disorders show attenuating risks of autism spectrum disorder ≥1 psychiatric disorder: ARR, 1.32 (95% CI, 0.86 to 2.24)[56] ≥2 psychiatric disorders: ARR, 0.99 (95% CI, 0.63 to 1.55)[56] ≥3 psychiatric disorders: ARR, 0.71 (95% CI, 0.43 to 1.17)[56]	2 cohorts, N>15,477[51, 56] (potential overlap of participants in the publications)	Moderate study limitations, imprecise (wide CIs), some consistency	Insufficient
Women with current or past psychiatric disorder	Sertraline vs. unexposed to antidepressants during pregnancy	Autism spectrum disorder without intellectual disability	27/912 (3.0%) vs. NR/12,325[51]	AOR, 1.52 (95% CI, 0.22 to 1.62)[51]	Stockholm Youth Cohort, N=16,667[51]	Moderate study limitations, imprecise (wide CIs), consistency unknown	Insufficient

AOR = adjusted odds ratio; ARR = adjusted risk ratio; CI = confidence interval; IPTW =inverse probability of treatment weighted; LMP = last menstrual period; n/N = number; NR = not reported; RCT = randomized controlled trials; UKU = Udvalg for Kliniske Undersøgelser; vs. = versus.

The two RCTs focused on postpartum exposure,[16, 23] while the remaining nine focused on exposure at various times during pregnancy. Two focused on first trimester exposures,[7, 72] one focused on first and second trimester exposures,[104] two focused on second and third trimester exposures[74, 75] (with 1 limiting third trimester exposure to the first half[75]), and four looked at exposure at any time during pregnancy.[51, 56, 57, 70] The two RCTs involved comparison with psychotherapy: one compared sertraline versus interpersonal psychotherapy,[16] while the other compared sertraline plus a brief dynamic psychotherapy with psychotherapy alone.[23] The nine cohort studies compared sertraline exposure to no medication exposure, although one looked at discontinuation during the first two trimesters.[104] Only the two RCTs reported doses, with one

reporting a mean dose between 65 and 70 mg[23] and the other reporting a median dose of 150 mg.[16]

The evidence for sertraline varied by outcome. Overall, there is low strength of evidence that sertraline increases the risk of postpartum hemorrhage for current or recent use.[74] Also, one low risk-of-bias RCT provided low strength of evidence of no increased side effects with sertraline compared with placebo.[23] The evidence for the remaining maternal outcome comparisons (attrition, preeclampsia, and incident gestational diabetes), as well as all of the fetal outcomes (major congenital anomalies, cardiac anomalies, or autism spectrum disorder), is insufficient. Evidence from four cohorts, when pooled, spanned the null for cardiac anomalies, but with intervals that included appreciable benefit and appreciable harm (pooled AOR, 1.08; 95% CI, 0.91 to 1.28; I^2, 0%; Figure B-6);[7, 57, 72, 106] as a result, we rated the evidence as insufficient.

Notably, two publications, likely reporting on the same population,[57, 70] reported nonsignificant results for craniosynostosis and ventricular/atrial septal defects in one publication[57] and statistically significant differences in the other.[70] The authors attribute differences in findings to differences in inclusion criteria and exposure groups.[57] A third study generally reported no significant differences for other birth defects but did not control for multiple comparisons.[106]

Two publications from Swedish birth cohorts, with potential overlaps in the cohort, found no association between paroxetine exposure during pregnancy among women with a current or past psychiatric disorder and autism spectrum disorder in offspring.[51, 56] Moreover, when the referent group was restricted to women with more than one psychiatric diagnosis, the point estimate for relative risk moved from 1.32 (≥1 disorder) to 0.71 (≥3 disorders).[56]

SSRIs: Trazodone

Overview

- The evidence for trazodone use during pregnancy, when analyzed individually, is insufficient to judge the risk of harms for maternal outcomes (postpartum hemorrhage or preeclampsia).

Detailed Results

Two publications reported on trazodone.[74, 75] These publications drew from one cohort (2000-2007 U.S. nationwide Medicaid Analytic eXtract [MAX] data). Both were nonrandomized observational studies and were rated as "some concerns" regarding risk of bias.[74, 75]

Both publications focused on exposure during pregnancy. One publication[74] also analyzed recent trazodone exposure (women with a supply of antidepressants on at least 1 day in the month before the delivery date but not on the delivery date) and past trazodone exposure (1 to 5 months prior to delivery). Publications compared pregnant women exposed to trazodone with women with nonpharmacologically treated depression[75] or mood disorder and anxiety.[74] One publication[75] compared pregnant women who continued versus discontinued trazodone during pregnancy.

The evidence for trazodone, when analyzed individually, is insufficient to judge the risk of harms for maternal outcomes (postpartum hemorrhage or preeclampsia) (Table B-26). The publications consistently found no association between trazodone exposure and maternal harms (postpartum hemorrhage, preeclampsia). Notably, there was no association detected with recent or current trazodone exposure in this publication.[74]

There was an insufficient number of studies to pool results.

Table B-26. Strength of evidence for harms: Trazodone versus no treatment

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Mood disorder or anxiety or bupropion-exposed women	Current trazodone exposure in pregnancy vs. unexposed women with mood disorder or anxiety	Postpartum hemorrhage	NR	ARR, 1.85 (95% CI, 0.90 to 3.80)[74]	1 cohort, n=69,183[74]	Moderate study limitations, imprecise (wide CIs), consistency unknown	Insufficient
Mood disorder or anxiety or bupropion-exposed women	Recent trazodone exposure in pregnancy vs. unexposed women with mood disorder or anxiety	Postpartum hemorrhage	NR	ARR, 2.01 (95% CI, 0.77 to 5.24)[74]	1 cohort, n=69,117[74]	Moderate study limitations, imprecise (wide CIs), consistency unknown	Insufficient
Mood disorder or anxiety or bupropion-exposed women	Past trazodone exposure in pregnancy vs. unexposed women with mood disorder or anxiety	Postpartum hemorrhage	NR	ARR, 0.61 (95% CI, 0.23 to 1.67)[74]	1 cohort, n=69,270[74]	Moderate study limitations, imprecise (wide CIs), consistency unknown	Insufficient
Depressed women	Trazodone exposure in pregnancy vs. unexposed women with depression	Preeclampsia	14/339 vs. 3,215/5,919[75]	ARR, 0.63 (95% CI, 0.38 to 1.05)[75]	1 cohort, n=59,558[75]	Moderate study limitations, imprecise (wide CIs), consistency unknown	Insufficient

ARR = adjusted risk ratio; CI = confidence interval; n = number; NR = not reported; vs. = versus.

SNRIs

Overview

- For SNRIs overall, evidence suggests an increased association of postpartum hemorrhage with exposure to SNRIs at the time of delivery (low for harms). It also suggests an increased association of spontaneous abortion and preeclampsia for SNRIs (low strength of evidence for harms).
- For SNRIs overall, the evidence is insufficient for maternal postpartum hemorrhage with recent or past exposure or child outcomes (major congenital anomalies, cardiac anomalies).

- For duloxetine exposure during pregnancy, the evidence is insufficient for duloxetine continuation versus discontinuation for child outcomes, specifically any congenital anomalies or cardiovascular anomalies.
- For venlafaxine, evidence suggests an increased association of postpartum hemorrhage with exposure to SNRIs at the time of delivery (low strength of evidence for harms). It also suggests an increased association with preeclampsia (low strength of evidence for harms). The evidence is insufficient to judge the risk of harms for gestational diabetes or for child outcomes (small for gestational age, cardiac anomalies, or autism spectrum disorder).

Detailed Results

Twelve publications reported on SNRIs.[7, 51, 56, 57, 64, 74, 75, 81, 83, 104, 106] Of these, three analyzed only the effects of SNRIs as a class,[7, 64, 81] three focused specifically on the effects of venlafaxine,[51, 83, 104] one focused on duloxetine exposure versus discontinuation,[98] three included analyses of both SNRIs as a class and venlafaxine more specifically,[57, 74, 106] one included analyses of venlafaxine and duloxetine,[56] and one included analyses of SNRIs as a class and both venlafaxine and duloxetine more specifically.[75] These studies drew from five cohorts (three from the Canadian QPC,[57, 64, 83] four from the U.S. Medicaid Analytic eXtract,[7, 74, 75, 98] and one each from a U.S. Kaiser Permanente Washington cohort,[104] the U.S. National Birth Defects Prevention Study,[106] a Swedish Stockholm youth cohort,[51] a Swedish birth cohort,[56] and a Canadian British Columbia birth cohort.[81] All were nonrandomized studies. Two studies were rated high risk of bias.[7, 57]

The evidence on the risk of maternal harms from SNRIs was reported in relation to spontaneous abortion, preeclampsia, gestational diabetes, and hemorrhage. One publication reported on the risk of spontaneous abortion during the first trimester for women exposed to SNRIs compared with women with a depression diagnosis during the 4 years before pregnancy and no prescription in the year before pregnancy.[64] The difference in the adjusted risk of spontaneous abortion prior to 20 weeks was calculated both with and without a correction for induced abortions. The risk adjustment for induced abortions resulted in a lower estimate of risk. In both analyses, the risk of spontaneous abortion was significantly higher in the exposed group. We rated our confidence in the findings as low strength of evidence for harms (Table B-27).

Table B-27. Strength of evidence for harms: SNRIs versus no treatment

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Pregnant women: SNRI exposure or depression diagnosis in past 4 years	SNRI exposure in 1st trimester vs. unexposed	Spontaneous abortion	20/90 (22%) vs. 720/7,034 (10%);[64] results corrected for induced abortions: 20/137 (15%) vs. 720/8,877 (8.1%)[64]	ARR, 2.1 (95% CI, 1.4 to 3.0); corrected for induced abortions ARR, 1.7 (95% CI, 1.2 to 2.6)[64]	1 cohort, n=7,134; corrected for inducted abortion, n=9,014[64]	Moderate study limitations, precise; consistency unknown	Low for harms with SNRIs
Pregnant women: SNRI exposure or depression diagnosis, through 2nd trimester	SNRI exposure through 2nd trimester vs. unexposed	Preeclampsia	107/1,216 (9%) vs. 3,215/59,219 (5%);[75] 23/408 (5.6%) vs. 1,569/65,392 (2.4%)[81]	ARR, 1.52 (95% CI, 1.26 to 1.83)[75]; ARR, 1.59 (95% CI, 1.26 to 3.03)[81]	2 cohorts: N=126,235[75, 81]	Moderate study limitations, precise; consistent	Low for harms with SNRIs
Pregnant women: venlafaxine exposure or depression diagnosis, through 2nd trimester	Venlafaxine exposure through 2nd trimester vs. unexposed	Preeclampsia	100/1,113 (9%) vs. 3,215/59,219 (5%)[75]	ARR, 1.57 (1.29 to 1.91)[75]	1 cohort: N=60,332[75]	Moderate study limitations, precise; consistency unknown	Low for harms with venlafaxine
Pregnant women: anti-depressant prescription fill during the 6 months before pregnancy	Venlafaxine exposure before gestational diabetes screening (24-28 weeks gestations) vs. unexposed	Gestational diabetes	15/104 (14%) vs. 90/1,211 (7%)[104]	ARR: 1.52 (0.87 to 2.68)[104]	1 cohort, N=1,315[104]	Moderate study limitations, imprecise (CIs span the null), consistency unknown	Insufficient
Pregnant women with mood or anxiety disorders	SNRI recent exposure (<1 month before delivery) vs. unexposed	Postpartum hemorrhage billing diagnosis	NR/217 (NR%) vs. 1,898/69,044 (2.8%)[74]	ARR, 1.21 (0.58 to 2.54)[74]	1 cohort: N=69,261[74]	Moderate study limitations, imprecise, consistency unknown	Insufficient
Pregnant women with mood or anxiety disorders	SNRI past exposure (>1 to 5 months before delivery) or unexposed	Postpartum hemorrhage billing diagnosis	12/423 (2.8%) vs. 1,898/69,044 (2.8%)[74]	ARR, 1.05 (0.60 to 1.83)[74]	1 cohort: N=69,467[74]	Moderate study limitations, imprecise, consistency unknown	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Pregnant women with mood or anxiety disorders	Venlafaxine current exposure at time of delivery vs. unexposed	Postpartum hemorrhage billing diagnosis	46/763 (6%) vs. 1,898/69,044 (2.8%)[74]	ARR, 2.24 (95% CI, 1.69 to 2.97)[74]	1 cohort, N=69,807[74]	Moderate study limitations, precise, consistency unknown	Low for harms with venlafaxine
Pregnant women with mood or anxiety disorders	Venlafaxine recent exposure (<1 month before delivery) vs. unexposed	Postpartum hemorrhage billing diagnosis	NR/237 (6%) vs. 1,898/69,044 (2.8%)[74]	ARR, 1.10 (95% CI, 0.53 to 2.30)[74]	1 cohort, N=69,281[74]	Moderate study limitations, imprecise, consistency unknown	Insufficient
Pregnant women with mood or anxiety disorders	Venlafaxine past exposure (>1 to 5 months before delivery) or unexposed	Postpartum hemorrhage billing diagnosis	12/458 (2.6%) vs. 1,898/69,044 (2.8%)[74]	ARR, 0.98 (95% CI, 0.56 to 1.70)[74]	1 cohort, N=69,502[74]	Moderate study limitations, imprecise, consistency unknown	Insufficient
Pregnant women with a psychiatric disorder diagnosis, used AD ≥30 days in prior year	Venlafaxine during 2nd trimester vs. unexposed	Small for gestational age	NA, case-control[83]	ARR, 2.55 (1.04 to 6.27)[83]	1 case-control: N=755[83]	Moderate study limitations, imprecise (few events, wide CIs); consistency unknown	Insufficient
Pregnant women: depression and/or anxiety diagnosis and exposure to antidepres-sants in the 12 months before pregnancy	SNRI exposure in the first trimester vs. unexposed	Major congenital anomaly	91/738 (12.3%) vs. 1,650/14,847 (11.1%)[57]	Through 11 years post-delivery: AOR, 1.10 (0.87 to 1.38)[57]	1 cohort: N=15,585[57]	High study limitations (high risk of bias[57]) imprecise (wide CIs); consistency unknown	Insufficient
Duloxetine in the first trimester vs. discontin-uation of duloxetine before the first trimester	Duloxetine, exposure in the first trimester	Any congenital malformations	Duloxetine: 128/2,532 (5.06%) vs. 114/2456 (4.64%)[98]	ARR, 1.09 (95% CI, 0.84 to 1.42)[98]	1 cohorts: N=4988[98]	Moderate study limitations, imprecise (wide CIs), consistency unknown	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women with depression or anxiety before pregnancy or exposure to anti-depressants outside of early pregnancy or duloxetine in the first trimester vs. discontinuation of duloxetine before the first trimester	Venlafaxine;[57] SNRI; exposure in the first trimester vs. unexposed;[7, 106] Duloxetine, exposure in the first trimester[98]	Cardiac anomalies	SNRI:69/1,497 (4.6%) vs. 1,497/180,564 (0.8%);[7] 59 cases/27 controls vs. 149 cases/125 controls[106] Venlafaxine: NR/738 vs. NR/14,847;[57] 47 cases/21 controls vs. 149 cases/125 controls[106] Duloxetine: 59/2,532 (2.33%) vs. 43/2,456 (1.75%)[98]	SNRI Propensity score AOR, 1.20 (0.91 to 1.57)[7] AOR, 1.14 (95% CI, 0.44 to 3.01)[106] Venlafaxine AOR, 0.80 (0.47 to 1.38)[57] AOR, 1.91 (95% CI, 1.05 to 3.45) SNRIs[106] Duloxetine ARR, 1.41 (95% CI, 0.92 to 2.17)[98]	3 cohorts, 1 case control: N=202,994[7, 57, 98, 106]	High study limitations (high risk of bias[57 7]), imprecise (wide CIs), inconsistent	Insufficient
Pregnant women: Any lifetime depression or anxiety diagnosis	Venlafaxine during pregnancy vs. unexposed women	Autism spectrum disorder	4/195 (2.1%) vs. 282/14,805 (1.9%);[56] 11/213 (5.1%) vs. 353/12,325 (2.9%)[51]	By 7- or 8-year followup ARR, 0.74 (0.32 to 1.72);[56] 4-year or more followup: AOR, 1.81 (0.89 to 3.71)[51] ≥1 psychiatric disorder: ARR, 1.36 (95% CI, 0.61 to 3.04)[56] ≥2 psychiatric disorders: ARR, 1.01 (0.44 to 2.29)[56] ≥3 psychiatric disorders: ARR, 0.74 (0.32 to 1.72)[56]	2 cohorts: N=27,538[51, 56]	Moderate study limitations, imprecise (wide CIs), inconsistent	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Pregnant women: Any lifetime psychiatric disorders	Duloxetine during pregnancy vs. unexposed women	Autism spectrum disorder	NR/52 (NR%) vs. control ≥1 psychiatric disorder: NR/24,285 (NR%); control ≥2 psychiatric disorders NR/5,839 (NR%); control ≥3 psychiatric disorders NR/5,839 (NR%)[56]	Results not presented for any comparison[56]	Duloxetine and control ≥1 psychiatric disorder: N=24,337; duloxetine and control ≥2 psychiatric disorders: N=5,891; duloxetine and control ≥3 psychiatric disorders: N=1946[56]	Moderate study limitations, no result estimates	Insufficient

AD = antidepressants; AOR = adjusted odds ratio; ARR = adjusted risk ratio; CI = confidence interval; dx = diagnosis; N = number; NA = not applicable; NR = not reported; SNRI = serotonin-norepinephrine reuptake inhibitor; vs. = versus.

Two publications, reporting on the risk of preeclampsia in independent cohorts, compared women with depression diagnoses while pregnant through the second trimester.[75, 81] Those exposed to SNRIs were found to be at significantly higher risk of preeclampsia in both analyses after controlling for potential confounders. We rated our confidence in the findings as low strength of evidence for harms. One of the publications also reported on risk of preeclampsia among the women exposed to venlafaxine more specifically.[75] Similarly, those exposed to venlafaxine were found to be at significantly higher risk of preeclampsia, and we rated our confidence in the findings as low strength of evidence for harms.

One publication compared the risk of hemorrhage among women with mood or anxiety disorders exposed to SNRIs at the time of delivery at ≤ 1 month prior to delivery and at 1 to 5 months prior to delivery compared with women with no exposure to antidepressants.[74] In analyses controlling for potential confounders, the risk of hemorrhage was significantly higher among women exposed to SNRIs at the time of delivery (low strength of evidence for harms), but the evidence was insufficient for grading the outcome when exposure was prior to delivery. In this publication, we found a similar pattern of findings in relation to venlafaxine more specifically.[74]

One publication reporting on gestational diabetes (N=1,315) found an increased risk from venlafaxine (ARR, 1.52), but the CI surrounding the estimate is large (imprecise). As a result, the evidence was graded as insufficient.

The evidence on the risk of child adverse outcomes from SNRIs reported on small for gestational age, major or any congenital anomalies, cardiac anomalies, and autism spectrum disorder. Each was graded as insufficient strength of evidence. Limited to one case-control study, women exposed to venlafaxine during the second trimester were found to be significantly more likely to give birth to children who were small for gestational age.[83] However, when the sample population was divided into subgroups of women who used ≤150 mg/day and those who used >150 mg/day during the second trimester, only women using the smaller dose were found to be at significantly increased risk of their child being small for gestational age. The authors speculated that the results could be the result of residual confounding by indication; women at

lower dosages have poorer control of their psychiatric condition. Because of the potential for residual confounding, we rated this outcome as insufficient, despite the statistical significant result. Also limiting the strength of the findings was small sample sizes. Only five of the venlafaxine cases and 12 of the control subjects had a child small for gestational age.

One study of congenital anomalies[57] also compared venlafaxine to controls in relation to organ specific anomalies: nervous system; eye, ear, face, and neck; circulatory system; respiratory system; digestive system; genital organs; urinary system; musculoskeletal system; craniosynostosis; ventricular/atrial septal defect; and cardiac anomalies discussed below. A significantly increased risk was found only in relation to respiratory anomalies (AOR, 2.17; 95% CI, 2.07 to 4.38). One study reported some differences in birth defects for SNRIs and venlafaxine but had small numbers of cases and controls, had imprecise results, and did not control for multiple comparisons.[106]

One study evaluated the risk of any congenital malformations when comparing the risk for women on duloxetine in the first trimester when compared with women who discontinued duloxetine. Discontinuation was defined as having a duloxetine prescription dispensed between 6 months and 60 days before the last menstrual period but not during the first trimester. The study found no statistically significant results and wide CIs. Four studies reported on cardiac anomalies following exposure to SNRIs as a drug class,[7, 106] duloxetine,[98] and venlafaxine.[57, 106] Given the heterogeneity in exposure, we did not pool the results. The results were rated as insufficient as a result of inconsistent and imprecise results. Two publications with potential overlaps in the cohorts[51, 56] reported inconsistent and imprecise results on autism spectrum disorder. These results were rated as insufficient as a result.

TCAs

Overview

- TCA exposure during pregnancy may be associated with an increased risk of preeclampsia compared with no treatment (low strength of evidence).
- For TCAs overall, the evidence is insufficient to judge the risk of harms for other maternal (spontaneous abortion, postpartum hemorrhage) or child outcomes (perinatal mortality, small for gestational age, major congenital anomalies, cardiac anomalies).
- For clomipramine and amitriptyline or nortriptyline exposure during pregnancy, the evidence is insufficient to judge the risk of harms for child outcomes (autism spectrum disorder).

Detailed Results

Twelve publications reported on TCAs;[7, 51, 56, 57, 64, 72, 74, 75, 79, 81, 83, 93] of these, none reported on TCAs as a class, and three focused on specific drugs (amitriptyline and nortriptyline, and clomipramine) (Table B-28).[51, 56, 74] These publications drew from four cohorts (four from the Canadian QPC,[57, 64, 83, 93] three from the U.S. Medicaid Analytic eXtract,[7, 74, 75] two each from the U.K. THIN[72, 79] and the Swedish Birth Cohort,[51, 56] and one from the Canadian British Columbia health utilization databases.[81] All were nonrandomized studies. Four were rated high risk of bias;[7, 57, 72, 79] others were rated as having some risk-of-bias concerns.

Table B-28. Strength of evidence for harms: TCAs versus no treatment

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Depressed or TCA-exposed women	TCA exposure in pregnancy vs. unexposed women with depression	Spontaneous abortion	20/112 (17.9%) vs. 720/7,034 (10.2%)[64] NR in second[79]	ARR, 1.5, 95% CI, 1.5 (0.96 to 2.2)[64] and 1.3 (99% CI, 1.1 to 1.5)[79]	2 cohorts; n=7,146 in one cohort,[64] NR in second[79]	Moderate study limitations (one high risk-of-bias study[79]), imprecise, consistent	Insufficient
Mood or anxiety disorder during pregnancy or exposed to amitriptyline	Current amitriptyline exposure (at delivery), or unexposed	Postpartum hemorrhage billing diagnosis	NR	ARR, 1.68 (95% CI, 0.89 to 3.16)[74]	1 cohort, N=69,220[74]	Moderate study limitations, precise, consistency unknown	Insufficient
Mood or anxiety disorder during pregnancy or exposed to amitriptyline	Recent amitriptyline exposure (<1 month before delivery) or unexposed	Postpartum hemorrhage billing diagnosis	NR	ARR, 1.13 (95% CI, 0.29 to 4.42)[74]	1 cohort, N=69,113[74]	Moderate study limitations, imprecision (wide CIs), consistency unknown	Insufficient
Mood or anxiety disorder during pregnancy or exposed to amitriptyline	Past amitriptyline exposure (>1 to 5 months before delivery) or unexposed	Postpartum hemorrhage billing diagnosis	NR	ARR, 1.08 (95% CI, 0.48 to 2.42)[74]	1 cohort, n=69,250[74]	Moderate study limitations, precision (wide CIs), consistency unknown	Insufficient
Depressed women	TCA exposure in pregnancy vs. unexposed women with depression in pregnancy	Preeclampsia	47/441 (10.7%) vs. 3,215//59,219 (5.4%);[75] 14/146 (9.59%) vs. 1,569/65,392 (2.40%)[81]	ARR, 1.62 (95% CI, 1.23 to 2.12)[75]; ARR, 3.23 (95% CI, 1.87 to 5.59)[81]	2 cohorts, n=125,198[75, 81]	Moderate study limitations, precise, consistent	Low for harms of TCA
Depressed or anxious or TCA-exposed women	TCA exposure in pregnancy vs. unexposed women with depression	Perinatal mortality	18/3,019 (0.6%) vs. 20/3647 (0.6%)[79]	ARR, 1.2 (99% CI, 0.5 to 2.7)	1 cohort, n=6,666[79]	High study limitations, imprecise (wide CIs), consistency unknown	Insufficient
History of psychiatric disorder or TCA-exposed women	TCA exposure in pregnancy vs. unexposed women with psychiatric disorder	Small for gestational age	Not applicable for case-control[93]	ARR, varies by trimester from 0.69 to 2.12, 95% CI, spans the null	1 case-control, n varies by trimester, >1,535[83]	Moderate study limitations, imprecise (wide CIs), consistency unknown	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
History of depression, depression or anxiety or psychiatric disorder or TCA-exposed women	TCA exposure during the first trimester vs. unexposed with history of depression, anxiety, or psychiatric disorder	Major congenital anomalies	51/382 (13.4%) vs. 1,650/14,847 (11.1%);[57] 74/2,428 (3.0%) vs. 380/13,432 (2.8%);[72] Not applicable for case-control[93]	Results not pooled because two publications[57, 93] potentially drawn from the same population AOR, 1.16 (95% CI, 0.86 to 1.56)[57] AOR, 1.02 (95% CI, 0.79 to 1.32)[72] AOR,0.78 (95% CI, 0.30 to 2.02)[93]	1 case-control,[93] 2 cohorts, n≥31,089[57, 72] N from two studies;[57, 72] (study samples may overlap)	High study limitations (two high risk-of-bias studies),[57, 93] imprecise (wide CIs), consistent	Insufficient
History of depression or anxiety or TCA-exposed women	TCA in first trimester vs. unexposed women with history of depression	Cardiac anomalies	20/2,428 (0.82%) vs. 112/13,432 (0.83%);[72] NR in other studies[7, 57]	Pooled AOR, 0.86 (95% CI, 0.65 to 1.13), I^2: 0%[7, 57, 72]	3 cohorts, n>15,860 (N=NR in two studies)[7, 57, 72]	High study limitations (all risk-of-bias studies),[7, 57, 72] imprecise (wide CIs), consistent	Insufficient
Psychiatric disorder or clomipramine -exposed women	Clomipramine vs. unexposed women with history of psychiatric disorder	Autism spectrum disorder	16/235 (6.8%) vs. 353/12,325 (2.9%);[51] NR in second study[56]	AOR, 1.76 (-95% CI, 1.01 to 3.05);[51] ARR, 3.36 (95% CI, 1.39 to 8.13), results not statistically significant when corrected for multiple testing ≥1 psychiatric disorder: ARR, 3.36 (95% CI, 1.39 to 8.13)[56] ≥2 psychiatric disorders: ARR, 2.53 (1.02 to 6.22)[56] ≥3 psychiatric disorders: ARR, 1.88 (0.7 to 4.73)[56]	2 cohorts, n=36,936[51, 56] (potential overlap of participants in the publications)	Moderate study limitations, imprecise, consistent	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Psychiatric disorder or amitriptyline or nortriptyline-exposed women	Amitriptyline or nortriptyline vs. unexposed women with history of psychiatric disorder	Autism spectrum disorder	NR	ARR, 0.47 (95% CI, 0.07 to 3.31) ≥1 psychiatric disorder: ARR, 0.47 (95% CI, 0.07 to 3.31)[56] ≥2 psychiatric disorders: ARR, 0.35 (0.05 to 2.49)[56] ≥3 psychiatric disorders: ARR, 0.25 (0.04 to 1.84)[56]	1 cohort, n=24,418[56]	Moderate study limitations, imprecise, consistency unknown	Insufficient

AOR = adjusted odds ratio; ARR = adjusted risk ratio; CI = confidence interval; n/N = number; NR = not reported; TCA = tricyclic antidepressant; vs. = versus.

All publications focused on exposure during pregnancy. Publications compared pregnant women exposed to TCAs with women with untreated depression,[7, 57, 64, 72, 75, 81] depression and anxiety,[56, 79] mood or anxiety disorders,[74] or history of a psychiatric disorder.[51, 83, 93] Studies specifying a history of disorders varied significantly in their definition. The most inclusive specified the control arm as having a lifetime history of at least one diagnosis of anxiety or depression but no drug exposure during pregnancy.[56] Among those specifying the control arm with respect to exposure during pregnancy, the allowable period of exposure also varied: no exposure during or in the year prior to pregnancy,[64] no exposure in the past year to 20 weeks gestation,[81] no exposure in the trimester of interest,[79, 83] and a history of anxiety or depression but no supply of antidepressants in the 5 months before delivery in another.[74]

The evidence from two studies[75, 81] suggests low strength of evidence for preeclampsia with TCAs; the risk of residual confounding cannot be ruled out. The evidence for TCAs, when analyzed individually or as a class, is insufficient to judge the risk of harms for maternal (spontaneous abortion, postpartum hemorrhage) or child outcomes (perinatal mortality, small for gestational age, major congenital anomalies, cardiac anomalies, or autism spectrum disorder) (Table B-28).

Two publications from the same data source (Quebec pregnancy, children cohort) reported on major congenital anomalies, but because they drew on different samples and used different designs, their results were reported separately. Notably, the results are not consistent in direction of effect, although neither publication demonstrates an association. Pooled results for cardiac anomalies also do not indicate an association (AOR, 0.86; 95% CI, 0.65 to 1.13; I^2, 0%; Figure B-7).[7, 57, 72]

Two publications from Swedish birth cohorts, with potential overlaps in the cohort, found no association between TCA exposure during pregnancy among women with a current or past psychiatric disorder and autism spectrum disorder in offspring.[51, 56] When the referent group was restricted to women with more than one psychiatric diagnosis, the point estimate for relative risk for clomipramine exposure moved from 3.36 (≥1 disorder with statistically significant results) to

1.88 (≥3 disorders with CIs spanning the null).[56] Similarly, the point estimate for amitriptyline/nortriptyline exposure also indicated reduced risk with more disorders. The relative risk moved from 0.47 (≥1 disorder with CIs spanning the null) to 0.25 (≥3 disorders also with CIs spanning the null).[56] This adjustment for confounding further suggests that the incidence of autism cannot be attributed to exposure to TCAs.

Brexanolone

Overview

- The prescribing information for brexanolone exposure for depression onset in the third trimester of pregnancy or within 4 weeks of birth includes a boxed warning regarding risk of excessive sedation or sudden loss of consciousness during administration of the drug.[150]
- Evidence was insufficient to judge the risks of any adverse events or dizziness in the brexanolone arms when compared with the. placebo arms.

Detailed Results

As noted in KQ 1, three RCTs (rated low risk of bias) reported on the harms of brexanolone versus placebo for depression symptoms with onset in the third trimester of pregnancy or within 4 weeks of birth (Table B-29).[17, 19] Brexanolone was administered as a 60-hour continuous infusion with a peak dose of either 60 μg/kg per hour or 90 μg/kg per hour. The study reported similar rates of any adverse events (pooled RR, 0.93; 95% CI, 0.72 to 1.21; I, 1.7%; Figure B-8) during infusion in the brexanolone and placebo groups and a higher rate of dizziness (pooled RR, 1.56; 95% CI, 0.52 to 4.66; I^2, 31.4%; Figure B-9) and loss of consciousness in the brexanolone versus placebo arms (pooled RR, 2.00; 95% CI, 0.78 to 5.16; I^2, 0%; Figure B-9). The prescribing information warns of excessive sedation or loss of consciousness in the active arm. Although results could not be pooled for excessive sedation or dose interruption based on the data in the published studies, the prescribing information notes that 5 percent of brexanolone-treated patients compared to 0 percent of placebo-treated patients had sedation or somnolence that required dose interruption.[151] Rates of loss of consciousness did not appear to increase with dose intensity: 5 percent of women randomized to BRX60 versus 3% for BRX90 experienced loss of consciousness. The pooled results for any adverse events and dizziness are imprecise and inconsistent and graded as insufficient.

Table B-29. Strength of evidence for harms: Brexanolone versus no placebo

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women with postpartum depression	Brexanolone vs. placebo	Any adverse event	BRX60: 19/38 (50%); BRX90: 51/102 (50%); Placebo: 54/107 (50.5%)	Pooled RR, 0.93, 95% CI, 0.72 to 1.21, I^2=1.7%	3 RCTs[17, 19]	Low study limitations, inconsistent, imprecise (wide CIs)	Insufficient
Women with postpartum depression	Brexanolone vs. placebo	Dizziness	BRX60: 6/38 (15.8%); BRX90: 13/102 (12.7%) Placebo: 8/107 (7.5%)	Pooled RR, 1.56, 95% CI, 0.52 to 4.66, I^2=31.4%	3 RCTs[17, 19]	Low study limitations, inconsistent, imprecise (wide CIs, few events)	Insufficient
Women with postpartum depression	Brexanolone vs. placebo	Dose interruption or reduction in some patients during the infusion due to sedation or somnolence	Treatment arm: 5% Placebo: 0 (from FDA prescribing information)[151]	Data not reported by study pooled RR not calculable)		Low study limitations, precision and consistency unknown	Low
	Brexanolone vs. placebo	Loss of consciousness	BRX60: 5%; BRX90: 3%; Placebo: 0% (from FDA prescribing information)[151]	Data not reported by study, cannot be pooled (from FDA prescribing information,[151] not reported in the appendix)	3 RCTs[17, 19]	Low study limitations, precision and consistency unknown	
	Brexanolone vs. placebo	Somnolence	BRX60: 7/38 (18.4%) BRX90: 8/102 (7.8%) Placebo: 5/107 (4.7%)	Pooled RR, 2.00, 95% CI, 0.78 to 5.16, I^2=0%	3 RCTs[17, 19]	Low study limitations, inconsistent, imprecise (wide CIs, few events)	

BRX = brexanolone for postpartum depression; CI = confidence interval; FDA = Food and Drug Administration; RCT = randomized controlled trial; RR = relative risk; vs. = versus.

Bupropion

Overview

- Evidence from one study suggests an increased risk of postpartum hemorrhage with past exposure (supply of drug 1 to 5 months prior to delivery) to bupropion compared with women with mood or anxiety disorders and no exposure to bupropion during pregnancy (low strength of evidence).
- The evidence is insufficient to judge the risk of harms for postpartum hemorrhage for current (supply of drug on delivery date) or recent exposure (supply of drug 1 month before delivery) to bupropion.

- The evidence is insufficient to judge the risk of harms for maternal outcomes (gestational diabetes, preeclampsia, postpartum hemorrhage) or child outcomes (any cardiac anomaly).

Detailed Results

Five publications reported on bupropion.[7, 74, 75, 104, 106] These publications drew from three cohorts (the 2000-2007 U.S. nationwide Medicaid Analytic eXtract data,[7, 74, 75] the Kaiser Permanente Washington Database,[104] and the National Birth Defects Prevention Study).[106] All were nonrandomized observational studies and were rated as "some concerns" regarding risk of bias.[7, 74, 75]

All publications focused on exposure during pregnancy. One publication[74] also analyzed current bupropion exposure (supply of drug on the delivery date), recent bupropion exposure (women with a supply of antidepressants on at least 1 day in the month before the delivery date but not on the delivery date), and past bupropion exposure (1 to 5 months before delivery). Publications compared pregnant women exposed to bupropion with women with nonpharmacologically treated depression[7, 75] or mood disorder and anxiety.[74] Two publications[75, 104]compared pregnant women who continued versus discontinued bupropion during pregnancy. One publication compared women exposed to bupropion during early pregnancy to women not exposed during early pregnancy.[106]

The evidence for bupropion, when analyzed individually is insufficient to judge the risk of harms for most maternal outcomes (postpartum hemorrhage, preeclampsia, or gestational diabetes) or child outcomes (any cardiac anomalies) (Table B-30). One study with moderate study limitations that did not adjust for multiple comparisons generally reported no difference in several other birth defects.[106]

The publications consistently found no association between bupropion exposure and maternal or child harms with the exception of increased risk of postpartum hemorrhage at one time point (past bupropion exposure[74]). Notably, there was no association detected with recent or current bupropion exposure in this publication.[74] In the one publication examining continuation versus discontinuation, bupropion continuation during pregnancy had no association with preeclampsia risk.

Table B-30. Strength of evidence for harms: Bupropion versus no treatment

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women taking anti-depressants at least 6 months before pregnancy	Bupropion continuation in pregnancy vs. discontinuation	Gestational Diabetes	21/217 (10%) vs. 90/1211 (7%)[104]	Weighted RR, 1.07 (95% CI, 0.63 to 1.81)[104]	1 cohort, N=1,438[104]	Moderate study limitations, imprecise (large CIs spanning the null), consistency unknown	Insufficient
Depressed or bupropion-exposed women	Bupropion exposure in pregnancy vs. unexposed women with depression	Any preeclampsia	153/2,622 (5.8%) vs. 3215/59,219 (5.4%)[75]	AOR, 1.09 (95% CI, 0.89 to 1.37)[75]	1 cohort, n=61,841[75]	Moderate study limitations, imprecise (wide CIs spanning the null), consistency unknown	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Depressed or bupropion-exposed women	Bupropion exposure in pregnancy vs. unexposed women with depression	Severe preeclampsia	34/2,622 (1.3%) vs. 976/59,219 (1.6%)[75]	AOR, 0.79 (95% CI, 0.56 to 1.12)[75]	1 cohort, n=61,841[75]	Moderate study limitations, imprecise (wide CIs spanning the null), consistency unknown	Insufficient
Depressed or bupropion-exposed women	Bupropion continuation in pregnancy vs. bupropion discontinuation	Preeclampsia	21/360 (5.8%) vs. 33/691 (4.8%)[75]	AOR, 1.10 (95% CI, 0.64 to 1.91)[75]	1 cohort, n=1,051[75]	Moderate study limitations, imprecise (wide CIs spanning the null), consistency unknown	Insufficient
Mood disorder or anxiety or bupropion-exposed women	Current bupropion exposure in pregnancy vs. bupropion unexposed women with mood disorder or anxiety	Postpartum hemorrhage	42/1,162 (3.6%) vs. 1,896/69,044 (2.7%) in[74]	ARR, 1.32 (95% CI, 0.98 to 1.79)	1 cohort, n=70,206[74]	Moderate study limitations, imprecise (wide CIs spanning the null), consistency unknown	Insufficient
Mood disorder or anxiety or bupropion-exposed women	Recent bupropion exposure in pregnancy vs. bupropion unexposed women with mood disorder or anxiety	Postpartum hemorrhage	21/660 (3.2%) vs. 1,896/69,044 (2.7%) in[74]	ARR, 1.17 (95% CI, 0.8 to 1.8)[74]	1 cohort, n=70,206[74]	Moderate study limitations, imprecise (wide CIs spanning the null), consistency unknown	Insufficient
Mood disorder or anxiety or bupropion-exposed women	Past bupropion exposure in pregnancy vs. bupropion unexposed women with mood disorder or anxiety	Postpartum hemorrhage	61/1,712 (3.6%) vs. 1,896/69,044 (2.7%) in[74]	ARR, 1.32 (95% CI, 1.02 to 1.69)[74]	1 cohort, n=70,206[74]	Moderate study limitations, precise, consistency unknown	Low for harms of bupropion
Depressed or bupropion-exposed women	Bupropion exposure in pregnancy vs. unexposed women with depression or unexposed in early pregnancy	Cardiac anomalies	NR;[7] 57 cases/45 controls vs.149 cases/125 controls[106]	AOR, 0.92 (95% CI, 0.69 to 1.22);[7] AOR, 1.06 (0.66 to 1.71)[106]	1 cohort,1 case-control, n NR in cohort[7] N in case-control=376[106]	Serious study limitations (high risk of bias[7]) imprecise (wide CIs spanning the null), consistency unknown	Insufficient

AOR = adjusted odds ratio; ARR = adjusted risk ratio; CI = confidence interval; n = number; vs. = versus.

