Comparative Effectiveness Review
Number 234

Management of Primary Headaches in Pregnancy

AHRQ
Agency for Healthcare
Research and Quality

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Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
5600 Fishers Lane
Rockville, MD 20857
www.ahrq.gov

Contract No. 290-2015-00002-I

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AHRQ Publication No. 20(21)-EHC026
November 2020

This report is based on research conducted by the Brown Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-2015-00002-I). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

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.

Suggested citation: Saldanha IJ, Roth JL, Chen KK, Zullo AR, Adam GP, Konnyu KJ, Cao W, Bhuma MR, Kimmel HJ, Mehta S, Riester MR, Sorial MN, Balk EM. Management of Primary Headaches in Pregnancy. Comparative Effectiveness Review No. 234. (Prepared by the Brown Evidence-based Practice Center under Contract No. 290-2015-00002-I.) AHRQ Publication No. 20(21)-EHC026. Rockville, MD: Agency for Healthcare Research and Quality; November 2020. DOI: https://doi.org/10.23970/AHRQEPCCER234. Posted final reports are located on the Effective Health Care Program search page.

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 www.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 Officers 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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Acknowledgments

The authors gratefully acknowledge the following individuals for their contributions to this project: Associate Editor Marian McDonagh, Ph.D., from the Pacific Northwest Evidence-based Practice Center, Portland, OR; Task Order Officers Jill Huppert, M.D., M.P.H., and Suchitra Iyer, Ph.D., from AHRQ; and EPC Program Director Stephanie Chang, M.D., M.P.H., from AHRQ.

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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Management of Primary Headaches in Pregnancy

Structured Abstract

Objectives. This systematic review (SR) evaluates the literature on pharmacologic and nonpharmacologic interventions to prevent or treat attacks of primary headaches (migraine, tension headache, cluster headache, and other trigeminal autonomic cephalgias) in women who are pregnant (or attempting to become pregnant), postpartum, or breastfeeding.

Data sources. We searched Medline®, Embase®, Cochrane CENTRAL, CINAHL®, and ClinicalTrials.gov to identify primary studies (comparative studies and single-group studies) in women who are pregnant (or attempting to become pregnant), postpartum, or breastfeeding with primary headache (direct evidence). We searched Medline, the Cochrane Database of Systematic Reviews, and Epistemonikos for existing SRs of harms of interventions in pregnant women regardless of indication (indirect evidence).

Review methods. We extracted study data into the Systematic Review Data Repository. We assessed the risk of bias and evaluated the strength of evidence (SoE) using standard methods. The PROSPERO protocol registration number is CRD42020158310.

Results. Our searches for direct and indirect evidence yielded 8,549 citations and 2,788 citations, respectively. Sixteen primary studies comprising 14,185 patients in total and 26 SRs met criteria. Risk of bias was high for most primary studies. We found no evidence addressing effectiveness of any intervention for *prevention of primary headaches*. We found one single-group study (of topiramate) and 11 SRs reporting potential harms of various interventions used for primary headache prevention during pregnancy. Antiepileptics (except lamotrigine), venlafaxine, tricyclic antidepressants, benzodiazepines, beta blockers, prednisolone, and oral magnesium may be associated with increased risk of fetal/child adverse effects, but calcium channel blockers and antihistamines may have low risk of adverse effects (indirect evidence; low to moderate SoE). For *treatment of acute attacks of primary headache*, we found three randomized controlled trials (RCTs), eight nonrandomized comparative studies (NRCSs), and four single-group studies. Combination metoclopramide and diphenhydramine may be more effective than codeine in reducing severity of migraine or tension headache; adverse effect profiles were similar (1 RCT; low SoE). Triptans used for migraine during pregnancy were not associated with spontaneous abortions or congenital anomalies (8 NRCSs; low SoE). Acetaminophen, prednisolone, indomethacin, ondansetron, antipsychotics, and intravenous magnesium may be associated with increased risk of fetal/child adverse effects, but low-dose aspirin (either during pregnancy or postpartum) may not be associated with increased risk (indirect evidence; low to moderate SoE). There is insufficient evidence to make conclusions about the benefits or harms of nonpharmacologic treatments used during pregnancy, including acupuncture (1 RCT); biofeedback, relaxation therapy, and physical therapy (1 RCT and 2 single-group studies); nerve blocks (1 single-group study); and transcranial magnetic stimulation (1 single-group study).

Conclusions. Evidence regarding the benefits and harms of all interventions in women who are pregnant (or attempting to become pregnant), postpartum, or breastfeeding is insufficient, or at

best of low strength of evidence. Future research is needed to identify the most effective and safe interventions for preventing or treating primary headaches in these populations of women.

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    - A single primary study provided insufficient (direct) evidence to make conclusions about the harms of topiramate when used for preventing primary headache during pregnancy, but use during pregnancy outside the primary headache context (indirect evidence) suggests increased risk of fetal/child adverse effects. Indirect evidence also suggests that other antiepileptics, such as carbamazepine, gabapentin, and valproate may have similar adverse effect profiles, but lamotrigine may have a low risk of adverse effects.
    - Venlafaxine, tricyclic antidepressants (any), benzodiazepines (any), beta blockers (any), prednisolone, and oral magnesium use during pregnancy may have increased risk of fetal/child adverse effects, but calcium channel blockers (any, but nifedipine in particular) and antihistamines (any) may have a low risk of adverse effects (indirect evidence).
- **Treatment** of patients with acute attacks of primary headache in women who are pregnant (or attempting to become pregnant), postpartum, or breastfeeding
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    - A single primary study found that compared with oral codeine, combination metoclopramide and diphenhydramine may be more effective to reduce migraine or tension headache severity during pregnancy, and may not be associated with greater serious or nonserious maternal harms; fetal/child harms were not reported. Indirect evidence found that antihistamines (any) during pregnancy (used for indications other than primary headache) may have a low risk of adverse effects.
    - Systematic reviews of harms (regardless of indication) report that acetaminophen, prednisolone, indomethacin, ondansetron, antipsychotics (any), and intravenous magnesium use during pregnancy may be associated with fetal/child adverse effects, but low-dose aspirin use may not be associated with increased risk of adverse effects.
  - Nonpharmacologic interventions
    - There is insufficient direct evidence to make conclusions about the benefits or harms of acupuncture, thermal biofeedback, relaxation therapy, physical therapy, peripheral nerve blocks, and transcranial magnetic stimulation when used for treatment of primary headache during pregnancy.
    - No indirect evidence regarding harms of nonpharmacologic interventions in pregnancy was identified.

Background and Purpose

Primary headaches (i.e., conditions in which the headache itself is the disorder) are common in pregnancy and comprise four types: migraine, tension headache, cluster headache, and other trigeminal autonomic cephalgias (TACs). Although tension headaches are more common, migraine is by far the most common primary headache to present to clinical practice. Primary headache and its treatments can have significant consequences for the mother and fetus or infant. Given the heightened sensitivity about the potential impact of drugs on the fetus or infant, there is a tension between treatment decisions that might be best for the mother and those best for the fetus/infant. The uncertainty about the comparative effectiveness and harms of various treatment options underscores the importance of identifying effective interventions to treat primary headaches during pregnancy.

This systematic review (SR) aims to inform healthcare providers, policymakers, and the American College of Obstetricians and Gynecologists (ACOG) as developers of clinical guidance about currently available evidence on interventions for preventing or treating acute attacks of primary headaches in women who are pregnant (or attempting to become pregnant), postpartum, or breastfeeding. The SR addresses both pharmacologic and nonpharmacologic interventions for migraine, tension headache, cluster headache, and other TACs.

Methods

We used methods consistent with those outlined in the Agency for Healthcare Research and Quality's Evidence-based Practice Center Methods Guidance (https://effectivehealthcare.ahrq.gov/products/cer-methods-guide/overview). Our searches covered published and unpublished primary studies (direct evidence) and case reports (supplemental evidence) in women who are pregnant (or attempting to become pregnant), postpartum, or breastfeeding from database inception to June 5, 2020. For additional information on harms, we also searched for relevant SRs of interventions in women in the same phase, regardless of the indication for which the intervention was used (indirect evidence), from database inception to June 5, 2020.

Results

We found 16 primary studies (14,185 patients), representing direct evidence (3 randomized controlled trials, 8 nonrandomized comparative studies [i.e., observational studies that compared 2 or more interventions], and 5 single-group studies [i.e., studies without a comparison group]), and 26 SRs of interventions for any indication during pregnancy, representing indirect evidence. We also identified 19 case reports, representing supplemental evidence. Most primary studies enrolled patients with migraine and some with migraine and/or tension headache.

Table A provides a high-level summary of findings, summarized below.

Prevention—antiepileptics: There was insufficient direct evidence to make conclusions about harms of topiramate when used for migraine (one single-group study). However, we identified indirect evidence (i.e., systematic reviews regardless of indication) that carbamazepine, gabapentin, topiramate, and valproate use during pregnancy had increased fetal/child adverse effects (all moderate strength of evidence [SoE], except for gabapentin, which had low SoE). Lamotrigine may have a lower risk of adverse effects: no increased risk of spontaneous abortion, stillbirth, preterm birth, or congenital anomalies (moderate SoE), although increased risk of autism/dyspraxia but not other neurodevelopmental adverse effects (moderate SoE).

Prevention—other pharmacologic interventions: We identified no direct evidence. We identified indirect evidence (i.e., systematic reviews regardless of indication) that the following,

when used during pregnancy, were associated with fetal/child adverse effects: venlafaxine (a serotonin and norepinephrine reuptake inhibitor; moderate SoE), tricyclic antidepressants (moderate SoE), benzodiazepines (low SoE), beta blockers (moderate SoE), prednisolone (low SoE), and oral magnesium (low SoE). But, calcium channel blockers (any, but nifedipine in particular) (low to moderate SoE for specific adverse effects) and antihistamines (moderate SoE) had low risks of maternal or fetal/child adverse effects.

Prevention—nonpharmacologic interventions: We found no direct or indirect evidence.

Treatment—triptans, ergot products, nonsteroidal anti-inflammatory drugs (NSAIDs: naproxen), and antihistamines (pizotifen): Eight observational NRCSs addressed adverse effects of triptans, ergot products, naproxen, and pizotifen, but none reported on treatment effectiveness. Among the studies that adjusted for underlying differences between study groups, child neurodevelopmental, behavioral, and social outcomes did not differ between use of any triptan during pregnancy and use only before pregnancy, except for worse emotionality and activity outcomes at 3 years of age with triptan use during pregnancy (low SoE). Triptan use during pregnancy was not associated with spontaneous abortion, elective or induced abortion, or major or minor congenital anomalies, compared with nonuse (low SoE). An existing SR found that triptan use was not associated with spontaneous abortion (moderate SoE), preterm birth (low SoE), or major congenital anomalies (moderate SoE). We also identified indirect evidence (not focused on primary headaches) regarding NSAIDs: indomethacin may be associated with neonatal periventricular leukomalacia, intraventricular hemorrhage, and necrotizing enterocolitis (low SoE), but low-dose aspirin was *not* associated with maternal (moderate SoE) or fetal/child adverse effects (low SoE).

Treatment—antiemetics (dopamine receptor antagonists), antihistamines, and opioids: One RCT found that, compared with codeine, combination metoclopramide and diphenhydramine reduced migraine or tension headache severity and was more likely to resolve headache (low SoE). No serious maternal adverse effects occurred (low SoE). We also identified indirect evidence (i.e., systematic reviews regardless of indication) that antihistamines were not associated with serious fetal/child adverse effects (moderate SoE).

Treatment—other pharmacologic interventions: We did not find any direct evidence. We identified indirect evidence (i.e., systematic reviews regardless of indication) that use of the following interventions during pregnancy may be associated with fetal/child adverse effects: acetaminophen (low SoE), prednisolone (low SoE), ondansetron (a 5HT3 antagonist antiemetic) (moderate SoE), antipsychotics (low to moderate SoE), and intravenous magnesium (low SoE).

Treatment—nonpharmacologic interventions: There was insufficient direct evidence to make conclusions about thermal biofeedback (one RCT and two single-group studies), acupuncture (one RCT), relaxation therapy (one RCT and two single-group studies), physical therapy (one RCT and one single-group study), peripheral nerve blocks (one single-group study), and transcranial magnetic stimulation (one single-group study). We found no indirect evidence.

Limitations

Evidence for intervention benefits and harms was often sparse or absent. Entire classes, such as tricyclic antidepressants, beta blockers, and calcium channel blockers, were not identified in any primary study of pregnant patients with primary headache. Similarly, no primary study addressed entire classes of nonpharmacologic agents, such as hydration and chemodenervation (see full report for full lists). Most studies focused on patients with migraine. We deemed individual studies to have high or moderate risk of bias, most commonly due to lack of adjustment for confounders; lack of blinding of participants, personnel, and outcome assessors; and/or incomplete outcome data.

Implications and Conclusions

Evidence regarding the benefits and harms of interventions in women who are pregnant or breastfeeding is insufficient or of at best low strength of evidence. The paucity of evidence emphasizes the need for further primary research to identify effective and safe pharmacologic and nonpharmacologic interventions for primary headaches during pregnancy. Future studies should either randomize patients or adequately account for important confounders and evaluate important maternal outcomes, such as headache-related symptoms, quality of life, functional outcomes, and important fetal/child adverse outcomes; we found negligible data for these outcomes.

Table A. High-level summary of benefits and harms of interventions

KQ	Intervention Type	Intervention Class	Intervention	Comparator	Condition	Maternal Benefits	Maternal AEs	Fetal/ Child AEs
1	Pharm	Antiepileptics	Topiramate	None	Migraine	-	-	?? (I)
				Nonuse	Various	-	-	↑ (++)
			Carbamazepine	Nonuse	Various	-	-	↑ (++)
			Gabapentin	Nonuse	Various	-	-	↑ (+)
			Lamotrigine	Nonuse	Various	-	-	↑ (++)
			Valproate	Nonuse	Various	-	-	↑ (++)
			Gabapentin	Nonuse	Various	-	-	↑ (+)
		SNRIs	Venlafaxine	Nonuse	Various	-	-	↑ (++)
		Tricyclic antidepressants	Any	Nonuse	Various	-	-	↑ (++)
		Benzodiazepines	Any	Nonuse	Various	-	-	↑ (+)
		Beta blockers	Any	Nonuse	Various	-	~ (+)	↑ (++)
		Calcium channel blockers	Any	Nonuse	Various	-	~ (+)	~ (++)
			Nifedipine	Nonuse	Various	-	-	~ (++)
		Corticosteroids	Prednisolone	Nonuse	Various	-	-	↑ (+)
		Antihistamines	Any	Nonuse	Various	-	-	~ (++)
		Oral magnesium	Oral magnesium	Nonuse	Various	-	~ (+)	↑ (+)
	Nonpharm	-	-	-	-	-	-	-
2	Pharm	Triptans, Ergot products, and NSAIDs	Sumatriptan	Naratriptan	Migraine	-	-	?? (I)
			Sumatriptan	Sumatriptan + naratriptan	Migraine	-	-	?? (I)
			Naratriptan	Sumatriptan + naratriptan	Migraine	-	-	?? (I)
			Any triptan	Any ergot product	Migraine	-	-	?? (I)
			Any triptan	Pizotifen	Migraine	-	-	?? (I)
			Any ergot product	Pizotifen	Migraine	-	-	?? (I)
			Any triptan during pregnancy	Any triptan before pregnancy only	Migraine	-	?? (I)	↑ (+)
			Sumatriptan during pregnancy	Sumatriptan before pregnancy only	Migraine	-	?? (I)	?? (I)
			Any triptan during pregnancy	No triptan	Migraine	-	?? (I)	↑ (+)
		Antiemetics (Dopamine antagonists), Antihistamines, Opioid-like analgesics	Metoclopramide + Diphenhydramine	Codeine	Migraine or tension HA	Maternal benefit (+)	~ (+)	-
		NSAIDs	Any	Nonuse	Various	-	~ (++)	-

KQ	Intervention Type	Intervention Class	Intervention	Comparator	Condition	Maternal Benefits	Maternal AEs	Fetal/ Child AEs
			Indomethacin	Nonuse	Various	-	-	↑ (+)
			Low-dose aspirin	Nonuse	Various	-	~ (++)	~ (+)
		Antiemetics (5HT3 antagonists	Ondansetron	Nonuse	Various	-	-	↑ (++)
		Antipsychotics	Any	Nonuse	Various	-	-	↑ (++)
		Corticosteroids	Prednisolone	Nonuse	Various	-	-	↑ (++)
		Analgesics/ Antipyretics	Acetaminophen	Nonuse	Various	-	-	↑ (+)
		IV magnesium	IV magnesium	Nonuse	Various	-	↑ (+)	-
		Antihistamines	Any	Nonuse	Various	-	-	~ (++)
	Nonpharm	Complementary, behavioral, and physical therapy	Acupuncture	Routine care	Migraine	?? (I)	-	?? (I)
			Thermal biofeedback, relaxation, physical therapy	Thermal biofeedback	Migraine or tension HA	?? (I)	-	-
			Thermal biofeedback and relaxation therapy	None	Migraine	?? (I)	-	-
		Procedures	Peripheral nerve blocks	None	Migraine	?? (I)	?? (I)	-
		Noninvasive neuromodulation devices	Transcranial magnetic stimulation	None	Migraine	?? (I)	-	-

For interventions with evidence of an increased risk of any fetal/child AE and evidence of no increased risk or unknown risk of other fetal/child AEs, this table includes only the indicator for increased risk. Table 38 in the full report includes further details.

Abbreviations: AE = adverse effect, HA = headache, IV = intravenous, KQ = Key Question, Nonpharm = nonpharmacologic, NSAID = nonsteroidal anti-inflammatory drug, Pharm = pharmacologic, SNRI = serotonin and norepinephrine reuptake inhibitor.

↑ = Increase in adverse effects, ~ = No increase in adverse effects, ?? = Direction unknown, - = No evidence, I = Insufficient strength of evidence, + = Low strength of evidence, ++ = Moderate strength of evidence, +++ = High strength of evidence (none in Table).

Introduction

Background

Headache, one of the most common symptoms in the general population, is also common during pregnancy. Primary headaches are conditions where the headache itself is the disorder. In contrast, secondary headaches are caused by an underlying disorder, such as stroke, venous thromboembolism,[1, 2] and pituitary tumors.[3, 4] Management of secondary headache in pregnancy generally targets the underlying disorder, and, thus, is not the focus of this systematic review (SR).

Primary headaches that occur in pregnant women are classified into four types: migraine, tension headache, cluster headache, and other trigeminal autonomic cephalgias (TACs).[5] At the end of Appendix A, we have provided a glossary of terms and abbreviations used in this report. The lifetime prevalence of migraine disorder among pregnant women is approximately 30 percent.[6, 7] While tension headaches are most common in pregnant women in the population, migraine is by far the most common primary headache for which pregnant women seek care, accounting for about 90 percent of visits for primary headaches.[2] Tension headache is a less common reason for seeking care, and cluster headache and other TACs are rare.[8] Primary headaches can be pre-existing (i.e., they began before pregnancy) or can occur for the first time during pregnancy, postpartum, or while breastfeeding. The stress of pregnancy and imminent infant care may exacerbate the frequency and/or severity of primary headaches.

Both pre-existing and pregnancy-onset primary headaches can have significant consequences for the mother, the fetus/child, and mother-child bonding.[8] In addition to the symptoms themselves, primary headaches can lead to social consequences, including reduced productivity, loss of employment, financial detriment, and impacted family life, and clinical consequences, including depression, spontaneous abortion, preterm birth, and low birth weight.[9]

Although outside of pregnancy migraine frequency and severity often vary with a woman's menstrual cycle, during pregnancy the course of migraine frequency and intensity can be more variable. In some cases, hormonal fluctuations can precipitate attacks of migraine and can make them more severe,[10, 11] while in others, elevated estrogen and endogenous opioid levels can improve migraine symptoms and/or reduce their frequency.[12-14]

Management approaches for primary headaches may harm the fetus and breastfed newborn. From a diagnostic standpoint, radiation and/or contrast agents (primarily neuroimaging) may harm the fetuses of pregnant women.[15-17] From a treatment standpoint, decisions during pregnancy, postpartum, and breastfeeding need to be made after consideration of both potential benefits and harms, which poses major decisional dilemmas. Regarding treatment for acute attacks of migraine, many of the commonly-prescribed drugs with the highest level of evidence in the general population can be harmful during pregnancy. For example, nonsteroidal antiinflammatory drugs (NSAIDs) have been shown to be associated with a higher risk of spontaneous abortion (when used early in pregnancy) and of developmental malformations in the fetus, such as premature closure of the ductus arteriosus and oligohydramnios (when used in the third trimester).[18] Similarly, sodium valproate, a commonly-used antiepileptic drug for prevention of migraine attacks, is contraindicated in pregnancy due to its teratogenicity and adverse neurocognitive outcomes in the offspring.[19, 20]

Other therapies used outside of pregnancy, such as complementary and alternative therapies and biologic drugs (e.g., monoclonal antibodies), have unclear and/or mixed safety profiles during pregnancy and lactation. Therapies that are commonly used in patients with migraine during pregnancy include pharmacologic therapies, such as acetaminophen, antihistamines, caffeine, and magnesium. The first-line agents used for prophylaxis (i.e., migraine prevention) are beta blockers,

such as metoprolol; low-dose tricyclic antidepressants, such as amitriptyline; and oral magnesium supplements.[21] Metoclopramide, alone or in combination with other therapies, is frequently used for treatment of acute attacks, particularly in inpatient and emergency settings.[22-24] While other pharmacologic agents, such as low-dose aspirin and intravenous magnesium, that were used in the past are now less frequently prescribed. Other nonpharmacologic interventions for treatment and prophylaxis include hydration, physical therapy, and acupuncture. Pericranial nerve blocks, including occipital nerve blocks, are also increasingly used for treatment and prophylaxis against headaches in pregnancy.[25]

Management of the other types of primary headache also presents decisional dilemmas. While patients with tension headache respond best to NSAIDs, they can be treated with acetaminophen, although often with only moderate success. Because cluster headache and other TACs are rare and inadequately studied during pregnancy, little is known about ideal treatments and prophylactic strategies for them. While some subtypes of TACs, such as paroxysmal hemicrania, hemicrania continua, and primary stabbing headache, respond to indomethacin (an NSAID), this drug is contraindicated in the latter phases of pregnancy. Little is known about nonpharmacologic treatments for primary headaches during pregnancy.

Unique aspects of the pregnancy and postpartum phases present challenges for managing primary headaches. Given the heightened sensitivity about the impact of pharmacotherapy on the developing fetus or breastfed infant, there is a tension between treatment decisions that might be best for the mother's health and those that might be best for the fetus/infant. Regardless of treatment, migraine during pregnancy has been shown to be associated with various adverse maternal outcomes, such as preeclampsia, hypertension, pulmonary embolism, stroke, myocardial infarction, unplanned cesarean section, and adverse neonatal outcomes, including preterm birth, low birth weight, and respiratory distress.[9] Sound risk-benefit assessments that optimize the health of both mother and fetus/child require clinical expertise and careful shared decision making between providers and patients.

The stresses on women during pregnancy and the ethical challenges in designing studies in this population have been obstacles to conducting studies to identify the most effective and safest therapies for these women and their offspring. Uncertainty about the comparative effectiveness and harms among various treatment options has meant that specific clinical practice guidelines for management of primary headaches during pregnancy do not exist. Existing guidelines on perinatal care from organizations, such as the American Academy of Pediatrics (AAP) and the American College of Obstetricians and Gynecologists (ACOG), do not discuss primary headaches.[26] Existing guidelines on the management of headache from the American Headache Society (AHS) do not discuss pregnancy.[27-29] To address the gap related to the overlap of primary headaches and pregnancy, ACOG nominated this SR.

Purpose and Scope of the Systematic Review

This SR assesses the prevention and acute treatment of primary headaches during pregnancy, postpartum, and breastfeeding. Specifically, the SR assesses: (1) the (comparative) benefits and harms of pharmacologic and nonpharmacologic interventions to *prevent* attacks of primary headache in women who have a history of primary headache and are pregnant (or attempting to become pregnant, i.e., in the preconception phase), postpartum, or breastfeeding; and (2) the (comparative) benefits and harms of pharmacologic and nonpharmacologic interventions to *treat* acute attacks of primary headache in women who are pregnant (or attempting to become pregnant), postpartum, or breastfeeding. The intended audience for this SR includes guideline developers, clinicians, and other providers of care for women with primary headaches and are pregnant, postpartum, and

breastfeeding. ACOG nominated the topic of this SR. The findings of this SR are intended to be used in development of ACOG clinical guidance.

Methods

Review Approach

The Evidence-based Practice Center conducted this systematic review (SR) based on the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews (available at https://effectivehealthcare.ahrq.gov/products/cer-methods-guide/overview). This SR is reported in accordance with the Preferred Items for Reporting in Systematic Reviews and Meta-Analyses (PRISMA),[30] A Measurement Tool to Assess Systematic Reviews (AMSTAR 2),[31] and any relevant extension statements.

The topic of this report and preliminary Key Questions (KQs) arose through a process involving the public and AHRQ (https://effectivehealthcare.ahrq.gov/about/epc/nomination/). Initially, a panel of Key Informants gave input on the KQs, including the outcomes, to be examined. AHRQ then posted these KQs and solicited public comment through its Effective Health Care (EHC) Program website (March 22, 2019, for 3 weeks) and on the Federal Register (November 22, 2019, for 1 month). AHRQ did not receive any comments. A Technical Expert Panel provided high-level content and methodological expertise throughout development of the SR protocol. The final protocol was posted on the EHC website at https://effectivehealthcare.ahrq.gov/products/headaches-pregnancy/protocol on November 12, 2019. We registered the protocol for this systematic review in PROSPERO (registration number CRD42020158310).

Key Questions

KQ 1:

What are the (comparative) benefits and harms of interventions *to prevent* attacks of primary headache in women who have a history of primary headache and are pregnant (or attempting to become pregnant), postpartum, or breastfeeding?

- **KQ 1a.** Do the (comparative) benefits and harms vary by phase (i.e., preconception, first trimester of pregnancy, second trimester of pregnancy, third trimester of pregnancy, postpartum, breastfeeding)?
- **KQ 1b.** Do the (comparative) benefits and harms vary by type of primary headache (i.e., migraine, tension headache, cluster headache, and other trigeminal autonomic cephalgias)?

KQ 2:

What are the (comparative) benefits and harms of interventions *to treat* acute attacks of primary headache in women who are pregnant (or attempting to become pregnant), postpartum, or breastfeeding?

- **KQ 2a.** Do the (comparative) benefits and harms vary by phase (i.e., preconception, first trimester of pregnancy, second trimester of pregnancy, third trimester of pregnancy, postpartum, breastfeeding)?
- **KQ 2b.** Do the (comparative) benefits and harms vary by type of primary headache (i.e., migraine, tension headache, cluster headache, and other trigeminal autonomic cephalgias)?

Contextual Question:

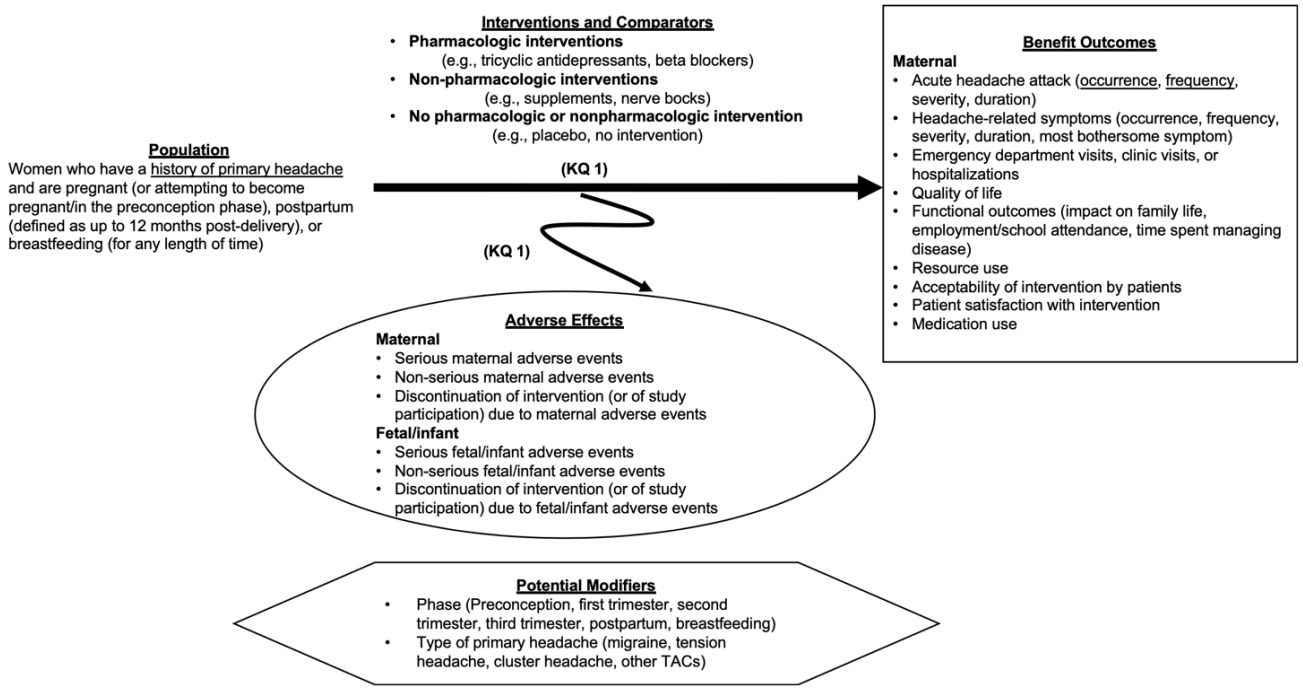
What is the available evidence concerning levels in maternal serum/blood, fetal/child serum/blood, breast milk, amniotic fluid, meconium, cord blood, or child urine of drugs used

to prevent or treat attacks of primary headache in women who are pregnant (or attempting to become pregnant), postpartum, or breastfeeding?

Analytic Frameworks

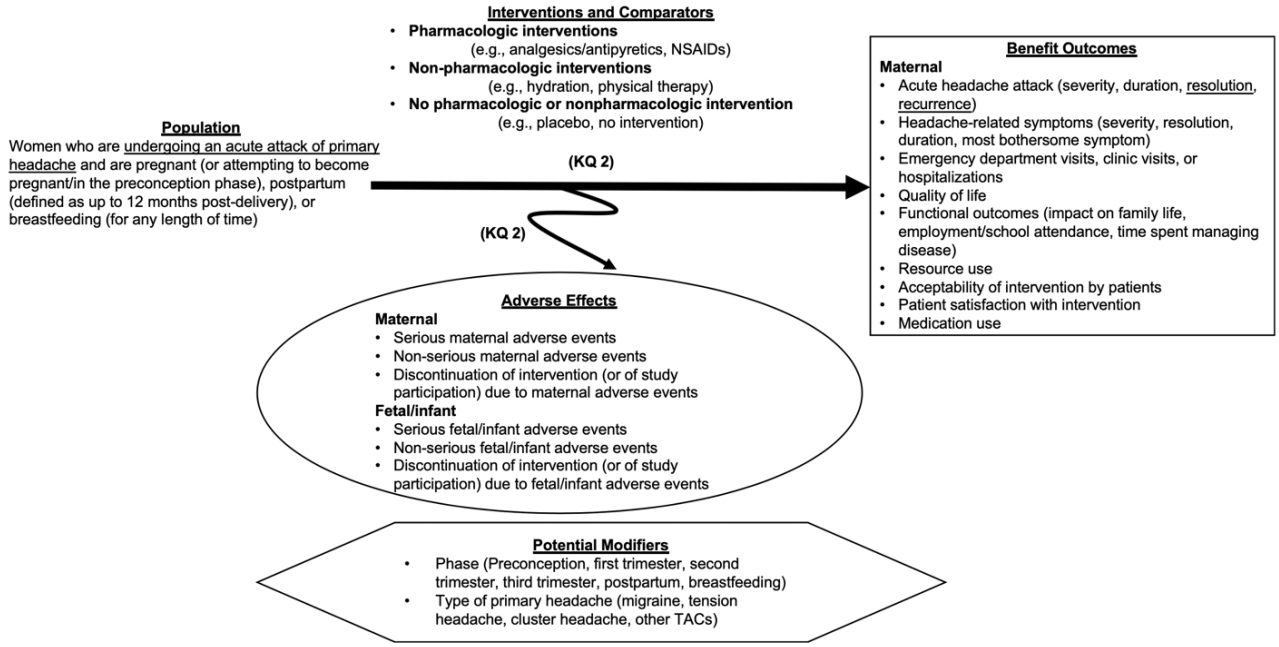
Figures 1 and 2 provide the analytic frameworks for KQs 1 and 2, respectively.

Figure 1. Analytic framework for KQ 1: Interventions to prevent attacks of primary headache during pregnancy, postpartum, and breastfeeding



Abbreviations: KQ = Key Question, TAC = trigeminal autonomic cephalgia.
Underlined text in regular font refers to aspects that are distinct to KQ 1.

Figure 2. Analytic framework for KQ 2: Interventions to treat attacks of primary headache during pregnancy, postpartum, and breastfeeding



Abbreviations: KQ = Key Question, NSAID = nonsteroidal anti-inflammatory drug, TAC = trigeminal autonomic cephalgia.
Underlined text in regular font refers to aspects that are distinct to KQ 2.

Study Selection

Appendix A provides full details on all search strategies, inclusion and exclusion criteria, and screening processes (for all types of evidence described above).

Direct Evidence (Primary Studies)

We searched for published primary studies for both KQs in Medline® (via PubMed®), Embase®, the Cochrane Central Register of Clinical Trials, and CINAHL®, and for unpublished studies in ClinicalTrials.gov. Searches were current as of June 5, 2020.

For KQ 1 (prevention), the population of interest was women who were pregnant (or attempting to become pregnant), postpartum, or breastfeeding and had a history of, but were not currently undergoing, an attack of primary headache (migraine, tension headache, cluster headache, or other trigeminal autonomic cephalgias [TACs]) in any setting. We were interested in various pharmacologic and nonpharmacologic interventions used to prevent primary headaches (irrespective of their approval status by the U.S. Food and Drug Administration or their availability in the U.S.), and their association with various effectiveness outcomes (for the mother, such as headache onset and functional outcomes) and harms (for the mother, such as cardiovascular adverse effects, and for the fetus/child, such as spontaneous abortion, congenital anomalies, and neurodevelopmental adverse effects) at any time. Randomized controlled trials (RCTs), nonrandomized comparative studies (NRCSs: prospective or retrospective cohort studies comparing two or more interventions), single-group studies (prospective or retrospective, without a comparison group), case control studies, and cross-sectional studies or surveys were eligible. Our criteria for KQ 2 (treatment) differed from

KQ 1 in that eligible patients were undergoing an ongoing attack of primary headache. Thus, the interventions and outcomes differed somewhat between the KQs.

Indirect Evidence (Systematic Reviews of Harms, Regardless of Indication)

For additional information about harms from the primary studies for both KQs, we searched for published SRs that have reported adverse effects to mother or child of interventions used in women who are pregnant, postpartum, or breastfeeding, regardless of the indication for which the intervention was used. To identify SRs, we searched Medline, the Cochrane Database of Systematic Reviews, and Epistemonikos through June 5, 2020. We did not enforce a date restriction when screening for eligible SRs, but we required that, at a minimum, SRs should have fulfilled each of the following four criteria:

1. Specified eligibility criteria for primary studies;
2. Conducted a comprehensive search (defined as searched at least two electronic databases and searched for unpublished studies through at least one source);
3. Assessed risk of bias in included studies using any instrument; and
4. Used appropriate methods for meta-analysis, if conducted.

Supplemental Evidence (Case Reports)

We included case reports as supplemental evidence only. From these, we simply report what occurred to individual patients in terms of headache progression and adverse effects (neither of which can be ascribed to individual interventions in case reports). We did not use case reports to inform conclusions in this SR. Instead, we separately summarized the supplemental evidence (briefly at the end of the Results section and in more detail in the Appendix B).

Data Extraction and Risk of Bias Assessment

For all types of evidence (primary studies, SRs, and case reports), one researcher extracted and entered data, which were confirmed by a second, independent researcher. We assessed risk of bias of the primary studies (but not case reports) and quality of the SRs using currently recommended study design-specific tools.

Direct Evidence (Primary Studies)

For RCTs, we used the Cochrane Risk of Bias Tool.[32] For NRCSs (whether prospective or retrospective cohort studies) and case-control studies, we used specific items of the Risk of Bias in Nonrandomized Studies of Interventions (ROBINS-I) tool[33] that pertain to confounding and selection bias, and items from the Cochrane Risk of Bias tool that relate to blinding, incomplete outcome data, selective outcome reporting, and other issues that could be related to bias. For single-group studies (i.e., noncomparative interventional studies, also known as single-arm studies), we used items from the Cochrane Risk of Bias tool that relate to participant loss to followup, selective outcome reporting, and other issues that could be related to bias. For all study designs, we also used items from the National Heart, Lung, and Blood Institute (NHLBI) tool focusing on the adequacy of descriptions of study eligibility criteria, interventions, and outcomes.[34]

Indirect Evidence (Systematic Reviews of Harms, Regardless of Indication)

We assessed the quality of the SRs using specific items from the A Measurement Tool to Assess Systematic Reviews, version 2 (AMSTAR 2).[31]

Data Synthesis and Analysis

In consultation with a panel of invited Key Informants and members of a Technical Expert Panel, we identified relevant outcomes and prioritized some outcomes for strength of evidence (SoE) assessment. Where appropriate, we calculated between-arm effect sizes based on reported within-arm data. Because of the overall paucity of evidence identified, our approach to synthesis was qualitative. The evidence base did not allow for meta-analysis.

Where applicable, we compared data reported in the direct evidence (i.e., primary studies) with data reported in the indirect evidence (i.e., SRs).

Grading the Strength of the Body of Evidence

We graded the SoE in both the direct evidence and the indirect evidence as per the AHRQ Methods Guide.[35, 36] The SoE for each conclusion is based on a qualitative combination of the summary risk of bias across all relevant studies, the consistency of the studies, the precision of the available estimates, and the directness of the evidence. When only one study addressed a given comparison, it was not possible to evaluate consistency. When only single-group studies addressed a given comparison, estimates were rated as indirect because of the lack of direct comparisons of interest. Although there was some variability in the definitions of various outcomes, such as pain severity, we deemed these to be sufficiently minor so as not to affect directness.

We graded SoE for acute headache attacks, headache-related symptoms, emergency department or clinic visits, hospitalizations, quality of life, serious maternal adverse effects or discontinuation of intervention (or of study participation) due to maternal adverse effects, and serious fetal/child adverse effects or discontinuation of intervention (or of study participation) due to fetal/child adverse effects. As noted, we did not use case reports to make conclusions, and, thus, we did not consider the case reports in the SoE assessments.

Basis for Conclusions

For each class of interventions for each KQ, we have based our conclusions regarding benefits and harms on: (1) the direct evidence—primary studies (not case reports) conducted in patients who were pregnant (or attempting to become pregnant), postpartum, or breastfeeding *with primary headache*; and (2) the indirect evidence—existing SRs of studies conducted in patients who were pregnant (or attempting to become pregnant), postpartum, or breastfeeding *regardless of indication*. In the one instance where we found a SR in this population of patients with primary headache (on triptan use), we have denoted that evidence as “SR Evidence” because it focused on our population of interest.

Results

Description of Included Evidence

Organization of Chapter

We have organized the Results Chapter by type of evidence (direct, indirect, and supplemental), as follows:

- **Direct Evidence (Primary Studies) and Indirect Evidence (Systematic Reviews [SRs] of Harms, Regardless of Indication)**: We describe the direct evidence and the indirect evidence because we use both these types of evidence to inform our conclusions. We have organized this first section, by Key Question (KQ) (first prevention [KQ 1], then treatment [KQ 2]). For each KQ, we provide Key Points. Subsections within KQs are organized by type of intervention (i.e., pharmacologic and nonpharmacologic, and within types, guided by the research identified, by groupings of intervention classes and comparisons). Each subsection includes the following components (in order):
  - A description of the direct evidence
  - A description of the indirect evidence
  - Results for maternal benefit and maternal and fetal/child harm outcomes
  - Where applicable, a comparison of how the harms reported in the direct evidence compare with those reported in the indirect evidence
  - A summary table of results from the direct evidence
  - An evidence profile (with strength of evidence [SoE]) of the direct evidence
  - A summary table of statistically significant adverse effects (harms) from the indirect evidence
  - An evidence profile (with SoE) of the indirect evidence.

  Detailed findings from the direct evidence (i.e., primary studies), including tables for study designs and arms, risk of bias, and all outcomes are in Appendix B. We call attention to specific Appendix Table numbers in the relevant subsections. Detailed findings from the indirect evidence (i.e., SRs regardless of indication), including tables for SR design and arms, SR quality, and all reported adverse effects (either statistically significant or otherwise) are also in Appendix B.
- **Supplemental Evidence (Case Reports)**: We provide a brief summary of the findings from the supplemental evidence (case reports). This summary is organized by KQ, and within each KQ, by type of outcomes (benefit outcomes versus harms). Details about the individual case reports and detailed tables are in Appendix B.

Literature Search Results

We conducted two separate literature searches – one for the primary studies and case reports, and the other for SRs. The electronic literature search for primary studies and case reports, combined with a handsearch of existing SRs, yielded 8,549 citations. The search for SRs yielded 2,788 citations.

In total, 16 primary studies (direct evidence), 26 SRs (indirect evidence), and 19 case reports (supplemental evidence) met criteria.

The 16 included primary studies, published between 1990 and 2018, comprised three randomized controlled trials (RCTs) (reported in five articles[37-41]), eight nonrandomized comparative studies

(NRCSs) (observational cohort studies, reported in 16 articles[42-57]), and five single-group studies (reported in six articles[25, 38, 58-61]). Of note, one article reported both an RCT and a single-group study (Marcus 1995).[38] The 16 primary studies included a total of 14,185 patients, all of whom were pregnant. No studies examined women who were attempting to become pregnant or who were postpartum or breastfeeding. The 16 included studies comprised three RCTs with 138 patients (ranging from 25 to 70 patients each), eight NRCSs with 13,907 patients (ranging from 123 to 5,900 patients each), and five single-group studies with 121 patients (ranging from 3 to 240 patients each). Table B-1 summarizes the design and arm details of all 16 primary studies. Tables B-2, B-3, B-4, and B-5 summarize the risk of bias assessment of all 16 primary studies.

The 26 included SRs, published between 2000 and 2020, assessed harms of pharmacologic interventions used during pregnancy (Table B-25), regardless of indication.[62-90] These included eight SRs that assessed nonsteroidal anti-inflammatory drugs (NSAIDs),[64, 66, 67, 70, 73-75, 81] two that assessed antiepileptics,[87-89] two that assessed beta blockers,[62, 90] two that assessed calcium channel blockers,[62, 65] two that assessed antiemetics (5HT3 antagonists),[76, 85] two that assessed antipsychotics,[68, 86] two that assessed antihistamines,[72, 77] and one each that assessed serotonin and norepinephrine reuptake inhibitors (SNRIs),[82, 83] tricyclic antidepressants,[82, 83] benzodiazepines,[69, 71] corticosteroids,[84] oral magnesium,[78] triptans,[79] analgesics/antipyretics,[80] and intravenous magnesium.[63] Only one of the 26 SRs, which addressed triptans,[79] was focused on studies of pregnant women with primary headache (migraine); the remaining 25 SRs included studies of pregnant women with various conditions. Twelve of the 26 SRs reported maternal adverse effects, and 23 reported fetal/child adverse effects.

Table B-25 summarizes the characteristics and arm details of all 26 SRs. Table B-26 summarizes the quality assessment of all 26 SRs (assessed using AMSTAR 2). Tables providing the adverse effects with statistically significant effect sizes, suggesting evidence of drug harms, are included within the descriptions of each intervention class in this report. Tables B-27 and B-28 provide the complete lists of maternal and fetal/child adverse effects, respectively, that were reported in the 26 SRs.

Details of the 19 included case reports[91-109] are provided in Tables B-29 and B-30.

Further details about the literature searches; included primary studies, SRs, and case reports; and excluded primary studies, SRs, and case reports (with reasons for their exclusion) are in Appendix B.

Direct Evidence (Primary Studies) and Indirect Evidence (Systematic Reviews of Harms, Regardless of Indication)

Key Question 1: Prevention of Primary Headache

Key Points

- No *direct or indirect evidence* evaluated the beneficial effects of interventions to prevent primary headache in women who are pregnant (or attempting to become pregnant), postpartum, or breastfeeding.
- There is insufficient *direct evidence* (studies of pregnant women with primary headaches) to make conclusions about the harms of **topiramate** during pregnancy (but see indirect evidence below).
- *Indirect evidence* (SRs of use during pregnancy regardless of indication) found that:
  - The following pharmacologic interventions have increased risks of maternal or fetal/child adverse effects:

        - **Antiepileptics**:
            - ◊ **Topiramate**: Increased risk of fetal death or spontaneous abortion (combined), fetal growth restriction, cleft lip/palate, and other major congenital anomalies (moderate SoE)
            - ◊ **Carbamazepine**: Increased risk of major and minor congenital anomalies (moderate SoE)
            - ◊ **Gabapentin**: Increased risk of congenital cardiovascular anomalies, hypospadias, and psychomotor developmental delay (low SoE)
            - ◊ **Lamotrigine**: Increased risk of autism/dyspraxia, but not other adverse effects (moderate SoE)
            - ◊ **Valproate**: Increased risk of fetal death or spontaneous abortion, major congenital malformations, cleft lip/palate, developmental delays, and autism/dyspraxia (moderate SoE)
        - **Venlafaxine**: Increased risk of preterm birth (moderate SoE)
        - **Tricyclic antidepressants (any)**: Increased risk of small for gestational age, major congenital anomalies, cardiovascular anomalies, neonatal convlusions, and neonatal respiratory distress, but not low birth weight (moderate SoE)
        - **Benzodiazepines (any)**: Increased risk of oral cleft and other major congenital anomalies (low SoE)
        - **Beta blockers (any)**: Increased risk of cardiovascular anomalies, cleft lip/palate, and neural tube defects, but no increased risk of preterm birth (moderate SoE)
        - **Prednisolone**: Increased risk of oral clefts, but not other major congenital anomalies (low SoE)
        - **Oral magnesium**: Increased risk of neonatal death, but not low birth weight (low SoE). No increased risk of maternal adverse effects (low SoE).
    - The following pharmacologic interventions have no increased risk of maternal or fetal/child AEs:
        - **Calcium channel blockers (any)**: No increased risk of maternal (low SoE) or fetal/child adverse effects (low to moderate SoE)
        - **Calcium channel blockers (nifedipine)**: No increased risk of fetal/child adverse effects (low to moderate SoE)
        - **Antihistamines (any)**: No increased risk of spontaneous abortion, stillbirth, preterm birth, low birth weight, or major congenital anomalies (moderate SoE)
- No *direct or indirect evidence* evaluated **nonpharmacologic interventions** to prevent primary headaches in women who are pregnant (or attempting to become pregnant), postpartum, or breastfeeding.

Only one of the 16 primary studies included in this SR (direct evidence) addressed prevention of primary headaches. This study, a single-group study, addressed a pharmacologic intervention – topiramate (an antiepileptic).[59] No primary studies addressed nonpharmacologic interventions for prevention.

Eleven existing SRs (indirect evidence) addressed interventions relevant to KQ 1. These included: antiepileptics, serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, benzodiazepines, beta blockers, calcium channel blockers, corticosteroids, antihistamines, and oral magnesium. No SRs addressed nonpharmacologic interventions used for prevention.

Key Question 1: Pharmacologic Interventions To Prevent Attacks of Primary Headache

Antiepileptics

Description of Direct Evidence for Antiepileptics

One retrospective single-group study reported the harms of an antiepileptic drug (topiramate) in pregnant patients with primary headache (Tables 1 and 2 and Tables B-1, B-5, B-6, and B-31).[59] The study did not report the drug's effect in preventing migraine.

Castilla-Puentes 2014 studied 81 pregnant women with a history of migraine in the U.S., U.K., Canada, Australia, and 36 other countries.[59] The patients received topiramate, but its dose, duration, route, and frequency were not reported. Patient age, race, trimester, gestational age, and parity were also not reported. We assessed the study at overall low risk of bias.

Description of Indirect Evidence for Antiepileptics

Two high-quality SRs (Veroniki 2017 [reported in two articles][87, 88] and Weston 2016[89]) assessed harms associated with antiepileptic use during pregnancy (regardless of indication) (Tables 3 and 4 and Tables B-26, B-27, B-28, and B-37).

Each of the SRs assessed five antiepileptics: valproate, topiramate, gabapentin, carbamazepine, and lamotrigine. Veroniki 2017 conducted a network meta-analysis, but Weston 2016 did not. Veroniki 2017 was thus able incorporate more studies (96 studies) than Weston 2016 (50 studies). We therefore summarize harms reported in Veroniki 2017 and supplement additional harms that were reported only in Weston 2016.

Maternal Benefit Outcomes of Antiepileptics

No primary study or SR reported on maternal benefit outcomes of antiepileptics.

Maternal Adverse Effects of Antiepileptics

No primary study or SR reported on maternal adverse effects of antiepileptics.

Fetal/Child Adverse Effects of Antiepileptics

In Castilla-Puentes 2014 (direct evidence), among the 81 pregnant women treated with topiramate to prevent migraines, 23 women (28.4%) lost their fetuses due to **spontaneous abortion** and another 10 women (12.3%) underwent **elective or induced abortion** (Table 1).

Castilla-Puentes 2014 also reported that, among the 81 infants exposed to topiramate during pregnancy (being used to prevent migraines), 10 infants (12.3%) had **congenital anomalies**. Two infants (2.5%) had cleft palate. The following anomalies were found in one infant (1.2%) each: hydrocephalus, meningomyelocele, spina bifida, an unspecified cardiovascular congenital anomaly, syndactyly, polydactyly, gastrointestinal obstruction, and pyloric stenosis (Table 1).

Fetal/Child Adverse Effects Reported in Indirect Evidence

Topiramate: Topiramate use was associated with **fetal death or spontaneous abortion** (odds ratio [OR] 23.6, 95% confidence interval [CI] 1.2 to 549.6), **fetal growth restriction** (OR 2.64, 95% CI 1.41 to 4.63), **major congenital anomalies** (OR 1.90, 95% CI 1.17 to 2.97), and **cleft lip/palate** (OR 6.12, 95% CI 1.89 to 19.05) (Table 3). Topiramate use was associated with hypospadias (OR 3.52, 95% CI 0.77 to 15.72), cognitive developmental delay (OR 3.14, 95% CI 0.45 to 16.53), and

psychomotor developmental delay (OR 3.89, 95% CI 0.41 to 24.27), but these were not statistically significant. However, topiramate use was not associated with congenital skeletal or limb defects.

Carbamazepine: Carbamazepine use was associated with **major congenital anomalies** (OR 1.37, 95% CI 1.10 to 1.71) and **minor congenital anomalies** (OR 10.8, 95% CI 1.4 to 373.9) (Table 3). Carbamazepine was also associated with cognitive developmental delay (OR 2.07, 95% CI 0.82 to 5.48), autism/dyspraxia (OR 5.76, 95% CI 0.76 to 73.43), language delay (OR 4.32, 95% CI 0.81 to 26.93), and attention deficit hyperactivity disorder (OR 2.32, 95% CI 0.70 to 7.86), but none of the ORs for these individual adverse effects were statistically significant.

Gabapentin: Gabapentin was associated with **congenital cardiovascular anomalies** (OR 5.98, 95% CI 1.34 to 19.73), **hypospadias** (OR 16.5, 95% CI 2.5 to 121.7), and **psychomotor developmental** delay (OR 9.03, 95% CI 1.00 to 62.78) (Table 3). Gabapentin was associated with cleft lip/palate (OR 5.14, 95% CI 0.16 to 38.06), club foot (OR 5.55, 95% CI 0.01 to 165.5), and inguinal hernia (OR 10.86, 95% CI 0.02 to 282.60), but these were not statistically significant.

Lamotrigine: There was no association between lamotrigine use and *in utero* (e.g., fetal death or spontaneous abortion [combined], fetal growth restriction), perinatal (e.g., preterm birth), or neonatal (e.g., congenital anomalies, inguinal hernia) adverse effects. Lamotrigine use was, however, associated with **autism/dyspraxia** (OR 8.88, 95% CI 1.28 to 112.0) (Table 3). Lamotrigine use was associated with language delay, but this was not statistically significant (OR 4.36, 95% CI 0.68 to 25.41).

Valproate: Valproate use was associated with increased fetal/child harms. These included **fetal death or spontaneous abortion (combined)** (OR 1.83, 95% CI 1.04 to 3.45), **congenital anomalies** (ORs exceeding 3.0), **neural tube defects** (RR 5.30, 95% CI 1.05 to 26.70), **hypospadias** (OR 2.58, 95% CI 1.24 to 5.76), **cleft lip/palate** (OR 3.26, 95% CI 1.38 to 7.57), **club foot** (OR 3.26, 95% CIC 1.38 to 7.57), and **minor anomalies** (OR 17.8, 95% CI 1.6 to 633.3). Valproate was also associated with **cognitive developmental delay**, **autism/dyspraxia**, **psychomotor developmental delay**, and **language delay** (all ORs exceeding 4) (Table 3).

Table 1. Antiepileptics: Summary of direct evidence regarding use to prevent primary headaches

Outcome*	Outcome Definition	Study, Year, Design, PMID	Intervention	n/N (%)
AEs – Spontaneous abortion or elective or induced abortion	Spontaneous abortion	Castilla-Puentes, 2014, Single-group study, 24598456	Topiramate	23/81 (28.4)
AEs – Elective or induced abortion	Elective or induced abortion			10/81 (12.3)
AEs – Fetal/child serious congenital anomalies	Any			10/81 (12.3)
	Various neurological, cardiovascular, malformations, gastrointestinal anomalies			Each either 1/81 (1.2) or 2/81 (2.5)

Abbreviations: AE = adverse effect, CS = cesarean section, PMID = PubMed identifier.

* No studies reported acute headache attack outcomes (occurrence, frequency, severity, duration), headache-related symptom outcomes (occurrence, frequency, severity, duration), emergency department or clinic visits, hospitalizations, quality of life, functional outcomes (impact on family life, work/school attendance, time spent managing disease), resource use, acceptability of intervention by patients, patient satisfaction with intervention, medication use, serious maternal AEs (any serious AE, cardiovascular), nonserious maternal AEs (any nonserious, nonobstetrical, preterm labor/CS, reduced breast milk, medication withdrawal symptoms), discontinuation due to maternal AEs, serious fetal/child AEs (any serious AE, stillbirth or fetal death, neonatal or infant death, preterm birth, low birth weight, perinatal complications, neurodevelopmental/behavioral/social), nonserious fetal/child AEs (any nonserious AE, breastfeeding delay/cessation/etc., poor infant attachment/bonding, medication withdrawal symptoms), or discontinuation due to fetal/child AEs.

Table 2. Antiepileptics: Evidence profile for direct evidence regarding use to prevent primary headaches

Topic	Comparison	Outcome	N Studies (Subjects)	RoB	Consistency	Precision	Directness	SoE	Conclusion
Benefits	-	-	0	-	-	-	-	None	None
Harms	Topiramate (no comparison)	Spontaneous abortion or elective or induced abortion	1 (81)	Low	N/A	Imprecise	Indirect	Insufficient	No conclusion made
		Fetal/child serious congenital anomalies	1 (81)	Low	N/A	Imprecise	Indirect	Insufficient	No conclusion made

Abbreviations: N/A = not applicable, RoB = risk of bias, SoE = strength of evidence.

Consistency was deemed N/A when it could not be assessed because only one study was one found.

Table B-31 provides the complete version of this Evidence Profile, including displaying outcomes for which no studies were identified.

Table 3. Antiepileptics: Summary of indirect evidence of fetal/child harms, statistically significant findings

SR, Year Published, PMID	Drug Class	Drug Name	Timing of Occurrence of Adverse Effect	Adverse Effect	N Studies	Effect Size (95% CI)
Veroniki, 2017, 28472982	Antiepileptics: Multiple mechanisms	Topiramate	*In utero*	Fetal death or spontaneous abortion (combined)	96	OR 23.6 (1.2, 549.6)
				Fetal growth restriction	96	OR 2.64 (1.41, 4.63)
			Neonatal	Congenital anomalies, Major	96	OR 1.90 (1.17, 2.97)
				Congenital anomalies, Cleft lip/palate	96	OR 6.12 (1.89, 19.1)
	Antiepileptic: Sodium channel modulators	Carbamazepine	Neonatal	Congenital anomalies, Major	96	OR 1.37 (1.10, 1.71)
				Congenital anomalies, Minor	96	OR 10.8 (1.4, 373.9)
	Antiepileptics: Calcium channel modulators	Gabapentin	Neonatal	Congenital anomalies, Cardiovascular	96	OR 5.98 (1.34, 19.7)
				Congenital anomalies, Hypospadias	96	OR 16.5 (2.5, 121.7)
			Child	Psychomotor developmental delay	96	OR 9.03 (1.00, 62.78)
	Antiepileptic: Sodium channel modulator	Lamotrigine	Child	Autism/dyspraxia	96	OR 8.88 (1.28, 112.0)
	Antiepileptics: Multiple mechanisms	Valproate	*In utero*	Fetal death or spontaneous abortion (combined)	96	OR 1.83 (1.04, 3.45)
			Neonatal	Congenital anomalies, Major	96	OR 3.04 (1.23, 7.07)
				Congenital anomalies, Hypospadias	96	OR 2.58 (1.24, 5.76)
				Congenital anomalies, Cleft lip/palate	96	OR 3.26 (1.38, 7.57)
				Congenital anomalies, Club foot	96	OR 3.26 (1.43, 8.25)
				Congenital anomalies, Minor	96	OR 17.8 (1.6, 633.3)
			Child	Cognitive developmental delay	96	OR 7.40 (3.00, 18.46)
				Autism/dyspraxia	96	OR 17.29 (2.40, 217.6)
				Psychomotor developmental delay	96	OR 4.16 (2.04, 8.75)
				Language delay	96	OR 7.95 (1.50, 49.1)
Weston, 2016, 27819746	Antiepileptics: Multiple mechanisms	Valproate	Neonatal	Congenital anomalies, Neural tube defects	6	RR 5.30 (1.05, 26.7)
				Congenital anomalies, Orofacial clefts	6	RD 0.03 (0.01, 0.05)

Abbreviations: CI = confidence interval, OR = odds ratio, PMID = PubMed identifier, RD = risk difference, RR = relative risk, SR = systematic review.