Mirtazapine

Overview

- The evidence is insufficient to judge the risk of harms for mirtazapine exposure during pregnancy for maternal (postpartum hemorrhage or preeclampsia) or child outcomes (preterm birth, low birth weight, NICU stay, autism spectrum disorder).

Detailed Results

Four publications reported on mirtazapine.[56, 74, 75, 95] These three publications drew from two cohorts (two publications from the U.S. Medicaid Analytic eXtract,[74, 75]one from the Swedish Birth Cohort,[56] and one from a cohort based in Turkey.[95] All were nonrandomized studies and were rated as having some risk of bias.

All publications focused on exposure during pregnancy. Publications compared pregnant women exposed to mirtazapine with women with untreated depression,[75] untreated mood disorder or anxiety,[74] unexposed to antidepressants, [56] or unmedicated psychiatric disorder.[95]

The evidence for mirtazapine is insufficient to judge the risk of harms for maternal (postpartum hemorrhage preeclampsia) or child outcomes (preterm birth, low birth weight, NICU stay, autism spectrum disorder) (Table B-31). When the referent group was restricted to women with more than one psychiatric diagnosis, the point estimate for relative risk for clomipramine exposure moved from 1.55 (≥1 disorder with CIs spanning the null) to 0.99 (≥3 disorders also with CIs spanning the null).[56] This adjustment for confounding further suggests that the incidence of autism cannot be attributed to exposure to mirtazapine.

Table B-31. Strength of evidence for harms: Mirtazapine versus no treatment

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women with mood disorder or anxiety	Mirtazapine exposure during pregnancy (current vs. unexposed women with mood disorder or anxiety (no medication in 5 months prior to delivery)	Postpartum hemorrhage	NR/129 (NR%) vs. 1,896/69,044 (2.7%)[74]	ARR, 0.87 (95% CI, 0.29 to 2.66)[74]	1 cohort, n=69,173[74]	Moderate study limitations, imprecision (wide CIs), consistency unknown	Insufficient
Women with mood disorder or anxiety	Mirtazapine exposure during pregnancy (recent, 1-30 days prior to delivery) vs. unexposed women with mood disorder or anxiety (no medication in 5 months prior to delivery)	Postpartum hemorrhage	0/57 (0%) vs. 1,896/69,044 (2.7%)[74]	ARR, NA[74]	1 cohort, n=69,101[74]	Moderate study limitations, likely imprecision (few treatment cases and no events), consistency unknown	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women with mood disorder or anxiety	Mirtazapine exposure during pregnancy (past exposure 1-5 months prior to delivery) vs. unexposed women with mood disorder or anxiety (no medication in 5 months prior to delivery)	Postpartum hemorrhage	NR/135 (NR%) vs. 1,896/69,044 (2.7%)[74]	ARR, 1.07 (95% CI, 0.4 to 2.82)[74]	1 cohort, n=69,179[74]	Moderate study limitations, imprecision (wide CIs), consistency unknown	Insufficient
Depressed women	Mirtazapine exposure during pregnancy vs. unexposed women with depression	Preeclampsia	14/253 (5.5%) vs. 3,215/59,219 (5.4%)[75]	ARR, 0.81 (95% CI, 0.5 to 1.34)[75]	1 cohort, n=59,472[75]	Moderate study limitations, imprecision (wide CIs), consistency unknown	Insufficient
Women with psychiatric diagnosis	Mirtazapine exposure during pregnancy vs. unmedicated psychiatric diagnosis	Preterm birth	1/15 vs. 3/19[95]	NR, p = 0.767[95]	1 cohort, n=3,439[95]	High study limitations (high risk of bias[95]), imprecision (wide CIs), consistency unknown	Insufficient
Women with psychiatric diagnosis	Mirtazapine exposure during pregnancy vs. unmedicated psychiatric diagnosis	Low birth weight	1/15 vs. 3/19[95]	NR, p=0.767[95]	1 cohort, n=34[95]	High study limitations (high risk of bias[95]), imprecision (wide CIs), consistency unknown	Insufficient
Women with psychiatric diagnosis	Mirtazapine exposure during pregnancy vs. unmedicated psychiatric diagnosis	NICU stay	2/15 vs. 3/19[95]	NR, p=0.619[95]	1 cohort, n=3,439[95]	High study limitations (high risk of bias[95]), imprecision (wide CIs), consistency unknown	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women exposed to antidepres-sants	Mirtazapine exposure during pregnancy vs. unexposed women with prior antidepressant prescription	Autism spectrum disorder	NR/625 (NR) vs. NR/24,285 (NR)[56] ≥1 psychiatric disorder: ARR, 1.55 (95% CI, 0.39 to 6.29)[56] ≥2 psychiatric disorders: ARR, 1.24 (95% CI, 0.30 to 5.06)[56] ≥3 psychiatric disorders: ARR, 0.99 (95% CI, 0.24 to 4.09)[56]	ARR, 1.55 (95% CI, 0.39 to 6.29)[56]	1 cohort, n=24,347[56]	Moderate study limitations, imprecision (wide CIs), consistency unknown	Insufficient

ARR = adjusted risk ratio; CI = confidence interval; n = number; NA = not applicable; NR = not reported; vs. = versus.

Mood Stabilizers

Overview

- The evidence for mood stabilizer exposure during pregnancy (mood stabilizers overall, lamotrigine, valproate, topiramate, carbamazepine, oxcarbazepine, lithium) is insufficient to judge the risk of harms for maternal (gestational diabetes, preeclampsia, placental abruption, preterm birth) and child outcomes (small for gestational age, IQ).

Detailed Results

Three studies reported on mood stabilizers.[47, 96, 97] One publication with moderate risk of bias presented results for mood stabilizer monotherapy as a drug class and for individual drugs (lamotrigine, valproate, topiramate, carbamazepine, oxcarbazepine, and lithium) across a range of disorders, including bipolar disorder, migraine, epilepsy, and neuropathic pain, drawing from a cohort of deliveries in the Medicaid Analytic eXtract database.[96] We requested and received subgroup results for women with a diagnosis of bipolar disorder through personal communication. A second moderate risk-of-bias study reported for lithium and antipsychotics on gestational diabetes in two Australian hospitals.[97] Additionally, one high risk-of-bias publication, focusing on lithium,[47] drew from a cohort in Sweden. The publication compared women exposed to mood stabilizers with women who had no exposure to mood stabilizers during pregnancy.[47] These results are insufficient to judge the risk of maternal (gestational diabetes, preeclampsia, placental abruption, preterm birth) and child (small for gestational age, IQ) outcomes from mood stabilizer therapy or lithium exposure (Table B-32).

Table B-32. Strength of evidence for harms: Mood stabilizers versus no treatment

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Pregnant women with bipolar disorder	Mood stabilizer monotherapy vs. no exposure to mood stabilizers	Preeclampsia	NR	ARR, 0.95 (95% CI, 0.79 to 1.15) (personal communication with author[96])	1 cohort, N NR	Moderate study limitations, likely imprecise (wide CIs, likely small sample size), consistency unknown	Insufficient
Pregnant women with bipolar disorder	Mood stabilizer monotherapy vs. no exposure to mood stabilizers	Placental abruption	NR	ARR, 1.32 (95% CI, 1.01 to 1.73) (personal communication with author[96])	1 cohort, N NR	Moderate study limitations, likely imprecise (wide CIs, likely small sample size), consistency unknown	Insufficient
Pregnant women with bipolar disorder	Mood stabilizer monotherapy vs. no exposure to mood stabilizers	Small for gestational age	NR	ARR, 0.80 (95% CI, 0.65 to 0.97) (personal communication with author[96])	1 cohort, N NR	Moderate study limitations, likely imprecise (wide CIs, likely small sample size), consistency unknown	Insufficient
Pregnant women with bipolar disorder	Mood stabilizer monotherapy vs. no exposure to mood stabilizers	Preterm birth	NR	ARR, 0.95 (95% CI, 0.87 to 1.04) (personal communication with author[96])	1 cohort, N NR	Moderate study limitations, likely imprecise (wide CIs, likely small sample size), consistency unknown	Insufficient
Lamotrigine-exposed women	Lamotrigine exposure during any trimester of pregnancy vs. no exposure	Gestational diabetes mellitus	10.5% vs. 8.8% [97]	RR, 1.19 (0.30 to 4.79)[97]	1 cohort , n<539[97]	Moderate study limitations, imprecise (wide CIs, small N) consistency unknown	
Pregnant women with bipolar disorder	Lamotrigine vs. no exposure to mood stabilizers	Preeclampsia	NR	ARR, 0.86 (95% CI, 0.63 to 1.16) (personal communication with author[96])	1 cohort, N NR	Moderate study limitations, likely imprecise (wide CIs, likely small sample size), consistency unknown	Insufficient
Pregnant women with bipolar disorder	Lamotrigine vs. no exposure to mood stabilizers	Placental abruption	NR	ARR, 1.28 (95% CI, 0.84 to 1.95) (personal communication with author[96])	1 cohort, N NR	Moderate study limitations, likely imprecise (wide CIs, likely small sample size), consistency unknown	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Pregnant women with bipolar disorder	Lamotrigine vs. no exposure to mood stabilizers	Small for gestational age	NR	ARR, 0.78 (95% CI, 0.58 to 1.07) (personal communication with author[96])	1 cohort, N NR [96]	Moderate study limitations, likely imprecise (wide CIs, likely small sample size), consistency unknown	Insufficient
Pregnant women with bipolar disorder	Lamotrigine vs. no exposure to mood stabilizers	Preterm birth	NR	ARR, 0.97 (95% CI, 0.84 to 1.13) (personal communication with author[96])	1 cohort, N NR	Moderate study limitations, likely imprecise (wide CIs, likely small sample size), consistency unknown	Insufficient
Pregnant women with bipolar disorder	Valproate vs. no exposure to mood stabilizers	Preeclampsia	NR	ARR, 1.01 (95% CI, 0.74 to 1.37) (personal communication with author[96])	1 cohort, N NR	Moderate study limitations, likely imprecise (wide CIs, likely small sample size), consistency unknown	Insufficient
Pregnant women with bipolar disorder	Valproate vs. no exposure to mood stabilizers	Placental abruption	NR	ARR, 1.67 (95% CI, 1.11 to 2.52) (personal communication with author[96])	1 cohort, N NR	Moderate study limitations, likely imprecise (wide CIs, likely small sample size), consistency unknown	Insufficient
Pregnant women with bipolar disorder	Valproate vs. no exposure to mood stabilizers	Small for gestational age	NR	ARR, 0.70 (95% CI, 0.49 to 1.00) (personal communication with author[96])	1 cohort, N NR	Moderate study limitations, likely imprecise (wide CIs, likely small sample size), consistency unknown	Insufficient
Pregnant women with bipolar disorder	Valproate vs. no exposure to mood stabilizers	Preterm birth	NR	ARR, 1.06 (95% CI, 0.92 to 1.23) (personal communication with author[96])	1 cohort, N NR	Moderate study limitations, likely imprecise (wide CIs, likely small sample size), consistency unknown	Insufficient
Pregnant women with bipolar disorder	Topiramate vs. no exposure to mood stabilizers	Preeclampsia	NR	ARR, 1.39 (95% CI, 0.94 to 2.06) (personal communication with author[96])	1 cohort, N NR	Moderate study limitations, likely imprecise (wide CIs, likely small sample size), consistency unknown	Insufficient
Pregnant women with bipolar disorder	Topiramate vs. no exposure to mood stabilizers	Placental abruption	NR	ARR, 1.29 (95% CI, 0.67 to 2.50) (personal communication with author[96])	1 cohort, N NR	Moderate study limitations, likely imprecise (wide CIs, likely small sample size), consistency unknown	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Pregnant women with bipolar disorder	Topiramate vs. no exposure to mood stabilizers	Small for gestational age	NR	ARR, 0.58 (95% CI, 0.33 to 1.01) (personal communication with author[96])	1 cohort, N NR	Moderate study limitations, likely imprecise (wide CIs, likely small sample size), consistency unknown	Insufficient
Pregnant women with bipolar disorder	Topiramate vs. no exposure to mood stabilizers	Preterm birth	NR	ARR, 0.77 (95% CI, 0.59 to 1.00) (personal communication with author[96])	1 cohort, N NR	Moderate study limitations, likely imprecise (wide CIs, likely small sample size), consistency unknown	Insufficient
Pregnant women with bipolar disorder	Carbama-zepine vs. no exposure to mood stabilizers	Preeclampsia	NR	ARR, 1.16 (95% CI, 0.57 to 2.34) (personal communication with author[96])	1 cohort, N NR	Moderate study limitations, likely imprecise (wide CIs, likely small sample size), consistency unknown	Insufficient
Pregnant women with bipolar disorder	Carbama-zepine vs. no exposure to mood stabilizers	Placental abruption	NR	ARR, 1.18 (95% CI, 0.37 to 3.74) (personal communication with author[96])	1 cohort, N NR	Moderate study limitations, likely imprecise (wide CIs, likely small sample size), consistency unknown	Insufficient
Pregnant women with bipolar disorder	Carbama-zepine vs. no exposure to mood stabilizers	Small for gestational age	NR	ARR, 1.45 (95% CI, 0.76 to 2.77) (personal communication with author[96])	1 cohort, N NR	Moderate study limitations, likely imprecise (wide CIs, likely small sample size), consistency unknown	Insufficient
Pregnant women with bipolar disorder	Carbama-zepine vs. no exposure to mood stabilizers	Preterm birth	NR	ARR, 1.05 (95% CI, 0.74 to 1.48) (personal communication with author[96])	1 cohort, N NR	Moderate study limitations, likely imprecise (wide CIs, likely small sample size), consistency unknown	Insufficient
Pregnant women with bipolar disorder	Oxcarba-zepine vs. no exposure to mood stabilizers	Preeclampsia	NR	ARR, 0.95 (95% CI, 0.63 to 1.44) (personal communication with author[96])	1 cohort, N NR	Moderate study limitations, likely imprecise (wide CIs, likely small sample size), consistency unknown	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Pregnant women with bipolar disorder	Oxcarba-zepine vs. no exposure to mood stabilizers	Placental abruption	NR	ARR, 1.05 (95% CI, 0.53 to 2.08) (personal communication with author[96])	1 cohort, N NR	Moderate study limitations, likely imprecise (wide CIs, likely small sample size), consistency unknown	Insufficient
Pregnant women with bipolar disorder	Oxcarba-zepine vs. no exposure to mood stabilizers	Small for gestational age	NR	ARR, 0.68 (95% CI, 0.42 to 1.11) (personal communication with author[96])	1 cohort, N NR	Moderate study limitations, likely imprecise (wide CIs, likely small sample size), consistency unknown	Insufficient
Pregnant women with bipolar disorder	Oxcarba-zepine vs. no exposure to mood stabilizers	Preterm birth	NR	ARR, 0.97 (95% CI, 0.79 to 1.20) (personal communication with author[96])	1 cohort, N NR	Moderate study limitations, likely imprecise (wide CIs, likely small sample size), consistency unknown	Insufficient
Lithium-exposed women	Lithium exposure during any trimester of pregnancy vs. no exposure	Gestational diabetes mellitus	11.8% vs. 8.8%[97]	RR, 1.33 (0.33 to 5.31)[97]	1 cohort , n<539[97]	Moderate study limitations, imprecise (wide CIs, small N) consistency unknown	Insufficient
Pregnant women with bipolar disorder	Lithium vs. no exposure to mood stabilizers	Preeclampsia	NR	ARR, 0.79 (95% CI, 0.51 to 1.23) (personal communication with author[96])	1 cohort, N NR, ≤4153	Moderate study limitations, likely imprecise (wide CIs, likely small sample size), consistency unknown	Insufficient
Pregnant women with bipolar disorder	Lithium vs. no exposure to mood stabilizers	Placental abruption	NR	ARR, 0.88 (95% CI, 0.46 to 1.66) (personal communication with author[96])	1 cohort, N NR	Moderate study limitations, likely imprecise (wide CIs, likely small sample size), consistency unknown	Insufficient
Pregnant women with bipolar disorder	Lithium vs. no exposure to mood stabilizers	Small for gestational age	NR	ARR, 0.95 (95% CI, 0.64 to 1.41) (personal communication with author[96])	1 cohort, N NR	Moderate study limitations, likely imprecise (wide CIs, likely small sample size), consistency unknown	Insufficient
Pregnant women with bipolar disorder	Lithium vs. no exposure to mood stabilizers	Preterm birth	NR	ARR, 0.83 (95% CI, 0.67 to 1.02) (personal communication with author[96])	1 cohort, N NR	Moderate study limitations, likely imprecise (wide CIs, likely small sample size), consistency unknown	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Mood disorders	Lithium exposure in pregnancy vs. unexposed women with mood disorders	Child's full-scale IQ at 4-5 years from the Wechsler Preschool and Primary Scale of Intelligence	Medians 107.5 vs. 98[47]	Regression coefficient for no lithium vs. lithium: -6.3, p=0.15[47]	1 cohort, n=27[47]	High study limitations (high risk of bias[47]), seriously imprecise (wide CIs, small sample size), consistency unknown	Insufficient

CI = confidence interval; n = number; vs. = versus.

Antipsychotics

Overview

- Evidence from one study with some risk-of-bias concerns suggests increased risk of gestational diabetes with continuing quetiapine or olanzapine compared with discontinuing either drug during pregnancy (low strength of evidence).
- Evidence from one study with some risk-of-bias concerns suggests increased risk of congenital anomalies with second-generation antipsychotics compared with no exposure to drugs for women with schizophrenia, bipolar disorder, or psychosis during pregnancy (low strength of evidence).
- The evidence for antipsychotics, when analyzed individually or as a class, is insufficient to judge the risk of harms for maternal (only diabetes is assessed, primarily gestational onset for second-generation antipsychotics overall, or other evaluated antipsychotics, specifically, aripiprazole, ziprasidone, and risperidone) or child outcomes (low birthweight, preterm birth, small for gestational age, large for gestational age, major congenital anomalies, or cardiac anomalies) for all evaluated antipsychotic exposure during pregnancy.

Detailed Results

Seven publications reported on antipsychotics;[43, 44, 50, 62, 85, 90, 97] of these, four reported on antipsychotics as a class (1 compared second-generation antipsychotics to a control,[50] 1 compared antipsychotics associated with increased risks of nongestational type 2 diabetes mellitus to control,[97] and 2 separately compared second-generation antipsychotics to a control and first-generation antipsychotics to a control[62, 85]), and four focused on specific antipsychotics compared with control.[43, 44, 62, 90] These publications drew from four cohorts (3 from the National Pregnancy Registry for Atypical Antipsychotics,[43, 44, 50] 2 from the U.S. Medicaid Analytic eXtract,[62, 90] 1 from the Taiwan National Health Insurance Research Database and birth certificate registry,[85] and 1 from a cohort based in Australia.[97] All were nonrandomized studies. Three were rated as high risk of bias,[43, 44, 85] while four had some concerns.[50, 62, 90, 97]

All publications focused on exposure during pregnancy; four limited their exposure to the first trimester.[43, 44, 50, 62] Publications compared pregnant women exposed to antipsychotics with those who discontinued an antipsychotic during the first half of pregnancy[90] or at variably defined periods of exposure (before pregnancy or 4, 6, or 8 weeks before pregnancy),[62] those with a psychiatric condition but no second-generation antipsychotic exposure (although they

could be exposed to first-generation antipsychotics),[79] or those with no psychiatric history and no receipt of an antipsychotic during pregnancy.[85]

The evidence for antipsychotics, when analyzed individually or as a class, is insufficient to judge the risk of harms for maternal (only diabetes is assessed, primarily gestational onset) or child outcomes (low birthweight, preterm birth, small for gestational age, or large for gestational age) (Table B-33). Most available evidence involves the newer second-generation antipsychotics.

Table B-33. Strength of evidence for harms: Antipsychotics versus no treatment

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women with a psychiatric condition	Second-generation antipsychotic exposure in first trimester vs. unexposed to second-generation antipsychotic	All diabetes (pre-gestational or gestational)	40/310 (12.9%) vs. 16/149 (10.7%)[50]	AOR (propensity score): 1.16 (95% CI, 0.59 to 2.28); AOR (logistic regressions): 0.9 (95% CI, 0.44 to 1.91)[50]	1 cohort, n=459[50]	Moderate study limitations, imprecise (wide CIs), consistency unknown	Insufficient
Women with a psychiatric condition	Second-generation antipsychotic exposure in first trimester vs. unexposed to second-generation antipsychotic	Gestational diabetes	33/303 (10.9%) vs. 16/149 (10.7%)[50]	AOR (propensity score): 0.79 (95% CI, 0.40 to 1.56); AOR (logistic regressions): 0.72 (95% CI, 0.34 to 1.53)[50]	1 cohort, n=452[50]	Moderate study limitations, imprecise (wide CIs), consistency unknown	Insufficient
Women with severe mental illness	Antipsychotics associated with increased risk of nongestational type 2 diabetes mellitus (quetiapine [high-dose], olanzapine, risperidone, or clozapine) vs. psychotic disorders only	Gestational diabetes	NR	ARR, 4.39 (95% CI, 1.8 to 10.69)[97]	1 cohort, n= NR, <539[97]	Moderate study limitations, imprecise (wide CIs), consistency unknown[97]	Insufficient
Women prescribed an second-generation antipsychotic	Aripiprazole continued vs. aripiprazole discontinued	Gestational diabetes	20/419 (4.8%) vs. 68/1,505 (4.5%)[90]	ARR, 0.82 (95% CI, 0.5 to 1.33)[90]	1 cohort, n=924[90]	Moderate study limitations, imprecise (wide CIs), consistency unknown	Insufficient
Women prescribed an second-generation antipsychotic	Ziprasidone continued vs. ziprasidone discontinued	Gestational diabetes	<11/167 (<6.6%) vs. 19/506 (3.8%)[90]	ARR, 0.76 (95% CI, 0.29 to 2.0)[90]	1 cohort, n=673[90]	Moderate study limitations, imprecise (wide CIs), consistency unknown	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women prescribed an second-generation antipsychotic	Quetiapine continued vs. quetiapine discontinued	Gestational diabetes	110/1543 (7.1%) vs. 122/2,990 (4.1%)[90]	ARR, 1.28 (95% CI, 1.01 to 1.62)[90]	1 cohort, n=4,533[90]	Moderate study limitations, precise, consistency unknown	Low for harms of continued quetiapine
Women prescribed an second-generation antipsychotic	Risperidone continued vs. risperidone discontinued	Gestational diabetes	23/359 (6.4%) vs. 60/1,465 (4.1%)[90]	ARR, 1.09 (95% CI, 0.7 to 1.7)[90]	1 cohort, n=1,824[90]	Moderate study limitations, imprecise (wide CIs), consistency unknown	Insufficient
Women prescribed an second-generation antipsychotic	Olanzapine continued vs. olanzapine discontinued	Gestational diabetes	46/384 (12.0%) vs. 49/1,041 (4.7%)[90]	ARR, 1.61 (95% CI, 1.13 to 2.29)[90]	1 cohort, n=1,425[90]	Moderate study limitations, precise, consistency unknown	Low for harms of continued quetiapine
Women with schizophrenia	First-generation antipsychotic vs. no antipsychotic	Preterm birth	35/194 (18.0%) vs. 37/454 (8.1%)[85]	AOR, 2.46 (95% CI, 1.5 to 4.11)[85]	1 cohort, n=648[85]	High study limitations (high risk of bias[85]) precise, consistency unknown	Insufficient
Women with schizophrenia	Second-generation antipsychotic vs. no antipsychotic	Preterm birth	6/48 (12.5%) vs. 37/454 (8.1%)[85]	AOR, 1.61 (95% CI, 0.63 to 4.12)[85]	1 cohort, n=696[85]	High study limitations (high risk of bias[85]) imprecise (wide CIs), consistency unknown	Insufficient
Women with schizophrenia	First-generation antipsychotic vs. no antipsychotic	Low birth weight	16/194 (8.2%) vs. 41/454 (9.0%)[85]	AOR, 0.95 (95% CI, 0.5 to 1.75)[85]	1 cohort, n=696[85]	High study limitations (high risk of bias[85]) imprecise (wide CIs), consistency unknown	Insufficient
Women with schizophrenia	Second-generation antipsychotic vs. no antipsychotic	Low birth weight	6/48 (12.5%) vs. 41/454 (9.0%)[85]	AOR, 1.71 (95% CI, 0.67 to 4.34)[85]	1 cohort, n=696[85]	High study limitations (high risk of bias[85]) imprecise (wide CIs), consistency unknown	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women with schizophrenia	First-generation antipsychotic vs. no antipsychotic	Small for gestational age	49/194 (25.3%) vs. 92/454 (20.3%)[85]	AOR, 1.39 (95% CI, 0.93 to 2.08)[85]	1 cohort, n=696[85]	High study limitations (high risk of bias[85]) imprecise (wide CIs), consistency unknown	Insufficient
Women with schizophrenia	Second-generation antipsychotic vs. no antipsychotic	Small for gestational age	10/48(20.8%) vs. 92/454 (20.3%)[85]	AOR, 1.15 (95% CI, 0.55 to 2.41)[85]	1 cohort, n=696[85]	High study limitations (high risk of bias[85]) imprecise (wide CIs), consistency unknown	Insufficient
Women with schizophrenia	First-generation antipsychotic vs. no antipsychotic	Large for gestational age	15/194 (7.7%) vs. 44/454 (9.7%)[85]	AOR, 0.72 (95% CI, 0.39 to 1.34)[85]	1 cohort, n=696[85]	High study limitations (high risk of bias[85]) imprecise (wide CIs), consistency unknown	Insufficient
Women with schizophrenia	Second-generation antipsychotic vs. no antipsychotic	Large for gestational age	3/48 (6.3%) vs. 44/454 (9.7%)[85]	AOR, 0.55 (95% CI, 0.16 to 1.85)[85]	1 cohort, n=696[85]	High study limitations (high risk of bias[85]) imprecise (wide CIs), consistency unknown	Insufficient
Women exposed to risperidone during or before pregnancy	Risperidone continued in first trimester vs. risperidone discontinued before pregnancy	Major congenital anomalies	44/895 (4.9%) vs. 72/1737 discontinued before pregnancy (4.1%)[62] N reduces in both arms as more restrictive definitions of control group are used (no prescriptions 4, 6, and 8 weeks before pregnancy)	AOR, 1.00 (95% CI, 0.70 to 1.43)[62] AOR increases when more restrictive definitions of control group are used (no prescriptions 4, 6, and 8 weeks before pregnancy) from 1.13 to 1.64; CIs wide in all cases and span the null	1 cohort, n=2,632[62]	Moderate study limitations imprecise (wide CIs), inconsistency unknown	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women exposed to risperidone during or before pregnancy	Risperidone continued in first trimester vs. risperidone discontinued before pregnancy	Cardiac anomalies	18/895 (2.0%) vs. 26/1,737 (discontinued before pregnancy) (1.5%)[62] N reduces in both arms as more restrictive definitions of control group are used (no prescriptions 4, 6, and 8 weeks before pregnancy)	AOR, 0.85. (95% CI, 0.49 to 1.46)[62] AOR increases with more restrictive definitions of control group are used (no prescriptions 4, 6, and 8 weeks before pregnancy) from 1.31 to 2.46; CIs wide in all cases and span the null	1 cohort, n=2,632[62]	Moderate study limitations imprecise (wide CIs), inconsistency unknown	Insufficient
Women with a psychiatric condition	Quetiapine exposure in first trimester vs. unexposed to second-generation antipsychotic	Major congenital anomalies	2/155 (1.3%) vs. 3/210 (1.4%)[43]	AOR, 0.9 (95% CI, 0.15 to 5.46)[43]	1 cohort, n=357[43]	High study limitations (high risk of bias[43]) imprecise (wide CIs), consistency unknown	Insufficient
Women with a psychiatric condition or women with schizophrenia, bipolar disorder, or psychosis	Second-generation antipsychotic exposure in first trimester vs. unexposed to second-generation antipsychotic	Major congenital anomalies	209/3,995 (5.2%) vs. 471/11,606 (4.1%)[62] 3/214 (1.4%) vs. 1/89 (1.1%)[44]	AOR, 1.16 (95% CI, 0.99 to 1.35)[62] AOR, 0.69 (95% CI, 0.06 to 8.09)[44]	2 cohorts, n=15,904[44, 62]	Moderate study limitations (one high risk of bias study[44] precise, inconsistent	Insufficient
Women with schizophrenia, bipolar disorder, or psychosis	First-generation antipsychotic exposure in first trimester vs. unexposed to first-generation antipsychotic	Major congenital anomalies	16/381 (4.2%) vs. 417/10,418 (4.0%)[62]	AOR, 0.93 (95% CI, 0.57 to 1.51)[62]	1 cohort, n=10,799[62]	Moderate study limitations imprecise (wide CIs), inconsistency unknown	Insufficient
Women with schizophrenia, bipolar disorder, or psychosis	Second-generation antipsychotic exposure in first trimester vs. unexposed to second-generation antipsychotic	Cardiac anomalies	79/3,995 (2.0%) vs. 169/11,606 (1.5%)[62]	AOR, 1.21 (95% CI, 0.93 to 1.57)[62]	1 cohort, n=15,601[62]	Moderate study limitations imprecise (wide CIs), inconsistency unknown	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women with schizophrenia, bipolar disorder, or psychosis	First-generation antipsychotic exposure in first trimester vs. unexposed to first-generation antipsychotic	Cardiac anomalies	≤10/381 (≤2.6%) vs. 152/10,418 (2.6%)[62]	AOR, 0.91 (95% CI, 0.43 to 1.91)[62]	1 cohort, n=10,799[62]	Moderate study limitations imprecise (wide CIs), inconsistency unknown	Insufficient

AOR = adjusted odds ratio; ARR = adjusted risk ratio; CI = confidence interval; n = number; vs. = versus.

For maternal diabetes, data are only available for second-generation antipsychotics, and one study (which compares continuing with discontinuing second-generation antipsychotics) showed an increased risk for quetiapine (N=4,533) and olanzapine (N=1,425).[90] The evidence is rated as low for the potential for harm: although metabolic effects of these drugs could potentially have resulted in diabetes, the potential for residual confounding limits our confidence. A smaller study (N not reported but <539) reported a higher and significant risk of gestational diabetes for women with exposure to antipsychotics (first generation or second generation). The study did not control for severity of the disorder and had wide CIs, suggesting lack of precision. As a result, we graded the evidence for the risk of gestational diabetes from antipsychotics as a drug as insufficient.

For birth anomalies, the larger[62] of two studies[44, 62] (moderate risk of bias) provided analyses in women with schizophrenia, bipolar disorder, or psychosis and adjusted for potential confounding. These results suggest a small increased risk of congenital anomalies with second-generation antipsychotics as a class and with risperidone in particular. Notably, however, the risk for second-generation antipsychotics is not consistently higher in all analyses; the findings could be explained by chance and residual confounding cannot be ruled out. Also, the study did not find increased risk for cardiac anomalies. Further, it found no increased risk for first-generation antipsychotics for congenital anomalies overall or cardiac anomalies. Although the risk with risperidone was higher among those who continued on medication compared with those who discontinued medication, confidence intervals included appreciable harm and appreciable benefit, suggesting imprecision.

Regarding preterm birth, one high risk-of-bias study showed a significantly increased risk of preterm birth with first-generation antipsychotics but not second-generation antipsychotics.[85] Overall, however, results are not consistent in direction or magnitude of effects.

Pharmacologic Combinations

Overview

- Two publications on pharmacologic combinations reported on child outcomes (major congenital anomalies, heart anomalies, or psychomotor development) on nonspecific or undefined pharmacologic interventions compared with inactive treatment.

Detailed Results

Two publications reported on pharmacologic combinations.[45, 72] These publications drew from two cohorts (1 from THIN[72] and 1 from the Women's Mental Health Program at the Emory University School of Medicine[45]). Both were nonrandomized studies and were rated as high risk of bias.

Both publications focused on exposure during pregnancy. One compared SSRIs plus TCAs with untreated depression on child harms of major congenital and heart anomalies.[72] One compared SSRIs plus non-SSRIs exposure with untreated major depressive disorder on child outcomes of infant psychomotor development.[45] Because we could not determine the clinical utility of the interventions, they are not discussed in further detail.

Nonspecific or Undefined Pharmacologic Intervention

Overview

- Thirty-nine publications reported on nonspecific or undefined pharmacologic interventions compared with no treatment. Because the clinical utility is limited, we did not judge the risk of harms for maternal or child outcomes.
- These studies reported on maternal (breastfeeding at discharge, conception, ectopic pregnancy, gestational diabetes, obstetrical and/or delivery complications, induced labor, spontaneous abortion, gestational hypertension, preeclampsia, postpartum hemorrhage, severe maternal morbidity, maternal ICU, maternal extended length of hospital stay) and child outcomes (preterm birth, attention-deficit/hyperactivity disorder, asthma, Apgar scores, autism, cardiac/heart anomalies, major congenital anomalies, intellectual disabilities, low birth weight, NICU admissions and/or discharge, neonatal abstinence syndrome, prematurity/gestational age, perinatal death, psychiatric disorders, neuromotor and/or psychomotor development or other early development indicators, severe neonatal morbidity or mortality, or small for gestational age/size for gestational age).

Detailed Results

Thirty-nine publications reported on nonspecific or undefined pharmacologic interventions.[6, 7, 9, 31, 33, 42, 45, 48, 49, 51-58, 60, 64, 65, 67, 68, 70, 73, 75, 77-79, 83, 84, 86, 89, 93, 94, 99, 101, 102, 104-106] These publications drew from 28 cohorts (1 from Antimanic Use During Pregnancy,[89] 2 from the Danish Medical Birth Registry,[49, 68] 2 from the Danish National Birth Cohort,[9, 60, 78] 1 from THIN,[79] 1 from the Hong Kong Clinical Data Analysis and Reporting System,[55] 1 from Kaiser Permanente Northern California,[67] 1 from Kaiser Permanente Washington,[104] 2 from the Lombardy healthcare utilization database,[54, 58] 1 from Massachusetts General Hospital,[86] 1 from Motherisk,[77] 1 from the National Birth Defects Study,[106] 4 from the QPC,[53, 57, 64, 93] 1 from RAMQ,[70] 1 from the Slone Epidemiology Center Birth Defects Study,[84] 1 from the Stockholm Youth Cohort,[51] 1 from the Swedish Medical Birth Register,[52] 1 from the Swedish National Registers,[56] 1 from Time to Conceive,[65] 3 from U.S. Medicaid Analytic eXtract,[6, 7, 75] 1 from the Women's and Children's Health Network,[48] 1 from the OptumLabs Data Warehouse,[99] 1 from the Manitoba Population Research Data Repository,[101] 1 from the IBM MarketScan Research Databases,[102] 1 from the a claims databases maintained by the Japan Medical Data Center,[105] 1 that included multiple Danish national[73]registries,[73] 2 that included multiple Canada-based databases,[31, 83] 2 from populations in Australia,[33, 42] and 2 from populations based in the United States[45, 94]). All were

nonrandomized studies and were rated as high risk of bias or having some concerns for risk of bias.

All 39 publications focused on exposure during pregnancy. Twenty-four publications examined any antidepressants use,[7, 31, 33, 42, 48, 49, 51-56, 58, 60, 64, 65, 67, 68, 73, 78, 83, 86, 99, 102, 104-106] one examined new antidepressants,[93] one examined antipsychotics,[33] seven examined intervention groups described as other antidepressants,[7, 57, 58, 75, 79, 83, 106] one examined an intervention described as antidepressant/antipsychotic,[42] one examined interventions described as other monotherapy,[64] three examined polytherapy/polypharmacy,[64, 75, 79] four examined non-SSRIs,[6, 45, 51, 70, 84] one examined SSRIs only,[45] one examined nonsertraline SSRIs,[70] one examined SSRIs plus non-SSRIs,[45] one examined antidepressants described as SSRIs or SNRIs,[101] two examined any psychotropic treatment,[89, 94] one examined multiple antidepressant classes,[106] two examined interventions described as co-exposure,[83, 93] and one examined an intervention described as unclear.[77] The included publications evaluated the maternal outcomes (breastfeeding at discharge, conception, obstetrical and/or delivery complications, ectopic pregnancy, gestational diabetes, induced labor, spontaneous abortion, or gestational hypertension, preeclampsia, postpartum hemorrhage, severe maternal morbidity, maternal ICU admission, maternal extended length of stay) and the child outcomes (preterm delivery, attention-deficit/hyperactivity disorder, asthma, Apgar scores, autism, behavior, cardiac anomalies, major congenital anomalies, neural tube defect, mood disorder, heart anomalies, intellectual disabilities, birth weight, neonatal abstinence syndrome, NICU admissions and/or discharge, prematurity/gestational age, perinatal death, psychiatric disorders, persistent pulmonary hypertension, intrauterine hypoxia and birth asphyxia, neonatal convulsions, neuromotor and/or psychomotor development, respiratory conditions, severe neonatal morbidity or mortality, or small for gestational age/size for gestational age). Because the interventions were not clearly defined, they are not evaluated any further given their limited clinical utility.

Key Question 4: Among reproductive-aged 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?

Anti-Anxiety Medications Versus Specific Active Comparators

Overview

- No included publications reported on the harms of anxiolytics compared with specific active comparators.

Sedative Hypnotics Versus Specific Active Comparators

Overview

- No included publications reported on the harms of sedative hypnotics compared with specific active comparators.

SSRIs Versus SNRIs

Overview

- The evidence is insufficient to judge the comparative harms of SSRIs versus SNRIs exposure during pregnancy for any reported maternal outcomes (preeclampsia, gestational hypertension, vaginal bleeding, diabetes during pregnancy, infection during pregnancy, or spontaneous abortion) or child outcomes (birth outcomes, childhood epilepsy, neonatal behavioral assessments, attention-deficit/hyperactivity disorder, or autism spectrum disorder).

Detailed Results

Eight publications reported on the comparative harms of SSRIs versus SNRIs during pregnancy (Table B-34).[53, 64, 81, 110, 112, 114, 124, 140] These studies drew from five cohorts (two from the Canadian QPC cohort,[53, 114] a second cohort using the same Canadian Quebec registry data,[64] one from an Australian cohort of women with depression receiving care at a hospital's outpatient clinics,[124] one from the Danish Medical Birth Registry,[110] one from a Canadian British Colombian pregnant women and newborn registry,[81] one from the United States and Canada MotherToBaby (MTB) USA data,[112] and one from the Australian Mercy Pregnancy and Emotional Wellbeing Study. All were rated high risk of bias.

Table B-34. Strength of evidence for comparative harms: SSRIs versus SNRIs

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Pregnant women who used SSRIs or SNRIs during pregnancy or who had depression	SSRI vs. SNRI	Preeclampsia	23/408 (5.6%) vs. 105/3,169 (3.3%)[81] Continued AD use ≥20 weeks of gestation: 4/157 (2.5%) vs. 2/21 (9.5%)[112]	RR, 0.59 (95% CI,0.38 to 0.91)[81] RR, 0.27 (95% CI, 0.052 to 1.37)[112]	2 cohorts; n=3,577 in one cohort,[81] n=252 in second[112]	Serious study limitations (high risk of bias[81, 112]), imprecise (few events), consistent	Insufficient
Pregnant women who used SSRIs or SNRIs during pregnancy	SSRI vs. SNRI	Gestational hypertension	Continued AD use ≥20 weeks of gestation: 11/157 (7.0%) vs 3/21 (14.6%)[112] 2/23 (8.3%) vs. 23/60 (39.1%)[140]	RR, 0.49 (95% CI, 0.15 to 1.62)[112] RR, 0.235. (95% CI, 0.06 to 0.89)[140]	2 cohorts, n=335[112, 140]	High study limitations (high risk of bias[112, 140]), imprecise (wide CIs), consistent	Insufficient
Pregnant women who used SSRIs or SNRIs during pregnancy	SSRI vs. SNRI	Vaginal bleeding	2/27 (7%) vs. 1/11 (9%)[124]	RR, 0.81 (95% CI, 0.08 to 8.09)	1 cohort, n=38[124]	High study limitations (high risk of bias[124]), seriously imprecise (few events, wide CIs), consistency unknown	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Pregnant women who used SSRIs or SNRIs during pregnancy	SSRI vs. SNRI	Diabetes during pregnancy	2/27 (7%) vs. 1/11 (9%)[124]	RR, 0.81 (95% CI, 0.082 to 8.09)	1 cohort, n=38[124]	High study limitations (high risk of bias[124]), seriously imprecise (few events, wide CIs), consistency unknown	Insufficient
Pregnant women who used SSRIs or SNRIs during pregnancy	SSRI vs. SNRI	Infection during pregnancy	1/27 (4%) vs. 1/11 (9%)[124]	RR, 0.41 (95% CI, 0.03 to 5.95)	1 cohort, n=38[124]	High study limitations (high risk of bias[124]), seriously imprecise (few events, wide CIs), consistency unknown	Insufficient
Pregnant women with depression	SSRI vs. SNRI	Spontaneous abortion	93/938 (10%) vs. 20/137 (15%)[64]	RR, 0.68 (95% CI, 0.434 to 1.064)	1 cohort, n=1075[64]	High study limitations (high risk of bias[64]), imprecise (wide CIs), consistency unknown	Insufficient
Pregnant women taking anti-depressants or with current or past (within 2 years) depression or dysthymia	SSRI vs. SNRI	Birth outcomes (small and large for gestational age, Apgar score)	NR	NR, no significant associa-tions	1 cohort, n=90[140]	High study limitations (high risk of bias[140]), likely imprecise, consistency unknown	Insufficient
Pregnant women who used SSRIs or SNRIs during pregnancy	SSRI vs. SNRI	Childhood epilepsy	82/9,728 (0.008%) vs. 5/582 (0.009%)[110]	RR, 0.98 (95% CI, 0.399 to 2.411)	1 cohort, n=10,310[110]	High study limitations (high risk of bias[110]), imprecise (wide CIs), consistency unknown	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Pregnant women who used SSRIs or SNRIs during pregnancy	SSRI vs. SNRI	Brazelton Neonatal Behavioral Assessment Scale domain means	Means ± standard deviations Autonomic: 5.52±0.98 vs. 5.47±1.59[124] Habituation: 6.62±1.80 vs. 6.46±1.65[124] Motor: 5.38±0.55 vs. 5.27±0.69[124] Range: 3.47±0.61 vs. 3.55±0.52[124] Reflexes: 0.74±0.08 vs. 0.72±0.11[124] Regulation: 5.91±1.13 vs. 6.09±1.32[124] Social-interactive: 6.10± 2.02 vs. 6.49±1.63[124]	Mean diff: 0.05 (95% CI, -0.78 to 0.88) Mean diff: 0.16 (95% CI, -1.074 to 1.394) Mean diff: 0.11 (95% CI, -0.305 to 0.52) Mean diff: -0.08 (95% CI, -0.49 to 0.331) Mean diff: 0.02 (95% CI, -0.043 to 0.083) Mean diff: -0.18 (95% CI, -1.011 to 0.651) Mean diff: -0.39 (95% CI, -1.736 to 0.956)	1 cohort, n=38[124]	High study limitations (high risk of bias[124]), seriously imprecise (few events, wide CIs), consistency unknown	Insufficient
Pregnant women who used SSRIs or SNRIs during pregnancy	SSRI vs. SNRI	Attention-deficit/hyper-activity disorder	86/1561 (5.5%) vs. 18/445 (4%)[53]	RR, 1.36 (95% CI, 0.829 to 2.239)	1 cohort, n=2,006[53]	High study limitations (high risk of bias[53]), imprecise (wide CIs), consistency unknown	Insufficient
Pregnant women who used SSRIs or SNRIs during pregnancy	SSRI vs. SNRI	Autism spectrum disorder	22/1583 (1.4%) vs. 2/447 (0.4%)[114]	RR, 3.11 (95% CI, 0.733 to 13.159)	1 cohort, n=2,030[114]	High study limitations (high risk of bias[114]), imprecise (wide CIs), consistency unknown	Insufficient

AD = antidepressants; CI = confidence interval; n = number; RR = relative risk; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; vs. = versus.

Two publications each reported on differences in the risk of preeclampsia and gestational hypertension. For preeclampsia, one study found a significantly lower risk from SSRIs,[81] and a

second found a lower but not significantly different risk in a comparison limited to women who continued using the medications for 20 or more weeks of gestation.[112] For gestational hypertension, one study found a significant lower risk with SSRIs,[140] and the second study did not show a reduced risk. No study controlled for any potential confounding for these two outcomes.

All other outcomes were reported in one study. One study found that the risk of miscarriage (correcting for induced abortions) was similar between the two groups.[64] Other outcomes included maternal risk of vaginal bleeding, diabetes during pregnancy, and infection during pregnancy and child risks including epilepsy; Brazelton Neonatal Behavioral Assessment Scale domains; attention-deficit/hyperactivity disorder; and autism spectrum disorder. No differences were found for any of these outcomes.

SSRIs Versus TCAs

Overview

- The evidence is insufficient to judge the comparative risk of harms from SSRIs versus TCAs exposure during pregnancy for maternal outcomes (preeclampsia or spontaneous abortion) and child outcomes (preterm birth, gestational age, small for gestational age, birthweight, perinatal complications, NICU, Apgar score, anomalies, attention-deficit/hyperactivity disorder, autism spectrum disorder, or epilepsy).

Detailed Results

Ten high risk-of-bias publications reported on the comparative harms of SSRIs versus TCAs in pregnancy.[53, 64, 81, 83, 86, 110, 114, 123, 126, 133] Four publications drew from Canadian cohorts from Quebec and British Columbia,[53, 64, 81, 83, 114] two from Danish registries,[110, 123] and three from U.S. cohorts.[86, 126, 133] All outcomes were reported in nonrandomized studies that did not control for confounding. The evidence was insufficient to grade maternal risk of preeclampsia and spontaneous abortion and child outcomes of preterm birth, small for gestational age, birthweight, perinatal complications, Apgar score, anomalies, NICU, attention-deficit/hyperactivity disorder, autism spectrum disorder, and epilepsy (Table B-35).

Table B-35. Strength of evidence for comparative harms: SSRIs versus TCAs

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Pregnant women with depression	SSRIs vs. TCAs	Preeclampsia	105/3,169 (3.3%) vs. 14/146 (9.6%)[81]	RR, 0.34 (95% CI, 0.20 to 0.59)[81]	1 cohort, n=3,315[81]	High study limitations (high risk of bias[81]), imprecise (wide CIs), consistency unknown	Insufficient
Pregnant women with depression	SSRIs vs. TCAs	Spontaneous abortion	93/938 (9.9%) vs. 20/147 (13.6%)[64]	RR, 0.73 (95% CI, 0.46 to 1.14)	1 cohort, n=1,085[64]	High study limitations (high risk of bias[64]), imprecise (wide CIs), consistency unknown	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Exposed to SSRIs in the first trimester vs. exposed to TCAs in the first trimester (full-term infants)	SSRIs vs. TCAs	Preterm	166/1,768 (9.4%) vs. 42/381 (11.0%)[126] 3/42 (7.1%) vs. 6/37 (16.2%)[86]	RR, 0.85 (95% CI, 0.62 to 1.17)[126] RR: 2.27 (95% CI, 0.61 to 8.44)[86]	2 cohort study, N=2,228[86, 126]	High study limitations (high risk of bias[86, 126]), imprecise (wide CIs), inconsistent	Insufficient
Exposed to SSRIs vs. exposed to TCAs	SSRIs vs. TCAs	Gestational age ≤ 36 weeks	12/185 (6.5%) vs. 10/209 (4.8%), mean difference: -0.3 [133]	RR, 1.36 (95% CI, 0.60 to 3.06); CIs for mean difference span the null[133]	1 cohort study, N=394[133]	High study limitations (high risk of bias[133]), precise, consistency unknown	Insufficient
Exposed to SSRIs vs. exposed to TCAs	SSRIs vs. TCAs	Birthweight (birthweight ≤2500 g or total birthweight[133] or undefined[86])	19/185 (10.3%) vs. 21/209 (10.0%), mean difference: -80 g[133]; 1/42 (2.4%) vs. 2/37 (5.4%)	RR, 1.02 (95% CI, 0.57 to 1.84); CIs for mean difference span the null[133]; RR: 2.27 (95% CI, 0.21 to 2.40)[86]	2 cohort study, N=473[86, 133]	High study limitations (high risk of bias[86, 133]), imprecise, consistent	Insufficient
Exposed to SSRIs in the first trimester vs. exposed to TCAs in the first trimester (full-term infants)	SSRIs vs. TCAs	One or perinatal complications	339/874 (38.8%) vs. 58/136 (42.6%)[126]	RR, 0.91 (95% CI, 0.74 to 1.12)	1 cohort study, N=1,010[126]	High study limitations (high risk of bias[126]), imprecise (wide CIs), consistency unknown	Insufficient
Pregnant women with a psychiatric disorder	SSRIs or TCA by trimester of exposure	Small for gestational age (<10th percentile)	Not applicable, case control	ORs range from 0.42 to 0.98, all CIs cross the null	1 case-control, n=172[83]	High study limitations (high risk of bias,[83] imprecise) wide CIs, consistency unknown	Insufficient
Exposed to SSRIs vs. exposed to TCAs	SSRIs vs. TCAs	Apgar scores measured at 1 (≤5) and 5 minutes (≤7)	Rates for low Apgar scores range from 10.8% to 14.6% in the SSRI arm to 4.8% to 6.7% in the TCA arm; mean difference range from -0.28 to -0.52[133]	RR ranges from 2.18 to 2.26, CIs do not cross the null; mean differences also do not cross the null[133]	1 cohort study, N=394[133]	High study limitations (high risk of bias[133]), precise, consistency unknown	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Exposed to SSRIs in the first trimester vs. exposed to TCAs in the first trimester (full-term infants)	SSRIs vs. TCAs	Anomalies (one or more anomalies, major congenital anomalies, minor anomalies)	Ranges from 3.7% to 13.4% in the SSRI arm vs. 3.4% to 12.0% in the TCA arm	RRs range from 1.08 to 1.45, all CIs cross the null[123, 126, 133]	3 cohort studies, N=5,651[123, 126, 133]	High study limitations (high risk of bias[123, 126, 133]), imprecise (wide CIs), consistent	Insufficient
Exposed to SSRIs vs. exposed to TCAs	SSRIs vs. TCAs	Special care nursery of NICU	5/42 (11.9%) vs. 11/37 (29.7%)	RR: 2.50 (95% CI, 0.96 to 6.52)[86]	1 cohort study, N=79[86]	High study limitations (high risk of bias[86]), imprecise (wide CIs), consistency unknown	Insufficient
Pregnant women with psychiatric disorders	SSRIs vs. TCAs	ADHD	86/1,561 (5.5%) vs. 16/227 (7%)[53]	RR, 0.78 (95% CI, 0.47 to 1.31)[53]	1 cohort n=1,788[53]	High study limitations (high risk of bias[53]), imprecise (wide CIs), consistency unknown	Insufficient
Pregnant women with psychiatric disorders	SSRIs vs. TCAs	ASD	22/1,583 (1.4%) vs. 2/229 (0.9%)[114]	RR, 1.5 9 (95% CI, 0.38 to 6.72)	1 cohort n=1,812[114]	High study limitations (high risk of bias[114]), imprecise (wide CIs), consistency unknown	Insufficient
Pregnant women exposed to SSRIs or TCAs	SSRIs vs. TCAs	Epilepsy	82/9,728 (0.8%) vs. 8/576 (1.4%)[110]	RR, 0.61 (95% CI, 0.30 to 1.25)[110]	1 cohort n=1,304[110]	High study limitations (high risk of bias[110]), imprecise (wide CIs), consistency unknown	Insufficient

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; CI = confidence interval; N = number; RR = relative risk; SNRI = selective norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant; vs. = versus.

SSRIs Versus SSRIs Plus Mirtazapine

Overview

- The evidence is insufficient to judge the comparative risk of harms from SSRIs versus SSRIs plus mirtazapine exposure during pregnancy for child outcomes (preterm birth, late-term birth, low birthweight, NICU stay, macrosomia, neonatal bilirubinemia).

Detailed Results

One high risk-of-bias publication reported on the comparative harms of SSRIs versus SSRIs plus mirtazapine in pregnancy in Turkey.[95] The study did not control for confounding. The evidence was insufficient for all reported outcomes (preterm birth, late-term birth, low birthweight, birthweight, NICU stay, macrosomia, neonatal bilirubinemia) (Table B-36).

Table B-36. Strength of evidence for comparative harms: SSRIs versus SSRIs plus mirtazapine

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Pregnant women exposed to SSRIs or mirtazapine	SSRIs vs. SSRIs plus mirtazapine	Preterm birth	3/40 (7.50%) vs. 1/18 (5.56%)[95]	RR, 1.35 (95% CI, 0.15, 12.11)[95]	1 cohort, n=58[95]	High study limitations (high risk of bias[95]), imprecise (wide CIs), consistency unknown	Insufficient
Pregnant women exposed to SSRIs or mirtazapine	SSRIs vs. SSRIs plus mirtazapine	Late-term birth	0/40 (0.00%) vs. 2/18 (11.11%)[95]	RR, 0.09 (95% CI, 0.005 to 1.84)[95]	1 cohort, n=58[95]	High study limitations (high risk of bias[95]), imprecise (wide CIs), consistency unknown	Insufficient
Pregnant women exposed to SSRIs or mirtazapine	SSRIs vs. SSRIs plus mirtazapine	Low birthweight	4/40 (10.00%) vs. 1/18 (5.56%)[95]	RR, 1.80(95% CI, 0.22 to 14.99)[95]	1 cohort, n=58[95]	High study limitations (high risk of bias[95]), imprecise (wide CIs), consistency unknown	Insufficient
Pregnant women exposed to mirtazapine or SSRIs plus mirtazapine	SSRIs vs. SSRIs plus mirtazapine	Birthweight	3,153.17 gm (SD: 435.17), n=40 vs. 3,191.38 gm (SD: 436.69, n=18)[95]	Mean difference: -38.21 (95% CI, -280.55 to 204.13)[95]	1 cohort, n=58[95]	High study limitations (high risk of bias[95]), imprecise (wide CIs), consistency unknown	Insufficient
Pregnant women exposed to SSRIs or mirtazapine	SSRIs vs. SSRIs plus mirtazapine	NICU stay	7/40 (17.50%) vs. 3/18 (16.67%)[95]	RR, 1.05 (95% CI, 0.31 to 3.60)[95]	1 cohort, n=58[95]	High study limitations (high risk of bias[95]), imprecise (wide CIs), consistency unknown	Insufficient
Pregnant women exposed to SSRIs or mirtazapine	SSRIs vs. SSRIs plus mirtazapine	Macrosomia	2/40 (5.00%) vs. 1/18 (5.56%)[95]	RR, 0.9 (95% CI, 0.09 to 9.30)[95]	1 cohort, n=58[95]	High study limitations (high risk of bias[95]), imprecise (wide CIs), consistency unknown	Insufficient
Pregnant women exposed to SSRIs or mirtazapine	SSRIs vs. SSRIs plus mirtazapine	Neonatal bilirubinemia	19/40 (47.50%) vs. 4/18 (22.22%)[95]	RR, 2.14 (95% CI, 0.85 to 5.38)[95]	1 cohort, n=58[95]	High study limitations (high risk of bias[95]), imprecise (wide CIs), consistency unknown	Insufficient

CI = confidence interval; n = number; NICU = neonatal intensive care unit; SD = standard deviation; SSRI = selective serotonin reuptake inhibitor; RR = relative risk; vs. = versus.

SSRIs Versus MAOIs

Overview

- The evidence is insufficient to judge the comparative risk of harms from SSRIs versus MAOI exposure during pregnancy for child outcomes (attention-deficit/hyperactivity disorder or autism spectrum disorder).

Detailed Results

Two publications from the Canadian QPC reported on the comparative harms from treatment with SSRIs versus MAOIs among pregnant women with psychiatric disorders (Table B-37).[53, 114] Child attention-deficit/hyperactivity disorder outcomes were reported in one publication,[114] and autism spectrum disorder outcomes were reported in a second.[53] Only one woman was included in the MAOI group, and the publications were rated as high risk of bias because the analyses did not control for confounding.

Table B-37. Strength of evidence for comparative harms: SSRIs versus MAOIs

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women with psychiatric disorders during pregnancy	SSRIs vs. MAOIs	ADHD	86/1,561 (5.5%) vs. 0/1 (0%)[53]	RD, 0.055 (95% CI, -0.55 to 0.66)[53]	1 cohort n=1,562	High study limitations (high risk of bias,[53] imprecise (wide CIs), consistency unknown	Insufficient
Women with psychiatric disorders during pregnancy	SSRIs vs. MAOIs	ASD	22/1,583 (0.4%) vs. 0/1 (0%)[114]	RD, 0.014 (95% CI, -0.59 to 0.61)	1 cohort n=1,583	High study limitations (high risk of bias,[114] imprecise (wide CIs), consistency unknown	Insufficient

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; CI = confidence interval; MAOI = monoamine oxidase inhibitors; n = number; RD = risk difference; SSRI = selective serotonin reuptake inhibitor; vs. = versus.

Citalopram Versus Bupropion

Overview

- The evidence is insufficient to judge the comparative risk of harms from citalopram versus bupropion exposure during pregnancy for child outcomes (congenital heart disease).

Detailed Results

One publication reported on the comparative harms of citalopram versus bupropion.[141] The study drew from a cohort of women who had undergone a fetal echocardiogram because of in utero exposure of the fetus to SSRIs or SNRIs.[141] The study was rated as high risk of bias. The study yielded insufficient strength of evidence to judge the risk of congenital heart disease (Table B-38).

Table B-38. Strength of evidence for comparative harms: Citalopram versus bupropion

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women who underwent fetal echocardiography because of an in-utero exposure to either SSRIs or SNRIs	Citalopram vs. bupropion	Congenital heart disease	2/5 (40.00%) vs. 0/3 (0%)[141]	Risk difference, 0.40 (95% CI, -0.11 to 0.91)[141]	1 cohort, n=8[141]	High study limitations (high risk of bias,[141] imprecise (wide CIs), consistency unknown	Insufficient

CI = confidence interval; n = number; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; vs. = versus.

Citalopram Versus Duloxetine

Overview

- The evidence is insufficient to judge the comparative risk of harms from citalopram versus duloxetine exposure during pregnancy for child outcomes (congenital heart disease).

Detailed Results

One publication reported on the comparative harms of citalopram versus duloxetine.[141] The study drew from a cohort of women who had undergone a fetal echocardiogram because of in utero exposure of the fetus to SSRIs or SNRIs.[141] The study was rated as high risk of bias. The study yielded insufficient strength of evidence to judge the risk of congenital heart disease (Table B-39).

Table B-39. Strength of evidence for comparative harms: Citalopram versus duloxetine

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women who underwent fetal echocardiography because of an in-utero exposure to either SSRIs or SNRIs	Citalopram vs. duloxetine	Congenital heart disease	2/5 (40.00%) vs. 0/1 (0%)[141]	Risk difference, 0.40 (95% CI, -0.32 to 1.12)[141]	1 cohort, n=4[141]	High study limitations (high risk of bias,[141] imprecise (wide CIs), consistency unknown	Insufficient

CI = confidence interval; n = number; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; vs. = versus.

Citalopram Versus Escitalopram

Overview

- The evidence is insufficient to judge the comparative risk of harms from citalopram versus escitalopram exposure during pregnancy for child outcomes (congenital heart disease).

Detailed Results

One publication reported on the comparative harms of citalopram versus escitalopram.[141] The study drew from a cohort of women who had undergone a fetal echocardiogram because of in utero exposure of the fetus to SSRIs or SNRIs.[141] The study was rated as high risk of bias. The study yielded insufficient strength of evidence to judge the risk of congenital heart disease (Table B-40).

Table B-40. Strength of evidence for comparative harms: Citalopram versus escitalopram

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women who underwent fetal echocardiography because of an in utero exposure to either SSRIs or SNRIs	Citalopram vs. escitalopram	Congenital heart disease	2/5 (40.00%) vs. 1/9 (11.11%)[141]	RR, 3.60 (95% CI, 0.42 to 30.51)[141]	1 cohort, n=14[141]	High study limitations (high risk of bias,[141] imprecise (wide CIs), consistency unknown	Insufficient

CI = confidence interval; n = number; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; RR = relative risk; vs. = versus.

Citalopram Versus Fluvoxamine

Overview

- The evidence is insufficient to judge the risk of child outcomes (specifically, autism spectrum disorder) when comparing exposure during pregnancy to citalopram or fluvoxamine during pregnancy.

Detailed Results

One high risk-of-bias publication reported on child harms, specifically autism spectrum disorder, of citalopram exposure compared with fluvoxamine exposure during pregnancy.[111] The publication drew from the QPC in Canada.[111] The study provided imprecise results on the risk of autism spectrum disorder; the evidence was rated as insufficient (Table B-41).

Table B-41. Strength of evidence for comparative harms: Citalopram versus fluvoxamine

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Pregnant women in second or third trimester exposed to citalopram or fluvoxamine[111]	Maternal exposure to citalopram vs. maternal exposure to fluvoxamine	Autism spectrum disorder among offspring	5/421 (1.2%) vs. 1/135 (2.9%)[111]	RR, 0.42 (95% CI, 0.005 to 3.46)[111]	1 cohort, N=556	High study limitations (high risk of bias[111]), imprecise, consistency unknown	Insufficient

CI = confidence interval; N = number; RR = relative risk; vs. = versus.

Citalopram Versus Fluoxetine

Overview

- The evidence is insufficient to judge the risk of child outcomes (congenital heart disease, autism spectrum disorder) when comparing exposure during pregnancy to citalopram or fluoxetine during pregnancy.

Detailed Results

One publication reported on the comparative harms of citalopram versus fluoxetine.[141] The study drew from a cohort of women who had undergone a fetal echocardiogram because of in utero exposure of the fetus to SSRIs or SNRIs.[141] The study was rated as high risk of bias. The study yielded insufficient strength of evidence to judge the risk of congenital heart disease

Two high risk-of-bias publications reported on child harms, specifically autism spectrum disorder, of citalopram exposure versus fluoxetine exposure during pregnancy.[111, 117] These studies both drew from large cohorts including Danish National registries[117] and the QPC in Canada.[111] Two studies provided inconsistent and imprecise results on the risk of autism spectrum disorder; the evidence was rated as insufficient (Table B-42).

Table B-42. Strength of evidence for comparative harms: Citalopram versus fluoxetine

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women who underwent fetal echocardio-graphy because of an in utero exposure to either SSRIs or SNRIs	Citalopram vs fluoxetine.	Congenital heart disease	2/5 (40.00%) vs. 2/9 (22.22%)[141]	RR, 1.80 (95% CI, 0.35 to 9.16)[141]	1 cohort, n=14[141]	High study limitations (high risk of bias,[141] imprecise (wide CIs), consistency unknown	Insufficient
Pregnant women in second or third trimester[111] or during pregnancy[117] exposed to citalopram or fluoxetine	Maternal exposure to citalopram vs. maternal exposure to fluoxetine	Autism spectrum disorder among offspring	5/421 (1.2%) vs. 5/171 (2.9%);[111] 14/1,751 (0.8%) vs. 18/160 (11.3%)[117]	RR, 0.41 (95% CI, 0.11 to 1.4);[111] RR, 7.1 (95% CI, 0.036 to 0.14)[117]	2 cohorts, N=2,503	High study limitations (high risk of bias[111, 117]), imprecise, inconsistent	Insufficient

CI = confidence interval; n = number; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; RR = relative risk; vs. = versus.

Citalopram Versus Paroxetine

Overview

- The evidence is insufficient to judge the risk of child outcomes (specifically, autism spectrum disorder and congenital heart disease) when comparing exposure during pregnancy to citalopram or paroxetine during pregnancy.

Detailed Results

Two high risk-of-bias publications reported on child harms, specifically autism spectrum disorder, of citalopram exposure compared with paroxetine exposure during pregnancy.[111, 117] These studies both drew from large cohorts, including Danish National registries[117] and the QPC in Canada.[111] Two studies provided consistent but imprecise results and had high study limitations; the evidence was rated as insufficient (Table B-43). One small high risk-of-bias study reported on congenital heart disease; the evidence was rated as insufficient.

Table B-43. Strength of evidence for comparative harms: Citalopram versus paroxetine

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Pregnant women in second or third trimester[111] or during pregnancy[117] exposed to citalopram or paroxetine	Maternal exposure to citalopram vs. maternal exposure to paroxetine	Autism spectrum disorder among offspring	5/421 (1.2%) vs. 11/744 (1.5%);[111] 14/1,751 (0.8%) vs. 7/871 (0.8%)[117]	RR, 0.80 (95% CI, 0.28 to 2.3);[111] RR, 0.99 (95% CI, 0.4 to 2.5)[117]	2 cohorts, N=3,787	High study limitations (high risk of bias[117]), imprecise, consistent	Insufficient
Women who underwent fetal echocardiography because of an in utero exposure to either SSRIs or SNRIs	Citalopram vs. paroxetine	Congenital heart disease	2/5 (40.00%) vs. 0/1	Risk difference 0.40 (95% CI, -0.32 to 1.12[141]	1 cohort, n=6[141]	High study limitations (high risk of bias,[141] imprecise (wide CIs), consistency unknown	Insufficient

CI = confidence interval; n = number; RR = relative risk; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; vs. = versus.

Citalopram Versus Sertraline

Overview

- The evidence is insufficient to judge the risk of child outcomes (specifically, autism spectrum disorder and congenital heart disease) when comparing exposure during pregnancy to citalopram or sertraline during pregnancy.

Detailed Results

Two high risk-of-bias publications reported on child harms, specifically autism spectrum disorder, of citalopram exposure compared with sertraline exposure during pregnancy.[111, 117] These studies both drew from large cohorts, including Danish National registries[117] and the QPC in Canada.[111] Two studies provided consistent but imprecise results and had high study limitations; the evidence was rated as insufficient (Table B-44). One small high risk-of-bias study reported on congenital heart disease; the evidence was rated as insufficient.

Table B-44. Strength of evidence for comparative harms: Citalopram versus sertraline

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Pregnant women in second or third trimester[111] or during pregnancy[117] exposed to citalopram or sertraline	Maternal exposure to citalopram vs. maternal exposure to sertraline	Autism spectrum disorder among offspring	5/421 (1.2%) vs. 1/292 (0.34%);[111] 14/1,751 (0.8%) vs. 9/1,576 (0.57%)[117]	RR, 3.5 (95% CI, 0.41 to 29.5)[111] RR, 1.4 (95% CI, 0.61 to 3.2)[117]	2 cohorts, N=4,040	High study limitations (high risk of bias[111, 117]), imprecise, consistent	Insufficient
Women who underwent fetal echocardiography because of an in utero exposure to either SSRIs or SNRIs	Citalopram vs. sertraline	Congenital heart disease	2/5 (40.00%) vs. 0/7 (0%)[141]	Risk difference, 0.40 (95% CI, -0.03 to 0.83[141]	1 cohort, n=12[141]	High study limitations (high risk of bias,[141] imprecise (wide CIs), consistency unknown	Insufficient

CI = confidence interval; n = number; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; RR = relative risk; vs. = versus.

Citalopram Versus Venlafaxine

Overview

- The evidence is insufficient to judge the comparative risk of harms from exposure during pregnancy to citalopram versus venlafaxine for child outcomes (congenital heart disease).

Detailed Results

One publication reported on the comparative harms of citalopram versus venlafaxine.[141] The study drew from a cohort of women who had undergone a fetal echocardiogram because of in utero exposure of the fetus to SSRIs or SNRIs.[141] The study was rated as high risk of bias. The study yielded insufficient strength of evidence to judge the risk of congenital heart disease (Table B-45).

Table B-45. Strength of evidence for comparative harms: Citalopram versus venlafaxine

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women who underwent fetal echocardiography because of an in utero exposure to either SSRIs or SNRIs	Citalopram vs. venlafaxine	Congenital heart disease	2/5 (40.00%) vs. 2/2 (100%)[141]	RR, 0.50 (95% CI, 0.17 to 1.46)[141]	1 cohort, N=7[141]	High study limitations (high risk of bias,[141] imprecise (wide CIs), consistency unknown	Insufficient

CI = confidence interval; N = number; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; RR = relative risk; vs. = versus.

Escitalopram Versus Bupropion

Overview

- The evidence is insufficient to judge the comparative risk of harms from exposure to escitalopram versus bupropion during pregnancy for child outcomes (congenital heart disease).

Detailed Results

One publication reported on the comparative harms of escitalopram versus bupropion.[141] The study drew from a cohort of women who had undergone a fetal echocardiogram because of in utero exposure of the fetus to SSRIs or SNRIs.[141] The study was rated as high risk of bias. The study yielded insufficient strength of evidence to judge the risk of congenital heart disease (Table B-46).

Table B-46. Strength of evidence for comparative harms: Escitalopram versus bupropion

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women who underwent fetal echocardiography because of an in utero exposure to either SSRIs or SNRIs	Escitalopram vs. bupropion	Congenital heart disease	1/9 (11.11%) vs. 0/3 (0.00%)[141]	Risk difference, 0.11 (95% CI, -0.28 to 0.50)[141]	1 cohort, n=12[141]	High study limitations (high risk of bias,[141] imprecise (wide CIs), consistency unknown	Insufficient

CI = confidence interval; n = number; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; vs. = versus.

Escitalopram Versus Paroxetine

Overview

- The evidence is insufficient to judge the risk of harms for child outcomes (congenital heart disease) for exposure to escitalopram versus paroxetine during pregnancy.

Detailed Results

One publication reported on the comparative harms of paroxetine versus escitalopram (Table B-47).[141] The study drew from a cohort of women who had undergone a fetal echocardiogram because of in utero exposure of the fetus to SSRIs or SNRIs.[141] The study was rated as high risk of bias. The study yielded insufficient strength of evidence to judge the risk of congenital heart disease.

Table B-47. Strength of evidence for comparative harms: Escitalopram versus paroxetine

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women who underwent fetal echocardiography because of an in utero exposure to either SSRIs or SNRIs center	Escitalopram vs. paroxetine	Congenital heart disease	1/9 (11%) vs. 0/1 (0%)[141]	Risk difference 0.11 (95% CI, -0.53-0.75)[141]	1 cohort study, N=10[141]	High study limitations (high risk of bias,[141] imprecise (wide CIs), consistency unknown	Insufficient

CI = confidence interval; N = number; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; vs. = versus.

Escitalopram Versus Sertraline

Overview

- The evidence is insufficient to judge the comparative risk of harms from exposure to escitalopram versus sertraline during pregnancy for child outcomes (congenital heart disease).

Detailed Results

One publication reported on the comparative harms of escitalopram versus sertraline.[141] The study drew from a cohort of women who had undergone a fetal echocardiogram because of in utero exposure of the fetus to SSRIs or SNRIs.[141] The study was rated as high risk of bias. The study yielded insufficient strength of evidence to judge the risk of congenital heart disease (Table B-48).

Table B-48. Strength of evidence for comparative harms: Escitalopram versus sertraline

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women who underwent fetal echocardiography because of an in utero exposure to either SSRIs or SNRIs	Escitalopram vs. sertraline	Congenital heart disease	1/9 (11.11%) vs. 0/7 (0.00%)[141]	Risk difference, 0.11 (95% CI, -0.17 to 0.39)[141]	1 cohort, n=16[141]	High study limitations (high risk of bias,[141] imprecise (wide CIs), consistency unknown	Insufficient

CI = confidence interval; n = number; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; vs. = versus.

Escitalopram Versus Duloxetine

Overview

- The evidence is insufficient to judge the comparative risk of harms from exposure to escitalopram versus duloxetine during pregnancy for child outcomes (congenital heart disease).

Detailed Results

One publication reported on the comparative harms of escitalopram versus duloxetine.[141] The study drew from a cohort of women who had undergone a fetal echocardiogram because of in utero exposure of the fetus to SSRIs or SNRIs.[141] The study was rated as high risk of bias. The study yielded insufficient strength of evidence to judge the risk of congenital heart disease (Table B-49).

Table B-49. Strength of evidence for comparative harms: Escitalopram versus duloxetine

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women who underwent fetal echocardiography because of an in utero exposure to either SSRIs or SNRIs	Escitalopram vs. duloxetine	Congenital heart disease	1/9 (11.11%) vs. 0/1 (0.00%)[141]	Risk difference 0.11 (95% CI, -0.53 to 0.75)[141]	1 cohort, n=10[141]	High study limitations (high risk of bias,[141] imprecise (wide CIs), consistency unknown	Insufficient

CI = confidence interval; n = number; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; vs. = versus.

Fluoxetine Versus Bupropion

Overview

- The evidence is insufficient to judge the comparative risk of harms from exposure during pregnancy to fluoxetine versus bupropion for child outcomes (congenital heart disease).

Detailed Results

One publication reported on the comparative harms of fluoxetine versus bupropion.[141] The study drew from a cohort of women who had undergone a fetal echocardiogram because of in utero exposure of the fetus to SSRIs or SNRIs.[141] The study was rated as high risk of bias. The study yielded insufficient strength of evidence to judge the risk of congenital heart disease (Table B-50).

Table B-50. Strength of evidence for comparative harms: Fluoxetine versus bupropion

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women who underwent fetal echocardiography because of an in utero exposure to either SSRIs or SNRIs	Fluoxetine vs. bupropion	Congenital heart disease	2/9 (22.22%) vs. 0/3 (0%)[141]	Risk difference, 0.22 (95% CI, -0.20 to 0.64)[141]	1 cohort, n=12[141]	High study limitations (high risk of bias,[141] imprecise (wide CIs), consistency unknown	Insufficient

CI = confidence interval; n = number; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; vs. = versus.

Fluoxetine Versus Duloxetine

Overview

- The evidence is insufficient to judge the comparative risk of harms from exposure during pregnancy to fluoxetine versus duloxetine for child outcomes (congenital heart disease).

Detailed Results

One publication reported on the comparative harms of fluoxetine versus duloxetine.[141] The study drew from a cohort of women who had undergone a fetal echocardiogram because of in utero exposure of the fetus to SSRIs or SNRIs.[141] The study was rated as high risk of bias. The study yielded insufficient strength of evidence to judge the risk of congenital heart disease (Table B-51).

Table B-51. Strength of evidence for comparative harms: Fluoxetine versus duloxetine

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women who underwent fetal echocardiography because of an in utero exposure to either SSRIs or SNRIs	Fluoxetine vs. duloxetine	Congenital heart disease	2/9 (22.22%) vs. 0/1 (0%)[141]	Risk difference, 0.22 (95% CI, -0.20 to 0.64)[141]	1 cohort, n=10[141]	High study limitations (high risk of bias,[141] imprecise (wide CIs), consistency unknown	Insufficient

CI = confidence interval; n = number; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; vs. = versus.

Fluoxetine Versus Escitalopram

Overview

- The evidence is insufficient to judge the comparative risk of harms from exposure during pregnancy to fluoxetine versus escitalopram for child outcomes (congenital heart disease).

Detailed Results

One publication reported on the comparative harms of fluoxetine versus escitalopram.[141] The study drew from a cohort of women who had undergone a fetal echocardiogram because of in utero exposure of the fetus to SSRIs or SNRIs.[141] The study was rated as high risk of bias. The study yielded insufficient strength of evidence to judge the risk of congenital heart disease (Table B-52).

Table B-52. Strength of evidence for comparative harms: Fluoxetine versus escitalopram

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women who underwent fetal echocardiography because of an in utero exposure to either SSRIs or SNRIs	Fluoxetine vs. escitalopram	Congenital heart disease	2/9 (22.22%) vs. 1/9 (11.11%)[141]	RR, 2.00 (95% CI, 0.22 to 18.33)[141]	1 cohort, n=18[141]	High study limitations (high risk of bias,[141] imprecise (wide CIs), consistency unknown	Insufficient

CI = confidence interval; n = number; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; RR = relative risk; vs. = versus.

Fluoxetine Versus Sertraline

Overview

- The evidence is insufficient to judge the comparative risk of harms from exposure during pregnancy to fluoxetine versus sertraline for child outcomes (congenital heart disease).

Detailed Results

One publication reported on the comparative harms of Fluoxetine versus sertraline.[141] The study drew from a cohort of women who had undergone a fetal echocardiogram because of in utero exposure of the fetus to SSRIs or SNRIs.[141] The study was rated as high risk of bias. The study yielded insufficient strength of evidence to judge the risk of congenital heart disease (Table B-53).