Table 4. Antiepileptics: Evidence profile for indirect evidence regarding harms of use during pregnancy

Drug	Outcome Category	Outcome	N SRs (N Studies)	RoB in Included Studies	Consistency	Precision	Directness	SoE	Conclusions
Topiramate	AEs – Fetal/ Child	Any	1 (96)	Low to moderate	Consistent	Precise	Indirect	Moderate	Increased fetal growth restriction
		Spontaneous abortion or elective or induced abortion	1 (96)	Low to moderate	Consistent	Precise	Indirect	Moderate	Increased spontaneous abortion
		Stillbirth or fetal death	1 (96)	Low to moderate	Consistent	Precise	Indirect	Moderate	Increased fetal death
		Preterm birth	1 (96)	Low to moderate	Consistent	Precise	Indirect	Moderate	No increased risk
		Congenital anomalies	1 (96)	Low to moderate	Consistent	Precise	Indirect	Moderate	Increased major anomalies and cleft lip/palate
		Neurodevelopmental/ behavioral/social	1 (96)	Low to moderate	Consistent	Imprecise	Indirect	Low	No increased risk of cognitive or developmental delays
Carba-mazepine	AEs – Fetal/ Child	Spontaneous abortion or elective or induced abortion	1 (96)	Low to moderate	Consistent	Precise	Indirect	Low	No increased risk
		Stillbirth or fetal death	1 (96)	Low to moderate	Consistent	Precise	Indirect	Low	No increased risk
		Preterm birth	1 (96)	Low to moderate	Consistent	Precise	Indirect	Low	No increased risk
		Congenital anomalies	1 (96)	Low to moderate	Consistent	Precise	Indirect	Moderate	Increased major and minor anomalies
		Neurodevelopmental/ behavioral/social	1 (96)	Low to moderate	Consistent	Precise	Indirect	Low	No increased risk
Gabapentin	AEs – Fetal/ Child	Any	1 (96)	Low to moderate	Consistent	Imprecise	Indirect	Low	No increased risk of fetal growth restriction
		Preterm birth	1 (96)	Low to moderate	Consistent	Precise	Indirect	Low	No increased risk
		Congenital anomalies	1 (96)	Low to moderate	Inconsistent	Imprecise	Indirect	Low	Increased cardiovascular anomalies and hypospadias, but not cleft lip/palate or club foot
		Neurodevelopmental/ behavioral/social	1 (96)	Low to moderate	Inconsistent	Precise	Indirect	Low	Increased psychomotor developmental delay, but not cognitive developmental delays
Lamotrigine	AEs – Fetal/ Child	Any	1 (96)	Low to moderate	Consistent	Precise	Indirect	Moderate	No increased risk
		Spontaneous abortion or elective or induced abortion	1 (96)	Low to moderate	Consistent	Precise	Indirect	Moderate	No increased risk
		Stillbirth or fetal death	1 (96)	Low to moderate	Consistent	Precise	Indirect	Moderate	No increased risk
		Preterm birth	1 (96)	Low to moderate	Consistent	Precise	Indirect	Moderate	No increased risk
		Congenital anomalies	1 (96)	Low to moderate	Consistent	Precise	Indirect	Moderate	No increased risk

Drug	Outcome Category	Outcome	N SRs (N Studies)	RoB in Included Studies	Consistency	Precision	Directness	SoE	Conclusions
		Neurodevelopmental/ behavioral/social	1 (96)	Low to moderate	Consistent	Precise	Indirect	Moderate	Increased autism/dyspraxia, but no increased risk of cognitive or psychomotor developmental delays, language delay, for attention deficit hyperactivity disorder
Valproate	AEs – Fetal/ Child	Spontaneous abortion or elective or induced abortion	1 (96)	Low to moderate	Consistent	Precise	Indirect	Moderate	Increased spontaneous abortion
		Stillbirth or fetal death	1 (96)	Low to moderate	Consistent	Precise	Indirect	Moderate	Increased fetal death
		Preterm birth	1 (96)	Low to moderate	Consistent	Precise	Indirect	Moderate	No increased risk
		Congenital anomalies	2 (96)	Low to moderate	Consistent	Precise	Indirect	Moderate	Increased major anomalies, hypospadias, cleft lip/palate, club foot, neural tube defects
		Neurodevelopmental/ behavioral/social	1 (96)	Low to moderate	Consistent	Precise	Indirect	Moderate	Increased cognitive delay, autism/dyspraxia, psychomotor developmental delay, language delay

Abbreviations: AE = adverse effect, RoB = risk of bias, SoE = strength of evidence, SR = systematic review.

When a range is provided for N studies, it implies that different numbers of studies reported data for the different individual measures of a given outcome.

Table B-37 provides the complete version of this Evidence Profile, including displaying outcomes for which no evidence was identified.

Serotonin and Norepinephrine Reuptake Inhibitors

Description of Direct Evidence for SNRIs

We did not find any primary studies on use of SNRIs for preventing attacks of primary headache in women who were pregnant (or attempting to become pregnant), postpartum, or breastfeeding.

Description of Indirect Evidence for SNRIs

One high-quality SR (McDonagh 2014) assessed harms associated with venlafaxine use during late pregnancy (regardless of indication) (Tables 5 and 6 and Tables B-26, B-27, B-28, and B-37).[82, 83]

Maternal Benefit Outcomes of SNRIs

No primary study or SR reported on maternal benefit outcomes of SNRIs.

Maternal Adverse Effects of SNRIs

No primary study or SR reported on maternal adverse effects of SNRIs.

Fetal/Child Adverse Effects of SNRIs

No primary study (direct evidence) reported on fetal/child adverse effects of SNRIs.

The McDonagh 2014 SR (indirect evidence) found that venlafaxine use in pregnant women (for any indication) was associated with **preterm birth** (OR 1.79, 95% CI 1.46 to 2.19) and **neonatal withdrawal symptoms** (OR 3.1, 95% CI 1.3 to 7.1) (Table 5).

Table 5. SNRIs: Summary of indirect evidence of fetal/child harms, statistically significant findings

SR, Year Published, PMID	Drug Class	Drug Name(s)	Timing of Occurrence of Adverse Effect	Adverse Effect	N Studies	Effect Size (95% CI)
McDonagh, 2014, 25004304	SNRIs	Venlafaxine	Perinatal	Preterm birth	2	OR 1.79 (1.46, 2.19)
			Neonatal	Neonatal withdrawal symptoms	1	OR 3.1 (1.3, 7.1)

Abbreviations: CI = confidence interval, OR = odds ratio, PMID = PubMed identifier, SNRI = serotonin and norepinephrine reuptake inhibitor, SR = systematic review.

Table 6. SNRIs: Evidence profile for indirect evidence regarding harms of use during pregnancy

Drug	Outcome Category	Outcome	N SRs (N Studies)	RoB in Included Studies	Consistency	Precision	Directness	SoE	Conclusions
Venlafaxine	AEs – Fetal/Child	Preterm birth	1 (2)	Moderate	Consistent	Precise	Indirect	Moderate	Increased preterm birth

Abbreviations: AE = adverse effect, RoB = risk of bias, SoE = strength of evidence, SNRI = serotonin and norepinephrine reuptake inhibitor, SR = systematic review.

Table B-37 provides the complete version of this Evidence Profile, including displaying outcomes for which no evidence was identified.

Tricyclic Antidepressants

Description of Direct Evidence for Tricyclic Antidepressants

We did not find any primary studies on use of tricyclic antidepressants for preventing attacks of primary headache in women who were pregnant (or attempting to become pregnant), postpartum, or breastfeeding.

Description of Indirect Evidence for Tricyclic Antidepressants

One high-quality SR (McDonagh 2014) assessed harms associated with (any) tricyclic antidepressant use during pregnancy (regardless of indication) (Tables 7 and 8 and Tables B-26, B-27, B-28, and B-37).[82, 83]

Maternal Benefit Outcomes of Tricyclic Antidepressants

No primary study or SR reported on maternal benefit outcomes of tricyclic antidepressants.

Maternal Adverse Effects of Tricyclic Antidepressants

No primary study or SR reported on maternal adverse effects of tricyclic antidepressants.

Fetal/Child Adverse Effects of Tricyclic Antidepressants

No primary study (direct evidence) reported on fetal/child adverse effects of tricyclic antidepressants.

The McDonagh 2014 SR (indirect evidence) found that (any) tricyclic antidepressant use in pregnant women (for any indication) was associated with **neonatal convulsions** (OR 7.82, 95% CI 2.81 to 21.8), **neonatal respiratory distress** (OR 2.11, 95% CI 1.57 to 2.83), **major congenital anomalies** (OR 1.31, 95% CI 1.04 to 1.65), and **cardiovascular anomalies** (OR 1.58, 95% CI 1.10 to 2.19) (Table 7). There was no increased risk of low birth weight, however. Tricyclic antidepressant use was also associated with the child being unable to sit without support at 6 months (relative risk [RR] 2.9, 95% CI 0.89 to 9.51), but this was not statistically significant.

Table 7. Tricyclic antidepressants: Summary of indirect evidence of fetal/child harms, statistically significant findings

SR, Year Published, PMID	Drug Class	Drug	Timing of Occurrence of Adverse Effect	Adverse Effect	N Studies	Effect Size (95% CI)
McDonagh, 2014, 25004304	Tricyclic antidepressants	Any	Neonatal	Neonatal convulsions	2	OR 7.82 (2.81, 21.8)
				Neonatal respiratory distress	2	OR 2.11 (1.57, 2.83)
				Congenital anomalies, Major	2	OR 1.31 (1.04, 1.65)
				Congenital anomalies, Cardiovascular	2	OR 1.58 (1.10, 2.29)

Abbreviations: CI = confidence interval, OR = odds ratio, PMID = PubMed identifier, SR = systematic review.

Table 8. Tricyclic antidepressants: Evidence profile for indirect evidence regarding harms of use during pregnancy

Drug	Outcome Category	Outcome	N SRs (N Studies)	RoB in Included Studies	Consistency	Precision	Directness	SoE	Conclusions
Tricyclic anti-depressants, any	AEs – Fetal/Child	Low birth weight	1 (2)	Moderate	Consistent	Precise	Indirect	Moderate	No increased risk of small for gestational age
		Congenital anomalies	1 (2)	Moderate	Consistent	Precise	Indirect	Moderate	Increased major and cardiovascular anomalies
		Perinatal complications	1 (2)	Moderate	Consistent	Precise	Indirect	Moderate	Increased neonatal convulsions and respiratory distress
		Neuro-developmental/ behavioral/ social	1 (1)	Moderate	N/A	Imprecise	Indirect	Insufficient	None

Abbreviations: AE = adverse effect, N/A = not applicable, RoB = risk of bias, SoE = strength of evidence, SR = systematic review.

Table B-37 provides the complete version of this Evidence Profile, including displaying outcomes for which no evidence was identified.

Benzodiazepines

Description of Direct Evidence for Benzodiazepines

We did not find any primary studies on use of benzodiazepines for preventing attacks of primary headache in women who were pregnant (or attempting to become pregnant), postpartum, or breastfeeding .

Description of Indirect Evidence for Benzodiazepines

One high-quality SR (Enato 2011), reported in two articles, assessed harms associated with (any) benzodiazepine use during the first trimester (regardless of indication) (Tables 9 and 10 and Tables B-26, B-27, B-28, and B-37).[69, 71]

Maternal Benefit Outcomes of Benzodiazepines

No primary study or SR reported on maternal benefit outcomes of benzodiazepines.

Maternal Adverse Effects of Benzodiazepines

No primary study or SR reported on maternal adverse effects of benzodiazepines.

Fetal/Child Adverse Effects of Benzodiazepines

No primary study (direct evidence) reported on fetal/child adverse effects of benzodiazepines.

The Enato 2011 SR (indirect evidence) reported that, in case-control studies included in the SR, benzodiazepine use during the first trimester was associated with **major congenital anomalies** (OR 3.01, 95% CI 1.32 to 6.84) and **oral clefts**, specifically (OR 1.79, 95% CI 1.13 to 2.82) (Table 9). However, cohort studies included in the SR did not show such associations.

Benzodiazepine use was not associated with cardiovascular anomalies (assessed in case-control studies only).

Table 9. Benzodiazepines: Summary of indirect evidence of fetal/child harms, statistically significant findings

SR, Year Published, PMID	Drug Class	Drug	Timing of Occurrence of Adverse Effect	Adverse Effect	N Studies	Effect Size (95% CI)
Enato, 2011, 21272436	Benzodiazepines	Any (First trimester)	Neonatal	Congenital anomalies, Major	9	CC studies: OR 3.01 (1.32, 6.84)
				Congenital anomalies, Oral cleft	6	CC studies: OR 1.79 (1.13, 2.82)

Abbreviations: CC = case-control, CI = confidence interval, OR = odds ratio, PMID = PubMed identifier, SR = systematic review.

Table 10. Benzodiazepines: Evidence profile for indirect evidence regarding harms of use during pregnancy

Drug	Outcome Category	Outcome	N SRs (N Studies)	RoB in Included Studies	Consistency	Precision	Directness	SoE	Conclusions
Benzo-diazepines, any	AEs – Fetal/Child	Congenital anomalies	1 (6-9)	Moderate	Consistent	Precise	Indirect	Low	Increased major congenital anomalies and oral cleft

Abbreviations: AE = adverse effect, RoB = risk of bias, SoE = strength of evidence, SR = systematic review.

Table B-37 provides the complete version of this Evidence Profile, including displaying outcomes for which no evidence was identified.

Beta Blockers

Description of Direct Evidence for Beta Blockers

We did not find any primary studies on use of beta blockers for preventing attacks of primary headache in women who were pregnant (or attempting to become pregnant), postpartum, or breastfeeding.

Description of Indirect Evidence for Beta Blockers

Two high-quality SRs (Yakoob 2013[90] and Abalos 2018[62]) assessed harms associated with (any) beta blocker use during pregnancy (regardless of indication) (Tables 11 and 12 and Tables B-26, B-27, B-28, and B-37).

Maternal Benefit Outcomes of Beta Blockers

No primary study or SR reported on maternal benefit outcomes of beta blockers.

Maternal Adverse Effects of Beta Blockers

No primary study (direct evidence) reported on maternal adverse effects of beta blockers.

The Abalos 2018 SR (indirect evidence) reported that beta blocker use was associated with placental abruption, but this was not statistically significant (RR 5.11, 95% CI 0.25 to 104.96). Beta blocker use was not associated with other adverse effects antepartum (e.g., hospitalization) or during delivery (e.g., induction of labor, cesarean section).

Fetal/Child Adverse Effects of Beta Blockers

No primary study (direct evidence) reported on fetal/child adverse effects of beta blockers.

Both SRs (indirect evidence) reported on fetal/child adverse effects. The Yakoob 2013 SR reported that beta blocker use was associated with **cardiovascular anomalies** (OR 2.01, 95% CI 1.18 to 3.42), **cleft lip or palate** (OR 3.11, 95% CI 1.79 to 5.43), and **neural tube defects** (OR 3.56, 95% CI 1.19 to 10.67) (Table 11). Beta blocker use was also associated with severe hypospadias, but this was not statistically significant (RR 2.27, 95% CI 0.69 to 7.46).

The Abalos 2018 SR reported on a different set of fetal/child adverse effects and found no increased association of beta blocker use with *in utero*, perinatal, and neonatal adverse effects. However, beta blocker use was associated with neonatal pulmonary edema (RR 5.23, 95% CI 0.25 to 107.39) and neonatal bradycardia (RR 2.20, 95% CI 0.68 to 7.16), but these were not statistically significant.

Table 11. Beta blockers: Summary of indirect evidence of fetal/child harms, statistically significant findings

SR, Year Published, PMID	Drug Class	Drug	Timing of Occurrence of Adverse Effect	Adverse Effect	N Studies	Effect Size (95% CI)
Yakoob 2013 23753416	Beta blockers	Any	Neonatal	Cardiovascular anomalies, Any	4	OR 2.01 (1.18, 3.42)
				Congenital anomalies, Cleft lip or palate	4	OR 3.11 (1.79, 5.43)
				Congenital anomalies, Neural tube defects	3	OR 3.56 (1.19, 10.67)

Abbreviations: CI = confidence interval, OR = odds ratio, PMID = PubMed identifier, SR = systematic review.

Table 12. Beta blockers: Evidence profile for indirect evidence regarding harms of use during pregnancy

Drug	Outcome Category	Outcome	N SRs (N Studies)	RoB in Included Studies	Consistency	Precision	Directness	SoE	Conclusions
Beta blockers, any	AEs – Maternal	Discontinuation due to AEs	1 (9)	Moderate	Consistent	Precise	Indirect	Low	No increased risk
	AEs – Fetal/Child	Perinatal complications	1 (1)	Moderate	N/A	Precise	Indirect	Insufficient	None
		Preterm birth	1 (4)	Moderate	Consistent	Precise	Indirect	Moderate	No increased risk
		Congenital anomalies	1 (1–5)	Low to moderate	Consistent	Precise	Indirect	Moderate	Increased cardiovascular anomalies, cleft lip/palate, and neural tube defects

Abbreviations: AE = adverse effect, N/A = not applicable, RoB = risk of bias, SoE = strength of evidence, SR = systematic review.

Table B-37 provides the complete version of this Evidence Profile, including displaying outcomes for which no evidence was identified.

Calcium Channel Blockers

Description of Direct Evidence for Calcium Channel Blockers

We did not find any primary studies on use of calcium channel blockers for preventing attacks of primary headache in women who were pregnant (or attempting to become pregnant), postpartum, or breastfeeding.

Description of Indirect Evidence for Calcium Channel Blockers

Two high-quality SRs assessed harms associated with calcium channel blocker use during pregnancy (regardless of indication): one SR (Abalos 2018[62]) examined any calcium channel blocker use and the other SR (Bellos 2020a[65]) examined nifedipine use, specifically (Table 13 and Tables B-26, B-27, B-28, and B-37).

Maternal Benefit Outcomes of Calcium Channel Blockers

No primary study or SR reported on maternal benefit outcomes of calcium channel blockers.

Maternal Adverse Effects of Calcium Channel Blockers

No primary study (direct evidence) reported on maternal adverse effects of calcium channel blockers.

The Abalos 2018 SR (indirect evidence) reported that (any) calcium channel blocker use was not associated with placental abruption or cesarean section. The Bellos 2020a SR (indirect evidence) reported that nifedipine use, specifically, was also not associated with placental abruption or cesarean section.

Fetal/Child Adverse Effects of Calcium Channel Blockers

No primary study (direct evidence) reported on fetal/child adverse effects of calcium channel blockers.

The Abalos 2018 SR (indirect evidence) reported that calcium channel blocker use was not associated with total fetal or neonatal death (including spontaneous abortion), preterm birth, small for gestational age, or neonatal outcomes, such as hypoglycemia, jaundice, or respiratory distress syndrome.

The Bellos 2020a SR (indirect evidence) reported that nifedipine use, specifically, was not associated with gestational age at delivery, preterm birth, small for gestational age, or perinatal death.

Table 13. Calcium channel blockers: Evidence profile for indirect evidence regarding harms of use during pregnancy

Drug	Outcome Category	Outcome	N SRs (N Studies)	RoB in Included Studies	Consistency	Precision	Directness	SoE	Conclusions
Calcium channel blockers, any	AEs – Maternal	Discontinuation due to AEs	1 (2)	Moderate	Consistent	Imprecise	Indirect	Low	No increased risk
	AEs – Fetal/Child	Perinatal complications	1 (1-3)	Low to moderate	Consistent	Precise	Indirect	Moderate	No increased risk of NICU admission, neonatal respiratory distress syndrome
		Spontaneous abortion or elective or induced abortion	1 (5)	Moderate	Consistent	Imprecise	Indirect	Low	No increased risk
		Stillbirth or fetal death	1 (5)	Moderate	Consistent	Imprecise	Indirect	Low	No increased risk
		Neonatal or infant death	1 (5)	Moderate	Consistent	Imprecise	Indirect	Low	No increased risk
		Preterm birth	1 (4)	Moderate	Consistent	Precise	Indirect	Low	No increased risk
Calcium channel blockers, nifedipine	AEs – Fetal/Child	Neonatal or infant death	1 (2)	Moderate	Consistent	Precise	Indirect	Moderate	No increased risk
		Preterm birth	1 (2)	Moderate	Consistent	Imprecise	Indirect	Low	No increased risk

Abbreviations: AE = adverse effect, NICU = neonatal intensive care unit, RoB = risk of bias, SoE = strength of evidence, SR = systematic review.

Table B-37 provides the complete version of this Evidence Profile, including displaying outcomes for which no evidence was identified.

Corticosteroids

Description of Direct Evidence for Corticosteroids

We did not find any primary studies on use of corticosteroids for preventing attacks of primary headache in women who were pregnant (or attempting to become pregnant), postpartum, or breastfeeding.

Description of Indirect Evidence for Corticosteroids

One high-quality SR (Park-Wyllie 2000) assessed harms associated with use of corticosteroids, specifically prednisolone, during pregnancy (regardless of indication) (Tables 14 and 15 and Tables B-26, B-27, B-28, and B-37).[84]

Maternal Benefit Outcomes of Corticosteroids

No primary study or SR reported on maternal benefit outcomes of corticosteroids.

Maternal Adverse Effects of Corticosteroids

No primary study or SR reported on maternal adverse effects of corticosteroids.

Fetal/Child Adverse Effects of Corticosteroids

No primary study (direct evidence) reported on fetal/child adverse effects of corticosteroids.

The Park-Wyllie 2000 SR (indirect evidence) reported that prednisolone use was associated with increased likelihood of **oral clefts** (OR 3.35, 95% CI 1.97 to 5.69), but not other major congenital anomalies (Table 14).

Table 14. Corticosteroids: Summary of indirect evidence of fetal/child harms, statistically significant findings

SR, Year Published, PMID	Drug Class	Drug	Timing of Occurrence of Adverse Effect	Adverse Effect	N Studies	Effect Size (95% CI)
Park-Wyllie, 2000, 11091360	Corticosteroids	Prednisolone	Neonatal	Congenital anomalies, Oral clefts	4	OR 3.35 (1.97, 5.69)

Abbreviations: CI = confidence interval, OR = odds ratio, PMID = PubMed identifier, SR = systematic review.

Table 15. Corticosteroids: Evidence profile for direct evidence regarding use to prevent primary headaches

Drug	Outcome Category	Outcome	N SRs (N Studies)	RoB in Included Studies	Consistency	Precision	Directness	SoE	Conclusions
Prednisolone	AEs – Fetal/Child	Congenital anomalies	1 (4-6)	Unclear	Inconsistent	Precise	Indirect	Low	Increased oral clefts, but no increased risk of other major anomalies

Abbreviations: AE = adverse effect, RoB = risk of bias, SoE = strength of evidence, SR = systematic review.

Table B-37 provides the complete version of this Evidence Profile, including displaying outcomes for which no evidence was identified.

Antihistamines

Description of Direct Evidence for Antihistamines

We did not find any primary studies on use of antihistamines for preventing attacks of primary headache in women who were pregnant (or attempting to become pregnant), postpartum, or breastfeeding.

Description of Indirect Evidence for Antihistamines

Two high-quality SRs (Etwel 2017[72] and Li 2019[77]) assessed harms associated with (any) antihistamine use during pregnancy (regardless of indication) (Table 16 and Tables B-26, B-27, B-28, and B-37).

Maternal Benefit Outcomes of Antihistamines

No primary study or SR reported on maternal benefit outcomes of antihistamines.

Maternal Adverse Effects of Antihistamines

No primary study or SR reported on maternal adverse effects of antihistamines.

Fetal/Child Adverse Effects of Antihistamines

No primary study (direct evidence) reported on fetal/child adverse effects of antihistamines.

The Etwel 2017 SR (indirect evidence) reported that antihistamine use was not associated with spontaneous abortion, stillbirth, preterm birth, low birth weight, or major congenital anomalies.

The Li 2019 SR (indirect evidence) reported that antihistamine use was not associated with congenital anomalies (overall) or hypospadias (in particular).

Table 16. Antihistamines: Evidence profile for direct evidence regarding use to prevent primary headaches

Drug	Outcome Category	Outcome	N SRs (N Studies)	RoB in Included Studies	Consistency	Precision	Directness	SoE	Conclusions
Antihistamines, any	AEs – Fetal/Child	Spontaneous abortion or elective or induced abortion	1 (8-13)	Low	Consistent	Precise	Indirect	Moderate	No increased risk of spontaneous abortion
		Stillbirth or fetal death	1 (8-13)	Low	Consistent	Precise	Indirect	Moderate	No increased risk of stillbirth
		Serious, Preterm birth	1 (9)	Low	Consistent	Precise	Indirect	Moderate	No increased risk
		Serious, Low birth weight	1 (3)	Low	Consistent	Precise	Indirect	Moderate	No increased risk
		Serious, Congenital anomalies	2 (43)	Low	Consistent	Precise	Indirect	Moderate	No increased risk of major congenital anomalies

Abbreviations: AE = adverse effect, RoB = risk of bias, SoE = strength of evidence, SR = systematic review.

Table B-37 provides the complete version of this Evidence Profile, including displaying outcomes for which no evidence was identified.

Oral Magnesium

Description of Direct Evidence for Oral Magnesium

We did not find primary studies on oral magnesium for preventing attacks of primary headache in women who were pregnant (or attempting to become pregnant), postpartum, or breastfeeding.

Description of Indirect Evidence for Oral Magnesium

One high-quality SR (Makredes 2014) assessed harms associated with oral magnesium sulphate use during pregnancy (regardless of indication) (Tables 17, 18, and 19 and Tables B-26, B-27, B-28, and B-37).[78]

Maternal Benefit Outcomes

No primary study or SR reported on maternal benefit outcomes of oral magnesium.

Maternal Adverse Effects of Oral Magnesium

No primary study or SR reported on maternal adverse effects of oral magnesium.

The Makredes 2014 SR (indirect evidence) reported that patients who used oral magnesium during pregnancy experienced a marginally **higher systolic blood pressure** (1 mm of Hg) than those who did not (Table 17). Oral magnesium use was not associated with other maternal adverse effects, such as gastrointestinal symptoms, hospitalizations, antepartum hemorrhage, or increased length of labor.

Fetal/Child Adverse Effects of Oral Magnesium

No primary study or SR reported on fetal/child adverse effects of oral magnesium.

The Makredes 2014 SR (indirect evidence) reported that oral magnesium use was associated with **neonatal death** (RR 2.21, 95% CI 1.02 to 4.75), but not spontaneous abortion, stillbirth, low birth weight, or neonatal intensive care unit admissions (Table 18).

Table 17. Oral magnesium: Summary of indirect evidence of maternal harms, statistically significant findings

SR, Year Published, PMID	Intervention Class	Intervention Name	Timing of Occurrence of Adverse Effect	Adverse Effect	N Studies	Effect Size (95% CI)
Makredes, 2014, 24696187	Oral magnesium	Oral magnesium sulphate	NR	Systolic blood pressure	3	MD 1 mm Hg (0.03, 1.97)

Abbreviations: CI = confidence interval, MD = mean difference, NR = not reported, PMID = PubMed identifier, SR = systematic review.

Table 18. Oral magnesium: Summary of indirect evidence of fetal/child harms, statistically significant findings

SR, Year Published, PMID	Intervention Class	Intervention Name	Timing of Occurrence of Adverse Effect	Adverse Effect	N Studies	Effect Size (95% CI)
Makredes, 2014, 24696187	Oral magnesium	Oral magnesium sulphate	Neonatal	Neonatal death	4	RR 2.21 (1.02, 4.75)

Abbreviations: CI = confidence interval, PMID = PubMed identifier, RR = relative risk, SR = systematic review.

Table 19. Oral magnesium: Evidence profile for indirect evidence regarding harms of use during pregnancy

Drug	Outcome Category	Outcome	N SRs (N Studies)	RoB in Included Studies	Consistency	Precision	Directness	SoE	Conclusions
Oral magnesium	AEs – Maternal	Any serious AE	1 (1-5)	Low to moderate	Inconsistent	Precise	Indirect	Low	No increased risk of hospitalization or eclampsia
	AEs – Fetal/Child	Spontaneous abortion or elective or induced abortion	1 (6)	Low to moderate	Consistent	Precise	Indirect	Low	No increased risk of spontaneous abortion
		Stillbirth or fetal death	1 (4)	Low to moderate	Consistent	Precise	Indirect	Low	No increased risk of stillbirth
		Neonatal or infant death	1 (4)	Low to moderate	Consistent	Precise	Indirect	Low	Increased neonatal death
		Low birth weight	1 (5)	Low to moderate	Consistent	Precise	Indirect	Low	No increased risk of low birth weight
		Perinatal complications	1 (3)	Low to moderate	Consistent	Precise	Indirect	Low	No increased risk of NICU admission

Abbreviations: AE = adverse effect, NICU = neonatal intensive care unit, RoB = risk of bias, SoE = strength of evidence, SR = systematic review.

Table B-37 provides the complete version of this Evidence Profile, including displaying outcomes for which no evidence was identified.

Other Pharmacologic Interventions for KQ 1

We did not find direct evidence (i.e., primary studies) or indirect evidence (i.e., SRs regardless of indication) on the use of the following pharmacologic interventions for preventing primary headaches in women who are pregnant (or attempting to be pregnant), postpartum, or breastfeeding: tetracyclic antidepressants, mood-stabilizing agents, other antihypertensive medications, N-methyl-D-aspartate (NMDA) receptor antagonists, and calcitonin gene-related peptide (CGRP) inhibitors.

Key Question 1: Nonpharmacologic Interventions To Prevent Attacks of Primary Headache

We did not find direct evidence (i.e., primary studies) or indirect evidence (i.e., SRs regardless of indication) addressing the use of nonpharmacologic interventions for preventing attacks of primary headaches in women who are pregnant (or attempting to become pregnant), postpartum, or breastfeeding. These included complementary therapy, behavioral therapy, physical therapy, procedures, noninvasive neuromodulation devices, chemodenervation, hydration, and supplements.

Key Question 2: Treatment of Primary Headache

Key Points

- **Pharmacologic interventions**
  - No *direct or indirect evidence* evaluated the beneficial effects or harms of pharmacologic interventions in women attempting to become pregnant or in women who were postpartum or breastfeeding.
  - *Direct evidence* (studies of pregnant women with primary headache) about pharmacologic interventions found that:
    - **Triptan** use for migraine during pregnancy, when compared with triptan nonuse or use only before pregnancy, may have a lower risk of adverse effects, except for increased child emotionality and hyperactivity at 3 years of age (low SoE).
    - **Combination metoclopramide and diphenhydramine** may be more effective (low SoE) and not more harmful (low SoE) than **codeine** for treatment of migraine or tension headache during pregnancy.
- **Nonpharmacologic interventions**
  - No *direct or indirect evidence* evaluated the beneficial effects or harms of nonpharmacologic interventions in women attempting to become pregnant or in women who were postpartum or breastfeeding.
  - There is *insufficient direct evidence* to make conclusions about the benefit or harms of **acupuncture**, **thermal biofeedback**, **relaxation therapy**, **physical therapy**, **peripheral nerve blocks**, or **transcranial magnetic stimulation** when used for treatment of primary headache during pregnancy.
  - No *indirect evidence* evaluated nonpharmacologic interventions for treatment of primary headache during pregnancy.

Fifteen of the 16 primary studies included in this SR (direct evidence) addressed KQ 2. These included nine primary studies addressing the following pharmacologic interventions: triptans,

ergot products, NSAIDs, antiemetics (dopamine receptor antagonists), antihistamines, and opioid analgesics, and six primary studies addressing the following nonpharmacologic interventions: complementary therapies, behavioral therapy, physical therapy, procedures, and noninvasive neuromodulation devices.

Eighteen existing SRs (indirect evidence) addressed the following pharmacologic interventions relevant to KQ 2: triptans, NSAIDs, antihistamines, antiemetics (5HT3 antagonists), antipsychotics, corticosteroids, analgesics/antipyretics, and intravenous magnesium. No SRs addressed nonpharmacologic interventions for KQ 2.

Key Question 2: Pharmacologic Interventions To Treat Attacks of Primary Headache

Fifteen of the 16 included primary studies (i.e., direct evidence) addressed KQ 2. These included nine studies of pharmacologic treatments (eight observational NRCSs of triptans, ergot products, and NSAIDs[42-57] and one RCT of antiemetics [dopamine receptor antagonists], antihistamines, and opioid-containing analgesics,[37, 39, 40]) and six studies of nonpharmacologic treatments (two RCTs[38, 41] and two single-group studies[38, 60, 61] of complementary, behavioral, and physical therapies, one single-group study[25] of nerve blocks, and one single-group study of noninvasive neuromodulation devices[58]), all in women who were pregnant.

Triptans, Ergot Products, NSAIDs (Naproxen), and Antihistamines (Pizotifen)

Description of Direct Evidence for Triptans, Ergot Products, NSAIDs (Naproxen), and Antihistamines (Pizotifen)

Eight primary studies (direct evidence), all observational NRCSs (described in 16 articles[42-57]), reported the harms of triptans, ergot products, NSAIDs (naproxen), and antihistamines (pizotifen) in pregnant patients with primary headaches (all with migraine). These included three prospective cohort studies[42, 44, 48, 52, 54] and five retrospective cohort studies.[43, 45-47, 49-51, 53, 55-57] The eight studies enrolled a total of 13,907 patients (Tables 20 and 21 and Tables B-1, B-3, B-4, B-10 to B-16, and B-32).

Ephross 2014, reported in three articles, studied 689 pregnant patients with migraine in 18 countries.[42, 44, 48] Patient data were obtained from the Sumatriptan, Naratriptan, and Treximet Pregnancy Registry. This study was funded by industry. The study compared three arms: subcutaneous sumatriptan (626 patients), oral naratriptan (57 patients), and a subcutaneous combination of sumatriptan and naproxen (6 patients). No information about treatment doses, frequencies, or durations, or patient age, race, trimester/gestational age, gravidity, or parity was reported. We assessed the study at overall high risk of bias because of serious risk of confounding bias and high risks of performance and detection biases due to lack of blinding of patients, study personnel, and outcome assessors. Furthermore, the treatments were not clearly described.

O'Quinn 1999 studied 168 pregnant patients with migraine in the U.S.[52] This study was funded by industry. The study compared subcutaneous sumatriptan use during the first trimester of pregnancy (76 patients) with its use before pregnancy only (92 patients). No information about treatment doses, frequencies, or durations, or patient age, race, gestational age, gravidity, or parity was reported. We assessed the study at overall high risk of bias because of serious risk

of confounding bias and high risk of performance bias due to lack of blinding of patients and study personnel. We rated the risk of detection bias as unclear. Furthermore, the participant eligibility criteria, treatments, and outcomes were not clearly described.

Shuhaiber 1998 studied 192 pregnant patients with migraine in the U.S. and Canada.[54] The funding source for this study was not reported. The study compared sumatriptan use (96 patients) with no triptan use (96 patients) during the first trimester of pregnancy. No information about treatment doses, frequencies, or durations was reported. Patient ages were similar in the triptan (mean 32.3 years) and no triptan arms (mean 31.7 years). No information about patient race, gestational age, gravidity, or parity was reported. We assessed the study at overall high risk of bias because of serious risk of confounding bias and high risks of performance and detection biases due to lack of blinding of patients, study personnel, and outcome assessors. We rated the risk of detection bias as unclear. Furthermore, the treatments were not clearly described.

Nezvalova-Henriksen 2013 studied 2,560 pregnant patients with migraine in Norway.[50] Patient data were obtained from the Norwegian Prescription Database and their birth outcomes were linked to the Medical Birth Registry of Norway. The funding source for this study was not reported. The study compared the use of any triptan use during pregnancy (1,465 patients) with use only before pregnancy (1,095 patients). No information about treatment doses, frequencies, or durations, or patient age, race, trimester/gestational age, gravidity, or parity was reported. We assessed the study at overall high risk of bias because of moderate risk of confounding bias and high risks of performance and detection biases due to lack of blinding of patients, study personnel, and outcome assessors. Furthermore, the treatments were not clearly described.

Nezvalova-Henriksen 2010, reported in five articles, studied 5,900 pregnant patients with migraine in Norway.[45, 49, 51, 56, 57] Patient data were obtained from the Norwegian Mother and Child Cohort Study and, like Nezvalova-Henriksen 2013, patient birth outcomes were linked to the Medical Birth Registry of Norway. Nezvalova-Henriksen 2010 was funded by nonindustry sources. The study compared three arms: any triptan use during pregnancy (1,045 patients), any triptan use only before pregnancy (805 patients), and no triptan use either during or before pregnancy (4,050 patients). No information about treatment doses, frequencies, or durations, or patient age, race, trimester/gestational age, gravidity, or parity was reported. We assessed the study at overall high risk of bias because of moderate risk of confounding bias; high risks of performance and detection biases due to lack of blinding of patients, study personnel, and outcome assessors; and high risk of attrition bias due to incomplete outcome data. Furthermore, the treatments were not clearly described.

Kallen 2011, reported in two articles, studied 3,368 pregnant patients with migraine in Sweden.[46, 47] Patient data and birth outcomes were obtained from the Swedish Medical Birth Register. Kallen 2011 was funded by a nonindustry source. The study compared three arms: any triptan use during pregnancy (2,777 patients), any ergot product use during pregnancy (527 patients), and pizotifen use during pregnancy (64 patients). No information about treatment doses, frequencies, or durations, or patient age, race, trimester/gestational age, gravidity, or parity was reported. We assessed the study at overall high risk of bias because of serious risk of confounding bias and high risks of performance and detection biases due to lack of blinding of patients, study personnel, and outcome assessors. Furthermore, the treatments were not clearly described.

Olesen 2000 studied 123 pregnant patients with migraine in Denmark.[53] Patient data and birth outcomes were obtained from the Pharmaco-epidemiological Prescription Database of North Jutland County, Denmark. Olesen 2000 was funded by nonindustry sources. The study

compared sumatriptan use during pregnancy (34 patients) with sumatriptan or ergotamine use only before pregnancy (89 patients). No information about treatment doses, frequencies, or durations was reported. Patient ages were similar in the sumatriptan during pregnancy (mean 29.6 years) and the sumatriptan or ergotamine before pregnancy arms (mean 28.4 years). No information about patient race, trimester/gestational age, gravidity, or parity was reported. We assessed the study at overall moderate risk of bias because of high risks of performance and detection biases due to lack of blinding of patients, study personnel, and outcome assessors. Furthermore, the treatments were not clearly described.

Spielmann 2018, reported in two articles, studied 907 pregnant patients with migraine in Germany.[43, 55] Patient data and birth outcomes were obtained from the German Embryotox System. The funding source for this study was not reported. The study compared triptan use during pregnancy (432 patients) with no use during pregnancy (475 patients). No information about treatment doses, frequencies, or durations was reported. Patient ages were similar in the triptan (median 33 years) and no triptan arms (median 32 years). No information about patient race, trimester/gestational age, gravidity, or parity was reported. We assessed the study at overall high risk of bias because of high risks of performance and detection biases due to lack of blinding of patients, study personnel, and outcome assessors, and high risk of attrition bias due to incomplete outcome data. Furthermore, the treatments were not clearly described.

We have organized the rest of this section on triptans, ergot products, and NSAIDs by timing of use of the drugs. First, we discuss studies that compared the use of drugs (or drug classes) with each other during pregnancy. Next, we discuss studies that compared the use of drugs (or drug classes) during pregnancy versus the same drugs (or drug classes) only before pregnancy. Finally, we discuss studies that compared the use of drugs (or drug classes) during pregnancy versus nonuse of the same drug (or drug classes) either during or before pregnancy. None of the studies described in this section reported on maternal benefit outcomes.

Description of SR Evidence for Triptans

One high-quality SR (Marchenko 2015) assessed harms associated with (any) triptan use during pregnancy (Table 22 and Tables B-26, B-27, B-28, and B-37).[79]

Description of Indirect Evidence for Antihistamines

Two high-quality SRs (Etwel 2017[72] and Li 2019[77]) assessed harms associated with (any) antihistamine use during pregnancy (regardless of indication) (Table 16 and Tables B-26, B-27, B-28, and B-37).

Sumatriptan Versus Naratriptan During Pregnancy

Description of Direct Evidence for Sumatriptan Versus Naratriptan During Pregnancy

One observational NRCS (Ephross 2014), reported in three articles, addressed this comparison in pregnant patients with migraine.[42, 44, 48] Although this study reported subgroup analyses by trimester of drug use, most patients (585/689 patients; 84.9%) were in the first trimester (Tables B-11 and B-13). No statistical analyses for subgroup differences were reported. Only fetal/child adverse effects were reported.

Description of SR Evidence for Sumatriptan Versus Naratriptan During Pregnancy

No SR reported on this comparison.

Maternal Benefit Outcomes of Sumatriptan Versus Naratriptan During Pregnancy

No primary study or SR reported on maternal benefit outcomes for this comparison.

Maternal Adverse Effects of Sumatriptan Versus Naratriptan During Pregnancy

No primary study or SR reported on maternal adverse effects for this comparison.

Fetal/Child Adverse Effects of Sumatriptan Versus Naratriptan During Pregnancy

Ephross 2014 (direct evidence) reported that **spontaneous abortion** occurred in 34 of 626 patients receiving sumatriptan (5.4%) and 5 of 57 patients receiving naratriptan (8.8%) (Table B-11). No adjusted effect sizes were reported.

Ephross 2014 also reported that **elective or induced abortion** occurred in patients 16 of 626 receiving sumatriptan (2.6%) and 1 of 57 patients receiving naratriptan (1.8%) (Table B-11). No adjusted effect sizes were reported.

Ephross 2014 also reported that **stillbirth or fetal death** occurred in patients 5 of 626 receiving sumatriptan (0.8%) and none of the 57 patients receiving naratriptan (Table B-11). No adjusted effect sizes were reported.

Ephross 2014 also reported that **major congenital anomalies** occurred in patients 19 of 626 patients receiving sumatriptan (3.0%) and 1 of 57 patients receiving naratriptan (1.8%) (Table B-13). No adjusted effect sizes were reported.

Sumatriptan Versus Combination Sumatriptan and Naproxen During Pregnancy

Direct Evidence for Sumatriptan Versus Combination Sumatriptan and Naproxen During Pregnancy

One observational NRCS (Ephross 2014), reported in three articles, addressed this comparison in pregnant patients with migraine, although only 6 patients received the combination treatment (Tables B-11 and B-13).[42, 44, 48] Although this study reported subgroup analyses by trimester of drug use, most patients (585/689 patients; 84.9%) were in the first trimester. No statistical analyses for subgroup differences were reported. The study reported fetal/child adverse effects only.

Description of SR Evidence for Sumatriptan Versus Combination Sumatriptan and Naproxen During Pregnancy

No SR reported on this comparison.

Maternal Benefit Outcomes of Sumatriptan Versus Combination Sumatriptan and Naproxen During Pregnancy

No primary study or SR reported on maternal benefit outcomes for this comparison.

Maternal Adverse Effects of Sumatriptan Versus Combination Sumatriptan and Naproxen During Pregnancy

No primary study or SR reported on maternal adverse effects for this comparison.

Fetal/Child Adverse Effects of Sumatriptan Versus Combination Sumatriptan and Naproxen During Pregnancy

Ephross 2014 (direct evidence) reported that **spontaneous abortion** occurred in 34 of 626 patients receiving sumatriptan (5.4%) and 1 of 6 patients receiving the sumatriptan and naproxen combination (16.7%) (Table B-11). No adjusted effect sizes were reported.

Ephross 2014 also reported that **elective or induced abortion** occurred in 16 of 626 patients receiving sumatriptan (2.6%) and none of the 6 patients receiving the sumatriptan and naproxen combination (Table B-11). No adjusted effect sizes were reported.

Ephross 2014 also reported that **stillbirth or fetal death** occurred in 5 of 626 patients receiving sumatriptan (0.8%) and none of the 6 patients receiving the sumatriptan and naproxen combination (Table B-11). No adjusted effect sizes were reported.

Ephross 2014 also reported that **major congenital anomalies** occurred in 19 of 626 patients receiving sumatriptan (3.0%) and none of the 6 patients receiving the sumatriptan and naproxen combination (Table B-13). No adjusted effect sizes were reported.

Naratriptan Versus Combination Sumatriptan and Naproxen During Pregnancy

Direct Evidence for Naratriptan Versus Combination Sumatriptan and Naproxen During Pregnancy

One observational NRCS (Ephross 2014), reported in three articles, addressed this comparison in pregnant patients in pregnant patients with migraine, although only 6 patients received the combination treatment (Tables B-11 and B-13).[42, 44, 48] Although this study reported subgroup analyses by trimester of drug use, most patients (585/689 patients; 84.9%) were in the first trimester. No statistical analyses for subgroup differences were reported. The study reported fetal/child adverse effects only.

Description of SR Evidence for Naratriptan Versus Combination Sumatriptan and Naproxen During Pregnancy

No SR reported on this comparison.

Maternal Benefit Outcomes of Naratriptan Versus Combination Sumatriptan and Naproxen During Pregnancy

No primary study or SR reported on maternal benefit outcomes for this comparison.

Maternal Adverse Effects of Naratriptan Versus Combination Sumatriptan and Naproxen During Pregnancy:

No primary study or SR reported on maternal adverse effects for this comparison.

Fetal/Child Adverse Effects of Naratriptan Versus Combination Sumatriptan and Naproxen During Pregnancy

Ephross 2014 (direct evidence) reported that **spontaneous abortion** occurred in 5 of 57 patients receiving naratriptan (8.8%) and one of 6 (16.7%) of patients receiving the sumatriptan and naproxen combination (Table B-11). No adjusted effect sizes were reported.

Ephross 2014 also reported that **elective or induced abortion** occurred in 1 of 57 patients receiving naratriptan (1.8%) and none of the 6 patients receiving the sumatriptan and naproxen combination (Table B-11). No adjusted effect sizes were reported.

Ephross 2014 also reported that **stillbirth or fetal death** did not occur in the patients receiving either naratriptan or the sumatriptan and naproxen combination (Table B-11).

Ephross 2014 also reported that **major congenital anomalies** occurred in 1 of 57 patients receiving naratriptan (1.8%) and none of the 6 patients receiving the sumatriptan and naproxen combination (Table B-13). No adjusted effect sizes were reported.

Any Triptan Versus Any Ergot Product During Pregnancy

Description of Direct Evidence for Any Triptan Versus Any Ergot Product During Pregnancy

One observational NRCS (Kallen 2011), reported in two articles, addressed this comparison in 3,368 pregnant patients with migraine (Tables B-11 to B-13).[46, 47] This study report subgroup results for specific triptans (sumatriptan, naratriptan, zolmitriptan, rizatriptan, almotriptan, and eletriptan) and specific ergot products (dihydroergotamine and ergotamine combinations), but did not report statistical analyses for differences between subgroups. The study reported fetal/child adverse effects only.

Description of SR Evidence for Any Triptan Versus Any Ergot Product During Pregnancy

No SR reported on this comparison.

Maternal Benefit Outcomes of Any Triptan Versus Any Ergot Product During Pregnancy

No primary study or SR reported on maternal benefit outcomes for this comparison.

Maternal Adverse Effects of Any Triptan Versus Any Ergot Product During Pregnancy

No primary study or SR reported on maternal adverse effects for this comparison.

Fetal/Child Adverse Effects of Any Triptan Versus Any Ergot Product During Pregnancy

Kallen 2011 (direct evidence) reported that **perinatal death** occurred in 5 of 658 patients receiving sumatriptan (0.75%) (Table B-11). Data for the other triptan subgroups or for the any ergot product arm were not reported.

Kallen 2011 also reported that **preterm birth (<37 weeks)** occurred in 34 of 658 patients receiving sumatriptan (5.1%) (Table B-12). Data for the other triptan subgroups or for the any ergot product arm were not reported.

Kallen 2011 also reported that **low birth weight (<2500 g)** occurred in 34 of 658 patients receiving sumatriptan (5.1%) (Table B-12). Data for the other triptan subgroups or for the any ergot product arm were not reported.

Kallen 2011 also reported that **congenital anomalies** occurred in 127 of 2,777 patients receiving any triptan (4.57%) and 21 of 527 patients receiving any ergot product (3.98%) (Table B-13). No adjusted effect sizes were reported.

Kallen 2011 also reported that **major congenital anomalies** occurred in 92 of 2,777 patients receiving any triptan (3.31%) and 17 of 527 patients receiving any ergot product (3.23%) (Table B-13). No adjusted effect sizes were reported.

Kallen 2011 also reported that **congenital cardiovascular anomalies** occurred in 29 of 2,777 patients receiving any triptan (1.04%) and 7 of 527 patients receiving any ergot product (1.33%) (Table B-13). No adjusted effect sizes were reported.

Kallen 2011 also reported that **ventricular septum defect and/or atrial septum defect** occurred in 12 of 2,777 patients receiving any triptan (0.61%) and 6 of 527 patients receiving any ergot product (1.14%) (Table B-13). No adjusted effect sizes were reported.

Any Triptan Versus Pizotifen During Pregnancy

Description of Direct Evidence for Any Triptan Versus Pizotifen During Pregnancy

One observational NRCS (Kallen 2011), reported in two articles, addressed this comparison in 3,368 pregnant patients with migraine (Tables B-11 to B-13).[46, 47] This study reported subgroup results for specific triptans (sumatriptan, naratriptan, zolmitriptan, rizatriptan, almotriptan, and eletriptan), but not statistical analyses for differences between subgroups. The study reported fetal/child adverse effects only.

Description of SR Evidence for Any Triptan Versus Pizotifen During Pregnancy

No SR reported on this comparison.

Maternal Benefit Outcomes of Any Triptan Versus Pizotifen During Pregnancy

No primary study or SR reported on maternal benefit outcomes for this comparison.

Maternal Adverse Effects of Any Triptan Versus Pizotifen During Pregnancy

No primary study or SR reported on maternal adverse effects for this comparison.

Fetal/Child Adverse Effects of Any Triptan Versus Pizotifen During Pregnancy

Kallen 2011 (direct evidence) reported that **perinatal death of newborns** occurred in 5 of 658 patients receiving sumatriptan (0.75%) (Table B-11). Data for the other triptan subgroups or for the pizotifen arm were not reported.

Kallen 2011 also reported that **preterm birth (<37 weeks)** occurred in 34 of 658 patients receiving sumatriptan (5.1%) (Table B-12). Data for the other triptan subgroups or for the pizotifen arm were not reported.

Kallen 2011 also reported that **low birth weight (<2500 g)** occurred in 34 of 658 patients receiving sumatriptan (5.1%) (Table B-12). Data for the other triptan subgroups or for the pizotifen arm were not reported.

Kallen 2011 also reported that **congenital anomalies** occurred in 127 of 2,777 (4.57%) percent of patients receiving any triptan and 3 of 64 patients receiving pizotifen (4.69%) (Table B-13). No adjusted effect sizes were reported.

Any Ergot Product Versus Pizotifen During Pregnancy

Description of Direct Evidence for Any Ergot Product Versus Pizotifen During Pregnancy

One observational NRCS (Kallen 2011), reported in two articles, addressed this comparison in 3,368 pregnant patients with migraine (Table B-13).[46, 47] This study reported subgroup results for specific triptans (sumatriptan, naratriptan, zolmitriptan, rizatriptan, almotriptan, and

eletriptan), but not statistical analyses for differences between subgroups. The study reported fetal/child adverse effects only.

Description of SR Evidence for Any Ergot Product Versus Pizotifen During Pregnancy

No SR reported on this comparison.

Maternal Benefit Outcomes of Any Ergot Product Versus Pizotifen During Pregnancy

No primary study or SR reported on maternal benefit outcomes for this comparison.

Maternal Adverse Effects of Any Ergot Product Versus Pizotifen During Pregnancy

No primary study or SR reported on maternal adverse effects for this comparison.

Fetal/Child Adverse Effects of Any Ergot Product Versus Pizotifen During Pregnancy

Kallen 2011 (direct evidence) reported that **congenital anomalies** occurred in 21 of 527 patients receiving any ergot product (3.98%) and 3 of 64 patients receiving pizotifen (4.69%) (Table B-13).[46, 47] No adjusted effect sizes were reported.

Any Triptan During Pregnancy Versus Any Triptan Before Pregnancy Only

Description of Direct Evidence for Any Triptan During Pregnancy Versus Any Triptan Before Pregnancy Only

Two observational NRCSs (Nezvalova-Henriksen 2013[50] and Nezvalova-Henriksen 2010 [reported in five articles][45, 49, 51, 56, 57]) addressed this comparison in a total of 8,460 pregnant patients with migraine (Tables 20 and 21 and Tables B-10 to B-15). Although these studies reported subgroup analyses by specific triptan and/or trimester of use, no statistical analyses for subgroup differences were reported. Both studies reported maternal as well as fetal/child adverse effects.

Description of SR Evidence for Any Triptan During Pregnancy Versus Any Triptan Before Pregnancy Only

No SR reported on this comparison.

Maternal Benefit Outcomes of Any Triptan During Pregnancy Versus Any Triptan Before Pregnancy Only

No primary study or SR reported on maternal benefit outcomes for this comparison.

Maternal Adverse Effects of Any Triptan During Pregnancy Versus Any Triptan Before Pregnancy Only

Both Nezvalova-Henriksen 2013 and Nezvalova-Henriksen 2010 (direct evidence) reported on the outcome of **postpartum hemorrhage (>500 mL)** (Table B-10). Nezvalova-Henriksen 2013 reported that the rates of postpartum hemorrhage were similar comparing women who used triptans during pregnancy with those who only used them before pregnancy (248 of 1,465 patients [16.9%] and 195 of 1,095 patients [17.8%], respectively). Nezvalova-Henriksen 2010,

however, reported that the rates were 255 of 1,045 patients (24.4%) and 63 of 805 patients (7.8%), respectively. In this study, women using triptans in the first trimester appeared to have higher rates of postpartum hemorrhage than those using it in the second and/or third trimester. In Nezvalova-Henriksen 2013, the rates of postpartum hemorrhage were similar across the triptans and across the subgroups, with somewhat higher rates in the zolmitriptan subgroups. No adjusted effect sizes were reported in either study for this outcome, either overall or within the subgroups.

Fetal/Child Adverse Effects of Any Triptan During Pregnancy Versus Any Triptan Before Pregnancy Only

Nezvalova-Henriksen 2010 (direct evidence) reported on **stillbirths** and **perinatal deaths** separately.[45, 49, 51, 56, 57] The rate of **stillbirth** was 2 of 805 patients in the triptans before pregnancy only arm (0.2%) and not reported for the triptans during pregnancy arm (Table B-11). The rates of **perinatal death** were 6 of 1,045 patients (0.6%) and 3 of 805 patients (0.4%) in the triptans during pregnancy and triptans before pregnancy only arms, respectively (Table B-11). No adjusted effect sizes were reported.

Nezvalova-Henriksen 2010 also reported on the outcome of **infant death by 1 year of age**. The rate of infant death was 5 of 1,045 patients in the triptans during pregnancy arm (0.5%). No infant deaths were reported in the triptans before pregnancy only arm (Table B-11).[45, 49, 51, 56, 57]

Both Nezvalova-Henriksen 2013 and Nezvalova-Henriksen 2010 (direct evidence) reported on the outcome of **preterm birth (<37 weeks)** (Table B-12). No patterns were observed in either study, except that preterm birth rates were somewhat higher rates in the zolmitriptan subgroups than the other subgroups in the Nezvalova-Henriksen 2013 study. No adjusted effect sizes were reported for this outcome.

Both Nezvalova-Henriksen 2013 and Nezvalova-Henriksen 2010 reported on the outcome of **low birth weight** (Table B-12). No patterns were observed in either study; rates of low birth weight were approximately 6 percent in both studies. No adjusted effect sizes were reported. Nezvalova-Henriksen 2013 also reported on the outcome of low birth weight for gestational age. The rates of **low birth weight for gestational age** were 132 of 1,465 patients (9.0%) and 91 of 1,095 patients (8.3%) in the triptans during pregnancy and triptans before pregnancy only arms, respectively. No adjusted effect sizes were reported for this outcome.

Nezvalova-Henriksen 2010 reported on the outcome of **Apgar score being less than 7 at both 1 minute and at 5 minutes after birth**. A larger proportion of newborns born to patients who used triptans during versus only before pregnancy had Apgar scores less than 7 at 1 minute (8.4% vs. 2.2%) and at 5 minutes (2.1% vs. 0.5%), but no adjusted effect sizes were reported for this outcome (Table B-12).

Nezvalova-Henriksen 2013 reported on **neonatal intensive care unit admission rates** for each of the triptans, by trimester of use only. No patterns were observed, and no adjusted effect sizes were reported for this outcome (Table B-12).

Both Nezvalova-Henriksen 2013 and Nezvalova-Henriksen 2010 reported on **congenital anomalies**. Nezvalova-Henriksen 2013 reported that the rates of **any congenital anomalies** were similar between triptan during pregnancy and triptan before pregnancy only arms (85 of 1,465 patients [5.7%] and 67 of 1,095 patients [6.1%]), but Nezvalova-Henriksen 2010 reported higher rates in the during pregnancy arm (Table B-13). No adjusted effect sizes were reported for this outcome.

Both Nezvalova-Henriksen 2013 and Nezvalova-Henriksen 2010 reported on **major congenital anomalies**. Nezvalova-Henriksen 2013 reported that the rates of major congenital anomalies were similar between triptan during pregnancy and triptans before pregnancy only

arms (51 of 1,465 patients [3.5%] and 50 of 1,095 patients [4.6%]), but Nezvalova-Henriksen 2010 reported higher rates in the during pregnancy arm (75 of 1,045 patients [7.2%]) (Table B-13). No adjusted effect sizes were reported for this outcome.

Nezvalova-Henriksen 2010 reported on **neurodevelopmental outcomes at 1.5 years and 3 years of age**, as measured by the Ages and Stages Questionnaire (ASQ). Compared with children whose mothers used triptans only before pregnancy, those whose mothers used triptans during pregnancy had similar **gross motor development** (adjusted RR for being above a Z-score of 1.5 on the ASQ: 0.86, 95% CI 0.23 to 3.19) and **fine motor development** (adjusted RR 0.85, 95% CI 0.52 to 1.37) at 3 years of age (Table B-14).

Nezvalova-Henriksen 2010 reported on various **behavioral and social outcomes at 1.5 years, 3 years, and 5 years of age**. These included **externalizing problems**, **internalizing problems, and emotionality** (measured using the Child Behavior Check List [CBCL]); **activity, shyness, and sociability** (measured using the Emotionality, Activity, and Shyness Temperament [EAST] Questionnaire), and **communication** (measured using the ASQ). At 3 years of age, compared with children of triptan users only before pregnancy, children of triptan users during pregnancy were more likely to have **emotionality problems** (adjusted RR 2.18, 95% CI 1.03 to 4.53) and **activity problems** (adjusted RR 1.70, 95% CI 1.02 to 2.80) (Table 20 and Table B-15).

Sumatriptan During Pregnancy Versus Sumatriptan Before Pregnancy Only

Description of Direct Evidence for Sumatriptan During Pregnancy Versus Sumatriptan Before Pregnancy Only

Two observational NRCSs (O'Quinn 1999 and Olesen 2000) addressed this comparison in a total of 291 pregnant patients with migraine (Tables B-10 to B-12).[52, 53] O'Quinn 1999 reported maternal adverse effects, while both studies reported fetal/child adverse effects.

Description of SR Evidence for Sumatriptan During Pregnancy Versus Sumatriptan Before Pregnancy Only

No SR reported on this comparison.

Maternal Benefit Outcomes of Sumatriptan During Pregnancy Versus Sumatriptan Before Pregnancy Only

No primary study or SR reported on maternal benefit outcomes for this comparison.

Maternal Adverse Effects of Sumatriptan During Pregnancy Versus Sumatriptan Before Pregnancy Only

O'Quinn 1999 (direct evidence) reported **abnormal pregnancy outcomes** occurred in 9 of 76 sumatriptan users during pregnancy (12%) and 19 of 92 sumatriptan users only before pregnancy (21%) (Table B-10). The authors did not, however, define abnormal pregnancy outcomes or report an adjusted effect size.