Table B-53. Strength of evidence for comparative harms: Fluoxetine versus sertraline

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women who underwent fetal echocardiography because of an in utero exposure to either SSRIs or SNRIs	Fluoxetine vs. sertraline	Congenital heart disease	2/9 (22.22%) vs. 0/7 (0%)[141]	Risk difference. 0.22 (95% CI, -0.09 to 0.54)[141]	1 cohort, n=16[141]	High study limitations (high risk of bias,[141] imprecise (wide CIs), consistency unknown	Insufficient

CI = confidence interval; n = number; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; vs. = versus.

Fluoxetine Versus Venlafaxine

Overview

- The evidence is insufficient to judge the comparative risk of harms from exposure during pregnancy to fluoxetine versus venlafaxine for child outcomes (congenital heart disease).

Detailed Results

One publication reported on the comparative harms of fluoxetine versus venlafaxine.[141] The study drew from a cohort of women who had undergone a fetal echocardiogram because of in utero exposure of the fetus to SSRIs or SNRIs.[141] The study was rated as high risk of bias. The study yielded insufficient strength of evidence to judge the risk of congenital heart disease (Table B-54).

Table B-54. Strength of evidence for comparative harms: Fluoxetine versus venlafaxine

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women who underwent fetal echocardiography because of an in utero exposure to either SSRIs or SNRIs	Fluoxetine vs. venlafaxine	Congenital heart disease	2/9 (22.22%) vs. 2/2 (100%)[141]	RR, 0.03 (95% CI, 0.09 to 0.98)[141]	1 cohort, n=11[141]	High study limitations (high risk of bias,[141] imprecise (wide CIs), consistency unknown	Insufficient

CI = confidence interval; n = number; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; RR = relative risk; vs. = versus.

Fluoxetine Versus Citalopram or Escitalopram

Overview

- The evidence is limited to one study and is insufficient to judge the comparative risk of harms from exposure during pregnancy to fluoxetine monotherapy versus citalopram or escitalopram monotherapy for maternal outcomes (convulsive seizures, nonconvulsive seizures, or spontaneous abortion or stillbirth) or child outcomes (congenital anomaly or birth weight) among women with epilepsy.

Detailed Results

One high risk-of-bias publication reported on the comparative harms of fluoxetine versus citalopram or escitalopram.[107] The population consisted of pregnant women with depression, anxiety, or bipolar disorder, as well as epilepsy, drawn from the Australian Antiepileptic Drugs in Pregnancy register. No significant differences were found in the risk of harms for any maternal (convulsive seizures, nonconvulsive seizures, spontaneous abortion, or stillbirth) or child outcomes (congenital anomalies or birth weight) (Table B-55).

Table B-55. Strength of evidence for comparative harms: Fluoxetine monotherapy versus SSRI monotherapy (citalopram or escitalopram)

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women with epilepsy and depression, anxiety or bipolar disorder	Fluoxetine only vs. SSRI monotherapy (citalopram or escitalopram)	Convulsive seizures: From enrollment to 7 months gestation From 7 months gestation to delivery	2/5 (40%) vs. 2/20 (10%)[107] 1/5 (20%) vs. 1/20 (5%)[107]	RR, 4 (95% CI, 0.73 to 21.84)[107] RR, 4 (95% CI, 0.30 to 53.47)[107]	1 cohort, n=25	High study limitations (high risk of bias[107]), seriously imprecise (few events, wide CIs), consistency unknown	Insufficient
Women with epilepsy and depression, anxiety or bipolar disorder	Fluoxetine only vs. SSRI monotherapy (citalopram or escitalopram)	Noncon-vulsive seizures: From enrollment to 7 months gestation From 7 months gestation to delivery	1/5 (20%) vs. 4/20 (20%)[107] 1/5 (20%) vs. 3/20 (15%)[107]	RR, 1 (95% CI, 0.14 to 7.10)[107] RR, 1.33 (95% CI, 0.173 to 10.254)[107]	1 cohort, n=25	High study limitations (high risk of bias[107]), seriously imprecise (few events, wide CIs), consistency unknown	Insufficient
Women with epilepsy and depression, anxiety or bipolar disorder	Fluoxetine only vs. SSRI monotherapy (citalopram or escitalopram)	Spontan-eous abortion	0/5 (0%) vs. 0/20 (0%)[107]	RR not calculable: no events	1 cohort, n=25	High study limitations (high risk of bias[107]), likely imprecise (small Ns), small Ns), consistency unknown	Insufficient
Women with epilepsy and depression, anxiety or bipolar disorder	Fluoxetine only vs. SSRI monotherapy (citalopram or escitalopram)	Stillbirth	0/5 (0%) vs. 0/20 (0%)[107]	RR not calculable: no events	1 cohort, n=25	High study limitations (high risk of bias[107]), likely imprecise (no events, small Ns), consistency unknown	Insufficient
Women with epilepsy and depression, anxiety or bipolar disorder	Fluoxetine only vs. SSRI monotherapy (citalopram or escitalopram)	Congenital anomaly	0/0 (0%) vs. 4/20 (19%)[107]	RD: 0.41 (95% CI, 0.03 to 6.56)[107]	1 cohort, n=25	High study limitations (high risk of bias[107]), seriously imprecise (few events, wide CIs), consistency unknown	Insufficient
Women with epilepsy and depression, anxiety or bipolar disorder	Fluoxetine only vs. SSRI monotherapy (citalopram or escitalopram)	Birth weight	Median ± IQR: 2,790±497 vs. 3,087±286[107]	Not calculable	1 cohort, n=25	High study limitations (high risk of bias[107]), likely imprecise, consistency unknown	Insufficient

CI = confidence interval; IQR = interquartile ratio; n = number; RD = risk difference; RR = relative risk; SSRI = selective serotonin reuptake inhibitor; vs. = versus.

Fluoxetine Versus Escitalopram or Fluvoxamine

Overview

- Based on evidence from a single study of the comparative risk of exposure during pregnancy to fluoxetine monotherapy versus fluvoxamine monotherapy among a sample of women with epilepsy, the evidence was insufficient in relation to maternal outcomes (convulsive seizures, nonconvulsive seizures, or spontaneous abortion or stillbirth) and child outcomes (congenital anomaly or birth weight). Based on the evidence from two studies, the comparative risk of autism spectrum disorder is also graded as insufficient.

Detailed Results

Three high risk-of-bias publications reported on the comparative harms of fluoxetine monotherapy versus fluvoxamine monotherapy.[107, 111, 117] One study combined fluvoxamine monotherapy or escitalopram monotherapy as the comparison group.[117] One analysis reported on a population of pregnant women with depression, anxiety, or bipolar disorder as well as epilepsy, drawn from the Australian Antiepileptic Drugs in Pregnancy register.[107] The authors found no significant differences in the risk of harms for any maternal (convulsive seizures, nonconvulsive seizures, spontaneous abortion, or stillbirth) or child outcomes (congenital anomalies or birth weight). Each of these outcomes was graded as insufficient strength of evidence.

Two publications reported on the relative risk of autism spectrum disorder. Data from the Danish Birth registry[117] were analyzed in one study, and data from the Canadian QPC were analyzed in the second.[111] A significantly smaller risk of autism spectrum disorder was found from fluvoxamine or escitalopram compared with fluoxetine in one study[117] but not in a second study where the comparison group was limited to fluvoxamine.[111] Both studies did not control for confounding, resulting in the comparison being graded as insufficient strength of evidence (Table B-56).

Table B-56. Strength of evidence for comparative harms: Fluoxetine monotherapy versus fluvoxamine monotherapy

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Pregnant women with epilepsy and depression, anxiety or bipolar disorder	Fluoxetine monotherapy vs. fluvoxamine monotherapy	Convulsive seizures: From enrollment to 7 months gestation From 7 months gestation to delivery	2/5 (40%) vs. 0/1 (0%)[107] 1/5 (20%) vs. 0/1 (0%)[107]	RD, 0.40 (95% CI, -0.32 to 1.12) RD, 0.20 (95% CI, -0.64 to 0.64)	1 cohort, n=6	High study limitations (high risk of bias[107]), seriously imprecise (few events, wide CIs), consistency unknown	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Pregnant women with epilepsy and depression, anxiety or bipolar disorder	Fluoxetine monotherapy vs. fluvoxamine monotherapy	Nonconvulsive seizures: From enrollment to 7 months gestation From 7 months gestation to delivery	1/5 (20%) vs. 0/1 (0%)[107] 1/5 (20%) vs. 0/1(0%)[107]	RD, 0.20 (95% CI, -0.64 to 0.64) RD, 0.20 (95% CI, -0.64 to 0.64)	1 cohort, n=6	High study limitations (high risk of bias[107]), seriously imprecise (few events, wide CIs), consistency unknown	Insufficient
Pregnant women with epilepsy and depression, anxiety or bipolar disorder	Fluoxetine monotherapy vs. fluvoxamine monotherapy	Spontaneous abortion	0/5 (0%) vs. 0/1(0%)[107]	RR not calculable: no events	1 cohort, n=6	High study limitations (high risk of bias[107]), likely imprecise (no events, small N), consistency unknown	Insufficient
Pregnant women with epilepsy and depression, anxiety or bipolar disorder	Fluoxetine monotherapy vs. fluvoxamine monotherapy	Stillbirth	0/5 (0%) vs. 0/1 (0%)[107]	RR not calculable: no events	1 cohort, n=6	High study limitations (high risk of bias[107]), likely imprecise (no events, small N), consistency unknown	Insufficient
Pregnant women with epilepsy and depression, anxiety or bipolar disorder	Fluoxetine monotherapy vs. fluvoxamine monotherapy	Congenital anomaly	0/5 (0%) vs. 0/1 (0%)[107]	RR not calculable: no events	1 cohort, n=6	High study limitations (high risk of bias[107]), likely imprecise (no events, small N), consistency unknown	Insufficient
Pregnant women with epilepsy and depression, anxiety or bipolar disorder	Fluoxetine monotherapy vs. fluvoxamine monotherapy	Birthweight	Median ± IQR: 2,790±497 vs. 3,310[107]	Difference not calculable	1 cohort, n=6	High study limitations (high risk of bias[107]), likely imprecise (small Ns), consistency unknown	Insufficient
Pregnant women taking fluoxetine, fluvoxamine or escitalopram	Fluoxetine monotherapy vs. fluvoxamine or escitalopram monotherapy;[117] Fluoxetine monotherapy vs. fluvoxamine[111]	Autism spectrum disorder	18/160 (11%) vs. 1/1,047(0.09%)[117] 5/171 (2.9%) vs. 1/35 (2.9%)[111]	RR, 117.79 (95% CI, 15.83 to 876.27) RR, 1.02 (95% CI, 0.12 to 8.49)	2 cohorts; n=1,207 in one cohort,[117] n=206 in one cohort[111]	High study limitations (high risk of bias[111, 117]), imprecise (wide CIs), consistent	Insufficient Low

CI = confidence interval; IQR = interquartile ratio; n = number; RD = risk difference; RR = relative risk; vs. = versus.

Paroxetine Versus Duloxetine

Overview

- The evidence is insufficient to judge the comparative risk of harms from exposure during pregnancy to paroxetine versus duloxetine for child outcomes (congenital heart disease).

Detailed Results

One publication reported on the comparative harms of paroxetine versus duloxetine.[141] The study drew from a cohort of women who had undergone a fetal echocardiogram because of in utero exposure of the fetus to SSRIs or SNRIs.[141] The study was rated as high risk of bias. The study yielded insufficient strength of evidence to judge the risk of congenital heart disease (Table B-57).

Table B-57. Strength of evidence for comparative harms: Paroxetine versus duloxetine

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women who underwent fetal echocardiography because of an in utero exposure to either SSRIs or SNRIs	Paroxetine vs. duloxetine	Congenital heart disease	0/1 (0%) vs. 0/1 (0%)[141]	RR not calculable[141]	1 cohort, n=2[141]	High study limitations (high risk of bias,[141] imprecise (small Ns), consistency unknown	Insufficient

CI = confidence interval; n = number; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; RR = relative risk; vs. = versus.

Paroxetine Versus Fluoxetine

Overview

- Based on evidence from single studies, the evidence is insufficient to judge the comparative risk of harms from exposure during pregnancy to paroxetine monotherapy versus fluoxetine monotherapy in relation to maternal outcomes (preeclampsia, convulsive seizures, nonconvulsive seizures, or spontaneous abortion or stillbirth) or child outcomes (congenital anomaly/congenital heart disease or birth weight). The evidence was graded as insufficient in relation to the comparative risk of autism spectrum disorder based on the findings from two unadjusted high risk-of-bias studies.

Detailed Results

Five publications reported on the comparative harms of paroxetine monotherapy versus fluoxetine monotherapy.[81, 107, 111, 117, 141] One medium risk-of-bias analysis reported on preeclampsia outcomes among women with depression, based on data in a Canadian British Columbia province-wide pregnancy and newborn database. The risk was not found to be significantly different between the two groups after adjusting for potential confounding characteristics.[81] One high risk-of-bias analysis reported on a population of pregnant women with depression, anxiety, or bipolar disorder as well as epilepsy, drawn from the Australian Antiepileptic Drugs in Pregnancy register.[107] In this study, the authors found no significant

differences in the risk of harms for any maternal (convulsive seizures, nonconvulsive seizures, spontaneous abortion, or still birth) or child outcomes (congenital anomalies or birth weight). Each of these outcomes was graded as insufficient strength of evidence study drew from a cohort of women who had undergone a fetal echocardiogram because of in utero exposure of the fetus to SSRIs or SNRIs.[141] The study was rated as high risk of bias. The study yielded insufficient strength of evidence to judge the risk of congenital heart disease (Table B-58).

Table B-58. Strength of evidence for comparative harms: Paroxetine monotherapy versus fluoxetine monotherapy

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Pregnant women with depression	Paroxetine monotherapy vs. fluoxetine monotherapy	Preeclampsia	NR	ARR, 1.70 (95% CI, 0.93 to 3.11)[81]	1 cohort, n=NR[81]	Moderate study limitations, imprecise (wide CIs), consistency unknown	Insufficient
Pregnant women with epilepsy and depression, anxiety or bipolar disorder	Paroxetine monotherapy vs. fluoxetine monotherapy	Convulsive seizures: From enrollment to 7 months gestation From 7 months gestation to delivery	2/7 (29%) vs. 2/5 (40%)[107] 2/7 (29%) vs. 1/5 (20%)[107]	RR, 0.20 (95% CI, 0.04 to 1.10)[107] RR, 0.20 (95% CI, 0.02 to 2.69)[107]	1 cohort, n=12[107]	High study limitations (high risk of bias[107]), seriously imprecise (few events, wide CIs), consistency unknown	Insufficient
Pregnant women with epilepsy and depression, anxiety or bipolar disorder	Paroxetine monotherapy vs. fluoxetine monotherapy	Nonconvulsive seizures: From enrollment to 7 months gestation From 7 months gestation to delivery	3/7 (43%) vs. 1/5 (20%)[107] 2/7 (29%) vs. 1/5 (20%)[107]	RR, 0.60 (95% CI, 0.08 to 4.66)[107] RR, 0.20 (95% CI, 0.015 to 2.69)[107]	1 cohort, n=12[107]	High study limitations (high risk of bias[107]), seriously imprecise (few events, wide CIs), consistency unknown	Insufficient
Pregnant women with epilepsy and depression, anxiety or bipolar disorder	Paroxetine monotherapy vs. fluoxetine monotherapy	Spontaneous abortion	0/7 (0%) vs. 0/5 (0%)[107]	RR not calculable: no events	1 cohort, n=12[107]	High study limitations (high risk of bias[107]), likely imprecise (no events, small N), consistency unknown	Insufficient
Pregnant women with epilepsy and depression, anxiety or bipolar disorder	Paroxetine monotherapy vs. fluoxetine monotherapy	Stillbirth	0/7 (0%) vs. 0/5 (0%)[107]	RR not calculable: no events	1 cohort, n=12[107]	High study limitations (high risk of bias[107]), likely imprecise (no events, small N), consistency unknown	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Pregnant women with epilepsy and depression, anxiety or bipolar disorder	Paroxetine monotherapy vs. fluoxetine monotherapy	Congenital anomaly	0/7 (0%) vs. 0/5 (0%)[107]	RR not calculable: no events	1 cohort, n=12[107]	High study limitations (high risk of bias[107]), likely imprecise (no events, small N), consistency unknown	Insufficient
Women who underwent fetal echocardiography because of an in utero exposure to either SSRIs or SNRIs	Paroxetine vs. fluoxetine	Congenital heart disease	0/1 (0%) vs. 2/9 (22.00%)[141]	Risk difference -0.22 (95% CI, -0.88 to 0.)[141]	1 cohort, n=10[141]	High study limitations (high risk of bias,[141] imprecise (wide CIs), consistency unknown	Insufficient
Pregnant women with epilepsy and depression, anxiety or bipolar disorder	Paroxetine monotherapy vs. fluoxetine monotherapy	Birth weight	Median ± IQR: 3,010±670 vs. 2,790±497[107]	Difference not calculable	1 cohort, n=12[107]	High study limitations (high risk of bias[107]), likely imprecise (small Ns), consistency unknown	Insufficient
Pregnant women taking paroxetine or fluoxetine	Paroxetine monotherapy vs. fluoxetine monotherapy	Autism spectrum disorder	11/744 (1.5%) vs. 5/171 (2.9%)[111] 7/871 (0.6%) vs. 18/160 (11%)[117]	RR, 0.51 (95% CI, 0.18 to 1.44)[111] RR, 0.07 (95% CI, 0.03 to 0.17)[117]	2 cohorts, n=915 in one cohort,[111] n=1,031 in one cohort[117]	High study limitations (high risk of bias[107]), imprecise (few events), consistent	Insufficient

ARR = adjusted risk ratio; CI = confidence interval; n = number; NR = not reported; NS = not significant; RR = relative risk; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; vs. = versus.

Two publications reported on the relative risk of autism spectrum disorder. Data from the Danish Birth registry[117] were analyzed in one study, and data from the Canadian QPC were analyzed in the second.[111] While both studies found the same direction of effect, a smaller risk of autism spectrum disorder from paroxetine compared with fluoxetine, the difference was statistically significant in one analysis but not in a second. Both studies were rated as high risk of bias and did not control for confounding, resulting in a grade of insufficient strength of evidence.

Paroxetine Versus Venlafaxine

Overview

- The evidence is insufficient to judge the risk of harms for maternal (spontaneous abortion) or child outcomes (congenital heart disease) for exposure during pregnancy to paroxetine versus venlafaxine.

Detailed Results

Two high risk-of-bias publication compared the maternal or infant harms of paroxetine versus other pharmacologic interventions for mental health disorders during pregnancy.[122, 141] One case-control study, set in Canada, quantified the association between dispensing of paroxetine or venlafaxine in early pregnancy and spontaneous abortion risk and found no difference between paroxetine versus venlafaxine.[122] One publication reported on the comparative harms of venlafaxine versus paroxetine.[141] The study drew from a cohort of women who had undergone a fetal echocardiogram because of in utero exposure of the fetus to SSRIs or SNRIs.[141] The study was rated as high risk of bias. The study yielded insufficient strength of evidence to judge the risk of congenital heart disease. The evidence was insufficient to judge harms for the outcome (Table B-59).

Table B-59. Strength of evidence for comparative harms: Paroxetine versus venlafaxine

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women who filled a prescription for an SSRI or SNRI in first trimester of pregnancy	Paroxetine vs. venlafaxine	Spontaneous abortion	84/569 (14.76%) vs, 33/161 (20.50%)[22]	OR 0.67 (95% CI, 0.43-1.05)[22]	1 case-control study, N=730[122]	High study limitations (high risk of bias[122]), imprecise (wide CIs), consistency unknown	Insufficient
Women who underwent fetal echocardiography because of an in utero exposure to either SSRIs or SNRIs	Venlafaxine vs. paroxetine	Congenital heart disease	2/2 (100%) vs. 0/1 (0%)[141]	Risk difference -1 (95% CI, -1.73 to -0.27)[141]	1 cohort, n=3[141]	High study limitations (high risk of bias,[141] imprecise (wide CIs), consistency unknown	Insufficient

CI = confidence interval; N = number; OR = odds ratio; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; vs. = versus.

Paroxetine Versus Citalopram or Escitalopram

Overview

- The evidence is insufficient to judge the risk of harms for child outcomes (stillbirth, birth weight, or congenital anomalies) for exposure during pregnancy to paroxetine versus citalopram or escitalopram.

Detailed Results

One high risk-of-bias publication from the Australian Pregnancy Register of Anti-Epileptic Drugs in Pregnancy[107] reported on outcomes among women with epilepsy who were treated with both anti-epileptic drugs (AEDs) and antidepressants for depression or anxiety. No differences were found in risk for stillbirth, median birthweight, or congenital anomalies for paroxetine compared with citalopram or escitalopram. The evidence was insufficient to judge harms for all outcomes (Table B-60).

Table B-60. Strength of evidence for comparative harms: Paroxetine versus citalopram or escitalopram

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Pregnant women with epilepsy and anxiety or depression, on AEDs	Paroxetine vs. citalopram or escitalopram	Stillbirths	0/7 (0%) vs. 0/21 (0%)[107]	No events[107]	1 cohort, N=28[107]	High study limitations (high risk of bias[107]), likely imprecise, consistency unknown	Insufficient
Pregnant women with epilepsy and anxiety or depression, on AEDs	Paroxetine vs. citalopram or escitalopram	Birthweight	Median (IQR) Paroxetine: 3,010 g (670) Citalopram or escitalopram: 3,087 g (286)[107]	Difference not calculable	1 cohort, N=28[107]	High study limitations (high risk of bias[107]), likely imprecise (small Ns), consistency unknown	Insufficient
Pregnant women with epilepsy and anxiety or depression, on AEDs	Paroxetine vs. citalopram or escitalopram	Congenital anomaly	Paroxetine: 0/7 (0%) Citalopram or escitalopram: 4/21 (19.0%)[107]	RD, -0.19 (95% CI, -0.43 to 0.05)[107]	1 cohort, N=28[107]	High study limitations (high risk of bias[107]), imprecise (wide CIs), consistency unknown	Insufficient

AED = anti-epileptic drug; CI = confidence interval; IQR = interquartile ratio; N = number; RD = risk difference; vs. = versus.

Paroxetine Versus Sertraline

Overview

- The evidence is insufficient to judge the risk of harms for child outcomes (birth weight, congenital anomalies, congenital heart disease, or autism spectrum disorder) for exposure during pregnancy to paroxetine versus sertraline.

Detailed Results

Four high risk-of-bias publications compared the maternal or infant harms of paroxetine versus sertraline for mental health disorders during pregnancy.[107, 111, 117, 141] A publication from the Australian Pregnancy Register of Anti-Epileptic Drugs in Pregnancy[107] reported on outcomes among women with epilepsy who were treated with both AEDs and antidepressants for depression or anxiety. No differences were found in risk for stillbirth, median birthweight, or congenital anomalies for paroxetine compared with sertraline. Two publications[111, 117] evaluated autism spectrum disorder diagnosis among children exposed in utero to sertraline versus

paroxetine and found no association. One study evaluated the risk of congenital heart disease among a cohort of women who had undergone a fetal echocardiogram because of in utero exposure of the fetus to SSRIs or SNRIs.[141] The evidence was insufficient to judge harms for all outcomes (Table B-61).

Table B-61. Strength of evidence for comparative harms: Paroxetine versus sertraline

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Pregnant women with epilepsy and anxiety or depression, on AEDs	Paroxetine vs. sertraline	Stillbirth	0/7 (0%) vs. 0/25 (0%)[107]	RR not calculable: no events	1 cohort, N=32[107]	High study limitations (high risk of bias,[107] likely imprecise, consistency unknown	Insufficient
Pregnant women with epilepsy and anxiety or depression, on AEDs	Paroxetine vs. sertraline	Birthweight	Median (IQR) Paroxetine: 3,010 g (670) Sertraline: 3,350 g (808)[107]	RR not calculable: no events	1 cohort, N=32[107]	High study limitations (high risk of bias,[107] likely imprecise (small Ns), consistency unknown	Insufficient
Pregnant women with epilepsy and anxiety or depression, on AEDs	Paroxetine vs. sertraline	Congenital anomaly	Paroxetine: 0/7 (0%) Sertraline: 3/25 (12.0%)[107]	RD, -0.12 (95% CI, -0.33 to 0.09)[107]	1 cohort, N=32[107]	High study limitations (high risk of bias[107]), imprecise (wide CIs), consistency unknown	Insufficient
Women who underwent fetal echocardiography because of an in utero exposure to either SSRIs or SNRIs	Paroxetine vs. sertraline	Congenital heart disease	0/1 (0%) vs. 0/7 (0%)[141]	RR not calculable: no events[141]	1 cohort, n=8[141]	High study limitations (high risk of bias,[141] imprecise (small Ns, no events), consistency unknown	Insufficient
Women exposed to antidepressants in 2nd/3rd trimester of pregnancy	Paroxetine vs. sertraline	Autism spectrum disorder	Paroxetine: 11/744 (1.5%) vs. sertraline: 1/292 (0.34%)[111] Paroxetine: 7/871 (0.8%) vs. sertraline: 9/1,576 (0.57%)[111]	RR, 4.3 (95% CI, 0.56 to 33.3)[111] RR, 1.41 (95% CI, 0.53 to 3.77)[117]	2 cohorts, N=3,483[111, 117]	High study limitations (high risk of bias[111, 117]), imprecise (wide CIs), consistent	Insufficient

AED = anti-epileptic drug; CI = confidence interval; IQR = interquartile ratio; N = number; RR = relative risk; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; vs. = versus.

Paroxetine Versus SNRIs

Overview

- The evidence is insufficient to judge the risk of harms for maternal (spontaneous abortion) or child outcomes (stillbirth, birth weight, or congenital anomalies) for exposure during pregnancy to paroxetine versus SNRIs.

Detailed Results

One high risk-of-bias publication from the Australian Pregnancy Register of Anti-Epileptic Drugs in Pregnancy[107] reported on outcomes among women with epilepsy who were treated with both AEDs and antidepressants for depression or anxiety. No differences were found in risk for stillbirth, median birthweight, or congenital anomalies for paroxetine compared with SNRIs. The evidence was insufficient to judge harms for all outcomes (Table B-62).

Table B-62. Strength of evidence for comparative harms: Paroxetine versus SNRIs

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Pregnant women with epilepsy and anxiety or depression, on AEDs	Paroxetine vs. SNRI monotherapy	Stillbirth	Paroxetine:0/7 (0%) SNRI monotherapy: 1/13 (7.7%)[107]	No difference[107]	1 cohort, N=20[107]	High study limitations (high risk of bias[107]), imprecise (wide CIs), consistency unknown	Insufficient
Pregnant women with epilepsy and anxiety or depression, on AEDs	Paroxetine vs. SNRI monotherapy	Birthweight	Median (IQR) Paroxetine: 3010 g (670) SNRI monotherapy: 3530 g (561)[107]	Difference not calculable	1 cohort, N=20[107]	High study limitations (high risk of bias[107]), likely imprecise (small Ns), consistency unknown	Insufficient
Pregnant women with epilepsy and anxiety or depression, on AEDs	Paroxetine vs. SNRI monotherapy	Congenital anomaly	Paroxetine: 0/7 (0%) SNRI monotherapy: 0/13 (0%)[107]	RD, 0 (95% CI, -0.19 to 0.19)[107]	1 cohort, N=20[107]	High study limitations (high risk of bias[107]), imprecise (wide CIs), consistency unknown	Insufficient

AED = anti-epileptic drug; CI = confidence interval; IQR = interquartile ratio; N = number; RD = risk difference; SNRI = serotonin-norepinephrine reuptake inhibitor; vs. = versus.

Paroxetine Versus Other SSRI Comparators

Overview

- The evidence is insufficient to judge the risk of harms for child outcomes (preterm birth, birth weight, congenital anomalies status, or respiratory distress) for exposure during pregnancy to paroxetine versus other SSRIs.

Detailed Results

Two high risk-of-bias publications compared the maternal or infant harms of paroxetine versus other SSRIs for mental health disorders during pregnancy.[87, 131] A Swedish Medical Birth Registry publication compared neonatal outcomes among women exposed to paroxetine versus other SSRIs (mainly citalopram) during pregnancy and reported no difference in preterm birth, low birthweight, small for gestational age, large for gestational age, or respiratory distress.[131] A high risk-of-bias case-control study within the QPC[87] evaluated major congenital and cardiac anomalies among pregnancies exposed to paroxetine versus other SSRIs in the first trimester and found no differences in outcomes (Table B-63).

Table B-63. Strength of evidence for comparative harms: Paroxetine versus other SSRIs

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Pregnant women with 1st trimester exposure to an antidepressant	Paroxetine vs. other SSRI antidepressant	Major congenital anomalies	Paroxetine: 43 cases, 499 controls Other SSRI antidepres-sants: 28 cases, 415 controls[87]	Crude OR 1.28 (95% CI, 0.78 to 2.11)[87]	1 case: control, n=985[87]	High study limitations (high risk of bias[87]), imprecise (wide CIs), consistency unknown	Insufficient
Pregnant women with 1st trimester exposure to an antidepressant	Paroxetine vs. other SSRI antidepressant	Major cardiac anomalies	Paroxetine: 10 cases, 499 controls Other SSRI antidepres-sants: 6 cases, 415 controls[87]	Crude OR 1.39 (95% CI, 0.50 to 4.14)[87]	1 case-control, n=930[87]	High study limitations (high risk of bias[87]), imprecise (wide CIs), consistency unknown	Insufficient
Women with antidepressant use in pregnancy	Paroxetine vs. other SSRIs, mainly citalopram	Preterm delivery <37 weeks	11/104 (10.6%) s. 38/449 (8.5%)[131]	RR, 1.25 (95% CI, 0.66 to 2.36)[131]	1 cohort, N=519[131]	High study limitations (high risk of bias[131]), imprecise (wide CIs), consistency unknown	Insufficient
Women with antidepressant use in pregnancy	Paroxetine vs. other SSRIs, mainly citalopram	Low birth weight	5/94 (5.3%) vs. 16/425 (3.8%)[131]	RR, 1.41 (95% CI, 0.53 to 3.76)[131]	1 cohort, N=519[131]	High study limitations (high risk of bias[131]), imprecise (wide CIs), consistency unknown	Insufficient
Women with antidepressant use in pregnancy	Paroxetine vs. other SSRIs, mainly citalopram	SGA	2/94 (2.3%) vs. 10/425 (2.4%)[131]	RR, 0.90 (95% CI, 0.20 to 4.06)[131]	1 cohort, N=519[131]	High study limitations (high risk of bias[131]), imprecise (wide CIs), consistency unknown	Insufficient
Women with antidepressant use in pregnancy	Paroxetine vs. other SSRIs, mainly citalopram	LGA	9/94 (9.6%) vs. 21/425 (4.9%)[131]	RR, 1.94 (95% CI, 0.92 to 4.09)[131]	1 cohort, N=519[131]	High study limitations (high risk of bias[131]), imprecise (wide CIs), consistency unknown	Insufficient
Women with antidepressant use in pregnancy	Paroxetine vs. other SSRIs, mainly citalopram	Respiratory distress	7/109 (6.4%) vs. 24/455 (5.3%)[131]	RR, 1.22 (95% CI, 0.54 to 2.75%)[131]	1 cohort, N=564[131]	High study limitations (high risk of bias[131]), imprecise (wide CIs), consistency unknown	Insufficient

CI = confidence interval; LGA = large for gestational age; n/N = number; OR = odds ratio; RR = relative risk; SGA = small for gestational age; SSRI = selective serotonin reuptake inhibitor; vs. = versus.

Paroxetine Versus TCAs

Overview

- The evidence is insufficient to judge the risk of harms for child outcomes (one or more congenital anomalies) for exposure to paroxetine versus TCAs during pregnancy.

Detailed Results

One high risk-of-bias study provided information on the risks of one or more congenital anomalies in women exposed to paroxetine or TCAs.[126] The study used data from five health maintenance organizations (HMOs) participating in the HMO Research Network's Center for Education and Research on Therapeutics. The evidence is insufficient to judge the risk of harms when comparing paroxetine with TCAs (Table B-64).

Table B-64. Strength of evidence for comparative harms: Paroxetine versus TCAs

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Exposed to paroxetine in the first trimester vs. exposed to TCAs in the first trimester (full-term infants)	Paroxetine vs. TCAs	One or more anomalies	26/182 (14.2%) vs. 20/167 (12.0%)[126]	RR, 1.19 (95% CI, 0.69 to 2.05)[126]	1 cohort study, N=349[126]	High study limitations (high risk of bias[126]), imprecise (wide CIs), consistency unknown	Insufficient

CI = confidence interval; N = number; RR = relative risk; TCA = tricyclic antidepressant; vs. = versus.

Fluoxetine Versus SNRIs

Overview

- The evidence is limited to one study and is insufficient to judge the comparative risk of harms from exposure to fluoxetine monotherapy versus SNRI monotherapy (venlafaxine or desvenlafaxine) during pregnancy for maternal outcomes (convulsive seizures, nonconvulsive seizures, spontaneous abortion, or still birth) or child outcomes (congenital anomaly or birth weight) among women with epilepsy.

Detailed Results

One high risk-of-bias publication reported on the comparative harms of fluoxetine monotherapy versus SNRI monotherapy (venlafaxine or desvenlafaxine).[107] The population in the analysis was pregnant women with depression, anxiety, or bipolar disorder as well as epilepsy, drawn from the Australian Antiepileptic Drugs in Pregnancy register. No significant differences were found in the risk of harms for any maternal (convulsive seizures, nonconvulsive seizures, spontaneous abortion, or still birth) or child outcomes (congenital anomalies or birth weight) (Table B-65).

Table B-65. Strength of evidence for comparative harms: Fluoxetine monotherapy versus SNRI monotherapy (venlafaxine or desvenlafaxine)

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women with epilepsy and depression, anxiety or bipolar disorder	Fluoxetine only vs. SNRI monotherapy (venlafaxine or desvenlafaxine)	Convulsive seizures: From enrollment to 7 months gestation From 7 months gestation to delivery	2/5 (40%) vs. 0/13 (0%)[107] 1/5 (20%) vs. 0/13 (0%)[107]	RD, 14.67 (95% CI, 0.65 to 208.21)[107] RD, 7 (95% CI, 0.33 to 148.46)[107]	1 cohort, n=18[107]	High study limitations (high risk of bias[107]), seriously imprecise (few events, wide CIs), consistency unknown	Insufficient
Women with epilepsy and depression, anxiety or bipolar disorder	Fluoxetine only vs. SNRI monotherapy (venlafaxine or desvenlafaxine)	Nonconvulsive seizures: From enrollment to 7 months gestation From 7 months gestation to delivery	1/5 (20%) vs. 1/13 (7.7%)[107] 1/5 (20%) vs. 0/13 (0%)[107]	RR, 2.6 (95% CI, 0.20 to 34.07)[107] RD, 7 (95% CI, 0.33 to 148.457)[107]	1 cohort, n=18[107]	High study limitations (high risk of bias[107]), seriously imprecise (few events, wide CIs), consistency unknown	Insufficient
Women with epilepsy and depression, anxiety or bipolar disorder	Fluoxetine only vs. SNRI monotherapy (venlafaxine or desvenlafaxine)	Spontaneous abortion	0/5 (0%) vs. 0/13 (0%)[107]	RR not calculable: no events	1 cohort, n=18[107]	High study limitations (high risk of bias[107]), likely imprecise (no events, small Ns), consistency unknown	Insufficient
Women with epilepsy and depression, anxiety or bipolar disorder	Fluoxetine only vs. SNRI monotherapy (venlafaxine or desvenlafaxine)	Still birth	0/5 (0%) vs. 1/13 (7.7%)[107]	RD, 0.78 (95% CI, 0.037 to 16.50)[107]	1 cohort, n=18[107]	High study limitations (high risk of bias[107]), seriously imprecise (few events, wide CIs), consistency unknown	Insufficient

CI = confidence interval; n/N = number; RD = risk difference; RR = relative risk; SNRI = serotonin-norepinephrine reuptake inhibitor; vs. = versus.

Fluoxetine Versus TCAs

Overview

- The evidence is insufficient to judge the comparative risk of harms from exposure to fluoxetine versus TCAs during pregnancy for any child outcomes (gestational age, birthweight, major congenital anomalies, or infant mental development).

Detailed Results

Two publications reported on the comparative harms of fluoxetine versus TCAs as a class.[134, 136] Both publications reported findings from the Canadian Motherisk cohort of women with

major depression. One publication reported on women who used one of the medications during the first trimester or longer.[39, 136] The third publication was limited to women who used one of the medications throughout their pregnancy.[134] The studies were rated as high risk of bias.

Results for four outcomes were reported in single studies. No significant differences were found in the risk of harms for any child outcomes (gestational age, birthweight, or major congenital anomalies). Differences in infant development based on the Bayley Mental Development Index were reported in two publications.[134, 136] While the sample sizes differed in the two publications, it is unknown whether they overlap. Both studies reported no significant differences between the two groups. The strength of evidence was rated as insufficient for all outcomes (Table B-66).

Table B-66. Strength of evidence for comparative harms: Fluoxetine versus TCAs

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Pregnant women with depression	Fluoxetine vs. TCAs	Gestational age (weeks)	Mean (SD): 39.4 (1.6) vs. 39.1 (2.3)[39]	Mean difference: 0.3 (95% CI, -0.34 to 0.94)[39]	1 cohort, n=85[39]	High study limitations (high risk of bias[39]), imprecise (wide CIs), inconsistency unknown	Insufficient
Pregnant women with depression	Fluoxetine vs. TCAs	Birthweight (gram)	Median±IQR: 3,421.9±664.1 vs. 3,515.9±672.3[39]	Mean difference: -94 (95% CI, -309.3 to 121.3)[39]	1 cohort, n=85[39]	High study limitations (high risk of bias[39]), imprecise (wide CIs), inconsistency unknown	Insufficient
Pregnant women with depression	Fluoxetine vs. TCAs	Major congenital anomalies	2/58 (3%) vs. 0.6 (% not calculable)[39]	Not calculated, likely typographic error in primary source	1 cohort, n=85[39]	High study limitations (high risk of bias[39]), likely imprecise (small Ns), inconsistency unknown	Insufficient
Women exposed to antidepressants in pregnancy	Fluvoxamine exposure vs. citalopram/ escitalopram exposure in pregnancy	Convulsive seizures in women with epilepsy at enrollment to 7 months gestation	0/1 (0%) vs. 2/20 (10%)[107]	RR, 0.48 (95% CI, 0.03 to 6.86)[107]	1 cohort, n=22[107]	High study limitations (high risk of bias[107]), seriously imprecise (wide CIs, few events), consistency unknown	Insufficient
Women exposed to antidepressants in pregnancy	Fluvoxamine exposure vs. citalopram/ escitalopram exposure in pregnancy	Convulsive seizures in women with epilepsy at 7 months to delivery	0/1 (0%) vs. 1/20 (5%)[107]	RR,0.29 (95% CI, 0.02 to 4.95)[107]	1 cohort, n=21[107]	High study limitations (high risk of bias[107]), seriously imprecise (wide CIs, few events), consistency unknown	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women exposed to antidepressants in pregnancy	Fluvoxamine exposure vs. citalopram/ escitalopram exposure in pregnancy	Non-convulsive seizures in women with epilepsy at enrollment to 7 months gestation	0/1 (0%) vs. 4/20 (20%)[107]	RR,0.86 (95% CI, 0.07 to 10.8)[107]	1 cohort, n=21[107]	High study limitations (high risk of bias[107]), seriously imprecise (wide CIs, few events), consistency unknown	Insufficient
Women exposed to antidepressants in pregnancy	Fluvoxamine exposure vs. citalopram/ escitalopram exposure in pregnancy	Non-convulsive seizures in women with epilepsy at 7 months to delivery	0/1 (0%) vs. 3/20 (15%)[107]	RR,0.67 (95% CI, 0.07 to 10.8)[107]	1 cohort, n=21[107]	High study limitations (high risk of bias[107]), seriously imprecise (wide CIs, few events), consistency unknown	Insufficient
Women exposed to antidepressants in pregnancy	Fluvoxamine exposure vs. citalopram/ escitalopram exposure in pregnancy	Birth weight	NR[107]	NR other than "specific ADDs were not associated with birth weight"[107]	1 cohort, n=21[107]	High study limitations (high risk of bias[107]), seriously imprecise (nonsignificant, small sample size), consistency unknown	Insufficient
Women exposed to antidepressants in pregnancy	Fluvoxamine exposure vs. citalopram/ escitalopram exposure in pregnancy	Congenital anomalies	0/1 (0%) vs. 4/21 (19.0%)[107]	ARR, 0.82 (95% CI, 0.06 to 10.35)[107]	1 cohort, n=22[107]	High study limitations (high risk of bias[107]), seriously imprecise (wide CIs, few events), consistency unknown	Insufficient
Women exposed to antidepressants in pregnancy	Fluvoxamine exposure vs. citalopram/ escitalopram exposure in pregnancy	Autism spectrum disorder	1/35 (2.9%) vs. 5/421 (1.2%)[111]	ARR, 0.42 (95% CI, 0.05 to 3.5)[111]	1 cohort, n=456[111]	High study limitations (high risk of bias[111]), seriously imprecise (wide CIs, few events), consistency unknown	Insufficient

ADD = attention deficit disorder; ARR = adjusted risk ratio; CI = confidence interval; n = number; NR = not reported; RD = risk difference; RR = relative risk; vs. = versus.

Fluvoxamine Versus Fluoxetine

Overview

- The evidence for exposure to fluvoxamine versus fluoxetine monotherapy during pregnancy is insufficient to judge the risk of harms for the maternal outcomes (spontaneous abortion, still birth, convulsive seizures in women with epilepsy, or nonconvulsive seizures in women with epilepsy) and child outcomes (birth weight, congenital anomalies, or autism spectrum disorder).

Detailed Results

Two publications reported on fluvoxamine versus fluoxetine monotherapy.[107, 111] These publications drew from two cohorts (the Australian Pregnancy Register of Antiepileptic Drugs[107] and the QPC[111]). Both were nonrandomized observational studies and were rated as high risk of bias.

Both publications focused on exposure during pregnancy. One study further examined outcomes at three time frames: enrollment to 7 months gestation, 7 months gestation to delivery, and within the first postnatal month.[107] Publications compared pregnant women exposed to fluvoxamine versus fluoxetine monotherapy.[107, 111]

The evidence for fluvoxamine versus fluoxetine monotherapy is insufficient to judge the risk of harms for the maternal outcomes (spontaneous abortion, still birth, convulsive seizures in women with epilepsy, or nonconvulsive seizures in women with epilepsy) and child outcomes (birth weight, congenital anomalies, or autism spectrum disorder) (Table B-67). These studies found no association between fluvoxamine versus fluoxetine monotherapy use in pregnancy with any outcome.

Table B-67. Strength of evidence for comparative harms: Fluvoxamine versus fluoxetine

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
ADD-exposed women	Fluvoxamine vs. fluoxetine monotherapy exposure in pregnancy	Spontaneous abortion	0/1 vs. 0/5[107]	RD, 0 (95% CI, -0.64 to 0.64)[107]	1 cohort, n=6[107]	High study limitations (high risk of bias[107]), seriously imprecise (wide CIs, few events), consistency unknown	Insufficient
ADD-exposed women	Fluvoxamine vs. fluoxetine monotherapy exposure in pregnancy	Still birth	0/1 vs. 0/5[107]	RD, 0 (95% CI, -0.64 to 0.64)[107]	1 cohort, n=6[107]	High study limitations (high risk of bias[107]), seriously imprecise (wide CIs, few events), consistency unknown	Insufficient
ADD-exposed women	Fluvoxamine vs. fluoxetine monotherapy exposure in pregnancy	Convulsive seizures in women with epilepsy at enrollment to 7 months gestation	0/1 vs. 2/5[107]	RD, 0.4 (95% CI, -0.32 to 1.12)[107]	1 cohort, n=6[107]	High study limitations (high risk of bias[107]), seriously imprecise (wide CIs, few events), consistency unknown	Insufficient
ADD-exposed women	Fluvoxamine vs. fluoxetine monotherapy exposure in pregnancy	Convulsive seizures in women with epilepsy at 7 months to delivery	0/1 vs. 1/5[107]	RD, 0.2 (95% CI, -0.49 to 0.89)[107]	1 cohort, n=6[107]	High study limitations (high risk of bias[107]), seriously imprecise (wide CIs, few events), consistency unknown	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
ADD-exposed women	Fluvoxamine vs. fluoxetine monotherapy exposure in pregnancy	Nonconvul-sive seizures in women with epilepsy at enrollment to 7 months gestation	0/1 vs. 1/5[107]	RR,0.2 (95% CI, -0.49 to 0.89)[107]	1 cohort, n=6[107]	High study limitations (high risk of bias[107]), seriously imprecise (wide CIs, few events), consistency unknown	Insufficient
ADD-exposed women	Fluvoxamine vs. fluoxetine monotherapy exposure in pregnancy	Nonconvul-sive seizures in women with epilepsy at 7 months to delivery	0/1 vs. 1/5[107]	RD, 0.2 (95% CI, -0.49 to 0.89)[107]	1 cohort, n=6[107]	High study limitations (high risk of bias[107]), seriously imprecise (wide CIs, few events), consistency unknown	Insufficient
ADD-exposed women	Fluvoxamine vs. fluoxetine monotherapy exposure in pregnancy	Birth weight	NR[107]	NR other than "specific ADDs were not associated with birth weight"[107]	1 cohort, n=6[107]	High study limitations (high risk of bias[107]), seriously imprecise (wide CIs, few events), consistency unknown	Insufficient
ADD-exposed women	Fluvoxamine vs. fluoxetine monotherapy exposure in pregnancy	Congenital anomalies	0/1 vs. 0/5[107]	RD, 0 (95% CI, -0.64 to 0.64)[107]	1 cohort, n=6[107]	High study limitations (high risk of bias[107]), seriously imprecise (wide CIs, few events), consistency unknown	Insufficient
ADD-exposed women	Fluvoxamine vs. fluoxetine monotherapy exposure in pregnancy	Autism spectrum disorder	1/35 vs. 5/171[111]	ARR, 1.02 (95% CI, 0.12 to 8.49)[111]	1 cohort, n=206[111]	High study limitations (high risk of bias[111]), imprecise, consistency unknown	Insufficient

ADD = attention deficit disorder; ARR = adjusted risk ratio; CI = confidence interval; n = number; RD = risk difference; RR = relative risk; vs. = versus.

Fluvoxamine Versus Paroxetine

Overview

- The evidence for exposure to fluvoxamine versus paroxetine monotherapy during pregnancy is insufficient to judge the risk of harms for the maternal outcomes (spontaneous abortion, still birth, convulsive seizures in women with epilepsy, or nonconvulsive seizures in women with epilepsy) and child outcomes (birth weight, congenital anomalies, or autism spectrum disorder).

Detailed Results

Two publications reported on fluvoxamine versus paroxetine monotherapy.[107, 111] These publications drew from two cohorts (the Australian Pregnancy Register of Antiepileptic Drugs[107] and the QPC[111]). Both were nonrandomized observational studies and were rated as high risk of bias.

Both publications focused on exposure during pregnancy. One study further examined outcomes at three time frames: enrollment to 7 months gestation, 7 months gestation to delivery, and within the first postnatal month.[107] Publications compared pregnant women exposed to fluvoxamine versus paroxetine monotherapy.[107, 111]

The evidence for fluvoxamine versus paroxetine monotherapy is insufficient to judge the risk of harms for the maternal outcomes (spontaneous abortion, still birth, convulsive seizures in women with epilepsy, or nonconvulsive seizures in women with epilepsy) and child outcomes (birth weight, congenital anomalies, or autism spectrum disorder) (Table B-68). These studies found no association between fluvoxamine versus paroxetine monotherapy use in pregnancy with any outcome.

Table B-68. Strength of evidence for comparative harms: Fluvoxamine versus paroxetine monotherapy

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
ADD-exposed women	Fluvoxamine vs. paroxetine monotherapy exposure in pregnancy	Spontaneous abortion	0/1 vs. 0/7[107]	RD, 0 (95% CI, -0.62 to 0.62)[107]	1 cohort, n=22[107]	High study limitations (high risk of bias[107]), seriously imprecise (wide CIs, few events), consistency unknown	Insufficient
ADD-exposed women	Fluvoxamine vs. paroxetine monotherapy exposure in pregnancy	Still birth	0/1 vs. 0/7[107]	RD, 0 (95% CI, 0.62 to 0.62)[107]	1 cohort, n=22[107]	High study limitations (high risk of bias[107]), seriously imprecise (wide CIs, few events), consistency unknown	Insufficient
ADD-exposed women	Fluvoxamine vs. paroxetine monotherapy exposure in pregnancy	Convulsive seizures in women with epilepsy at enrollment to 7 months gestation	0/1 vs. 2/7[107]	RD, 0.29 (95% CI, -0.39 to 0.97)[107]	1 cohort, n=8[107]	High study limitations (high risk of bias[107]), seriously imprecise (wide CIs, few events), consistency unknown	Insufficient
ADD-exposed women	Fluvoxamine vs. paroxetine monotherapy exposure in pregnancy	Convulsive seizures in women with epilepsy at 7 months to delivery	0/1 vs. 2/7[107]	RD, 0.29 (95% CI, -0.39 to 0.97)[107]	1 cohort, n=8[107]	High study limitations (high risk of bias[107]), seriously imprecise (wide CIs, few events), consistency unknown	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
ADD-exposed women	Fluvoxamine vs. paroxetine monotherapy exposure in pregnancy	Nonconvulsive seizures in women with epilepsy at enrollment to 7 months gestation	0/1 vs. 3/7[107]	RR, 0.43 (95% CI, -0.26 to 1.12)[107]	1 cohort, n=8[107]	High study limitations (high risk of bias[107]), seriously imprecise (wide CIs, few events), consistency unknown	Insufficient
ADD-exposed women	Fluvoxamine vs. paroxetine monotherapy exposure in pregnancy	Nonconvulsive seizures in women with epilepsy at 7 months to delivery	0/1 vs. 2/7[107]	RD, 0.29 (95% CI, -0.39 to 0.97)[107]	1 cohort, n=8[107]	High study limitations (high risk of bias[107]), seriously imprecise (wide CIs, few events), consistency unknown	Insufficient
ADD-exposed women	Fluvoxamine vs. paroxetine monotherapy exposure in pregnancy	Birth weight	NR[107]	NR other than "specific ADDs were not associated with birth weight"[107]	1 cohort, n=8[107]	High study limitations (high risk of bias[107]), seriously imprecise (wide CIs, few events), consistency unknown	Insufficient
ADD-exposed women	Fluvoxamine vs. paroxetine monotherapy exposure in pregnancy	Congenital anomalies	0/1 vs. 0/7[107]	RD, 0 (95% CI, -0.62 to 0.62)[107]	1 cohort, n=8[107]	High study limitations (high risk of bias[107]), seriously imprecise (wide CIs, few events), consistency unknown	Insufficient
ADD-exposed women	Fluvoxamine vs. paroxetine monotherapy exposure in pregnancy	Autism spectrum disorder	1/35 vs. 11/744[111]	ARR, 1.93 (95% CI, 0.26 to 14.55)[111]	1 cohort, n=779[111]	High study limitations (high risk of bias[111]), seriously imprecise (wide CIs, few events), consistency unknown	Insufficient

ARR = adjusted risk ratio; CI = confidence interval; n = number; NR = not reported; RD = risk difference; RR = relative risk; vs. = versus.

Fluvoxamine Versus Sertraline

Overview

- The evidence for exposure to fluvoxamine versus sertraline monotherapy during pregnancy is insufficient to judge the risk of harms for the maternal outcomes (spontaneous abortion, still birth, convulsive seizures in women with epilepsy, or nonconvulsive seizures in women with epilepsy) and child outcomes (birth weight, congenital anomalies, or autism spectrum disorder).

Detailed Results

Two publications reported on fluvoxamine versus sertraline monotherapy.[107, 111] These publications drew from two cohorts (the Australian Pregnancy Register of Antiepileptic Drugs[107] and the QPC[111]). Both were nonrandomized observational studies and were rated as high risk of bias.

Both publications focused on exposure during pregnancy. One study further examined outcomes at three time frames: enrollment to 7 months gestation, 7 months gestation to delivery, and within the first postnatal month.[107] Publications compared pregnant women exposed to fluvoxamine versus sertraline monotherapy.[107, 111]

The evidence for fluvoxamine versus sertraline monotherapy is insufficient to judge the risk of harms for the maternal outcomes (spontaneous abortion, still birth, convulsive seizures in women with epilepsy, or nonconvulsive seizures in women with epilepsy) and child outcomes (birth weight, congenital anomalies, or autism spectrum disorder) (Table B-69). These studies found no association between fluvoxamine versus sertraline monotherapy use in pregnancy with any outcome.

Table B-69. Strength of evidence for comparative harms: Fluvoxamine versus sertraline monotherapy

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
ADD-exposed women	Fluvoxamine vs. sertraline monotherapy exposure in pregnancy	Spontaneous abortion	0/1 vs. 0/25[107]	RD, 0 (95% CI, -0.60 to 0.60)[107]	1 cohort, n=26[107]	High study limitations (high risk of bias[107]), seriously imprecise (wide CIs, few events), consistency unknown	Insufficient
ADD-exposed women	Fluvoxamine vs. sertraline monotherapy exposure in pregnancy	Still birth	0/1 vs. 0/25[107]	RD, 0 (95% CI, -0.60 to 0.60)[107]	1 cohort, n=26[107]	High study limitations (high risk of bias[107]), seriously imprecise (wide CIs, few events), consistency unknown	Insufficient
ADD-exposed women	Fluvoxamine vs. sertraline monotherapy exposure in pregnancy	Convulsive seizures in women with epilepsy at enrollment to 7 months gestation	0/1 vs. 2/25[107]	RD, 0.08 (95% CI, -0.53 to 0.69)[107]	1 cohort, n=26[107]	High study limitations (high risk of bias[107]), seriously imprecise (wide CIs, few events), consistency unknown	Insufficient
ADD-exposed women	Fluvoxamine vs. sertraline monotherapy exposure in pregnancy	Convulsive seizures in women with epilepsy at 7 months to delivery	0/1 vs. 1/25[107]	RD, 0.29 (95% CI, -0.57 to 0.65)[107]	1 cohort, n=26[107]	High study limitations (high risk of bias[107]), seriously imprecise (wide CIs, few events), consistency unknown	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
ADD-exposed women	Fluvoxamine vs. sertraline monotherapy exposure in pregnancy	Nonconvulsive seizures in women with epilepsy at enrollment to 7 months gestation	0/1 vs. 3/25[107]	RR,0.43 (95% CI, -0.49 to 0.73)[107]	1 cohort, n=26[107]	High study limitations (high risk of bias[107]), seriously imprecise (wide CIs, few events), consistency unknown	Insufficient
ADD-exposed women	Fluvoxamine vs. sertraline monotherapy exposure in pregnancy	Nonconvulsive seizures in women with epilepsy at 7 months to delivery	0/1 vs. 1/25[107]	RD, 0.29 (95% CI, -0.57 to 0.65)[107]	1 cohort, n=26[107]	High study limitations (high risk of bias[107]), seriously imprecise (wide CIs, few events), consistency unknown	Insufficient
ADD-exposed women	Fluvoxamine vs. sertraline monotherapy exposure in pregnancy	Birth weight	NR[107]	NR other than "specific ADDs were not associated with birth weight"[107]	1 cohort, n=26[107]	High study limitations (high risk of bias[107]), seriously imprecise (wide CIs, few events), consistency unknown	Insufficient
ADD-exposed women	Fluvoxamine vs. sertraline monotherapy exposure in pregnancy	Congenital anomalies	0/1 vs. 3/25[107]	RD, 0.12 (95% CI, -0.49 to 0.73)[107]	1 cohort, n=26[107]	High study limitations (high risk of bias[107]), seriously imprecise (wide CIs, few events), consistency unknown	Insufficient
ADD-exposed women	Fluvoxamine vs. sertraline monotherapy exposure in pregnancy	Autism spectrum disorder	1/35 vs. 1/292[111]	ARR, 8.34 (95% CI, 0.53 to 130.45)[111]	1 cohort, n=327[111]	High study limitations (high risk of bias[111]), seriously imprecise (wide CIs, few events), consistency unknown	Insufficient

ADD = attention deficit disorder; ARR = adjusted risk ratio; CI = confidence interval; NR = not reported; RD = risk difference; RR = relative risk; vs. = versus.

Fluvoxamine Versus SNRI (Venlafaxine or Desvenlafaxine)

Overview

- The evidence for exposure to fluvoxamine versus SNRI monotherapy during pregnancy is insufficient to judge the risk of harms for the maternal outcomes (spontaneous abortion, still birth, convulsive seizures in women with epilepsy, or nonconvulsive seizures in women with epilepsy) and child outcomes (birth weight or congenital anomalies).

Detailed Results

One publication reported on fluvoxamine versus SNRI monotherapy (venlafaxine or desvenlafaxine).[107] This publication drew from one cohort (the Australian Pregnancy Register of Antiepileptic Drugs[107]), which was a nonrandomized observational study and was rated as high risk of bias.

This publication focused on exposure during pregnancy and further examined outcomes at three time frames: enrollment to 7 months gestation, 7 months gestation to delivery, and within the first postnatal month.[107] This publication compared pregnant women exposed to fluvoxamine versus SNRI monotherapy.[107]

The evidence for fluvoxamine versus SNRI monotherapy is insufficient to judge the risk of harms for the maternal outcomes (spontaneous abortion, still birth, convulsive seizures in women with epilepsy, or nonconvulsive seizures in women with epilepsy) and child outcomes (birth weight or congenital anomalies) (Table B-70). This study found no association between fluvoxamine versus SNRI monotherapy use in pregnancy with any outcome.

Table B-70. Strength of evidence for comparative harms: Fluvoxamine versus SNRI (venlafaxine or desvenlafaxine)

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
ADD-exposed women	Fluvoxamine exposure vs. SNRI monotherapy (venlafaxine or desvenlafaxine) exposure in pregnancy	Spontaneous abortion	0/1 vs. 0/13[107]	RD, 0 (95% CI, -0.62 to 0.62)[107]	1 cohort, n=14[107]	High study limitations (high risk of bias[107]), seriously imprecise (wide CIs, few events), consistency unknown	Insufficient
ADD-exposed women	Fluvoxamine exposure vs. SNRI monotherapy (venlafaxine or desvenlafaxine) exposure in pregnancy	Still birth	0/1 vs. 1/13[107]	RD, 0 (95% CI, 0.62 to 0.62)[107]	1 cohort, n=14[107]	High study limitations (high risk of bias[107]), seriously imprecise (wide CIs, few events), consistency unknown	Insufficient
ADD-exposed women	Fluvoxamine exposure vs. SNRI monotherapy (venlafaxine or desvenlafaxine) exposure in pregnancy	Convulsive seizures in women with epilepsy at enrollment to 7 months gestation	0/1 vs. 0/13[107]	RR, 0.48 (95% CI, 0.03 to 6.86)[107]	1 cohort, n=14[107]	High study limitations (high risk of bias[107]), seriously imprecise (wide CIs, few events), consistency unknown	Insufficient
ADD-exposed women	Fluvoxamine exposure vs. SNRI monotherapy (venlafaxine or desvenlafaxine) exposure in pregnancy	Convulsive seizures in women with epilepsy at 7 months to delivery	0/1 vs. 0/13[107]	RR, 0.29 (95% CI, 0.02 to 4.95)[107]	1 cohort, n=14[107]	High study limitations (high risk of bias[107]), seriously imprecise (wide CIs, few events), consistency unknown	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
ADD-exposed women	Fluvoxamine exposure vs. SNRI monotherapy (venlafaxine or desvenlafaxine) exposure in pregnancy	Nonconvulsive seizures in women with epilepsy at enrollment to 7 months gestation	0/1 vs. 1/13[107]	RR, 0.86 (95% CI, 0.07 to 10.8)[107]	1 cohort, n=14[107]	High study limitations (high risk of bias[107]), seriously imprecise (wide CIs, few events), consistency unknown	Insufficient
ADD-exposed women	Fluvoxamine exposure vs. SNRI monotherapy (venlafaxine or desvenlafaxine) exposure in pregnancy	Nonconvulsive seizures in women with epilepsy at 7 months to delivery	0/1 vs. 0/13[107]	RR, 0.67 (95% CI, 0.07 to 10.8)[107]	1 cohort, n=14[107]	High study limitations (high risk of bias[107]), seriously imprecise (wide CIs, few events), consistency unknown	Insufficient
ADD-exposed women	Fluvoxamine exposure vs. SNRI monotherapy (venlafaxine or desvenlafaxine) exposure in pregnancy	Birth weight	NR[107]	NR other than "specific ADDs were not associated with birth weight"[107]	1 cohort, n=14[107]	High study limitations (high risk of bias[107]), seriously imprecise (wide CIs, few events), consistency unknown	Insufficient
ADD-exposed women	Fluvoxamine exposure vs. SNRI monotherapy (venlafaxine or desvenlafaxine) exposure in pregnancy	Congenital anomalies	0/1 vs. 0/13[107]	ARR, 0.82 (95% CI, 0.06 to 10.35)[107]	1 cohort, n=14[107]	High study limitations (high risk of bias[107]), seriously imprecise (wide CIs, few events), consistency unknown	Insufficient

ADD = attention deficit disorder; ARR = adjusted risk ratio; CI = confidence interval; n = number; NR = not reported; RD = risk difference; RR = relative risk; SNRI = serotonin-norepinephrine reuptake inhibitor; vs. = versus.

Sertraline Only Versus Citalopram or Escitalopram Only

Overview

- The evidence is limited to two studies and is insufficient to judge the comparative risk of harms from exposure to sertraline only versus citalopram or escitalopram only during pregnancy for maternal outcomes (convulsive seizures, nonconvulsive seizures, or spontaneous abortion or still birth) or child outcomes (congenital anomaly, birth weight, or congenital heart disease) among women with epilepsy.

Detailed Results

Two high risk-of-bias publications reported on the comparative harms of sertraline versus citalopram or escitalopram only.[107, 141]

For one study, the population consisted of pregnant women with depression, anxiety, or bipolar disorder, as well as epilepsy, drawn from the Australian Antiepileptic Drugs in Pregnancy register. This publication focused on exposure during pregnancy and further examined outcomes at 3 time frames: enrollment to 7 months gestation, 7 months gestation to

delivery, and within the first postnatal month. This publication compared pregnant women exposed to sertraline versus citalopram or escitalopram only.[107]

The second study consisted of pregnant women who underwent fetal echocardiography because of an in utero exposure at any point during pregnancy to either SSRIs or SNRIs in a retrospective review of institutional medical records at Children's Hospital of New Orleans.[141]

The evidence is insufficient to judge the comparative risk of harms from sertraline only versus citalopram or escitalopram only for maternal outcomes (convulsive seizures, nonconvulsive seizures, or spontaneous abortion or still birth) or child outcomes (congenital anomaly, birth weight, or congenital heart disease) among women with epilepsy (Table B-71).

Table B-71. Strength of evidence for comparative harms: Sertraline monotherapy versus SSRI monotherapy (citalopram or escitalopram)

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women with epilepsy and depression, anxiety or bipolar disorder	Sertraline only vs. SSRI monotherapy (citalopram or escitalopram)	Convulsive seizures: From enrollment to 7 months gestation From 7 months gestation to delivery	2/25 (8%) vs. 2/20 (10%)[107] 1/25 (4%) vs. 1/20 (5%)[107]	RR, 0.8 (95% CI, 0.12 to 5.19)[107] RR, 0.8 (95% CI, 0.05 to 12.01)[107]	1 cohort, n=45[107]	High study limitations (high risk of bias[107]), seriously imprecise (few events, wide CIs), consistency unknown	Insufficient
Women with epilepsy and depression, anxiety or bipolar disorder	Sertraline only vs. SSRI monotherapy (citalopram or escitalopram)	Nonconvulsive seizures: From enrollment to 7 months gestation From 7 months gestation to delivery	3/25 (12%) vs. 4/20 (20%)[107] 1/25 (4%) vs. 3/20 (15%)[107]	RR, 0.60 (95% CI, 0.15 to 2.38)[107] RR, 0.27 (95% CI, 0.03 to 2.37)[107]	1 cohort, n=45[107]	High study limitations (high risk of bias[107]), seriously imprecise (few events, wide CIs), consistency unknown	Insufficient
Women with epilepsy and depression, anxiety or bipolar disorder	Sertraline only vs. SSRI monotherapy (citalopram or escitalopram)	Spontaneous abortion	0/25 (0%) vs. 0/21 (0%)[107]	RR not calculable: no events	1 cohort, n=46[107]	High study limitations (high risk of bias[107]), likely imprecise (no events, small Ns), consistency unknown	Insufficient
Women with epilepsy and depression, anxiety or bipolar disorder	Sertraline only vs. SSRI monotherapy (citalopram or escitalopram)	Still birth	0/25 (0%) vs. 0/21 (0%)[107]	RR not calculable: no events	1 cohort, n=46[107]	High study limitations (high risk of bias[107]), likely imprecise (no events, small Ns), consistency unknown	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women with epilepsy and depression, anxiety or bipolar disorder	Sertraline only vs. SSRI monotherapy (citalopram or escitalopram)	Congenital anomaly	3/25 (12%) vs. 4/21 (19%)[107]	RR, 0.63 (95% CI, 0.16 to 2.50)[107]	1 cohort, n=46[107]	High study limitations (high risk of bias[107]), seriously imprecise (few events, wide CIs), consistency unknown	Insufficient
Women with epilepsy and depression, anxiety or bipolar disorder	Sertraline only vs. SSRI monotherapy (citalopram or escitalopram)	Birth weight	Median±IQR: 3,350±808 vs. 3,087±286[107]	Difference not calculable	1 cohort, n=45[107]	High study limitations (high risk of bias[107]), likely imprecise (small Ns), consistency unknown	Insufficient
Women who underwent fetal echocardiography because of an in-utero exposure to either SSRIs or SNRIs	Sertraline vs. SSRI monotherapy (citalopram or escitalopram); sertraline vs. citalopram; sertraline vs. escitalopram	Congenital heart disease	Sertraline vs. citalopram or escitalopram 0/7 (0%) vs. 3/14 (21%);[141] Sertraline vs. citalopram, 0/7 (0%) vs. 2/5 (40%);[141] Sertraline vs. escitalopram 0/7 (0%) vs. 1/9 (11%)[141]	Risk difference for sertraline vs. citalopram or escitalopram, -0.21 (95% CI, -0.49 to 0.06); for sertraline vs. citalopram, -0.20 (95% CI, -0.59 to 0.19); for sertraline vs. escitalopram, 0.11 95% CI, -0.39 to 0.17)[141]	1 cohort (n=40)[141]	High study limitations (high risk of bias[141]), likely imprecise (small Ns), consistency unknown	Insufficient

CI = confidence interval; IQR = interquartile ratio; n = number; RR = relative risk; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; vs. = versus.

Sertraline Versus Duloxetine

Overview

- The evidence is insufficient to judge the comparative risk of harms from exposure to sertraline versus duloxetine during pregnancy for child outcomes (congenital heart disease).

Detailed Results

One publication reported on the comparative harms of sertraline versus duloxetine.[141] The study drew from a cohort of women who had undergone a fetal echocardiogram because of in utero exposure of the fetus to SSRIs or SNRIs.[141] The study was rated as high risk of bias. The study yielded insufficient strength of evidence to judge the risk of congenital heart disease (Table B-72).

Table B-72. Strength of evidence for comparative harms: Sertraline versus duloxetine

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women who underwent fetal echocardiography because of an in utero exposure to either SSRIs or SNRIs	Sertraline vs. duloxetine	Congenital heart disease	0/7 (0%) vs. 0/1 (0%)[141]	RR not calculable: no events[141]	1 cohort, n=2[141]	High study limitations (high risk of bias,[141] imprecise (wide CIs), consistency unknown	Insufficient

CI = confidence interval; n = number; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; RR = relative risk; vs. = versus.

Sertraline Versus Escitalopram or Fluvoxamine

Overview

- The evidence is insufficient to judge the comparative risk of harms of exposure to sertraline versus escitalopram or fluvoxamine during pregnancy for child outcomes (autism spectrum disorder).

Detailed Results

One high risk-of-bias publication reported on the comparative harms of sertraline versus escitalopram or fluvoxamine.[117] The population consisted of pregnant women with depression or anxiety exposed to antidepressants during pregnancy. The sample was drawn from multiple Danish National registries.

The evidence is insufficient to judge the comparative risk of harms from sertraline versus escitalopram or fluvoxamine for child outcomes (autism spectrum disorder [Table B-73]).

Table B-73. Strength of evidence for comparative harms: Sertraline versus escitalopram or fluvoxamine

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women exposed to SSRIs during pregnancy[117]	Maternal exposure to sertraline vs. escitalopram or fluvoxamine	Autism spectrum disorder among offspring	9/1,576 (0.6%) vs. 1/1047 (0.1%)[117]	RR, 5.98 (95% CI, 0.76 to 47.12)[117]	1 cohort, N=2,623[117]	High study limitations (high risk of bias[117]), seriously imprecise (few events, CIs span the null), consistency unknown	Insufficient

CI = confidence interval; N = number; RR = relative risk; SSRI = selective serotonin reuptake inhibitor; vs. = versus.

Sertraline Versus Fluoxetine

Overview

- The strength of evidence is insufficient for judging a smaller risk of child autism spectrum disorder from exposure to sertraline monotherapy versus fluoxetine monotherapy during pregnancy.
- Among a sample of women with epilepsy, the evidence was insufficient in relation to maternal outcomes (convulsive seizures, nonconvulsive seizures, or spontaneous abortion or still birth) and child outcomes (congenital anomaly or birth weight).

Detailed Results

Four publications reported on the comparative harms of sertraline monotherapy versus fluoxetine monotherapy.[81, 107, 111, 117] Three studies were rated high risk of bias.[107, 111, 117] One medium risk-of-bias analysis reported on preeclampsia outcomes among women with depression based on data in a Canadian British Columbia province-wide pregnancy and newborn database.[81] The risk was not found to be significantly different between the two groups after adjusting for potential confounding characteristics. One high risk-of-bias analysis reported on a population of pregnant women with depression, anxiety, or bipolar disorder as well epilepsy, drawn from the Australian Antiepileptic Drugs in Pregnancy register.[107] The authors found no significant differences in the risk of harms for any maternal (convulsive seizures, nonconvulsive seizures, spontaneous abortion, or still birth) or child outcomes (congenital anomalies or birth weight). Each of these outcomes was graded as insufficient strength of evidence.

Two publications reported on the relative risk of autism spectrum disorder. Data from the Danish Birth registry[117] were analyzed in one study, and data from the Canadian QPC were analyzed in the second.[111] A significantly smaller risk of autism spectrum disorder was found from sertraline compared with fluoxetine in both analyses, although we have contacted the author regarding the accuracy of the data and are awaiting a response. While both studies were rated as high risk of bias and did not control for confounding, differences in effect sizes were large. However, the uncertainty regarding accuracy resulted in the comparison being graded as insufficient (Table B-74).

Table B-74. Strength of evidence for comparative harms: Sertraline monotherapy versus fluoxetine monotherapy

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Pregnant women with depression	Sertraline monotherapy vs. fluoxetine monotherapy	Preeclampsia	NR	ARR, 1.83 (95% CI, 0.92 to 3.64)[81]	1 cohort, n=NR[81]	Moderate study limitations imprecise (wide CIs), consistency unknown	Insufficient
Pregnant women with epilepsy and depression, anxiety or bipolar disorder	Sertraline monotherapy vs. fluoxetine monotherapy	Convulsive seizures: From enrollment to 7 months gestation From 7 months gestation to delivery	2/25 (8%) vs. 2/5 (40%)[107] 1/25 (4%) vs. 1/5 (20%)[107]	RR, 0.2 (95% CI, 0.04 to 1.10)[107] RR, 0.2 (95% CI, 0.02 to 2.69)[107]	1 cohort, n=30[107]	High study limitations (high risk of bias[107]), seriously imprecise (few events, wide CIs), consistency unknown	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Pregnant women with epilepsy and depression, anxiety or bipolar disorder	Sertraline monotherapy vs. fluoxetine monotherapy	Nonconvulsive seizures: From enrollment to 7 months gestation From 7 months gestation to delivery	3/25 (12%) vs. 1/5 (20%)[107] 1/25 (4%) vs. 1/5 (20%)[107]	RR, 0.6 (95% CI, 0.077 to 4.66)[107] RR, 0.2 (95% CI, 0.015 to 2.69)[107]	1 cohort, n=30[107]	High study limitations (high risk of bias[107]), seriously imprecise (few events, wide CIs), consistency unknown	Insufficient
Pregnant women with epilepsy and depression, anxiety or bipolar disorder	Sertraline monotherapy vs. fluoxetine monotherapy	Spontaneous abortion	0/25 (0%) vs. 0/5 (0%)[107]	RR not calculable: no events	1 cohort, n=30[107]	High study limitations (high risk of bias[107]), likely imprecise (small N), consistency unknown	Insufficient
Pregnant women with epilepsy and depression, anxiety or bipolar disorder	Sertraline monotherapy vs. fluoxetine monotherapy	Stillbirth	0/25 (0%) vs. 0/5 (0%)[107]	RR not calculable: no events	1 cohort, n=30[107]	High study limitations (high risk of bias[107]), likely imprecise (small N), consistency unknown	Insufficient
Pregnant women with epilepsy and depression, anxiety or bipolar disorder	Sertraline monotherapy vs. fluoxetine monotherapy	Congenital anomaly	3/25 (12%) vs. 0/5 (0%)[107]	RD, 0.12 (95% CI, -0.14 to 0.38)[107]	1 cohort, n=30[107]	High study limitations (high risk of bias[107]), seriously imprecise (few events, wide CIs), consistency unknown	Insufficient
Pregnant women with epilepsy and depression, anxiety or bipolar disorder	Sertraline monotherapy vs. fluoxetine monotherapy	Birth weight	Median±IQR: 3,330±808 vs. 2,790±497[107]	Difference not calculable	1 cohort, n=30[107]	High study limitations (high risk of bias[107]), likely imprecise (small N), consistency unknown	Insufficient
Pregnant women taking fluoxetine or sertraline	Sertraline monotherapy vs. fluoxetine monotherapy	Autism spectrum disorder	9/1,576 (0.6%) vs. 18/160 (11%)[117] 1/292 (0.3%) vs. 5/171 (2.9%)[111]	RR, 0.05 (95% CI, 0.02 to 0.11)[117] RR, 0.12 (95% CI, 0.01 to 0.99)[111]	2 cohorts; n=1,736 in one cohort,[117] n=463 in one cohort[111]	High study limitations (high risk of bias, potential inaccuracy in data,[111, 117] precise, consistent	Insufficient

ARR = adjusted risk ratio; CI = confidence interval; IQR = interquartile ratio; n = number; NR = not reported; RD = risk difference RR = relative risk; vs. = versus.

Sertraline Versus Nonsertraline SSRIs

Overview

- The evidence is insufficient to judge the comparative risk of harms from exposure to sertraline versus nonsertraline SSRIs during pregnancy for child outcomes (major congenital abnormalities).

Detailed Results

One high risk-of-bias publication reported on the comparative harms of sertraline versus nonsertraline SSRIs.[70] The population consisted of pregnant women with depression or anxiety identified in the year prior to pregnancy who were exposed to antidepressants during pregnancy. The sample was drawn from Canada's QPC.

The evidence is insufficient to judge the comparative risk of harms from sertraline only versus nonsertraline SSRIs for child outcomes (major congenital abnormalities) (Table B-75).

Table B-75. Strength of evidence for comparative harms: Sertraline versus nonsertraline SSRIs

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women with depression or anxiety in the year prior to pregnancy	Exposed to sertraline vs. exposed to non-sertraline SSRIs	Major congenital anomalies	45/366 (12.3%) vs. 236/1,963 (12.0%)[70]	ARR, 1.02 (95% CI, 0.76 to 1.38)[70]	1 cohort, N=2,329[70]	High study limitations (high risk of bias,[70] imprecise (CIs span the null), consistency unknown	Insufficient

ARR = adjusted risk ratio; CI = confidence interval; N = number; SSRI = selective serotonin reuptake inhibitor; vs. = versus.

Sertraline Only Versus SNRI Monotherapy (Venlafaxine or Desvenlafaxine)

Overview

- The evidence is limited to one study and is insufficient to judge the comparative risk of harms from exposure to sertraline only versus SNRI monotherapy (venlafaxine or desvenlafaxine) during pregnancy for maternal outcomes (convulsive seizures, nonconvulsive seizures, or spontaneous abortion or still birth) or child outcomes (congenital anomaly or birth weight) among women with epilepsy.

Detailed Results

One high risk-of-bias publication reported on the comparative harms of sertraline versus SNRI monotherapy (venlafaxine or desvenlafaxine).[107] The population consisted of pregnant women with depression, anxiety, or bipolar disorder, as well as epilepsy, drawn from the Australian Antiepileptic Drugs in Pregnancy register.

This publication focused on exposure during pregnancy and further examined outcomes at 3 time frames: enrollment to 7 months gestation, 7 months gestation to delivery, and within the

first postnatal month. This publication compared pregnant women exposed to sertraline versus SNRI monotherapy.