Fetal/Child Adverse Effects of Sumatriptan During Pregnancy Versus Sumatriptan Before Pregnancy Only

O'Quinn 1999 (direct evidence) reported that the rates of **spontaneous abortions** were 8 of 76 sumatriptan users during pregnancy (10.5%) and 11 of 92 sumatriptan users only before pregnancy (12%) (Table B-11). No adjusted effect sizes were reported.

Olesen 2000 (direct evidence) reported higher rates of **preterm births (<37 weeks)** in infants of sumatriptan users during pregnancy (5 of 34 patients; 14.7%) than infants of users before pregnancy only (3 of 89 patients; 3.4%) (adjusted OR 6.3, 95% CI 1.2 to 32.0) (Table 20 and Table B-12).

Olesen 2000 also reported similar rates of **low birth weight (<2,500 g)** in infants of sumatriptan users during pregnancy (1 of 34 patients; 3.4%) than infants of users only before pregnancy (5 of 89 patients; 5.8%) (adjusted OR 0.9, 95% CI 0.1 to 11.8) (Table 20 and Table B-12).

Any Triptan During Pregnancy Versus No Triptan During or Before Pregnancy

Description of Direct Evidence for Any Triptan During Pregnancy Versus No Triptan During or Before Pregnancy

Three observational NRCSs (Shuhaiber 1997, Nezvalova-Henriksen 2010, and Spielmann 2018) addressed this comparison in a total of 6,999 pregnant patients with migraine (Tables B-10 to B-16).[43, 45, 49, 51, 54-57] Although Nezvalova-Henriksen 2010 reported subgroup analyses by trimester of triptan use, no statistical analyses for subgroup differences were reported. One study reported maternal adverse effects, while all three studies reported fetal/child adverse effects.

Description of SR Evidence for Any Triptan During Pregnancy Versus No Triptan During or Before Pregnancy

One high-quality SR (Marchenko 2015) assessed harms associated with (any) triptan use during pregnancy (Table 22 and Tables B-26, B-27, B-28, and B-37).[79]

Maternal Benefit Outcomes of Any Triptan During Pregnancy Versus No Triptan During or Before Pregnancy

No primary study or SR reported on maternal benefit outcomes for this comparison.

Maternal Adverse Effects of Any Triptan During Pregnancy Versus No Triptan During or Before Pregnancy

Nezvalova-Henriksen 2010 (direct evidence) reported on the outcome of **postpartum hemorrhage (>500 mL)**. The rate of postpartum hemorrhage was 255 of 1,045 triptan users (24.4%) and not reported for nonusers (Table B-10). Women using triptans in the first trimester appeared to have higher rates of postpartum hemorrhage than those using it in the second or third trimester, but statistical analyses of subgroup differences were not reported.

The SR did not report maternal adverse effects.

Fetal/Child Adverse Effects of Any Triptan During Pregnancy Versus No Triptan During or Before Pregnancy

Two studies (Shuhaiber 1998 and Spielmann 2018) (direct evidence) reported on **spontaneous abortions.** Spielmann 2018 reported that rates of spontaneous abortions were similar between triptan users and nonusers (adjusted hazard ratio [HR] 1.41, 95% CI 0.9 to 2.2) (Table 20 and Table B-11). Shuhaiber 1998 also reported similar rates in the two arms, but did not report an adjusted effect size.

Two studies (Shuhaiber 1998 and Spielmann 2018) (direct evidence) reported on **elective or induced abortions** that were likely to be related to drug use. Spielmann 2018 reported that rates

of elective or induced abortions were similar between triptan users and nonusers (adjusted HR 1.58, 95% CI 0.8 to 3.0) (Table 20 and Table B-11). Shuhaiber 1998 also reported similar rates in the two arms, but did not report an adjusted effect size.

Two studies (Nezvalova-Henriksen 2010 and Spielmann 2018) (direct evidence) reported on the outcome of **stillbirth**. Spielmann 2018 reported that the rates of stillbirth were 0.2 percent in each arm. No adjusted effect sizes were reported (Table B-11). Nezvalova-Henriksen 2010 also reported on this outcome, but there were no stillbirths in either the triptan user or nonuser arms. Nezvalova-Henriksen 2010 (direct evidence) also reported on the outcome of perinatal death. The rate of perinatal death was 6 of 1,045 triptan users (0.6%) and not reported for nonusers.

Nezvalova-Henriksen 2010 (direct evidence) reported on the outcome of **infant death by 1 year of age**. The rate of infant death was 5 of 1,045 triptan users (0.5%). Infant deaths were not reported in the nonuser arm (Table B-11).

Nezvalova-Henriksen 2010 (direct evidence) reported on the outcome of **preterm birth (<37 weeks)**. The rate of preterm birth was 86 of 1,045 triptan users (8.2%) (Table B-12). Preterm births were not reported for the nonuser arm.

Nezvalova-Henriksen 2010 (direct evidence) reported on the outcome of **low birth weight**. The rate of low birth weight was 65 of 1,045 triptan users (6.2%) (Table B-12). Birth weights were not reported for the nonuser arm.

Nezvalova-Henriksen 2010 (direct evidence) reported on the outcome of **Apgar score being less than 7 at both 1 minute and at 5 minutes after birth**. The proportion of newborns born to patients who used triptans had Apgar scores of 8.4 percent vs. 2.2 percent at 1 minute and 5 minutes, respectively (Table B-12). Apgar scores were not reported for the nonuser arm.

Two studies (Nezvalova-Henriksen 2010 and Spielmann 2018) (direct evidence) reported **congenital anomalies**. Nezvalova-Henriksen 2010 reported a 7.2% rate of any anomalies in infants in the triptan user arm, but no data were reported for the nonuser arm. Spielmann reported similar rates of any congenital anomalies between triptan users and nonusers (adjusted OR 1.00, 95% CI 0.51 to 2.10). (Table 20 and Table B-13).

All three studies (Shuhaiber 1999, Nezvalova-Henriksen 2010, and Spielmann 2018) (direct evidence) reported data on **major congenital anomalies**. Spielmann 2018 reported similar rates of major congenital anomalies between infants of users and nonusers (adjusted OR 1.01, 95% CI 0.3 to 3.3) (Table 20 and Table B-13). The other two studies also reported similar rates of major congenital anomalies in the two arms (Table 9).

Spielmann 2018 (direct evidence) reported similar rates of **(unnamed) genetic birth defects** between infants of triptan users and nonusers (adjusted OR 1.10, 95% CI 0.2 to 6.6) (Table 20 and Table B-13).

Two studies (Shuhaiber 1999 and Spielmann 2018) (direct evidence) reported on **minor congenital anomalies**. Spielmann 2018 reported similar rates of minor congenital anomalies (e.g., congenital finger hypoplasia, club foot) between infants of triptan users and nonusers (adjusted OR 1.48, 95% CI 0.5 to 4.4) (Table 20 and Table B-13). Shuhaiber 1999 also reported similar rates of **minor congenital anomalies** (e.g., brown marks, red marks) in the two arms, but a between-group effect size was not reported.

Nezvalova-Henriksen 2010 (direct evidence) reported on **neurodevelopmental outcomes** at 1.5 years and 3 years of age, as measured by the ASQ. Compared with children of nonusers, children of triptan users during pregnancy had similar gross motor development (adjusted RR for being above a Z-score of 1.5 on the ASQ: 0.58, 95% CI 0.17 to 2.03) and fine motor

development (adjusted RR 0.85, 95% CI 0.56 to 1.29) at 3 years of age (Table 20 and Tables B-14).

Nezvalova-Henriksen 2010 (direct evidence) reported on various **behavioral and social outcomes at 1.5 years, 3 years, and 5 years of age**. These outcomes included **externalizing problems**, **internalizing problems**, and **emotionality** (measured using the CBCL); **activity, shyness, and sociability** (measured using the Emotionality, Activity, and Shyness Temperament [EAST] Questionnaire), and communication (measured using the ASQ). Triptan use, compared with nonuse, was not associated with differences in most of these outcomes, except for emotionality and activity. At 3 years of age, compared with children of triptan nonusers, children of triptan users during pregnancy were more likely to have **emotionality problems** (adjusted RR 2.51, 95% CI 1.27 to 4.90) and **activity problems (hyperactivity)** (adjusted RR 1.57, 95% CI 1.04 to 2.36) (Table 20 and Tables B-15 and B-16) At 5 years of age, there were no differences between groups in these outcomes.

Fetal/Child Adverse Effects Reported in SR Evidence for Triptans

The Marchenko 2015 SR reported that (any) triptan use was not associated with spontaneous abortion, preterm birth, or major congenital anomalies.

The findings in the Marchenko 2015 SR are consistent with the findings in the three primary studies that we identified for the same comparison of triptan use versus nonuse (Shuhaiber 1997, Nezvalova-Henriksen 2010, and Spielmann 2018). In these three primary studies, triptan use was not associated with an increased likelihood of spontaneous abortion, elective or induced abortion, or major or minor congenital anomalies.

Fetal/Child Adverse Effects Reported in Indirect Evidence for Antihistamines

The Etwel 2017 and Li 2019 SRs (indirect evidence) reported that (any) antihistamine use was not associated with spontaneous abortion, stillbirth, preterm birth, low birth weight, or major congenital anomalies.

The findings in the Etwel 2017 and Li 2019 SRs are consistent with the findings in the primary study that we identified for the use of pizotifen (a specific antihistamine) (Kallen 2011).

Table 20. Triptans: Summary of direct evidence regarding fetal/child harms

Outcome*	Outcome Definition	Study, Year, Design, PMID	Arm	n/N (%) or Mean (SD)	Adj Effect Size (95% CI)
Fetal/child death	Spontaneous abortion	Spielmann, 2018, NRCS, 28758416	Triptans: Any (during pregnancy)	50/432 (11.6)	Adj HR 1.41 (0.2, 2.2)
			No triptans during or before pregnancy	37/475 (7.8)	
	Elective or induced abortion		Triptans: Any (during pregnancy)	23/432 (5.3)	Adj HR 1.58 (0.8, 3.0)
			No triptans during or before pregnancy	17/475 (3.6)	
Preterm birth	<37 w	Olesen, 2000. NRCS, 10759898	Triptans: Sumatriptan (during pregnancy)	5/34 (14.7)	Adj OR 6.3 (1.2, 32.0)
			No sumatriptan during or before pregnancy	3/89 (3.4)	
Low birth weight	<2500 g		Triptans: Sumatriptan (during pregnancy)	1/34 (3.4)	Adj OR 0.9 (0.1, 11.8)
			No sumatriptan during or before pregnancy	5/89 (5.8)	
Congenital anomalies	Any	Spielmann, 2018, NRCS, 28758416	Triptans: Any (during pregnancy)	25/372 (6.7)	Adj OR 1.00 (0.51, 2.10)
			No triptans during or before pregnancy	28/431 (6.5)	
	Major		Triptans: Any (during pregnancy)	9/367 (2.5)	Adj OR 1.01 (0.3, 3.3)
			No triptans during or before pregnancy	12/429 (2.8)	
	Genetic birth defects		Triptans: Any (during pregnancy)	5/369 (1.4)	Adj OR 1.10 (0.2, 6.6)
			No triptans during or before pregnancy	4/429 (0.9)	
	Minor		Triptans: Any (during pregnancy)	11/364 (3.0)	Adj OR 1.48 (0.5, 4.4)
			No triptans during or before pregnancy	12/427 (2.8)	
Neurodevelopmental AEs	Gross motor development at 3 y	Nezvalova-Henriksen 2010, NRCS, 20132339	Triptans: Any (during pregnancy)	6/495 (1.2)	Vs. Triptans before pregnancy only RR 0.86 (0.23, 3.19) Vs. No Triptans RR 0.58 (0.17, 2.03)
			Triptans: Any (before pregnancy only)	30/1002 (3.0)	
			No triptans during or before pregnancy	122/4050 (3.0)	
	Fine motor development at 3 y		Triptans: Any (during pregnancy)	47/495 (9.5)	Vs. Triptans before pregnancy only Adj RR 0.85 (0.52, 1.37) Vs. No Triptans Adj RR 0.85 (0.56, 1.29)
			Triptans: Any (before pregnancy only)	94/1002 (9.4)	
			No triptans during or before pregnancy	373/4050 (9.2)	

Outcome*	Outcome Definition	Study, Year, Design, PMID	Arm	n/N (%) or Mean (SD)	Adj Effect Size (95% CI)
Social and behavioral AEs	Externalizing problems at 3 y	Nezvalova-Henriksen 2010, NRCS, 20132339	Triptans: Any (during pregnancy)	101/1085 (9.3)	Adj RR 0.99 (0.77, 1.27)
			No triptans (during or before pregnancy)	297/3354 (8.9)	
	Externalizing problems at 5 y		Triptans: Any (during pregnancy)	25/340 (7.4)	Adj RR 0.68 (0.44, 1.05)
			No triptans (during or before pregnancy)	15/1457 (10.6)	
	Internalizing problems at 3 y		Triptans: Any (during pregnancy)	47/495 (9.5)	Vs. Triptans before pregnancy only Adj RR 0.69 (0.41, 1.14) Vs. No Triptans Adj RR 1.02 (0.66, 1.57)
			Triptans: Any (before pregnancy only)	108/1002 (10.8)	
			No triptans (during or before pregnancy)	425/4050 (10.5)	
	Emotionality at 3 y on the CBCL		Triptans: Any (during pregnancy)	31/495 (6.3)	Vs. Triptans before pregnancy only Adj RR 2.18 (1.03, 4.53) Vs. No Triptans Adj RR 2.51 (1.27, 4.90)
			Triptans: Any (before pregnancy only)	47/1002 (4.7)	
			No triptans (during or before pregnancy)	158/4050 (3.9)	
	Emotionality at 5 y		Triptans: Any (during pregnancy)	49.7 (9.9)	Adj NMD –1.02 (–2.3, 0.29)
			No triptans (during or before pregnancy)	50.5 (10.0)	
	Activity at 3 y on the EAST Questionnaire		Triptans: Any (during pregnancy)	41/495 (8.3)	Vs. Triptans before pregnancy only Adj RR 1.70 (1.02, 2.80) Vs. No Triptans Adj RR 1.57 (1.04, 2.36)
			Triptans: Any (before pregnancy only)	47/1002 (4.7)	
			No triptans (during or before pregnancy)	215/4050 (5.3)	
	Activity at 5 y		Triptans: Any (during pregnancy)	49.3 (10.2)	Adj NMD –0.06 (–1.35, 1.23)
			No triptans (during or before pregnancy)	50.1 (10.2)	
	Shyness at 3 y		Triptans: Any (during pregnancy)	61/495 (12.3)	Vs. Triptans before pregnancy only Adj RR 0.92 (0.52, 1.63) Vs. No Triptans RR 1.30 (0.81, 2.08)
			Triptans: Any (before pregnancy only)	96/1002 (9.6)	
			No triptans (during or before pregnancy)	312/4050 (7.7)	
	Shyness at 5 y		Triptans: Any (during pregnancy)	50.1 (10.0)	Adj NMD –0.71 (–0.28, 0.65)
			No triptans (during or before pregnancy)	50.5 (10.1)	

Outcome*	Outcome Definition	Study, Year, Design, PMID	Arm	n/N (%) or Mean (SD)	Adj Effect Size (95% CI)
Social and behavioral AEs (continued)	Sociability at 3 y	Nezvalova-Henriksen 2010, NRCS, 20132339	Triptans: Any (during pregnancy)	31/495 (6.3)	Vs. Triptans before pregnancy only Adj RR 0.70 (0.40, 1.38) Vs. No Triptans Adj RR 1.13 (0.70, 1.82)
			Triptans: Any (before pregnancy only)	64/1002 (6.4)	
			No triptans (during or before pregnancy)	247/4050 (6.1)	
	Sociability at 5 y		Triptans: Any (during pregnancy)	51.0 (10.4)	Adj NMD 1.66 (–0.30, 3.02)
			No triptans (during or before pregnancy)	49.6 (10.5)	
	Communication at 3 y		Triptans: Any (during pregnancy)	23/495 (4.6)	Vs. Triptans before pregnancy only Adj RR 1.22 (0.56, 2.68) Vs. No Triptans Adj RR 0.97 (0.48, 1.95)
			Triptans: Any (before pregnancy only)	45/1002 (4.5)	
			No triptans (during or before pregnancy)	211/4050 (5.2)	

Abbreviations: Adj = adjusted, AE = adverse effect, CBCL = Child Behavior Checklist, CI = confidence interval, EAST = Emotionality, Activity, and Shyness Temperament, HR = hazard ratio, min = minutes, NMD = net mean difference, NRCS = nonrandomized comparative study, OR = odds ratio, PMID = PubMed identifier, RR = relative risk, y = years, SD = standard deviation.

This table provides only data pertaining to outcomes with reported adjusted effect sizes. For full data, please refer to individual evidence tables. (Tables B-10 to B-16).

* No studies reported acute headache attack outcomes (severity, duration, resolution, recurrence), headache-related symptom outcomes (severity, duration, resolution, recurrence), emergency department or clinic visits, hospitalizations, quality of life, functional outcomes (impact on family life, work/school attendance, time spent managing disease), resource use, acceptability of intervention by patients, patient satisfaction with intervention, medication use, serious maternal AEs (any serious, cardiovascular), nonserious maternal AEs (any nonserious, nonobstetrical, preterm labor/CS, reduced breast milk, medication withdrawal symptoms), discontinuation due to maternal AEs, serious fetal/child AEs (any serious AE, perinatal complications), nonserious fetal/child AEs (any nonserious AE, breastfeeding delay/cessation/etc., poor infant attachment/bonding, medication withdrawal symptoms), or discontinuation due to fetal/child AEs.

Table 21. Triptans, ergot products, NSAIDs (naproxen), and antihistamines (pizotifen): Evidence profile for direct evidence regarding use to treat primary headaches

Topic	Comparison	Outcome Category	Outcome	N Studies (Subjects)	RoB	Consistency	Precision	Directness	SoE	Conclusions
Benefits	-	-	-	0	-	-	-	-	None	None
Harms	Sumatriptan vs. naratriptan (during pregnancy)	AEs – Fetal/Child	Spontaneous abortion or elective or induced abortion	1 (689)	High	N/A	N/A	Direct	Insufficient	No conclusion made
			Stillbirth or fetal death	1 (689)	High	N/A	N/A	Direct	Insufficient	No conclusion made
			Congenital anomalies	1 (689)	High	N/A	N/A	Direct	Insufficient	No conclusion made
	Sumatriptan vs. sumatriptan and naproxen combination (during pregnancy)	AEs – Fetal/Child	Spontaneous abortion or elective or induced abortion	1 (689)	High	N/A	N/A	Direct	Insufficient	No conclusion made
			Stillbirth or fetal death	1 (689)	High	N/A	N/A	Direct	Insufficient	No conclusion made
			Congenital anomalies	1 (689)	High	N/A	N/A	Direct	Insufficient	No conclusion made
	Naratriptan vs. sumatriptan and naproxen combination (during pregnancy)	AEs – Fetal/Child	Spontaneous abortion or elective or induced abortion	1 (689)	High	N/A	N/A	Direct	Insufficient	No conclusion made
			Stillbirth or fetal death	1 (689)	High	N/A	N/A	Direct	Insufficient	No conclusion made
			Congenital anomalies	1 (689)	High	N/A	N/A	Direct	Insufficient	No conclusion made
	Any triptan vs. any ergot product (during pregnancy)	AEs – Fetal/Child	Stillbirth or fetal death	1 (3368)	High	N/A	N/A	Direct	Insufficient	No conclusion made
			Preterm birth	1 (3368)	High	N/A	N/A	Direct	Insufficient	No conclusion made
			Low birth weight	1 (3368)	High	N/A	N/A	Direct	Insufficient	No conclusion made
			Congenital anomalies	1 (3368)	High	N/A	N/A	Direct	Insufficient	No conclusion made
	Any triptan vs. pizotifen (during pregnancy)	AEs – Fetal/Child	Stillbirth or fetal death	1 (3368)	High	N/A	N/A	Direct	Insufficient	No conclusion made
			Preterm birth	1 (3368)	High	N/A	N/A	Direct	Insufficient	No conclusion made
			Low birth weight	1 (3368)	High	N/A	N/A	Direct	Insufficient	No conclusion made
			Congenital anomalies	1 (3368)	High	N/A	N/A	Direct	Insufficient	No conclusion made
	Any ergot product vs. pizotifen (during pregnancy)	AEs – Fetal/Child	Congenital anomalies	1 (5900)	High	N/A	N/A	Direct	Insufficient	No conclusion made

Topic	Comparison	Outcome Category	Outcome	N Studies (Subjects)	RoB	Consistency	Precision	Directness	SoE	Conclusions
Harms (continued)	Any triptan (during pregnancy) vs. any triptan (before pregnancy)	AEs – Maternal	Serious AEs	2 (8460)	High	N/A	N/A	Direct	Insufficient	No conclusion made
		AEs – Fetal/Child	Stillbirth or fetal death	1 (5900)	High	N/A	N/A	Direct	Insufficient	No conclusion made
			Neonatal or infant death	1 (5900)	High	N/A	N/A	Direct	Insufficient	No conclusion made
			Preterm birth	2 (8460)	High	N/A	N/A	Direct	Insufficient	No conclusion made
			Low birth weight	2 (8460)	High	N/A	N/A	Direct	Insufficient	No conclusion made
			Congenital anomalies	2 (8460)	High	N/A	N/A	Direct	Insufficient	No conclusion made
			Perinatal complications	2 (8460)	High	N/A	N/A	Direct	Insufficient	No conclusion made
			Neurodevelopmental/ behavioral/social AEs	1 (5900)	High	N/A	Imprecise	Direct	Low	Similar gross motor and fine motor development, but worse emotionality and activity outcomes (hyperactivity) at 3 years of age for use during pregnancy versus before pregnancy.
	Sumatriptan (during pregnancy) vs. sumatriptan (before pregnancy)	AEs – Maternal	Serious Maternal AEs	1 (168)	High	N/A	N/A	Direct	Insufficient	No conclusion made
		AEs – Fetal/Child	Spontaneous abortion	1 (168)	High	N/A	N/A	Direct	Insufficient	No conclusion made
			Preterm birth	1 (123)	Moderate	N/A	Imprecise	Direct	Insufficient	No conclusion made
			Low birth weight	1 (123)	Moderate	N/A	Imprecise	Direct	Insufficient	No conclusion made

Topic	Comparison	Outcome Category	Outcome	N Studies (Subjects)	RoB	Consistency	Precision	Directness	SoE	Conclusions
Harms (continued)	Any triptan (during pregnancy) vs. no triptans (during or before pregnancy)	AEs – Maternal	Serious Maternal AEs	1 (5900)	High	N/A	N/A	Indirect	Insufficient	No conclusion made
		AEs – Fetal/Child	Spontaneous abortion or elective or induced abortion	2 (1099)	High	N/A	N/A	Direct	Low	No difference for spontaneous or elective abortion
			Stillbirth or fetal death	2 (6807)	High	N/A	N/A	Direct	Insufficient	No adjusted between-arm estimates available
			Neonatal or infant death	1 (5900)	High	N/A	N/A	Direct	Insufficient	No adjusted between-arm estimates available
			Preterm birth	1 (5900)	High	N/A	N/A	Indirect	Insufficient	No conclusion made
			Low birth weight	1 (5900)	High	N/A	N/A	Indirect	Insufficient	No conclusion made
			Congenital anomalies	3 (6999)	High	N/A	Imprecise	Direct	Low	No difference for any, major, minor, and genetic birth defects. spontaneous or elective abortion.
			Perinatal complications	1 (5900)	High	N/A	N/A	Indirect	Insufficient	No conclusion made
			Neurodevelopmental/ behavioral/social AEs	1 (5900)	High	N/A	N/A	Direct	Low	Similar gross motor and fine motor development, but worse emotionality and activity (hyperactivity) for use during pregnancy versus nonuse (during or before pregnancy).

Abbreviations: AE = adverse effect, N/A = not applicable, NS = not statistically significant, RoB = risk of bias, SoE = strength of evidence.

Consistency was deemed "N/A" when it could not be assessed because only one study was found. Consistency was also deemed "N/A" in some instances where more than one study was found because at least one of the studies did not report adjusted between-arm effect sizes, precluding an assessment of consistency.

Table B-32 provides the complete version of this Evidence Profile, including displaying outcomes for which no studies were identified.

Table 22. Triptans: Evidence profile for existing systematic review regarding harms

Drug	Outcome Category	Outcome	N SRs (N Studies)	RoB in Included Studies	Consistency	Precision	Directness	SoE	Conclusion
Triptans, any	AEs – Fetal/Child	Spontaneous abortion or elective or induced abortion	1 (2)	Unclear	Consistent	Precise	Direct	Moderate	No increased risk of spontaneous abortion
		Preterm birth	1 (3)	Unclear	Inconsistent	Imprecise	Direct	Low	No increased risk
		Congenital anomalies	1 (3)	Unclear	Consistent	Precise	Direct	Moderate	No increased risk of major anomalies

Abbreviations: AE = adverse effect, RoB = risk of bias, SoE = strength of evidence, SR = systematic review.

Table B-37 provides the complete version of this Evidence Profile, including displaying outcomes for which no evidence was identified.

NSAIDs (Any, Indomethacin, and Low-Dose Aspirin)

Description of Direct Evidence for NSAIDs (Any, Indomethacin, and Low-Dose Aspirin)

We did not find any primary studies on use of "any" NSAID or of indomethacin or low-dose aspirin for treating attacks of primary headache in women who were pregnant (or attempting to become pregnant), postpartum, or breastfeeding.

Description of Indirect Evidence for NSAIDs (Any, Indomethacin, and Low-Dose Aspirin)

Eight SRs (six of high quality[66, 70, 73-75, 81] and two of moderate quality[64, 67]) assessed harms associated with use of any NSAID (one medium-quality SR), indomethacin (one high-quality SR), and low-dose aspirin (five high-quality SRs and one moderate-quality SR) (regardless of indication) (Tables 23 and 24 and Tables B-26, B-27, B-28, and B-37). One of these SRs (Bellos 2020b[64]) examined NSAID use in the postpartum period; the rest examined NSAID use during pregnancy.

Maternal Benefit Outcomes of NSAIDs (Any, Indomethacin, and Low-Dose Aspirin)

No primary study or SR reported on maternal benefit outcomes of "any" NSAID or of indomethacin or low-dose aspirin.

Maternal Adverse Effects of NSAIDs (Any, Indomethacin, and Low-Dose Aspirin)

No primary study (direct evidence) reported on maternal adverse effects of "any" NSAID or of indomethacin or low-dose aspirin.

The Bellos 2020b SR (indirect evidence) reported that use of "any" NSAID in the postpartum period was not associated with postpartum hypertension.

No SR (indirect evidence) reported on maternal adverse effects of indomethacin.

Five SRs (Henderson 2014, Coomarasamy 2003, Duley 2007, Hamulyak 2020, and Maze 2019) (indirect evidence) reported that low-dose aspirin use during pregnancy was not associated

with adverse effects antepartum (e.g., placental abruption or other antepartum bleeding), during delivery (e.g., cesarean section), or postpartum (e.g., postpartum hemorrhage).

Fetal/Child Adverse Effects of NSAIDs (Any, Indomethacin, and Low-Dose Aspirin)

No primary study (direct evidence) reported on fetal/child adverse effects of indomethacin or low-dose aspirin.

The Bellos 2020b SR (indirect evidence) did not report on fetal/child adverse effects of "any" NSAID.

The Hammers 2015 SR (indirect evidence) reported that indomethacin use during pregnancy was associated with **neonatal complications**, such as **periventricular leukomalacia** (RR 1.59, 95% CI 1.17 to 2.17), **Grade III-IV intraventricular hemorrhage** (RR 1.29, 95% CI 1.06 to 1.56), and **necrotizing enterocolitis** (RR 1.36, 95% CI 1.08 to 1.71) (Table 23). Indomethacin use was not associated with neonatal mortality, sepsis, or patent ductus arteriosus.

Five SRs (indirect evidence) reported that low-dose aspirin use during pregnancy was not associated with adverse effects *in utero* (e.g., spontaneous abortion, fetal growth restriction), perinatal (e.g., low birth weight, small for gestational age), or during infant/child growth (e.g., gross motor function, fine motor problems, behavioral problems). The Duley 2007 SR (indirect evidence) reported that low-dose aspirin use during pregnancy was associated with hearing problems in the child, but this was not statistically significant (RR 2.54, 95% CI 0.10 to 62.10).

Table 23. NSAIDs (indomethacin and low-dose aspirin): Summary of indirect evidence of fetal/child harms, statistically significant findings

SR, Year Published, PMID	Intervention Class	Intervention Name	Timing of Occurrence of Adverse Effect	Adverse Effect	N Studies	Effect Size (95% CI)
Hammers, 2015, 25448524	NSAIDs	Indomethacin	Neonatal	Periventricular leukomalacia	9	RR 1.59 (1.17, 2.17)
				Intraventricular hemorrhage: Grade III-IV	16	RR 1.29 (1.06, 1.56)
				Necrotizing enterocolitis	18	RR 1.36 (1.08, 1.71)

Abbreviations: CI = confidence interval, IV = intravenous, NSAID = nonsteroidal antiinflammatory drug, PMID = PubMed identifier, RR = relative risk, SR = systematic review.

Low-dose aspirin was not found to be statistically significantly associated with fetal/child harms, and is thus omitted from this table.

Table 24. NSAIDs (indomethacin and low-dose aspirin): Evidence profile for indirect evidence regarding harms of use during pregnancy

Drug	Outcome Category	Outcome	N SRs (N Studies)	RoB in Included Studies	Consistency	Precision	Directness	SoE	Conclusions
Any	AEs – Maternal	Cardiovascular	1 (4)	Moderate	Consistent	Precise	Indirect	Moderate	No increased risk of postpartum hypertension
Indomethacin	AEs – Fetal/Child	Neonatal or infant death	1 (15)	Unclear	Consistent	Precise	Indirect	Low	No increased risk of neonatal death
		Congenital anomalies	1 (17)	Unclear	Consistent	Precise	Indirect	Low	No increased risk of patent ductus arteriosus
		Perinatal complications	1 (9-18)	Unclear	Consistent	Precise	Indirect	Low	Increased risk of periventricular leukomalacia, Grade III-IV intraventricular hemorrhage, and necrotizing enterocolitis
Low-dose aspirin	AEs – Maternal	Any serious AE	1 (3)	Low	Consistent	Precise	Indirect	Moderate	No increased risk of hospitalization
	AEs – Fetal/Child	Spontaneous abortion or elective or induced abortion	3 (3-28)	Low to moderate	Consistent	Precise	Indirect	Low	No increased risk of spontaneous abortion
		Stillbirth or fetal death	3 (3-28)	Low to moderate	Consistent	Precise	Indirect	Low	No increased risk of stillbirth, perinatal mortality
		Neonatal or infant death	3 (3-28)	Low to moderate	Consistent	Precise	Indirect	Low	No increased risk of infant death
		Preterm birth	4 (9)	Low to moderate	Consistent	Precise	Indirect	Low	No increased risk
		Low birth weight	2 (8)	Low to moderate	Inconsistent	Precise	Indirect	Low	No increased risk
		Perinatal complications	1 (8-15)	Low to moderate	Inconsistent	Precise	Indirect	Low	No increased risk of NICU admission, intraventricular hemorrhage, other neonatal bleed
		Neurodevelopmental/ behavioral/ social	1 (1)	Low	N/A	Imprecise	Indirect	Low	No increased risk of gross motor, fine motor, language, hearing, speech, etc.

Abbreviations: AE = adverse effect, NICU = neonatal intensive care unit, NSAID = nonsteroidal antiinflammatory drug, RoB = risk of bias, SoE = strength of evidence, SR = systematic review.

Table B-37 provides the complete version of this Evidence Profile, including displaying outcomes for which no evidence was identified.

Antiemetics (Metoclopramide), Antihistamines (Diphenhydramine), and Opioid Analgesics (Codeine)

Description of Direct Evidence for Metoclopramide, Diphenhydramine, and Codeine

One RCT, described in three articles,[37, 39, 40] reported on the effects and harms of metoclopramide, diphenhydramine, and codeine in pregnant patients with primary headaches (Tables 25 and 26 and Tables B-1, B-2, B-7 to 9, and B-33).

Childress 2018, reported in three articles, studied 70 pregnant women with either migraine or tension headache in the U.S.[37, 39, 40] The study did not report how many patients had migraine and how many had tension headache. Other eligibility criteria included being in the second or third trimester, normotensive, and headaches not relieved by acetaminophen. Patients were randomized to a combination of metoclopramide (a dopamine receptor antagonist antiemetic) 10 mg and diphenhydramine (an antihistamine) 25 mg intravenously, as a single dose, or to codeine (an opioid-containing analgesic) 30 mg orally, as a single dose. Patients in either arm could receive a second dose of the same intervention, if the pain was not relieved. Patients were relatively young (median age 23 years) and majority black (76%). The median gravidity was 3 and parity 1. The median gestational ages were 31.9 weeks in the combination arm and 28.4 weeks in the codeine arm. We assessed the study at overall high risk of bias due to lack of blinding of patients, study personnel, and outcome assessors, and due to selective outcome reporting.

Description of Indirect Evidence for Diphenhydramine

Two high-quality SRs (Etwel 2017[72] and Li 2019[77]) assessed fetal/child harms associated with (any) antihistamine use during pregnancy (regardless of indication) (Table 16 and Tables B-26, B-27, B-28, and B-37). The SRs did not report maternal benefit outcomes or maternal adverse effects.

Maternal Benefit Outcomes of Metoclopramide, Diphenhydramine, and Codeine

Childress 2018 (direct evidence) reported on the effect of treatment on **severity of acute headache attacks** over 24 hours using a visual analog scale (VAS) from 0 to 10 (maximum pain). Patients in the combination metoclopramide and diphenhydramine treatment arm experienced greater reductions in pain than did patients in the codeine arm, as measured by the net mean difference (NMD), i.e., the between-arm difference in the within-arm changes (difference-in-difference). The NMDs were statistically significant at 30 minutes (−3.0, 95% CI −4.2 to −1.8), at 1 hour (−2.1, 95% CI −3.3 to −0.9), and at 12 hours (−1.6, 95% CI −2.9 to −0.3), but not at 6 hours or 24 hours. At 24 hours, all patients in both arms experienced at least a 2-point reduction in pain on the VAS (Table 25).

Childress 2018 also reported that patients in the combination treatment arm were more likely than patients in the codeine arm to experience **relief from headache with one dose** (OR 1.37, 95% CI 1.07 to 1.75) and to experience **complete resolution of headache at 24 hours** (OR 5.42, 95% CI 1.86 to 15.76) (Table 25). Combination treatment also provided **relief from headache** 42.2 minutes sooner (95% CI 20.7 to 63.7) than codeine treatment.

Childress 2018 also found **lower recurrence of headache** by 24 hours in patients in the combination treatment arm (13 of 34 patients; 38.2%) than the codeine arm (19 of 32 patients;

59.4%), but the between-arm comparison was not statistically significant (OR 0.42, 95% CI 0.16 to 1.14) (Table 25).

Childress 2018 also found **lower use of nonstudy medications by 24 hours** in patients in the combination treatment arm (7 of 34 patients; 20.6%) than the codeine arm (12 of 32 patients; 37.5%), but the between-arm comparison was not statistically significant (OR 0.43, 95% CI 0.14 to 1.29) (Table 25).

Maternal Adverse Effects of Metoclopramide, Diphenhydramine, and Codeine

Childress 2018 (direct evidence) reported that **no serious maternal adverse effects** occurred within 24 hours in either arm (Table 25). Reported nonserious adverse effects included fatigue, dizziness, agitation, nausea, and intravenous site pain (Table 25). Within 24 hours, 44.1 percent of the 34 women in the combination drug arm and 31.3 percent of the 32 women in the opioid arms had nonserious adverse effects. The between-arm comparison was not statistically significant (OR 1.74, 95% CI 0.63 to 4.76).

The Etwel 2017 and Li 2019 SRs (indirect evidence) reported that (any) antihistamine use was not associated with spontaneous abortion, stillbirth, preterm birth, low birth weight, or major congenital anomalies.

Table 25. Combination metoclopramide and diphenhydramine versus codeine: Summary of direct evidence regarding use to treat primary headaches

Outcome*	Definition	Study, Year, Design, PMID	Arm	n/N (%) or Mean (SD)	Effect Size (95% CI)
Severity of acute headache attacks	Pain score on VAS (0–10), 30 min	Childress, 2018, RCT, 29723901	Comb metoclopramide & diphenhydramine	3.0 (2.8)	NMD –3.0 (–4.2, –1.8) †
			Codeine	5.8 (2.3)	
	Pain score on VAS (0–10), 1 hr		Comb metoclopramide & diphenhydramine	2.2 (2.3)	NMD –2.1 (–3.3, –0.9) †
			Codeine	4.1 (3.0)	
	Pain score on VAS (0–10), 6 hr		Comb metoclopramide & diphenhydramine	1.8 (NR)	NMD –0.9 (–2.2, 0.4) †
			Codeine	2.5 (NR)	
	Pain score on VAS (0–10), 12 hr		Comb metoclopramide & diphenhydramine	1.3 (2.5)	NMD –1.6 (–2.9, –0.3)
			Codeine	2.7 (3.0)	
	Pain score on VAS (0–10), 24 hr		Comb metoclopramide & diphenhydramine	2.1 (NR)	NMD –1.0 (–2.3, 0.3) †
			Codeine	2.9 (NR)	
	Reduction >=2 on VAS (0–10), 24 hr		Comb metoclopramide & diphenhydramine	34/34 (100)	No nonevents
			Codeine	32/32 (100)	
Resolution of acute headache attack	Relief with 1 dose		Comb metoclopramide & diphenhydramine	32/34 (94.1)	OR 1.37 (1.07, 1.75)
			Codeine	22/32 (68.8)	
	Time to relief		Comb metoclopramide & diphenhydramine	20.2 min (13.4)	MD –42.2 min (–63.7, –20.7)
			Codeine	62.4 min (62.2)	
	Complete resolution at 24 hr		Comb metoclopramide & diphenhydramine	26/34 (76.5)	OR 5.42 (1.86, 15.76)
			Codeine	12/32 (37.5)	
Recurrence of acute headache attacks	Recurrence of headache at 24 hr		Comb metoclopramide & diphenhydramine	13/34 (38.2)	OR 0.42 (0.16, 1.14)
			Codeine	19/32 (59.4)	
Medication use	Use of nonstudy medication		Comb metoclopramide & diphenhydramine	7/34 (20.6)	OR 0.43 (0.14, 1.29)
			Codeine	12/32 (37.5)	
AEs – Maternal – Serious, Any	Any serious AE		Comb metoclopramide & diphenhydramine	0/34 (0.0)	No events
			Codeine	0/34 (0.0)	
AEs – Maternal – Nonserious, Any	Any nonserious maternal AE		Comb metoclopramide & diphenhydramine	15/34 (44.1)	OR 1.74 (0.63, 4.76)
			Codeine	10/32 (31.3)	

Abbreviations: AE = adverse effect, CI = confidence interval, Comb = combination, hr = hours, MD = mean difference, min = minutes, NMD = net mean difference, NR = not reported, OR = odds ratio, PMID = PubMed identifier, RCT = randomized controlled trial, SD = standard deviation, VAS = visual analog scale.

* No studies reported acute headache attack outcomes (duration), headache-related symptom outcomes (severity, duration, resolution, recurrence), emergency department or clinic visits, hospitalizations, quality of life, functional outcomes (impact on family life, work/school attendance, time spent managing disease), resource use, acceptability of intervention by patients, patient satisfaction with intervention, serious maternal AEs (cardiovascular), nonserious maternal AEs (nonobstetrical, preterm labor/CS, reduced breast milk, medication withdrawal symptoms), discontinuation due to maternal AEs, serious fetal/child AEs (any serious AE, spontaneous abortion or elective or induced abortion, stillbirth or fetal death, neonatal or infant death, preterm birth, low birth weight, congenital anomalies, perinatal complications, neurodevelopmental/behavioral/social), nonserious fetal/child AEs (any nonserious AE, breastfeeding delay/cessation/etc., poor infant attachment/bonding, medication withdrawal symptoms), or discontinuation due to fetal/child AEs.

† Calculated by us based on reported arm-specific data.

Table 26. Combination metoclopramide and diphenhydramine versus codeine: Evidence profile for direct evidence regarding use to prevent primary headaches

Topic	Comparison	Outcome Category	Outcome	N Studies (Subjects)	RoB	Consistency	Precision	Directness	SoE	Conclusion
Benefits	Combination of metoclopramide and diphenhydramine vs. codeine	Acute headache attacks	Severity of acute headache attacks	1 (70)	High	N/A	Imprecise	Direct	Low	Severity reduced more in combination arm
			Resolution of acute headache attacks	1 (70)	High	N/A	Imprecise	Direct	Low	More and quicker resolution in combination arm
			Recurrence of acute headache attacks	1 (70)	High	N/A	Imprecise	Direct	Low	Recurrence lower in combination arm, but NS
Harms	Combination of metoclopramide and diphenhydramine vs. codeine	AEs – Maternal	Any serious AE	1 (70)	High	N/A	Imprecise	Direct	Low	No events in either arm

Abbreviations: AE = adverse effect, N/A = not applicable, NS = not statistically significant, RoB = risk of bias, SoE = strength of evidence.

Consistency was deemed "N/A" when it could not be assessed because only one study was one found.

Table B-33 provides the complete version of this Evidence Profile, including displaying outcomes for which no studies were identified.

Antiemetics (5HT3 Antagonists)

Description of Direct Evidence for Antiemetics (5HT3 Antagonists)

We did not find any primary studies on use of antiemetics (5HT3 antagonists) for treating attacks of primary headache in women who were pregnant (or attempting to become pregnant), postpartum, or breastfeeding.

Description of Indirect Evidence for Antiemetics (5HT3 Antagonists)

Two high-quality SRs (Kaplan 2019[76] and Picot 2020[85]) assessed harms associated with use of antiemetics (5HT3 antagonists), specifically ondansetron, during pregnancy (regardless of indication) (Tables 27 and 28 and Tables B-26, B-27, B-28, and B-37).

The search for Kaplan 2019 was conducted in 2016, while that for Picot 2020 was run in 2019. Picot 2020 was thus able to include more relevant studies than Kaplan 2019 (12 versus 9). We therefore summarize harms reported in Picot 2020.

Maternal Benefit Outcomes of Antiemetics (5HT3 Antagonists)

No primary study or SR reported on maternal benefit outcomes of antiemetics (5HT3 antagonists).

Maternal Adverse Effects of Antiemetics (5HT3 Antagonists)

No primary study or SR reported on maternal adverse effects of antiemetics (5HT3 antagonists).

Fetal/Child Adverse Effects of Antiemetics (5HT3 Antagonists)

No primary study (direct evidence) reported on fetal/child adverse effects of antiemetics (5HT3 antagonists).

The Picot 2020 SR (indirect evidence) reported that use of ondansetron was associated with various congenital anomalies, such as ventricular septum defect, hypoplastic left heart, orofacial clefts, diaphragmatic hernia, and respiratory system anomalies.

Table 27. Antiemetics (5HT3 antagonists): Summary of indirect evidence of fetal/child harms, statistically significant findings

SR, Year Published, PMID	Intervention Class	Intervention Name	Timing of Occurrence of Adverse Effect	Adverse Effect	N Studies	Effect Size (95% CI)
Picot, 2020, 32420702	Antiemetics: 5HT3 Antagonists	Ondansetron	Neonatal	Congenital anomalies, Ventricular septum defect	6	OR 1.11 (1.00, 1.23)
				Congenital anomalies, Hypoplastic left heart	3	OR 1.49 (1.03, 2.17)
				Congenital anomalies, Orofacial clefts (any)	4	OR 1.22 (1.00, 1.49)
				Congenital anomalies, Diaphragmatic hernia	3	OR 1.71 (1.18, 2.49)
				Congenital anomalies, Respiratory system anomalies	2	OR 1.13 (1.01, 1.27)

Abbreviations: CI = confidence interval, OR = odds ratio, PMID = PubMed identifier, SR = systematic review.

Table 28. Antiemetics (5HT3 antagonists): Evidence profile for indirect evidence regarding harms of use during pregnancy

Drug	Outcome Category	Outcome	N SRs (N Studies)	RoB in Included Studies	Consistency	Precision	Directness	SoE	Conclusions
Ondansetron	AEs – Fetal/Child	Congenital anomalies	2 (16)	Moderate	Consistent	Precise	Indirect	Moderate	Increased risk of cardiovascular anomalies, orofacial clefts, diaphragmatic hernia, and respiratory system anomalies

Abbreviations: AE = adverse effect, RoB = risk of bias, SoE = strength of evidence, SR = systematic review.

Table B-37 provides the complete version of this Evidence Profile, including displaying outcomes for which no evidence was identified.

Antipsychotics

Description of Direct Evidence for Antipsychotics

We did not find any primary studies on use of antipsychotics for treating attacks of primary headache in women who were pregnant (or attempting to become pregnant), postpartum, or breastfeeding.

Description of Indirect Evidence for Antipsychotics

Two SRs (one of high quality [Coughlin 2015][68] and one of moderate quality [Terrana 2015][86]) assessed harms associated with (any) antipsychotic use during pregnancy (regardless of indication) (Tables 29 and 30 and Tables B-26, B-27, B-28, and B-37).

Maternal Benefit Outcomes of Antipsychotics

No primary study or SR reported on maternal benefit outcomes of antipsychotics.

Maternal Adverse Effects of Antipsychotics

No primary study or SR reported on maternal adverse effects of antipsychotics.

Fetal/Child Adverse Effects of Antipsychotics

No primary study (direct evidence) reported on fetal/child adverse effects of antipsychotics.

Both SRs (indirect evidence) reported that antipsychotic use was associated with increased likelihood of **preterm birth (<37 weeks)** (ORs approximately 1.9) and **major congenital anomalies** (ORs approximately 2.1). Coughlin 2015 also reported that antipsychotic use was associated somewhat **lower birth weight** (mean difference [MD] –58 g, CI –103 to –12) and increased likelihood of infants being **small for gestational age** (OR 2.44, 95% CI 1.22 to 4.86). Terrana 2015 also reported an association for small for gestational age, but this was not statistically significant (OR 1.58, 95% CI 0.91 to 2.74). Finally, Coughlin 2015 also reported an increased likelihood of **congenital cardiovascular anomalies** (OR 2.09, 95% CI 1.50 to 2.91) (Table 29).

Table 29. Antipsychotics: Summary of indirect evidence of fetal/child harms, statistically significant findings

SR, Year Published, PMID	Intervention Class	Intervention Name	Timing of Occurrence of Adverse Effect	Adverse Effect	N Studies	Effect Size (95% CI)
Coughlin, 2015, 25932852	Antipsychotics	Any	Perinatal	Preterm birth (<37 weeks)	7	OR 1.86 (1.45, 2.39)
				Birth weight	3	MD –58 g (–103, –12)
				Small for gestational age	4	OR 2.44 (1.22, 4.86)
			Neonatal	Congenital anomalies, Major	7	OR 2.12 (1.25, 3.57)
				Congenital anomalies, Cardiovascular	4	OR 2.09 (1.50, 2.91)

Abbreviations: CI = confidence interval, IV = intravenous, MD = mean difference, OR = odds ratio, PMID = PubMed identifier, SR = systematic review.

Table 30. Antipsychotics: Evidence profile for indirect evidence regarding harms of use during pregnancy

Drug	Outcome Category	Outcome	N SRs (N Studies)	RoB in Included Studies	Consistency	Precision	Directness	SoE	Conclusions
Antipsychotics, any	AEs – Fetal/Child	Spontaneous abortion or elective or induced abortion	2 (7)	Moderate	Inconsistent	Precise	Indirect	Low	No increased risk of spontaneous abortion
		Stillbirth or fetal	2 (7)	Moderate	Inconsistent	Precise	Indirect	Low	No increased risk of stillbirth
		Preterm birth	2 (7)	Moderate	Consistent	Precise	Indirect	Moderate	Increased preterm birth
		Low birth weight	2 (3)	Moderate	Consistent	Precise	Indirect	Moderate	Increased risk of low birth weight, small for gestational age
		Congenital anomalies	2 (4-7)	Moderate	Inconsistent	Precise	Indirect	Low	Increased major and cardiovascular anomalies

Abbreviations: AE = adverse effect, RoB = risk of bias, SoE = strength of evidence, SR = systematic review.

Table B-37 provides the complete version of this Evidence Profile, including displaying outcomes for which no evidence was identified.

Corticosteroids

Description of Direct Evidence for Corticosteroids

We did not find any primary studies on use of corticosteroids for preventing attacks of primary headache in women who were pregnant (or attempting to become pregnant), postpartum, or breastfeeding.

Description of Indirect Evidence for Corticosteroids

One high-quality SR (Park-Wyllie 2000) assessed harms associated with use of corticosteroids, specifically prednisolone, during pregnancy (regardless of indication) (Tables 14 and 15 and Tables B-26, B-27, B-28, and B-37).[84]

Maternal Benefit Outcomes of Corticosteroids

No primary study or SR reported on maternal benefit outcomes of corticosteroids.

Maternal Adverse Effects of Corticosteroids

No primary study or SR reported on maternal adverse effects of corticosteroids.

Fetal/Child Adverse Effects of Corticosteroids

No primary study (direct evidence) reported on fetal/child adverse effects of corticosteroids.

The Park-Wyllie 2000 SR (indirect evidence) reported that prednisolone use was associated with increased likelihood of **oral clefts** (OR 3.35, 95% CI 1.97 to 5.69), but not other major congenital anomalies (Table 14).

Analgesics/Antipyretics

Description of Direct Evidence for Analgesics/Antipyretics

We did not find any primary studies on use of analgesics/antipyretics for treating attacks of primary headache in women who were pregnant (or attempting to become pregnant), postpartum, or breastfeeding.

Description of Indirect Evidence for Analgesics/Antipyretics

One moderate-quality SR (Masarwa 2018) assessed harms associated with analgesic/antipyretic, specifically acetaminophen, use during pregnancy (regardless of indication) (Tables 31 and 32 and Tables B-26, B-27, B-28, and B-37).[80]

Maternal Benefit Outcomes of Analgesics/Antipyretics

No primary study or SR reported on maternal benefit outcomes of analgesics/antipyretics.

Maternal Adverse Effects of Analgesics/Antipyretics

No primary study or SR reported on maternal adverse effects of analgesics/antipyretics.

Fetal/Child Adverse Effects of Analgesics/Antipyretics

No primary study (direct evidence) reported on fetal/child adverse effects of corticosteroids.

The Masarwa 2018 SR (indirect evidence) reported that acetaminophen use was associated with **attention deficit hyperactivity disorder** (RR 1.34, 95% CI 1.21 to 1.47), **hyperactivity symptoms** (RR 1.24, 95% CI 1.04 to 1.43), **autism spectrum disorder** (RR 1.19, 95% CI 1.14 to 1.25), and **conduct disorder** (RR 1.23, 95% CI 1.04 to 1.42) (Table 31). No other harms were reported in this SR.

Table 31. Analgesics/antipyretics (acetaminophen): Summary of indirect evidence of fetal/child harms, statistically significant findings

SR, Year Published, PMID	Intervention Class	Intervention Name	Timing of Occurrence of Adverse Effect	Adverse Effect	N Studies	Effect Size (95% CI)
Masarwa, 2018, 29688261	Analgesic/ Antipyretic	Acetaminophen	Child	Attention deficit hyperactivity disorder	6	RR 1.34 (1.21, 1.47)
				Hyperactivity symptoms	4	RR 1.24 (1.04, 1.43)
				Autism spectrum disorder	5	RR 1.19 (1.14, 1.25)
				Conduct disorder	4	RR 1.23 (1.04, 1.42)

Abbreviations: CI = confidence interval, PMID = PubMed identifier, RR = relative risk, SR = systematic review.

Table 32. Analgesics/antipyretics (acetaminophen): Evidence profile for indirect evidence of fetal/child harms, statistically significant findings

Drug	Outcome Category	Outcome	N SRs (N Studies)	RoB in Included Studies	Consistency	Precision	Directness	SoE	Conclusions
Acetaminophen	AEs – Fetal/Child	Neuro-developmental/ behavioral/ social	1 (4-6)	Moderate	Inconsistent	Precise	Indirect	Low	Increased attention deficit hyperactivity disorder, hyperactivity symptoms, autism spectrum disorder, and conduct disorder

Abbreviations: AE = adverse effect, RoB = risk of bias, SoE = strength of evidence, SR = systematic review.

Table B-37 provides the complete version of this Evidence Profile, including displaying outcomes for which no evidence was identified.

Intravenous Magnesium

Description of Direct Evidence for Intravenous Magnesium

We did not find any primary studies on use of intravenous magnesium for treating attacks of primary headache in women who were pregnant (or attempting to become pregnant), postpartum, or breastfeeding.

Description of Indirect Evidence for Intravenous Magnesium

One high-quality SR (Bain 2014) assessed harms associated with intravenous magnesium sulphate use during pregnancy (regardless of indication) (Tables 33 and 34 and Tables B-26, B-27, B-28, and B-37).[63]

Maternal Benefit Outcomes of Intravenous Magnesium

No primary study or SR reported on maternal benefit outcomes of intravenous magnesium.

Maternal Adverse Effects of Intravenous Magnesium

The Bain 2014 SR (indirect evidence) reported that, compared with patients who had not been prescribed intravenous magnesium, those who had were more likely to experience an **adverse effect** (RR 4.62, 95% CI 2.42 to 8.83) and to discontinue the intervention due to adverse effects (RR 2.77, 95% CI 2.32 to 3.30). Adverse effects with notable effect sizes included **flushing and/or warmth** (RR 6.94, 95% CI 4.19 to 11.49), **muscle weakness** (RR 15.81, 95% CI 7.36 to 33.96), and **sweating** (RR 6.37, 95% CI 1.96 to 20.65) (Table 33). Intravenous magnesium use was not associated with increased incidence of cesarean section or postpartum hemorrhage.

Fetal/Child Adverse Effects of Intravenous Magnesium

No primary study or SR reported on fetal/child adverse effects of intravenous magnesium.

Table 33. Intravenous magnesium: Summary of indirect evidence of maternal harms, statistically significant findings

SR, Year Published, PMID	Intervention Class	Intervention Name	Timing of Occurrence of Adverse Effect	Adverse Effect	N Studies	Effect Size (95% CI)
Bain, 2013, 24139447	Intravenous magnesium	Intravenous magnesium sulphate	NR	Any adverse effect	4	RR 4.62 (2.42, 8.83)
				Discontinuation due to adverse effects	5	RR 2.77 (2.32, 3.30)
				Respiratory depression/ other respiratory problems	5	RR 1.41 (1.07, 1.86)
				Hypotension	3	RR 1.52 (1.10, 2.11)
				Tachycardia	1	RR 1.53 (1.03, 2.29)
				Flushing and/or warmth	5	RR 6.94 (4.19, 11.49)
				Nausea and/or vomiting	4	RR 5.50 (2.29, 13.22)
				Muscle weakness	3	RR 15.81 (7.36, 34.0)
				Drowsiness or confusion	3	RR 2.46 (1.83, 3.29)
				Headache	2	RR 2.21 (1.27, 3.86)
				Thirst or mouth dryness	2	RR 2.38 (1.59, 3.56)
				Dizziness	2	RR 2.62 (1.63, 4.21)
				Sweating	2	RR 6.37 (1.96, 20.65)
				Itching and/or tingling	1	RR 14.5 (2.0, 113.4)
				Blurred vision	1	RR 2.34 (1.32, 4.14)

Abbreviations: CI = confidence interval, NR = not reported, PMID = PubMed identifier, RR = relative risk, SR = systematic review.

Table 34. Intravenous magnesium: Evidence profile for indirect evidence regarding harms of use during pregnancy

Drug	Outcome Category	Outcome	N SRs (N Studies)	RoB in Included Studies	Consistency	Precision	Directness	SoE	Conclusions
IV magnesium	AEs – Maternal	Any serious AE	1 (4-5)	Unclear	Unclear	Precise	Indirect	Low	Increased respiratory depression/other respiratory problems, but no increased risk of increased respiratory arrest or death
		Cardiovascular	1 (4-5)	Unclear	Unclear	Imprecise	Indirect	Low	Increased hypotension, tachycardia, but no increased risk of increased cardiac arrest or death
		Discontinuation due to AEs	1 (5)	Unclear	Unclear	Precise	Indirect	Low	Increased discontinuation due to AEs

Abbreviations: AE = adverse effect, IV = intravenous, RoB = risk of bias, SoE = strength of evidence, SR = systematic review.

Table B-37 provides the complete version of this Evidence Profile, including displaying outcomes for which no evidence was identified.

Other Pharmacologic Interventions for KQ 2

We did not find any direct evidence (i.e., primary studies) or indirect evidence (i.e., SRs regardless of indication) for the following pharmacologic interventions for treating attacks of primary headaches in women who are pregnant (or attempting to become pregnant), postpartum, or breastfeeding: central nervous system stimulants, muscle relaxants, butalbital-containing

analgesics, sympathomimetic amines, topical anesthetics, somatostatin analogs, and over-the-counter analgesics.

Key Question 2: Nonpharmacologic Interventions To Treat Attacks of Primary Headache

Complementary, Behavioral, and Physical Therapies

Description of Direct Evidence for Complementary, Behavioral, and Physical Therapies

We found four studies (two RCTs[38, 41] and two single-group studies[38, 60, 61]) that reported on the benefits and harms of complementary, behavioral, and physical therapies in a total of 92 pregnant patients with primary headaches (Tables 35 and 36 and Table B-34).

Silva 2012 was an RCT of 43 pregnant women experiencing attacks of tension headaches in Brazil.[41] Eligibility criteria included being 15 to 30 weeks of gestation and experiencing tension headache of at least 4 on a VAS of 0 to 10 (maximum pain). Patients were randomized to either complementary therapy (acupuncture through 15 needles of 40 mm length and 0.2 mm diameter for 25 min, once a week for 8 weeks; 20 patients) or conventional treatment (routine care; 23 patients). The arms were similar in terms of age (mean 27.3 and 25.3 years in the acupuncture and routine care arms, respectively), gestational age (mean 19.8 and 19.4 years, respectively), gravidity (mean 2 each), and parity (mean 1 each). Race distributions were not reported. We assessed the study at overall high risk of bias because the random sequence generation process was not reported, and patients, study personnel, and outcome assessors were not blinded.

The second study described in Marcus 1995, hereafter called Marcus (Study 2) 1995, was an RCT of 25 pregnant women experiencing attacks of either migraine (nine patients), tension headache (seven patients), or coexisting migraine and tension headache (nine patients) in the U.S.[38] Other eligibility criteria included being in the second or third trimester and experiencing at least one headache attack a week or at least five headache attacks a month. Patients were randomized to either of two arms: (1) a combination of complementary therapy (thermal biofeedback), behavioral therapy (relaxation therapy), and physical therapy; and (2) complementary therapy (thermal biofeedback) only. In both arms, sessions lasted for 1 hour and occurred four times over the course of 2 months. The arms were similar in terms of age (mean 28.6 and 29.2 years in the combination and complementary only arms, respectively) and gestational age (mean 17.6 and 19.8 years, respectively). Race, trimester, gravidity, and parity distributions were not reported. We assessed the study at overall high risk of bias because the random sequence generation and allocation concealment processes were not reported; patients, study personnel, and outcome assessors (for subjective outcomes) were not blinded; and there was incomplete outcome data.