The evidence is insufficient to judge the comparative risk of harms from sertraline only versus SNRI monotherapy (venlafaxine or desvenlafaxine) for maternal outcomes (convulsive seizures, nonconvulsive seizures, or spontaneous abortion or still birth) or child outcomes (congenital anomaly or birth weight) among women with epilepsy (Table B-76).

Table B-76. Strength of evidence for comparative harms: Sertraline monotherapy versus SNRI monotherapy (venlafaxine or desvenlafaxine)

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women with epilepsy and depression, anxiety or bipolar disorder	Sertraline only vs. SNRI monotherapy (venlafaxine or desvenlafaxine)	Convulsive seizures: From enrollment to 7 months gestation From 7 months gestation to delivery	2/25 (8%) vs. 0/13 (0%)[107] 1/25 (4%) vs. 0/13 (0%)[107]	RD: 0.08 (95% CI, -0.07 to 0.23)[107] RD, 0.04 (95% CI, -0.09 to 0.17)[107]	1 cohort, n=38[107]	High study limitations (high risk of bias[107]), seriously imprecise (few events, wide CIs), consistency unknown	Insufficient
Women with epilepsy and depression, anxiety or bipolar disorder	Sertraline only vs. SNRI monotherapy (venlafaxine or desvenlafaxine)	Nonconvulsive seizures: From enrollment to 7 months gestation From 7 months gestation to delivery	3/25 (12%) vs. 1/13 (8%)[107] 1/25 (4%) vs. 0/13 (0%)[107]	RR, 1.56 (95% CI, 0.18 to 13.55)[107] RD, 0.04 (95% CI, -0.09 to 0.17)[107]	1 cohort, n=38[107]	High study limitations (high risk of bias[107]), seriously imprecise (few events, wide CIs), consistency unknown	Insufficient
Women with epilepsy and depression, anxiety or bipolar disorder	Sertraline only vs. SNRI monotherapy (venlafaxine or desvenlafaxine)	Spontaneous abortion	0/25 (0%) vs. 0/13 (0%)[107]	RR not calculable: no events	1 cohort, n=38[107]	High study limitations (high risk of bias[107]), likely imprecise (no events, small Ns), consistency unknown	Insufficient
Women with epilepsy and depression, anxiety or bipolar disorder	Sertraline only vs. SNRI monotherapy (venlafaxine or desvenlafaxine)	Still birth	0/25 (0%) vs. 1/13 (8%)[107]	RD, -0.08 (95% CI, -0.24 to 0.09)[107]	1 cohort, n=38[107]	High study limitations (high risk of bias[107]), likely imprecise (no events, small Ns), consistency unknown	Insufficient
Women with epilepsy and depression, anxiety or bipolar disorder	Sertraline only vs. SNRI monotherapy (venlafaxine or desvenlafaxine)	Congenital anomaly	3/25 (12%) vs. 0/13 (0%)[107]	RD, 0.12 (95%CI -0.04 to 0.28)[107]	1 cohort, n=38[107]	High study limitations (high risk of bias[107]), seriously imprecise (few events, wide CIs), consistency unknown	Insufficient
Women with epilepsy and depression, anxiety or bipolar disorder	Sertraline only vs. SNRI monotherapy (venlafaxine or desvenlafaxine)	Birth weight	Median ± IQR: 3,350±808 vs. 3,087±286[107]	Difference not calculable	1 cohort, n=45[107]	High study limitations (high risk of bias[107]), likely imprecise (small Ns), consistency unknown	Insufficient

CI = confidence interval; n = number; RD = risk difference; RR = relative risk; SNRI = serotonin-norepinephrine reuptake inhibitor; vs. = versus.

Sertraline Versus Bupropion

Overview

- The evidence is insufficient to judge the comparative risk of harms of exposure to sertraline versus bupropion during pregnancy for child outcomes (congenital heart defect).

Detailed Results

One high risk-of-bias retrospective chart review of institutional medical records at Children's Hospital of New Orleans reported on the comparative effectiveness of sertraline versus bupropion for women with an in utero exposure of the fetus to SSRIs or SNRIs.[141]

The evidence is insufficient to judge the comparative risk of harms from sertraline only versus bupropion for child outcomes (congenital heart defects) (Table B-77).

Table B-77. Strength of evidence for comparative harms outcomes: Sertraline versus bupropion

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women who underwent fetal echocardiography because of an in utero exposure to either SSRIs or SNRIs	Sertraline vs. duloxetine	Congenital heart disease	0/7 (0%) vs. 0/1 (0%)[141]	RR not calculable	1 cohort (n=8)[141]	High study limitations (high risk of bias[141]), likely imprecise (no events, small Ns), consistency unknown	Insufficient

CI = confidence interval; n = number; RR = relative risk; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; vs. = versus.

Sertraline Versus Nortriptyline

Overview

- One high risk-of-bias trial did not report any differences between sertraline and nortriptyline exposure during pregnancy for any adverse events (insufficient).

Detailed Results

One RCT (rated high risk of bias) reported on the comparative effectiveness of sertraline versus nortriptyline for women with postpartum depression.[36] Some women may also have had chronic depression: the study began including women with chronic depression after the trial started. Women were treated with a fixed dose strategy of 25 mg/d of sertraline or 10 mg/d of nortriptyline initially. The dose was escalated to 50 mg/d of sertraline or 25 mg/d of nortriptyline after 2 days and then gradually increased up to a maximum of 200 mg/d of sertraline and 150 mg/d nortriptyline if response or side effects did not prohibit further escalation. Although the study reported no differences in adverse events, it was not powered to test for equivalence. The study had higher attrition in the sertraline arm than in the nortriptyline arm (23/55 [41.8%] vs. 13/54 [24.1%]). The authors noted that the proportion of women withdrawing by personal choice differed significantly between groups (20% vs. 6%, p=0.03), but other reasons for withdrawal,

like side effects, did not differ between groups. We graded the evidence as insufficient as a result of imprecision and potential for bias due to attrition (Table B-78).

Table B-78. Strength of evidence for comparative harms outcomes: Sertraline versus nortriptyline

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women with postpartum depression (with or without chronic depression)	Sertraline vs. nortriptyline	Asberg Side Effects Rating Scale (any adverse events)	0/55 (0%) vs. 0/54 (0%)[36]	No events in either arm[36]	1 trial, N=108[36]	High study limitations (high risk of bias,[36] imprecise, consistency unknown	Insufficient
Women with postpartum depression (with or without chronic depression)	Sertraline vs. nortriptyline	Overall study withdrawal	23/55 (41.8%) vs. 13/54 (24.1%)[36]	RR, 1.73 (95% CI, 0.99 to 3.06)[36]	1 trial, N=108[36]	High study limitations (high risk of bias,[36] imprecise, consistency unknown	Insufficient

CI = confidence interval; N = number; RR = relative risk; vs. = versus.

Duloxetine Versus SSRIs

Overview

- The evidence is insufficient to judge the comparative risk of harms from duloxetine versus SSRIs during pregnancy for maternal (preeclampsia and postpartum hemorrhage) and child outcomes (preterm birth, being small for gestational age, cardiovascular anomalies, and major anomalies).

Detailed Results

One publication, with some risk-of-bias concerns reported on the comparative harms of second trimester use of duloxetine versus SSRIs as a class, from a cohort study of women in the Medicaid Analytic eXtract for 2004-2013.[98]

Maternal outcomes include preeclampsia and postpartum hemorrhage; child outcomes include preterm birth, being small for gestational age, cardiovascular anomalies, and major anomalies. Each of these outcomes with the exception of cardiovascular anomalies was evaluated in a single study; all with the exception of one study on cardiovascular anomalies showed no association. The strength of evidence for all outcomes was rated as insufficient (Table B-79).

Table B-79. Strength of evidence for comparative harms: Duloxetine versus SSRIs

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women exposed to SSRIs vs. duloxetine during pregnancy	Duloxetine vs. SSRIs	Preeclampsia	Early exposure: 119/2,104 (5.66%) vs. 2,540/70,926 (3.58%)[98] Late exposure: 42/662 (6.34%) vs. 1,835/4,8672 (3.77%)[98]	ARR for early exposure: 1.16 (95% CI, 0.96 to 1.40)[98] ARR for late exposure: (1.05, 95% CI, 0.77 to 1.44)[98]	1 cohort (n=14,391)[98]	Moderate study limitations, imprecise (wide CIs), consistency unknown	Insufficient
Women exposed to SSRIs vs. duloxetine during pregnancy	Duloxetine vs. SSRIs	Postpartum hemorrhage	33/869 (3.80%) vs. 1879/65,303 (2.88%)[98]	ARR, 1.48 (95% CI, 1.03 to 2.12)[98]	1 cohort (n=66,172)[98]	Moderate study limitations, imprecise (wide CIs), consistency unknown	Insufficient
Women exposed to SSRIs vs. duloxetine during pregnancy	Duloxetine vs. SSRIs	Preterm birth	Early exposure: 282/1,989 (14.18%) vs. 9013/67,222 (13.41%)[98] Late exposure: 128/621 (20.61%) vs. 7,685/46,098 (16.67%)[98]	ARR for early exposure: 0.95 (95% CI, 0.84 to 1.06)[98] ARR for late exposure: (1.02, 95% CI, 0.87 to 1.21)[98]	1 cohort (n=115,930[98]	Moderate study limitations, imprecise (wide CIs), consistency unknown	Insufficient
Women exposed to SSRIs vs. duloxetine during pregnancy	Duloxetine vs. SSRIs	Small for gestational age	Early exposure: 60/1,989 (3.02%) vs. 1697/67,222 (2.52%)[98] Late exposure: 18/621 (2.90%) vs. 1189/46,098 (2.58%)[98]	ARR for early exposure: 1.26 (95% CI, 0.97 to 1.64)[98] ARR for late exposure: (1.17, 95% CI, 0.73 to 1.88)[98]	1 cohort (n=115,930)[98]	Moderate study limitations, imprecise (wide CIs), consistency unknown	Insufficient
Women exposed to SSRIs vs. duloxetine during pregnancy	Duloxetine vs. SSRIs	Any congenital malformations	99/1966 (5.04%) vs. 2,192/52,018 (4.21%)[98]	ARR, 1.09 (95% CI, 0.89 to 1.35[98]	1 cohort (n=53,984)[98]	Moderate study limitations, imprecise (wide CIs), consistency unknown	Insufficient
Women exposed to SSRIs vs. duloxetine during pregnancy	Duloxetine vs. SSRIs	Cardiovascular anomalies	46/1,966 (2.34%) vs. 810/52,018 (1.56%)[98]	ARR, 1.27 (95% CI, 0.93 to 1.74[98]	1 cohort (n=53,984)[98]	Moderate study limitations, imprecise (wide CIs), consistency unknown	Insufficient

ARR = adjusted relative risk; CI = confidence interval; n = number; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; vs. = versus.

Duloxetine Versus Venlafaxine

Overview

- The evidence is insufficient to judge the comparative risk of harms from duloxetine versus venlafaxine during pregnancy for maternal (preeclampsia and postpartum hemorrhage) and child outcomes (preterm birth, being small for gestational age, cardiovascular anomalies, and major anomalies).

Detailed Results

Two publications reported on the comparative harms of duloxetine versus venlafaxine.[98, 141] One is a cohort study of women in the Medicaid Analytic eXtract for 2004-2013.[98] The second is a cohort of women who had undergone a fetal echocardiogram because of in utero exposure of the fetus to SSRIs or SNRIs.[141] One study was rated as high risk of bias.[141]

Maternal outcomes include preeclampsia and postpartum hemorrhage; child outcomes include preterm birth, being small for gestational age, cardiovascular anomalies, and major anomalies. Each of these outcomes with the exception of cardiovascular anomalies was evaluated in a single study; all with the exception of one study on cardiovascular anomalies showed no association. The studies on cardiovascular anomalies were inconsistent in direction of the association. The strength of evidence for all outcomes was rated as insufficient (Table B-80).

Table B-80. Strength of evidence for comparative harms: Duloxetine versus venlafaxine

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women exposed to venlafaxine vs. duloxetine during pregnancy	Duloxetine vs. venlafaxine	Preeclampsia	Early exposure: 161/2,927 (5.50%) vs. 357/7,642 (4.67%)[98] Late exposure: 55/879 (6.26%) vs. 185/2,943 (6.29%)[98]	ARR for early exposure: 0.96 (95% CI, 0.8 to 1.16)[98] ARR for late exposure: 0.8 (95% CI, 0.59 to 1.08)[98]	1 cohort (n=14,391)[98]	Moderate study limitations, imprecise (wide CIs), consistency unknown	Insufficient
Women exposed to venlafaxine vs. duloxetine during pregnancy	Duloxetine vs. venlafaxine	Postpartum hemorrhage	34/948 (3.59%) vs. 135/3,573 (3.78%)[98]	ARR: 1.04 (95% CI, 0.69 to 1.56)[98]	1 cohort (n=4,521)	Moderate study limitations, imprecise (wide CIs), consistency unknown	Insufficient
Women exposed to venlafaxine vs. duloxetine during pregnancy	Duloxetine vs. venlafaxine	Preterm birth	Early exposure: 402/2,779 (14.47%) vs. 1,008/7,258 (13.89%)[98] Late exposure: 167/828 (20.17%) vs. 559/2,770 (20.18%)[98]	ARR for early exposure: 0.94 (95% CI, 0.84 to 1.06)[98] ARR for late exposure: 0.88 (95% CI, 0.75 to 1.04)[98]	1 cohort (n=13,635)	Moderate study limitations, imprecise (wide CIs), consistency unknown	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women exposed to venlafaxine vs. duloxetine during pregnancy	Duloxetine vs. venlafaxine	Small for gestational age	Early exposure: 79/2,779 (2.84 %) vs. 166/7,258 (2.29%)[98] Late exposure: 26/828 (3.14 %) vs. 61/2,770 (2.20%)[98]	ARR for early exposure: 1.18 (95% CI, 0.90 to 1.56)[98] ARR for late exposure: 1.32 (95% CI, 0.83 to 2.09)[98]	1 cohort (n=13,635)[98]	Moderate study limitations, imprecise (wide CIs), consistency unknown	Insufficient
Women exposed to venlafaxine vs. duloxetine during pregnancy	Duloxetine vs. venlafaxine	Any congenital malformations	127/2,467 (5.15%) vs. 270/6,369 (4.24%)[98]	ARR: 1.09 (95% CI, 0.88 to 1.36)[98]	1 cohort (n=8,836)[98]	Moderate study limitations, imprecise (wide CIs), consistency unknown	Insufficient
Women exposed to venlafaxine vs. duloxetine during pregnancy	Duloxetine vs. venlafaxine	Congenital heart disease/cardiovascular anomalies	0/1 (0%) vs. 2/2 (100%);[141] 58/2,467 (2.35%) vs. 96/6,369 (1.51%)[152]	RR: 0.30 (95% CI, 0.30 to 3.49):[141] ARR: 1.17 (95% CI, 0.84 to 1.63)[98]	2 cohorts (n=8,839)	Moderate study limitations (high risk of bias[141]), imprecise, inconsistent	Insufficient

ARR = adjusted relative risk; CI = confidence interval; n = number; RR = relative risk; vs. = versus.

Venlafaxine Versus SSRIs

Overview

- The evidence is insufficient to judge the comparative risk of harms from venlafaxine versus SSRIs during pregnancy for maternal spontaneous abortion and child outcomes (preterm delivery, gestational age, birthweight, small for gestational age, any congenital malformations, and any major congenital malformations).

Detailed Results

Three publications reported on the comparative harms of second trimester use of venlafaxine versus SSRIs as a class. One was a cohort study of women participating in the Motherisk Program, providing pregnancy counseling in centers in selected sites in North America, Europe, and Brazil.[135] The second was a case-control study using the Canadian Quebec Pregnancy Registry.[83] Both studies were rated as high risk of bias. A third publication, rated as having some concerns for risk of bias, reported on the comparative harms of venlafaxine versus SSRIs during pregnancy. The study cohort was drawn from surveillance data collected by the U.K. Teratology Information Service.[144]

Outcomes include differences in the risk of maternal spontaneous abortion, preterm delivery, child gestational age, birth weight, being small for gestational age, any congenital malformations, and major anomalies. Each of these outcomes, with the exception of spontaneous abortion, was evaluated in a single study and none showed an association. Two studies reported

on spontaneous abortion and were consistent in not reporting an association between exposure to venlafaxine and spontaneous abortion when compared with SSRIs. However, wide CIs for both studies effects spanned appreciable benefit and appreciable harm, so we graded the evidence as imprecise and the overall evidence as insufficient. The strength of evidence for all outcomes was rated as insufficient (Table B-81).

Table B-81. Strength of evidence for comparative harms: Venlafaxine versus SSRIs

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Pregnant women with depression, pregnant women who used SSRIs or venlafaxine during pregnancy	Venlafaxine or SSRI, first trimester exposure[135]	Spontaneous abortion	18/150 (12%) vs. 16/150 (10.7%)[135] 46/281 (16.37%) vs. 144/843 (17.1%)[144]	RR, 1.1 (95% CI, 0.60 to 2.12)[135] AOR, 1.0 (95% CI, 0.655 to 1.53)[144]	2 cohorts, n=1,424[135, 144]	Moderate study limitations (high risk of bias[135]) imprecise (wide CIs), consistent	Insufficient
Pregnant women who used SSRIs or venlafaxine during pregnancy	Venlafaxine vs. SSRI during first or second trimester	Preterm delivery	33/198 (16.7%) vs. 81/614 (13.2%)[144]	AOR, 1.32 (95% CI, 0.844 to 2.06)[144]	1 cohort, n=812[144]	Moderate study limitations imprecise (wide CIs), inconsistency unknown	Insufficient
Pregnant women with depression	Venlafaxine or SSRI, second trimester exposure	Gestational age at birth (weeks)	Mean (SD): 39 (2) vs. 38 (2)[135]	NR	1 cohort, n=300	High study limitations (high risk of bias,[135] imprecise) wide CIs, consistency unknown	Insufficient
Pregnant women with a psychiatric disorder	Venlafaxine or SSRI, second trimester exposure	Birthweight (g)	Mean (SD): 3,332 (609) vs. 3,429 (482)[135]	NR	1 cohort, N=300[135]	High study limitations (high risk of bias,[135] imprecise) wide CIs, consistency unknown	Insufficient
Pregnant women who used SSRIs or venlafaxine during pregnancy	Venlafaxine vs. SSRI	Term infants with low birth weight	4/133 (3.01%) vs. 22/438 (5.02%)[144]	AOR, 0.610 (95% CI, 0.175 to 1.64)[144]	1 cohort, n=600[144]	Moderate study limitations imprecise (wide CIs), inconsistency unknown	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Pregnant women with a psychiatric disorder (second trimester) or exposed to venlafaxine or SSRIs (during pregnancy)	Venlafaxine vs. SSRI during second trimester	SGA (<10th percentile)	5 cases/12 controls vs. 24 cases/131 controls[83] 12/133 (9.02%) vs. 55/438 (12.6%)[144]	OR, 3.19, 95% CI, 0.93 to 10.90[83] AOR, 0.714 (95% CI, 0.353 to 1.35)[144]	1 cohort, 1 case-control, n=772[83, 144]	Moderate study limitations (high risk of bias,[83] imprecise) wide CIs, inconsistent	Insufficient
Pregnant women with a psychiatric disorder (second trimester) or exposed to venlafaxine or SSRIs (during pregnancy)	Venlafaxine vs. SSRI during second trimester	Major anomaly	2/150 (1.6%) vs. 3/150 (2.4%)[135] 4/281 (1.42%) vs. 14/838 (1.67%)[144]	RR, 0.67 (95% CI, 0.11 to 3.93)[135] AOR, 0.864 (95% CI, 0.243 to 2.44[144]	1 cohort, n=1,419[135, 144]	Moderate study limitations (high risk of bias,[135] imprecise) wide CIs, consistent	Insufficient
Pregnant women who used SSRIs or venlafaxine during pregnancy	Venlafaxine vs. SSRI during first or second trimester	Any congenital malformation	7/281 (2.49%) vs. 33/838 (3.94%)[144]	AOR, 0.641 (95% CI, 0.257 to 1.39)[144]	1 cohort, n=1,119[144]	Moderate study limitations imprecise (wide CIs), inconsistency unknown	Insufficient
Pregnant women who used SSRIs or venlafaxine during first pregnancy trimester	Venlafaxine vs. SSRI during first or second trimester	Any congenital malformation	7/270 (2.59%) vs. 28/716 (3.9%)[144]	AOR, 0.567 (95% CI, 0.209 to 1.30)[144]	1 cohort, n=986[144]	Moderate study limitations imprecise (wide CIs), inconsistency unknown	Insufficient

AOR = adjusted odds ratio; CI = confidence interval; n = number; NR = not reported; RR = relative risk; SD = standard deviation; SSRI = selective serotonin reuptake inhibitor; vs. = versus.

Venlafaxine Versus Bupropion

Overview

- The evidence is insufficient to judge the comparative risk of harms from venlafaxine versus bupropion during pregnancy for child outcomes (congenital heart disease).

Detailed Results

One publication reported on the comparative harms of venlafaxine versus bupropion.[141] The study drew from a cohort of women who had undergone a fetal echocardiogram because of in utero exposure of the fetus to SSRIs or SNRIs.[141] The study was rated as high risk of bias. The study yielded insufficient strength of evidence to judge the risk of congenital heart disease (Table B-82).

Table B-82. Strength of evidence for comparative harms: Venlafaxine versus bupropion

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women who underwent fetal echocardiography because of an in utero exposure to either SSRIs or SNRIs	Venlafaxine vs. bupropion	Congenital heart disease	2/2 (100%) vs. 0/3 (0%)[141]	Risk difference, 1.00 (95% CI, 0.47 to 1.53)[141]	1 cohort, n=5[141]	High study limitations (high risk of bias,[141] imprecise (wide CIs), consistency unknown	Insufficient

CI = confidence interval; n = number; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; vs. = versus.

Venlafaxine Versus Escitalopram

Overview

- The evidence is insufficient to judge the comparative risk of harms from venlafaxine versus escitalopram during pregnancy for child outcomes (congenital heart disease)

Detailed Results

One publication reported on the comparative harms of venlafaxine versus escitalopram.[141] The study drew from a cohort of women who had undergone a fetal echocardiogram because of in utero exposure of the fetus to SSRIs or SNRIs.[141] The study was rated as high risk of bias. The study yielded insufficient strength of evidence to judge the risk of congenital heart disease (Table B-83).

Table B-83. Strength of evidence for comparative harms: Venlafaxine versus escitalopram

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women who underwent fetal echocardiography because of an in utero exposure to either SSRIs or SNRIs	Venlafaxine vs. escitalopram	Congenital heart disease	2/2 (100%) vs. 1/9 (11.11%)[141]	RR, 5.56 (95% CI, 1.17 to 26.43)[141]	1 cohort, n=11[141]	High study limitations (high risk of bias,[141] imprecise (wide CIs), consistency unknown	Insufficient

CI = confidence interval; n = number; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; vs. = versus.

Venlafaxine Versus Sertraline

Overview

- The evidence is insufficient to judge the comparative risk of harms from venlafaxine versus sertraline during pregnancy for child outcomes (congenital heart disease).

Detailed Results

One publication reported on the comparative harms of venlafaxine versus sertraline.[141] The study drew from a cohort of women who had undergone a fetal echocardiogram because of in utero exposure of the fetus to SSRIs or SNRIs.[141] The study was rated as high risk of bias. The study yielded insufficient strength of evidence to judge the risk of congenital heart disease (Table B-84).

Table B-84. Strength of evidence for comparative harms: Venlafaxine versus sertraline

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women who underwent fetal echocardiography because of an in utero exposure to either SSRIs or SNRIs	Venlafaxine vs. sertraline	Congenital heart disease	2/2 (100%) vs. 0/7 (0%)[141]	Risk difference 1.00 (95% CI, -0.55 to 1.45)[141]	1 cohort, n=9[141]	High study limitations (high risk of bias,[141] imprecise, wide CIs, consistency unknown	Insufficient

CI = confidence interval; n = number; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; vs. = versus.

SNRIs Versus MAOIs

Overview

- The evidence is insufficient to judge the comparative risk of harms from SNRIs versus MAOIs during pregnancy for child outcomes (attention-deficit/hyperactivity disorder or autism spectrum disorder).

Detailed Results

Two publications from the Canadian QPC reported on the comparative harms from treatment with SNRIs versus MAOIs among pregnant women with psychiatric disorders.[53, 114] Child attention-deficit/hyperactivity disorder outcomes were reported in one publication,[114] and autism spectrum disorder outcomes were reported in a second.[53] Only one woman was included in the MAOI group and the publications were rated as high risk of bias because the analyses did not control for confounding, leading to insufficient ratings (Table B-85).

Table B-85. Strength of evidence for comparative harms: SNRIs versus MAOIs

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Psychiatric disorder	SNRIs vs. MAOIs	ADHD	18/445 (4%) vs. 0/1 (0%)[53]	RD, 0.04 (95% CI, -0.56 to 0.64)[53]	1 cohort n=446[53]	High study limitations (high risk of bias,[53] imprecise (wide CIs), consistency unknown	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Psychiatric disorder	SNRIs vs. MAOIs	ASD	2/447 (0.4%) vs. 0/1 (0%)[114]	RD, 0.004 (95% CI, -0.60 to 0.60)[114]	1 cohort n=448[114]	High study limitations (high risk of bias,[114] imprecise (wide CIs), consistency unknown	Insufficient

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; CI = confidence interval; MAOI = monoamine oxidase inhibitors; n = number; RD = risk difference; SNRI = serotonin-norepinephrine reuptake inhibitor; vs. = versus.

SNRIs Versus TCAs

Overview

- The evidence is insufficient to judge the comparative risk of harms from SNRIs versus TCAs during pregnancy for maternal outcomes (preeclampsia or spontaneous abortion) and child outcomes (attention-deficit/hyperactivity disorder or autism spectrum disorder).

Detailed Results

Four high risk-of-bias publications reported on the comparative harms of SNRIs versus TCAs in pregnancy.[53, 64, 81, 114] These studies drew from three cohorts (2 from the Canadian QPC,[53, 114] a second cohort using the same Canadian Quebec registry data[64] and 1 from a Canadian British Colombian pregnant women and newborn registry).[81] All outcomes were reported in a single nonrandomized study that did not control for confounding. These include maternal risk of preeclampsia and spontaneous abortion and child risk of attention-deficit/hyperactivity disorder and autism spectrum disorder. No differences were found for any of these outcomes (Table B-86).

Table B-86. Strength of evidence for comparative harms: SNRIs versus TCAs

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Pregnant women with depression	SNRIs vs. TCAs	Preeclampsia	23/408 (5.6%) vs. 14/146 (9.6%)[81]	RR, 0.59 (95% CI, 0.31 to 1.11)[81]	1 cohort, n=554[81]	High study limitations (high risk of bias[81]), imprecise (wide CIs), consistency unknown	Insufficient
Pregnant women with depression	SNRIs vs. TCAs	Spontaneous abortion	20/137 (15%) vs. 20/147 (14%)[64]	RR, 1.07 (95% CI, 0.60 to 1.91)[64]	1 cohort, n=284[64]	High study limitations (high risk of bias[64]), imprecise (wide CIs), consistency unknown	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Pregnant women with psychiatric disorders	SNRIs vs. TCAs	ADHD	18/445 (4%) vs. 16/227 (7%)[53]	RR, 0.57 (95% CI, 0.30 to 1.10)[53]	1 cohort n=672[53]	High study limitations (high risk of bias[53]), imprecise (wide CIs), consistency unknown	Insufficient
Pregnant women with psychiatric disorders	SNRIs vs. TCAs	ASD	2/447 (0.4%) vs. 2/229 (0.9%)[114]	RR, 0.51 (95% CI, 0.07 to 3.61)[114]	1 cohort n=676[114]	High study limitations (high risk of bias[114]), imprecise (wide CIs), consistency unknown	Insufficient

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; CI = confidence interval; n = number; RR = relative risk; SNRI = serotonin-norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant; vs. = versus.

MAOIs Versus TCAs

Overview

- The evidence is insufficient to judge the comparative risk of harms from MAOIs versus TCAs during pregnancy for child outcomes (attention-deficit/hyperactivity disorder or autism spectrum disorder).

Detailed Results

Two publications from the Canadian QPC reported on the comparative harms from treatment with MAOIs versus TCAs among pregnant women with psychiatric disorders.[53, 114] Child attention-deficit/hyperactivity disorder outcomes were reported in one publication,[114] and autism spectrum disorder outcomes were reported in a second.[53] Only one woman was included in the MAOI group, and the publications were rated as high risk of bias because the analyses did not control for confounding (Table B-87).

Table B-87. Strength of evidence for comparative harms: MAOIs versus TCAs

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Psychiatric disorder	MAOIs vs. TCAs	ADHD	0/1 (0%) vs. 16/227 (7.0%)[53]	RD, -0.07 (95% CI, -0.67 to 0.53)[53]	1 cohort n=227[53]	High study limitations (high risk of bias,[53] imprecise (wide CIs), consistency unknown	Insufficient
Psychiatric disorder	MAOIs vs. TCAs	ASD	0/1 (0%) vs. 2/229 (0.9%)[114]	RD, -0.009 (95% CI, -0.61 to 0.59)[114]	1 cohort n=230[114]	High study limitations (high risk of bias,[114] imprecise (wide CIs), consistency unknown	Insufficient

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; CI = confidence interval; MAOI = monoamine oxidase inhibitors; n = number; RD = risk difference; RR = relative risk; TCA = tricyclic antidepressant; vs. = versus.

Venlafaxine Versus TCAs

Overview

- The evidence is insufficient to judge the comparative risk of harms from venlafaxine versus TCAs during pregnancy for the child outcome of small for gestational age.

Detailed Results

One publication reported on the comparative harms of second trimester use of venlafaxine versus TCAs as a class; a case-control study using the Canadian QPC.[83] The study was rated as high risk of bias.

The one outcome reported in this study is small for gestational age.[83] The strength of evidence was rated as insufficient (Table B-88).

Table B-88. Strength of evidence for comparative harms: Venlafaxine versus TCAs

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Pregnant women with a psychiatric disorder	Venlafaxine or TCAs, 2nd trimester exposure	Small for gestational age (<10th percentile)	5 case/17controls vs. 1 cases/10 controls[83]	OR, 5.71 (95% CI, 0.53 to 61.41)[83]	1 case-control, n=27[83]	High study limitations (high risk of bias[83]), seriously imprecise (few events, wide CIs), consistency unknown	Insufficient

CI = confidence interval; n = number; OR = odds ratio; TCA = tricyclic antidepressant; vs. = versus.

Bupropion Versus Duloxetine

Overview

- The evidence is insufficient to judge the comparative risk of harms from bupropion versus duloxetine during pregnancy for child outcomes (congenital heart disease).

Detailed Results

One publication reported on the comparative harms of bupropion versus duloxetine.[141] The study drew from a cohort of women who had undergone a fetal echocardiogram because of in utero exposure of the fetus to SSRIs or SNRIs.[141] The study was rated as high risk of bias. The study yielded insufficient strength of evidence to judge the risk of congenital heart disease (Table B-89).

Table B-89. Strength of evidence for comparative harms: Bupropion versus duloxetine

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women who underwent fetal echocardiography because of an in utero exposure to either SSRIs or SNRIs	Bupropion vs. duloxetine	Congenital heart disease	0/3 (0%) vs. 0/1 (0%)[141]	RR not calculable: no events[141]	1 cohort, n=4[141]	High study limitations (high risk of bias,[141] likely imprecise (no events, small Ns), consistency unknown)	Insufficient

CI = confidence interval; RR = relative risk; SNRI = serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; vs = versus.

Bupropion Versus Paroxetine

Overview

- The evidence is insufficient to judge the comparative risk of harms from bupropion versus paroxetine during pregnancy for child outcomes (congenital heart disease).

Detailed Results

One publication reported on the comparative harms of bupropion versus paroxetine.[141] The study drew from a cohort of women who had undergone a fetal echocardiogram because of in utero exposure of the fetus to SSRIs or SNRIs.[141] The study was rated as high risk of bias. The study yielded insufficient strength of evidence to judge the risk of congenital heart disease (Table B-90).

Table B-90. Strength of evidence for comparative harms: Bupropion versus paroxetine

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women who underwent fetal echocardiography because of an in utero exposure to either SSRIs or SNRIs	Bupropion vs. paroxetine	Congenital heart disease	0/3 (0%) vs. 0/1 (0%)[141]	RR not calculable: no events[141]	1 cohort, n=4[141]	High study limitations (high risk of bias,[141] likely imprecise (no events, small Ns), consistency unknown	Insufficient

CI = confidence interval; n = number; RR = relative risk; SNRI = serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; vs. = versus.

Bupropion Versus Sertraline

Overview

- The evidence is insufficient to judge the comparative risk of harms from bupropion versus sertraline during pregnancy for child outcomes (congenital heart disease).

Detailed Results

One publication reported on the comparative harms of bupropion versus sertraline.[141] The study drew from a cohort of women who had undergone a fetal echocardiogram because of in utero exposure of the fetus to SSRIs or SNRIs.[141] The study was rated as high risk of bias. The study yielded insufficient strength of evidence to judge the risk of congenital heart disease (Table B-91).

Table B-91. Strength of evidence for comparative harms: Bupropion versus sertraline

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women who underwent fetal echocardiography because of an in utero exposure to either SSRIs or SNRIs	Bupropion vs. sertraline	Congenital heart disease	0/3 (0%) vs. 0/7 (0%)[141]	RR not calculable: no events[141]	1 cohort, n=10[141]	High study limitations (high risk of bias,[141] likely imprecise (no events, small Ns), consistency unknown	Insufficient

CI = confidence interval; n = number; RR = relative risk; SNRI = serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; vs. = versus.

Brexanolone Versus Specific Active Comparators

Overview

- No included publications reported on the harms of brexanolone compared with specific active comparators.

Mirtazapine Versus SSRIs

Overview

- The evidence is insufficient to judge the risk of harms for maternal (spontaneous abortion or stillbirth) or child outcomes (preterm birth late-term birth, low birthweight, major birth defects, NICU stay, macrosomia, neonatal bilirubinemia) for mirtazapine versus SSRIs during pregnancy.

Detailed Results

One publication reported on mirtazapine compared with SSRIs.[116] The study drew from a cohort from the European Network of Teratology Information Services. The study was nonrandomized and was rated as high risk of bias. The publication focused on exposure to mirtazapine compared with exposure to SSRIs during pregnancy.[116] A second high risk-of-bias publication reported on the comparative harms of SSRIs versus mirtazapine in pregnancy in

Turkey.[95] The study did not control for confounding. The evidence is insufficient to judge the risk of harms for maternal (spontaneous abortion or stillbirth) or child outcomes (preterm birth late-term birth, low birthweight, birthweight, major birth defects, NICU stay, macrosomia, neonatal bilirubinemia) for mirtazapine versus SSRIs (Table B-92).

Table B-92. Strength of evidence for comparative harms: Mirtazapine versus SSRIs

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women exposed to therapeutic agents during pregnancy	Mirtazapine exposure during pregnancy vs. SSRI exposure during pregnancy	Spontaneous abortion or stillbirth	39/323 (12.1%) vs. 41/342 (12%)[116]	OR, 1.01 (95% CI, (0.63 to 1.61)[116]	1 cohort, n=665[116]	High study limitations (high risk of bias[116]), imprecise, consistent	Insufficient
Women exposed to therapeutic agents during pregnancy	Mirtazapine exposure during pregnancy vs. SSRI exposure during pregnancy	Preterm delivery	31/279 (11.1%) vs. 32/302 (10.6%)[116] 1/16 (6.25%) vs. 3/40 (7.50%)[95]	OR, 1.06 (95% CI, (0.63 to 1.78);[116] the OR did not change after adjusting for concomitant drug treatment RR, 0.83 (95% CI, 0.09 to 7.43)[95]	2 cohorts, n=637[95, 116]	High study limitations (high risk of bias[95, 116]), imprecise, consistent	Insufficient
Pregnant women exposed to mirtazapine or SSRIs	Mirtazapine exposure during pregnancy vs. SSRI exposure during pregnancy	Late-term birth	2/16 (12.50%) vs. 0/40 (0.00%)[95]	Risk difference, 0.13 (95% CI, -0.05 to 0.30)[95]	1 cohort, n=56[95]	High study limitations (high risk of bias[95]), imprecise (wide CIs), consistency unknown	Insufficient
Women exposed to therapeutic agents during pregnancy	Mirtazapine exposure during pregnancy vs. SSRI exposure during pregnancy	Major birth defects	13/292 (4.4%) vs. 13/307 (4.2%)[116]	OR, 1.05 (95% CI, 0.48 to 2.31)[116] The OR did not change after adjusting for concomitant drug treatment	1 cohort, n=599[116]	High study limitations (high risk of bias[116]), imprecise (wide CIs),, consistent	Insufficient
Pregnant women exposed to mirtazapine or SSRIs	Mirtazapine exposure during pregnancy vs. SSRI exposure during pregnancy	Low birthweight	1/16 (6.25%) vs. 4/40 (10.00%)[95]	RR, 0.63 (95% CI, 0.08 to 5.17)[95]	1 cohort, n=56[95]	High study limitations (high risk of bias[95]), imprecise (wide CIs), consistency unknown	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women exposed to therapeutic agents during pregnancy	Mirtazapine exposure during pregnancy vs. SSRI exposure during pregnancy	Birth weight (grams)	39 (IQR 38-40) vs. 39 (IQR 38-40)[116] 3,251.25 gm (SD: 502.27, n=16 vs. 3,153.17 gm (SD: 435.17), n=40[95]	No difference between groups;[116] mean difference, 98.08 (955 CI, -165.60 to 361.76)[95] The OR did not change after adjusting for concomitant drug treatment[116]	2 cohorts, n=652[95, 116]	High study limitations (high risk of bias[95, 116]), imprecise (wide CIs), consistent	Insufficient
Women exposed to therapeutic agents during pregnancy	Mirtazapine exposure during pregnancy vs. SSRI exposure during pregnancy	Gestational age (weeks)	3,320 (IQR 2,979-3,636) vs. 3,320 (IQR 2,910-3,629)[116]	Difference not calculable; no difference between groups[116] The OR did not change after adjusting for concomitant drug treatment	1 cohort, n=596[116]	High study limitations (high risk of bias[116]), imprecise, consistent	Insufficient
Pregnant women exposed to mirtazapine or SSRIs	Mirtazapine exposure during pregnancy vs. SSRI exposure during pregnancy	NICU stay	2/16 (12.50%) vs. 7/40 (17.50%)[95]	RR, 0.71 (95% CI, 0.17 to 3.08)[95]	1 cohort, n=56[95]	High study limitations (high risk of bias[95]), imprecise (wide CIs), consistency unknown	Insufficient
Pregnant women exposed to mirtazapine or SSRIs	Mirtazapine exposure during pregnancy vs. SSRI exposure during pregnancy	Macrosomia	0/16 (0.00%) vs. 2/40 (5.00%)[95]	Risk difference, -0.05 (95% CI, -0.16 to 0.06)[95]	1 cohort, n=56[95]	High study limitations (few events, small Ns[95]), imprecise (wide CIs), consistency unknown	Insufficient
Pregnant women exposed to mirtazapine or SSRIs	Mirtazapine exposure during pregnancy vs. SSRI exposure during pregnancy	Neonatal bilirubinemia	3/16 (18.75%) vs. 19/40 (47.50%)[95]	RR, 0.39 (95% CI, 0.14 to 1.15)[95]	1 cohort, n=56[95]	High study limitations (high risk of bias[95]), imprecise (wide CIs), consistency unknown	Insufficient

CI = confidence interval; IQR = interquartile ratio; n = number; OR = odds ratio; RR = relative risk; SSRI = selective serotonin reuptake inhibitor; vs. = versus.