The first study described in Marcus 1995[38] (and in another article[61]), hereafter called Marcus (Study 1) 1995, was a prospective single-group study of 19 pregnant women in the U.S. Participating women were experiencing attacks of either migraine (15 patients), tension headache (three patients), or coexisting migraine and tension headache (one patient). The patients received the same intervention as arm 1 in Marcus (Study 1) 1995 (i.e., a combination of complementary therapy [thermal biofeedback], behavioral therapy [relaxation therapy], and physical therapy); sessions lasted for 1 hour and occurred four times over the course of 2 months. The mean patient

and gestational ages were 31.7 years and 17.7 weeks, respectively. Race, trimester, gravidity, and parity distributions were not reported. We assessed the study at overall low risk of bias.

Hickling 1990 was a prospective single-group study of five pregnant women with migraine in their first or second trimester in the U.S.[60] The patients received a combination of complementary therapy (thermal biofeedback) and behavioral therapy (muscle relaxation); sessions occurred 4 to 12 times. The mean patient age and parity were 34 years and 1, respectively. One patient (20%) was in her first trimester and four patients were in their second trimester. Race, gestational age, and gravidity distributions were not reported. We assessed the study at overall low risk of bias.

We have organized the rest of this section on complementary, behavioral, and physical therapies (direct evidence) by type of complementary therapy. First, we discuss the study that compared use versus nonuse of acupuncture. Next, we discuss the two studies that addressed the combination of thermal biofeedback, relaxation therapy, and physical therapy. Finally, we discuss the study that addressed the combination of thermal biofeedback and relaxation therapy.

Description of Indirect Evidence for Complementary, Behavioral, and Physical Therapies

We did not identify any SRs of complementary, behavioral, and physical therapies in pregnancy (indirect evidence).

Acupuncture Use Versus Nonuse

Description of Direct Evidence for Acupuncture Use Versus Nonuse

One RCT (Silva 2012) compared acupuncture use versus nonuse in 43 pregnant patients with migraine (Tables B-17 to B-19).[41] Silva 2012 reported maternal benefit outcomes as well fetal/child adverse effects.

Description of Indirect Evidence for Acupuncture Use Versus Nonuse

We did not identify any SR (indirect evidence).

Maternal Benefit Outcomes of Acupuncture Use Versus Nonuse

Silva 2012 (direct evidence) reported the effect of acupuncture on **severity of acute headache attacks** using a VAS from 0 to 10 (maximum pain). Compared with patients receiving routine care, patients receiving acupuncture experienced a greater reduction in severity of pain (MD 2.2, 95% CI 0.3 to 4.7) and were more likely to experience a reduction of average pain intensity by 25 percent or more (OR 4.36, 95% CI 1.11 to 17.13) (Table 35).

Silva 2012 also reported that, compared with patients receiving routine care, patients receiving acupuncture had a greater reduction in **number of acetaminophen doses used** (MD 5.4, 95% CI 1.3 to 9.5) and were more likely to reduce their acetaminophen by 50 percent or more (OR 6.61, 95% CI 1.74 to 25.1) (Table 35).

Maternal Adverse Acupuncture Use Versus Nonuse

No primary study or SR reported on maternal adverse effects of acupuncture use.

Fetal/Child Adverse Effects of Acupuncture Use Versus Nonuse

Silva 2012 (direct evidence) reported that **birth weight** was similar in infants of patients treated and not treated with acupuncture (MD 98 g, 95% CI –141 to 336) (Table 35).

Silva 2012 also reported that **Apgar scores** were similar in infants of patients treated and not treated with acupuncture, both at 1 minute (MD 0, 95% CI –0.5 to 0.5) and 5 minutes after birth (MD 0, 95% CI –0.1 to 0.1) (Table 35).

Combination Thermal Biofeedback, Relaxation Therapy, and Physical Therapy

Description of Direct Evidence for Combination Thermal Biofeedback, Relaxation Therapy, and Physical Therapy

Two studies, one RCT (Marcus [Study 2] 1995[38]) and one single-group study (Marcus [Study 1] 1995[38, 61]) addressed the use of a combination of thermal biofeedback, relaxation therapy, and physical therapy in a total of 44 patients with migraine and/or tension headache (Table 7). Both studies reported on maternal benefit outcomes, but neither study reported maternal or fetal/child adverse effects.

Description of Indirect Evidence for Combination Thermal Biofeedback, Relaxation Therapy, and Physical Therapy

We did not identify any SR (indirect evidence).

Maternal Benefit Outcomes of Combination of Thermal Biofeedback, Relaxation Therapy, and Physical Therapy

Both studies (direct evidence) reported on **severity of headache** using the VAS (0 to 10) and the Headache Index.[38, 61] Marcus [Study 2] 1995 (the RCT) reported that at the 2-month time-point, compared with patients only receiving thermal biofeedback, patients receiving the combination treatment experienced a greater reduction in their *worst* headache score in the past 2 weeks (NMD –3.4, 95% CI –5.61 to –1.19) and in the number of days in the past 2 weeks with a headache of at least 1 on the VAS (NMD –5.60, 95% CI –8.74 to –2.46). However, the arms were similar in terms of reductions in their *average* headache score over the past weeks (using the Headache Index) (NMD –0.86, 95% CI –1.95 to 0.23). Marcus [Study 1] 1995 (the single-group study) also reported reductions in these three measures of pain at 2 months, and that 79 percent of patients had significant improvements in pain score (Table 35).

Marcus [Study 2] 1995 (direct evidence), the RCT, reported that the **likelihood of using any medication for headache** at 2 months was similar between patients receiving the combination treatment and those only receiving thermal biofeedback (OR 0.50, 95% CI 0.09 to 2.73) (Table 35).

Maternal Adverse Effects of Combination of Thermal Biofeedback, Relaxation Therapy, and Physical Therapy

No primary study or SR reported on maternal adverse effects.

Fetal/Child Adverse Effects of Combination of Thermal Biofeedback, Relaxation Therapy, and Physical Therapy

No primary study or SR reported on fetal/child adverse effects.

Combination Thermal Biofeedback and Relaxation Therapy

Description of Direct Evidence for Combination Thermal Biofeedback and Relaxation Therapy

One study (Hickling 1990), a single-group study, reported on the use of a combination of thermal biofeedback and relaxation therapy in five pregnant patients with migraine (Tables B-20 to B-22).[60] The study only reported maternal benefit outcomes.

Description of Indirect Evidence for Combination Thermal Biofeedback and Relaxation Therapy

We did not identify any SR (indirect evidence).

Description of Direct Evidence for Maternal Benefit Outcomes of Combination Thermal Biofeedback and Relaxation Therapy

Hickling 1990 (direct evidence) reported on the **severity of headache** using an atypical VAS of 0 to 5 (maximum pain). The mean average pain score of patients' worst headache reduced from 2.9 before the intervention to 0.5 and 0.3 after the intervention and after delivery, respectively. The mean worst headache score reduced from 3.9 before the intervention to 0.6 and 0.9 after the intervention and after delivery, respectively (Table 35).

Hickling 1990 reported that the mean **duration of headache** reduced from 20.6 hours before the intervention to 1.2 hours and 4.8 hours after the intervention and after delivery, respectively (Table 35).

Hickling 1990 reported that the mean **number of headache-free days** per week increased from 2.8 before the intervention to 7, both after the intervention and after delivery (Table 35).

Maternal Adverse Effects of Combination Thermal Biofeedback and Relaxation Therapy

No primary study or SR reported on maternal adverse effects.

Fetal/Child Adverse Effects of Combination Thermal Biofeedback and Relaxation Therapy

No primary study or SR reported on fetal/child adverse effects.

Procedures

Description of Direct Evidence for Procedures

We found only one study, a retrospective single-group study, that reported the effects and harms of nerve blocks in 13 pregnant patients with migraine in the U.S. (Tables 35 and 36 and Tables B-20, B-21, B-22, and B-35).[25] Govindappagari 2014 studied patients who had previously tried other forms of treatment that failed. Patients received greater occipital, auriculotemporal, supraorbital, and supratrochlear nerve injections with local anesthetics (1–2% lidocaine or 0.5% bupivacaine). The mean age of patients was 28 years, but their race and gravidity were not reported. The mean gestational age of the patients was 23.5 weeks. Most women (61.5%) were nulliparous. We assessed the study at overall low risk of bias.

Description of Indirect Evidence for Procedures

We did not identify any SR (indirect evidence).

Maternal Benefit Outcomes of Procedures

Govindappagari 2014 (direct evidence) reported on the effect of peripheral nerve blocks on **severity of acute headache attacks** using a VAS from 0 to 10 (maximum pain). Compared with baseline, the severity of pain was significantly lower both immediately after the procedure (mean change –4.0, standard deviation [SD] 2.6) and at 24 hours (mean change –4.0, SD 4.4) (Table 35).

Maternal Adverse Effects of Procedures

Govindappagari 2014 (direct evidence) reported that none of the 13 patients who received nerve blocks experienced **serious adverse effects** immediately post-procedure (Table 35).

One of the 13 patients who received nerve blocks (7.7%) experienced a **vasovagal syncopal episode with nausea** immediately post-procedure (Table 35).

Fetal/Child Adverse Effects of Procedures

Govindappagari 2014 (direct evidence) reported that infants of two of the 13 patients (15.3%) were born **preterm** (Table 35).

Noninvasive Neuromodulation Devices

Description of Direct Evidence for Noninvasive Neuromodulation Devices

We found only one study, a prospective single-group study, that reported the effects and harms of transcranial magnetic stimulation in three pregnant patients with migraine in the U.K. (Tables 35 and 36 and Tables B-23, B-24, and B-36).[58] Bhola 2015 studied patients who had previously tried other forms of treatment that failed. Patients received up to two pulses of transcranial (over the back of the head) magnetic stimulation of 0.9 T. Pulses were separated by at least 15 minutes. Patients could receive up to 16 single pulses or eight double pulses per day, on as many migraine days as needed. The mean age of patients was 30.3 years, and all were in their second trimester, but mean gestational age was not reported. Patient race, gravidity, and parity status were also not reported. We assessed the study at overall moderate risk of bias.

Description of Indirect Evidence for Noninvasive Neuromodulation Devices

We did not identify any SR (indirect evidence).

Maternal Benefit Outcomes of Noninvasive Neuromodulation Devices

Bhola 2015 (direct evidence) reported that all three patients who received transcranial magnetic stimulation experienced **resolution of their acute migraine** (Table 35).

All three patients who received transcranial magnetic stimulation experienced **resolution of their acute migraine-related symptoms** (Table 35).

Maternal Adverse Effects of Noninvasive Neuromodulation Devices

Bhola 2015 (direct evidence) reported that none of the three patients who received transcranial magnetic stimulation experienced adverse effects (Table 35).

Fetal/Child Adverse Effects of Noninvasive Neuromodulation Devices

No primary study or SR reported on fetal/child adverse effects.

Table 35. Nonpharmacologic interventions: Summary of direct evidence regarding use to treat primary headaches

Outcome*	Outcome Measurement	Time-Point	Study, Year, Design, PMID	Intervention(s)	n/N (%) or Mean (SD)	Effect Size (95% CI) or Effect Size (SD)
Severity of acute headache attacks	Reduction in pain on a VAS (0–10)	8 wk	Silva, 2012, RCT, no PMID	Acupuncture	3.9 (3.4)	MD 2.2 (0.3, 4.7)
				Routine care	1.7 (4.4)	
	25% reduction in pain on a VAS (0 to 10)	8 wk		Acupuncture	16/20 (80.0)	OR 4.36 (1.11, 17.13)
				Routine care	11/23 (47.8)	
	Worst pain score on a VAS (0–10) in past 2 wk	2 mo	Marcus [Study 2] 1995, RCT, 8600478	Combination thermal biofeedback, relaxation therapy, & physical therapy	2.3 (3.1)	NMD –3.4 (–5.61, –1.19)
				Thermal biofeedback	5.7 (3.3)	
	Worst pain score on a VAS (0–10) in past 2 wk	Baseline	Marcus [Study 1] 1995, Single-group study, 8600478	Combination thermal biofeedback, relaxation therapy, & physical therapy	7.7 (2.0)	NR
		2 mo			4.2 (3.8)	
	Number of days in past 2 wk with headache >1 on a VAS (0–10)	2 mo	Marcus [Study 2] 1995, RCT, 8600478	Combination thermal biofeedback, relaxation therapy, & physical therapy	2.9 (4.3)	NMD –5.60 (–8.74, –2.46)
				Thermal biofeedback	7.7 (NR)	
	Number of days in past 2 wk with headache >1 on a VAS (0–10)	Baseline	Marcus [Study 1] 1995, 8600478	Combination thermal biofeedback, relaxation therapy, & physical therapy	8.0 (3.5)	NR
		2 mo			2.9 (4.0)	
	Headache score average over 2 wk on Headache Index	2 mo	Marcus [Study 2] 1995, RCT, 8600478	Combination thermal biofeedback, relaxation therapy, & physical therapy	0.44 (0.70)	NMD –0.86 (–1.95, 0.23)
				Thermal biofeedback	1.8 (2.0)	
	Headache score average over 2 wk on Headache Index	Baseline	Marcus [Study 1] 1995, Single-group study, 8600478	Combination thermal biofeedback, relaxation therapy, & physical therapy	1.7 (1.3)	NR
		2 mo			0.45 (0.77)	
	Average of worst headache on a VAS (0–5)	Baseline	Hickling, 1990, Single-group study, 2401622	Combination thermal biofeedback & relaxation therapy	2.9 (0.6)	NR
		After int			0.5 (1.1)	
		After delivery			0.3 (0.7)	
	Worst headache on a VAS (0–5)	Baseline			3.9 (1.0)	NR
		After int			0.6 (1.3)	
		After delivery			0.9 (1.3)	
	Pain, VAS (0–10) pre-procedure	Pre-procedure	Govindappagari, 2014, Single-group study, 25415168	Peripheral nerve blocks	8.4 (1.8)	-
		Post-procedure			4.5 (3.8)	MD -4.0 (2.6)
		24 hr			4.5 (4.5)	MD -4.0 (4.4)

Outcome*	Outcome Measurement	Time-Point	Study, Year, Design, PMID	Intervention(s)	n/N (%) or Mean (SD)	Effect Size (95% CI) or Effect Size (SD)
Duration of acute headache attacks	Duration in hr	Baseline	Hickling, 1990, Single-group study, 2401622	Combination thermal biofeedback & relaxation therapy	20.6 hr (16.0)	NR
		After int			1.2 hr (2.7)	
		After delivery			4.8 hr (10.7)	
Resolution of acute headache	Number of headache-free days per week	Baseline	Hickling, 1990, Single-group study, 2401622	Combination thermal biofeedback & relaxation therapy	2.8 d/wk (2.6)	NR
		After int			7 d/wk (0)	
		After delivery			7 d/wk (0)	
	NR	NR	Bhola, 2015, Single-group study, 26055242	Transcranial magnetic stimulation	3/3 (100)	-
Resolution of headache-related symptoms	NR	NR	Bhola, 2015, Single-group study, 26055242	Transcranial magnetic stimulation	3/3 (100)	-
Medication use	Reduction in number of acetaminophen doses	8 wk	Silva, 2012, RCT, no PMID	Acupuncture	6.0 (9.0)	MD 5.4 (1.3, 9.5)
				Routine care	0.6 (3.3)	
	50% reduction in number of acetaminophen doses	8 wk	Silva, 2012, RCT, no PMID	Acupuncture	14/20 (70.0)	OR 6.61 (CI 1.74, 25.1)
				Routine care	6/23 (26.1)	
	Use of any medication for headache	2 mo	Marcus [Study 2] 1995, RCT, 8600478	Combination of thermal biofeedback, relaxation therapy, and physical therapy	4/11 (36.4)	OR 0.50 (0.09, 2.73)
				Thermal biofeedback	10/14 (71.4)	
AEs – Maternal – Serious, Any	Any serious AE	Post-procedure	Govindappagari, 2014, Single-group study, 25415168	Peripheral nerve blocks	0/13 (0.0)	-
AEs – Maternal – Nonserious, Any	Vasovagal near syncopal episode with nausea	Post-procedure			1/13 (7.7)	-
AEs – Maternal – Any	NR	NR	Bhola, 2015, Single-group study, 26055242	Transcranial magnetic stimulation	0/13 (0.0)	-
Preterm birth	Birth at <37 wk gestation	At birth	Govindappagari, 2014, Single-group study, 25415168	Peripheral nerve blocks	2/13 (15.3)	-
Low birth weight	Birth weight	At birth	Silva, 2012, RCT, no PMID	Acupuncture	3244 g (336)	MD 98 g (–141, 336)
				Routine care	3146 g (424)	
Perinatal complications	Apgar score	At 1 min after birth		Acupuncture	9 (0)	MD 0 (–0.5, 0.5)
				Routine care	9 (1)	
		At 5 min after birth		Acupuncture	10 (0)	MD 0 (–0.1, 0.1)
				Routine care	10 (0)	

Abbreviations: AE = adverse effect, CI = confidence interval, d = days, hr = hours, int = intervention, MD = mean difference, min = minutes, mo = months, NMD = net mean difference, NR = not reported, OR = odds ratio, PMID = PubMed identifier, RCT = randomized controlled trial, SD = standard deviation, VAS = visual analog scale, wk = weeks.

* No studies reported acute headache outcomes (recurrence), headache-related symptom(severity, duration, resolution, recurrence), emergency department or clinic visits, hospitalizations, quality of life, functional outcomes (family life, work/school attendance, time spent managing disease), resource use, acceptability of int by patients, patient satisfaction with int, serious maternal AEs (any AE, cardiovascular), nonserious maternal AEs (any nonserious AE, nonobstetrical, preterm labor/CS, reduced breast milk, medication withdrawal symptoms), discontinuation due to maternal AEs, serious fetal/child AEs (any serious AE, death, preterm birth, congenital anomalies, neurodevelopmental/behavioral/social), nonserious fetal/child AEs (any nonserious AE, breastfeeding delay/cessation/etc., poor infant attachment/bonding, medication withdrawal symptoms), or discontinuation due to fetal/child AEs.

Table 36. Nonpharmacologic interventions: Evidence profile for direct evidence regarding use to treat primary headaches

Topic	Comparison	Outcome Category	Outcome	N Studies (Subjects)	RoB	Consistency	Precision	Directness	SoE	Conclusions
Benefits	Acupuncture vs. routine care	Acute headache attack	Severity of acute headache attacks	1 (43)	High	N/A	Imprecise	Direct	Insufficient	No conclusion made
	Combination thermal biofeedback, relaxation therapy, and physical therapy vs. thermal biofeedback	Acute headache attack	Severity of acute headache attacks	2 (44)	High	N/A	Imprecise	Direct	Insufficient	No conclusion made
	Combination of thermal biofeedback and relaxation therapy (no comparison)	Acute headache attack	Severity of acute headache attacks	1 (5)	Low	N/A	Imprecise	Indirect	Insufficient	No conclusion made
			Duration of acute headache attacks	1 (5)	Low	N/A	Imprecise	Indirect	Insufficient	No conclusion made
			Resolution of acute headache attack	1 (5)	Low	N/A	Imprecise	Indirect	Insufficient	No conclusion made
	Peripheral nerve blocks (no comparison)	Acute headache attack	Severity of acute headache attacks	1 (13)	Low	N/A	Imprecise	Indirect	Insufficient	No conclusion made
	Transcranial magnetic stimulation (No comparison)	Acute headache attack	Acute headache attacks – Resolution	1 (3)	Moderate	N/A	N/A	Indirect	Insufficient	No conclusion made
		Headache-related symptoms	Headache-related symptoms – Resolution	1 (3)	Moderate	N/A	N/A	Indirect	Insufficient	No conclusion made
Harms	Acupuncture vs. routine care	AEs – Fetal/Child	Low birth weight	1 (43)	High	N/A	Imprecise	Direct	Insufficient	No conclusion made
			Perinatal complications	1 (43)	High	N/A	Imprecise	Direct	Insufficient	No conclusion made
	Peripheral nerve blocks (no comparison)	AEs – Maternal	Any serious AEs	1 (13)	Low	N/A	Imprecise	Indirect	Insufficient	No conclusion made
		AEs – Fetal/Child	Preterm birth	1 (13)	Low	N/A	Imprecise	Indirect	Insufficient	No conclusion made
	Transcranial magnetic stimulation (No comparison)	AEs – Maternal	Any serious AEs	1 (3)	Moderate	N/A	N/A	Indirect	Insufficient	No conclusion made

Abbreviations: AE = adverse effect, N/A = not applicable, RoB = risk of bias, SoE = strength of evidence.

Consistency was deemed "N/A" when it could not be assessed because only one study was one found. Consistency was also deemed "N/A" when two studies were found because one of the studies was a single-group study for which no between-arm effect size was feasible, precluding an assessment of consistency.
Tables B-34 and B-35 provide the complete versions of this Evidence Profile, including displaying outcomes for which no studies were identified

Other Nonpharmacologic Interventions for KQ 2

We did not find any direct evidence (i.e., primary studies) or indirect evidence (i.e., SRs regardless of indication) specifically for hydration and supplements for treating attacks of primary headaches in women who are pregnant (or attempting to become pregnant), postpartum, or breastfeeding.

Supplemental Evidence (Case Reports)

We identified 19 case reports,[91-109] of which five reported on interventions relevant to KQ 1 only, seven reported on interventions relevant to KQ 2 only, and seven reported on interventions relevant to both KQs. Overall, thirteen case reports reported on benefit outcomes intervention effects and six on adverse effects.

The text in Appendix B and Tables B-29 and B-30 provide detailed descriptions of the case reports. Here we provide a simple summary of what occurred to individual patients in terms of headache progression and adverse effects.

Because case reports do not provide evidence of whether the benefit or harms reported can be ascribed to individual interventions, and generally represent cherry-picked "interesting" examples, this evidence is not considered in our conclusions about effects, harms, or strength of evidence.

Case Reports Specific to Key Question 1 (Prevention of Primary Headache)

Summary of Benefit Outcomes

Four case reports described benefits of preventive interventions for primary headaches.

- Migraines were prevented in one woman who received complementary therapy (chiropractic therapy, massage therapy), hydration and advice to avoid triggering foods and sleep with an orthopedic pillow, and in one woman who received onabotulinumtoxinA.
- Cluster headache was prevented in one woman who received methylprednisolone.
- Other trigeminal autonomic cephalgia (TAC) headache was prevented in one woman who received nerve blocks and methylprednisolone.

Summary of Harms

- One case report described harms of an intervention used for prevention of primary headaches. The patient, who had migraine and received valproate, had an induced abortion of a fetus that was detected as having a cardiac defect.

Case Reports Specific to Key Question 2 (Treatment of Primary Headache)

Summary of Benefit Outcomes

Five case reports described benefits of interventions used for treatment of primary headaches.

- Migraines were treated in one woman who received a butalbital, acetaminophen, and caffeine combination, a second woman who received sumatriptan, a third woman who received

acetaminophen and ibuprofen, and a fourth woman who received intravenous prochlorperazine and magnesium.
- In one woman, an unspecified primary postpartum headache was treated using intravenous saline and ketorolac.

Summary of Harms

Two case reports described harms of interventions used for treatment of primary headaches.
- One woman with migraine treated with acetaminophen, ergotamine, caffeine, and mecloxamine during the first trimester lost her newborn 13 hours after birth due to cardiopulmonary arrest, and another woman with migraine treated with acetaminophen and codeine during her second trimester had an infant born with neonatal abstinence syndrome, which resolved without requiring pharmacologic therapy.

Case Reports Addressing Both Key Question 1 (Prevention of Primary Headache) and Key Question 2 (Treatment of Primary Headache)

Summary of Benefit Outcomes

Four case reports described benefits of interventions used for both prevention and treatment of primary headaches.
- Migraines were prevented and/or treated in one woman who received sphenopalantine ganglion block, another woman who received oral magnesium supplements, and a third woman who received labetalol.
- In one woman, cluster headache was prevented using occipital nerve stimulation device and treated using sumatriptan.

Summary of Harms

Three case reports described harms of interventions used for both prevention and treatment of primary headaches.
- One woman with migraine who received candesartan, pramipexole, and amitriptyline (as prevention) and zolmitriptan and metoclopramide (as treatment) had a baby with renal tubular dysgenesis, hypoplasia of the skull and the lungs, and hyaline membranes of the lungs; a second woman who received acetaminophen, codeine, propranolol, ergotamine, and caffeine had a baby with severe malformations and paraplegia; and a third woman receiving bisoprolol, naproxen, sumatriptan, and acetaminophen had an infant with various birth defects.

Discussion

Findings in Relation to the Decisional Dilemmas

We identified a sparse body of evidence addressing the many interventions of interest in this systematic review (SR). This included 16 primary studies providing direct evidence of benefits and harms in pregnant women with primary headache, and 26 existing SRs that provided indirect evidence of harms in pregnant women regardless of indication. Table 37 maps out the investigated interventions for both Key Questions (KQs), by type of evidence (direct and indirect) and specific study design (for direct evidence). Table 38 provides a summary of the identified direct and indirect evidence addressing pharmacologic and nonpharmacologic interventions for prevention (KQ 1) or treatment of primary headaches (KQ 2).

Table 37. Map of direct and indirect evidence identified in this systematic review

Topic (KQ)	Type	Class	Intervention(s)	Direct Evidence: RCTs N_S (N_P)	Direct Evidence: NRCSs N_S (N_P)	Direct Evidence: Single-group studies N_S (N_P)	Indirect Evidence: SRs N_{SR} (N_S*)
Prevention (KQ 1)	Pharm	**Antiepileptics**	Topiramate, Carbamazepine, Gabapentin, Lamotrigine, Valproate	-	-	1 (81)	2 (146)
		SNRIs	Venlafaxine	-	-	-	1 (2)
		Tricyclic antidepressants	Any	-	-	-	1 (2)
		Tetracyclic antidepressants	-	-	-	-	-
		Mood-stabilizing agents	-	-	-	-	-
		Benzodiazepines	Any	-	-	-	1 (26)
		Beta blockers	Any	-	-	-	2 (76)
		Calcium channel blockers	Any, Nifedipine	-	-	-	2 (85)
		Other antihypertensive medications	-	-	-	-	-
		Corticosteroids	Prednisolone	-	-	-	1 (10)†
		Antihistamines	Any	-	-	-	2 (63)†
		Oral magnesium	Magnesium	-	-	-	1 (10)
		NMDA receptor antagonists	-	-	-	-	-
		CGRP inhibitors	-	-	-	-	-
	Non-pharm	Complementary therapy	-	-	-	-	-
		Behavioral therapy	-	-	-	-	-
		Physical therapy	-	-	-	-	-
		Procedures	-	-	-	-	-
		Noninvasive neuromodulation devices	-	-	-	-	-
		Chemodenervation	-	-	-	-	-
		Hydration	-	-	-	-	-
		Supplements	-	-	-	-	

Topic (KQ)	Type	Class	Intervention(s)	Direct Evidence: RCTs N_S (N_P)	Direct Evidence: NRCSs N_S (N_P)	Direct Evidence: Single-group studies N_S (N_P)	Indirect Evidence: SRs N_{SR} (N_S*)
Treatment (KQ 2)	Pharm	**Triptans**	Any, Sumatriptan, Naratriptan	-	8 (13,907)	-	1 (6)
		Ergot products	Any	-	1 (3,368)	-	-
		NSAIDs	Naproxen	-	1 (689)	-	-
		NSAIDs	Any, Indomethacin, Low-dose aspirin	-	-	-	8 (174)
		Antiemetics: Dopamine receptor antagonists	Metoclopramide	1 (70)	-	-	-
		Antihistamines	Any	1 (70)	1 (3,368)	-	2 (63)†
		Opioid containing analgesics	Codeine	1 (70)	-	-	-
		Antiemetics: 5HT3 antagonists	Ondansetron	-	-	-	2 (20)
		Antipsychotics	Any	-	-	-	2 (22)
		Corticosteroids	Prednisolone	-	-	-	1 (10)†
		Analgesics/antipyretics	Acetaminophen	-	-	-	1 (7)
		Intravenous magnesium	Intravenous Magnesium	-	-	-	1 (143)
		Central nervous system stimulants	-	-	-	-	-
		Muscle relaxants	-	-	-	-	-
		Butalbital-containing analgesics	-	-	-	-	-
		Sympathomimetic amines	-	-	-	-	-
		Topical anesthetics	-	-	-	-	-
		Somatostatin analogs	-	-	-	-	-
		Other over-the-counter analgesics	-	-	-	-	-
	Nonpharm	**Complementary therapy**	Thermal biofeedback	2 (68)	-	2 (24)	-
		Behavioral therapy	Relaxation therapy	1 (25)	-	2 (24)	-
		Physical therapy	Physical therapy	1 (25)	-	1 (19)	-
		Procedures	Peripheral nerve blocks	-	-	1 (13)	-
		Noninvasive neuromodulation devices	Transcranial magnetic stimulation	-	-	1 (3)	-
		Hydration	-	-	-	-	-
		Supplements	-	-	-	-	-

Abbreviations: CGRP = calcitonin gene-related peptide, KQ = Key Question, N_{CR} = number of case reports, NMDA = N-methyl-D-aspartate, Nonpharm = nonpharmacologic, N_P = number of participants, NRCS = nonrandomized comparative study, N_S = number of studies, NSAID = nonsteroidal antiinflammatory drug, N_{SR} = number of systematic reviews, Pharm = pharmacologic, RCT = randomized controlled trial, SNRI = serotonin and norepinephrine reuptake inhibitor, SR = systematic review.

Intervention classes in bold font are those for which we identified at least one primary study (direct evidence) or SR (indirect evidence).

Direct evidence = primary studies in women who are pregnant (or attempting to become pregnant), postpartum, or breastfeeding with primary headache. Indirect evidence = systematic reviews in women who are pregnant (or attempting to become pregnant), postpartum, or breastfeeding regardless of indication.

* Does not account for overlap of studies across existing SRs.
† SRs addressing interventions that can be used for either prevention or treatment of primary headache are counted in both categories.

Table 38. Summary of direct and indirect evidence identified in this systematic review

KQ	Intervention Type	Intervention Class	Intervention Name	Comparator	Type of Evidence	Condition	Maternal Benefits	Maternal Harms	Fetal/Child Harms	
1	Pharm	Antiepileptics	Topiramate	-	Direct	Migraine	-	-	??	Spontaneous or elective/induced abortion, congenital anomalies (I)
				Nonuse	Indirect	Various	-	-	↑	Spontaneous or elective/induced abortion, stillbirth/fetal death, preterm birth, congenital anomalies (++)
									~	Neurodevelopmental AEs (+)
			Carbamazepine	Nonuse	Indirect	Various	-	-	↑	Congenital anomalies (++)
									~	Spontaneous or elective/induced abortion, preterm birth, , neurodevelopmental AEs (+)
			Gabapentin	Nonuse	Indirect	Various	-	-	↑	Congenital anomalies, neurodevelopmental AEs (+)
									~	Fetal growth restriction, preterm birth (+)
			Lamotrigine	Nonuse	Indirect	Various	-	-	↑	Neurodevelopmental AEs (++)
									~	Spontaneous or elective/induced abortion, stillbirth/fetal death, preterm birth, congenital anomalies (++)
			Valproate	Nonuse	Indirect	Various	-	-	↑	Spontaneous or elective/induced abortion, stillbirth/fetal death, congenital anomalies, neurodevelopmental AEs (++)
									~	Preterm birth (++)
		SNRIs	Venlafaxine	Nonuse	Indirect	Various	-	-	↑	Preterm birth (++)
		Tricyclic antidepressants	Any	Nonuse	Indirect	Various	-	-	↑	Congenital anomalies and perinatal complications (++)
									~	Low birth weight (++)
									??	Neurodevelopmental AEs (I)
		Benzodiazepines	Any	Nonuse	Indirect	Various	-	-	↑	Congenital anomalies (+)
		Beta blockers	Any	Nonuse	Indirect	Various	-	~ Discontinuation due to AEs (+)	↑	Congenital anomalies (++)
									~	Preterm birth (++)
									??	Perinatal complications (I)
		Calcium channel blockers	Any	Nonuse	Indirect	Various	-	~ Discontinuation due to AEs (+)	~	Perinatal complications (++)
									~	Spontaneous/elective/induced abortion, stillbirth/fetal death, neonatal/infant death, or preterm birth (+)
			Nifedipine	Nonuse	Indirect	Various	-	-	~	Neonatal/infant death (++)
									~	Preterm birth (+)
		Corticosteroids	Prednisolone	Nonuse	Indirect	Various	-	-	↑	Congenital anomalies (+)
		Antihistamines	Any	Nonuse	Indirect	Various	-	-	~	Spontaneous or elective/induced abortion, stillbirth/fetal death, preterm birth, low birth weight, congenital anomalies (++)
		Oral magnesium	Oral magnesium	Nonuse	Indirect	Various	-	~ Discontinuation due to AEs (+)	↑	Neonatal/infant death (+)
									~	Spontaneous or elective/induced abortion, stillbirth/fetal death, low birth weight, perinatal complications (+)
	Nonpharm	-	-	-	-	-	-	-		N/E

KQ	Intervention Type	Intervention Class	Intervention Name	Comparator	Type of Evidence	Condition	Maternal Benefits	Maternal Harms	Fetal/Child Harms	
2	Pharm	Triptans, Ergot products, and NSAIDs	Sumatriptan	Naratriptan	Direct	Migraine	-	-	??	Spontaneous or elective/induced abortion, stillbirth/fetal death, congenital anomalies (I)
			Sumatriptan	Sumatriptan + Naproxen	Direct	Migraine	-	-	??	Spontaneous or elective/induced abortion, stillbirth/fetal death, congenital anomalies (I)
			Naratriptan	Sumatriptan + Naproxen	Direct	Migraine	-	-	??	Spontaneous or elective/induced abortion, stillbirth/fetal death, congenital anomalies (I)
			Any triptan	Any ergot product	Direct	Migraine	-	-	??	Stillbirth/fetal death, preterm birth, low birth weight, congenital anomalies (I)
			Any triptan	Pizotifen	Direct	Migraine	-	-	??	Stillbirth/fetal death, preterm birth, low birth weight, congenital anomalies (I)
			Any ergot product	Pizotifen	Direct	Migraine	-	-	??	Congenital anomalies (I)
			Any triptan during pregnancy	Any triptan before pregnancy only	Direct	Migraine	-	?? Serious AEs (I)	↑	Behavioral and social AEs (+)
									??	Spontaneous or elective/induced abortion, preterm birth, low birth weight (I)
			Sumatriptan during pregnancy	Sumatriptan before pregnancy only	Direct	Migraine	-	?? Serious AEs (I)	??	Stillbirth/fetal death, neonatal/infant death, preterm birth, low birth weight, congenital anomalies, perinatal complications (I)
			Any triptan during pregnancy	No triptan use during or before pregnancy	Direct	Migraine	-	?? Serious AEs (I)	↑	Behavioral and social AEs (+)
									~	Spontaneous or elective/induced abortion, congenital anomalies (+)
									??	Preterm birth, low birth weight, perinatal complications (I)
					Existing SR	Migraine	-	-	~	Spontaneous or elective/induced abortion, congenital anomalies (++)
									~	Preterm birth (+)
		Antiemetics (Dopamine antagonists), Antihistamines, Opioid-like analgesics	Metoclopramide + Diphenhydramine	Codeine	Direct	Migraine or tension HA	Effective in improving severity, resolution, and recurrence of acute HA (+)	~ Serious AEs (+)		-
		NSAIDs	Any	Nonuse	Indirect	Various	-	~ Cardiovascular AEs (++)		-
			Indomethacin	Nonuse	Indirect	Various	-	-	↑	Perinatal complications (+)
									~	Neonatal/infant death, congenital anomalies (+)
			Low-dose aspirin	Nonuse	Indirect	Various	-	~ Serious AEs (++)	~	Spontaneous or elective/induced abortion, stillbirth/fetal death, neonatal/infant death, preterm birth, low birth weight, perinatal complications, or neurodevelopmental AEs (+)
		Antiemetics (5HT3 antagonists	Ondansetron	Nonuse	Indirect	Various	-	-	↑	Congenital anomalies (++)
		Antipsychotics	Any	Nonuse	Indirect	Various	-	-	↑	Preterm birth, low birth weight (++)
									↑	Congenital anomalies (+)
									~	Spontaneous or elective/induced abortion, stillbirth/fetal death (+)
		Corticosteroids	Prednisolone	Nonuse	Indirect	Various	-	-	↑	Congenital anomalies (++)
		Analgesics/Antipyretics	Acetaminophen	Nonuse	Indirect	Various	-	-	↑	Neurodevelopmental, behavioral, and social AEs (+)
		Intravenous magnesium	Intravenous magnesium	Nonuse	Indirect	Various	-	↑ Serious AEs (+)		-
		Antihistamines	Any	Nonuse	Indirect	Various	-	-	~	Spontaneous or elective/induced abortion, stillbirth/fetal death, preterm birth, low birth weight, congenital anomalies (++)

KQ	Intervention Type	Intervention Class	Intervention Name	Comparator	Type of Evidence	Condition	Maternal Benefits	Maternal Harms	Fetal/Child Harms	
	Nonpharm	Complementary therapy	Acupuncture	Routine care	Direct	Migraine	?? Severity of acute attack (I)	-	??	Low birth weight and perinatal complications (I)
		Complementary therapy, Behavioral therapy, and Physical therapy	Thermal biofeedback, Relaxation therapy, and Physical therapy	Thermal biofeedback	Direct	Migraine and/or tension HA	?? Severity of acute attack (I)	-		-
		Complementary therapy and Behavioral therapy,	Thermal biofeedback and Relaxation therapy	-	Direct	Migraine	?? Severity, duration, and resolution of acute attacks (I)	-		-
		Procedures	Peripheral nerve blocks	-	Direct	Migraine	?? Severity of acute attack	?? Serious AEs	??	Preterm birth (I)
		Noninvasive neuromodulation devices	Transcranial magnetic stimulation	-	Direct	Migraine	?? Resolution of acute attack and HA-related symptoms (I)	-	??	Serious AEs (I)

Abbreviations: AE = adverse effect, HA = headache, KQ = Key Question, N/E = no evidence, Nonpharm = nonpharmacologic, NSAID = nonsteroidal antiinflammatory drug, Pharm = pharmacologic, SNRI = serotonin and norepinephrine reuptake inhibitor, SR = systematic review

Clarifications: ↑ = Increase, ~ = No increase, ?? = Direction unknown, I = Insufficient strength of evidence, + = Low strength of evidence, ++ = Moderate strength of evidence, +++ = High strength of evidence (none in Table), Direct = evidence from primary studies in pregnant women with primary headache, Indirect = evidence from SRs in pregnant women regardless of indication. We did not search for SRs of benefits for any intervention class or intervention.

For **prevention** of acute attacks of primary headache in patients who are pregnant (or attempting to become pregnant), postpartum, or breastfeeding with a history of primary headache (KQ 1), we found no direct evidence for effectiveness of pharmacologic interventions. While we found insufficient direct evidence regarding the harms of topiramate, indirect evidence suggested that topiramate and other antiepileptics (carbamazepine, gabapentin, and valproate) used during pregnancy may be associated with increased risk of fetal/infant adverse effects. However, one antiepileptic (lamotrigine) may not be associated with increased risk of serious adverse effects, except for neurodevelopmental adverse effects, for which there may be increased risk. Indirect evidence also suggested that venlafaxine, tricyclic antidepressants, benzodiazepines, beta blockers, prednisolone, and oral magnesium used during pregnancy may be associated with increased risk of fetal/infant adverse effects, but calcium channel blockers and antihistamines may not be. We found no direct or indirect evidence for the effectiveness or harms of nonpharmacologic interventions when used for prevention.

For **treatment** of acute attacks of primary headache in patients who are pregnant (or attempting to become pregnant), postpartum, or breastfeeding (KQ 2), we found direct evidence that, when used during pregnancy, combination metoclopramide and diphenhydramine may be more effective than codeine in reducing migraine or tension headache severity, and may have a lower risk of maternal adverse effects; but, fetal/infant adverse effects were not reported. While we did not find any evidence for effectiveness of triptans, direct and existing SR evidence suggested that triptan use for migraine may have a low risk of adverse effects, except for increased child emotionality and hyperactivity at 3 years of age. SRs of harms of medications regardless of indication suggested that indomethacin, ondansetron, antipsychotics, prednisolone, acetaminophen, and intravenous magnesium, when used during pregnancy, may be associated with increased risk of fetal/infant adverse effects, but low-dose aspirin and antihistamines may not be. Regarding nonpharmacologic treatments for primary headache, we found insufficient direct evidence (and no indirect evidence) to make conclusions about the benefits or harms of acupuncture, thermal biofeedback, relaxation therapy, physical therapy, peripheral nerve blocks, or transcranial magnetic stimulation when used during pregnancy.

Caveats to Indirect Evidence (Systematic Reviews of Harms, Regardless of Indication)

We suggest caution in interpretation of the findings from the indirect evidence (existing SRs of harms of interventions in pregnancy regardless of indication) for various reasons.

First, although obvious, it is worth repeating that the evidence examined in these SRs is not exclusively based on patients with primary headache. It is possible that the harms of interventions may be different in pregnant patients with primary headaches (and their offspring) than pregnant patients with other conditions (and their offspring).

Second, findings regarding classes of drugs (e.g., tricyclic antidepressants, beta blockers – those denoted by “any”) apply to classes as wholes, rather than to individual drugs (or doses) within a class, which may have greater (or lesser) risks of adverse effects than other drugs (or doses) in the same class. A concern in this context is that pharmacodynamic profiles and associated degrees of cross-placental and/or breast milk transmission can be variable across drugs within a class and across doses of a drug.

Third, the SRs included variable numbers of studies, and frequently only a subset of the studies (often one or two) included in a given SR contributed data to estimates of specific harms for specific interventions.

Fourth, it is possible, even likely, that some relevant studies of harms in pregnancy were not included in the SRs we identified. Some potential reasons for this include that the SRs may have had narrow eligibility criteria, included studies may have underreported harms, and newer studies may have been published after the searches for the SRs were run. Another reason might be that the existence of established harms for decades, such as harms of indomethacin on premature closure of the ductus arteriosus when used after 32 weeks of gestation, may have contributed to the lack of quality SRs. Updating these SRs was beyond the scope of the current SR.

Fifth, because we required included SRs to have fulfilled minimum quality criteria, we likely excluded some insufficient-quality SRs of harms.

Sixth, although we required SRs to fulfill minimum quality criteria, even well-conducted SRs cannot overcome methodological limitations of studies that they include. For example, the one SR on harms of acetaminophen conducted a meta-analysis of observational studies on the association between acetaminophen use during pregnancy and neurodevelopmental adverse effects in the child. The positive association that remained despite adjustment for potential confounders provides a potential signal, but the moderate risk of bias of the included studies contributed to our assessment of an overall low strength of evidence for this association.

Notwithstanding these caveats, the indirect evidence from the SRs we identified contributes supplemental information that can be particularly valuable in making conclusions about drugs for which we did not find primary evidence (as we have done above in the section—*Findings in Relation to the Decisional Dilemmas).* For drugs for which we identified both direct and indirect evidence (i.e., topiramate, antihistamines, and triptans), the harms were generally consistent in both types of evidence.

Supplemental Evidence (Case Reports)

We identified 19 case reports and summarized them as supplemental evidence, but have not used them to make conclusions because of three major limitations.

First, due to the combination of the lack of a comparison group, the singular sample size, and the nonexperimental setting (i.e., they were not N-of-1 trials), it is highly inappropriate (and even impossible) to make inferences about treatment effectiveness or harms from a case report.

Second, most case reports that we identified involved the use of multiple interventions, often in combination, as attempts to prevent and/or treat primary headache. Teasing apart which intervention (or combination of interventions) was associated with which outcomes in this setting is unfeasible and, more so, inappropriate.

Third, case reports are subject to publication bias and a lack of generalizability in that the cases that are reported, almost by definition, are the select ones that the authors found to be interesting in terms of beneficial effects and/or harms of a given treatment(s). For descriptive information of the individual cases, we refer the reader to the section—*Supplemental Evidence (Case Reports)*—and to Appendix B.

Strengths and Limitations

Strengths and Limitations of the Evidence Base

The limitations of the evidence we identified vastly outnumber its strengths. A major limitation is that, for most interventions, direct evidence about the effectiveness and/or harms in

patients who are pregnant (or attempting to become pregnant), postpartum, or breastfeeding is sparse or absent. We did not identify any primary studies for entire classes of pharmacologic agents: analgesics/antipyretics, tricyclic antidepressants, beta blockers, calcium channel blockers, other antihypertensive medications, serotonin and norepinephrine reuptake inhibitors (SNRIs), benzodiazepines, central nervous system stimulants, muscle relaxants, N-methyl-D-aspartate (NMDA) receptor antagonists, calcitonin gene-related peptide (CGRP) inhibitors, mood-stabilizing agents, tetracyclic antidepressants, corticosteroids, butalbital-containing analgesics, sympathomimetic amines, topical anesthetics, antipsychotics, somatostatin analogs, and intravenous magnesium. Similarly, no primary studies addressed entire classes of nonpharmacologic agents: supplements, chemodenervation, and hydration therapy. However, as discussed above, some of these interventions were described in the indirect evidence.

Where evidence was identified, all studies included women exposed to the interventions (or comparators) during pregnancy; we did not find evidence in women attempting to become pregnant or when postpartum or breastfeeding (except for some studies of triptans [direct evidence] that compared treatments during versus before pregnancy and one SR [indirect evidence] that examined nonsteroidal anti-inflammatory drug (NSAID) use in the postpartum period). In terms of type of primary headache, most primary studies focused on migraine and some focused on tension headache, but none focused on cluster headache or other trigeminal autonomic cephalgias (TACs).

A related limitation of the sparse evidence base is that the studies we identified did not report data for many of our outcomes of interest. Unreported or rarely reported maternal outcomes include headache-related symptoms (nausea/vomiting, photosensitivity, dizziness), quality of life, functional outcomes (impact on family life, impact on employment/school attendance, time spent managing disease), resource use, acceptability of intervention, satisfaction with intervention, and certain adverse effects (stroke, myocardial infarction, reduced breast milk production, and maternal symptoms related to withdrawal of medication). Unreported or rarely reported fetal/child adverse effects include breastfeeding outcomes (delayed initiation, cessation, reduced frequency, reduced volume), poor infant attachment/bonding, and neonatal signs related to withdrawal of medication. Relatedly, few studies reported on the long-term effects and harms of the interventions for mother or child.

Three limitations with the evidence base pertain specifically to the included nonrandomized comparative studies (NRCSs). First, few of the NRCSs reported adjusted between-arm effect sizes. In the absence of the individual patient data, we were unable to calculate adjusted effect sizes. While feasible in some instances (i.e., when arm-specific data were reported), we did not consider it appropriate to calculate unadjusted effect sizes because the populations of women in the treatment arms were generally dissimilar on one or more important confounders. The primary headache disorders result in the use of interventions (for prevention or treatment). While interventions can cause harms that were investigated in this SR, the underlying disorders themselves can cause some of the harms, irrespective of exposure to interventions. This issue can contribute to confounding. Moreover, nonrandomized studies are prone to unmeasured confounding, which can only be accounted for satisfactorily by well-conducted randomized controlled trials (RCTs). Second, triptans, which were the most studied classes of pharmacologic interventions, were discussed by the included studies only in the context of their harms. Currently, their use in clinical practice appears to be based on their effectiveness in nonpregnant populations; the findings of the current SR suggest the absence of evidence of their effectiveness in pregnant women. Third, none of the NRCSs reported information about the doses, durations,

and routes of administration. This is likely because most of the NRCSs were registry-based studies that might not have had access to such information, but the absence of such information can weaken conclusions.

We assessed most of the primary studies at an overall high risk of bias. The main reasons were because of a high risk of serious confounding; because participants, care providers, and/or outcome assessors were not blinded; and because of incomplete outcome data. Furthermore, the participant eligibility criteria, interventions, and outcomes were often inadequately described.

Finally, the included SRs of harms of pharmacologic interventions (indirect evidence) reported limited information regarding the doses, timings, durations, and routes of administration during pregnancy. Consequently, the estimates of harms obtained from these SRs were restricted to use versus nonuse of specific drugs or drug classes. We were unable to make conclusions regarding relative harms of various doses, timings, durations, and routes of administration.

Strengths and Limitations of the Systematic Review Process

We followed contemporary standards for SRs, including multiple stakeholder engagement in KQ development and refinement and careful adherence to recommended methods for literature searching, screening, data extraction, risk of bias assessment, data (narrative) synthesis, and strength of evidence (SoE) assessment. In anticipation of a sparse evidence base, we were very inclusive in our eligibility criteria, especially in terms of study designs, including RCTs, NRCSs, and single-group studies of interventions for primary headaches in pregnancy (as direct evidence); SRs of harms of interventions in pregnancy regardless of indication (as indirect evidence); and case reports (as supplemental evidence).

For all interventions examined in this SR, the paucity of the evidence precluded us from being able to be conduct meta-analyses (either pairwise or network) or make definitive conclusions about treatment effectiveness or harms of the various interventions.

Despite our comprehensive search and approach to using indirect evidence to find harms from SRs regardless of indication, some well-accepted harms of treatment were not addressed. For example, we did not find a SR that fulfilled our minimum quality criteria and provided evidence for the association between indomethacin and increased risk of premature closure of the ductus arteriosus (despite indomethacin being an effective treatment to close a patent ductus arteriosus in neonates[110]). Searching for primary studies of harms (or benefits) of medications regardless of indication during pregnancy was beyond the scope of this review.

Applicability

In addition to the sparseness of the evidence discussed above, a few factors may limit the applicability of our findings. As discussed, the limited information about doses, durations, and frequencies of the interventions reported in the NRCSs (especially triptans) constrains our ability to make definitive conclusions about individual triptans.

The population in the studies included in this SR were varied in terms of the trimester and gestational age, which limits our ability to apply our findings specifically to different trimesters of pregnancy.

Most primary studies in this SR were conducted in the U.S., Canada, or Europe. Various contextual factors may impact the effectiveness of treatments. It is unclear to what extent the findings of this SR might apply outside of these high-income settings.

Implications for Clinical Practice

Although we used both direct and indirect evidence to inform our conclusions in this SR, we emphasize that the direct evidence is sparse. There is surprisingly little directly useful evidence for guiding clinical practice for women with primary headache who are pregnant (or attempting to become pregnant), postpartum, or breastfeeding. This paucity of information also applies to medications more recently approved for migraine by the Food and Drug Administration, such as CGRP inhibitors, noninvasive neuromodulation devices, and botulinum toxin, and some that are available over the counter, such as acetaminophen. Our *a priori* approach to examining harms of relevant medications in this review was restricted to harms reported in (1) primary studies of women with primary headache who were pregnant (or attempting to become pregnant), postpartum, or breastfeeding, and (2) existing SRs that met minimal quality criteria in this population of women regardless of indication. Thus, as discussed above, some harms, such as the risks of NSAIDs when used after 32 weeks of gestation, may not have been found in our search of these two sources of evidence.

Given the paucity of information regarding estimates of the effectiveness of various interventions to prevent or treat primary headaches, decision makers will need to rely on the evidence from the general population. This is especially true for interventions for prevention of primary headaches and for treatments of primary headaches other than migraine, for which we found limited studies among pregnant, postpartum, or breastfeeding women. Ideally, high SoE information from studies of pregnant women with migraine (or other types of primary headache) would inform this decision, but there is generally sparse information for this population. Thus, decision makers are left to extrapolate from studies of pregnant women with mostly other conditions regarding the safety of the interventions, especially regarding potential harms to the fetus or infant. However, the risks involved in using the same drugs for treatment of other conditions (e.g., seizures, psychosis, depression) may not translate well to the risks for women with primary headaches because the underlying risks of fetal/child adverse effects may differ. Treatment doses and durations often differ by indication. Concomitant drug use (and thus drug-drug interactions) are likely to differ. Psychosocial behaviors, such as smoking, substance use, and caffeine intake, may also differ. Nevertheless, clinicians, patients, and policymakers are left with the options of making treatment decisions based on: (1) extrapolating information about harms from studies where these drugs were used for other indications (not included as direct evidence in this SR, but summarized as indirect evidence through examination of published SRs); and/or (2) depending on what is known about the levels of the various drugs in maternal serum/blood or that are transmitted to the fetus through amniotic fluid and/or cord blood, or to the infant through breast milk.

We did not consider levels of various drugs in maternal serum/blood or in other fluids transmitted to the fetus/infant as relevant outcomes in our SR. However, especially given the absence of studies examining interventions for primary headache in breastfeeding women, we recognize that decision makers may be interested in drug levels in various fluids. We found that the most complete resource with data about levels of the various drugs is the Drugs and Lactation Database (LactMed®, available at https://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm). Because the data in LactMed are readily available and are being continually updated, we refer the interested reader there for current information on specific drugs of interest. LactMed contains extensive information about the levels of drugs that are of interest to the current SR. This information is reported in LactMed for specific drugs, often at the level of individual studies and/or specific body fluids. Data are often reported for individual (deidentified) women at

various time-points. While LactMed is frequently used by clinicians and sometimes incorporated into discussions with patients about potential risks, it should be noted that for many drugs, the association between levels of drug exposure in body fluids and harms, either short- or long-term, is not well established. In other words, drug levels are, at best, intermediate outcomes and may not correlate well with harms to the offspring.

We encourage clinicians to inform patients about the limitations of existing research on interventions for preventing or treating primary headaches during pregnancy, postpartum, or breastfeeding phases. Given the limitations of the evidence, the patient's values and preferences and the clinician's expertise and experience are even more important. A related important aspect that should be considered is the severity of the primary headache, which could shift the balance between benefits and harms of a given intervention, or comparative benefits and harms between a set of interventions, under consideration.

Implications for Research

The sparseness of the direct evidence addressing the interventions addressed in this comprehensive SR is striking. It does not imply, however, that interventions are not beneficial or harmful. Because interventions may affect pregnant women (and their offspring) differently than non-pregnant individuals, there is an important and urgent research need for direct evidence in pregnancy, postpartum, or breastfeeding phases.

Research is needed both for pharmacologic and nonpharmacologic interventions. Triptans, the most studied classes of pharmacologic interventions, were discussed by the included studies only in the context of their harms. Currently, their use in clinical practice appears to be based on their effectiveness in nonpregnant populations; the findings of the current SR suggests the absence of evidence in pregnant women. We found low strength of evidence that combination metoclopramide and diphenhydramine was more effective and no more harmful than codeine when used for treating migraine or tension headache. In an era of heightened concern about opioid use, the evidence suggests that it is possible that this combination is a viable alternative to codeine for pregnant women experiencing migraine or tension headache.

For some interventions, although we concluded that studies provided insufficient evidence to make conclusions, these studies found a signal of potential effectiveness and/or safety that should be explored in future research. These include topiramate for prevention of primary headache, and acupuncture, thermal biofeedback, behavioral therapy, physical therapy, peripheral nerve blocks, and transcranial magnetic stimulation for treatment.

Because of the absence of studies addressing prevention or treatment of cluster headache and other TACs in pregnant women, researchers should also design studies that, either entirely or in part, enroll these patients. When enrolled as part of a larger study, subgroup-specific data for these types of primary headache, should be reported.

It is important that future studies either randomize patients (after considering the ethical issues in this population) to minimize selection bias, or report between-arm estimates of treatment effect that adequately account for important confounders, such as age and severity of headache attack (or of history of headaches). Studies should also, where feasible, conduct blinding of participants, care providers, and outcome assessors to minimize the likelihood of performance and detection biases. Given the concern regarding exposing the fetus to potentially harmful pharmacologic interventions, we recognize that RCTs will likely continue to be infrequent. As an alternative to randomization, when observational studies, such as those using patient registries, are conducted, they should be adequately designed and analyzed to compare

treatments. Such analyses should appropriately account for differences between comparison groups of patients that are inherently different. Ideally, propensity score analyses (or similar rigorous techniques) should be used to adequately adjust for these differences. A propensity score analysis, for example, estimates the likelihood that each patient had one or the other intervention (conditional on their measured characteristics) and controls for this likelihood. These analyses generally require relatively large numbers of patients for whom there are granular data about risk factors for outcomes. Additionally, while registry data will likely continue to be important in identifying harms, researchers should report more details about disease severity as well as intervention doses, durations, and frequencies.

When reporting studies, it is also important that authors adhere to relevant reporting guidelines so that adequate details about the population, interventions (and comparators), and outcomes are clearly described.

Future studies should also evaluate other important maternal outcomes, such as headache-related symptoms (e.g., photosensitivity), quality of life, functional outcomes (e.g., impact on employment/school attendance), and patient satisfaction with intervention; adverse effects on breastfeeding, such as decreased milk supply; and some important fetal/child adverse outcomes. None of the studies included in this SR addressed these outcomes.

Conclusions

We were able to make few specific conclusions in this SR, most of which were based on low strength of evidence. Future research should identify the most effective and safe interventions for preventing or treating primary headaches in this population.

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110. Cooke L, Steer P, Woodgate P. Indomethacin for asymptomatic patent ductus arteriosus in preterm infants. Cochrane Database Syst Rev. 2003(2):Cd003745. doi: 10.1002/14651858.Cd003745. PMID: 12804488.

Appendix A. Methods

Details of Study Selection

Search Strategy (Details)

Search Strategy for Primary Studies

We searched for published primary studies for both Key Questions (KQs) in Medline (via PubMed), the Cochrane Central Register of Clinical Trials, Embase, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL). Duplicate citations were removed prior to screening. Searches did not have any date or language restrictions. Search strategies included filters to remove nonhuman studies. The searches included medical subject headings (MeSH) or Emtree terms, along with free-text words, related to pregnancy, postpartum, breastfeeding, headache, migraine, tension headache, cluster headache, and other trigeminal autonomic cephalgias (TACs). The searches were independently peer reviewed. The exact search terms used for identifying primary studies in each database are listed below. To identify additional eligible studies, we also reviewed the reference lists of relevant existing systematic reviews (SRs). Searches for primary studies will be updated upon submission of this draft report for public review.

Medline (via **PubMed**)
Last run June 5, 2020

("Breast Feeding"[Mesh]
OR "Fertilization"[Mesh]
OR "Gestational age"[Mesh]
OR "Lactation"[Mesh]
OR "Maternal Behavior"[Mesh]
OR "Maternal exposure"[Mesh]
OR "Maternal-Fetal Exchange"[Mesh]
OR "Perinatal Care"[Mesh]
OR "Pregnancy"[Mesh]
OR "pregnancy complications"[Mesh]
OR "pregnancy trimesters"[Mesh]
OR breastfeeding
OR "fetal growth"
OR "gestational age"
OR postpartum
OR pregnancy
OR pregnant
OR trimester
OR lactation
OR polycystic ovary syndrome
OR IVF
OR "In Vitro Fertilization"
OR insemination

OR “Polycystic Ovary Syndrome”[Mesh]
OR “Fertilization in Vitro”[Mesh])

AND

(Migraine
OR "Migraine Disorders"[Mesh]
OR "Tension-Type Headache"[Mesh]
OR "Cluster Headache"[Mesh]
OR headache
OR “Headache Disorders, Primary”[Mesh]
OR ((tension OR cluster) AND headache))

Cochrane CENTRAL
Last run June 5, 2020

((breastfeeding
OR “fetal growth”
OR “gestational age”
OR postpartum
OR pregnancy
OR pregnant
OR trimester
OR lactation
OR polycystic ovary syndrome
OR IVF
OR “In Vitro Fertilization”
OR insemination)
AND
(Migraine
OR headache))
NOT ("post-dural" or "post dural" or postdural) and puncture))

CINAHL
Last run June 5, 2020

((breastfeeding
OR “fetal growth”
OR “gestational age”
OR postpartum
OR pregnancy
OR pregnant
OR trimester
OR lactation

OR polycystic ovary syndrome
OR IVF
OR “In Vitro Fertilization”
OR insemination)
AND
(Migraine
OR headache))
NOT ("post-dural" or "post dural" or postdural) and puncture))

EMBASE
Last run June 5, 2020

#1 'breastfeeding'/exp OR 'breastfeeding'
#2 'fetus growth'/de
#3 'gestational age'/de
#4 'puerperium'
#5 postpartum
#6 'pregnancy'/de
#7 'pregnant woman'/de
#8 trimester
#9 'lactation'/de
#10 'ovary polycystic disease'/de
#11 'in vitro fertilization'/de
#12 'insemination'
#13 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12
#14 'migraine'/de
#15 'headache'/de
#16 #14 OR #15
#17 #13 AND #16
#18 #13 AND #16 AND ([article]/lim OR [article in press]/lim) AND [humans]/lim
#19 'postdural puncture headache'
#20 #18 NOT #19

We also searched the ClinicalTrials.gov registry for unpublished study protocols, unpublished study results, and ongoing studies using the following exact terms.

CLINICALTRIALS.GOV
Last run June 5, 2020

(headache
OR migraine) [in condition field]

AND

(breastfeeding
OR “fetal growth”
OR “gestational age”
OR postpartum
OR pregnancy
OR pregnant
OR trimester
OR lactation
OR polycystic ovary syndrome
OR IVF
OR “In Vitro Fertilization”
OR insemination) [in other terms field]

We also asked all members of the Technical Expert Panel (TEP) to review our list of included studies and suggest any additional studies that might be relevant, which we checked against our list of citations and, where applicable, added to our list. Non-English language articles were screened by readers of the relevant languages or after translation via Google Translate (https://translate.google.com/), where possible. Additional articles suggested to us in any language from any source, during peer and public review, will be screened applying identical eligibility criteria.

Search Strategy for SRs

To supplement information about adverse effects from the primary studies for both KQs, we searched for published SRs that have reported adverse effects of interventions, regardless of the indication for which the intervention was used, i.e., we did not restrict to primary headache (or even headache). We searched for SRs in Medline (via PubMed), the Cochrane Database of Systematic Reviews, and Epistemonikos. Duplicate citations were removed prior to screening. Searches did not have any date or language restrictions. The searches included MeSH and free-text words related to pregnancy, postpartum, breastfeeding, and each of the interventions and classes of interventions of interest (for both KQs). The exact search terms used for identifying SRs in each database are listed below. Searches for SRs will be updated upon submission of this draft report for public review.

Medline (via **PubMed**)
Last run June 5, 2020

(“Breast Feeding”[Mesh]
OR “Fertilization”[Mesh]
OR “Gestational age”[Mesh]
OR “Lactation”[Mesh]
OR “Maternal Behavior”[Mesh]
OR “Maternal exposure”[Mesh]
OR “Maternal-Fetal Exchange”[Mesh]
OR “Perinatal Care”[Mesh]
OR “Pregnancy”[Mesh]

OR “pregnancy complications”[Mesh]
OR “pregnancy trimesters”[Mesh]
OR breastfeeding
OR “fetal growth”
OR “gestational age”
OR postpartum
OR pregnancy
OR pregnant
OR trimester
OR lactation)

AND

(“Antidepressive agents, Tricyclic”[Mesh]
OR “Adrenergic beta-Antagonists”[Mesh]
OR “Calcium Channel Blockers”[Mesh]
OR “Anticonvulsants”[Mesh]
OR “Serotonin Uptake Inhibitors”[Mesh]
OR “Benzodiazepines”[Mesh]
OR “Anti-Inflammatory Agents, Non-Steroidal”[Mesh]
OR “Neuromuscular Blocking Agents”[Mesh]
OR “Histamine Antagonists”[Mesh]
OR “Central Nervous System Stimulants”[Mesh]
OR “Tryptamines”[Mesh]
OR “narcotics”[Mesh]
OR “Analgesics, Opioid”[Mesh]
OR “Antimanic Agents”[Mesh]
OR “Antipsychotic Agents”[Mesh]
OR “Antiemetics”[Mesh]
OR “Anesthetics, Local”[Mesh]
OR “Analgesics”[Mesh]
OR “Tricyclic antidepressants”
OR amitriptyline
OR nortriptyline
OR imipramine
OR “Beta blockers”
OR metoprolol
OR propranolol
OR nadolol
OR atenolol
OR timolol
OR nebivolol
OR “Calcium channel blockers”
OR verapamil
OR nimodipine
OR nifedipine

OR nicardipine
OR lisinopril
OR candesartan
OR Antiepileptic*
OR “divalproex sodium”
OR “valproic acid”
OR “sodium valproate”
OR topiramate
OR carbamazepine
OR lamotrigine
OR gabapentin
OR ((Serotonin OR norepinephrine) AND “reuptake inhibitor”)
OR venlafaxine
OR duloxetine
OR benzodiazepines
OR clonazepam
OR (NMDA AND receptor AND (inhibitor OR antagonist))
OR memantine
OR (CGRP AND (inhibitor OR antagonist))
OR erenumab
OR fremanezumab
OR galcanezumab
OR riboflavin
OR “coenzyme Q10”
OR melatonin
OR feverfew
OR “herbal supplement”
OR feverfew
OR butterbur
OR frankincense
OR cannabidiol
OR cyproheptadine
OR acetaminophen
OR paracetamol
OR (Nonsteroidal AND (antiinflammatory OR anti-inflammatory))
OR NSAID
OR Excedrin
OR ibuprofen
OR naproxen
OR aspirin
OR celecoxib
OR ketorolac
OR indomethacin
OR ketoprofen
OR diclofenac
OR “mefenamic acid”

OR Midrin
OR isometheptene
OR dichloralphenazone
OR Antiemetics
OR metoclopramide
OR Antihistamines
OR meclizine
OR dimenhydrinate
OR diphenhydramine
OR promethazine
OR prochlorperazine
OR (("Central Nervous System" OR "CNS") AND "Stimulant")
OR caffeine
OR "muscle relaxant"
OR baclofen
OR cyclobenzaprine
OR tizanidine
OR metaxolone
OR carisoprodol
OR "neuromuscular block"
OR OnabotulinumtoxinA
OR botox
OR AbobotulinumtoxinA
OR dysport
OR magnesium
OR corticosteroids
OR methylprednisolone
OR triamcinolone
OR prednisolone
OR prednisone
OR triptans
OR sumatriptan
OR frovatriptan
OR naratriptan
OR rizatriptan
OR almotriptan
OR eletriptan
OR zolmitriptan
OR narcotics
OR opioids
OR codeine
OR nalbuphine
OR butorphanol
OR hydrocodone
OR oxycodone
OR morphine

OR meperidine
OR tramadol
OR Fioricet
OR Fiorinal
OR butalbital
OR dihydroergotamine
OR ergotamine
OR (“5HT3” AND (“inhibitor” OR “antagonist”))
OR ondansetron
OR “Sympathomimetic Amine”
OR isometheptene
OR “topical anesthetics”
OR lidocaine
OR bupivacaine
OR Antipsychotics
OR chlorpromazine
OR droperidol
OR olanzapine
OR antimanic
OR lithium
OR “Tetracyclic antidepressant”
OR mirtazapine
OR “Somatostatin analog”
OR octreotide)

AND

("drug-related side effects and adverse reactions"[MESH]
OR “abnormalities, drug-induced”[MESH]
OR birth defect
OR congenital abnormality
OR ((adverse or undesirable or harm or harms or harmful or toxic or injurious or serious or fatal)
AND (effect* or reaction* or event* or outcome* or incident*)))
OR Pharmacokinetic* OR pharmacodynamic* OR "Pharmacokinetics"[Mesh]
OR “Breast milk”
OR “Milk, Human”[Mesh]
OR “human milk”
OR “Fetal blood”[Mesh]
OR “fetal blood”
OR “cord blood”
OR “amniotic fluid”
OR “Amniotic Fluid”[Mesh])

AND

(systematic[sb] OR meta-analysis[pt] OR meta-analysis as topic[mh] OR meta-analysis[mh] OR meta analy* OR metanaly* OR metaanaly* OR met analy* OR (systematic AND (review* OR overview*)) OR "Review Literature as Topic"[Mesh] OR cochrane[tiab] OR embase[tiab] OR (psychlit[tiab] or psyclit[tiab]) OR (psychinfo[tiab] or psycinfo[tiab]) OR (cinahl[tiab] or cinhal[tiab] OR “cumulative index to nursing and allied health”) OR science citation index[tiab] OR ibids[tiab] OR “international bibliographic information on dietary supplements” OR cancerlit[tiab] OR reference list*[tiab] OR bibliograph*[tiab] OR hand-search*[tiab] OR relevant journals[tiab] OR manual search*[tiab] OR ((selection OR inclusion OR exclusion) AND criteria[tiab]) OR data extraction[tiab] OR relevant journals OR "Systematic Review" [Publication Type])

Epistemonikos and **Cochrane** (same strategy for both databases)
Last run June 5, 2020

(breastfeeding
OR “fetal growth”
OR “gestational age”
OR postpartum
OR pregnancy
OR pregnant
OR trimester
OR lactation)

AND

(“Tricyclic antidepressants”
OR amitriptyline
OR nortriptyline
OR imipramine
OR “Beta blockers”
OR metoprolol
OR propranolol
OR nadolol
OR atenolol
OR timolol
OR nebivolol
OR “Calcium channel blockers”
OR verapamil
OR nimodipine
OR nifedipine
OR nicardipine
OR lisinopril
OR candesartan
OR Antiepileptic*
OR “divalproex sodium”

OR “valproic acid”
OR “sodium valproate”
OR topiramate
OR carbamazepine
OR lamotrigine
OR gabapentin
OR ((Serotonin OR norepinephrine) AND “reuptake inhibitor”)
OR venlafaxine
OR duloxetine
OR benzodiazepines
OR clonazepam
OR (NMDA AND receptor AND (inhibitor OR antagonist))
OR memantine
OR (CGRP AND (inhibitor OR antagonist))
OR erenumab
OR fremanezumab
OR galcanezumab
OR riboflavin
OR “coenzyme Q10”
OR melatonin
OR feverfew
OR “herbal supplement”
OR feverfew
OR butterbur
OR frankincense
OR cannabidiol
OR cyproheptadine
OR acetaminophen
OR paracetamol
OR (Nonsteroidal AND (antiinflammatory OR anti-inflammatory))
OR NSAID
OR Excedrin
OR ibuprofen
OR naproxen
OR aspirin
OR celecoxib
OR ketorolac
OR indomethacin
OR ketoprofen
OR diclofenac
OR “mefenamic acid”
OR Midrin
OR isometheptene
OR dichloralphenazone
OR Antiemetics
OR metoclopramide

OR Antihistamines
OR meclizine
OR dimenhydrinate
OR diphenhydramine
OR promethazine
OR prochlorperazine
OR (("Central Nervous System" OR "CNS") AND "Stimulant")
OR caffeine
OR "muscle relaxant"
OR baclofen
OR cyclobenzaprine
OR tizanidine
OR metaxolone
OR carisoprodol
OR "neuromuscular block"
OR OnabotulinumtoxinA
OR botox
OR AbobotulinumtoxinA
OR dysport
OR magnesium
OR corticosteroids
OR methylprednisolone
OR triamcinolone
OR prednisolone
OR prednisone
OR triptans
OR sumatriptan
OR frovatriptan
OR naratriptan
OR rizatriptan
OR almotriptan
OR eletriptan
OR zolmitriptan
OR narcotics
OR opioids
OR codeine
OR nalbuphine
OR butorphanol
OR hydrocodone
OR oxycodone
OR morphine
OR meperidine
OR tramadol
OR Fioricet
OR Fiorinal
OR butalbital

OR dihydroergotamine
OR ergotamine
OR ("5HT3" AND ("inhibitor" OR "antagonist"))
OR ondansetron
OR "Sympathomimetic Amine"
OR isometheptene
OR "topical anesthetics"
OR lidocaine
OR bupivacaine
OR Antipsychotics
OR chlorpromazine
OR droperidol
OR olanzapine
OR antimanic
OR lithium
OR "Tetracyclic antidepressant"
OR mirtazapine
OR "Somatostatin analog"
OR octreotide)

AND

(birth defect
OR congenital abnormality
OR ((adverse or undesirable or harm or harms or harmful or toxic or injurious or serious or fatal) AND (effect* or reaction* or event* or outcome* or incident*))
OR Pharmacokinetic*
OR pharmacodynamic*
OR "Breast milk"
OR "human milk"
OR "fetal blood"
OR "cord blood"
OR "amniotic fluid")

Inclusion and Exclusion Criteria (Details)

Inclusion and Exclusion Criteria for KQ 1 (Prevention of Primary Headache)

Population(s)

- Women who are pregnant (or attempting to become pregnant/in the preconception phase), postpartum (defined as up to 12 months postdelivery), or breastfeeding (for any length of time) with history of primary headache
  - Migraine, tension headache, cluster headache or other trigeminal autonomic cephalgia (TACs)

    - Women attempting to become pregnant include those actively planning pregnancy, by any method, who may wish to use only treatments found to be safe and effective during pregnancy.
- Exclude: Women with history of secondary headache of any origin

Interventions

- Pharmacologic interventions
    - Tricyclic antidepressants (e.g., amitriptyline, nortriptyline, imipramine)
    - Serotonin and norepinephrine reuptake inhibitors (SNRIs) (e.g., venlafaxine, duloxetine)
    - Beta blockers (e.g., metoprolol, propranolol, nadolol, atenolol, timolol, nebivolol)
    - Calcium channel blockers (e.g., verapamil, nimodipine, nifedipine, nicardipine)
    - Other antihypertensive medications (e.g., lisinopril, candesartan, clonidine)
    - Antiepileptic drugs (e.g., divalproex sodium, sodium valproate, valproic acid, topiramate, gabapentin, carbamazepine, lamotrigine)
    - Benzodiazepines (e.g., clonazepam)
    - N-methyl-D-aspartate (NMDA) receptor antagonists (e.g., memantine)
    - Calcitonin gene-related peptide (CGRP) inhibitors (e.g., erenumab, fremanezumab, galcanezumab)
    - Antihistamines (e.g., cyproheptadine)
    - Mood-stabilizing agents (e.g., lithium)
    - Tetracyclic antidepressants (e.g., mirtazapine)
    - Corticosteroids (e.g., methylprednisolone, triamcinolone acetonide, combinations of local anesthetics and corticosteroids)
    - Oral magnesium
    - Other pharmacologic interventions used to prevent primary headaches (whether or not available or approved in the United States)
- Nonpharmacologic interventions
    - Supplements (e.g., riboflavin, coenzyme Q10, melatonin, feverfew, butterbur, frankincense)
    - Procedures (e.g., occipital nerve blocks, sphenopalatine ganglion blocks, trigger point injections)
    - Chemodenervation (e.g., onabotulinumtoxin A, abobotulinumtoxin A)
    - Physical therapy
    - Hydration
    - Noninvasive neuromodulation devices (e.g., transcutaneous electrical nerve stimulation, transcranial magnetic stimulation, transcutaneous vagal stimulation, remote electrical neurostimulation)
    - Behavioral therapy (e.g., cognitive behavioral therapy, diet therapy, sleep therapy, exercise therapy, support group therapy)
    - Complementary therapies (e.g., biofeedback, acupuncture, mindfulness-based stress reduction)
    - Other nonpharmacologic interventions used to prevent primary headaches

Comparators

- Pharmacologic interventions
    - Other class

    - Other drug within class
    - Same drug(s), different route, treatment duration, initiation time, or other aspect
    - As comparator to nonpharmacologic intervention
- Nonpharmacologic interventions
    - Other nonpharmacologic intervention class
    - Other nonpharmacologic intervention, within class
    - As comparator to pharmacologic intervention
- No pharmacologic or nonpharmacologic interventions
    - Placebo
    - No intervention

Outcomes

(* denotes important outcomes that were considered when developing Strength of Evidence tables)**:**

- Acute headache attacks*
    - Occurrence of acute headache attacks
    - Frequency of acute headache attacks
    - Severity of acute headache attacks
    - Duration of acute headache attacks
- Headache-related symptoms (e.g., nausea/vomiting, photosensitivity, dizziness)*
    - Occurrence of headache-related symptoms
    - Frequency of headache-related symptoms
    - Severity of headache-related symptoms
    - Duration of headache-related symptoms
    - Most bothersome symptom
- Emergency department visits, clinic visits, or hospitalizations*
- Quality of life*
- Functional outcomes
    - Impact on family life
    - Employment/school attendance
    - Time spent managing disease
- Resource use
- Acceptability of intervention by patients
- Patient satisfaction with intervention
- Medication use
- Adverse effects
    - Maternal
        - Serious maternal adverse effects*
            - "Serious" adverse effects (including those that are composite outcomes), as defined by study authors
            - Cardiovascular outcomes, such as stroke, myocardial infarction
        - Nonserious maternal adverse effects
            - Nonobstetrical (e.g., maternal weight gain, tachycardia, hypertension, gastrointestinal)
            - Preterm labor, cesarean section
            - Reduced breast milk production

        - Symptoms related to withdrawal of medication
    - Discontinuation of intervention (or of study participation) due to maternal adverse effects*
- Fetal/Child
    - Serious fetal/child adverse effects*
        - "Serious" adverse effects (including those that are composite outcomes), as defined by study authors
        - Spontaneous abortion or elective or induced abortion (<20 weeks)
        - Stillbirth or fetal death (≥20 weeks)
        - Neonatal or infant death
        - Preterm birth
        - Low birth weight for gestational age
        - Congenital anomalies
        - Perinatal complications, e.g., low APGAR score, respiratory distress, admission to neonatal intensive care unit (NICU)
        - Neurodevelopmental, behavioral, or social – gross motor development, fine motor development, social, emotional, or cognitive delay or disability
    - Nonserious fetal/child adverse effects
        - Breastfeeding – delayed initiation, cessation, reduced frequency, reduced volume of breast milk
        - Poor infant attachment/bonding
        - Symptoms related to withdrawal of medication
    - Discontinuation of intervention (or of study participation) due to fetal/child adverse effects*

Potential Modifiers

- Phase
    - Preconception
    - First trimester
    - Second trimester
    - Third trimester
    - Postpartum
    - Breastfeeding
- Type of primary headache
    - Migraine
    - Tension headache
    - Cluster headache
    - Other TACs

Timing

- Any

Setting

- Any

Design

- Direct Evidence

- Randomized controlled trials (RCTs)
- Nonrandomized comparative studies (NRCSs)
- Single-group studies
- N-of-1 trials
- Case-control studies
- Cross-sectional studies/surveys
- Prospective or retrospective (all applicable study types)

- Indirect Evidence
  - For adverse effects, we searched for existing SRs that reported adverse effects of individual interventions used during pregnancy, postpartum, or breastfeeding, regardless of their indication (i.e., for any disease/condition, not only primary headaches). We did not enforce a date restriction when screening for eligible SRs, but we required that, SRs should have fulfilled each of the following four minimum criteria:
    1. Specified eligibility criteria for primary studies,
    2. Conducted a comprehensive search (defined as searched at least two electronic databases and searched for unpublished studies through at least one source),
    3. Assessed risk of bias in included studies using any instrument, and
    4. Used appropriate methods for meta-analysis, if conducted.
- Supplemental Evidence
  - Case reports or series of individually-reported case reports

Inclusion and Exclusion Criteria for KQ 2 (Treatment of Primary Headache)

Population(s)

- Women who are pregnant (or attempting to become pregnant/in the preconception phase), postpartum (defined as up to 12 months postdelivery), or breastfeeding (for any length of time) with acute attacks of primary headache
  - Migraine, tension headache, cluster headache, or other trigeminal autonomic cephalgia (TACs)
  - Women attempting to become pregnant include those actively planning pregnancy, by any method, who may wish to use only treatments found to be safe and effective during pregnancy.
- Exclude: Women with attacks of secondary headache of any origin

Interventions

- Pharmacologic interventions
  - Analgesics/antipyretics (e.g., acetaminophen)
  - Nonsteroidal antiinflammatory drugs (NSAIDs) (e.g., ibuprofen, naproxen, aspirin, celecoxib, ketorolac, indomethacin, ketoprofen, diclofenac, mefenamic acid)
  - Other over-the-counter analgesics (e.g., combination aspirin, acetaminophen, and caffeine; combination acetaminophen, isometheptene, and dichloralphenazone)
  - Antiemetics: dopamine receptor antagonists (e.g., metoclopramide, promethazine, prochlorperazine, droperidol, chlorpromazine)
  - Antiemetics: 5HT3 antagonists (e.g., ondansetron)
  - Antihistamines (e.g., meclizine, diphenhydramine, dimenhydrinate, promethazine, pizotifen)

    - Central nervous system stimulants (e.g., caffeine)
    - Muscle relaxants (e.g., baclofen, tizanidine, metaxalone, carisoprodol)
    - Corticosteroids (e.g., prednisolone, prednisolone, methylprednisolone, dexamethasone, betamethasone)
    - Triptans/Serotonin receptor agonists (e.g., sumatriptan, frovatriptan, naratriptan, rizatriptan, almotriptan, eletriptan, zolmitriptan, combination sumatriptan and naproxen)
    - Opioid containing analgesics (e.g., codeine, hydrocodone, oxycodone, morphine, meperidine, tramadol, butorphanol, nalbuphine)
    - Butalbital-containing analgesics (e.g., butalbital; combination butalbital and acetaminophen; combination butalbital, aspirin, and caffeine)
    - Ergot products (e.g., dihydroergotamine, ergotamine, combination ergotamine and caffeine)
    - Sympathomimetic amines (e.g., isometheptene)
    - Topical anesthetics (e.g., lidocaine)
    - Antipsychotics (e.g., chlorpromazine, olanzapine)
    - Somatostatin analogs (e.g., octreotide)
    - Intravenous magnesium
    - Other pharmacologic interventions used to treat acute attacks of primary headache (whether or not available or approved in the United States)
- Nonpharmacologic interventions
    - Hydration
    - Physical therapy
    - Procedures (e.g., occipital nerve blocks, sphenopalatine ganglion blocks, trigger point injections)
    - Noninvasive neuromodulation devices (e.g., transcutaneous electrical nerve stimulation, transcranial magnetic stimulation, transcutaneous vagal stimulation, remote electrical neurostimulation)
    - Behavioral therapy (e.g., cognitive behavioral therapy, diet therapy, sleep therapy, exercise therapy, support group therapy)
    - Supplements (e.g., cannabidiol)
    - Complementary therapies (e.g., biofeedback, acupuncture, mindfulness-based stress reduction)
    - Other nonpharmacologic interventions used to treat acute attacks of primary headache

Comparators

- Pharmacologic interventions
    - Other class
    - Other drug within class
    - Same drug(s), different route, treatment duration, initiation time, or other aspect
    - As comparator to nonpharmacologic intervention
- Nonpharmacologic interventions
    - Other nonpharmacologic intervention class
    - Other nonpharmacologic intervention, within class
    - As comparator to pharmacologic intervention
- No pharmacologic or nonpharmacologic interventions
    - Placebo

- No intervention

Outcomes

(* denotes important outcomes that were considered when developing Strength of Evidence tables):

- Acute headache attack*
  - Severity of acute headache attack
  - Duration of acute headache attack
  - Resolution of acute headache attack
  - Recurrence of headache attacks
- Headache-related symptoms (e.g., nausea/vomiting, photosensitivity)*
  - Severity of headache-related symptoms
  - Duration of headache-related symptoms
  - Resolution of headache-related symptoms
  - Recurrence of headache-related symptoms
  - Most bothersome symptom
- Emergency department visits, clinic visits, or hospitalizations*
- Quality of life*
- Functional outcomes
  - Impact on family life
  - Employment/school attendance
  - Time spent managing disease
- Resource use
- Acceptability of intervention by patients
- Patient satisfaction with intervention
- Medication use
- Adverse effects
  - Maternal
    - Serious maternal adverse effects*
      - "Serious" adverse effects (including those that are composite outcomes), as defined by study authors
      - Cardiovascular outcomes, such as stroke, myocardial infarction
    - Nonserious maternal adverse effects
      - Nonobstetrical (e.g., maternal weight gain, tachycardia, hypertension, gastrointestinal)
      - Preterm labor, cesarean section
      - Reduced breast milk production
      - Symptoms related to withdrawal of medication
    - Discontinuation of intervention (or of study participation) due to maternal adverse effects*
  - Fetal/child
    - Serious fetal/ child adverse effects*
      - "Serious" adverse effects (including those that are composite outcomes), as defined by study authors
      - Spontaneous abortion or elective or induced abortion (<20 weeks)
      - Stillbirth or fetal death (≥20 weeks)

    - Neonatal or infant death
    - Preterm birth
    - Low birth weight for gestational age
    - Congenital anomalies
    - Perinatal complications, e.g., low APGAR score, respiratory distress, admission to NICU
    - Neurodevelopmental, behavioral, or social – gross motor development, fine motor development, social, emotional, or cognitive delay or disability
  - Nonserious fetal/child adverse effects
    - Breastfeeding – delayed initiation, cessation, reduced frequency, reduced volume of breast milk
    - Poor infant attachment/bonding
    - Symptoms related to withdrawal of medication
  - Discontinuation of intervention (or of study participation) due to fetal/child adverse effects*

Potential Modifiers

- Phase
  - Preconception
  - First trimester
  - Second trimester
  - Third trimester
  - Postpartum
  - Breastfeeding
- Type of primary headache
  - Migraine
  - Tension headache
  - Cluster headache
  - Other TACs

Timing

- Any

Setting

- Any

Design

- Direct Evidence:
  - RCTs
  - NRCSs
  - Single-group studies
  - N-of-1 trials
  - Case-control studies
  - Cross-sectional studies/surveys
  - Prospective or retrospective (all applicable study types)
- Indirect Evidence:

- For adverse effects, we searched for existing SRs that reported adverse effects of individual interventions used during pregnancy, postpartum, or breastfeeding, regardless of their indication (i.e., for any disease/condition, not only primary headaches). We did not enforce a date restriction when screening for eligible SRs, but we required that, at a minimum, SRs should have fulfilled each of the following four criteria:
  5. Specified eligibility criteria for primary studies,
  6. Conducted a comprehensive search (defined as searched at least two electronic databases and searched for unpublished studies through at least one source),
  7. Assessed risk of bias in included studies using any instrument, and
  8. Used appropriate methods for meta-analysis, if conducted.

- Supplemental Evidence:
  - Case reports or series of individually-reported case reports

Screening Process (Details)

We screened abstracts in the Abstrackr online software platform (http://abstrackr.cebm.brown.edu/). We created two projects in Abstrackr, one each for primary studies and SRs. For each project, we conducted two rounds of pilot screening. During each pilot round, the entire team screened the same 100 abstracts and discussed conflicts, with the goal of training the team in the nuances of the eligibility criteria and refining them to maximize clarity and efficiency of the screening process. After the pilot rounds, we screened all remaining abstracts in duplicate. The Abstrackr software has machine-learning capabilities that predict the likelihood of relevance of each unscreened abstract. Daily, Abstrackr sorts the unscreened abstracts by likely relevance so that the most relevant abstracts are presented to screeners first. This made the process of screening more efficient and enabled us to capture the large majority of relevant articles relatively early in the abstract screening process.

Potentially-relevant citations were retrieved in full text. Each of these full-text articles were rescreened by one team member with verification by another.

Data Extraction (Details)

We extracted data from eligible primary studies into the Systematic Review Data Repository (https://srdr.ahrq.gov) and data from eligible SRs into Google Sheets (https://docs.google.com/spreadsheets). For each article, one researcher extracted and entered data, which were confirmed by a second, independent researcher. Each individual primary study/SR that was reported in multiple articles was extracted as a single record. In the instance where two studies were reported within a single article, each study was extracted separately.

For each primary study, we extracted article-identifying information, study design features, funding source, population characteristics and sample sizes, intervention and comparator names and descriptions, and relevant benefit and harms outcomes and their definitions.

For each SR, we extracted article-identifying information; information pertaining to our four minimum criteria (i.e., specification of study eligibility criteria, comprehensiveness of search, assessment of risk of bias in included studies, and methods used for meta-analysis, if conducted); other features of the SR related to its quality (see following section); year of last search; number of included studies; number of included studies of women in preconception, pregnant, postpartum, or breastfeeding phases; population characteristics; intervention names and descriptions; and relevant harms outcomes and their definitions.

For both primary studies and SRs, we extracted, as available, data on phase (i.e., preconception, First trimester of pregnancy, second trimester of pregnancy, third trimester of pregnancy, postpartum, breastfeeding) and type of primary headache (i.e., migraine, tension headache, cluster headache, other TACs).

Risk of Bias Assessment (Details)

Risk of Bias Assessment for Primary Studies

We evaluated each study for risk of bias and methodological quality. Because we included a variety of study designs, we incorporated items from three different existing commonly-used tools and tailored the set of items for each study design. The three tools were the Cochrane Risk of Bias Tool,[1] the Risk of Bias in Nonrandomized Studies (ROBINS-I) Tool,[2] and the National Heart, Lung, and Blood Institute (NHLBI) Quality Assessment Tool.[3]

For RCTs, we used all the items from the Cochrane Risk of Bias Tool,[1] focusing on issues related to randomization and allocation concealment methodology; blinding of patients, study personnel/care providers, objective outcome assessors, and subjective outcome assessors; incomplete outcome data; selective outcome reporting; and other issues that could be related to bias. We also used items from the NHLBI Tool focusing on the adequacy of descriptions of study eligibility criteria, interventions, and outcomes.[3]

For NRCSs, we used specific sections of the ROBINS-I Tool[2] that pertain to confounding and selection bias. ROBINS-I requires the identification of specific confounders of interest for the SR. For the purpose of assessing for the presence of potential confounding in studies, we considered age, severity of headache (or history of headache), and frequency of headache (or history of headache). Because NRCSs, like RCTs, can be impacted by the lack of blinding and by participant loss to followup, we also used the items from the Cochrane Risk of Bias Tool[1] that focus on issues related to blinding of patients, study personnel/care providers, objective outcome assessors, and subjective outcome assessors; incomplete outcome data; selective outcome reporting; and other issues that could be related to bias. We also used items from the NHLBI Tool that pertain to the adequacy of descriptions of study eligibility criteria, interventions, and outcomes.[3]

For single-group studies, we used the items from the Cochrane Risk of Bias Tool[1] that pertain to issues of participant loss to followup, specifically, incomplete outcome data, selective outcome reporting, and other issues that could be related to bias. We also used items from the NHLBI Tool focusing on the adequacy of descriptions of study eligibility criteria, interventions, and outcomes.[3]

We did not conduct a risk of bias assessment for case reports because we did not use them to inform conclusions.

Quality Assessment for SRs

We assessed the quality of the SRs using specific items from the A Measurement Tool to Assess Systematic Reviews, version 2 Tool (AMSTAR 2).[4] For each SR, we assessed whether the SR authors: described the eligibility criteria for included studies (AMSTAR 2 item 1); conducted a comprehensive literature search (item 4); conducted duplicate screening of studies (item 5); conducted duplicate data extraction (independently or with verification) (item 6); adequately described the details of included studies (item 8); used a satisfactory technique for assessing risk of bias in included studies (item 9); assessed the potential impact of risk of bias

(item 12); used appropriate meta-analysis methods (if conducted) (item 11); explained or discussed any heterogeneity (item 14); and reported SR conflict of interest (item 16).

Because we only included SRs that fulfilled each of our minimum criteria, the AMSTAR 2 items pertaining to these criteria (items 1, 2, 9, and 11) were always assessed as "Yes."

Data Synthesis and Analysis (Details)

We summarized the evidence qualitatively. We described each study included in the *de novo* SR narratively and using summary and evidence tables describing the study design features, participant characteristics, descriptions of interventions, outcome results, and risk of bias/methodological quality.

We described each existing SR (for adverse effects of interventions) narratively and using summary tables describing the SR's eligibility criteria, included studies, interventions, adverse effects, and reported effect sizes.

For the identified RCTs and NRCSs addressing Key Questions 1 and 2, we extracted information about the effects of interventions (pharmacologic and nonpharmacologic interventions) versus their comparators, primarily with odds ratios (ORs) or relative risks (RRs) for dichotomous outcomes (e.g., resolution of headache), "net mean differences" (NMDs, i.e., between-intervention comparison of within-intervention changes) for continuous outcomes with both pre- and post-intervention data (e.g., severity of headache), and mean differences for continuous outcomes with only post-intervention data (e.g., duration of hospitalization).

Where effect sizes were not reported for RCTs, we calculated unadjusted between-arm effect sizes based on reported arm-specific data (if feasible). When necessary for NMDs, standard errors (SEs) of the differences were estimated from reported standard deviations (or SEs) of baseline and final values. We assumed a correlation of 0.5 between baseline and final values in patients receiving a given intervention. Thus, we used the following equation to estimate the SE:

$$SE^2_{difference} = (SE_A)^2 + (SE_B)^2 - 2 \cdot r \cdot (SE_A) \cdot (SE_B)$$

where r=0.5 (the assumed correlation) and A and B index the correlated measurements (baseline and final time points).

Where effect sizes were not reported for NRCSs, we only did this if the arms were sufficiently similar at baseline on important prognostic factors for the unadjusted effect sizes to be meaningful.

For single-group studies, between-arm effect sizes are not relevant. However, we extracted (and, where possible, calculated) within-arm changes in outcomes in these studies.

No effect sizes are relevant for case reports; we have described these studies narratively (and in summary tables). We have not used the case reports to inform conclusions.

If we identified sufficient studies reporting sufficiently similar results, we would have conducted a Bayesian network meta-analysis comparing the different interventions to each other and to placebo (or no intervention).

Grading the Strength of the Body of Evidence (Details)

We evaluated the Strength of Evidence (SoE) addressing each major comparison for each KQ. These evaluations included the relative benefits and harms (both maternal and fetal/child) for all pharmacologic and nonpharmacologic interventions for which we found studies. We graded the SoE as per the Agency for Healthcare Research and Quality (AHRQ) Methods Guide.[5, 6] We assessed SoE for each outcome category that we, with input from the TEP, determined *a priori* to be important. These categories included acute headache attacks;

headache-related symptoms; emergency department visits, clinic visits, or hospitalizations; quality of life; serious maternal adverse effects or discontinuation of intervention (or of study participation) due to maternal adverse effects; and serious fetal/child adverse effects or discontinuation of intervention (or of study participation) due to fetal/child adverse effects.

For each SoE assessment, we considered the number of studies, their study designs, the study limitations (i.e., risk of bias and overall methodological quality), the directness of the evidence to the KQs, the consistency of study results, the precision of any estimates of effect, the likelihood of reporting bias, other limitations, and the overall findings across studies. When only one study was identified, we rated the consistency as 'not applicable (N/A).' When a single-group study was the only study identified, we rated the directness as 'indirect.' Based on these assessments, we assigned a SoE rating as being either high, moderate, low, or insufficient to estimate an effect.

We conducted SoE assessments of the evidence reported in the SRs in as similar fashion to our SoE assessment of the primary studies. When assessing RoB in the SRs, our assessments focused on the reported RoB among the studies in the SRs. By default, we rated the evidence in the SRs as indirect because they were not restricted to studies of patients with primary headache. The only exception to this was the one SR on triptans, which was focused on patients with migraine.

Outcomes with highly imprecise estimates, highly inconsistent findings across studies, or with data from only one study were deemed to have insufficient evidence to allow a conclusion (with the exception that particularly large and generalizable single studies could provide at least low SoE). This approach is consistent with the concept that for imprecise evidence "any estimate of effect is very uncertain," the definition of Very Low quality evidence per GRADE.[7]

Peer Review and Public Commentary

Experts in neurology, obstetrics and gynecology, maternal and fetal medicine, and primary care, and individuals representing stakeholder and user communities were invited to provide external peer review of this SR. AHRQ and an Associate Editor from a fellow Evidence-based Practice Center also provided comments. The draft report was posted on the AHRQ Website to elicit public comment for 4 weeks (from June 2 to June 30, 2020. We addressed all reviewer comments, revising the text as appropriate. A disposition of comments table of peer and public comments is posted on the EHC Website.

Glossary of Terms and Abbreviations

Terms

Acute headache attack	An occurrence of headache with moderate to severe pain intensity
Breastfeeding	The phase during which, according to the included studies, women were breastfeeding their infant(s)
Postpartum	The phase between delivery and up to 12 months post-delivery
Preconception	The phase during which women are attempting to become pregnant
Primary headaches	Conditions where the headache itself is the disorder
Secondary headache	Headaches that are caused by an underlying disorder, such as stroke, venous thromboembolism, and pituitary tumors

Abbreviations

AAP	American Academy of Pediatrics
ACOG	American College of Obstetricians and Gynecologists
AHRQ	Agency for Healthcare Research and Quality
AHS	American Headache Society
AMSTAR 2	A Measurement Tool to Assess Systematic Reviews 2
ASQ	Ages and Stages Questionnaire
BCBS	Blue Cross Blue Shield
CBCL	Child Behavior Check List
CINAHL	Cumulative Index to Nursing and Allied Health Literature
COI	conflicts of interest
EAST	Emotionality, Activity, and Shyness Temperament
EPC	Evidence-based Practice Center
EHC	Effective Health Care Program
FDA	Food and Drug Administration
HR	hazard ratio
KI	key informant
KQ	key question
MD	mean difference
MeSH	medical subject heading
NMD	net mean difference
NHLBI	National Heart, Lung, and Blood Institute
NICU	neonatal intensive care unit
NLM	National Library of Medicine
NICHD	National Institute of Child Health and Human Development
NRCS	nonrandomized comparative study
NSAID	nonsteroidal anti-inflammatory drug
OB/GYN	obstetrician and gynecologist
OR	odds ratio
RCT	randomized controlled trial
ROBINS-I	Risk of Bias in Nonrandomized Studies of Interventions
RR	relative risk
SD	standard deviation
SE	standard error
SoE	strength of evidence
SR	systematic review
SUNCT	short-lasting, unilateral, neuralgiform headache with conjunctival injection and tearing
TAC	trigeminal autonomic cephalgia
TEP	Technical Expert Panel
TOO	Task Order Officer
VAS	Visual Analog Scale
WMD	weighted mean difference

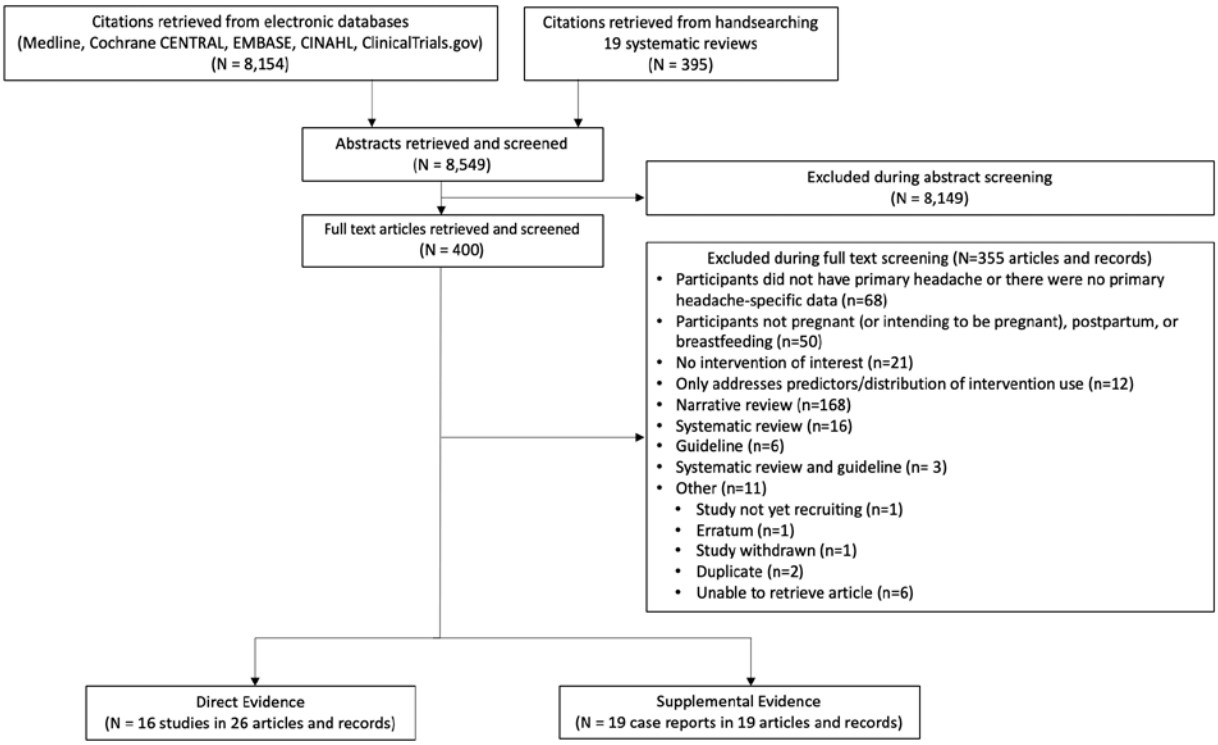
Appendix B. Results

Results of Literature Searches

Primary Search

As illustrated by Figure B-1, our primary electronic search retrieved a combined 8,154 unique citations. An additional 395 citations were retrieved from handsearching 19 relevant SRs that were identified during this search. All told, 8,549 unique abstracts were retrieved and screened. Of these, 400 were deemed potentially relevant and retrieved in full text. After full-text screening, we identified 16 primary studies that were reported in 26 articles (direct evidence)[8-33] and 19 case reports that were reported in 19 articles (supplemental evidence).[34-52]

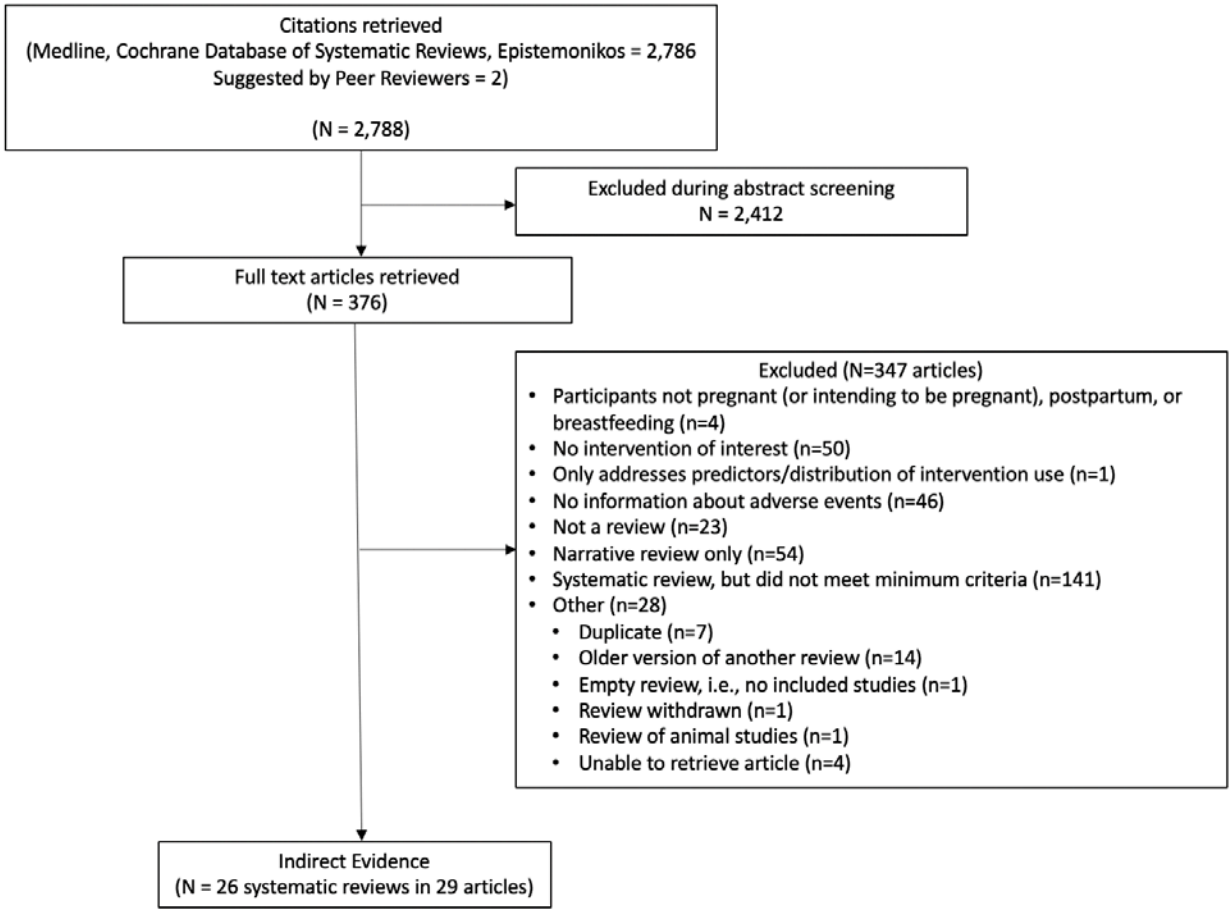
Figure B-1. Flow diagram for primary studies



SRs

Our separate search for SRs is illustrated by the flow diagram in Figure B-2. Our electronic searches retrieved 2,788 unique citations, of which 376 were deemed potentially relevant and retrieved in full text. After full-text screening, we included 26 SRs that were reported in 29 articles (indirect evidence).[53-81]

Figure B-2. Flow diagram for SRs



Description of Included Studies

Primary Studies

The 16 included primary studies, published between 1990 and 2018, comprised three RCTs (reported in five articles[10, 19, 20, 28, 30]), eight NRCSs (reported in 16 articles[11-13, 15, 17, 18, 21-26, 29, 31-33]), and five single-group studies (reported in six articles[8, 9, 14, 16, 19, 27]). Of note, one article reported both an RCT and a single-group study (Marcus 1995).[19]

The 16 primary studies included a total of 14,185 patients. These included three RCTs with 138 patients (ranging from 25 to 70 patients each), eight NRCSs with 13,907 patients (ranging from 123 to 5,900 patients each), and five single-group studies with 121 patients (ranging from 5 to 240 patients each).

All three RCTs enrolled patients with tension headache and evaluated treatments (KQ 2). Two of the RCTs also included patients with migraine.[10, 19, 20, 28]All eight NRCSs enrolled patients with migraine and evaluated treatments (KQ 2). Among the five single-group studies, one examined prevention of acute migraine in patients with a history of migraine (KQ 1),[9] while the other four examined treatment of either acute migraine (three studies [8, 14, 16]) or acute migraine and tension headache (one study[19, 27]) (KQ 2).

Average patient ages, when reported in the studies, ranged from 23 to 34 years. Only one of the 16 studies, an RCT, reported on the racial distribution of the patients, 76 percent of whom were black.[10, 20, 28] Most studies did not report data on the mean gravidity or parity of patients. Among the four studies that reported this information, mean gravidity and parity were usually 3 and 1, respectively.[10, 14, 16, 20, 28, 30]

In terms of natal phase considered, all the 16 included studies considered treatments during pregnancy. Trimesters and gestational ages varied across studies, with some studies considering patients in various trimesters as eligible. Four NRCSs,[15, 22-26, 32, 33] three of which were registry studies,[15, 22-24, 26, 32, 33] examined the issue of timing of treatments by comparing the use of specific pharmacologic interventions (mostly triptans) during pregnancy with their use before pregnancy.

Only one of the 16 included studies addressed interventions to prevent attacks of primary headache in patients with a history of primary headaches (KQ 1). This study, a single-group study, addressed pharmacologic interventions (antiepileptics).[9] None of the included studies addressed nonpharmacologic interventions for KQ 1.

Fifteen of the 16 included studies addressed interventions to treat patients experiencing attacks of primary headache. These included nine studies that addressed pharmacologic interventions (one RCT that addressed antiemetics, antihistamines, and opioid-containing analgesics[10, 20, 28] and eight NRCSs that addressed triptans, ergot products, and NSAIDs[11-13, 15, 17, 18, 21-26, 29, 31-33]) and six studies that addressed nonpharmacologic interventions (two RCTs[19, 30] and two single-group studies[16, 19, 27] that addressed complementary, behavioral, and physical therapies, one single-group study that addressed nerve blocks,[14] and one single-group study that addressed noninvasive neuromodulation devices[8]).

Among the 11 comparative studies (three RCTs and eight NRCSs), seven studies included active comparators only,[10, 13, 17-20, 23, 25, 26, 28] three studies included inactive (i.e., routine care) comparators only,[12, 29-31] and one study included both active and inactive comparators.[15, 22, 24, 32, 33]

All three RCTs[10, 19, 20, 28, 30] and four[8, 14, 16, 19, 27] of the five single-group studies reported adequate information about the dose, frequency, and intensity of the interventions. However, none of the eight NRCSs,[11-13, 15, 17, 18, 21-26, 29, 31-33] most of which were registry-based studies, reported this information.

Among all 16 studies, six were exclusively conducted in the U.S.,[10, 14, 16, 19, 20, 25, 27, 28] two exclusively in Norway,[15, 22-24, 32, 33] one each exclusively in Germany,[12, 31] Denmark,[26] Sweden,[17, 18], Brazil,[30] and the U.K.[8] The other three studies were international (one in the U.S. and Canada;[29] one in the U.S., Canada, U.K., and 36 other countries;[11, 13, 21] and one in the U.S., U.K., Sweden, Germany, and 14 other countries).[9]

Among the six registry-based NRCSs specifically (a total of 13,547 patients), two were exclusively in Norway (2,560 patients[23] and 5,900 patients[15, 22, 24, 32, 33]), one was exclusively in Sweden (3,368 patients),[17, 18] one was exclusively in Denmark (123 patients), one was exclusively in Germany (907 patients),[12, 31] and one was international (U.S., U.K., Sweden, Germany, and 14 other countries; 689 patients).[11, 13, 21]

Among all 16 included studies, four were funded by industry sources,[8, 11, 13, 21, 25] five by nonindustry sources,[15, 17-19, 22, 24, 26, 27, 32, 33] and two reported that they were not funded.[10, 20, 21, 28, 31] The remaining five studies did not report their funding sources.[9, 14, 23, 29, 30]

Table B-1. Included primary studies – Summary of design and arm details

Study, Year, PMID, Country, Funding	Design	Funding	Population description	Arm	Arm Details	Sample Size	Age (years)	Race	Trimester	Gestational Age	Gravidity	Parity	Type of Primary Headache
Childress, 2018, 29723901, U.S.	Randomized controlled trial	None	Second or third trimester, normotensive, migraine or tension headache not relieved by acetaminophen	Combination of antiemetic and antihistamine	Metoclopramide 10 mg intravenous and Diphenhydramine 25 mg intravenous, as a single dose; Second dose only if needed	35	Median 23 (IQR 21, 25)	White: 20%, Black: 80%	Second: NR Third: NR	Median 31.9 (IQR 25.7, 34.6)	Median 3 (IQR 1, 4)	Median 1 (IQR 0, 2)	Migraine: NR Tension headache: NR
				Opioid-containing analgesic	Codeine 30 mg oral as a single dose; Second dose only if needed	35	Median 23.5 (IQR 21, 27)	White: 28.6 %, Black: 71.4 %	Second: NR Third: NR	Median 28.4 (IQR 19.1, 32.9)	Median 3 (IQR 2, 4)	Median 1 (IQR 1, 2)	Migraine: NR Tension headache: NR
Silva, 2012, no PMID, Brazil	Randomized controlled trial	NR	15–30 w gestation with tension headache (>=4 on a scale of 0–10)	Complementary therapy	Acupuncture 15 needles of 40 mm (length) and 0.2 mm (diameter) diameter for 25 min, once a week for 8 weeks	20	27.3 (4.3)	NR	Second: 100%	19.8 (4.0)	2.0 (2.7)	1.0 (2.0)	Tension headache: 100%
				Conventional treatment	Routine care	23	25.3 (6.1)	NR	Second: 100%	19.4 (4.1)	2.0 (2.0)	1.0 (2.0)	Tension headache: 100%

Study, Year, PMID, Country, Funding	Design	Funding	Population description	Arm	Arm Details	Sample Size	Age (years)	Race	Trimester	Gestational Age	Gravidity	Parity	Type of Primary Headache
Marcus (Study 2), 1995, 8600478, U.S.	Randomized controlled trial	Nonindustry (National Headache Foundation)	First or Second trimester; migraine headache, tension headache, or coexisting migraine and tension headache; >=1 headache per week or >=5 headaches per month	Combination of complementary therapy, behavioral therapy, and. physical therapy	Combination of thermal biofeedback, relaxation therapy, and physical therapy; sessions lasted for 1 hour 4 times over 2 months	11	28.6 (6.3)	NR	First: NR Second: NR	17.6 (4.9)	NR	NR	Migraine: 27.3%, Tension headache: 36.4%, Migraine and tension headache coexisting: 36.4%
				Complementary therapy	Thermal biofeedback for 1 hour 4 times over 2 months	14	29.2 (4.8)	NR	First: NR Second: NR	19.8 (4.4)	NR	NR	Migraine: 42.9%, Tension headache: 21.4%, Migraine and tension headache coexisting: 35.7%
Ephross, 2014, 24805878, 18 countries	Nonrandomized comparative study (Prospective)	Industry (Glaxo-Smith-Kline)	Pregnant women with migraine in the Sumatriptan, Naratriptan, and Treximet Pregnancy Registry	Triptans: Sumatriptan	Subcutaneous	626	NR	NR	NR	NR	NR	NR	Migraine: 100%
				Triptans: Naratriptan	Oral	57	NR	NR	NR	NR	NR	NR	Migraine: 100%

Study, Year, PMID, Country, Funding	Design	Funding	Population description	Arm	Arm Details	Sample Size	Age (years)	Race	Trimester	Gestational Age	Gravidity	Parity	Type of Primary Headache
				Combination of Triptans (Sumatriptan) and NSAIDs (Naproxen)	Subcutaneous	6	NR	NR	NR	NR	NR	NR	Migraine: 100%
O'Quinn, 1999, 10728620, U.S.	Nonrandomized comparative study (Prospective)	Industry (Glaxo-Wellcome Research Unit)	Pregnant women with migraine	Triptans: Sumatriptan	During first trimester, subcutaneous	76	NR	NR	NR	NR	NR	NR	Migraine: 100%
				Triptans: Sumatriptan (before pregnancy only)	Before pregnancy only, subcutaneous	92	NR	NR	NR	NR	NR	NR	Migraine: 100%
Shuhaiber, 1998, 9710039, U.S. and Canada	Nonrandomized comparative study (Prospective)	NR	Pregnant women with migraine who contacted a Teratogen Information Service	Triptans: Sumatriptan	During first trimester	96	Mean 32.3, SD 4.9	NR	First: 100%	NR	NR	NR	Migraine: 100%
				No Triptans	Did not use before or during pregnancy	96	Mean 31.7, SD 4.5	NR	First: 100%	NR	NR	NR	Migraine: 100%
Nezvalova-Henriksen, 2013, 23884894, Norway	Nonrandomized comparative study (Retrospective)	NR	Pregnant women with migraine in the Norwegian Prescription Database	Triptans: Any	Sumatriptan, rizatriptan, eletriptan, or zolmitriptan during pregnancy	1465	NR	NR	NR	NR	NR	NR	Migraine: 100%
				Triptans: Any (Before pregnancy only)	Sumatriptan, rizatriptan, eletriptan, or zolmitriptan before pregnancy only	1095	NR	NR	NR	NR	NR	NR	Migraine: 100%

Study, Year, PMID, Country, Funding	Design	Funding	Population description	Arm	Arm Details	Sample Size	Age (years)	Race	Trimester	Gestational Age	Gravidity	Parity	Type of Primary Headache
Nezvalova-Henriksen 2010, 20132339, Norway	Nonrandomized comparative study (Retrospective)	Nonindustry (Norwegian Ministry of Health, NIH, Norwegian Research Council)	Pregnant women with migraine in the Norwegian Mother and Child Cohort Study	Triptans: Any	During pregnancy	1045	NR	NR	NR	NR	NR	NR	Migraine: 100%
				Triptans: Any (before pregnancy only)	Before pregnancy only	805	NR	NR	NR	NR	NR	NR	Migraine: 100%
				No Triptans	Did not use before or during pregnancy	4050	NR	NR	NR	NR	NR	NR	Migraine: 100%
Kallen, 2011, 21751829, Sweden	Nonrandomized comparative study (Retrospective)	Nonindustry (Evy and Gunnar Sandberg Foundation)	Pregnant women with migraine in the Swedish Medical Birth Register	Triptans: Any	Sumatriptan, naratriptan, zolmitriptan, rizatriptan, almotriptan, or eletriptan	2777	NR	NR	NR	NR	NR	NR	Migraine: 100%
				Ergot Products: Any	Dihydroergotamine or ergotamine combinations	527	NR	NR	NR	NR	NR	NR	Migraine: 100%
				Antihistamines: Pizotifen	Pizotifen	64	NR	NR	NR	NR	NR	NR	Migraine: 100%

Study, Year, PMID, Country, Funding	Design	Funding	Population description	Arm	Arm Details	Sample Size	Age (years)	Race	Trimester	Gestational Age	Gravidity	Parity	Type of Primary Headache
Olesen 2000 10759898, Denmark	Nonrandomized comparative study (Retrospective)	Nonindustry (Helsefonden, Pharmacy Foundation; EU BIOMED Programme, Danish Medical Research Council, North Jutland Research Council)	Pregnant women with migraine in the Pharmaco-Epidemiological Prescription Database of North Jutland County, Denmark	Triptans: Sumatriptan	During pregnancy	34	Mean 29.6	NR	NR	NR	NR	NR	Migraine: 100%
				Triptans: Sumatriptan or Ergot Products: Ergotamine (before pregnancy only)	Before pregnancy only	89	Mean 28.4	NR	NR	NR	NR	NR	Migraine: 100%
Spielmann, 2018, 28758416, Germany	Nonrandomized comparative study (Retrospective)	None	Pregnant women with migraine in the German Embryotox system	Triptans: Any	Sumatriptan, zolmitriptan, rizatriptan, naratriptan, frovatriptan, eletriptan, or almotriptan	432	Median 33 (IQR 30, 37)	NR	NR	NR	NR	NR	Migraine: 100%
				No Triptans	Any other drug for migraine	475	Median 32 (IQR 29, 36)	NR	NR	NR	NR	NR	Migraine: 100%

Study, Year, PMID, Country, Funding	Design	Funding	Population description	Arm	Arm Details	Sample Size	Age (years)	Race	Trimester	Gestational Age	Gravidity	Parity	Type of Primary Headache
Castilla-Puentes, 2014, 24598456, U.S., U.K., Canada, Australia, and 36 other countries	Single-group (Retrospective)	Industry (Janssen; previously Johnson & Johnson)	Pregnant women with a history of migraine	Antiepileptics: Topiramate	Topiramate monotherapy (dose, duration, route, frequency not reported)	81	NR	NR	NR	NR	NR	NR	History of migraine: 100%
Govindappagari, 2014, 1, U.S.	Single-group (Retrospective)	NR	Pregnant women with migraine in whom other forms of treatment previously had failed	Nerve blocks: Peripheral	Greater occipital, auriculotemporal, supraorbital, and supratrochlear nerve injections with local anesthetics (1–2% lidocaine or 0.5% bupivacaine)	13	Mean 28, Range 18, 36	NR	NR	Mean=23.5 Range=7, 37	NR	Nulliparous: 61.5% Multiparous: 38.4%	Migraine: 100%
Marcus (Study 1), 1995, 8600478, U.S.	Single-group (Prospective)	Nonindustry (National Headache Foundation)	First or second trimester; Migraine, tension headache, or coexisting migraine and tension headache; >=1 headache per week or 5 headaches per month	Combination of complementary therapy, behavioral therapy, and. physical therapy	Combination of thermal biofeedback, relaxation therapy, and physical therapy; sessions lasted for 1 hour 4 times over 2 months	19	Mean 31.7, SD 5.4	NR	First: NR Second: NR	17.7 (4.2)	NR	NR	Migraine: 78.9%, Tension headache: 15.8%, Migraine and tension headache combined: 5.2%

Study, Year, PMID, Country, Funding	Design	Funding	Population description	Arm	Arm Details	Sample Size	Age (years)	Race	Trimester	Gestational Age	Gravidity	Parity	Type of Primary Headache
Hickling, 1990, 2401622, U.S.	Single-group (Prospective)	NR	First or second trimester; Migraine	Combination of complementary therapy and behavioral therapy	Combination of thermal biofeedback and progressive muscle relaxation, 4–12 sessions	5	Mean 34, SD 4.9	NR	First: 20% Second: 80%	NR	NR	Mean 1.0 (SD 1.4)	Migraine: 100%
Bhola, 2015, 26055242, U.K.	Single-group (Prospective)	Industry (eNeura, Inc.)	Second trimester; Migraine	Transcranial magnetic stimulation	Magnetic field pulse of 0.9 T transcranially over the back of the head, up to 2 pulses separated by at least 15 mins, up to 16 single pulses or 8 double pulses per day, on as many migraine days as needed	3	Mean 30.3, SD 1.5	NR	Second: 100%	NR	NR	NR	Migraine: 100%

Abbreviations: IQR = interquartile range, min = minutes, NR = not reported, PMID = PubMed identifier, SD = standard deviation.