Mirtazapine Versus SSRIs Plus Mirtazapine

Overview

- The evidence is insufficient to judge the comparative risk of harms from mirtazapine plus SSRIs vs. mirtazapine during pregnancy for child outcomes (preterm birth, late-term birth, low birthweight, NICU stay, macrosomia, neonatal bilirubinemia).

Detailed Results

One high risk-of-bias publication reported on the comparative harms of mirtazapine versus SSRIs plus mirtazapine in pregnancy in Turkey.[95] The study did not control for confounding. The evidence was insufficient for all reported outcomes (preterm birth, late-term birth, low birthweight, NICU stay, macrosomia, neonatal bilirubinemia) (Table B-93).

Table B-93. Strength of evidence for comparative harms: Mirtazapine versus SSRIs plus mirtazapine

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Pregnant women exposed to mirtazapine or SSRIs plus mirtazapine	Mirtazapine vs. SSRIs plus mirtazapine	Preterm birth	1/16 (6.25%) vs. 1/18 (5.56%)[95]	RR, 1.13 (95% CI, 0.08 to 16.55)[95]	1 cohort, n=34[95]	High study limitations (high risk of bias[95]), imprecise (wide CIs), consistency unknown	Insufficient
Pregnant women exposed to mirtazapine or SSRIs plus mirtazapine	Mirtazapine vs. SSRIs plus mirtazapine	Late-term birth	2/16 (12.50%) vs. 2/18 (11.11%)[95]	RR, 1.13 (95% CI, 0.18 to 7.09)[95]	1 cohort, n=34[95]	High study limitations (high risk of bias[95]), imprecise (wide CIs), consistency unknown	Insufficient
Pregnant women exposed to mirtazapine or SSRIs plus mirtazapine	Mirtazapine vs. SSRIs plus mirtazapine	Low birthweight	1/16 (6.25%) vs. 1/18 (5.56%)[95]	RR, 1.13 (95% CI, 0.08 to 16.55)[95]	1 cohort, n=34[95]	High study limitations (high risk of bias[95]), imprecise (wide CIs), consistency unknown	Insufficient
Pregnant women exposed to mirtazapine or SSRIs plus mirtazapine	Mirtazapine vs. SSRIs plus mirtazapine	Birthweight	3251.25 gm (SD: 502.27), n=16 vs. 3191.38 gm (SD: 436.69, n=18)[95]	Mean difference, 59.87 (95% CI, -255.68 to 375.42)[95]	1 cohort, n=34[95]	High study limitations (high risk of bias[95]), imprecise (wide CIs), consistency unknown	Insufficient
Pregnant women exposed to mirtazapine or SSRIs plus mirtazapine	Mirtazapine vs. SSRIs plus mirtazapine	NICU stay	2/16 (12.50%) vs. 3/18 (16.67%)[95]	RR, 0.75 (95% CI, 0.14 to 3.94)[95]	1 cohort, n=34[95]	High study limitations (high risk of bias[95]), imprecise (wide CIs), consistency unknown	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Pregnant women exposed to mirtazapine or SSRIs plus mirtazapine	Mirtazapine vs. SSRIs plus mirtazapine	Macrosomia	0/16 (0%) vs. 1/18 (5.56%)[95]	Risk difference:, -0.06 (95% CI, -0.20 to 0.09)[95]	1 cohort, n=34[95]	High study limitations (high risk of bias[95]), imprecise (wide CIs), consistency unknown	Insufficient
Pregnant women exposed to mirtazapine or SSRIs plus mirtazapine	Mirtazapine vs. SSRIs plus mirtazapine	Neonatal bilirubinemia	3/16 (18.75%) vs. 4/18 (22.22%)[95]	RR, 0.84 (95% CI, 0.22 to 3.21)[95]	1 cohort, n=34[95]	High study limitations (high risk of bias[95]), imprecise (wide CIs), consistency unknown	Insufficient

CI = confidence interval; n = number; RR = relative risk; SSRI = selective serotonin reuptake inhibitor; vs. = versus.

Lithium Versus Lamotrigine

Overview

- The evidence from one high risk-of-bias study indicates a higher risk of overall and cardiac fetal anomalies with lithium during pregnancy (low strength of evidence), which can inform the decision to switch a medication in a successfully treated individual.
- The evidence from one high risk-of-bias was insufficient to judge the comparative risk of harms from lithium versus lamotrigine during pregnancy for gestational diabetes.

Detailed Results

One high risk-of-bias publication comparing lithium with lamotrigine[108] drew from a cohort in the United States. The publication, which focused on first-trimester exposure,[108] found a substantially higher risk for fetal cardiac anomalies and overall congenital anomalies with lithium.[108] The strength of evidence is low because of the limitations of the study (Table B-94).

Another high risk-of-bias publication comparing lithium or lamotrigine exposure during any trimester of pregnancy to no exposure did not find a significantly increased risk of gestational diabetes with exposure to either lithium or lamotrigine.[97] The strength of the evidence is low due to the small sample size, wide CIs, and lack of adjustment for possible confounders.

Table B-94. Strength of evidence for comparative harms: Lithium versus lamotrigine

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women exposed to psychotropic exposure medication during any trimester	Lithium vs. lamotrigine	Gestational diabetes	2/17 (11.7%) vs. 2/19 (10.5%)[97]	RR, 1.12 (0.18 to 7.09)[97]	1 cohort, n=36[97]	High study limitations (high risk of bias,[97] imprecise (wide CIs, small N) consistency unknown	Insufficient
Lithium or lamotrigine-exposed women	Lithium vs. lamotrigine exposure in first-trimester pregnancy	Fetal cardiac anomalies	16/663 (2.4%) vs. 27/1,945 (1.4%)[108]	ARR, 2.25 (95% CI, 1.17 to 4.34)[108]	1 cohort, n=2,608[108]	High study limitations (high risk of bias,[108] precise, large effect size, consistency unknown	Low for harms with lithium
Lithium or lamotrigine-exposed women	Lithium vs. lamotrigine exposure in first-trimester pregnancy	Overall congenital anomalies	38/663 (5.7%) vs. 76/1,945 (3.9%)[108]	ARR, 1.85 (95% CI, 1.23 to 2.78)[108]	1 cohort, n=2,608[108]	High study limitations (high risk of bias,[108] precise, large effect size, consistency unknown	Low for harms with lithium
Lithium or lamotrigine-exposed women	Lithium vs. lamotrigine exposure in first-trimester pregnancy	Noncardiac fetal anomalies	22/663 (3.3%) vs. 49/1,945 (2.5%)[108]	ARR, 1.63 (95% CI, 0.96 to 2.78)[108]	1 cohort, n=2,608[108]	High study limitations (high risk of bias,[108] imprecise, consistency unknown	Insufficient

ARR = adjusted risk ratio; CI = confidence interval; n = number; RR = relative risk; vs. = versus.

Haloperidol Versus Olanzapine

Overview

- The evidence for haloperidol versus olanzapine during pregnancy is insufficient to judge the risk of harms for the child outcomes reported (high birth weight, low birth weight, neonatal complications [respiratory], NICU admission, preterm birth, mean Apgar score at 1 minute, or mean Apgar score at 5 minutes).

Detailed Results

One publication reported on the comparative harms of haloperidol versus olanzapine in a sample collected at the Emory Women's Mental Health Program.[127] The study was a nonrandomized cohort study and was rated high risk of bias. The study did not require a diagnosis of schizophrenia but required antipsychotic exposure during pregnancy and a stable dose at delivery per laboratory confirmation for >5 elimination half-lives at delivery as determined by high-performance liquid chromatography. Only fetal outcomes were reported.

The evidence for haloperidol versus olanzapine is insufficient to judge the risk of harms for the child outcomes reported (high birth weight, low birth weight, neonatal complications [respiratory], NICU admission, preterm birth, mean Apgar score at 1 minute, or mean Apgar

score at 5 minutes) (Table B-95). These studies found no association between haloperidol versus olanzapine use in pregnancy with any outcome.

Table B-95. Strength of evidence for comparative harms: Haloperidol versus olanzapine

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women exposed to an antipsychotic during pregnancy (with a stable dose at delivery per laboratory confirmation)	Haloperidol exposure vs. olanzapine exposure	High birth weight (>4,000 grams)	1/13 (7.7%) vs. 1/14 (7.1%)[127]	Calculated RR, 1.07 (95% CI, 0.07 to 15.5)[127]	1 cohort, n=27[127]	High study limitations (high risk of bias[116]), seriously imprecise (few events, wide CIs), consistency unknown	Insufficient
		Low birth weight (<2,500 grams)	0/13 (0%) vs. 4/14 (28.6%)[127]	Calculated RR, 0.22 (95% CI, 0.007 to 2.02)[127]	1 cohort, n=27[127]	High study limitations (high risk of bias[116]), seriously imprecise (few events, wide CIs), consistency unknown	Insufficient
		Neonatal complications (respiratory)	1/13 (7.7%) vs. 4/14 (28.6%)[127]	Calculated RR, 0.27 (95% CI, 0.03 to 2.11)[127]	1 cohort, n=27[127]	High study limitations (high risk of bias[116]), seriously imprecise (few events, wide CIs), consistency unknown	Insufficient
		NICU admission	0/13 (0%) vs. 4/14 (28.6%)[127]	Calculated RR, 0.12 (95% CI, 0.07 to 2.02)[127]	1 cohort, n=27[127]	High study limitations (high risk of bias[116]), seriously imprecise (few events, wide CIs), consistency unknown	Insufficient
		Preterm birth (<37 weeks)	0/13 (0%) vs. 3/14 (21.4%)[127]	Calculated RR, 0.15 (95% CI, 0.008 to 2.71)[127]	1 cohort, n=27[127]	High study limitations (high risk of bias[116]), seriously imprecise (few events, wide CIs), consistency unknown	Insufficient
		Mean Apgar score at 1 minute	7.4 (n=13) vs. 7.6 (n=14)[127]	Calculated mean difference: -0.2 (95% CI, -1.52 to 1.12)[127]	1 cohort, n=27[127]	High study limitations (high risk of bias[116]), imprecise (wide CIs), consistent	Insufficient
		Mean Apgar score at 5 minutes	8.9 (n=13) vs. 8.8 (n=14)[127]	Calculated mean difference: 0.10 (95% CI, -0.17 to 0.37)[127]	1 cohort, n=27[127]	High study limitations (high risk of bias[116]), imprecise (wide CIs), consistent	Insufficient

CI = confidence interval; n = number; NICU = neonatal intensive care unit; RR = relative risk; vs. = versus.

Haloperidol Versus Quetiapine

Overview

- The evidence for haloperidol versus quetiapine during pregnancy is insufficient to judge the risk of harms for the child outcomes reported (high birth weight, low birth weight, neonatal complications [respiratory], NICU admission, preterm birth, mean Apgar score at 1 minute, or mean Apgar score at 5 minutes).

Detailed Results

One publication reported on the comparative harms of haloperidol versus quetiapine in a sample collected at the Emory Women's Mental Health Program.[127] The study was a nonrandomized cohort study and was rated high risk of bias. The study did not require a diagnosis of schizophrenia but required antipsychotic exposure during pregnancy and a stable dose at delivery per laboratory confirmation for >5 elimination half-lives at delivery as determined by high-performance liquid chromatography. Only fetal outcomes were reported.

The evidence for haloperidol versus quetiapine is insufficient to judge the risk of harms for the child outcomes reported (high birth weight, low birth weight, neonatal complications [respiratory], NICU admission, preterm birth, mean Apgar score at 1 minute, or mean Apgar score at 5 minutes) (Table B-96). These studies found no association between haloperidol versus quetiapine use in pregnancy with any outcome.

Table B-96. Strength of evidence for comparative harms: Haloperidol versus quetiapine

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women exposed to an antipsychotic during pregnancy (with a stable dose at delivery per laboratory confirmation)	Haloperidol exposure vs. quetiapine exposure	High birth weight (>4,000 grams)	1/13 (7.7%) vs. 0/21 (0%)[127]	Calculated RR, 4.71 (95% CI, 0.21 to 107.8)[127]	1 cohort, n=34[127]	High study limitations (high risk of bias[116]), seriously imprecise (few events, wide CIs), consistency unknown	Insufficient
		Low birth weight (<2,500 grams)	0/13 (0%) vs. 1/21 (4.8%)[127]	Calculated RR, 0.52 (95% CI, 0.02 to 11.98)[127]	1 cohort, n=34[127]	High study limitations (high risk of bias[116]), seriously imprecise (few events, wide CIs), consistency unknown	Insufficient
		Neonatal complications (respiratory)	1/13 (7.7%) vs. 7/21 (33.3%)[127]	Calculated RR, 0.23 (95% CI, 0.03 to 1.67)[127]	1 cohort, n=34[127]	High study limitations (high risk of bias[116]), seriously imprecise (few events, wide CIs), consistency unknown	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women exposed to an antipsychotic during pregnancy (with a stable dose at delivery per laboratory confirmation) (continued)	Haloperidol exposure vs. quetiapine exposure (continued)	NICU admission	0/13 (0%) vs. 2/21 (9.5%)[127]	Calculated RR, 0.31(95% CI, 0.02 to 6.07)[127]	1 cohort, n=34[127]	High study limitations (high risk of bias[116]), seriously imprecise (few events, wide CIs), consistency unknown	Insufficient
		Preterm birth (<37 weeks)	0/13 (0%) vs. 1/21 (4.8%)[127]	Calculated RR, 0.52 (95% CI, 0.02 to 11.98)[127]	1 cohort, n=34[127]	High study limitations (high risk of bias[116]), seriously imprecise (few events, wide CIs), consistency unknown	Insufficient
		Mean Apgar score at 1 minute	7.4 (n=13) vs. 7.6 (n=21)[127]	Calculated mean difference: -0.2 (95% CI, -1.17 to 0.77)[127]	1 cohort, n=34[127]	High study limitations (high risk of bias[116]), imprecise (wide CIs), consistent	Insufficient
		Mean Apgar score at 5 minutes	8.9 (n=13) vs. 8.9 (n=21)[127]	Calculated mean difference: 0 (95% CI, -0.25 to 0.25)[127]	1 cohort, n=34[127]	High study limitations (high risk of bias[116]), imprecise (wide CIs), consistent	Insufficient

CI = confidence interval; n = number; NICU = neonatal intensive care unit; RR = relative risk; vs. = versus.

Haloperidol Versus Risperidone

Overview

- The evidence for haloperidol versus risperidone during pregnancy is insufficient to judge the risk of harms for the child outcomes reported (high birth weight, low birth weight, neonatal complications [respiratory], NICU admission, preterm birth, mean Apgar score at 1 minute, or mean Apgar score at 5 minutes).

Detailed Results

One publication reported on the comparative harms of haloperidol versus risperidone in a sample collected at the Emory Women's Mental Health Program.[127] The study was a nonrandomized cohort study and was rated high risk of bias. The study did not require a diagnosis of schizophrenia but required antipsychotic exposure during pregnancy and a stable dose at delivery per laboratory confirmation for >5 elimination half-lives at delivery as determined by high-performance liquid chromatography. Only fetal outcomes were reported.

The evidence for haloperidol versus risperidone is insufficient to judge the risk of harms for the child outcomes reported (high birth weight, low birth weight, neonatal complications [respiratory], NICU admission, preterm birth, mean Apgar score at 1 minute, or mean Apgar score at 5 minutes) (Table B-97). Mean Apgar scores have uncertain clinical value when compared with ordinal measures of <7 versus ≥7. These studies found no association between haloperidol versus risperidone use in pregnancy with any outcome.

Table B-97. Strength of evidence for comparative harms: Haloperidol versus risperidone

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women exposed to an antipsychotic during pregnancy (with a stable dose at delivery per laboratory confirmation)	Haloperidol exposure vs. risperidone exposure	High birth weight (>4,000 grams)	1/13 (7.7%) vs. 0/6 (0%)[127]	Calculated RR, 1.5 (95% CI, 0.07 to 32.3)[127]	1 cohort, n=19[127]	High study limitations (high risk of bias[116]), seriously imprecise (few events, wide CIs), consistency unknown	Insufficient
		Low birth weight (<2,500 grams)	0/13 (0%) vs. 1/6 (16.7%)[127]	Calculated RR, 0.17 (95% CI, 0.007 to 3.59)[127]	1 cohort, n=19[127]	High study limitations (high risk of bias[116]), seriously imprecise (few events, wide CIs), consistency unknown	Insufficient
		Neonatal complications (respiratory)	1/13 (7.7%) vs. 0/6 (0%)[127]	Calculated RR, 1.5 (95% CI, 0.07 to 32.3)[127]	1 cohort, n=19[127]	High study limitations (high risk of bias[116]), seriously imprecise (few events, wide CIs), consistency unknown	Insufficient
		NICU admission	0/13 (0%) vs. 0/6 (0%)[127]	No events	1 cohort, n=19[127]	High study limitations (high risk of bias[116]), imprecise (no events), consistent	Insufficient
		Preterm birth (<37 weeks)	0/13 (0%) vs. 0/6 (0%)[127]	No events	1 cohort, n=19[127]	High study limitations (high risk of bias[116]), imprecise (no events), consistent	Insufficient
		Mean Apgar score at 1 minute	7.4 (n=13) vs. 8.7 (n=6)[127]	Calculated mean difference: -1.3 (95% CI, -2.87 to 2.67)[127]	1 cohort, n=19[127]	High study limitations (high risk of bias[116]), imprecise (wide CIs), consistent	Insufficient
		Mean Apgar score at 5 minutes	8.9 (n=13) vs. 9.2 (n=6)[127]	Calculated mean difference: -0.3 (95% CI, -0.62 to 0.02)[127]	1 cohort, n=19[127]	High study limitations (high risk of bias[116]), imprecise (wide CIs), consistent	Insufficient

CI = confidence interval; n = number; NICU = neonatal intensive care unit; RR = relative risk; vs. = versus.

Aripiprazole Versus Risperidone

Overview

- The evidence for aripiprazole versus risperidone during pregnancy is insufficient to judge the risk of harms for developing gestational diabetes.

Detailed Results

One publication reported on the comparative harms of aripiprazole versus risperidone in a sample collected from two Australian tertiary obstetric hospitals (Mercy Hospital for Women in Melbourne, Victoria, and King Edward Memorial Hospital in Perth, Western Australia).[97] The study was a retrospective cohort study and was rated high risk of bias. The study required a charted mental health disorder diagnosis. Only the single maternal outcome was reported.

The evidence for aripiprazole versus risperidone is insufficient to judge the risk of harms for developing gestational diabetes (Table B-98). This study found no association between aripiprazole versus risperidone use in pregnancy with any outcome.

Table B-98. Strength of evidence for comparative harms: Aripiprazole versus risperidone

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women exposed to psychotropic exposure medication during any trimester	Aripiprazole exposure vs. risperidone exposure	Gestational diabetes diagnosed at 28 weeks gestation	1/14 (7.1%) vs. 4/14 (28.6%)[97]	Calculated RR, 0.25 (95% CI,0.03 to 1.97)[97]	1 cohort, n=28[97]	High study limitations (high risk of bias[97]), seriously imprecise (few events, wide CIs), consistency unknown	Insufficient

CI = confidence interval; n = number; RR = relative risk; vs. = versus.

Clozapine Versus Aripiprazole

Overview

- The evidence for clozapine versus aripiprazole during pregnancy is insufficient to judge the risk of harms for developing gestational diabetes.

Detailed Results

One publication reported on the comparative harms of clozapine versus aripiprazole in a sample collected from two Australian tertiary obstetric hospitals (Mercy Hospital for Women in Melbourne, Victoria, and King Edward Memorial Hospital in Perth, Western Australia).[97] The study was retrospective cohort study and was rated high risk of bias. The study required a charted mental health disorder diagnosis. Only the single maternal outcome was reported.

The evidence for clozapine versus aripiprazole is insufficient to judge the risk of harms for developing gestational diabetes (Table B-99). This study found an increased association between clozapine and gestational diabetes when compared with aripiprazole use in pregnancy. High study limitations, imprecision due to small study sizes, and no information on consistency limit our confidence in these results.

Table B-99. Strength of evidence for comparative harms: Clozapine versus aripiprazole

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women exposed to psychotropic exposure medication during any trimester	Clozapine exposure vs. aripiprazole exposure	Gestational diabetes diagnosed at 28 weeks gestation	8/11 (72.7%) vs. 1/14 (7.1%)[97]	Calculated RR, 10.18 (95% CI, 1.49 to 69.67)[97]	1 cohort, n=25[97]	High study limitations (high risk of bias[97]), seriously imprecise (few events, wide CIs), consistency unknown	Insufficient

CI = confidence interval; n = number; RR = relative risk; vs. = versus.

Clozapine Versus Risperidone

Overview

- The evidence for clozapine versus risperidone during pregnancy is insufficient to judge the risk of harms for developing gestational diabetes.

Detailed Results

One publication reported on the comparative harms of clozapine versus risperidone in a sample collected from two Australian tertiary obstetric hospitals (Mercy Hospital for Women in Melbourne, Victoria, and King Edward Memorial Hospital in Perth, Western Australia).[97] The study was a retrospective cohort study and was rated high risk of bias. The study required a charted mental health disorder diagnosis. Only the single maternal outcome was reported.

The evidence for clozapine versus risperidone is insufficient to judge the risk of harms for developing gestational diabetes (Table B-100). This study found an increased association between clozapine and gestational diabetes when compared with risperidone use in pregnancy. High study limitations, imprecision due to small study sizes, and no information on consistency limit our confidence in these results.

Table B-100. Strength of evidence for comparative harms: Clozapine versus risperidone

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women exposed to psychotropic exposure medication during any trimester	Clozapine exposure vs. risperidone exposure	Gestational diabetes diagnosed at 28 weeks gestation	8/11 (72.7%) vs. 4/14 (28.6%)[97]	Calculated RR, 2.55 (95% CI, 1.03 to 6.28)[97]	1 cohort, n=25[97]	High study limitations (high risk of bias[97]), seriously imprecise (few events, wide CIs), consistency unknown	Insufficient

CI = confidence interval; n = number; RR = relative risk; vs. = versus.

Olanzapine Versus Aripiprazole

Overview

- The evidence for olanzapine versus aripiprazole during pregnancy is insufficient to judge the risk of harms for developing gestational diabetes.

Detailed Results

One publication reported on the comparative harms of olanzapine versus aripiprazole in a sample collected from two Australian tertiary obstetric hospitals (Mercy Hospital for Women in Melbourne, Victoria, and King Edward Memorial Hospital in Perth, Western Australia).[97] The study was a retrospective cohort study and was rated high risk of bias. The study required a charted mental health disorder diagnosis. Only the single maternal outcome was reported.

The evidence for olanzapine versus aripiprazole is insufficient to judge the risk of harms for developing gestational diabetes (Table B-101). This study found no association between olanzapine versus aripiprazole use in pregnancy with any outcome.

Table B-101. Strength of evidence for comparative harms: Olanzapine versus aripiprazole

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women exposed to psychotropic exposure medication during any trimester	Olanzapine exposure vs. aripiprazole exposure	Gestational diabetes diagnosed at 28 weeks gestation	9/49 (18.4%) vs. 1/14 (7.1%)[97]	Calculated RR, 2.57 (95% CI, 0.36 to 18.60)[97]	1 cohort, n=63[97]	High study limitations (high risk of bias[97]), seriously imprecise (few events, wide CIs), consistency unknown	Insufficient

CI = confidence interval; n = number; RR = relative risk; vs. = versus.

Olanzapine Versus Clozapine

Overview

- The evidence for olanzapine versus clozapine during pregnancy is insufficient to judge the risk of harms for developing gestational diabetes.

Detailed Results

One publication reported on the comparative harms of olanzapine versus clozapine in a sample collected from two Australian tertiary obstetric hospitals (Mercy Hospital for Women in Melbourne, Victoria, and King Edward Memorial Hospital in Perth, Western Australia).[97] The study was a retrospective cohort study and was rated high risk of bias. The study required a charted mental health disorder diagnosis. Only the single maternal outcome was reported.

The evidence for olanzapine versus clozapine is insufficient to judge the risk of harms for developing gestational diabetes (Table B-102). This study found a reduced association between exposure to olanzapine and gestational diabetes when compared with clozapine use in pregnancy. High study limitations, imprecision due to small study sizes, and no information on consistency limit our confidence in these results.

Table B-102. Strength of evidence for comparative harms: Olanzapine versus clozapine

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women exposed to psychotropic exposure medication during any trimester	Olanzapine exposure vs. clozapine exposure	Gestational diabetes diagnosed at 28 weeks gestation	9/49 (18.4%) vs. 8/11 (72.7%)[97]	Calculated RR,: 0.25 (0.13 to 0.51) vs. 8.23 (4.55 to 14.86)[97]	1 cohort, n=60[97]	High study limitations (high risk of bias[97]), seriously imprecise (few events, wide CIs, small Ns), consistency unknown	Insufficient

CI = confidence interval; n = number; RR = relative risk; vs. = versus.

Olanzapine Versus Quetiapine

Overview

- The evidence for olanzapine versus quetiapine during pregnancy is insufficient to judge the risk of harms for the child outcomes reported (high birth weight, low birth weight, neonatal complications [respiratory], NICU admission, preterm birth, or gestational diabetes).

Detailed Results

Two publications reported on the comparative harms of olanzapine versus quetiapine, one in a sample collected at the Emory Women's Mental Health Program in a nonrandomized prospective cohort study[127] and the other from two Australian tertiary obstetric hospitals (Mercy Hospital for Women in Melbourne, Victoria, and King Edward Memorial Hospital in Perth, Western Australia) in a retrospective cohort study.[97] Both studies were rated high risk of bias.

The Emory study did not require a diagnosis of schizophrenia but required antipsychotic exposure during pregnancy and a stable dose at delivery per laboratory confirmation, and it only reported fetal outcomes for >5 elimination half-lives at delivery as determined by high-performance liquid chromatography.[127] The Australian study required a charted mental health disorder diagnosis the single maternal outcomes.

The evidence for olanzapine versus quetiapine is insufficient to judge the risk of harms for the child outcomes reported (high birth weight, low birth weight, neonatal complications [respiratory], NICU admission, preterm birth, or gestational diabetes) (Table B-103). These studies found no association between olanzapine versus quetiapine use in pregnancy with any outcome.

Table B-103. Strength of evidence for comparative harms: Olanzapine versus quetiapine

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women exposed to psychotropic exposure medication during any trimester	Olanzapine exposure vs. quetiapine exposure	Gestational diabetes diagnosed at 28 weeks gestation	9/49 (18.4%) vs. 10/96 (10.4%)[97]	Calculated RR, 1.76 (95% CI, 0.77 to 4.05)[97]	1 cohort, n=145[97]	High study limitations (high risk of bias[97]), seriously imprecise (few events, wide CIs), consistency unknown	Insufficient
Women exposed to an antipsychotic during pregnancy (with a stable dose at delivery per laboratory confirmation)	Olanzapine exposure vs. quetiapine exposure	High birth weight (>4,000 grams)	1/14 (7.1%) vs. 0/21 (0%)[127]	Calculated RR, 4.4 (95% CI, 0.19 to 100.9)[127]	1 cohort, n=34[127]	High study limitations (high risk of bias[116]), imprecise (no events), consistent	Insufficient
		Low birth weight (<2,500 grams)	4/14 (28.6%) vs. 1/21 (4.8%)[127]	Calculated RR, 6 (95% CI, 0.75 to 48.2)[127]	1 cohort, n=34[127]	High study limitations (high risk of bias[116]), imprecise (no events), consistent	Insufficient
		Neonatal complications (respiratory)	4/14 (28.6%) vs. 7/21 (33.3%)[127]	Calculated RR, 0.86 (95% CI, 0.31 to 2.39)[127]	1 cohort, n=34[127]	High study limitations (high risk of bias[116]), imprecise (no events), consistent	Insufficient
		NICU admission	4/14 (28.6%) vs. 2/21 (9.5%)[127]	Calculated RR), 3 (95% CI, 0.63 to 14.2)[127]	1 cohort, n=34[127]	High study limitations (high risk of bias[116]), imprecise (no events), consistent	Insufficient
		Preterm birth (<37 weeks)	3/14 (21.4%) vs. 1/21 (4.8%)[127]	Calculated RR, 4.5 (95% CI, 0.52 to 39.0)[127]	1 cohort, n=34[127]	High study limitations (high risk of bias[116]), imprecise (no events), consistent	Insufficient

CI = confidence interval; n = number; NICU = neonatal intensive care unit; RR = relative risk; vs. = versus.

Olanzapine Versus Risperidone

Overview

- The evidence for olanzapine versus risperidone during pregnancy is insufficient to judge the risk of harms for the child outcomes reported (high birth weight, low birth weight,

neonatal complications [respiratory], NICU admission, preterm birth, or development of gestational diabetes).

Detailed Results

Two publications reported on the comparative harms of olanzapine versus risperidone, one in a sample collected at the Emory Women's Mental Health Program in a nonrandomized prospective cohort study[127] and the other from two Australian tertiary obstetric hospitals (Mercy Hospital for Women in Melbourne, Victoria, and King Edward Memorial Hospital in Perth, Western Australia) in a retrospective cohort study.[97] Both studies were rated high risk of bias.

The Emory study did not require a diagnosis of schizophrenia but required antipsychotic exposure during pregnancy and a stable dose at delivery per laboratory confirmation, and it only reported fetal outcomes for >5 elimination half-lives at delivery as determined by high-performance liquid chromatography.[127] The Australian study required a charted mental health disorder diagnosis the single maternal outcomes.

The evidence for olanzapine versus risperidone is insufficient to judge the risk of harms for the child outcomes reported (high birth weight, low birth weight, neonatal complications [respiratory], NICU admission, preterm birth, or gestational diabetes) (Table B-104). These studies found no association between olanzapine versus risperidone use in pregnancy with any outcome.

Table B-104. Strength of evidence for comparative harms: Olanzapine versus risperidone

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women exposed to an antipsychotic during pregnancy (with a stable dose at delivery per laboratory confirmation)	Olanzapine exposure vs. risperidone exposure	High birth weight (>4,000 grams)	1/14 (7.7%) vs. 0/6 (0%)[127]	Calculated RR, 1.4 (95% CI, 0.06 to 30.2)[127]	1 cohort, n=20[127]	High study limitations (high risk of bias[116]), seriously imprecise (few events, wide CIs), consistency unknown	Insufficient
		Low birth weight (<2,500 grams)	4/14 (28.6%) vs. 1/6 (16.7%)[127]	Calculated RR, 1.7 (95% CI, 0.24 to 12.3)[127]	1 cohort, n=20[127]	High study limitations (high risk of bias[116]), seriously imprecise (few events, wide CIs), consistency unknown	Insufficient
		Neonatal complications (respiratory)	4/14 (28.6%) vs. 0/6 (0%)[127]	Calculated RR, 4.2 (95% CI, 0.26 to 67.7)[127]	1 cohort, n=20[127]	High study limitations (high risk of bias[116]), seriously imprecise (few events, wide CIs), consistency unknown	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women exposed to an antipsychotic during pregnancy (with a stable dose at delivery per laboratory confirmation) (continued)		NICU admission	4/14 (28.6%) vs. 0/6 (0%)[127]	Calculated RR, 4.2 (95% CI, 0.26 to 67.7)[127]	1 cohort, n=20[127]	High study limitations (high risk of bias[116]), seriously imprecise (few events, wide CIs), consistency unknown	Insufficient
		Preterm birth (<37 weeks)	3/14 (21.4%) vs. 0/6 (0%)[127]	Calculated RR, 3.3 (95% CI, 0.19 to 55.0)[127]	1 cohort, n=20[127]	High study limitations (high risk of bias[116]), seriously imprecise (few events, wide CIs), consistency unknown	Insufficient
Women exposed to psychotropic exposure medication during any trimester	Olanzapine exposure vs. risperidone exposure	Gestational diabetes diagnosed at 28 weeks gestation	9/49 (18.4%) vs. 4/14 (28.6%)[97]	Calculated RR, 0.64 (95% CI, 0.23 to 1.78)[97]	1 cohort, n=63[97]	High study limitations (high risk of bias[97]), seriously imprecise (few events, wide CIs), consistency unknown	Insufficient

CI = confidence interval; n = number; NICU = neonatal intensive care unit; RR = relative risk; vs. = versus.

Quetiapine Versus Clozapine

Overview

- The evidence for quetiapine versus clozapine during pregnancy is insufficient to judge the risk of harms for developing gestational diabetes.

Detailed Results

One publication reported on the comparative harms of quetiapine versus clozapine in a sample collected from two Australian tertiary obstetric hospitals (Mercy Hospital for Women in Melbourne, Victoria, and King Edward Memorial Hospital in Perth, Western Australia).[97] The study was a retrospective cohort study and was rated high risk of bias. The study required a charted mental health disorder diagnosis. Only the single maternal outcome was reported.

The evidence for quetiapine versus clozapine is insufficient to judge the risk of harms for developing gestational diabetes (Table B-105). This study found a reduced association between exposure to quetiapine and gestational diabetes when compared with clozapine use in pregnancy. High study limitations, imprecision due to small study sizes, and no information on consistency limit our confidence in these results.

Table B-105. Strength of evidence for comparative harms: Quetiapine versus clozapine

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women exposed to psychotropic exposure medication during any trimester	Quetiapine exposure vs. clozapine exposure	Gestational diabetes diagnosed at 28 weeks gestation	10/96 (10.4%) vs. 8/11 (72.7%)[97]	Calculated RR, 0.14 (95% CI, 0.07 to 0.29)[97]	1 cohort, n=107[97]	High study limitations (high risk of bias[97]), seriously imprecise (few events, small Ns), consistency unknown	Insufficient

CI = confidence interval; n = number; RR = relative risk; vs. = versus.

Quetiapine Versus Aripiprazole

Overview

- The evidence for quetiapine versus aripiprazole during pregnancy is insufficient to judge the risk of harms for developing gestational diabetes.

Detailed Results

One publication reported on the comparative harms of quetiapine versus aripiprazole in a sample collected from two Australian tertiary obstetric hospitals (Mercy Hospital for Women in Melbourne, Victoria, and King Edward Memorial Hospital in Perth, Western Australia).[97] The study was a retrospective cohort study and was rated high risk of bias. The study required a charted mental health disorder diagnosis. Only the single maternal outcome was reported.

The evidence for quetiapine versus aripiprazole is insufficient to judge the risk of harms for developing gestational diabetes (Table B-106). This study found no association between olanzapine versus aripiprazole use in pregnancy with any outcome.

Table B-106. Strength of evidence for comparative harms: Quetiapine versus aripiprazole

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women exposed to psychotropic exposure medication during any trimester	Quetiapine exposure vs. aripiprazole exposure	Gestational diabetes diagnosed at 28 weeks gestation	10/96 (10.4%) vs. 1/14 (7.1%)[97]	Calculated RR, 1.46 (95% CI, 0.20 to 10.54)[97]	1 cohort, n=110[97]	High study limitations (high risk of bias[97]), seriously imprecise (few events, wide CIs), consistency unknown	Insufficient

CI = confidence interval; n = number; RR = relative risk; vs. = versus.

Quetiapine Versus Risperidone

Overview

- The evidence for quetiapine versus risperidone during pregnancy is insufficient to judge the risk of harms for the child outcomes reported (high birth weight, low birth weight,

neonatal complications [respiratory], NICU admission, preterm birth, or gestational diabetes).

Detailed Results

Two publications reported on the comparative harms of quetiapine versus risperidone, one in a sample collected at the Emory Women's Mental Health Program in a nonrandomized prospective cohort study[127] and the other from two Australian tertiary obstetric hospitals (Mercy Hospital for Women in Melbourne, Victoria, and King Edward Memorial Hospital in Perth, Western Australia) in a retrospective cohort study.[97] Both studies were rated high risk of bias.

The Emory study did not require a diagnosis of schizophrenia but required antipsychotic exposure during pregnancy and a stable dose at delivery per laboratory confirmation, and it only reported fetal outcomes for >5 elimination half-lives at delivery as determined by high-performance liquid chromatography.[127] The Australian study required a charted mental health disorder diagnosis the single maternal outcomes.

The evidence for quetiapine versus risperidone is insufficient to judge the risk of harms for the child outcomes reported (high birth weight, low birth weight, neonatal complications [respiratory], NICU admission, preterm birth, or gestational diabetes) (Table B-107). These studies found no association between olanzapine versus risperidone use in pregnancy with any outcome.

Table B-107. Strength of evidence for comparative harms: Quetiapine versus risperidone

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women exposed to psychotropic exposure medication during any trimester	Quetiapine exposure vs. risperidone exposure	Gestational diabetes diagnosed at 28 weeks gestation	10/96 (10.4%) vs. 4/14 (28.6%)[97]	Calculated RR, 0.36 (95% CI, 0.13 to 1.01)[97]	1 cohort, n=110[97]	High study limitations (high risk of bias[97]), seriously imprecise (few events, wide CIs), consistency unknown	Insufficient
Women exposed to an antipsychotic during pregnancy (with a stable dose at delivery per laboratory confirmation)	Quetiapine exposure vs. risperidone exposure	High birth weight (>4,000 grams)	0/21 (0%) vs. 0/6 (0%)[127]	No events	1 cohort, n=27[127]	High study limitations (high risk of bias[116]), imprecise (no events), consistent	Insufficient
		Low birth weight (<2,500 grams)	1/21 (4.8%) vs. 1/6 (16.7%)[127]	Calculated RR, 0.29 (95% CI, 0.02 to 3.92)[127]	1 cohort, n=27[127]	High study limitations (high risk of bias[116]), seriously imprecise (few events, wide CIs), consistency unknown	Insufficient
		Neonatal complications (respiratory)	7/21 (33.3%) vs. 0/6 (0%)[127]	Calculated RR, 4.8 (95% CI, 0.31 to 73.4)[127]	1 cohort, n=27[127]	High study limitations (high risk of bias[116]), seriously imprecise (few events, wide CIs), consistency unknown	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women exposed to an antipsychotic during pregnancy (with a stable dose at delivery per laboratory confirmation) (continued)		NICU admission	2/21 (9.5%) vs. 0/6 (0%)[127]	Calculated RR, 1.6 (95% CI, 0.09 to 29.3)[127]	1 cohort, n=27[127]	High study limitations (high risk of bias[116]), seriously imprecise (few events, wide CIs), consistency unknown	Insufficient
		Preterm birth (<37 weeks)	1/21 (4.8%) vs. 0/6 (0%)[127]	Calculated RR, 0.95 (95% CI, 0.04 to 20.9)[127]	1 cohort, n=27[127]	High study limitations (high risk of bias[116]), seriously imprecise (few events, wide CIs), consistency unknown	Insufficient

CI = confidence interval; n = number; NICU = neonatal intensive care unit; RR = relative risk; vs. = versus.