Table B-2. Risk of bias assessment for primary studies – Randomized controlled trials (RCTs)

KQ, Int Type	Study, Year, PMID	Random Sequence Generation	Allocation Concealment	Blinding of Participants	Blinding of Personnel/ Care Providers	Blinding of Outcome Assessors (Objective Outcomes)	Blinding of Outcome Assessors (Subjective Outcomes)	Incomplete Outcome Data	Selective Outcome Reporting	Other Bias	Eligibility Criteria Prespecified and Clearly Described	Intervention Clearly Described and Consistently Delivered	Outcomes Prespecified, Clearly Defined, Valid, Reliable, and Consistently Assessed	OVERALL RISK OF BIAS
KQ 2, Pharm	Childress, 2018, 29723901	Low	Low	High	High	High	High	Low	High	Low	Yes	Yes	Yes	**HIGH**
KQ 2, Nonpharm	Silva, 2012, no PMID	Unclear	Low	High	High	High	High	Low	Low	Low	Yes	Yes	Yes	**HIGH**
	Marcus (Study 2), 1995, 8600478	Unclear	Unclear	High	High	Unclear	High	High	Low	Low	Yes	Yes	Yes	**HIGH**

Abbreviations: Int = intervention KQ = Key Question, Nonpharm = nonpharmacologic, Pharm = pharmacologic, PMID = PubMed identifier, RCT = randomized controlled trial.
Ratings are color coded for emphasis only.

From the Cochrane Risk of Bias Tool (each item rated as Low, High, Unclear, or N/A [none in Table])

- Random sequence generation (selection bias): Selection bias (biased allocation to interventions) due to inadequate generation of a randomized sequence;
- Allocation concealment (selection bias): Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment;
- Blinding of participants (performance bias): Performance bias due to knowledge of the allocated interventions by participants during the study;
- Blinding of personnel/care providers (performance bias): Performance bias due to knowledge of the allocated interventions by personnel/care providers during the study;
- Blinding of outcome assessor (detection bias): Detection bias due to knowledge of the allocated interventions by outcome assessors during the study;
- Incomplete outcome data (attrition bias): Attrition bias due to amount, nature, or handling of incomplete outcome data;
- Selective outcome reporting (outcome reporting bias): Bias arising from outcomes being selectively reported based on the direction and/or strength of the results;
- Other Bias: Bias due to problems not covered elsewhere in the table.

From the National Heart, Lung, and Blood Institute (NHLBI) Quality Assessment Tool (each item rated as Yes, No [none in Table], or Unclear [none in Table])

- Eligibility criteria prespecified and clearly described: Potentially related to selection bias;
- Intervention clearly described and delivered consistently: Potentially related to performance bias;
- Outcomes prespecified, clearly defined, valid, reliable, and assessed consistently: Potentially related to detection bias.

Overall risk of bias assessed as **HIGH**, **MODERATE** (none in Table), or **LOW** (none in Table).

Table B-3. Risk of bias assessment for primary studies – Nonrandomized comparative studies (NRCSs), assessment of confounding and section bias

KQ, Int Type	Study, Year, PMID	1.1 Potential for Any Confounding?	1.2 Potential for Time-Varying Confounding?	1.3 Intervention Switches Related to Prognostic Factors?	1.4 Appropriate Analysis Method for Confounding?	1.5 Appropriate Confounding Variables Used?	1.6 Inappropriate Control of Post-Intervention Variables?	Judgement – Risk of Bias Related to Confounding	2.1 Participant Selection Based on Post-Intervention Variables?	2.2 Post-Intervention Variables Associated with Intervention?	2.3 Post-Intervention Variables Associated with Outcome?	2.4 Start and Follow-Up (Duration) Coincide	2.5 Appropriate Adjustment for Selection Bias	Judgement – Risk of Bias Related to Selection Bias
KQ 2, Pharm	Ephross, 2014, 24805878	Yes	No	N/A	No	No	No	**Serious**	No	N/A	N/A	Yes	N/A	**Low**
	O'Quinn, 1999, 10728620	Yes	No	N/A	No	No	No	**Serious**	No	N/A	N/A	Yes	N/A	**Low**
	Shuhaiber, 1998, 9710039	Yes	No	N/A	No	No	No	**Serious**	No	N/A	N/A	Yes	N/A	**Low**
	Nezvalova-Henriksen, 2013, 23884894	Yes	No	N/A	Yes	Yes	No	**Moderate**	No	N/A	N/A	Yes	N/A	**Low**
	Nezvalova-Henriksen 2010, 20132339	Yes	No	N/A	Yes	Yes	No	**Moderate**	No	N/A	N/A	Yes	N/A	**Low**
	Kallen, 2011, 21751829	Yes	No	N/A	No	No	No	**Serious**	No	N/A	N/A	Yes	N/A	**Low**
	Olesen 2000, 1075989	Yes	No	N/A	Yes	Yes	No	**Low**	No	N/A	N/A	Yes	N/A	**Low**
	Spielmann, 2018, 28758416	Yes	No	N/A	Yes	Yes	No	**Low**	No	N/A	N/A	Yes	N/A	**Low**

Abbreviations: Int = intervention, KQ = Key Question, N/A = Not applicable, NI = no information, NRCS = nonrandomized comparative study, Pharm = pharmacologic, PMID = PubMed identifier, PN = probably no, PY = probably yes.

Judgements are color coded for emphasis only. Signaling questions are not color coded for simplicity and because they are only used to inform the judgements.

Responses to Risk of Bias in Nonrandomized Studies of Interventions (ROBINS-I) signaling questions 1.1 to 1.6 and 2.1 to 2.5 are in regular font. (each item rated as Yes, PY, NI, PN, No, or N/A)

Judgements about confounding and selection bias are in **bold font**. Each judgement is rated as **Low**, **Moderate**, **Serious**, **Critical** (none in Table), or **NI** (none in Table).

Table B-4. Risk of bias assessment for primary studies – Nonrandomized comparative studies (NRCSs), assessment of remaining biases and quality

KQ, Type of Intervention	Study, Year, PMID	Blinding of Participants	Blinding of Personnel/ Care Providers	Blinding of Outcome Assessors (Objective Outcomes)	Blinding of Outcome Assessors (Subjective Outcomes)	Incomplete Outcome Data	Selective Outcome Reporting	Other Bias	Eligibility Criteria Prespecified and Clearly Described	Intervention Clearly Described and Consistently Delivered	Outcomes Prespecified, Clearly Defined, Valid, Reliable, and Consistently Assessed	OVERALL RISK OF BIAS
KQ 2, Pharm	Ephross, 2014, 24805878	High	High	High	N/A	Low	Low	Low	Yes	No	Yes	**HIGH**
	O'Quinn, 1999, 10728620	High	High	Unclear	N/A	Low	Unclear	Low	No	No	No	**HIGH**
	Shuhaiber, 1998, 9710039	High	High	High	High	Low	Low	Low	Yes	No	Yes	**HIGH**
	Nezvalova-Henriksen, 2013, 23884894	High	High	High	High	Low	Low	Low	Yes	No	Yes	**HIGH**
	Nezvalova-Henriksen, 2010, 20132339	High	High	High	High	High	Low	Low	Yes	No	Yes	**HIGH**
	Kallen, 2011, 21751829	High	High	High	N/A	Low	Low	Low	Yes	No	Yes	**HIGH**
	Olesen, 2000 1075989	High	High	High	N/A	Low	Low	Low	Yes	No	Yes	**MODERATE**
	Spielmann, 2018, 28758416	High	High	High	High	High	Low	Low	Yes	No	Yes	**HIGH**

Abbreviations: KQ = Key Question, N/A = not applicable, NRCS = nonrandomized comparative study, Pharm = pharmacologic, PMID = PubMed identifier.
Ratings are color coded for emphasis only.
From the Cochrane Risk of Bias Tool (each item rated as Low, High, Unclear, or N/A)

- Blinding of participants (performance bias): Performance bias due to knowledge of the allocated interventions by participants during the study;
- Blinding of personnel/care providers (performance bias): Performance bias due to knowledge of the allocated interventions by personnel/care providers during the study;
- Blinding of outcome assessor (detection bias): Detection bias due to knowledge of the allocated interventions by outcome assessors during the study;
- Incomplete outcome data (attrition bias): Attrition bias due to amount, nature or handling of incomplete outcome data;
- Selective outcome reporting (outcome reporting bias): Bias arising from outcomes being selectively reported based on the direction and/or strength of the results;
- Other Bias: Bias due to problems not covered elsewhere in the table.

From the National Heart, Lung, and Blood Institute (NHLBI) Quality Assessment Tool (each item rated as Yes, No, Unclear [none in Table], or No Data [none in Table])

- Eligibility criteria prespecified and clearly described: potentially related to selection bias;
- Intervention clearly described and delivered consistently: potentially related to performance bias;
- Outcomes prespecified, clearly defined, valid, reliable, and assessed consistently: potentially related to detection bias.

Overall risk of bias assessed as **HIGH**, **MODERATE**, or **LOW** (none in Table).

Table B-5. Risk of bias assessment for primary studies – Single-group studies

KQ, Type of Intervention	Study, Year, PMID	Incomplete Outcome Data	Selective Outcome Reporting	Other Bias	Eligibility Criteria Prespecified and Clearly Described	Intervention Clearly Described and Consistently Delivered	Outcomes Prespecified, Clearly Defined, Valid, Reliable, and Consistently Assessed	OVERALL RISK OF BIAS
KQ 1, Pharm	Castilla-Puentes, 2014, 24598456	Low	Low	Low	Yes	No Data	Yes	**LOW**
KQ 2, Nonpharm	Govindappagari, 2014, 25415168	Low	Low	Low	No	Yes	Yes	**LOW**
	Marcus (Study 1), 1995, 8600478	Low	Low	Low	Yes	Yes	Yes	**LOW**
	Hickling, 1990, 2401622	Low	Low	Low	No Data	No Data	Yes	**LOW**
	Bhola, 2015, 26055242, U.K.	Low	Low	Low	Yes	Yes	No	**MODERATE**

Abbreviations: Nonpharm = nonpharmacologic, Pharm = pharmacologic, PMID = PubMed identifier.
Ratings are color coded for emphasis only.
From the Cochrane Risk of Bias Tool (each item rated as Low, High [none in Table], Unclear [none in Table], or N/A [none in Table])

- Incomplete outcome data (attrition bias): Attrition bias due to amount, nature or handling of incomplete outcome data;
- Selective outcome reporting (outcome reporting bias): Bias arising from outcomes being selectively reported based on the direction and/or strength of the results;
- Other Bias: Bias due to problems not covered elsewhere in the table.

From the National Heart, Lung, and Blood Institute (NHLBI) Quality Assessment Tool (each item rated as Yes, No, Unclear [none in Table], or No Data)

- Eligibility criteria prespecified and clearly described: potentially related to selection bias;
- Intervention clearly described and delivered consistently: potentially related to performance bias;
- Outcomes prespecified, clearly defined, valid, reliable, and assessed consistently: potentially related to detection bias.

Overall risk of bias assessed as **HIGH** (none in Table), **MODERATE**, or **LOW**.

Table B-6. Key Question 1: Pharmacologic interventions: Antiepileptics – Adverse effects, categorical

Study, Year, Design PMID	Maternal or Fetal/Child	Adverse Effect	Category of Congenital Anomaly	Time	Arm	Subgroup	n/N (%)	Effect Size (95% CI)	P Value
Castilla-Puentes, 2014, Single-group study, 24598456	Fetal/Child	Spontaneous abortion	-	NR	Antiepileptics: Topiramate	All participants	23/81 (28.4)	N/A	N/A
Castilla-Puentes, 2014, Single-group study, 24598456	Fetal/Child	Elective or induced abortion	-	NR	Antiepileptics: Topiramate	All participants	10/81 (12.3)	N/A	N/A
Castilla-Puentes, 2014, Single-group study, 24598456	Fetal/Child	Congenital anomalies, Any	-	At birth	Antiepileptics: Topiramate	All participants	10/81 (12.3)	N/A	N/A
Castilla-Puentes, 2014, Single-group study, 24598456	Fetal/Child	Congenital anomalies, Hydrocephalus	Neurological	At birth	Antiepileptics: Topiramate	All participants	1/81 (1.2)	N/A	N/A
Castilla-Puentes, 2014, Single-group study, 24598456	Fetal/Child	Congenital anomalies, Meningomyelocele	Neurological	At birth	Antiepileptics: Topiramate	All participants	1/81 (1.2)	N/A	N/A
Castilla-Puentes, 2014, Single-group study, 24598456	Fetal/Child	Congenital anomalies, Spina bifida	Neurological	At birth	Antiepileptics: Topiramate	All participants	1/81 (1.2)	N/A	N/A
Castilla-Puentes, 2014, Single-group study, 24598456	Fetal/Child	Congenital anomalies, Cardiovascular	Cardiovascular	At birth	Antiepileptics: Topiramate	All participants	1/81 (1.2)	N/A	N/A
Castilla-Puentes, 2014, Single-group study, 24598456	Fetal/Child	Congenital anomalies, Syndactyly	Malformation	At birth	Antiepileptics: Topiramate	All participants	1/81 (1.2)	N/A	N/A
Castilla-Puentes, 2014, Single-group study, 24598456	Fetal/Child	Congenital anomalies, Polydactyly	Malformation	At birth	Antiepileptics: Topiramate	All participants	1/81 (1.2)	N/A	N/A
Castilla-Puentes, 2014, Single-group study, 24598456	Fetal/Child	Congenital anomalies, Cleft palate	Malformation	At birth	Antiepileptics: Topiramate	All participants	2/81 (2.5)	N/A	N/A
Castilla-Puentes, 2014, Single-group study, 24598456	Fetal/Child	Congenital anomalies, Gastrointestinal obstruction	Gastrointestinal	At birth	Antiepileptics: Topiramate	All participants	1/81 (1.2)	N/A	N/A
Castilla-Puentes, 2014, Single-group study, 24598456	Fetal/Child	Congenital anomalies, Pyloric stenosis	Gastrointestinal	At birth	Antiepileptics: Topiramate	All participants	1/81 (1.2)	N/A	N/A

Abbreviations: CI = confidence interval, N/A = not applicable, PMID = PubMed identifier.

Table B-7. Key Question 2: Pharmacologic interventions: Antiemetics, antihistamines, opioid analgesics – Categorical outcomes

Study, Year, Design, PMID	Outcome	Outcome Definition	Time	Arm	Subgroup	n/N (%)	Effect Size (95% CI)	P value
Childress, 2018, RCT, 29723901	Severity of acute headache	Reduction in pain score by >=2 points on a VAS (0-10)	24 h	Combination of metoclopramide and diphenhydramine	All participants	34/34 (100)	No nonevents	
				Codeine	All participants	32/32 (100)		
Childress, 2018, RCT, 29723901	Resolution of acute headache	Relief from headache with one dose	NR	Combination of metoclopramide and diphenhydramine	All participants	32/34 (94.1)	OR 1.37 (1.07, 1.75)[i]	0.016[i]
				Codeine	All participants	22/32 (68.8)		
Childress, 2018, RCT, 29723901	Resolution of acute headache	Relief from headache with two doses	NR	Combination of metoclopramide and diphenhydramine	All participants	2/34 (5.9)	OR 0.44 (0.07, 2.57)[i]	0.360[i]
				Codeine	All participants	4/32 (12.5)		
Childress, 2018, RCT, 29723901	Resolution of acute headache	Complete resolution of headache	24 h	Combination of metoclopramide and diphenhydramine	All participants	26/34 (76.5)	OR 5.42 (1.86, 15.76)[i]	0.002[i]
				Codeine	All participants	12/32 (37.5)		
Childress, 2018, RCT, 29723901	Recurrence of acute headache	Recurrence of headache	24 h	Combination of metoclopramide and diphenhydramine	All participants	13/34 (38.2)	OR 0.42 (0.16, 1.14)[i]	0.088[i]
				Codeine	All participants	19/32 (59.4)		
Childress, 2018, RCT, 29723901	Medication use	Use of nonstudy headache medication	24 h	Combination of metoclopramide and diphenhydramine	All participants	7/34 (20.6)	OR 0.43 (0.14, 1.29)[i]	0.134[i]
				Codeine	All participants	12/32 (37.5)		

Abbreviations: CI = confidence interval, h = hours, IQR = interquartile range, OR = odds ratio, PMID = PubMed identifier, RCT = randomized controlled trial, VAS = visual analog scale.

[i] Calculated by us based on reported arm-specific data. This was done only for studies with arms with baseline characteristics considered by us to be similar.

Table B-8. Key Question 2: Pharmacologic interventions: Antiemetics, antihistamines, opioid analgesics – Continuous outcomes

Study, Year, Design, PMID	Outcome	Outcome Definition	Time	Arm	Subgroup	N	Result, Mean (SD)	Effect Size (95% CI)	P value
Childress, 2018, RCT, 29723901	Severity of acute headache	Pain score on a VAS (0-10)	Baseline	Combination of metoclopramide and diphenhydramine	All participants	35	7.6 (NR)	-	-
				Codeine	All participants	35	7.4 (NR)		
			30 min	Combination of metoclopramide and diphenhydramine	All participants	35	3.0 (2.8)	NMD –3.0 (–4.2, –1.8)[i]	<0.001[i]
				Codeine	All participants	35	5.8 (2.3)		
			1 h	Combination of metoclopramide and diphenhydramine	All participants	35	2.2 (2.3)	NMD –2.1 (–3.3, –0.9)[i]	0.001
				Codeine	All participants	35	4.1 (3.0)		
			6 h	Combination of metoclopramide and diphenhydramine	All participants	33	1.8 (NR)	NMD –0.9 (–2.2, 0.4)[i]	0.165[i]
				Codeine	All participants	32	2.5 (NR)		
			12 h	Combination of metoclopramide and diphenhydramine	All participants	33	1.3 (2.5)	NMD –1.6 (–2.9, –0.3)[i]	0.016[i]
				Codeine	All participants	31	2.7 (3.0)		
			24 h	Combination of metoclopramide and diphenhydramine	All participants	34	2.1 (NR)	NMD –1.0 (–2.3, 0.3)[i]	0.128[i]
				Codeine	All participants	32	2.9 (NR)		
Childress, 2018, RCT, 29723901	Resolution of acute headache	Time to headache relief in min	24 h	Combination of metoclopramide and diphenhydramine	All participants	35	20.2 min (13.4)	MD –42.2 min (–63.7. –20.7)[i]	<0.001[i]
				Codeine	All participants	35	62.4 min (62.2)		

Abbreviations: CI = confidence interval, h = hours, MD = mean difference, min = minutes, NMD = net mean difference, NR = not reported, PMID = PubMed identifier, RCT = randomized controlled trial, SD = standard deviation, VAS = visual analog scale.

[i] Calculated by us based on reported arm-specific data. This was done only for studies with arms with baseline characteristics considered by us to be similar.

Table B-9. Key Question 2: Pharmacologic interventions: Antiemetics, antihistamines, opioid analgesics – adverse effects, categorical

Study, Year, Design, PMID	Maternal or Infant/ Child?	Outcome	Time	Arm	Subgroup	n/N (%)	Effect Size (95% CI)	P value
Childress, 2018, RCT, 29723901	Maternal	Serious adverse effects	24 h	Combination of metoclopramide and diphenhydramine	All participants	0/34 (0.0)	No events	-
				Codeine	All participants	0/34 (0.0)		
Childress, 2018, RCT, 29723901	Maternal	Nonserious adverse effects (fatigue, dizziness, agitation, nausea, or intravenous site pain)	24 h	Combination of metoclopramide and diphenhydramine	All participants	15/34 (44.1)	OR 1.74 (0.63, 4.76)[i]	0.283[i]
				Codeine	All participants	10/32 (31.3)		

Abbreviations: CI = confidence interval, h = hours, OR = odds ratio, PMID = PubMed identifier.

[i] Calculated by us based on reported arm-specific data. This was done only for studies with arms with baseline characteristics considered by us to be similar.

Table B-10. Key Question 2: Pharmacologic interventions: Triptans, ergot products, and NSAIDs – Maternal adverse effects, categorical

Study, Year, Design, PMID	Outcome	Time	Arm	Subgroup	n/N (%)	Adj Effect Size (95% CI)	Adj P value
O'Quinn, 1999, NRCS, 10728620	Abnormal pregnancy outcome	NR	Triptans: Sumatriptan	All participants	9/76 (12)	NR	NR
			Triptans: Sumatriptan (before pregnancy only)	All participants	19/92 (21)		
Nezvalova-Henriksen, 2013, NRCS, 23884894	Postpartum hemorrhage >500 ml	Delivery	Triptans: Any	All participants (Any triptan, Any trimester)	248/1465 (16.9)	NR	NR
				Any Triptan, First trimester	204/1210 (16.9)		
				Any Triptan, Second trimester	65/304 (21.4)		
				Any Triptan, Third trimester	24/185 (13.0)		
				Sumatriptan, Any trimester	100/575 (17.4)		
				Sumatriptan, First trimester	71/415 (17.1)		
				Sumatriptan, Second trimester	40/173 (23.1)		
				Sumatriptan, Third trimester	11/104 (10.6)		
				Rizatriptan, Any trimester	49/334 (14.7)		
				Rizatriptan, First trimester	45/310 (14.5)		
				Rizatriptan, Second trimester	9/43 (20.9)		
				Rizatriptan, Third trimester	5/26 (19.2)		
				Eletriptan, Any trimester	30/207 (14.5)		
				Eletriptan, First trimester	29/189 (15.3)		
				Eletriptan, Second trimester	4/33 (12.1)		
				Eletriptan, Third trimester	2/21 (9.5)		
				Zolmitriptan, Any trimester	34/156 (21.8)		
				Zolmitriptan, First trimester	33/144 (22.9)		
				Zolmitriptan, Second trimester	6/26 (23.1)		
				Zolmitriptan, Third trimester	2/17 (11.8)		
			Triptans: Any (Before pregnancy only)	All participants	195/1095 (17.8)		
Nezvalova-Henriksen 2010, NRCS, 20132339	Postpartum hemorrhage >500 ml	Delivery	Triptans: Any	All participants	255/1045 (24.4)	NR	NR
				First trimester	228/455 (50.1)	NR	NR
				Second and/or Third trimester	41/229 (17.9)	NR	NR
			Triptans: Any (before pregnancy only)	All participants	63/805 (7.8)	NR	NR
			No Triptans	All participants	NR	NR	NR

Abbreviations: Adj = adjusted, CI = confidence interval, NR = not reported, NRCS = nonrandomized comparative study, PMID = PubMed identifier.

Table B-11. Key Question 2: Pharmacologic interventions: Triptans, ergot products, and NSAIDs – Fetal/child adverse effects (fetal death, spontaneous abortion, elective or induced abortion, stillbirth, and infant death), categorical

Study, Year, Design, PMID	Outcome	Time	Arm	Subgroup	n/N (%)	Adj Effect Size (95% CI)	Adj P value
Ephross, 2014, NRCS, 24805878	Spontaneous abortion	NR	Triptans: Sumatriptan	All participants	34/626 (5.4)	NR	NR
				First trimester	34/528 (6.4)		
				Second trimester	0/78 (0.0)		
				Third trimester	0/16 (0.0)		
				Unknown trimester	0/4 (0.0)		
			Triptans: Naratriptan	All participants	5/57 (8.8)	NR	NR
				First trimester	5/52 (9.6)		
				Second trimester	0/5 (0.0)		
				Third trimester	0/0 (0.0)		
				Unknown trimester	0/0 (0.0)		
			Combination of Triptans (Sumatriptan) and NSAIDs (Naproxen)	All participants	1/6 (16.7)	NR	NR
				First trimester	1/5 (20.0)		
				Second trimester	0/1 (0.0)		
				Third trimester	0/0 (0.0)		
				Unknown trimester	0/0 (0.0)		
Ephross, 2014, NRCS, 24805878	Elective or induced abortion	NR	Triptans: Sumatriptan	All participants	16/626 (2.6)	NR	NR
				First trimester	15/528 (2.8)		
				Second trimester	0/78 (0.0)		
				Third trimester	0/16 (0.0)		
				Unknown trimester	1/4 (25.0)		
			Triptans: Naratriptan	All participants	1/57 (1.8)	NR	NR
				First trimester	1/52 (1.9)		
				Second trimester	0/5 (0.0)		
				Third trimester	0/0 (0.0)		
				Unknown trimester	0/0 (0.0)		
			Combination of Triptans (Sumatriptan) and NSAIDs (Naproxen)	All participants	0/6 (0.0)	NR	NR
				First trimester	0/5 (0.0)		
				Second trimester	0/1 (0.0)		
				Third trimester	0/0 (0.0)		
				Unknown trimester	0/0 (0.0)		
Ephross, 2014, NRCS, 24805878	Stillbirth or fetal death	NR	Triptans: Sumatriptan	All participants	5/626 (0.8)	NR	NR
				First trimester	5/528 (1.0)		
				Second trimester	0/78 (0.0)		
				Third trimester	0/16 (0.0)		
				Unknown trimester	0/4 (0.0)		

Study, Year, Design, PMID	Outcome	Time	Arm	Subgroup	n/N (%)	Adj Effect Size (95% CI)	Adj P value
			Triptans: Naratriptan	All participants	0/57 (0.0)	NR	NR
				First trimester	0/52 (0.0)		
				Second trimester	0/5 (0.0)		
				Third trimester	0/0 (0.0)		
				Unknown trimester	0/0 (0.0)		
			Combination of Triptans (Sumatriptan) and NSAIDs (Naproxen)	All participants	0/6 (0.0)	NR	NR
				First trimester	0/5 (0.0)		
				Second trimester	0/1 (0.0)		
				Third trimester	0/0 (0.0)		
				Unknown trimester	0/0 (0.0)		
O'Quinn, 1999, NRCS, 10728620	Spontaneous abortion	NR	Triptans: Sumatriptan	All participants	8/76 (10.5)	NR	NR
			Triptans: Sumatriptan (before pregnancy only)	All participants	11/92 (12)		
Shuhaiber, 1998, NRCS, 9710039	Spontaneous abortion	NR	Triptans: Sumatriptan	All participants	11/96 (11.5)	NR	NR
			No Triptans	All participants	6/96 (6.3)		
Shuhaiber, 1998, NRCS, 9710039	Elective or induced abortion	NR	Triptans: Sumatriptan	All participants	4/96 (4.2)	NR	NR
			No Triptans	All participants	2/96 (2.1)		
Nezvalova-Henriksen 2010, NRCS, 20132339	Stillbirth	At birth	Triptans: Any	All participants	0/1045 (0.0)	NR	NR
				First trimester	0/455 (0.0)		
				Second and/or third trimester	0/229 (0.0)		
			Triptans: Any (before pregnancy only)	All participants	2/805 (0.2)		
			No Triptans	All participants	NR		
Nezvalova-Henriksen 2010, NRCS, 20132339	Perinatal death	At birth	Triptans: Any	All participants	6/1045 (0.6)	NR	NR
				First trimester	6/455 (1.3)		
				Second and/or third trimester	3/229 (1.3)		
			Triptans: Any (before pregnancy only)	All participants	3/805 (0.4)		
			No Triptans	All participants	NR		
Nezvalova-Henriksen 2010, NRCS, 20132339	Infant death	1 y of age	Triptans: Any	All participants	5/1045 (0.5)	NR	NR
				First trimester	5/455 (1.1)		
				Second and/or third trimester	2/229 (0.9)		
			Triptans: Any (before pregnancy only)	All participants	0/805 (0.0)		

Study, Year, Design, PMID	Outcome	Time	Arm	Subgroup	n/N (%)	Adj Effect Size (95% CI)	Adj P value
			No Triptans	All participants	NR		
Kallen, 2011, NRCS, 21751829	Perinatal death	At birth	Triptans: Any	All participants	NR	NR	NR
				Sumatriptan	5/658 (0.75)		
				Naratriptan	NR		
				Zolmitriptan	NR		
				Rizatriptan	NR		
				Almotriptan	NR		
				Eletriptan	NR		
			Ergot Products: Any	All participants	NR		
				Dihydroergotamine	NR		
				Ergotamine combinations	NR		
			Antihistamines: Pizotifen	All participants	3/64 (4.69)		
Spielmann, 2018, NRCS, 28758416	Spontaneous abortion	NR	Triptans: Any	All participants	50/432 (11.6)	Adj HR 1.41 (0.9, 2.2)	
				First trimester	49/387 (12.7)		
			No Triptans	All participants	37/475 (7.8)		
Spielmann, 2018, NRCS, 28758416	Elective or induced abortion	NR	Triptans: Any	All participants	23/432 (5.3)	Adj HR 1.58 (0.8, 3.0)	NR
				First trimester	23/387 (5.9)		
			No Triptans	All participants	17/475 (3.6)		
Spielmann, 2018, NRCS, 28758416	Stillbirth	At birth	Triptans: Any	All participants	1/432 (0.2)	NR	NR
				First trimester	1/387 (0.3)		
			No Triptans	All participants	1/475 (0.2)		

Abbreviations: Adj = adjusted, CI = confidence interval, h = hours, HR = hazard ratio, m = months, NR = not reported, NRCS = nonrandomized comparative study, OR = odds ratio, PMID = PubMed identifier, y = years.

Table B-12. Key Question 2: Pharmacologic interventions: Triptans, ergot products, and NSAIDs – Fetal/child adverse effects (perinatal complications and signs of infant distress), categorical

Study, Year, Design, PMID	Outcome	Outcome Definition	Time	Arm	Subgroup	n/N (%)	Adj Effect Size (95% CI)	Adj P value
Nezvalova-Henriksen, 2013, NRCS, 23884894	Preterm birth	<37 w	At birth	Triptans: Any	All participants (Any triptan, Any trimester)	92/1465 (6.3)	NR	NR
					Any Triptan, First trimester	76/1210 (6.3)		
					Any Triptan, Second trimester	27/304 (8.9)		
					Any Triptan, Third trimester	12/185 (6.5)		
					Sumatriptan, Any trimester	41/575 (7.1)		
					Sumatriptan, First trimester	32/415 (7.7)		
					Sumatriptan, Second trimester	11/173 (6.4)		
					Sumatriptan, Third trimester	7/104 (6.7)		
					Rizatriptan, Any trimester	18/334 (5.4)		
					Rizatriptan, First trimester	17/310 (5.5)		
					Rizatriptan, Second trimester	6/43 (14.0)		
					Rizatriptan, Third trimester	2/26 (7.7)		
					Eletriptan, Any trimester	9/207 (4.3)		
					Eletriptan, First trimester	7/189 (3.7)		
					Eletriptan, Second trimester	3/33 (9.1)		
					Eletriptan, Third trimester	1/21 (4.8)		
					Zolmitriptan, Any trimester	14/156 (9.0)		
					Zolmitriptan, First trimester	13/144 (9.0)		
					Zolmitriptan, Second trimester	5/26 (19.2)		
					Zolmitriptan, Third trimester	0/17 (0.0)		
				Triptans: Any (Before pregnancy only)	All participants	108/1095 (9.9)		
Nezvalova-Henriksen, 2013, NRCS, 23884894	Low birth weight	<2500 g	At birth	Triptans: Any	All participants (Any triptan, Any trimester)	75/1465 (5.1)	NR	NR
					Any Triptan, First trimester	61/1210 (5.0)		
					Any Triptan, Second trimester	22/304 (7.2)		
					Any Triptan, Third trimester	8/185 (4.3)		
					Sumatriptan, Any trimester	31/575 (5.4)		
					Sumatriptan, First trimester	23/415 (5.5)		
					Sumatriptan, Second trimester	11/173 (6.4)		
					Sumatriptan, Third trimester	3/104 (2.9)		
					Rizatriptan, Any trimester	16/334 (4.8)		
					Rizatriptan, First trimester	15/310 (4.8)		
					Rizatriptan, Second trimester	1/43 (2.3)		
					Rizatriptan, Third trimester	3/26 (11.5)		
					Eletriptan, Any trimester	7/207 (3.4)		

Study, Year, Design, PMID	Outcome	Outcome Definition	Time	Arm	Subgroup	n/N (%)	Adj Effect Size (95% CI)	Adj P value
					Eletriptan, First trimester	6/189 (3.2)		
					Eletriptan, Second trimester	3/33 (9.1)		
					Eletriptan, Third trimester	0/21 (0.0)		
					Zolmitriptan, Any trimester	11/156 (7.1)		
					Zolmitriptan, First trimester	9/144 (6.2)		
					Zolmitriptan, Second trimester	4/26 (15.4)		
					Zolmitriptan, Third trimester	1/17 (5.9)		
				Triptans: Any (Before pregnancy only)	All participants	66/1095 (6.0)		
Nezvalova-Henriksen, 2013, NRCS, 23884894	Low birth weight for gestational age	<tenth percentile for gestational age	At birth	Triptans: Any	All participants (Any triptan, Any trimester)	132/1465 (9.0)	NR	NR
					Any Triptan, First trimester	110/1210 (9.1)		
					Any Triptan, Second trimester	27/304 (8.9)		
					Any Triptan, Third trimester	20/185 (10.8)		
					Sumatriptan, Any trimester	48/575 (8.3)		
					Sumatriptan, First trimester	33/415 (8.0)		
					Sumatriptan, Second trimester	16/173 (9.2)		
					Sumatriptan, Third trimester	11/104 (10.6)		
					Rizatriptan, Any trimester	36/334 (10.8)		
					Rizatriptan, First trimester	36/310 (11.6)		
					Rizatriptan, Second trimester	2/43 (4.7)		
					Rizatriptan, Third trimester	4/26 (15.4)		
					Eletriptan, Any trimester	21/207 (10.1)		
					Eletriptan, First trimester	20/189 (10.6)		
					Eletriptan, Second trimester	4/33 (12.1)		
					Eletriptan, Third trimester	1/21 (4.8)		
					Zolmitriptan, Any trimester	13/156 (8.3)		
					Zolmitriptan, First trimester	13/144 (9.0)		
					Zolmitriptan, Second trimester	2/26 (7.7)		
					Zolmitriptan, Third trimester	1/17 (5.9)		
				Triptans: Any (Before pregnancy only)	All participants	91/1095 (8.3)		
Nezvalova-Henriksen, 2013, NRCS, 23884894	NICU admission	-	At birth	Triptans: Any	All participants (Any triptan, Any trimester)	NR	NR	NR
					Any Triptan, First trimester	100/1210 (8.3)		
					Any Triptan, Second trimester	31/304 (10.2)		
					Any Triptan, Third trimester	16/185 (8.6)		

Study, Year, Design, PMID	Outcome	Outcome Definition	Time	Arm	Subgroup	n/N (%)	Adj Effect Size (95% CI)	Adj P value
					Sumatriptan, Any trimester	NR		
					Sumatriptan, First trimester	41/415 (9.9)		
					Sumatriptan, Second trimester	14/173 (8.1)		
					Sumatriptan, Third trimester	5/104 (4.8)		
					Rizatriptan, Any trimester	NR		
					Rizatriptan, First trimester	23/310 (7.4)		
					Rizatriptan, Second trimester	5/43 (11.6)		
					Rizatriptan, Third trimester	4/26 (15.4)		
					Eletriptan, Any trimester	NR		
					Eletriptan, First trimester	15/189 (7.9)		
					Eletriptan, Second trimester	4/33 (12.1)		
					Eletriptan, Third trimester	1/21 (4.8)		
					Zolmitriptan, Any trimester	NR		
					Zolmitriptan, First trimester	12/144 (8.3)		
					Zolmitriptan, Second trimester	4/26 (15.4)		
					Zolmitriptan, Third trimester	4/17 (23.5)		
				Triptans: Any (Before pregnancy only)	All participants	120/1095 (11.0)		
Nezvalova-Henriksen 2010, NRCS, 20132339	Preterm birth	<37 w	At birth	Triptans: Any	All participants	86/1045 (8.2)	NR	NR
					First trimester	82/455 (18.0)		
					Second and/or Third trimester	55/229 (24.0)		
				Triptans: Any (before pregnancy only)	All participants	30/805 (3.7)		
				No Triptans	All participants	NR		
Nezvalova-Henriksen 2010, NRCS, 20132339	Low birth weight	<2500 g	At birth	Triptans: Any	All participants	65/1045 (6.2)	NR	NR
					First trimester	63/455 (13.9)		
					Second and/or Third trimester	40/229 (17.5)		
				Triptans: Any (before pregnancy only)	All participants	19/805 (2.3)		
				No Triptans	All participants	NR		
Nezvalova-Henriksen 2010, NRCS, 20132339	Apgar score <7	-	1 min after birth	Triptans: Any	All participants	88/1045 (8.4)	NR	NR
					First trimester	81/455 (17.8)		
					Second and/or Third trimester	55/229 (24.0)		

Study, Year, Design, PMID	Outcome	Outcome Definition	Time	Arm	Subgroup	n/N (%)	Adj Effect Size (95% CI)	Adj P value
				Triptans: Any (before pregnancy only)	All participants	18/805 (2.2)		
				No Triptans	All participants	NR		
			5 min after birth	Triptans: Any	All participants	22/1045 (2.1)	NR	NR
					First trimester	20/455 (4.4)		
					Second and/or Third trimester	11/229 (4.8)		
				Triptans: Any (before pregnancy only)	All participants	4/805 (0.5)		
				No Triptans	All participants	NR		
Kallen, 2011, NRCS, 21751829	Preterm birth	<37 w	At birth	Triptans: Any	All participants	NR	NR	NR
					Sumatriptan	34/658 (5.1)		
					Naratriptan	NR		
					Zolmitriptan	NR		
					Rizatriptan	NR		
					Almotriptan	NR		
					Eletriptan	NR		
				Ergot Products: Any	All participants	NR		
					Dihydroergotamine	NR		
					Ergotamine combinations	NR		
				Antihistamines: Pizotifen	All participants	NR		
Kallen, 2011, NRCS, 21751829	Low birth weight	<2500 g	At birth	Triptans: Any	All participants	NR	NR	NR
					Sumatriptan	34/658 (5.1)		
					Naratriptan	NR		
					Zolmitriptan	NR		
					Rizatriptan	NR		
					Almotriptan	NR		
					Eletriptan	NR		
				Ergot Products: Any	All participants	NR		
					Dihydroergotamine	NR		
					Ergotamine combinations	NR		
				Antihistamines: Pizotifen	All participants	NR		
Olesen, 2000, NRCS, 10759898	Preterm birth	<37 w	At birth	Triptans: Sumatriptan	All participants	5/34 (14.7)	Adj OR 6.3 (1.2, 32.0)	NR

Study, Year, Design, PMID	Outcome	Outcome Definition	Time	Arm	Subgroup	n/N (%)	Adj Effect Size (95% CI)	Adj P value
				Triptans: Sumatriptan or Ergot Products: Ergotamine (before pregnancy only)	All participants	3/89 (3.4)		
Olesen, 2000, NRCS, 10759898	Low birth weight	<2500 g	At birth	Triptans: Sumatriptan	All participants	1/34 (3.4)	Adj OR 0.9 (0.1, 11.8)	NR
				Triptans: Sumatriptan or Ergot Products: Ergotamine (before pregnancy only)	All participants	5/89 (5.8)		

Abbreviations: Adj = adjusted, CI = confidence interval, m = months, NICU = neonatal intensive care unit, NR = not reported, NRCS = nonrandomized comparative study, OR = odds ratio, PMID = PubMed identifier, RR = relative risk, w = weeks, y = years.

Table B-13. Key Question 2: Pharmacologic interventions: Triptans, ergot products, and NSAIDs – Fetal/child adverse effects (congenital anomalies), categorical

Study, Year, Design, PMID	Outcome	Time	Arm	Subgroup	n/N (%)	Adj Effect Size (95% CI)	Adj P value
Ephross, 2014, NRCS, 24805878	Major anomalies	At birth	Triptans: Sumatriptan	All participants	19/626 (3.0)	NR	NR
				First trimester	16/528 (3.0)		
				2nd trimester	3/78 (3.8)		
				3rd trimester	0/16 (0.0)		
				Unknown trimester	0/4 (0.0)		
			Triptans: Naratriptan	All participants	1/57 (1.8)		
				First trimester	1/52 (1.9)		
				2nd trimester	0/5 (0.0)		
				3rd trimester	0/0 (0.0)		
				Unknown trimester	0/0 (0.0)		
			Combination of Triptans (Sumatriptan) and NSAIDs (Naproxen)	All participants	0/6 (0.0)		
				First trimester	0/5 (0.0)		
				2nd trimester	0/1 (0.0)		
				3rd trimester	0/0 (0.0)		
				Unknown trimester	0/0 (0.0)		
Shuhaiber, 1998, NRCS, 9710039	Major anomalies	At birth	Triptans: Sumatriptan	All participants	1/82 (1.2)	NR	>=0.05
			No Triptans	All participants	4/90 (4.4)		
Shuhaiber, 1998, NRCS, 9710039	Minor anomalies – Brown marks	At birth	Triptans: Sumatriptan	All participants	2/82 (2.4)	NR	>=0.05
			No Triptans	All participants	4/90 (4.4)		
Shuhaiber, 1998, NRCS, 9710039	Minor anomalies – Red marks	At birth	Triptans: Sumatriptan	All participants	6/82 (7.3)	NR	>=0.05
			No Triptans	All participants	1/82 (1.2)		
Nezvalova-Henriksen, 2013, NRCS, 23884894	Any anomaly	At birth	Triptans: Any	All participants (Any triptan, Any trimester)	85/1465 (5.7)	NR	NR
				Any Triptan, First trimester	72/1210 (6.0)		
				Sumatriptan, Any trimester	35/575 (6.1)		
				Sumatriptan, First trimester	28/415 (6.7)		
				Rizatriptan, Any trimester	15/334 (4.5)		
				Rizatriptan, First trimester	14/310 (4.5)		
				Eletriptan, Any trimester	8/207 (3.9)		
				Eletriptan, First trimester	8/189 (4.2)		
				Zolmitriptan, Any trimester	12/156 (7.7)		
				Zolmitriptan, First trimester	11/144 (7.6)		
			Triptans: Any (Before pregnancy only)	All participants	67/1095 (6.1)		

Study, Year, Design, PMID	Outcome	Time	Arm	Subgroup	n/N (%)	Adj Effect Size (95% CI)	Adj P value
Nezvalova-Henriksen, 2013, NRCS, 23884894	Major anomalies	At birth	Triptans: Any	All participants (Any triptan, Any trimester)	51/1465 (3.5)	NR	NR
				Any Triptan, First trimester	43/1210 (3.6)		
				Sumatriptan, Any trimester	19/575 (3.3)		
				Sumatriptan, First trimester	15/415 (3.6)		
				Rizatriptan, Any trimester	11/334 (3.3)		
				Rizatriptan, First trimester	10/310 (3.2)		
				Eletriptan, Any trimester	4/207 (1.9)		
				Eletriptan, First trimester	4/189 (2.1)		
				Zolmitriptan, Any trimester	8/156 (5.1)		
				Zolmitriptan, First trimester	7/144 (4.9)		
			Triptans: Any (Before pregnancy only)	All participants	50/1095 (4.6)		
Nezvalova-Henriksen 2010, NRCS, 20132339	Any anomaly	At birth	Triptans: Any	All participants	75/1045 (7.2)	NR	NR
				First trimester	69/455 (15.2)		
				2nd and/or 3rd trimester	49/229 (21.4)		
			Triptans: Any (before pregnancy only)	All participants	22/805 (2.7)		
			No Triptans	All participants	NR		
Nezvalova-Henriksen 2010, NRCS, 20132339	Major anomalies	At birth	Triptans: Any	All participants	75/1045 (4.4)	NR	NR
				First trimester	43/455 (9.5)		
				2nd and/or 3rd trimester	30/229 (13.1)		
			Triptans: Any (before pregnancy only)	All participants	11/805 (1.4)		
			No Triptans	All participants	NR		
Kallen, 2011, NRCS, 21751829	Any anomaly	At birth	Triptans: Any	All participants	127/2777 (4.57)	NR	NR
				Sumatriptan	107/2257 (4.74)		
				Naratriptan	1/22 (4.55)		
				Zolmitriptan	12/362 (3.31)		
				Rizatriptan	7/157 (4.46)		
				Almotriptan	1/6 (16.67)		
				Eletriptan	3/14 (21.43)		
			Ergot Products: Any	All participants	21/527 (3.98)		
				Dihydroergotamine	5/135 (3.70)		
				Ergotamine combinations	16/388 (4.12)		
			Antihistamines: Pizotifen	All participants	3/64 (4.69)		

Study, Year, Design, PMID	Outcome	Time	Arm	Subgroup	n/N (%)	Adj Effect Size (95% CI)	Adj P value
Kallen, 2011, NRCS, 21751829	Major anomalies	At birth	Triptans: Any	All participants	92/2777 (3.31)	NR	NR
			Ergot Products: Any	All participants	17/527 (3.23)		
			Antihistamines: Pizotifen	All participants	NR		
Kallen, 2011, NRCS, 21751829	Any cardiovascular anomalies	At birth	Triptans: Any		29/2777 (1.04)	NR	NR
			Ergot Products: Any	All participants	7/527 (1.33)		
			Antihistamines: Pizotifen	All participants	NR		
Kallen, 2011, NRCS, 21751829	Ventricular septum defect and/or atrial septum defect	At birth	Triptans: Any		17/2777 (0.61)	NR	NR
			Ergot Products: Any	All participants	6/527 (1.14)		
			Antihistamines: Pizotifen	All participants	NR		
Spielmann, 2018, NRCS, 28758416	Any anomaly	At birth	Triptans: Any	All participants	25/372 (6.7)	Adj OR 1.00 (0.51, 2.1)	NR
				First trimester	24/438 (7.3)		
			No Triptans	All participants	28/431 (6.5)		
Spielmann, 2018, NRCS, 28758416	Major anomalies	At birth	Triptans: Any	All participants	9/367 (2.5)	Adj OR 1.01 (0.3, 3.3)	NR
				First trimester	8/323 (2.5)		
			No Triptans	All participants	12/429 (2.8)		
Spielmann, 2018, NRCS, 28758416	Minor anomalies	At birth	Triptans: Any	All participants	11/364 (3.0)	Adj OR 1.48 (0.5, 4.4)	NR
				First trimester	11/320 (3.4)		
			No Triptans	All participants	12/427 (2.8)		
Spielmann, 2018, NRCS, 28758416	Genetic birth defect	At birth	Triptans: Any	All participants	5/369 (1.4)	Adj OR 1.10 (0.2, 6.6)	NR
				First trimester	5/325 (1.5)		
			No Triptans	All participants	4/429 (0.9)		
Spielmann, 2018, NRCS, 28758416	Ventricular septum defect	At birth	Triptans: Any	All participants	1/367 (0.3)	NR	NR
				First trimester	NR		
			No Triptans	All participants	NR		
Spielmann, 2018, NRCS, 28758416	Atrial septum defect	At birth	Triptans: Any	All participants	1/367 (0.3)	NR	NR
				First trimester	NR		
			No Triptans	All participants	NR		
Spielmann, 2018, NRCS, 28758416	Pulmonary artery stenosis	At birth	Triptans: Any	All participants	1/367 (0.3)	NR	NR
				First trimester	NR		
			No Triptans	All participants	NR		
Spielmann, 2018, NRCS, 28758416	Cataract	At birth	Triptans: Any	All participants	1/367 (0.3)	NR	NR

Study, Year, Design, PMID	Outcome	Time	Arm	Subgroup	n/N (%)	Adj Effect Size (95% CI)	Adj P value
				First trimester	NR		
			No Triptans	All participants	NR		
Spielmann, 2018, NRCS, 28758416	Microphthalmy	At birth	Triptans: Any	All participants	1/367 (0.3)	NR	NR
				First trimester	NR		
			No Triptans	All participants	NR		
Spielmann, 2018, NRCS, 28758416	Cleft lip and palate	At birth	Triptans: Any	All participants	1/367 (0.3)	NR	NR
				First trimester	NR		
			No Triptans	All participants	NR		
Spielmann, 2018, NRCS, 28758416	Club foot	At birth	Triptans: Any	All participants	1/367 (0.3)	NR	NR
				First trimester	NR		
			No Triptans	All participants	NR		
Spielmann, 2018, NRCS, 28758416	Congenital finger hypoplasia	At birth	Triptans: Any	All participants	1/367 (0.3)	NR	NR
				First trimester	NR		
			No Triptans	All participants	NR		
Spielmann, 2018, NRCS, 28758416	Patent foramen ovale	At birth	Triptans: Any	All participants	1/367 (0.3)	NR	NR
				First trimester	NR		
			No Triptans	All participants	NR		
Spielmann, 2018, NRCS, 28758416	Poland syndrome	At birth	Triptans: Any	All participants	1/367 (0.3)	NR	NR
				First trimester	NR		
			No Triptans	All participants	NR		
Spielmann, 2018, NRCS, 28758416	Polydactyly of toes	At birth	Triptans: Any	All participants	1/367 (0.3)	NR	NR
				First trimester	NR		
			No Triptans	All participants	NR		
Spielmann, 2018, NRCS, 28758416	Renal agenesis	At birth	Triptans: Any	All participants	1/367 (0.3)	NR	NR
				First trimester	NR		
			No Triptans	All participants	NR		
Spielmann, 2018, NRCS, 28758416	Syndactyly	At birth	Triptans: Any	All participants	1/367 (0.3)	NR	NR
				First trimester	NR		
			No Triptans	All participants	NR		

Abbreviations: Adj = adjusted, CI = confidence interval, m = months, NR = not reported PMID = PubMed identifier, NRCS = nonrandomized comparative study, OR = odds ratio, RR = relative risk, y = years.

Table B-14. Key Question 2: Pharmacologic interventions: Triptans, ergot products, and NSAIDs – Fetal/child adverse effects (neurodevelopmental outcomes), categorical

Study, Year, Design, PMID	Outcome	Outcome Definition	Time	Arm	Subgroup	n/N (%)	Adj Effect Size (95% CI)	Adj P value
Nezvalova-Henriksen, 2010, NRCS, 20132339	Gross motor development	Z-score >=1.5 on the ASQ	1.5 y	Triptans: Any	All participants	8/495 (1.6)	NR	NR
				Triptans: Any (before pregnancy only)	All participants	33/1002 (3.3)		
				No Triptans	All participants	93/4050 (2.3)		
			3 y	Triptans: Any	All participants	6/495 (1.2)	Vs Triptans before pregnancy only Adj RR 0.86 (0.23, 3.19) Vs No Triptans Adj RR 0.58 (0.17, 2.03)	NR
				Triptans: Any (before pregnancy only)	All participants	30/1002 (3.0)		
				No Triptans	All participants	122/4050 (3.0)		
Nezvalova-Henriksen, 2010, NRCS, 20132339	Fine motor development	Z-score >=1.5 on the ASQ	1.5 y	Triptans: Any	All participants	69/495 (13.9)	NR	NR
				Triptans: Any (before pregnancy only)	All participants	116/1002 (11.6)		
				No Triptans	All participants	466/4050 (11.5)		
			3 y	Triptans: Any	All participants	47/495 (9.5)	Vs Triptans before pregnancy only Adj RR 0.85 (0.52, 1.37) Vs No Triptans Adj RR 0.85 (0.56, 1.29)	NR
				Triptans: Any (before pregnancy only)	All participants	94/1002 (9.4)		
				No Triptans	All participants	373/4050 (9.2)		

Abbreviations: Adj = adjusted, ASQ = Ages and Stages Questionnaire, CI = confidence interval, m = months, NRCS = nonrandomized comparative study, PMID = PubMed identifier, RR = relative risk, y = years.

Table B-15. Key Question 2: Pharmacologic interventions: Triptans, ergot products, and NSAIDs – Fetal/child adverse effects (behavioral and social outcomes), categorical

Study, Year, Design, PMID	Outcome	Outcome Definition	Time	Arm	Subgroup	n/N (%)	Adj Effect Size (95% CI)	Adj P value
Nezvalova-Henriksen 2010, NRCS, 20132339	Externalizing behavior problems	Clinically significant on the CBCL	3 y	Triptans: Any	All participants	101/1085 (9.3)	Vs No Triptans Adj RR 0.99 (0.77, 1.27)	NR
					First trimester	40/304 (13.2)	Vs No Triptans Adj RR 1.75 (0.98, 3.14)	NR
					Second and/or third trimester	11/137 (8.0)	NR	
				Triptans: Any (before pregnancy only)	All participants	297/3354 (8.9)		
				No Triptans	All participants	NR		
			5 y	Triptans: Any	All participants	25/340 (7.4)	Vs No Triptans Adj RR 0.68 (0.44, 1.05)	NR
					First trimester	NR		
					Second and/or third trimester	NR		
				Triptans: Any (before pregnancy only)	All participants	NR		
				No Triptans	All participants	15/1457 (10.6)		
Nezvalova-Henriksen 2010, NRCS, 20132339	Externalizing behavior problems	Z-score >=1.5 on the CBCL	1.5 y	Triptans: Any	All participants	54/495 (11.0)	NR	NR
				Triptans: Any (before pregnancy only)	All participants	78/1002 (7.8)		
				No Triptans	All participants	328/4050 (8.1)		
			3 y	Triptans: Any	All participants	50/495 (10.0)	NR	NR
				Triptans: Any (before pregnancy only)	All participants	65/1002 (6.5)		
				No Triptans		308/4050 (7.6)		
Nezvalova-Henriksen 2010, NRCS, 20132339	Internalizing behavior problems	Clinically significant on the CBCL	3 y	Triptans: Any	All participants	27/396 (6.8)	Vs No Triptans Adj RR 1.04 (0.80, 1.35)	NR
					First trimester	20/304 (6.6)	Vs No Triptans Adj RR 1.27 (0.57, 2.82)	NR
					Second and/or third trimester	7/137 (5.1)	Vs No Triptans Adj RR 0.70 (0.16, 3.14)	NR

Study, Year, Design, PMID	Outcome	Outcome Definition	Time	Arm	Subgroup	n/N (%)	Adj Effect Size (95% CI)	Adj P value
				Triptans: Any (before pregnancy only)	All participants	260/3354 (7.8)		
				No Triptans	All participants	NR		
			5 y	Triptans: Any	All participants	42/343 (12.2)	Vs No Triptans Adj RR 0.97 (0.68, 1.37)	NR
					First trimester	NR		
					Second and/or third trimester	NR		
				Triptans: Any (before pregnancy only)	All participants	NR		
				No Triptans	All participants	169/1482 (11.4)		
Nezvalova-Henriksen, 2010, NRCS, 20132339	Internalizing behavior problems	Z-score >=1.5 on the CBCL	1.5 y	Triptans: Any	All participants	40/495 (8.1)	NR	NR
				Triptans: Any (before pregnancy only)	All participants	62/1002 (6.2)		
				No Triptans	All participants	352/4050 (8.7)		
			3 y	Triptans: Any	All participants	47/495 (9.5)	Vs Triptans before pregnancy only Adj RR 0.69 (0.41, 1.14) Vs No Triptans Adj RR 1.02 (0.66, 1.57)	NR
				Triptans: Any (before pregnancy only)	All participants	108/1002 (10.8)		
				No Triptans		425/4050 (10.5)		
Nezvalova-Henriksen, 2010, NRCS, 20132339	Emotionality	Z-score >=1.5 on the CBCL	1.5 y	Triptans: Any	All participants	16/495 (3.2)	NR	NR
				Triptans: Any (before pregnancy only)	All participants	53/1002 (5.3)		
				No Triptans	All participants	207/4050 (5.1)		
			3 y	Triptans: Any	All participants	31/495 (6.3)	Vs Triptans before pregnancy only Adj RR 2.18 (1.03, 4.53) Vs No Triptans Adj RR 2.51 (1.27, 4.90)	NR
				Triptans: Any (before pregnancy only)	All participants	47/1002 (4.7)		

Study, Year, Design, PMID	Outcome	Outcome Definition	Time	Arm	Subgroup	n/N (%)	Adj Effect Size (95% CI)	Adj P value
				No Triptans	All participants	158/4050 (3.9)		
Nezvalova-Henriksen, 2010, NRCS, 20132339	Activity	Z-score >=1.5 on the EAST Questionnaire	1.5 y	Triptans: Any	All participants	46/495 (9.2)	NR	NR
				Triptans: Any (before pregnancy only)	All participants	97/1002 (9.7)		
				No Triptans	All participants	397/4050 (9.8)		
			3y	Triptans: Any	All participants	41/495 (8.3)	Vs Triptans before pregnancy only Adj RR 1.70 (1.02, 2.80) Vs No Triptans Adj RR 1.57 (1.04, 2.36)	NR
				Triptans: Any (before pregnancy only)	All participants	47/1002 (4.7)		
				No Triptans	All participants	215/4050 (5.3)		
Nezvalova-Henriksen, 2010, NRCS, 20132339	Shyness	Z-score >=1.5 on the EAST Questionnaire	1.5 y	Triptans: Any	All participants	24/495 (4.9)	NR	NR
				Triptans: Any (before pregnancy only)	All participants	35/1002 (3.5)		
				No Triptans	All participants	162/4050 (4.0)		
			3 y	Triptans: Any	All participants	61/495 (12.3)	Vs Triptans before pregnancy only Adj RR 0.92 (0.52, 1.63) Vs No Triptans Adj RR 1.30 (0.81, 2.08)	NR
				Triptans: Any (before pregnancy only)	All participants	96/1002 (9.6)		
				No Triptans	All participants	312/4050 (7.7)		
Nezvalova-Henriksen, 2010, NRCS, 20132339	Sociability	Z-score >=1.5 on the EAST Questionnaire	1.5 y	Triptans: Any	All participants	44/495 (8.8)	NR	NR
				Triptans: Any (before pregnancy only)	All participants	68/1002 (6.8)		
				No Triptans	All participants	377/4050 (9.3)		

Study, Year, Design, PMID	Outcome	Outcome Definition	Time	Arm	Subgroup	n/N (%)	Adj Effect Size (95% CI)	Adj P value
			3y	Triptans: Any	All participants	31/495 (6.3)	Vs Triptans before pregnancy only Adj RR 0.70 (0.40, 1.38) Vs No Triptans Adj RR 1.13 (0.70, 1.82)	NR
				Triptans: Any (before pregnancy only)	All participants	64/1002 (6.4)		
				No Triptans	All participants	247/4050 (6.1)		
Nezvalova-Henriksen, 2010, NRCS, 20132339	Communication development	Z-score >=1.5 on the ASQ	1.5 y	Triptans: Any	All participants	17/495 (3.4)	NR	NR
				Triptans: Any (before pregnancy only)	All participants	41/1002 (4.1)		
				No Triptans	All participants	154/4050 (3.8)		
			3 y	Triptans: Any	All participants	23/495 (4.6)	Vs Triptans before pregnancy only Adj RR 1.22 (0.56, 2.68) Vs No Triptans Adj RR 0.97 (0.48, 1.95)	NR
				Triptans: Any (before pregnancy only)	All participants	45/1002 (4.5)		
				No Triptans	All participants	211/4050 (5.2)		
Nezvalova-Henriksen, 2010, NRCS, 20132339	Communication	Clinically-significant communication problems on the ASQ	5 y	Triptans: Any	All participants	27/347 (7.8)	Vs No Triptans Adj RR 0.77 (0.50, 1.18)	NR
				Triptans: Any (before pregnancy only)	All participants	NR		
				No Triptans	All participants	135/1479 (9.1)		

Abbreviations: Adj = adjusted, ASQ = Ages and Stages Questionnaire, CBCL = Child Behavior Checklist, CI = confidence interval, EAST = Emotionality, Activity, and Shyness Temperament, m = months, NRCS = nonrandomized comparative study, PMID = PubMed identifier, RR = relative risk, y = years.

Table B-16. Key Question 2: Pharmacologic interventions: Triptans, ergot products, and NSAIDs – Fetal/infant adverse effects (behavioral and social outcomes), continuous

Study, Year, Design, PMID	Outcome	Time	Arm	Subgroup	N	Result, Mean (SD)	Adj Effect Size (95% CI)	Adj P value
Shuhaiber, 1998, NRCS, 9710039	Preterm birth – Gestational age at delivery	At birth	Triptans: Sumatriptan	All participants	96	39.2 w (2.2)	NR	NR
			No Triptans	All participants	96	38.8 w (2.6)		
Nezvalova-Henriksen, 2010, NRCS, 20132339	Behavioral/Social – Emotionality on the EAST Questionnaire	5 y of age	Triptans: Any	All participants	345	49.7 (9.9)	Vs. No Triptans Adj NMD –1.02 (–2.3, 0.29)	NR
			Triptans: Any (before pregnancy only)	All participants	NR	NR (NR)		
			No Triptans	All participants	1483	50.5 (10.0)		
Nezvalova–Henriksen, 2010, NRCS, 20132339	Behavioral/Social – Activity on the EAST Questionnaire	5 y of age	Triptans: Any	All participants	351	49.3 (10.2)	Vs. No Triptans Adj NMD –0.06 (–1.35, 1.23)	NR
			Triptans: Any (before pregnancy only)	All participants	NR	NR (NR)		
			No Triptans	All participants	1493	50.1 (10.2)		
Nezvalova–Henriksen, 2010, NRCS, 20132339	Behavioral/Social – Shyness on the EAST Questionnaire	5 y of age	Triptans: Any	All participants	348	50.1 (10.0)	Vs. No Triptans Adj NMD –0.71 (–2.08, 0.65)	NR
			Triptans: Any (before pregnancy only)	All participants	NR	NR (NR)		
			No Triptans	All participants	1480	50.5 (10.1)		
Nezvalova–Henriksen, 2010, NRCS, 20132339	Behavioral/Social – Sociability on the EAST Questionnaire	5 y of age	Triptans: Any	All participants	349	51.0 (10.4)	Vs. No Triptans Adj NMD 1.66 (–0.30, 3.02)	NR
			Triptans: Any (before pregnancy only)	All participants	NR	NR (NR)		
			No Triptans	All participants	1492	49.6 (10.5)		

Abbreviations: Adj = adjusted, CI = confidence interval, EAST = Emotionality, Activity, and Shyness Temperament, h = hours, IQR = interquartile range, m = months, ND = net mean difference, NRCS = nonrandomized comparative study, PMID = PubMed identifier, VAS = visual analog scale, y = years.

Table B-17. Key Question 2: Nonpharmacologic interventions: Complementary, behavioral, and physical therapies – Categorical outcomes

Study, Year, Design, PMID	Outcome	Outcome Definition	Time	Arm	Subgroup	n/N (%)	Effect Size (95% CI)	P value
Silva, 2012, RCT, no PMID	Severity of acute headache	Reduction of average pain intensity by >=25% on a VAS (0-10)	8 w	Acupuncture	All participants	16/20 (80.0)	OR 4.36 (1.11, 17.13)[i]	0.035[i]
				Routine care	All participants	11/23 (47.8)		
Silva, 2012, RCT, no PMID	Medication use	Reduction of acetaminophen use by >=50%	8 w	Acupuncture	All participants	14/20 (70.0)	OR 6.61 (1.74, 25.1)[i]	0.006[i]
				Routine care	All participants	6/23 (26.1)		
Marcus (Study 2), 1995, RCT, 8600478	Medication use	Use of any medication for headache	Baseline	Thermal biofeedback, relaxation therapy, and physical therapy	All participants	4/11 (36.4)	-	-
				Thermal biofeedback	All participants	10/14 (71.4)		
			2 m	Thermal biofeedback, relaxation therapy, and physical therapy	All participants	3/11 (27.3)	OR 0.50 (0.09, 2.73)[i]	0.423[i]
				Thermal biofeedback	All participants	6/14 (42.9)		
Marcus (Study 1), 1995, Single-group study, 8600478	Severity of acute headache	Significant improvement in pain score on Headache Index (0-10)	2 m	Thermal biofeedback, relaxation therapy, and physical therapy	All participants	15/19 (79)	N/A	N/A

Abbreviations: CI = confidence interval, m = months, N/A = not applicable, NRCS = nonrandomized comparative study, OR = odds ratio, PMID = PubMed identifier, RCT = randomized controlled trial, VAS = visual analog scale, w = weeks.

[i] Calculated by us based on reported arm-specific data. This was done only for studies with arms with baseline characteristics considered by us to be similar.

Table B-18. Key Question 2: Nonpharmacologic interventions: Complementary, behavioral, and physical therapies – Continuous outcomes

Study, Year, Design, PMID	Outcome	Outcome Definition	Time	Arm	Subgroup	N	Result, Mean (SD)	Effect Size (95% CI)	P value
Silva, 2012, RCT, no PMID	Severity of acute headache	Reduction in pain score on a VAS (0–10)	8 w	Acupuncture	All participants	20	3.9 (3.4)	MD 2.2 (0.3, 4.7)[i]	0.035[i]
				Routine care	All participants	23	1.7 (4.4)		
Silva, 2012, RCT, no PMID	Medication use	Reduction in number of 500 mg acetaminophen doses	8 w	Acupuncture	All participants	20	6.0 (9.0)	MD 5.4 (1.3, 9.5)[i]	0.011[i]
				Routine care	All participants	23	0.6 (3.3)		
Marcus (Study 2), 1995, RCT, 8600478	Severity of acute headache	Worst pain score on a VAS (0–10) in past 2 w	Baseline	Combination of thermal biofeedback, relaxation therapy, and physical therapy	All participants	11	7.8 (2.1)	-	-
				Thermal biofeedback	All participants	14	7.8 (1.5)		
			2 m	Combination of physical therapy, complementary therapy, and behavioral therapy	All participants	11	2.3 (3.1)	NMD –3.4 (–5.61, –1.19)[i]	0.003[i]
				Thermal biofeedback	All participants	14	5.7 (3.3)		
Marcus (Study 2), 1995, RCT, 8600478	Severity of acute headache	Number of days in past 2 w with headache >1 on a VAS (0–10)	Baseline	Combination of thermal biofeedback, relaxation therapy, and physical therapy	All participants	11	11.2 (3.7)	-	-
				Thermal biofeedback	All participants	14	10.4 (3.9)		
			2 m	Combination of thermal biofeedback, relaxation therapy, and physical therapy	All participants	11	2.9 (4.3)	NMD –5.60 (–8.74, –2.46)[i]	<0.001[i]
				Thermal biofeedback	All participants	14	7.7 (NR, assumed same as baseline)		
Marcus (Study 2), 1995, RCT, 8600478	Severity of acute headache	Headache score average over 2 w on Headache Index	Baseline	Combination of thermal biofeedback, relaxation therapy, and physical therapy	All participants	11	2.0 (0.77)		
				Thermal biofeedback	All participants	14	2.5 (1.80)		
			2 m	Combination of thermal biofeedback, relaxation therapy, and physical therapy	All participants	11	0.44 (0.70)	NMD –0.86 (–1.95, 0.23)[i]	0.122[i]

Study, Year, Design, PMID	Outcome	Outcome Definition	Time	Arm	Subgroup	N	Result, Mean (SD)	Effect Size (95% CI)	P value
				Thermal biofeedback	All participants	14	1.8 (2.0)		
Marcus (Study 1), 1995, RCT, 8600478	Severity of acute headache	Worst headache score on a VAS (0–10) in past 2 w	Baseline	Combination of thermal biofeedback, relaxation therapy, and physical therapy	All participants	19	7.7 (2.0)	-	-
			2 m	Combination of thermal biofeedback, relaxation therapy, and physical therapy	All participants	19	4.2 (3.8)	-	-
Marcus (Study 1), 1995, RCT, 8600478	Severity of acute headache	Number of days in past 2 weeks with headache >1 on a VAS (0-10)	Baseline	Combination of thermal biofeedback, relaxation therapy, and physical therapy	All participants	19	8.0 (3.5)	-	-
			2 m	Combination of thermal biofeedback, relaxation therapy, and physical therapy	All participants	19	2.9 (4.0)	-	-
Marcus (Study 1), 1995, RCT, 8600478	Severity of acute headache	Pain score average over 2 weeks on Headache Index (0-10)	Baseline	Combination of thermal biofeedback, relaxation therapy, and physical therapy	All participants	19	1.7 (1.3)	-	-
			2 m	Combination of thermal biofeedback, relaxation therapy, and physical therapy	All participants	19	0.45 (0.77)	-	-
Hickling, 1990, Single-group study, 2401622	Severity of acute headache	Average of worst headache on a VAS (0-5)	Baseline	Combination of thermal biofeedback and progressive muscle relaxation	All participants	5	2.9 (0.6)	-	-
			After intervention	Combination of thermal biofeedback and progressive muscle relaxation	All participants	5	0.5 (1.1)	-	-
			After delivery	Combination of thermal biofeedback and progressive muscle relaxation	All participants	5	0.3 (0.7)	-	-
Hickling, 1990, Single-group study, 2401622	Severity of acute headache	Worst headache on a VAS (0-5)	Baseline	Combination of thermal biofeedback and progressive muscle relaxation	All participants	5	3.9 (1.0)	-	-
			After intervention	Combination of thermal biofeedback and progressive muscle relaxation	All participants	5	0.6 (1.3)	-	-
			After delivery	Combination of thermal biofeedback and progressive muscle relaxation	All participants	5	0.9 (1.3)	-	-

Study, Year, Design, PMID	Outcome	Outcome Definition	Time	Arm	Subgroup	N	Result, Mean (SD)	Effect Size (95% CI)	P value
Hickling, 1990, Single-group study, 2401622	Acute headache duration	Duration in hours	Baseline	Combination of thermal biofeedback and progressive muscle relaxation	All participants	5	20.6 h (16.0)	-	-
			After intervention	Combination of thermal biofeedback and progressive muscle relaxation	All participants	5	1.2 h (2.7)	-	-
			After delivery	Combination of thermal biofeedback and progressive muscle relaxation	All participants	5	4.8 h (10.7)	-	-
Hickling, 1990, Single-group study, 2401622	Resolution of acute headache	Number of headache-free days per week	Baseline	Combination of thermal biofeedback and progressive muscle relaxation	All participants	5	2.8 d/w (2.6)	-	-
			After intervention	Combination of thermal biofeedback and progressive muscle relaxation	All participants	5	7 d/w (0)	-	-
			After delivery	Combination of thermal biofeedback and progressive muscle relaxation	All participants	5	7 d/w (0)	-	-

Abbreviations: CI = confidence interval, d = days h = hours, IQR = interquartile range, m = months, MD = mean difference, NMD = net mean difference, PMID = PubMed identifier, RCT = randomized controlled trial, VAS = visual analog scale, w = weeks.
[i] Calculated by us based on reported arm-specific data. This was done only for studies with arms with baseline characteristics considered by us to be similar

Table B-19. Key Question 2: Nonpharmacologic interventions: Complementary, behavioral, and physical therapies – Adverse effects, continuous

Study, Year, Design, PMID	Maternal or Fetal/ Child	Outcome	Time	Arm	Subgroup	N	Result, Mean (SD)	Effect Size (95% CI)	P value
Silva, 2012, RCT, no PMID	Fetal/Child	Birth weight	At birth	Acupuncture	All participants	20	3244 g (336)	MD 98 (–141, 336)[i]	0.411[i]
				Routine care	All participants	23	3146 g (424)		
Silva, 2012, RCT, no PMID	Fetal/Child	Apgar score	1 min after birth	Acupuncture	All participants	20	9 (0)	MD 0 (–0.5, 0.5)[i]	1[i]
				Routine care	All participants	23	9 (1)		
			5 min after birth	Acupuncture	All participants	20	10 (0)	MD 0 (–0.1, 0.1)[i]	1[i]
				Routine care	All participants	23	10 (0)		

Abbreviations: CI = confidence interval, h = hours, IQR = interquartile range, m = months, MD = mean difference, min = minutes, PMID = PubMed identifier, RCT = randomized controlled trial, w = weeks.
[i] Calculated by us based on reported arm-specific data. This was done only for studies with arms with baseline characteristics considered by us to be similar.

Table B-20. Key Question 2: Nonpharmacologic interventions: Nerve blocks – Continuous outcomes

Study, Year, Design, PMID	Outcome	Time	Arm	Subgroup		N	Mean (SD)	Mean (SD) Change from Baseline	P value
Govindappagari, Single-group study, 2014, 25415168	Acute headache – Severity (VAS, 0–9)	Pre-procedure	Nerve blocks: Peripheral	All participants		13	8.4 (1.8)	N/A	-
		Post-procedure	Nerve blocks: Peripheral	All participants		13	4.5 (3.8)	-4.0 (2.6)	<0.001
		24 h	Nerve blocks: Peripheral	All participants		13	4.5 (4.5)	-4.0 (4.4)	0.007

Abbreviations: CI = confidence interval, h = hours, N/A = not applicable, PMID = PubMed identifier, SD = standard deviation, VAS = visual analog scale.

Table B-21. Key Question 2: Nonpharmacologic interventions: Nerve blocks – Maternal adverse effects, categorical

Study, Year, Design, PMID	Outcome	Time	Arm	Subgroup	n/N (%)
Govindappagari, 2014, Single-group study, 25415168	Serious adverse effects	Post-procedure	Nerve blocks: Peripheral	All participants	0/13 (0.0)
Govindappagari, 2014, Single-group study, 25415168	Vasovagal near syncopal episode with nausea	Post-procedure	Nerve blocks: Peripheral	All participants	1/13 (7.7)

Abbreviations: PMID = PubMed identifier.

Table B-22. Key Question 2: Nonpharmacologic interventions: Nerve blocks – Fetal/child adverse effects, categorical

Study, Year, Design, PMID	Outcome	Time	Arm	Subgroup	n/N (%)
Govindappagari, 2014, Single-group study, 25415168	Preterm birth	29 w	Nerve blocks: Peripheral	All participants	2/13 (15.3)

Abbreviations: PMID = PubMed identifier, w = weeks.

Table B-23. Key Question 2: Nonpharmacologic interventions: Noninvasive neuromodulation devices – Categorical outcomes

Study, Year, Design, PMID	Outcome	Time	Arm	Subgroup	n/N (%)
Bhola, 2015, Single-group study, 26055242	Resolution of acute headache	NR	Transcranial magnetic stimulation	All participants	3/3 (100)
Bhola, 2015, Single-group study, 26055242	Resolution of headache-related symptoms	NR	Transcranial magnetic stimulation	All participants	3/3 (100)

Abbreviations: PMID = PubMed identifier, NR = not reported.

Table B-24. Key Question 2: Nonpharmacologic interventions: Noninvasive neuromodulation devices – Maternal adverse effects, categorical

Study, Year, Design, PMID	Outcome	Time	Arm	Subgroup	n/N (%)
Bhola, 2015, Single-group study, 26055242	Maternal adverse events, Any	NR	Transcranial magnetic stimulation	All participants	0/3 (0)

Abbreviations: PMID = PubMed identifier, NR = not reported.

SRs (Indirect Evidence)

The 26 included SRs were published between 2000 and 2020 in 29 articles (Table B-27).[53-81] The SRs included a total of 740 studies (not accounting for overlap of studies between some SRs), with a median of 14.5 studies per SR (IQR 10 to 37).

In terms of natal phase considered, only three of the 26 SRs focused on the effects of interventions received during a particular phase (two SRs[57, 81] focused on the first trimester and one SR[55] focused on the postpartum period).

All 26 SRs addressed pharmacologic interventions. These included eight SRs that assessed NSAIDs,[55, 57, 58, 61, 64-66, 72] two that assessed antiepileptics,[78-80] two that assessed beta blockers,[53, 81] two that assessed calcium channel blockers,[53, 56] two that assessed antiemetics (5HT3 antagonists),[67, 76] two that assessed antipsychotics,[59, 77] two that assessed antihistamines,[63, 68] and one each that assessed serotonin and norepinephrine reuptake inhibitors (SNRIs),[73, 74] tricyclic antidepressants,[73, 74] benzodiazepines,[60, 62] corticosteroids,[75] oral magnesium,[69] triptans,[70] analgesics/antipyretics,[71] and intravenous magnesium.[54] Of note, one SR addressed both tricyclic antidepressants and SNRIs,[73, 74] and one SR addressed both beta blockers and calcium channel blockers.[53]

Among all 26 SRs, 12 SRs reported maternal adverse effects, while 23 reported fetal/child adverse effects.

Table B-26 provides the results of our quality assessment of all 26 SRs (using AMSTAR 2).

Table B-27 provides all maternal adverse effects and Table B-28 provides all fetal/child adverse effects reported in the 26 SRs.

Table B-25. Included SRs – Summary of design and arm details

Review, Year Published, PMID	Number of Databases Searched	Year of Last Search	Number of Included Studies	Intervention Class (Subclass)	Intervention Name	Maternal Adverse Effects Reported	Fetal/ Child Adverse Effects Reported
McDonagh, 2014, 25004304	6	2013	15	SNRIs	Venlafaxine	No	Yes
				Tricyclic antidepressants	Any	No	Yes
Yakoob, 2013, 23753416	5	2011	13	Beta blockers	Any	No	Yes
Abalos, 2018, 30277556	6	2017	63	Beta blockers	Any	Yes	Yes
				Calcium channel blockers	Any	Yes	Yes
Bellos, 2020a, 32199925	5	2019	22	Calcium channel blockers	Nifedipine	Yes	Yes
Veroniki, 2017, 28472982	3	2017	96	Antiepileptics (Multiple mechanisms of action)	Valproate	No	Yes
					Topiramate	No	Yes
				Antiepileptics (Calcium channel modulators)	Gabapentin	No	Yes
				Antiepileptics (Sodium channel modulators)	Carbamazepine	No	Yes
					Lamotrigine	No	Yes
Weston, 2016, 27819746	6	2015	50	Antiepileptics (Multiple mechanisms)	Valproate	No	Yes
					Topiramate	No	Yes
				Antiepileptics (Calcium channel modulators)	Gabapentin	No	Yes
				Antiepileptic (Sodium channel modulators)	Carbamazepine	No	Yes
					Lamotrigine	No	Yes
Enato, 2011, 21272436	3	2011	26	Benzodiazepines	Any	No	Yes
Masarwa, 2018, 29688261	3	2017	7	Analgesics/Antipyretics	Acetaminophen	No	Yes
Bellos, 2020b, 32068930	4	2019	10	NSAIDs	Any	Yes	No
Hammers, 2015, 25448524	2	2014	27	NSAIDs	Indomethacin	No	Yes
Chaemsaithong, 2019, 31494125	5	2018	8	NSAIDs	Aspirin (Low dose)	No	Yes
Henderson, 2014, 24711050	6	2014	23	NSAIDs	Aspirin (Low dose)	Yes	Yes
Coomarasamy, 2003, 12798543	6	2001	14	NSAIDs	Aspirin (Low dose)	Yes	Yes
Duley, 2007, 17443552	3	2010	59	NSAIDs	Aspirin (Low dose)	Yes	Yes
Hamulyak, 2020, 32358837	4	2019	11	NSAIDs	Aspirin (Low dose)	Yes	Yes
Maze, 2019, 31584685	3	2018	22	NSAIDs	Aspirin (Low dose)	Yes	No
Kaplan, 2019, 30849498	3	2016	8	Antiemetics (5HT3 antagonists)	Ondansetron	No	Yes
Picot, 2020, 32420702	2	2019	12	Antiemetics (5HT3 antagonists)	Ondansetron	No	Yes
Etwel, 2017, 27878468	2	2015	37	Antihistamines	Any	No	Yes
Li, 2019, 31909512	4	2019	26	Antihistamines	Any	No	Yes
Park-Wyllie, 2000, 11091360	3	1999	10	Corticosteroids	Prednisolone	No	Yes
Marchenko, 2015, 25644494	17	2013	6	Triptans	Any	No	Yes
Coughlin, 2015, 25932852	3	2013	10	Antipsychotics	Any	No	Yes
Terrana, 2015, 26274044	2	2014	12	Antipsychotics	Any	No	Yes
Bain, 2013, 24139447	10	2012	143	Intravenous magnesium	Intravenous magnesium sulphate	Yes	No

Review, Year Published, PMID	Number of Databases Searched	Year of Last Search	Number of Included Studies	Intervention Class (Subclass)	Intervention Name	Maternal Adverse Effects Reported	Fetal/ Child Adverse Effects Reported
Makredes, 2014, 24696187	3	2013	10	Oral magnesium	Oral magnesium sulphate	Yes	Yes

Abbreviations: Nonpharm = nonpharmacologic, NR = not reported, NSAID = nonsteroidal anti-inflammatory drug, Pharm = pharmacologic, PMID = PubMed identifier, SNRIs

Table B-26. Included systematic reviews – Quality assessment using AMSTAR 2 criteria

Int Type	Review, Year, PMID	Eligibility Criteria[a]	Lit Search[b]	Duplicate Screening[c]	Duplicate Data Extraction[d]	Study Details Described[e]	Assessed Risk of Bias[f]	Assessed Impact of Risk of Bias[g]	Appropriate Meta-Analysis Methods[h]	Explained/ Discussed Heterogeneity[i]	COI[j]	OVERALL QUALITY
Pharm	McDonagh, 2014, 25004304	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	HIGH
	Yakoob, 2013, 23753416	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	HIGH
	Abalos, 2018, 30277556	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	HIGH
	Bellos, 2020a, 32199925	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	HIGH
	Veroniki, 2017, 28472982	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	HIGH
	Weston, 2016, 27819746	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	HIGH
	Enato, 2011, 21272436	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	HIGH
	Masarwa, 2018, 29688261	Yes	Yes	Yes	Unclear	Unclear	Yes	No	Yes	Yes	Yes	MODERATE
	Bellos, 2020b, 32068930	Yes	Yes	Unclear	Unclear	Yes	Yes	No	Yes	Yes	Yes	MODERATE
	Hammers, 2015, 25448524	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	HIGH
	Chaemsaithong, 2019, 31494125	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	HIGH
	Henderson, 2014, 24711050	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	HIGH
	Coomarasamy, 2003, 12798543	Yes	Yes	Yes	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	MODERATE
	Duley, 2007, 17443552	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	HIGH
	Hamulyak, 2020, 32358837	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	HIGH
	Maze, 2019, 31584685	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	HIGH
	Kaplan, 2019, 30849498	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	HIGH
	Picot, 2020, 32420702	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	HIGH
	Etwel, 2017, 27878468	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	HIGH
	Li, 2019, 31909512	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	HIGH
	Park-Wyllie, 2000, 11091360	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	HIGH
	Marchenko, 2015, 25644494	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	HIGH
	Coughlin, 2015, 25932852	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	HIGH
	Terrana, 2015, 26274044	Yes	Yes	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	MODERATE
	Bain, 2013, 24139447	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	Yes	HIGH
	Makredes, 2014, 24696187	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	HIGH

Abbreviations: AMSTAR 2 = A Measurement Tool to Assess Systematic Reviews, version 2 Tool, COI = conflicts of interest, Int = intervention, Lit = literature, Nonpharm = Nonpharmacologic, Pharm = Pharmacologic, PMID = PubMed identifier.

Ratings based on AMSTAR 2. Ratings of individual items: Yes = item explicitly done (or of good quality), No = item not done (or of poor quality), Unclear = not reported, N/A = not applicable. Ratings of overall quality: **HIGH**, **MODERATE**, and **LOW** (none in Table).

Ratings are color coded for emphasis only. Other abbreviations are defined in the footnotes.

a Did the authors specify research questions and inclusion criteria for the SR? (AMSTAR 2 item 1)

b Did the SR authors use a comprehensive literature search strategy? (AMSTAR 2 item 4)

c Did the SR authors perform study selection in duplicate? (AMSTAR 2 item 5)

d Did the SR authors perform data extraction in duplicate, either independently or through verification? (AMSTAR 2 item 6)

e Did the SR authors describe the included studies in adequate detail? (AMSTAR 2 item 8)

f Did the SR authors use a satisfactory technique for assessing the risk of bias in individual studies that were included in the SR? (AMSTAR 2 item 9)
g Did the SR authors assess the potential impact of risk of bias in individual studies on the summary results, interpretation, discussion? (AMSTAR 2 item 12)
h If meta-analysis (MA) was performed did the SR authors use appropriate methods for statistical combination of results? (AMSTAR 2 item 11) See subsequent footnotes.
i Did the SR authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the SR? (AMSTAR 2 item 14)
j Did the SR authors report the lack of significant potential of conflict of interest (COI) regarding conducting the SR? (AMSTAR 2 item 16)

Table B-27. SRs addressing pharmacologic interventions – All reported maternal adverse effects

Review, Year Published, PMID	Drug Class	Drug Name(s)	Timing of Occurrence of Adverse Effect	Adverse Effect	N studies	Effect Size (95% CI)	Conclusion
Abalos, 2018, 30277556	Beta blockers	Any	NR	Adverse effects, Any	7	RR 3.14 (0.66, 15.02)	NS
				Discontinuation due to adverse effects	9	RR 1.85 (0.61, 5.57)	NS
			Antepartum	Hospitalization during pregnancy	1	RR 0.84 (0.57, 1.24)	NS
				Placental abruption	3	RR 5.11 (0.25, 104.96)	NS
			Delivery	Induction of labor or cesarean section	2	RR 0.97 (0.84, 1.12)	NS
				Induction of labor	3	RR 0.98 (0.83, 1.17)	NS
				Cesarean section	8	RR 1.06 (0.86, 1.31)	NS
	Calcium channel blockers	Any	NR	Adverse effects, Any	1	RR 0.96 (0.60, 1.52)	NS
				Discontinuation due to adverse effects	2	RR 4.02 (0.45, 35.97)	NS
			Antepartum	Placental abruption	1	RR 1.52 (0.26, 8.87)	NS
			Delivery	Cesarean section	3	RR 0.94 (0.79, 1.11)	NS
Bellos, 2020a, 32199925	Calcium channel blockers	Nifedipine	Antepartum	Placental abruption	2	OR 0.29 (0.15, 0.58)	Intervention better
			Delivery	Cesarean section	2	OR 0.85 (0.56, 1.29)	NS
Bellos, 2020b, 32068930	NSAIDs	Any	Postpartum	Postpartum hypertension	4	OR 1.52 (0.77, 3.01)	NS
				Postpartum systolic blood pressure	4	MD -3.03 mm Hg (-6.21, 0.15)	NS
				Postpartum diastolic blood pressure	4	MD -2.28 mm Hg (-4.44, -0.13)	Intervention better
				Postpartum mean arterial pressure	4	MD -0.38 mm Hg (-1.88, 1.11)	NS
Henderson, 2014, 24711050	NSAIDs	Aspirin (Low dose)	Antepartum	Placental abruption	11	RR 1.17 (0.93, 1.48)	NS
			Postpartum	Postpartum hemorrhage	NR	NR	NS
Coomarasamy, 2003, 12798543	NSAIDs	Aspirin (Low dose)	Antepartum	Placental abruption or other antepartum bleeding	7	OR 0.98 (0.37, 1.30)	NS
Duley, 2007, 17443552	NSAIDs	Aspirin (Low dose)	Antepartum	Placental abruption	16	RR 1.10 (0.89, 1.37)	NS
				Hospitalization during pregnancy	3	RR 1.03 (0.97, 1.10)	NS
			Delivery	Cesarean section	24	RR 1.02 (0.98, 1.06)	NS
				Induction of labor	5	RR 1.03 (0.98, 1.08)	NS
Hamulyak, 2020, 32358837	NSAIDs	Aspirin (Low dose)	Antepartum	Adverse effect, Any	1	RR 1.29 (0.60, 2.77)	NS
Maze, 2019, 31584685	NSAIDs	Aspirin (Low dose)	Antepartum	Thrombosis	4	OR 0.8 (0.1, 4.3)	NS

Review, Year Published, PMID	Drug Class	Drug Name(s)	Timing of Occurrence of Adverse Effect	Adverse Effect	N studies	Effect Size (95% CI)	Conclusion
Bain, 2013, 24139447	Intravenous magnesium	Intravenous magnesium sulphate	NR	**Adverse effect, Any**	**4**	**RR 4.62 (2.42, 8.83)**	**Intervention worse**
				Death	5	RR 0.53 (0.26, 1.09)	NS
				Absent or reduced tendon reflexes	3	RR 1.01 (0.71, 1.44)	NS
				Slurred speech	1	RR 3.04 (0.13, 73.42)	NS
				Pulmonary edema	4	RR 1.12 (0.72, 1.74)	NS
				Discontinuation due to adverse effects	**5**	**RR 2.77 (2.32, 3.30)**	**Intervention worse**
				Respiratory arrest	4	RR 2.50 (0.49, 12.9)	NS
				Respiratory depression/other respiratory problems	**5**	**RR 1.41 (1.07, 1.86)**	**Intervention worse**
				Cardiac arrest	4	RR 0.80 (0.21, 2.98)	**NS**
				Hypotension	**3**	**RR 1.52 (1.10, 2.11)**	**Intervention worse**
				Tachycardia	**1**	**RR 1.53 (1.03, 2.29)**	**Intervention worse**
				Flushing and/or warmth	**5**	**RR 6.94 (4.19, 11.49)**	**Intervention worse**
				Nausea and/or vomiting	**4**	**RR 5.50 (2.29, 13.22)**	**Intervention worse**
				Muscle weakness	**3**	**RR 15.81 (7.36, 33.96)**	**Intervention worse**
				Drowsiness or confusion	**3**	**RR 2.46 (1.83, 3.29)**	**Intervention worse**
				Headache	**2**	**RR 2.21 (1.27, 3.86)**	**Intervention worse**
				Thirst or mouth dryness	**2**	**RR 2.38 (1.59, 3.56)**	**Intervention worse**
				Dizziness	**2**	**RR 2.62 (1.63, 4.21)**	**Intervention worse**
				Sweating	**2**	**RR 6.37 (1.96, 20.65)**	**Intervention worse**
				Itching and/or tingling	**1**	**RR 14.5 (2.0, 113.4)**	**Intervention worse**
				Blurred vision	**1**	**RR 2.34 (1.32, 4.14)**	**Intervention worse**
			Delivery	Cesarean section	10	RR 1.04 (1.00, 1.08)	NS
			Postpartum	Postpartum hemorrhage	4	RR 0.94 (0.87, 1.04)	NS
Makredes, 2014, 24696187	Oral magnesium	Oral magnesium sulphate	NR	Gastrointestinal symptoms	4	RR 0.88 (0.69, 1.12)	NS
				Systolic blood pressure	**3**	**MD 1 mm Hg (0.03, 1.97)**	**Intervention worse**
				Diastolic blood pressure	3	MD 0.23 mm Hg (-0.67, 1.13)	NS
				Hospitalizations	3	RR 0.65 (0.48, 1.86)	NS
			Antepartum	Pregnancy-induced hypertension	3	RR 0.39 (0.11, 1.41)	NS
				Eclampsia	1	RR 0.14 (0.01, 2.70)	NS
				Antepartum hemorrhage	2	RR 0.53 (0.09, 3.15)	NS
			Delivery	Length of labor	2	MD 0.00 h (-0.50, 0.50)	NS

Abbreviations: CI = confidence interval, m = months, MD = mean difference, NR = not reported, NS = no statistically significant difference in adverse effects between intervention and control, NSAID = nonsteroidal anti-inflammatory drug, PMID = PubMed identifier, OR = odds ratio, RR = relative risk.

Adverse effects, effect sizes, and conclusions in bold font have effect sizes that are statistically significantly higher (at the 5% level) in the drug arm, suggestive of harm.

Table B-28. SRs addressing pharmacologic interventions – All reported fetal/child adverse effects

Review, Year Published, PMID	Drug Class	Drug Name (s)	Timing of Occurrence of Adverse Effect	Adverse Effect	N Studies	Effect Size (95% CI)	Conclusion
McDonagh, 2014, 25004304	Tricyclic Antidepressants	Any	Perinatal	Small for gestational age	2	OR 0.97 (0.64, 1.46)	NS
			Neonatal	**Neonatal convulsions**	**2**	**OR 7.82 (2.81, 21.8)**	**Intervention worse**
				Neonatal respiratory distress	**2**	**OR 2.11 (1.57, 2.83)**	**Intervention worse**
				Congenital anomalies, All or major	**2**	**OR 1.31 (1.04, 1.65)**	**Intervention worse**
				Congenital anomalies, Cardiovascular	**2**	**OR 1.58 (1.10, 2.29)**	**Intervention worse**
			Child	Inability to sit without support at 6 months	1	OR 2.9 (0.89, 9.51)	NS
				Motor or speech delays	1	OR 1.0 (0.14, 7.17)	NS
				Autism spectrum disorder	1	OR 1.6 (0.5, 4.5)	NS
	Serotonin and norepinephrine reuptake inhibitors (SNRIs)	Venlafaxine (late pregnancy)	Perinatal	**Preterm birth**	**2**	**OR 1.79 (1.46, 2.19)**	**Intervention worse**
			Neonatal	**Neonatal withdrawal symptoms**	**1**	**OR 3.1 (1.3, 7.1)**	**Intervention worse**
Yakoob, 2013, 23753416	Beta blockers	Any	Neonatal	Congenital anomalies, All or major	5	OR 1.00 (0.91, 1.10)	NS
				Congenital anomalies, Severe hypospadias	1	OR 2.27 (0.69, 7.46)	NS
				Cardiovascular anomalies, Any	**4**	**OR 2.01 (1.18, 3.42)**	**Intervention worse**
				Congenital anomalies, Cleft lip or palate	**4**	**OR 3.11 (1.79, 5.43)**	**Intervention worse**
				Congenital anomalies, Neural tube defects	**3**	**OR 3.56 (1.19, 10.7)**	**Intervention worse**
Abalos, 2018, 30277556	Beta blockers	Any	In utero, Neonatal	Fetal or neonatal death, including spontaneous abortion	29	RR 0.72 (0.50, 1.04)	NS
			Perinatal	Preterm birth (<37 weeks)	4	RR 0.90 (0.61, 1.32)	NS
				Small for gestational age	9	RR 1.30 (0.86, 1.97)	NS
			Neonatal	NICU admission	3	RR 1.07 (0.82, 1.41)	NS
				Neonatal hypoglycemia	2	RR 0.71 (0.13, 3.83)	NS
				Neonatal bradycardia	2	RR 2.20 (0.68, 7.16)	NS
				Neonatal jaundice	1	RR 0.53 (0.19, 1.47)	NS
				Neonatal pulmonary edema	1	RR 5.23 (0.25, 107.4)	NS
				Neonatal respiratory distress syndrome	6	RR 0.32 (0.13, 0.83)	Intervention better
	Calcium channel blockers	Any	In utero, Neonatal	Fetal or neonatal death, including spontaneous abortion	5	RR 0.77 (0.28, 2.10)	NS
			Perinatal	Preterm birth (<37 weeks)	4	RR 1.01 (0.86, 1.18)	NS
				Small for gestational age	3	RR 0.83 (0.60, 1.16)	NS
			Neonatal	NICU admission	3	RR 1.18 (0.87, 1.62)	NS
				Neonatal hypoglycemia	1	RR 0.69 (0.39, 1.21)	NS

Review, Year Published, PMID	Drug Class	Drug Name (s)	Timing of Occurrence of Adverse Effect	Adverse Effect	N Studies	Effect Size (95% CI)	Conclusion
				Neonatal jaundice	1	RR 0.62 (0.35, 1.10)	NS
				Neonatal respiratory distress syndrome	1	RR 0.20 (0.01, 4.06)	NS
Bellos, 2020a, 32199925	Calcium channel blockers	Nifedipine	Perinatal	Gestational age at delivery	2	SMD -0.64 (-1.96, 0.68)	NS
				Preterm birth	2	OR 1.06 (0.50, 2.27)	NS
				Small for gestational age	2	OR 1.28 (0.79, 2.09)	NS
				Perinatal death	2	OR 0.71 (0.34, 1.49)	NS
Veroniki, 2017, 28472982	Antiepileptics: Multiple mechanisms	Valproate	In utero	**Fetal death or spontaneous abortion**	**96**	**OR 1.83 (1.04, 3.45)**	**Intervention worse**
				Fetal growth restriction	96	OR 1.28 (0.86, 1.95)	NS
			Perinatal	Preterm birth	96	OR 0.96 (0.65, 1.37)	NS
			Neonatal	**Congenital anomalies, Major**	**96**	**OR 3.04 (1.23, 7.07)**	**Intervention worse**
				Congenital anomalies, Cardiovascular	96	OR 1.54 (0.98, 2.37)	NS
				Congenital anomalies, Hypospadias	**96**	**OR 2.58 (1.24, 5.76)**	**Intervention worse**
				Congenital anomalies, Cleft lip/palate	**96**	**OR 3.26 (1.38, 7.57)**	**Intervention worse**
				Congenital anomalies, Club foot	**96**	**OR 3.26 (1.43, 8.25)**	**Intervention worse**
				Congenital anomalies, Minor	**96**	**OR 17.8 (1.6, 633.3)**	**Intervention worse**
				Inguinal hernia	96	OR 1.64 (0.39, 10.02)	NS
				Undescended testes	96	OR 1.10 (0.33, 3.78)	NS
			Child	**Cognitive developmental delay**	**96**	**OR 7.40 (3.00, 18.46)**	**Intervention worse**
				Autism/dyspraxia	**96**	**OR 17.29 (2.40, 217.6)**	**Intervention worse**
				Psychomotor developmental delay	**96**	**OR 4.16 (2.04, 8.75)**	**Intervention worse**
				Language delay	**96**	**OR 7.95 (1.50, 49.13)**	**Intervention worse**
				Attention deficit hyperactivity disorder	96	OR 2.84 (0.82, 9.99)	NS
	Antiepileptics: Multiple mechanisms	Topiramate	In utero	**Fetal death or spontaneous abortion**	**96**	**OR 23.6 (1.2, 549.6)**	**Intervention worse**
				Fetal growth restriction	**96**	**OR 2.64 (1.41, 4.63)**	**Intervention worse**
			Perinatal	Preterm birth	96	OR 1.38 (0.73, 2.35)	NS
			Neonatal	**Congenital anomalies, Major**	**96**	**OR 1.90 (1.17, 2.97)**	**Intervention worse**
				Congenital anomalies, Cardiovascular	96	OR 0.66 (0.16. 2.11)	NS
				Congenital anomalies, Hypospadias	96	OR 3.52 (0.77, 15.72)	NS
				Congenital anomalies, Cleft lip/palate	**96**	**OR 6.12 (1.89, 19.1)**	**Intervention worse**
				Congenital anomalies, Club foot	96	OR 1.77 (0.16, 11.44)	NS
				Inguinal hernia	96	OR 1.52 (0.13, 14.90)	NS
				Undescended testes	96	OR 0.14 (0.00, 2.72)	NS
			Child	Cognitive developmental delay	96	OR 3.14 (0.45, 16.53)	NS
				Psychomotor developmental delay	96	OR 3.89 (0.41, 24.27)	NS
	Antiepileptics: Calcium channel modulators	Gabapentin	In utero	Fetal growth restriction	96	OR 1.37 (0.44, 3.61)	NS
			Perinatal	Preterm birth	96	OR 1.93 (0.88, 4.05)	NS

Review, Year Published, PMID	Drug Class	Drug Name (s)	Timing of Occurrence of Adverse Effect	Adverse Effect	N Studies	Effect Size (95% CI)	Conclusion
			Neonatal	Congenital anomalies, Major	96	OR 1.00 (0.47, 1.89)	NS
				Congenital anomalies, Cardiovascular	**96**	**OR 5.98 (1.34, 19.73)**	**Intervention worse**
				Congenital anomalies, Hypospadias	**96**	**OR 16.5 (2.5, 121.7)**	**Intervention worse**
				Congenital anomalies, Cleft lip/palate	96	OR 5.14 (0.16, 38.06)	NS
				Congenital anomalies, Club foot	96	OR 5.55 (0.01, 165.50)	NS
				Inguinal hernia	96	OR 10.86 (0.02, 282.60)	NS
			Child	Cognitive developmental delay	96	OR 1.46 (0.04, 13.48)	NS
				Psychomotor developmental delay	**96**	**OR 9.03 (1.00, 62.78)**	**Intervention worse**
	Antiepileptic: Sodium channel modulators	Carbamazepine	In utero	Fetal death or spontaneous abortion	96	OR 1.25 (0.73, 2.36)	NS
				Fetal growth restriction	96	OR 1.15 (0.77, 1.67)	NS
			Perinatal	Preterm birth	96	OR 1.10 (0.77, 1.56)	NS
			Neonatal	**Congenital anomalies, Major**	**96**	**OR 1.37 (1.10, 1.71)**	**Intervention worse**
				Congenital anomalies, Cardiovascular	96	OR 0.93 (0.62, 1.43)	NS
				Congenital anomalies, Hypospadias	96	OR 1.09 (0.53, 2.61)	NS
				Congenital anomalies, Cleft lip/palate	96	OR 1.39 (0.56, 3.15)	NS
				Congenital anomalies, Club foot	96	OR 1.64 (0.68, 3.42)	NS
				Congenital anomalies, Minor	**96**	**OR 10.8 (1.4, 373.9)**	**Intervention worse**
				Inguinal hernia	96	OR 1.54 (0.40, 8.78)	NS
				Undescended testes	96	OR 0.53 (0.14, 1.96)	NS
			Child	Cognitive developmental delay	96	OR 2.07 (0.82, 5.48)	NS
				Autism/dyspraxia	96	OR 5.76 (0.76, 73.43)	NS
				Psychomotor developmental delay	96	OR 1.68 (0.85, 3.41)	NS
				Language delay	96	OR 4.32 (0.81, 26.93)	NS
				Attention deficit hyperactivity disorder	96	OR 2.32 (0.70, 7.86)	NS
	Antiepileptic: Sodium channel modulators	Lamotrigine	In utero	Fetal death or spontaneous abortion	96	OR 1.38 (0.70, 2.88)	NS
				Fetal growth restriction	96	OR 0.90 (0.56, 1.42)	NS
			Perinatal	Preterm birth	96	OR 1.05 (0.70, 1.48)	NS
			Neonatal	Congenital anomalies, Major	96	OR 0.96 (0.72, 1.25)	NS
				Congenital anomalies, Cardiovascular	96	OR 0.55 (0.32, 0.95)	Intervention better
				Congenital anomalies, Hypospadias	96	OR 0.66 (0.23, 2.26)	NS
				Congenital anomalies, Cleft lip/palate	96	OR 1.21 (0.45, 3.20)	NS
				Congenital anomalies, Club foot	96	OR 0.70 (0.12, 2.89)	NS
				Inguinal hernia	96	OR 0.86 (0.17, 5.92)	NS
				Undescended testes	96	OR 0.31 (0.05, 1.66)	NS
			Child	Cognitive developmental delay	96	OR 0.93 (0.09, 5.10)	NS
				Autism/dyspraxia	**96**	**OR 8.88 (1.28, 112.0)**	**Intervention worse**
				Psychomotor developmental delay	96	OR 1.86 (0.72, 4.76)	NS
				Language delay	96	OR 4.36 (0.68, 25.41)	NS
				Attention deficit hyperactivity disorder	96	OR 1.63 (0.41, 6.06)	NS

Review, Year Published, PMID	Drug Class	Drug Name (s)	Timing of Occurrence of Adverse Effect	Adverse Effect	N Studies	Effect Size (95% CI)	Conclusion
Weston, 2016, 27819746	Antiepileptics: Multiple mechanisms	Valproate	Neonatal	Congenital anomalies, Skeletal or limb defects	6	RR 2.57 (0.82, 8.04)	NS
				Congenital anomalies, Major	N/A	Not extracted because Veroniki 2017 reported data for this harm.	N/A
				Congenital anomalies, Neural tube defects	**6**	**RR 5.30 (1.05, 26.7)**	**Intervention worse**
				Congenital anomalies, Cardiovascular	N/A	Not extracted because Veroniki 2017 reported data for this harm.	N/A
				Congenital anomalies, Orofacial clefts	**6**	**RD 0.03 (0.01, 0.05)**	**Intervention worse**
		Topiramate	Neonatal	Congenital anomalies, Major	N/A	Not extracted because Veroniki 2017 reported data for this harm.	N/A
				Congenital anomalies, Neural tube defects	N/A	Not extracted because Veroniki 2017 reported data for this harm.	N/A
				Congenital anomalies, Cardiovascular	N/A	Not extracted because Veroniki 2017 reported data for this harm.	N/A
				Congenital anomalies, Orofacial clefts	N/A	Not extracted because Veroniki 2017 reported data for this harm.	N/A
				Congenital anomalies, Skeletal or limb defects	1	RR 1.10 (0.05, 26.45)	NS
	Antiepileptics: Calcium channel modulators	Gabapentin	Neonatal	Congenital anomalies, Major	N/A	Not extracted because Veroniki 2017 reported data for this harm.	N/A
	Antiepileptic: Sodium channel modulators	Carbamazepine	Neonatal	Congenital anomalies, Neural tube defects	7	RR 0.91 (0.15, 5.61)	NS
				Congenital anomalies, Cardiovascular	N/A	Not extracted because Veroniki 2017 reported data for this harm.	N/A
				Congenital anomalies, Orofacial clefts	N/A	Not extracted because Veroniki 2017 reported data for this harm.	N/A
				Congenital anomalies, Skeletal or limb defects	7	RR 0.73 (0.18, 3.01)	NS
				Congenital anomalies, Major	N/A	Not extracted because Veroniki 2017 reported data for this harm.	N/A
		Lamotrigine	Neonatal	Congenital anomalies, Major	N/A	Not extracted because Veroniki 2017 reported data for this harm.	N/A

Review, Year Published, PMID	Drug Class	Drug Name (s)	Timing of Occurrence of Adverse Effect	Adverse Effect	N Studies	Effect Size (95% CI)	Conclusion
				Congenital anomalies, Neural tube defects	2	No events	N/A
				Congenital anomalies, Cardiovascular	N/A	Not extracted because Veroniki 2017 reported data for this harm.	N/A
				Congenital anomalies, Orofacial clefts	N/A	Not extracted because Veroniki 2017 reported data for this harm.	N/A
				Congenital anomalies, Skeletal or limb defects	2	RR 0.72 (0.12, 4.12)	NS
Enato, 2011, 21272436	Benzodiazepines	Any (First trimester)	Neonatal	**Congenital anomalies, Major**	9	Cohort studies: OR 1.06 (0.91, 1.25) **CC studies: OR 3.01 (1.32, 6.84)**	Cohort studies: NS **CC studies: Intervention worse**
				Congenital anomalies, Cardiovascular	9	CC studies: OR 1.27 (0.69, 2.32)	NS
				Congenital anomalies, Oral cleft	6	Cohort studies: OR 1.19 (0.34, 4.15) **CC studies: OR 1.79 (1.13, 2.82)**	Cohort studies: NS **CC studies: Intervention worse**
Masarwa, 2018, 29688261	Analgesic/ Antipyretic	Acetaminophen	Child	**Attention deficit hyperactivity disorder**	**6**	**RR 1.34 (1.21, 1.47)**	**Intervention worse**
				Hyperactivity symptoms	**4**	**RR 1.24 (1.04, 1.43)**	**Intervention worse**
				Autism spectrum disorder	**5**	**RR 1.19 (1.14, 1.25)**	**Intervention worse**
				Conduct disorder	**4**	**RR 1.23 (1.04, 1.42)**	**Intervention worse**
Hammers, 2015, 25448524	NSAIDs	Indomethacin	Neonatal	Neonatal mortality	15	RR 1.04 (0.77, 1.41)	NS
				Sepsis	12	RR 1.12 (0.94, 1.34)	NS
				Patent ductus arteriosus	17	RR 1.14 (0.97, 1.35)	NS
				Bronchopulmonary dysplasia	7	RR 1.12 (0.79, 1.59)	NS
				Respiratory distress syndrome	12	RR 0.92 (0.77, 1.08)	NS
				Periventricular leukomalacia	**9**	**RR 1.59 (1.17, 2.17)**	**Intervention worse**
				Intraventricular hemorrhage: All Grades	11	RR 1.17 (0.89, 1.56)	NS
				Intraventricular hemorrhage: Grade III-IV	**16**	**RR 1.29 (1.06, 1.56)**	**Intervention worse**
				Necrotizing enterocolitis	**18**	**RR 1.36 (1.08, 1.71)**	**Intervention worse**
Chaemsaithong, 2019, 31494125	NSAIDs	Aspirin (Low dose, First trimester)	In utero	Fetal growth restriction	8	RR 1.06 (0.58, 1.95)	NS
			Perinatal	Preterm birth (<37 w)	8	RR 0.53 (0.36, 0.79)	Intervention better

Review, Year Published, PMID	Drug Class	Drug Name (s)	Timing of Occurrence of Adverse Effect	Adverse Effect	N Studies	Effect Size (95% CI)	Conclusion
Henderson, 2014, 24711050	NSAIDs	Aspirin (Low dose)	In utero	Fetal intracranial hemorrhage	10	RR 0.84 (0.61,1.16)	NS
			Perinatal	Perinatal mortality	18	RR 0.92 (0.76, 1.11)	NS
			Neonatal	Hospitalization	NR	NR	NS
			Child	Developmental outcomes	NR	NR	NS
Coomarasamy, 2003, 12798543	NSAIDs	Aspirin (Low dose)	Perinatal	Preterm birth (<37 w)	N/A	Not extracted because Chaemsaithong 2019 reported data for this harm.	N/A
			Perinatal	Birth weight	8	WMD 215 g (90, 341)	Intervention better
Duley, 2007, 17443552	NSAIDs	Aspirin (Low dose)	In utero, Perinatal	Spontaneous abortion or stillbirth	28	RR 0.96 (0.78, 1.18)	NS
			Perinatal	Low birth weight (<2500 g)	6	RR 0.93 (0.83, 1.05)	NS
				Preterm birth (<37 w)	N/A	Not extracted because Chaemsaithong 2019 reported data for this harm.	N/A
				Small for gestational age	36	RR 0.90 (0.83, 0.98)	Intervention better
			Neonatal	NICU admission	15	RR 0.95 (0.90, 1.01)	NS
				Intraventricular hemorrhage	10	RR 0.88 (0.63, 1.22)	NS
				Other neonatal bleed	8	RR 1.13 (0.83, 1.52)	NS
			Child	Infant death (after discharge)	3	RR 0.53 (0.21, 1.34)	NS
				Child hospitalization (at 12 months)	1	RR 0.94 (0.83, 1.08)	NS
				Child hospitalization (at 18 months)	1	RR 0.99 (0.89, 1.11)	NS
				Poor gross motor function	1	RR 0.82 (0.57, 1.17)	NS
				Poor fine motor function	1	RR 0.98 (0.84, 1.14)	NS
				Poor language expression	1	RR 0.94 (0.74, 1.19)	NS
				Poor language comprehension	1	RR 0.95 (0.80, 1.13)	NS
				Language problems, Undefined	1	RR 0.99 (0.69, 1.42)	NS
				Hearing problems	1	RR 2.54 (0.10, 62.10)	NS
				Sight problems	1	RR 0.85 (0.25, 2.90)	NS
				Respiratory problems	1	RR 1.48 (0.98, 2.23)	NS
				Behavior problems (at 18 months)	1	RR 0.87 (0.75, 1.01)	NS
				Malformations (at 18 months)	1	RR 0.74 (0.27, 2.02)	NS
				Poor growth (at 18 months)	2	RR 0.94 (0.84, 1.07)	NS
Hamulyak, 2020, 32358837	NSAIDs	Aspirin (Low dose)	In utero	Intrauterine growth restriction	1	RR 0.27 (0.03, 2.13)	NS
				Spontaneous abortion	1	RR 1.33 (0.34, 5.21)	NS

Review, Year Published, PMID	Drug Class	Drug Name (s)	Timing of Occurrence of Adverse Effect	Adverse Effect	N Studies	Effect Size (95% CI)	Conclusion
			Perinatal	Preterm birth	1	OR 5.29 (0.27, 102.5)	NS
			Neonatal	Adverse effects, Any	1	OR 1.06 (0.07, 15.60)	NS
Kaplan, 2019, 30849498	Antiemetics: 5HT3 Antagonists	Ondansetron	Neonatal	Congenital anomalies, Major	2	OR 1.21 (0.56, 2.58)	NS
				Congenital anomalies, Cardiovascular	2	OR 1.66 (0.30, 9.09)	NS
				Congenital anomalies, Hypospadias	4	OR 1.61 (0.69, 3.75)	NS
				Congenital anomalies, Genitourinary	4	OR 1.55 (0.89, 2.69)	NS
				Congenital anomalies, Orofacial clefts	3	OR 0.89 (0.32, 2.50)	NS
Picot, 2020, 32420702	Antiemetics: 5HT3 Antagonists	Ondansetron	Neonatal	Congenital anomalies, Major	7	OR 1.02 (0.98, 1.05)	NS
				Congenital anomalies, Cardiovascular (any)	6	OR 1.16 (0.97, 1.39)	NS
				Congenital anomalies, Ventricular septum defect	**6**	**OR 1.11 (1.00, 1.23)**	**Intervention worse**
				Congenital anomalies, Atrial septum defect	5	OR 1.08 (0.83, 1.41)	NS
				Congenital anomalies, Hypoplastic left heart	**3**	**OR 1.49 (1.03, 2.17)**	**Intervention worse**
				Congenital anomalies, Orofacial clefts (any)	**4**	**OR 1.22 (1.00, 1.49)**	**Intervention worse**
				Congenital anomalies, Cleft lip	7	OR 1.00 (0.83, 1.20)	NS
				Congenital anomalies, Cleft palate	6	OR 1.27 (0.86, 1.88)	NS
				Congenital anomalies, Diaphragmatic hernia	**3**	**OR 1.71 (1.18, 2.49)**	**Intervention worse**
				Congenital anomalies, Respiratory system anomalies	**2**	**OR 1.13 (1.01, 1.27)**	**Intervention worse**
Etwel, 2017, 27878468	Antihistamines	Any	In utero	Spontaneous abortion	13	OR 1.00 (0.83, 1.20)	NS
			Perinatal	Stillbirth	8	OR 1.23 (0.48, 3.18)	NS
				Preterm birth	9	OR 0.96 (0.76, 1.20)	NS
				Low birth weight	3	OR 1.20 (0.63, 2.29)	NS
			Neonatal	Congenital anomalies, Major	32	OR 1.07 (0.98, 1.16)	NS
Li, 2019, 31909512	Antihistamines	Any	Neonatal	Congenital anomalies, Any	11	OR 1.05 (0.83, 1.34)	NS
				Congenital anomalies, Hypospadias	2	OR 1.09 (0.60, 1.96)	NS
Park-Wyllie, 2000, 11091360	Corticosteroids	Prednisolone	Neonatal	Congenital anomalies, Major	6	OR 1.45 (0.80, 2.60)	NS
				Congenital anomalies, Oral clefts	**4**	**OR 3.35 (1.97, 5.69)**	**Intervention worse**
Marchenko, 2015, 25644494	Triptans	Any	In utero	Spontaneous abortion	2	OR 1.27 (0.58, 2.79)	NS
			Perinatal	Preterm birth	3	OR 0.90 (0.35, 2.30)	NS
			Neonatal	Congenital anomalies, Major	3	OR 0.84 (0.61, 1.16)	NS
Coughlin, 2015, 25932852	Antipsychotics	Any	In utero	Spontaneous abortion	4	OR 1.05 (0.61, 1.81)	NS

Review, Year Published, PMID	Drug Class	Drug Name (s)	Timing of Occurrence of Adverse Effect	Adverse Effect	N Studies	Effect Size (95% CI)	Conclusion
			Perinatal	Stillbirth	5	OR 1.18 (0.88, 1.57)	NS
				Gestational age at birth	3	MD -0.21 w (-0.44, 0.01)	NS
				Preterm birth (<37 weeks)	**7**	**OR 1.86 (1.45, 2.39)**	**Intervention worse**
				Birth weight	**3**	**MD -58 g (-103, -12)**	**Intervention worse**
				Small for gestational age	**4**	**OR 2.44 (1.22, 4.86)**	**Intervention worse**
				Large for gestational age	4	OR 2.50 (0.77, 8.16)	NS
			Neonatal	**Congenital anomalies, Major**	**7**	**OR 2.12 (1.25, 3.57)**	**Intervention worse**
				Congenital anomalies, Cardiovascular	**4**	**OR 2.09 (1.50, 2.91)**	**Intervention worse**
Terrana, 2015, 26274044	Antipsychotics	Any	In utero	Spontaneous abortion	NR	OR 1.10 (0.74, 1.64)	NS
			Perinatal	Stillbirth	NR	OR 0.79 (0.22, 2.83)	NS
				Preterm birth	N/A	Not extracted because Coughlin 2015 reported data for this harm.	N/A
				Small for gestational age	NR	OR 1.58 (0.91, 2.74)	NS
				Large for gestational age	NR	OR 2.68 (0.56, 12.85)	NS
			Neonatal	Congenital anomalies, Major	N/A	Not extracted because Coughlin 2015 reported data for this harm.	N/A
Makredes, 2014, 24696187	Supplements	Oral magnesium sulphate	In utero	Spontaneous abortion	6	RR 0.85 (0.49, 1.49)	NS
			Perinatal	Stillbirth	4	RR 0.73 (0.43, 1.25)	NS
				Low birth weight	5	RR 0.95 (0.83, 1.09)	NS
			Neonatal	NICU admission	3	RR 0.74 (0.50, 1.11)	NS
				Neonatal death	**4**	**RR 2.21 (1.02, 4.75)**	**Intervention worse**

Abbreviations: CI = confidence interval, CC = case-control, MD = mean difference, m = months, NICU = neonatal intensive care unit, N/A = not applicable, NICU = neonatal intensive care unit, NR = not reported, NS = no statistically significant difference in adverse effects between intervention and control, NSAIDs = nonsteroidal antiinflammatory drugs, OR = odds ratio, PMID = PubMed identifier, RR = relative risk, SMD = standardized mean difference, w = weeks, WMD = weighted mean difference.