First-Generation Antipsychotics Versus Second-Generation Antipsychotics

Overview

- The evidence for first-generation antipsychotics (as a class) versus second-generation antipsychotics (as a class) during pregnancy is insufficient to judge the risk of harms for the child outcomes reported (large for gestational age, low birth weight, small for gestational age preterm birth, or abnormal neuromotor development).

Detailed Results

Three publications reported on the comparative harms of first-generation antipsychotics versus second-generation antipsychotics,[85, 119, 125] but only two provided usable data.[85, 119] These samples were drawn from the Emory Women's Mental Health Program[119] and the Taiwan National Health Insurance Research Dataset.[85] The studies were each nonrandomized cohort studies. One was rated some concern,[119] and one was rated high risk of bias.[85]

Both publications focused on exposure during pregnancy. One study providing data required a maternal diagnosis of schizophrenia,[85] while the other only required exposure to antipsychotics during pregnancy without a confirmed schizophrenia diagnosis.[119] Only fetal outcomes alone were reported.

The evidence for first-generation antipsychotics versus second-generation antipsychotics is insufficient to judge the risk of harms for the child outcomes reported (large for gestational age, low birth weight, small for gestational age preterm birth, or abnormal neuromotor development) (Table B-108). These studies found no association between first-generation antipsychotics versus second-generation antipsychotics use in pregnancy with any outcome.

Table B-108. Strength of evidence for comparative harms: First-generation antipsychotics versus second-generation antipsychotics

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women exposed to an antipsychotic during pregnancy	First-generation antipsychotic vs. second-generation antipsychotic	Abnormal neuromotor development (measured by INFANIB, higher score is better)	NR	After controlling for maternal psychiatric history using the severity/ chronicity index, results revealed a modest but nonsignificant difference (F2,21=2.96; p=0.10), with adjusted means suggesting higher scores for first-generation antipsychotic-exposed infants (mean [SE]=67.1 [1.84]) than with second-generation antipsychotic-exposed infants (mean [SE]=62.9 [1.60])[119]	1 cohort, n=21[119]	Moderate study limitations, likely imprecise (small Ns), consistency unknown	Insufficient
Women with schizophrenia and exposed to an antipsychotic during pregnancy	First-generation antipsychotic vs. second-generation antipsychotic	Large for gestational age (birthweight >10th percentile for gestational age)	15/194 (7.7%) vs. 3/48 (6.3%)[85]	Calculated RR, 1.23 (95% CI, 0.37 to 4.10)[127]	1 cohort, n=242[127]	High study limitations (high risk of bias[127]), seriously imprecise (few events, wide CIs), consistency unknown	Insufficient
		Low birth weight (<2,500 grams)	16/194 (8.2%) vs. 6/48 (12.5%)[85]	Calculated RR, 0.66 (95% CI, 0.27 to 1.60)[127]	1 cohort, n=242[127]	High study limitations (high risk of bias[127]), seriously imprecise (few events, wide CIs), consistency unknown	Insufficient
		Small for gestational age (birthweight <10th percentile for gestational age)	49/194 (25.3%) vs. 10/48 (20.8%)[85]	Calculated RR, 1.21 (95% CI, 0.66 to 2.21)[127]	1 cohort, n=242[127]	High study limitations (high risk of bias[127]), seriously imprecise (few events, wide CIs), consistency unknown	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women with schizophrenia and exposed to an antipsychotic during pregnancy (continued)		Preterm birth	35/194 (18.0%) vs. 6/48 (12.5%)[85]	Calculated RR, 1.44 (95% CI, 0.64 to 3.23)[127]	1 cohort, n=242[127]	High study limitations (high risk of bias[127]), seriously imprecise (few events, wide CIs), consistency unknown	Insufficient

CI = confidence interval; INFANIB = Infant Neurological International Battery; n = number; RR = relative risk; SE = standard error; vs. = versus.

Second-Generation Antipsychotics Versus Mood Stabilizers

Overview

- The evidence for specific second-generation antipsychotics versus specific mood stabilizers during pregnancy is insufficient to judge the risk of harms for developing gestational diabetes.

Detailed Results

One publication reported on the comparative harms of a number of second-generation antipsychotics (quetiapine, olanzapine, risperidone, clozapine, or aripiprazole) versus mood stabilizers (lithium or lamotrigine), respectively, in a sample collected from two Australian tertiary obstetric hospitals (Mercy Hospital for Women in Melbourne, Victoria, and King Edward Memorial Hospital in Perth, Western Australia).[97] The study was a retrospective cohort study and rated high risk of bias. The study required a charted mental health disorder diagnosis. Only the single maternal outcome was reported. There were 10 specific comparisons available of a single agent versus a single agent (Table B-109).

The evidence for specific second-generation antipsychotics versus specific mood stabilizers is insufficient to judge the risk of harms for developing gestational diabetes (Table B-109). This study found no association between olanzapine versus aripiprazole use in pregnancy. One study found an increased association between gestational diabetes and exposure to clozapine when compared with exposure to lamotrigine or lithium. High study limitations, imprecision due to small study sizes, and no information on consistency limit our confidence in these results.

Table B-109. Strength of evidence for comparative harms: Second-generation antipsychotics versus mood stabilizers

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women exposed to psychotropic exposure medication during any trimester	Olanzapine exposure vs. lithium exposure	Gestational diabetes diagnosed at 28 weeks gestation	9/49 (18.4%) vs. 2/17 (11.7%)[97]	Calculated RR, 1.56 (95% CI, 0.37 to 6.52)[97]	1 cohort, n=66[97]	High study limitations (high risk of bias[97]), seriously imprecise (few events, wide CIs), consistency unknown	Insufficient
Women exposed to psychotropic exposure medication during any trimester	Olanzapine exposure vs. lamotrigine exposure	Gestational diabetes diagnosed at 28 weeks gestation	9/49 (18.4%) vs. 2/19 (10.5%)[97]	Calculated RR, 1.74 (95% CI, 0.41 to 7.35)[97]	1 cohort, n=68[97]	High study limitations (high risk of bias[97]), seriously imprecise (few events, wide CIs), consistency unknown	Insufficient
Women exposed to psychotropic exposure medication during any trimester	Quetiapine exposure vs. lithium exposure	Gestational diabetes diagnosed at 28 weeks gestation	10/96 (10.4%) vs. 2/17 (11.7%)[97]	Calculated RR, 0.99 (95% CI, 0.24 to 4.16)[97]	1 cohort, n=113[97]	High study limitations (high risk of bias[97]), seriously imprecise (few events, wide CIs), consistency unknown	Insufficient
Women exposed to psychotropic exposure medication during any trimester	Quetiapine exposure vs. lamotrigine exposure	Gestational diabetes diagnosed at 28 weeks gestation	10/96 (10.4%) vs. 2/19 (10.5%)[97]	Calculated RR, 0.89 (95% CI, 0.21 to 3.69)[97]	1 cohort, n=115[97]	High study limitations (high risk of bias[97]), seriously imprecise (few events, wide CIs), consistency unknown	Insufficient
Women exposed to psychotropic exposure medication during any trimester	Aripiprazole exposure vs. lithium exposure	Gestational diabetes diagnosed at 28 weeks gestation	1/14 (7.1%) vs. 2/17 (11.7%)[97]	Calculated RR, 0.61 (95% CI, 0.06 to 6.02)[97]	1 cohort, n=31[97]	High study limitations (high risk of bias[97]), seriously imprecise (few events, wide CIs), consistency unknown	Insufficient
Women exposed to psychotropic exposure medication during any trimester	Aripiprazole exposure vs. lamotrigine exposure	Gestational diabetes diagnosed at 28 weeks gestation	1/14 (7.1%) vs. 2/19 (10.5%)[97]	Calculated RR, 0.68 (95% CI, 0.07 to 6.76)[153]	1 cohort, n=33[97]	High study limitations (high risk of bias[97]), seriously imprecise (few events, wide CIs), consistency unknown	Insufficient

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by Arm	Results	Study Design and Sample Size	Factors That Affect the Strength of Evidence	Overall Evidence Strength (Direction of Effect)
Women exposed to psychotropic exposure medication during any trimester	Clozapine exposure vs. lithium exposure	Gestational diabetes diagnosed at 28 weeks gestation	8/11 (72.7%) vs. 2/17 (11.7%)[97]	Calculated RR, 6.18 (95% CI, 1.60 to 23.87)[97]	1 cohort, n=28[97]	High study limitations (high risk of bias[97]), seriously imprecise (few events, wide CIs), consistency unknown	Insufficient
Women exposed to psychotropic exposure medication during any trimester	Clozapine exposure vs. lamotrigine exposure	Gestational diabetes diagnosed at 28 weeks gestation	8/11 (72.7%) vs. 2/19 (10.5%)[97]	Calculated RR, 6.91 (95% CI, 1.77 to 26.92)[97]	1 cohort, n=30[97]	High study limitations (high risk of bias[97]), seriously imprecise (few events, wide CIs), consistency unknown	Insufficient
Women exposed to psychotropic exposure medication during any trimester	Risperidone exposure vs. lithium exposure	Gestational diabetes diagnosed at 28 weeks gestation	4/14 (28.6%) vs. 2/17 (11.7%)[97]	Calculated RR, 2.43 (95% CI, 0.52 to 11.36)[97]	1 cohort, n=31[97]	High study limitations (high risk of bias[97]), seriously imprecise (few events, wide CIs), consistency unknown	Insufficient
Women exposed to psychotropic exposure medication during any trimester	Risperidone exposure vs. lamotrigine exposure	Gestational diabetes diagnosed at 28 weeks gestation	4/14 (28.6%) vs. 2/19 (10.5%)[97]	Calculated RR, 2.71 (95% CI, 0.58 to 12.80)[97]	1 cohort, n=33[97]	High study limitations (high risk of bias[97]), seriously imprecise (few events, wide CIs), consistency unknown	Insufficient

CI = confidence interval; n = number; RR = relative risk; vs. = versus.

Pharmacologic Combinations

Overview

- Six publications reported on child outcomes (breastfeeding difficulty, transient neonatal symptoms, 5-minute Apgar <9, NICU admission, respiratory distress, birth weight, gestational age, internalizing problems, or congenital heart disease) for women receiving pharmacologic combinations.

Detailed Results

Six publications reported on pharmacologic combinations.[45, 115, 120, 129, 132, 141] These publications drew from six cohorts (3 from the British Columbia Children's and Women's Health Centre,[120, 129, 132] 1 from The Women's Mental Health Program at the Emory University School of Medicine,[45] and 2 cohorts based in the United States).[115] All were nonrandomized studies and were rated as high risk of bias.

All six publications focused on exposure during pregnancy. Three compared SSRIs plus clonazepam with SSRIs,[120, 129, 132] one compared SSRIs plus benzodiazepine with SSRIs,[115] one

compared SSRIs plus non-SSRIs with SRIs only, and one compared combinations of antidepressants (e.g., fluoxetine and bupropion, sertraline and paroxetine, and venlafaxine and bupropion with individual SSRIs [e.g., citalopram, escitalopram, fluoxetine, sertraline, or paroxetine] or SNRIs [e.g., venlafaxine, bupropion, or duloxetine]).[141] These studies evaluated the outcomes of breastfeeding difficulty, transient neonatal symptoms, 5-minute Apgar <9, NICU admission, respiratory distress, birth weight, gestational age, internalizing problems, infant psychomotor development, and congenital heart disease. These studies are not evaluated any further due to limited clinical utility.

Nonspecific or Undefined Pharmacologic Interventions

Overview

- Thirty-one publications reported on nonspecific or undefined pharmacologic interventions compared with another active treatment. Because the clinical utility is limited, we do not judge the risk of harms for maternal or child outcomes.

Detailed Results

Thirty-one publications reported on nonspecific/undefined pharmacologic interventions compared with another active treatment.[42, 45, 53, 55, 64, 70, 83, 84, 87, 96, 97, 107, 109-114, 117-119, 121, 123, 128, 130, 137, 138, 142, 143, 145, 146] These publications drew from 24 cohorts (1 from the Australian Pregnancy Register of Antiepileptic Drugs in Pregnancy,[107] 1 from the Danish Medical Birth Registry,[110] one from the Emory Women's Mental Health Program,[119] 1 from the U.S. Medicaid Analytic eXtract,[96] 2 from the U.S. Food and Drug Administration Adverse Event Reporting System,[143] 1 from the Hong Kong Clinical Data Analysis and Reporting System,[55] 1 from Ingenix Research Data Mart [claims data from UnitedHealthcare],[146] 5 from Motherisk,[77, 121, 128, 130, 138] 1 from Blue Cross Blue Shield of Michigan claims data,[145] 1 from the Norwegian Mother and Child Cohort Study,[142] 5 from the QPC,[53, 64, 87, 111, 114] 1 from RAMQ,[70] 1 from the Slone Epidemiology Center Birth Defects Study,[84] 1 from the national Quality Register of Assisted Reproductions,[113] 1 from MoBa,[118] 1 from MTB,[112] 2 that included multiple Danish national registries,[117, 123] 1 from birth registries in Sweden,[137] 1 that included multiple Canada-based databases,[83] 1 from a population in the United States,[45] and 3 from populations in Australia).[42, 97, 109] All were nonrandomized studies and were rated as high risk of bias[42, 45, 53, 70, 84, 87, 107, 109-114, 117, 118, 121, 123, 128, 130, 137, 138] or having some concerns for risk of bias.[55, 64, 83, 119]

All 31 publications focused on exposure during pregnancy. Six publications examined any antidepressants use,[42, 55, 109, 111, 119 , 143, 145] eight examined interventions groups described as other antidepressants,[53, 83, 87, 114, 121, 128, 130, 146] one examined an intervention described as other antidepressants/TCAs,[118] three publications examined an intervention described as antidepressant plus antipsychotics,[42, 55, 109] one examined an intervention described as antidepressants co-exposed with benzodiazepines,[146] two examined interventions described as other monotherapy,[64, 107] nine examined polytherapy/polypharmacy or undescribed combinations,[53, 96, 107, 114, 123, 137, 138, 154, 155] three examined non-SSRIs,[55, 70, 113] one examined non-SSRIs and non-SSRIs plus SSRIs,[45] one examined nonsertraline and nonsertraline SSRIs,[70] one examined any psychotropic treatment,[137] one examined interventions described as other psychotropic medication,[97] one examined an intervention described as co-exposure,[83] two examined interventions described as other,[110, 123] two examined interventions described as other monotherapy,[64, 107] and one examined an intervention described as only SNRI/TCA/MAOI/others.[111] The included publications

evaluated the maternal outcomes of anemia, gestational diabetes, spontaneous abortion, gestational hypertension, preeclampsia, vaginal bleeding, placental abruption, postpartum hemorrhage, and the child outcomes of preterm delivery, attention-deficit/hyperactivity disorder, Apgar scores, autism, cardiac anomalies, convulsive seizures, epilepsy, major congenital anomalies, heart anomalies, birth weight, NICU admissions, gestational age/prematurity, perinatal death, neuromotor and psychomotor development, and small for gestational age. Because the interventions were not clearly defined, they are not evaluated any further due to limited clinical utility.

Meta-Analysis

Figure B-2. Pooled odds ratios for cardiac anomalies for SSRIs versus no treatment

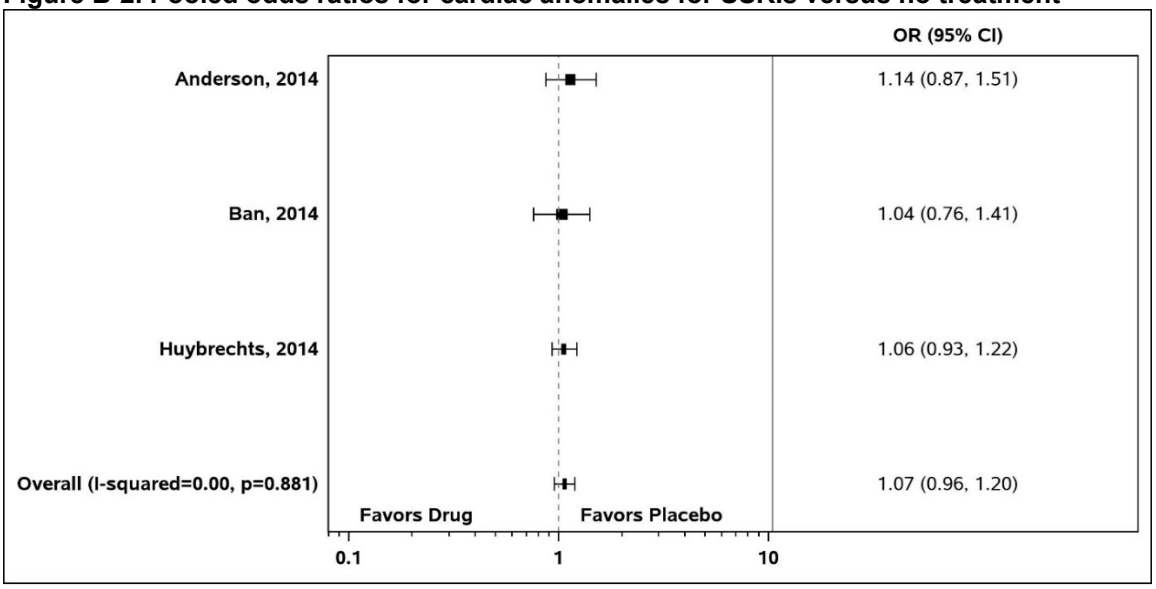


Figure B-3. Pooled odds ratios for cardiac anomalies for citalopram versus no treatment

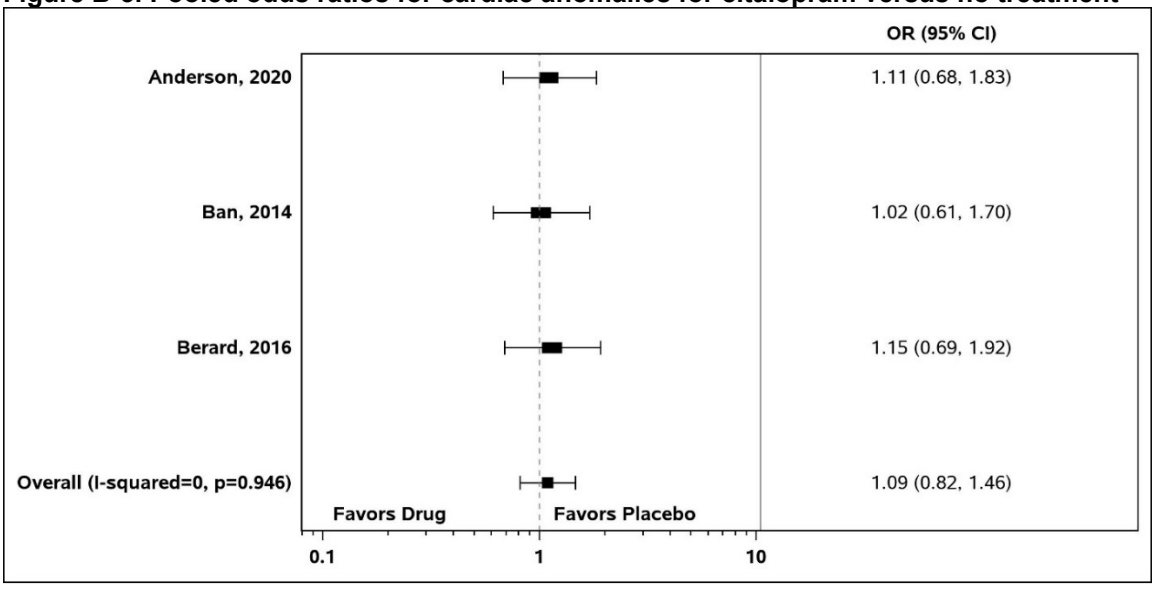


Figure B-4. Pooled odds ratios for cardiac anomalies for fluoxetine versus no treatment

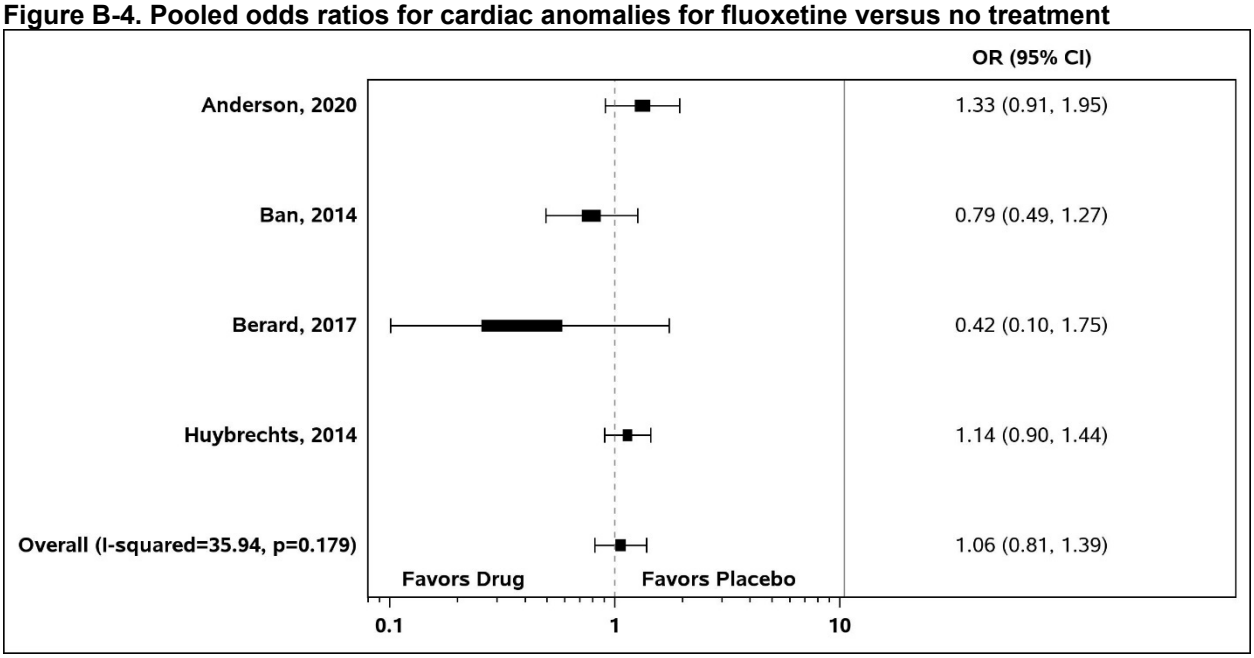


Figure B-5. Pooled odds ratios for cardiac anomalies for paroxetine versus placebo

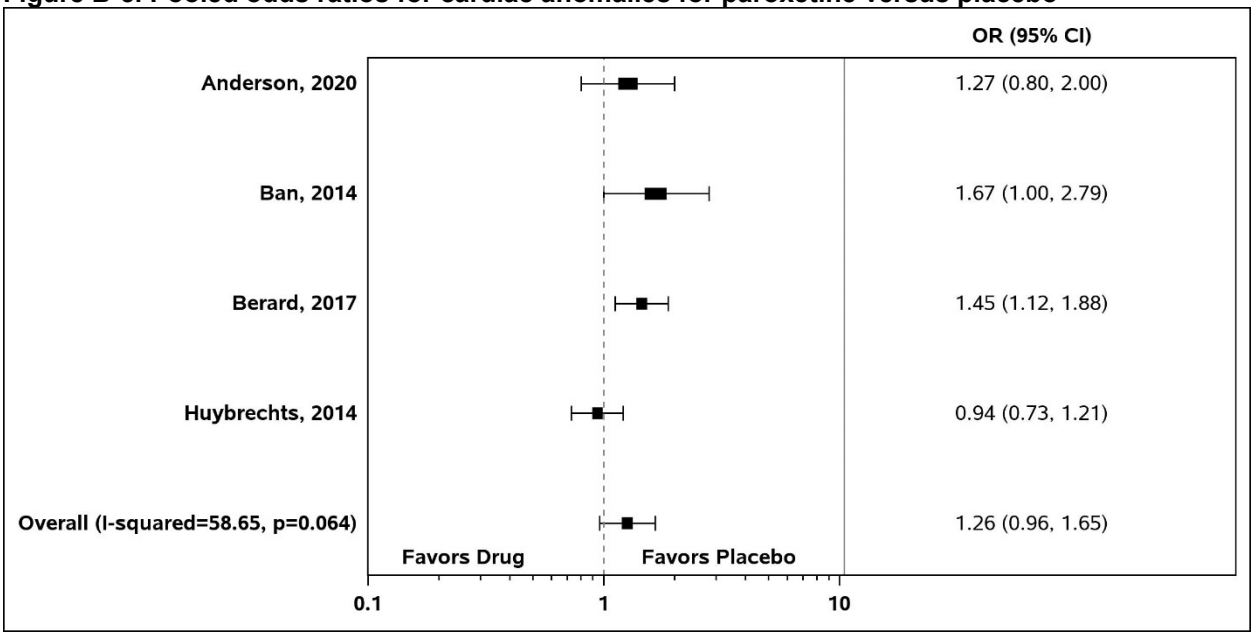


Figure B-6. Pooled odds ratios for cardiac anomalies for sertraline versus placebo

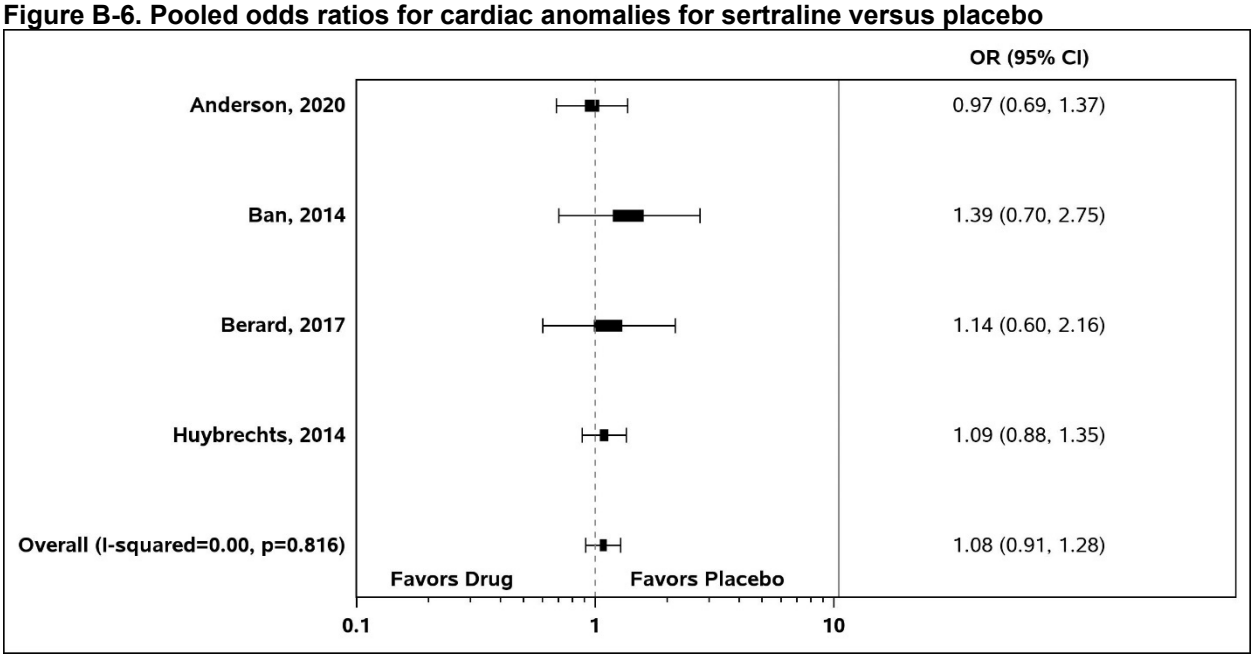


Figure B-7. Pooled odds ratios for cardiac anomalies for tricyclic antidepressants versus placebo

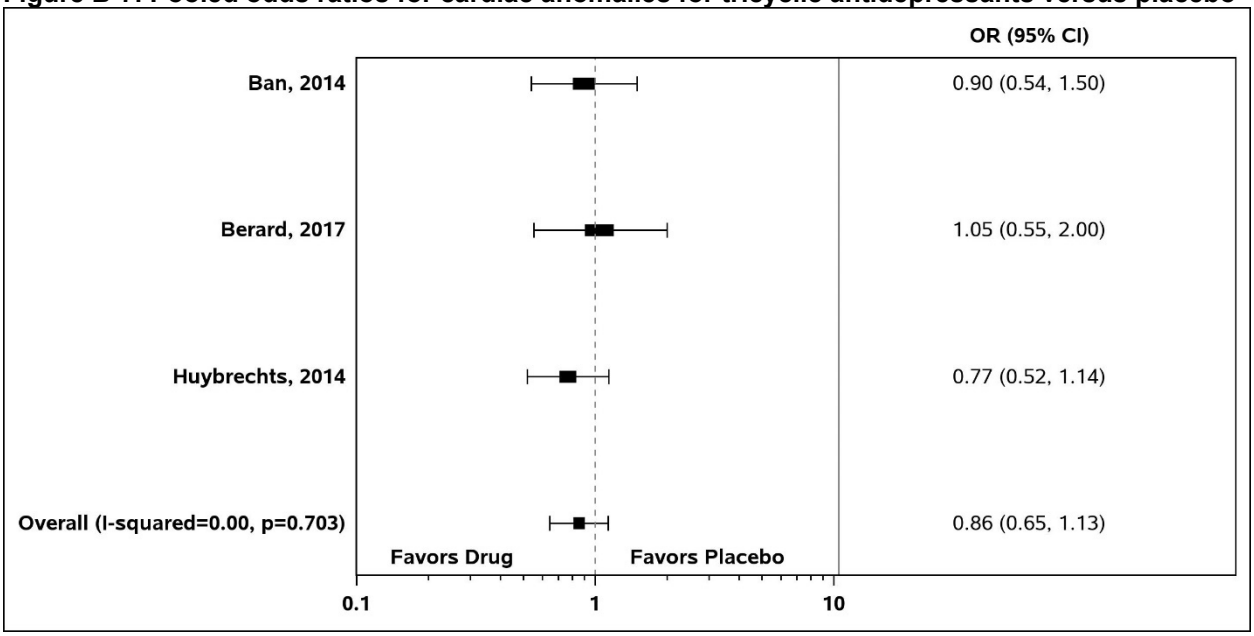


Figure B-8. Pooled relative risks for adverse events for brexanolone versus placebo

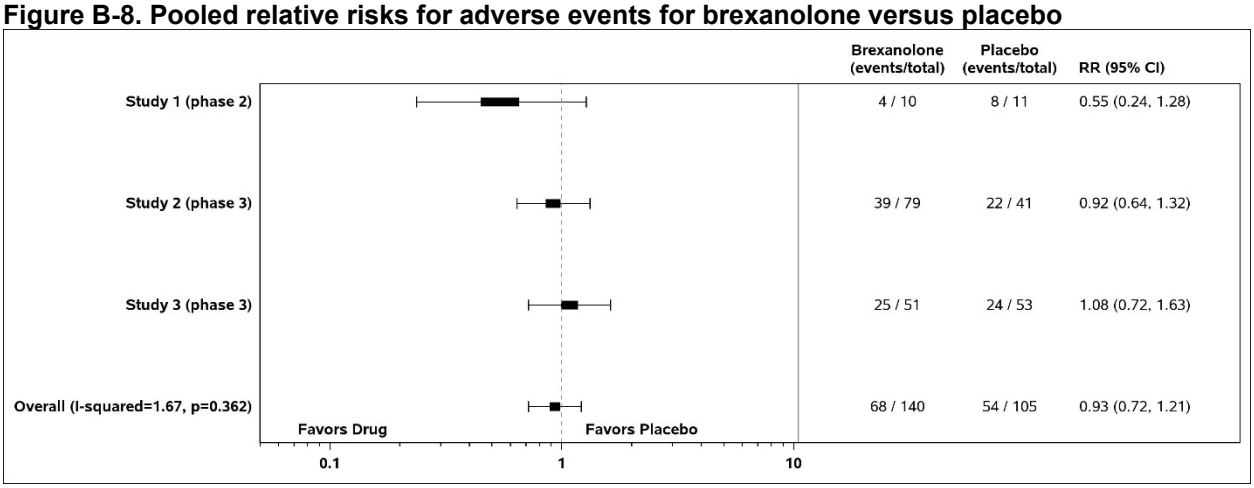


Figure B-9. Pooled relative risks for dizziness for brexanolone versus placebo

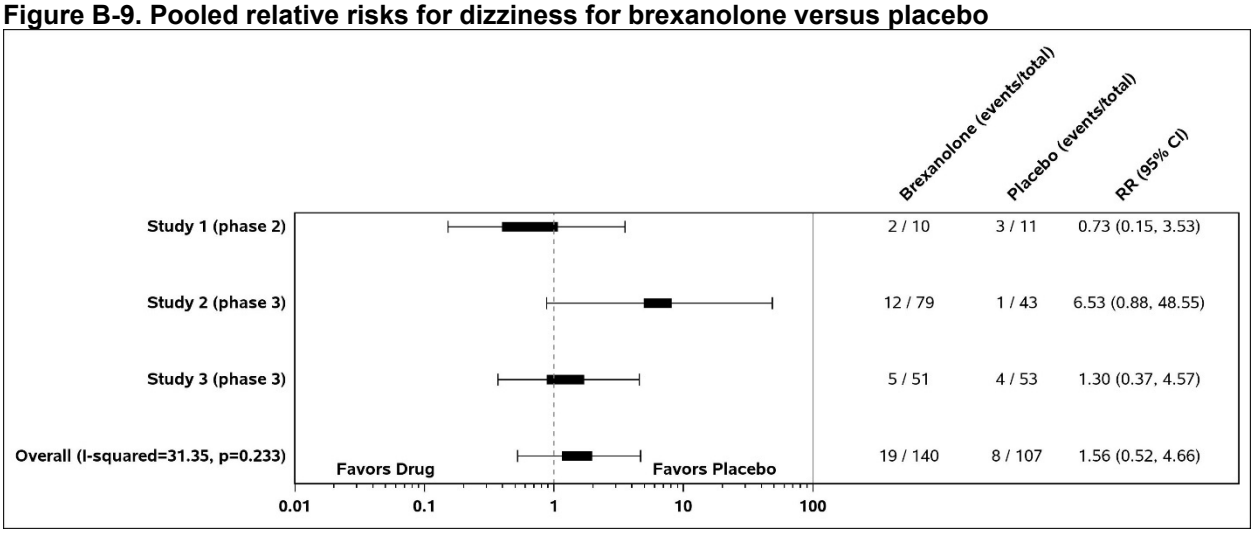
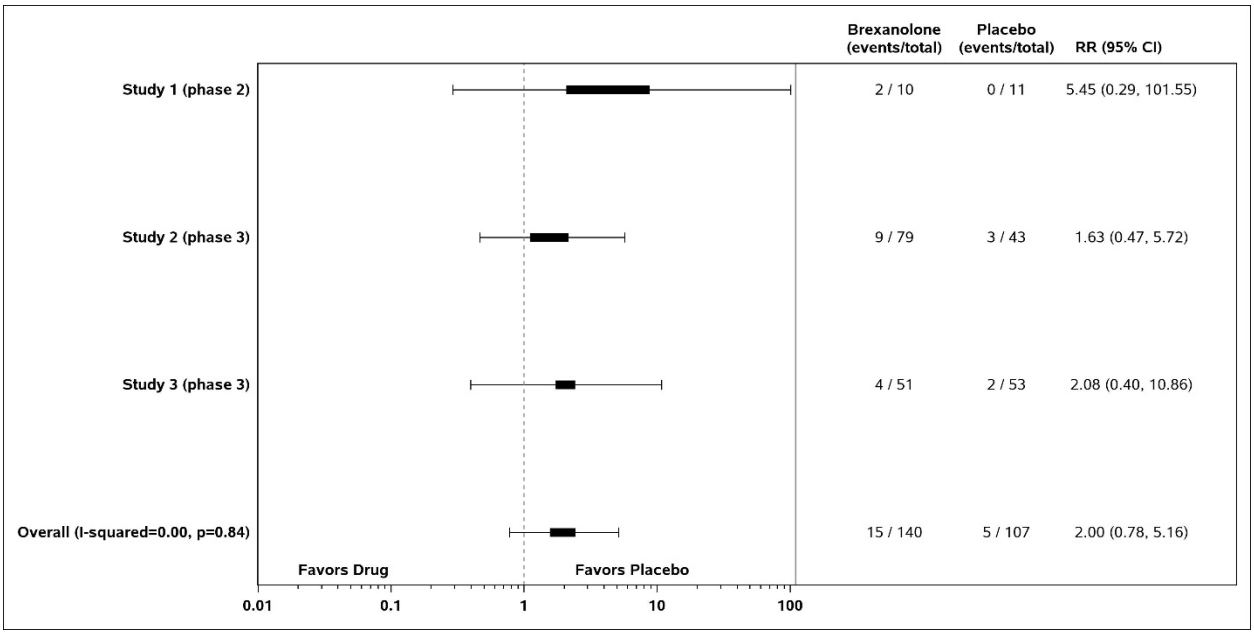


Figure B-10. Pooled relative risks for somnolence for brexanolone versus placebo



Excluded Studies

X1: Not Original Research

X2: Ineligible Population

X3: Ineligible Intervention

X4: Ineligible Comparator

X5: Ineligible Outcome

X6: Ineligible Time Frame

X7: Ineligible Study Design

X8: Not English

X9: Abstract Only

X10: Overlapping Arms

X11: Irretrievable

X12: Indirect Comparison

X13: Dose-Comparison Only

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5. Erratum: SSRI treatment during pregnancy: Deceleration of weight gain due to depression or drug? (American Journal of Psychiatry (2006) 163 (986-991)). Am J Psychiatry. 2006;163(10):1843. Exclusion Code: X1.
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22. Erratum: brexanolone injection in post-partum depression: two multicentre, double-blind, randomised, placebo-controlled, phase 3 trials (The Lancet (2018) 392(10152) (1058-1070), (S0140673618315514) (10.1016/S0140-6736(18)31551-4)). Lancet. 2018;392(10153):1116. doi: 10.1016/S0140-6736%2818%2932288-8. PMID: CN-01922333. Exclusion Code: X1.

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