Adverse effects, effect sizes, and conclusions in **bold** font have effect sizes that are statistically significantly higher (at the 5% level) in the drug arm, suggestive of harm.

Supplemental Evidence (Case Reports – Details)

We identified 19 case reports,[34-52] of which five reported on KQ 1 only, seven reported on KQ 2 only, and seven reported on both KQs. Thirteen case reports discussed intervention effects (Table B-29) and six reported on adverse effects (Table B-30).

We identified 19 case reports,[34-52] of which five reported on interventions relevant to KQ 1 only, seven reported on interventions relevant to KQ 2 only, and seven reported on interventions relevant to both KQs. Thirteen case reports reported on benefit outcomes intervention effects and six on adverse effects. In the following subsections we describe the case reports and highlight (using *italicized* text) the interventions that were the focus of the case reports. As a reminder, we have not based our conclusions on case reports. We simply report what occurred to individual patients in terms of headache progression and adverse effects (neither of which can be ascribed to individual interventions in case reports).

Case Reports Specific to Key Question 1 (Prevention of Primary Headache)

Case Reports Specific to Key Question 1: Benefits

Four case reports described benefits of interventions intended to prevent primary headaches in pregnant patients.[34, 35, 49, 52] Two reports were of patients with migraine,[34, 47] one with cluster headache,[35] and one with another TAC.[52] Table B-29 summarizes the details of the case reports.

Cases With History of Migraine

Alcantra 2009 reported on a 24 year-old patient in her 3second week of pregnancy, who had a history of migraine headaches that had worsened since she became pregnant.[34] She had been treating her headaches unsuccessfully with NSAIDs plus codeine (1,000 mg/day) and caffeine. She had also tried osteopathy and physical therapy with no improvement. The investigators described in detail starting a regimen of *chiropractic care* and *massage therapy* three times a week for 6 weeks, along with advice to drink *water*, *avoid triggering foods*, and *sleep with an orthopedic pillow*. The patient reported a reduction in pain on a VAS from 8 or 9 (of 10) to 2, and a reduction in headache attacks form one a day to one every 3 days, which subsequently reduced to one every 5 days. She also reported reduced use of the maximum dose of analgesics.

Robinson 2014 reported on a 26 year-old patient with a history of migraines that were not responsive to treatment, including promethazine, metoclopramide, isometheptene mucate (65 mg), dichloralphenazone (100 mg) plus acetaminophen (325 mg), and a compound of butalbital, acetaminophen, and caffeine.[49] She had been successfully treated with *onabotulinumtoxinA* before her pregnancy to prevent migraines, but this treatment was stopped when she became pregnant due to concerns about unknown risks. In her 18th week of pregnancy, she resumed treatment because she had been having five or six headaches a week. She received a total dose of 71 U and reported near resolution of her headaches until delivery. The investigators reported that there were no birth and early childhood short- or long-term adverse effects.

Cases With History of Cluster Headache

Asioli 2019 reported on a 25 year-old patient in her third trimester, with cluster headache, who had been using sumatriptan before pregnancy.[35] The investigators describe treatment with *methylprednisolone* (60 mg) injected into the suboccipital area on the first, second, and fifth day

of treatment. The patient's headache attacks reduced in frequency from four a day before treatment to two a day on the first day, one a day on the fourth day, and one a day during labor a month later.

Cases With History of Other TACs

Yalin 2018 reported on a 29 year-old patient with a history of seasonal headaches that were short-lasting, unilateral, and neuralgiform with conjunctival injection and tearing (SUNCT).[52] When 30 weeks pregnant, she had a headache attack that lasted a week. She was treated with *supra- and infra-orbital nerve blocks* with *lidocaine* (10 mg), *bupivacaine* (5 mg), and *methylprednisolone* (40 mg). She gave birth to a healthy baby, was able to breastfeed successfully, and reported attacks completely diminished after the injection and did not recur through 1 year.

Case Reports Specific to Key Question 1: Harms

One case report described the harms associated with interventions for prevention of primary headache.[51]

Ten Berg reported on a 35 year-old patient whose fetus was detected with a cardiac defect at the 18-week ultrasound, which lead to induced abortion due to poor prognosis. The woman was taking 1,200 mg/day of *valproate* for her migraine; she had taken lower doses (900 mg/day) with her previous two pregnancies, which were uncomplicated.

Case Reports Specific to Key Question 2 (Treatment of Primary Headache)

Case Reports Specific to Key Question 2: Benefits

Five case reports described benefits of interventions intended to treat primary headaches in pregnant patients.[39-41, 48, 50] Four reported on treatment in patients with migraine headaches and one in a patient with an unspecified primary headache.

Evans 2003 reported on a 38 year-old patient with migraine with aura, including three attacks in a prior pregnancy.[40] She experienced nine attacks over 2 months during her second trimester of the current pregnancy. She was treated with a *butalbital, acetaminophen, and caffeine compound*. This resolved her migraine headache within a few hours.

Evans 2000 reported on a 25 year-old patient, 10 weeks pregnant, with migraine headaches about once a week.[39] The patient had a 10-year history of migraine. The patient was treated with *sumatriptan* (50 mg), which gave her full headache relief.

Evans 2001 reported on a 32 year-old patient with a postpartum migraine. She had a history of bitemporal throbbing headaches, which were relieved by *acetaminophen* before her pregnancy.[41] She reported having no headaches during her pregnancy. She was able to relieve postpartum migraine headaches with *ibuprofen*.

Rozen 2003 reported on a 27 year-old patient in her second trimester of pregnancy with migraine with aura.[50] She was prescribed intravenous *prochlorperazine* and *magnesium sulfate*, which reduced her symptoms of aura and resolved her headache completely.

Richardson 2017 reported on a 22 year-old patient with unspecified primary postpartum headaches.[48] She had been experiencing daily headaches for 2.5 weeks, since the infant was 3 days old. The headaches were not resolved with acetaminophen, ibuprofen, or caffeine. The patient was breastfeeding. Treatment with a liter of intravenous saline and 500 mg of caffeine

sodium benzoate over 1 hour was also not effective. She was subsequently treated with *saline* and *ketorolac* (30 mg), which reduced her pain from 6 to 7 (of 10) to 3 on a VAS.

Case Reports Specific to Key Question 2: Harms

Two case reports described the harms of interventions intended to treat primary headaches in pregnant patients.[37, 46]

Demeriel 2012 reported on a patient (age not reported) whose an infant was born at 32 weeks' gestation and died 13 hours after birth from cardiopulmonary arrest.[37] In her first trimester, the woman had experienced migraine attacks that were treated with a combination of *acetaminophen*, *ergotamine tartrate*, *caffeine*, and *mecloxamine citrate*.

Nair 2012 reported 30 year-old patient with migraine headaches that were treated with six tablets a day of a combination of *acetaminophen* and *codeine* during the second trimester of her pregnancy.[46] Her infant was born with neonatal abstinence syndrome, which resolved without requiring pharmacologic therapy.

Case Reports Addressing Both Key Question 1 (Prevention of Primary Headache) and Key Question 2 (Treatment of Primary Headache)

Case Reports Addressing Both Key Question 1 and Key Question 2: Benefits

Four case reports described the effect of interventions intended to prevent and treat primary headaches in pregnant patients.[36, 38, 45, 47] Three reports were of patients with migraine headaches and one with cluster headache.

Levin 2018 reported on a 32 year-old woman with new-onset migraine in late pregnancy that initially responded to a combination of *butalbital*, *acetaminophen*, and *caffeine* every 4 hours; *aspirin*; and/or *methylprednisolone* once a day.[45]However, this regimen was not effective for the 5 days before admission. She was treated with a *sphenopalatine ganglion block*. Treatment consisted of a 4% *lidocaine* solution administered through each nostril, repeated three times every 15 minutes. The patient did not experience immediate improvement in pain, but 4 hours later, pain (measured through a VAS) decreased from 10 (of 10) to 2. The next morning, however, the pain was 8. The procedure was repeated. Fifteen minutes later, the pain decreased to 5.5, and 4 hours later, to 2. She was followed for 6 months and experienced no further migraine symptoms. The only adverse effect she experienced was mild discomfort from the lidocaine applicators.

Papadopoulos 2017 reported on a 28 year-old patient in her 18th week of pregnancy with a history of migraine.[47] Her headaches began 2 months earlier. The mild ones had responded to *acetaminophen*, *water*, and *acupuncture*, but the major ones had not. The patient was given an *oral magnesium phosphate supplement* for prevention and treatment (dose and frequency not reported). The patient reported no significant headaches in the first week and one debilitating migraine attack in the second week, which did not respond to extra doses of magnesium (two tablets every 2 hours up to a maximum of twelve tablets per day). For the 2 days following the debilitating attack in her second week, the patient experienced mild headaches that responded to the higher dose of magnesium. The patient reported one headache in the second through sixth weeks, the severity of which was ameliorated by taking extra doses of magnesium.

Dey 2002 reported on a 32 year-old patient with a history of migraine since puberty and progressively worsening migraines over the past 6 weeks.[38] Before pregnancy, she had used acetaminophen, ibuprofen, codeine, combination analgesics, sumatriptan, verapamil, and

propranolol with varying levels of effectiveness, but she stopped all medications upon becoming pregnant. To address the pain, she was prescribed biofeedback, relaxation, and avoidance of headache triggers, along with acetaminophen and oxycodone (subsequently hydromorphone) on an as-needed basis. She was also prescribed *labetalol* in increasing doses until she reported improvement in headache frequency and intensity. Before treatment, she reported headaches 5 days per week with pain between 6 and 10 (of 10) on a VAS. After a week on labetalol, she reported headaches 3 days per week with pain at 5 on the VAS. Her requirement for hydromorphone was also reduced from 8 to 10 mg to 2 to 4 mg per migraine attack. She delivered a healthy baby.

De Coo 2016 reported on a 32 year-old woman with cluster headache, who had been using sumatriptan to control her headaches from preconception through 4 weeks after delivery.[36] The investigators implanted an *occipital nerve stimulation device* 18 months the woman became pregnant. After device implantation, the attack frequency decreased from nine per week to one per week. During pregnancy, the frequency of her attacks further reduced to one every 2 weeks. She eliminated sumatriptan use in the first trimester and used it only once in her second trimester. The device battery was not recharged at 35 weeks, and the patient's attack frequency increased to one per day, which did not decline until birth. The patient resumed *sumatriptan* use for acute attacks after birth and did not breastfeed. She became attack free again at 4 weeks after birth. Acute attacks were treated with oxygen and, when that was not successful, sumatriptan.

Case Reports Addressing Both Key Question 1 and Key Question 2: Harms

Three case reports described the harms of interventions intended to prevent and treat primary headaches in pregnant patients.[42-44]

Haaland 2010 reported on a 35 year-old woman with migraine who previously had a missed abortion and subsequently a baby with renal tubular dysgenesis, hypoplasia of the skull and the lungs, and hyaline membranes of the lungs. The patient was receiving *candesartan* (1 mg/day), *pramipexole* (0.18 mg/3x), and *amitriptyline* (25 mg/day) as migraine prevention, and *zolmitriptan* (dose not reported) and *metoclopramide* (dose not reported) as treatment during attacks.[42]

In the other two case reports (Hughes 1988[43] and Kajantie 2004[44]), pharmaceutical treatments for migraine prevention or treatment were associated with fetal deformations. Hughes 1988 reported on a patient (age not reported) with severe migraine headaches that were treated with *acetaminophen*, *codeine*, *propranolol*, *ergotamine*, and *caffeine* during pregnancy.[43] The fetus had severe malformations, including arrested cerebral maturation, and the baby girl had paraplegia. Kajantie 2004 reported on a 24 year-old patient who suffered from recurrent migraines that were treated with *bisoprolol*, *naproxen*, and *sumatriptan* through the first weeks of pregnancy and *acetaminophen* thereafter until birth.[44] Her infant had birth defects, including bilateral cleft lip and palate, marked hypertelorism, a broad nose, and a bilateral, asymmetric hypoplasia of the toes.

Table B-29. Case reports addressing treatment effects

KQ	Study, Year, PMID, Country	Age (years)	Phase at Beginning of Intervention	Type of Headache	Intervention Type	Intervention Class	Intervention	Follow-up Time	Headache Results	Birth Results
1	Alcantara, 2009, 19880080, Canada	24	Third trimester	Migraine headache	Nonpharm	• Chiropractic therapy • Hydration therapy • Complementary therapies	• Chiropractic care (spinal manipulative therapy, 3 times/week for 6 weeks) • Water • Massage and trigger point therapy, Sleep posture, Orthopedic pillow • Avoidance of triggering foods	Delivery	• Decrease in headache frequency from 1 attack/day to 1 attack/3 days • Pain VAS : reduced from 8–9/10 to 2/10	
1	Robinson, 2014, 24902141, U.S.	26	Second trimester	Migraine headache	Nonpharm	• Chemodenervation	• OnabotulinumtoxinA (71 U)	Delivery	Near resolution	Normal fetal movements throughout the pregnancy; no notable intrauterine growth restriction; 1/5 minute Apgar score of 1/9, respectively, had vigorous muscular movements with good tone, required no special care, and was discharged home the same day. A review of the child's medical charts from 07/2007 through 09/2013 was notable for normal neuromuscular development with all developmental

KQ	Study, Year, PMID, Country	Age (years)	Phase at Beginning of Intervention	Type of Headache	Intervention Type	Intervention Class	Intervention	Follow-up Time	Headache Results	Birth Results
										milestones being met as expected with no evidence or concern
1	Asioli, 2019, 3116401, Italy	25	Third trimester	Cluster headache	Pharm	• Corticosteroids (Medium anti-inflammatory potency)	• Methylprednisolone (60 mg, slow-release in 3 injections: first, third, and fifth day)	Infant 6 months old	• 2 attacks 1 day after first treatment; 1 attack 4 days after first treatment; 1 attack during labor; Clinical control 10 months after the birth proved no recurrence of attacks	Newborn was healthy and no birth defects were reported
1	Yalin, 2018, 29450873, Turkey	29	Third trimester	Other TACs	Nonpharm	• Nerve blocks	• Supra- and infraorbital nerve block	Weaning	• Attacks diminished after the first injection, and recurrence was not observed for 1 year	Delivered a healthy baby girl, and the delivery was uneventful
1 & 2	Levin, 2018, 29634560, U.S.	32	Third trimester	Migraine headache	Nonpharm	• Nerve blocks	• Sphenopalatine ganglion block (0.5mL of 4% lidocaine solution; 3 times/15 minutes)	Infant 5 months old	• 4 hours after first dose VAS decreased to 2 of 10; next morning VAS was 8 of 10 • 15 minutes after second treatment later, the pain (VAS) decreased to 5.5 of 10, and	

KQ	Study, Year, PMID, Country	Age (years)	Phase at Beginning of Intervention	Type of Headache	Intervention Type	Intervention Class	Intervention	Follow-up Time	Headache Results	Birth Results
									4 hours later to 2 of 10 • At 6 months no return of migraine symptoms.	
1 & 2	Papadopoulos, 2017, No PMID, Australia	28	Second trimester	Migraine headache	Nonpharm	• Oral magnesium	• Magnesium sulfate (low elemental dose)	17 weeks pregnancy	• No significant headaches in first week; one debilitating migraine in second week, did not respond to extra doses of the magnesium supplement (two tablets every two hours up to a maximum of twelve tablets per day). For the following two days she experienced mild headaches which did respond to a higher dose of magnesium; one headache in third to sixth weeks, the severity of which was	

KQ	Study, Year, PMID, Country	Age (years)	Phase at Beginning of Intervention	Type of Headache	Intervention Type	Intervention Class	Intervention	Follow-up Time	Headache Results	Birth Results
									ameliorated by taking extra doses of magnesium	
1 & 2	Dey, 2002, 1242217, U.S.	32	Second trimester	Migraine headache	Pharm	• Opioid-containing analgesics • Beta blockers	• Hydromorphone (8-10 mg, as needed for 6 weeks) • Labetalol (150 mg 2/day for 6 weeks)	Delivery	Pain VAS: 6-10 of 10 at 24 weeks 5 of 10 at 25 weeks	LFTs, fetal and obstetrical parameters within normal limits. Healthy baby at 38 weeks.
1 & 2	De Coo, 2016, 25834272, Netherlands	32	Preconception	Cluster headache	Nonpharm	• Nerve Blocks	• Occipital nerve stimulation	Infant 4 weeks old	Second trimester 1 attack/2weeks; third trimester 1 attack/6 weeks; postpartum 1 day frequent severe attacks; attack-free after 4 weeks	parturition was uncomplicated except for a surgical removal of the placenta; baby made a good start and did not have any birth defects
1 & 2	De Coo, 2016, 25834272, Netherlands	32	Preconception	Cluster headache	Pharm	• Triptans/Serotonin receptor agonists	• Sumatriptan	Infant 4 weeks old	Successful acute treatment; once during pregnancy and once postpartum (breastfeeding suspended)	
1 & 2	De Coo, 2016, 25834272, Netherlands	32	Preconception	Cluster headache	Nonpharm	• Oxygen therapy	• Oxygen (9 L/min)	Infant 4 weeks old	Successful acute treatment; until the day after birth	
2	Evans, 2003, 12864766, U.S.	38	Second trimester	Migraine headache	Pharm + nonpharm	• Butalbital-containing analgesics • Sleep therapy	• Butalbital, acetaminophen, caffeine compound	28 weeks pregnancy	Resolution after a few hours	

KQ	Study, Year, PMID, Country	Age (years)	Phase at Beginning of Intervention	Type of Headache	Intervention Type	Intervention Class	Intervention	Follow-up Time	Headache Results	Birth Results
							• Sleep therapy			
2	Evans, 2000, 11135034, U.S.	25	Preconception	Migraine headache	Pharm	• Triptans/Serotonin receptor agonists	• Sumatriptan (50 mg)	NR	Complete relief	
2	Evans, 2001, 11554965, U.S.	35	Postpartum	Migraine headache	Pharm	• NSAIDs	• Ibuprofen	NR	Decreased but did not resolve headache	
2	Rozen, 2003, 12940813, U.S.	27	Second trimester	Migraine headache	Pharm + nonpharm	• Antiemetics: Dopamine receptor antagonists • Oral magnesium	• Prochlorperazine • Magnesium sulfate	NR	Complete resolution	
2	Richardson, 2017, 29095177, U.S.	22	Postpartum	NR	Pharm + nonpharm	• NSAIDs • Hydration therapy	• Ketorolac (30 mg, IV) • NaCl 0.9% (125 ml/hr, IV)	NR	Pain VAS decreased to 3/10	

Abbreviations: CNS = central nervous system; hr = hour, IV = intravenous, LFT = liver function test, Nonpharm = nonpharmacologic NR = not reported, NSAID = nonsteroidal anti-inflammatory drug, Pharm = pharmacologic, PMID = PubMed identifier, TAC = trigeminal autonomic cephalgia, VAS = visual analog scale

Table B-30. Case reports addressing adverse effects

KQ	Study, Year, PMID, Country	Age (years)	Phase at Beginning of Intervention	Type of Headache	Intervention Type	Drug/Intervention Class	Interventions	Follow-up Time	Adverse Effect
1	Ten Berg, 2005, 15712340, Netherlands	35	Preconception	Migraine headache	Pharm	• Antiepileptic drugs	• Valproate (1200 mg/day in two equal dosages)	Termination	A fetal cardiac defect with a hypoplastic right ventricle and anomaly of the ascending aorta. Due to poor prognosis pregnancy was terminated at 20 3/7 weeks.
1 & 2	Haaland, 2010, 20063032, Norway	35	Preconception	Migraine headache	Pharm	• Renin-angiotensin-aldosterone system inhibitors • Tricyclic antidepressants	• Candesartan (16 mg/day) • pramipexole (0.18mg/3x) • Amitriptyline (25 mg/day)	Termination	Miscarriage
1 & 2	Haaland, 2010, 20063032, Norway	35	Preconception	Migraine headache	Pharm	• Triptans/Serotonin receptor agonists • Dopamine receptor antagonists	• Zolmitriptan • Metoclopramide (during attacks)	Termination	Miscarriage
1 & 2	Hughes, 1988, 3398007, Canada	NR	Preconception	Migraine headache	Pharm	• Analgesics/Antipyretics • Opioid-containing analgesics • Beta blockers • Ergotamine • CNS stimulants	• Acetaminophen (325 mg; 6-20/day) • Codeine (8 mg; 6-20/day) • Propranolol (40mg 2/day) • Ergotamine (2mg 1-4/week) • Caffeine (100mg 1-4/week)	20 weeks pregnancy	Infant was clinically microcephalic with a head circumference of 31 cm and the anterior fontanelle was almost closed. Infant was paraplegic with underdeveloped and hypotonic lower limbs. The anal, knee, and ankle reflexes were absent. Sensation was absent up to the level of the knees and it was variably absent on the thighs. The findings suggested a spinal cord abnormality and it was estimated to be in the upper lumbar region. Both hips were dislocated and there was a marked equinovarus deformity bilaterally.

KQ	Study, Year, PMID, Country	Age (years)	Phase at Beginning of Intervention	Type of Headache	Intervention Type	Drug/Intervention Class	Interventions	Follow-up Time	Adverse Effect
1 & 2	Kajantie, 2004, 15194960, Finland	24	NR	Migraine headache	Pharm	• Beta blockers • NSAIDs • Triptans/Serotonin receptor agonists	• Bisoprolol • Naproxen • Sumatriptan	Through fifth premenstrual week	Wide bilateral cleft lip and palate, marked hypertelorism and a broad nose; bilateral, asymmetric toe abnormalities
1 & 2	Kajantie, 2004, 15194960, Finland	24	NR	Migraine headache	Pharm	• Over-the-counter analgesics	• Acetaminophen	Until delivery	Wide bilateral cleft lip and palate, marked hypertelorism and a broad nose; bilateral, asymmetric toe abnormalities
2	Demirel, 2012, 22417229, Turkey	NR	First trimester	Migraine headache	Pharm	• Over-the-counter analgesics	• Acetaminophen 325 mg, ergotamine tartrate 0.75 mg, caffeine 80 mg, and mecloxamine citrate 20 mg combination	4 weeks pregnancy	Infant death: 13 hours after birth from cardiopulmonary arrest
2	Nair, 2012, 23633904, Canada	30	Third trimester	Migraine headache	Pharm	• Analgesics/Antipyretics • Opioid-containing analgesics	• Acetaminophen, codeine combination (up to 6/day)	Until delivery	Neonatal abstinence syndrome. Infant recovered without requiring pharmacologic therapy

Abbreviations: Nonpharm = nonpharmacologic, Pharm = pharmacologic, PMID = PubMed identifier, NR = not reported.

Details on Strength of Evidence

Primary Studies

Table B-31. Key Question 1: Pharmacologic interventions: Antiepileptics – Full evidence profile

Topic	Comparison	Outcome	N Studies (Subjects)	RoB	Consistency	Precision	Directness	SoE	Conclusions
Benefits	Topiramate (No comparison)	Acute headache attacks – Occurrence	0	-	-	-	-	-	-
		Acute headache attacks – Frequency	0	-	-	-	-	-	-
		Acute headache attacks – Severity	0	-	-	-	-	-	-
		Acute headache attacks – Duration	0	-	-	-	-	-	-
		Headache-related symptoms – Occurrence	0	-	-	-	-	-	-
		Headache-related symptoms – Frequency	0	-	-	-	-	-	-
		Headache-related symptoms – Severity	0	-	-	-	-	-	-

Topic	Comparison	Outcome	N Studies (Subjects)	RoB	Consistency	Precision	Directness	SoE	Conclusions
		Headache-related symptoms – Duration	0	-	-	-	-	-	-
		Emergency department or clinic visits	0	-	-	-	-	-	-
		Hospitalizations	0	-	-	-	-	-	-
		Quality of life	0	-	-	-	-	-	-
Harms	Topiramate (No comparison)	AEs – Maternal – Serious, Any	0	-	-	-	-	-	-
		AEs – Maternal – Serious, Cardiovascular	0	-	-	-	-	-	-
		AEs – Maternal – Discontinuation due to AEs	0	-	-	-	-	-	-
		AEs – Maternal – Serious, Cardiovascular	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Any	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Spontaneous abortion or elective or induced abortion	1 (81)	Moderate	Not applicable	Imprecise	Indirect	Insufficient	No conclusion made
		AEs – Fetal/Child – Serious, Stillbirth or fetal death	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Neonatal or infant death	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Preterm birth	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Low birth weight	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Congenital anomalies	1 (81)	Moderate	Not applicable	Imprecise	Indirect	Insufficient	No conclusion made
		AEs – Fetal/Child – Serious, Perinatal complications	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Neurodevelopmental/Behavioral/Social	0	-	-	-	-	-	-
		AEs – Fetal/Child – Discontinuation due to AEs	0	-	-	-	-	-	-

Abbreviations: AE = adverse effect, RoB = risk of bias, SoE = strength of evidence.

Table B-32. Key Question 2: Pharmacologic interventions: Triptans, ergot products, and NSAIDs, full evidence profile

Topic	Comparison	Outcome	N Studies (Subjects)	RoB	Consistency	Precision	Directness	SoE	Conclusions
Benefits	Sumatriptan vs. Naratriptan (During Pregnancy)	Acute headache attacks – Severity	0	-	-	-	-	-	-
		Acute headache attacks – Duration	0	-	-	-	-	-	-
		Acute headache attacks – Resolution	0	-	-	-	-	-	-
		Acute headache attacks – Recurrence	0	-	-	-	-	-	-
		Headache-related symptoms – Severity	0	-	-	-	-	-	-
		Headache-related symptoms – Duration	0	-	-	-	-	-	-
		Headache-related symptoms – Resolution	0	-	-	-	-	-	-
		Headache-related symptoms – Recurrence	0	-	-	-	-	-	-

Topic	Comparison	Outcome	N Studies (Subjects)	RoB	Consistency	Precision	Directness	SoE	Conclusions
		Emergency department or clinic visits	0	-	-	-	-	-	-
		Hospitalizations	0	-	-	-	-	-	-
		Quality of life	0	-	-	-	-	-	-
Benefits	2: Sumatriptan vs. Sumatriptan and Naproxen Combination (During Pregnancy)	Acute headache attacks – Severity	0	-	-	-	-	-	-
		Acute headache attacks – Duration	0	-	-	-	-	-	-
		Acute headache attacks – Resolution	0	-	-	-	-	-	-
		Acute headache attacks – Recurrence	0	-	-	-	-	-	-
		Headache-related symptoms – Severity	0	-	-	-	-	-	-
		Headache-related symptoms – Duration	0	-	-	-	-	-	-
		Headache-related symptoms – Resolution	0	-	-	-	-	-	-
		Headache-related symptoms – Recurrence	0	-	-	-	-	-	-
		Emergency department or clinic visits	0	-	-	-	-	-	-
		Hospitalizations	0	-	-	-	-	-	-
		Quality of life	0	-	-	-	-	-	-
Benefits	Naratriptan vs. Sumatriptan and Naproxen Combination (During Pregnancy)	Acute headache attacks – Severity	0	-	-	-	-	-	-
		Acute headache attacks – Duration	0	-	-	-	-	-	-
		Acute headache attacks – Resolution	0	-	-	-	-	-	-
		Acute headache attacks – Recurrence	0	-	-	-	-	-	-
		Headache-related symptoms – Severity	0	-	-	-	-	-	-
		Headache-related symptoms – Duration	0	-	-	-	-	-	-
		Headache-related symptoms – Resolution	0	-	-	-	-	-	-
		Headache-related symptoms – Recurrence	0	-	-	-	-	-	-
		Emergency department or clinic visits	0	-	-	-	-	-	-
		Hospitalizations	0	-	-	-	-	-	-
		Quality of life	0	-	-	-	-	-	-
Benefits	Any Triptan vs. Any Ergot Product (During Pregnancy)	Acute headache attacks – Severity	0	-	-	-	-	-	-
		Acute headache attacks – Duration	0	-	-	-	-	-	-
		Acute headache attacks – Resolution	0	-	-	-	-	-	-
		Acute headache attacks – Recurrence	0	-	-	-	-	-	-
		Headache-related symptoms – Severity	0	-	-	-	-	-	-
		Headache-related symptoms – Duration	0	-	-	-	-	-	-
		Headache-related symptoms – Resolution	0	-	-	-	-	-	-
		Headache-related symptoms – Recurrence	0	-	-	-	-	-	-
		Emergency department or clinic visits	0	-	-	-	-	-	-

Topic	Comparison	Outcome	N Studies (Subjects)	RoB	Consistency	Precision	Directness	SoE	Conclusions
		Hospitalizations	0	-	-	-	-	-	-
		Quality of life	0	-	-	-	-	-	-
Benefits	Any Triptan vs. Pizotifen (During Pregnancy)	Acute headache attacks – Severity	0	-	-	-	-	-	-
		Acute headache attacks – Duration	0	-	-	-	-	-	-
		Acute headache attacks – Resolution	0	-	-	-	-	-	-
		Acute headache attacks – Recurrence	0	-	-	-	-	-	-
		Headache-related symptoms – Severity	0	-	-	-	-	-	-
		Headache-related symptoms – Duration	0	-	-	-	-	-	-
		Headache-related symptoms – Resolution	0	-	-	-	-	-	-
		Headache-related symptoms – Recurrence	0	-	-	-	-	-	-
		Emergency department or clinic visits	0	-	-	-	-	-	-
		Hospitalizations	0	-	-	-	-	-	-
		Quality of life	0	-	-	-	-	-	-
Benefits	Any Ergot Product vs. Pizotifen (During Pregnancy)	Acute headache attacks – Severity	0	-	-	-	-	-	-
		Acute headache attacks – Duration	0	-	-	-	-	-	-
		Acute headache attacks – Resolution	0	-	-	-	-	-	-
		Acute headache attacks – Recurrence	0	-	-	-	-	-	-
		Headache-related symptoms – Severity	0	-	-	-	-	-	-
		Headache-related symptoms – Duration	0	-	-	-	-	-	-
		Headache-related symptoms – Resolution	0	-	-	-	-	-	-
		Headache-related symptoms – Recurrence	0	-	-	-	-	-	-
		Emergency department or clinic visits	0	-	-	-	-	-	-
		Hospitalizations	0	-	-	-	-	-	-
		Quality of life	0	-	-	-	-	-	-
Benefits	Any Triptan (During Pregnancy) vs. Any Triptan (Before Pregnancy)	Acute headache attacks – Severity	0	-	-	-	-	-	-
		Acute headache attacks – Duration	0	-	-	-	-	-	-
		Acute headache attacks – Resolution	0	-	-	-	-	-	-
		Acute headache attacks – Recurrence	0	-	-	-	-	-	-
		Headache-related symptoms – Severity	0	-	-	-	-	-	-
		Headache-related symptoms – Duration	0	-	-	-	-	-	-
		Headache-related symptoms – Resolution	0	-	-	-	-	-	-
		Headache-related symptoms – Recurrence	0	-	-	-	-	-	-
		Emergency department or clinic visits	0	-	-	-	-	-	-
		Hospitalizations	0	-	-	-	-	-	-
		Quality of life	0	-	-	-	-	-	-

Topic	Comparison	Outcome	N Studies (Subjects)	RoB	Consistency	Precision	Directness	SoE	Conclusions
Effectiveness	Sumatriptan (During Pregnancy) vs. Sumatriptan (Before Pregnancy)	Acute headache attacks – Severity	0	-	-	-	-	-	-
		Acute headache attacks – Duration	0	-	-	-	-	-	-
		Acute headache attacks – Resolution	0	-	-	-	-	-	-
		Acute headache attacks – Recurrence	0	-	-	-	-	-	-
		Headache-related symptoms – Severity	0	-	-	-	-	-	-
		Headache-related symptoms – Duration	0	-	-	-	-	-	-
		Headache-related symptoms – Resolution	0	-	-	-	-	-	-
		Headache-related symptoms – Recurrence	0	-	-	-	-	-	-
		Emergency department or clinic visits	0	-	-	-	-	-	-
		Hospitalizations	0	-	-	-	-	-	-
		Quality of life	0	-	-	-	-	-	-
Effectiveness	Any Triptan (During Pregnancy) vs. No Triptans (During or Before Pregnancy)	Acute headache attacks – Severity	0	-	-	-	-	-	-
		Acute headache attacks – Duration	0	-	-	-	-	-	-
		Acute headache attacks – Resolution	0	-	-	-	-	-	-
		Acute headache attacks – Recurrence	0	-	-	-	-	-	-
		Headache-related symptoms – Severity	0	-	-	-	-	-	-
		Headache-related symptoms – Duration	0	-	-	-	-	-	-
		Headache-related symptoms – Resolution	0	-	-	-	-	-	-
		Headache-related symptoms – Recurrence	0	-	-	-	-	-	-
		Emergency department or clinic visits	0	-	-	-	-	-	-
		Hospitalizations	0	-	-	-	-	-	-
		Quality of life	0	-	-	-	-	-	-
Harms	Sumatriptan vs. Naratriptan (During Pregnancy)	AEs – Maternal – Serious, Any	0	-	-	-	-	-	-
		AEs – Maternal – Serious, Cardiovascular	0	-	-	-	-	-	-
		AEs – Maternal – Discontinuation due to AEs	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Any	0						
		AEs – Fetal/Child – Serious, Spontaneous abortion or elective or induced abortion	1 (689)	High	Not applicable	Not applicable	Direct	Insufficient	No conclusion made
		AEs – Fetal/Child – Serious, Stillbirth or fetal death	1 (689)	High	Not applicable	Not applicable	Direct	Insufficient	No conclusion made
		AEs – Fetal/Child – Serious, Neonatal or infant death	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Preterm birth	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Low birth weight	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Congenital anomalies	1 (689)	High	Not applicable	Not applicable	Direct	Insufficient	No conclusion made
		AEs – Fetal/Child – Serious, Perinatal complications	0	-	-	-	-	-	-

Topic	Comparison	Outcome	N Studies (Subjects)	RoB	Consistency	Precision	Directness	SoE	Conclusions
		AEs – Fetal/Child – Serious, Neurodevelopmental/Behavioral/Social	0	-	-	-	-	-	-
		AEs – Fetal/Child – Discontinuation due to AEs	0	-	-	-	-	-	-
Harms	Sumatriptan vs. Sumatriptan and Naproxen Combination (During Pregnancy)	AEs – Maternal – Serious, Any	0	-	-	-	-	-	-
		AEs – Maternal – Serious, Cardiovascular	0	-	-	-	-	-	-
		AEs – Maternal – Discontinuation due to AEs	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Any	0						
		AEs – Fetal/Child – Serious, Spontaneous abortion or elective or induced abortion	1 (689)	High	Not applicable	Not applicable	Direct	Insufficient	No conclusion made
		AEs – Fetal/Child – Serious, Stillbirth or fetal death	1 (689)	High	Not applicable	Not applicable	Direct	Insufficient	No conclusion made
		AEs – Fetal/Child – Serious, Neonatal or infant death	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Preterm birth	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Low birth weight	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Congenital anomalies	1 (689)	High	Not applicable	Not applicable	Direct	Insufficient	No conclusion made
		AEs – Fetal/Child – Serious, Perinatal complications	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Neurodevelopmental/Behavioral/Social	0	-	-	-	-	-	-
		AEs – Fetal/Child – Discontinuation due to AEs	0	-	-	-	-	-	-
Harms	Naratriptan vs. Sumatriptan and Naproxen Combination (During Pregnancy)	AEs – Maternal – Serious, Any	0	-	-	-	-	-	-
		AEs – Maternal – Serious, Cardiovascular	0	-	-	-	-	-	-
		AEs – Maternal – Discontinuation due to AEs	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Any	0						
		AEs – Fetal/Child – Serious, Spontaneous abortion or elective or induced abortion	1 (689)	High	Not applicable	Not applicable	Direct	Insufficient	No conclusion made
		AEs – Fetal/Child – Serious, Stillbirth or fetal death	1 (689)	High	Not applicable	Not applicable	Direct	Insufficient	No conclusion made
		AEs – Fetal/Child – Serious, Neonatal or infant death	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Preterm birth	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Low birth weight	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Congenital anomalies	1 (689)	High	Not applicable	Not applicable	Direct	Insufficient	No conclusion made
		AEs – Fetal/Child – Serious, Perinatal complications	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Neurodevelopmental/Behavioral/Social	0	-	-	-	-	-	-
		AEs – Fetal/Child – Discontinuation due to AEs	0	-	-	-	-	-	-

Topic	Comparison	Outcome	N Studies (Subjects)	RoB	Consistency	Precision	Directness	SoE	Conclusions
Harms	Any Triptan vs. Any Ergot Product (During Pregnancy)	AEs – Maternal – Serious, Any	0	-	-	-	-	-	-
		AEs – Maternal – Serious, Cardiovascular	0	-	-	-	-	-	-
		AEs – Maternal – Discontinuation due to AEs	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Any	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Spontaneous abortion or elective or induced abortion	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Stillbirth or fetal death	1 (3368)	High	Not applicable	Not applicable	Direct	Insufficient	No conclusion made
		AEs – Fetal/Child – Serious, Neonatal or infant death	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Preterm birth	1 (3368)	High	Not applicable	Not applicable	Direct	Insufficient	No conclusion made
		AEs – Fetal/Child – Serious, Low birth weight	1 (3368)	High	Not applicable	Not applicable	Direct	Insufficient	No conclusion made
		AEs – Fetal/Child – Serious, Congenital anomalies	1 (3368)	High	Not applicable	Not applicable	Direct	Insufficient	No conclusion made
		AEs – Fetal/Child – Serious, Perinatal complications	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Neurodevelopmental/Behavioral/Social	0	-	-	-	-	-	-
		AEs – Fetal/Child – Discontinuation due to AEs	0	-	-	-	-	-	-
Harms	Any Triptan vs. Pizotifen (During Pregnancy)	AEs – Maternal – Serious, Any	0	-	-	-	-	-	-
		AEs – Maternal – Serious, Cardiovascular	0	-	-	-	-	-	-
		AEs – Maternal – Discontinuation due to AEs	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Any	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Spontaneous abortion or elective or induced abortion	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Stillbirth or fetal death	1 (3368)	High	Not applicable	Not applicable	Direct	Insufficient	No conclusion made
		AEs – Fetal/Child – Serious, Neonatal or infant death	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Preterm birth	1 (3368)	High	Not applicable	Not applicable	Direct	Insufficient	No conclusion made
		AEs – Fetal/Child – Serious, Low birth weight	1 (3368)	High	Not applicable	Not applicable	Direct	Insufficient	No conclusion made
		AEs – Fetal/Child – Serious, Congenital anomalies	1 (3368)	High	Not applicable	Not applicable	Direct	Insufficient	No conclusion made
		AEs – Fetal/Child – Serious, Perinatal complications	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Neurodevelopmental/Behavioral/Social	0	-	-	-	-	-	-
		AEs – Fetal/Child – Discontinuation due to AEs	0	-	-	-	-	-	-
Harms	Any Ergot Product vs. Pizotifen (During Pregnancy)	AEs – Maternal – Serious, Any	0	-	-	-	-	-	-

Topic	Comparison	Outcome	N Studies (Subjects)	RoB	Consistency	Precision	Directness	SoE	Conclusions
		AEs – Maternal – Serious, Cardiovascular	0	-	-	-	-	-	-
		AEs – Maternal – Discontinuation due to AEs	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Any	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Spontaneous abortion or elective or induced abortion	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Stillbirth or fetal death	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Neonatal or infant death	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Preterm birth	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Low birth weight	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Congenital anomalies	1 (5900)	High	Not applicable	Not applicable	Direct	Insufficient	No conclusion made
		AEs – Fetal/Child – Serious, Perinatal complications	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Neurodevelopmental/Behavioral/Social	0	-	-	-	-	-	-
		AEs – Fetal/Child – Discontinuation due to AEs	0	-	-	-	-	-	-
Harms	Any Triptan (During Pregnancy) vs. Any Triptan (Before Pregnancy)	AEs – Maternal – Serious, Any	2 (8460)	High	Not applicable	Not applicable	Direct	Insufficient	No conclusion made
		AEs – Maternal – Serious, Cardiovascular	0	-	-	-	-	-	-
		AEs – Maternal – Discontinuation due to AEs	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Any	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Spontaneous abortion or elective or induced abortion	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Stillbirth or fetal death	1 (5900)	High	Not applicable	Not applicable	Direct	Insufficient	No conclusion made
		AEs – Fetal/Child – Serious, Neonatal or infant death	1 (5900)	High	Not applicable	Not applicable	Direct	Insufficient	No conclusion made
		AEs – Fetal/Child – Serious, Preterm birth	2 (8460)	High	Not applicable	Not applicable	Direct	Insufficient	No conclusion made
		AEs – Fetal/Child – Serious, Low birth weight	2 (8460)	High	Not applicable	Not applicable	Direct	Insufficient	No conclusion made
		AEs – Fetal/Child – Serious, Congenital anomalies	2 (8460)	High	Not applicable	Not applicable	Direct	Insufficient	No conclusion made
		AEs – Fetal/Child – Serious, Perinatal complications	2 (8460)	High	Not applicable	Not applicable	Direct	Insufficient	No conclusion made
		AEs – Fetal/Child – Serious, Neurodevelopmental/Behavioral/Social	1 (5900)	High	Not applicable	Imprecise	Direct	Low	Similar gross motor and fine motor development, but worse emotionality and activity outcomes for at 3 years for use during pregnancy versus before pregnancy.
		AEs – Fetal/Child – Discontinuation due to AEs	0	-	-	-	-	-	-

Topic	Comparison	Outcome	N Studies (Subjects)	RoB	Consistency	Precision	Directness	SoE	Conclusions
Harms	Sumatriptan (During Pregnancy) vs. Sumatriptan (Before Pregnancy)	AEs – Maternal – Serious, Any	1 (168)	High	Not applicable	Not applicable	Direct	Insufficient	No conclusion made
		AEs – Maternal – Serious, Cardiovascular	0	-	-	-	-	-	-
		AEs – Maternal – Discontinuation due to AEs	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Any	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Spontaneous abortion or elective or induced abortion	1 (168)	High	Not applicable	Not applicable	Direct	Insufficient	No conclusion made
		AEs – Fetal/Child – Serious, Stillbirth or fetal death	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Neonatal or infant death	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Preterm birth	1 (123)	Moderate	Not applicable	Imprecise	Direct	Insufficient	No conclusion made
		AEs – Fetal/Child – Serious, Low birth weight	1 (123)	Moderate	Not applicable	Imprecise	Direct	Insufficient	No conclusion made
		AEs – Fetal/Child – Serious, Congenital anomalies	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Perinatal complications	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Neurodevelopmental/Behavioral/Social	0	-	-	-	-	-	-
		AEs – Fetal/Child – Discontinuation due to AEs	0	-	-	-	-	-	-
Harms	Any Triptan (During Pregnancy) vs. No Triptans (During or Before Pregnancy)	AEs – Maternal – Serious, Any	1 (5900)	High	Not applicable	Not applicable	Indirect	Insufficient	No conclusion made
		AEs – Maternal – Serious, Cardiovascular	0	-	-	-	-	-	-
		AEs – Maternal – Discontinuation due to AEs	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Any	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Spontaneous abortion or elective or induced abortion	2 (1099)	High	N/A	N/A	Direct	Low	No difference for spontaneous or elective abortion
		AEs – Fetal/Child – Serious, Stillbirth or fetal death	2 (6807)	High	N/A	N/A	Direct	Low	No adjusted between-arm estimates
		AEs – Fetal/Child – Serious, Neonatal or infant death	1 (5900)	High	N/A	N/A	Direct	Low	No adjusted between-arm estimates available
		AEs – Fetal/Child – Serious, Preterm birth	1 (5900)	High	Not applicable	Not applicable	Indirect	Insufficient	No conclusion made
		AEs – Fetal/Child – Serious, Low birth weight	1 (5900)	High	Not applicable	Not applicable	Indirect	Insufficient	No conclusion made
		AEs – Fetal/Child – Serious, Congenital anomalies	3 (6999)	High	Not applicable	Imprecise	Direct	Low	No difference for any, major, minor, and genetic birth defects. spontaneous or elective abortion.

Topic	Comparison	Outcome	N Studies (Subjects)	RoB	Consistency	Precision	Directness	SoE	Conclusions
		AEs – Fetal/Child – Serious, Perinatal complications	1 (5900)	High	Not applicable	Not applicable	Indirect	Insufficient	No conclusion made
		AEs – Fetal/Child – Serious, Neurodevelopmental/Behavioral/Social	1 (5900)	High	Not applicable	Imprecise	Direct	Low	Similar gross motor and fine motor development, but worse emotionality and activity for use during pregnancy versus nonuse (during or before pregnancy).
		AEs – Fetal/Child – Discontinuation due to AEs	0	-	-	-	-	-	-

Abbreviations: AE = adverse effect, NS = not statistically significant, RoB = risk of bias, SoE = strength of evidence.
Consistency was deemed "N/A" when it could not be assessed because only one study was one found. Consistency was also deemed "N/A" when in some instances where more than one study was found because at least one of the studies did not report adjusted between-arm effect sizes, precluding an assessment of consistency.
Precision was deemed "N/A" when it could not be assessed because adjusted between-arm effect sizes were not reported.

Table B-33. Key Question 2: Pharmacologic interventions: Antiemetics, antihistamines, opioid analgesics – Full evidence profile

Topic	Comparison	Outcome	N Studies (Subjects)	RoB	Consistency	Precision	Directness	SoE	Conclusions
Benefits	Combination of metoclopramide and diphenhydramine vs. codeine	Acute headache attacks – Severity	1 (70)	High	Not applicable	Imprecise	Direct	Low	Severity reduced more in combination arm
		Acute headache attacks – Duration	0	-	-	-	-	-	-
		Acute headache attacks – Resolution	1 (70)	High	Not applicable	Imprecise	Direct	Low	Resolution more likely and sooner in combination arm
		Acute headache attacks – Recurrence	1 (70)	High	Not applicable	Imprecise	Direct	Low	Recurrence lower in combination arm, but NS
		Headache-related symptoms – Severity	0	-	-	-	-	-	-
		Headache-related symptoms – Duration	0	-	-	-	-	-	-
		Headache-related symptoms – Resolution	0	-	-	-	-	-	-
		Headache-related symptoms – Recurrence	0	-	-	-	-	-	-
		Emergency department or clinic visits	0	-	-	-	-	-	-
		Hospitalizations	0	-	-	-	-	-	-
		Quality of life	0	-	-	-	-	-	-
Harms	Combination of metoclopramide and diphenhydramine vs. codeine	AEs – Maternal – Serious, Any	1 (70)	High	Not applicable	Imprecise	Direct	Low	No events in either arm
		AEs – Maternal – Serious, Cardiovascular	0	-	-	-	-	-	-
		AEs – Maternal – Discontinuation due to AEs	0	-	-	-	-	-	-

Topic	Comparison	Outcome	N Studies (Subjects)	RoB	Consistency	Precision	Directness	SoE	Conclusions
		AEs – Fetal/Child – Serious, Any	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Spontaneous abortion or elective or induced abortion	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Stillbirth or fetal death	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Neonatal or infant death	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Preterm birth	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Low birth weight	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Congenital anomalies	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Perinatal complications	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Neurodevelopmental/Behavioral/Social	0	-	-	-	-	-	-
		AEs – Fetal/Child – Discontinuation due to AEs	0	-	-	-	-	-	-

Abbreviations: AE = adverse effect, NS = not statistically significant, RoB = risk of bias, SoE = strength of evidence.

Table B-34. Key Question 2: Nonpharmacologic interventions: Complementary, behavioral, and physical therapies – Full evidence profile

Topic	Comparison	Outcome	N Studies (Subjects)	RoB	Consistency	Precision	Directness	SoE	Conclusions
Benefits	1. Acupuncture vs. Routine Care	Acute headache attacks – Severity	1 (43)	High	Not applicable	Imprecise	Direct	Insufficient	No conclusion made
		Acute headache attacks – Duration	0	-	-	-	-	-	-
		Acute headache attacks – Resolution	0	-	-	-	-	-	-
		Acute headache attacks – Recurrence	0	-	-	-	-	-	-
		Headache-related symptoms – Severity	0	-	-	-	-	-	-
		Headache-related symptoms – Duration	0	-	-	-	-	-	-
		Headache-related symptoms – Resolution	0	-	-	-	-	-	-
		Headache-related symptoms – Recurrence	0	-	-	-	-	-	-
		Emergency department or clinic visits	0	-	-	-	-	-	-
		Hospitalizations	0	-	-	-	-	-	-
		Quality of life	0	-	-	-	-	-	-
Benefits	2. Combination of thermal biofeedback, relaxation therapy, and physical therapy	Acute headache attacks – Severity	2 (44)	High	Not applicable	Imprecise	Direct	Insufficient	No conclusion made
		Acute headache attacks – Duration	0	-	-	-	-	-	-
		Acute headache attacks – Resolution	0	-	-	-	-	-	-
		Acute headache attacks – Recurrence	0	-	-	-	-	-	-
		Headache-related symptoms – Severity	0	-	-	-	-	-	-
		Headache-related symptoms – Duration	0	-	-	-	-	-	-
		Headache-related symptoms – Resolution	0	-	-	-	-	-	-
		Headache-related symptoms – Recurrence	0	-	-	-	-	-	-
		Emergency department or clinic visits	0	-	-	-	-	-	-
		Hospitalizations	0	-	-	-	-	-	-
		Quality of life	0	-	-	-	-	-	-
Benefits	3. Combination of thermal biofeedback and relaxation therapy	Acute headache attacks – Severity	1 (5)	Low	Not applicable	Imprecise	Indirect	Insufficient	No conclusion made
		Acute headache attacks – Duration	1 (5)	Low	Not applicable	Imprecise	Indirect	Insufficient	No conclusion made
		Acute headache attacks – Resolution	1 (5)	Low	Not applicable	Imprecise	Indirect	Insufficient	No conclusion made
		Acute headache attacks – Recurrence	0	-	-	-	-	-	-
		Headache-related symptoms – Severity	0	-	-	-	-	-	-
		Headache-related symptoms – Duration	0	-	-	-	-	-	-
		Headache-related symptoms – Resolution	0	-	-	-	-	-	-
		Headache-related symptoms – Recurrence	0	-	-	-	-	-	-
		Emergency department or clinic visits	0	-	-	-	-	-	-
		Hospitalizations	0	-	-	-	-	-	-
		Quality of life	0	-	-	-	-	-	-

Topic	Comparison	Outcome	N Studies (Subjects)	RoB	Consistency	Precision	Directness	SoE	Conclusions
Harms	1. Acupuncture vs. Routine Care	AEs – Maternal – Serious, Any	0	-	-	-	-	-	-
		AEs – Maternal – Serious, Cardiovascular	0	-	-	-	-	-	-
		AEs – Maternal – Discontinuation due to AEs	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Any	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Spontaneous abortion or elective or induced abortion	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Stillbirth or fetal death	0	-	-	-	-	-	-
		AEs – Fetal/Child – Neonatal or infant death	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Preterm birth	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Low birth weight	1 (43)	High	Not applicable	Imprecise	Direct	Insufficient	No conclusion made
		AEs – Fetal/Child – Serious, Congenital anomalies	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Perinatal complications	1 (43)	High	Not applicable	Imprecise	Direct	Insufficient	No conclusion made
		AEs – Fetal/Child – Serious, Neurodevelopmental	0	-	-	-	-	-	-
		AEs – Fetal/Child – Discontinuation due to AEs	0	-	-	-	-	-	-
Harms	2. Combination of thermal biofeedback, relaxation therapy, and physical therapy	AEs – Maternal – Serious, Any	0	-	-	-	-	-	-
		AEs – Maternal – Serious, Cardiovascular	0	-	-	-	-	-	-
		AEs – Maternal – Discontinuation due to AEs	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Any	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Spontaneous abortion or elective or induced abortion	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Stillbirth or fetal death	0	-	-	-	-	-	-
		AEs – Fetal/Child – Neonatal or infant death	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Preterm birth	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Low birth weight	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Congenital anomalies	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Perinatal complications	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Neurodevelopmental	0	-	-	-	-	-	-
		AEs – Fetal/Child – Discontinuation due to AEs	0	-	-	-	-	-	-
Harms	3. Combination of thermal biofeedback and relaxation therapy	AEs – Maternal – Serious, Any	0	-	-	-	-	-	-
		AEs – Maternal – Serious, Cardiovascular	0	-	-	-	-	-	-
		AEs – Maternal – Discontinuation due to AEs	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Any	0	-	-	-	-	-	-

Topic	Comparison	Outcome	N Studies (Subjects)	RoB	Consistency	Precision	Directness	SoE	Conclusions
		AEs – Fetal/Child – Serious, Spontaneous abortion or elective or induced abortion	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Stillbirth or fetal death	0	-	-	-	-	-	-
		AEs – Fetal/Child – Neonatal or infant death	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Preterm birth	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Low birth weight	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Congenital anomalies	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Perinatal complications	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Neurodevelopmental/Behavioral/Social	0	-	-	-	-	-	-
		AEs – Fetal/Child – Discontinuation due to AEs	0	-	-	-	-	-	-

Abbreviations: AE = adverse effect, min = minutes, RoB = risk of bias, SoE = strength of evidence.

Table B-35. Key Question 2: Nonpharmacologic interventions: Procedures, full evidence profile

Topic	Comparison	Outcome	N Studies (Subjects)	RoB	Consistency	Precision	Directness	SoE	Conclusions
Benefits	Nerve blocks (No comparison)	Acute headache attacks – Severity	1 (13)	Low	Not applicable	Not applicable	Indirect	Insufficient	No conclusion made
		Acute headache attacks – Duration	0	-	-	-	-	-	-
		Acute headache attacks – Resolution	0	-	-	-	-	-	-
		Acute headache attacks – Recurrence	0	-	-	-	-	-	-
		Headache-related symptoms – Severity	0	-	-	-	-	-	-
		Headache-related symptoms – Duration	0	-	-	-	-	-	-
		Headache-related symptoms – Resolution	0	-	-	-	-	-	-
		Headache-related symptoms – Recurrence	0	-	-	-	-	-	-
		Emergency department or clinic visits	0	-	-	-	-	-	-
		Hospitalizations	0	-	-	-	-	-	-
		Quality of life	0	-	-	-	-	-	-
Harms	Nerve blocks (No comparison)	AEs – Maternal – Serious, Any	1 (13)	Low	Not applicable	Not applicable	Indirect	Insufficient	No conclusion made
		AEs – Maternal – Serious, Cardiovascular	0	-	-	-	-	-	-
		AEs – Maternal – Discontinuation due to AEs	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Any	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Spontaneous abortion or elective or induced abortion	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Stillbirth or fetal death	0	-	-	-	-	-	-

Topic	Comparison	Outcome	N Studies (Subjects)	RoB	Consistency	Precision	Directness	SoE	Conclusions
		AEs – Fetal/Child – Neonatal or infant death	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Preterm birth	1 (13)	Low	Not applicable	Not applicable	Indirect	Insufficient	No conclusion made
		AEs – Fetal/Child – Serious, Low birth weight	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Congenital anomalies	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Perinatal complications	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Neurodevelopmental/Behavioral/Social	0	-	-	-	-	-	-
		AEs – Fetal/Child – Discontinuation due to AEs	0	-	-	-	-	-	-

Abbreviations: AE = adverse effect, NS = not statistically significant, RoB = risk of bias, SoE = strength of evidence.

Table B-36. Key Question 2: Nonpharmacologic interventions: Noninvasive neuromodulation devices, full evidence profile

Topic	Comparison	Outcome	N Studies (Subjects)	RoB	Consistency	Precision	Directness	SoE	Conclusions
Benefits	Transcranial magnetic stimulation (No comparison)	Acute headache attacks – Severity	0	-	-	-	-	-	-
		Acute headache attacks – Duration	0	-	-	-	-	-	-
		Acute headache attacks – Resolution	1 (3)	Moderate	Not applicable	Not applicable	Indirect	Insufficient	No conclusion made
		Acute headache attacks – Recurrence	0	-	-	-	-	-	-
		Headache-related symptoms – Severity							
		Headache-related symptoms – Duration	0	-	-	-	-	-	-
		Headache-related symptoms – Resolution	1 (3)	Moderate	Not applicable	Not applicable	Indirect	Insufficient	No conclusion made
		Headache-related symptoms – Recurrence	0	-	-	-	-	-	-
		Emergency department or clinic visits	0	-	-	-	-	-	-
		Hospitalizations	0	-	-	-	-	-	-
		Quality of life	0	-	-	-	-	-	-
Harms	Transcranial magnetic stimulation (No comparison)	AEs – Maternal – Serious, Any	1 (3)	Moderate	Not applicable	Not applicable	Indirect	Insufficient	No conclusion made
		AEs – Maternal – Serious, Cardiovascular	0	-	-	-	-	-	-
		AEs – Maternal – Discontinuation due to AEs	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Any	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Spontaneous abortion or elective or induced abortion	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Stillbirth or fetal death	0	-	-	-	-	-	-
		AEs – Fetal/Child – Neonatal or infant death	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Preterm birth	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Low birth weight	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Congenital anomalies	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Perinatal complications	0	-	-	-	-	-	-
		AEs – Fetal/Child – Serious, Neurodevelopmental/Behavioral/Social	0	-	-	-	-	-	-
		AEs – Fetal/Child – Discontinuation due to AEs	0	-	-	-	-	-	-

Abbreviations: AE = adverse effect, NS = not statistically significant, RoB = risk of bias, SoE = strength of evidence.

Systematic Reviews

Table B-37. Systematic reviews of harms of pharmacologic interventions (regardless of indication) – Full evidence profile

Class	Drug	Outcome	N SRs (N Studies)	RoB	Consistency	Precision	Directness	SoE	Conclusions
Tricyclic antidepressants	Any	AEs – Maternal – Serious, Any	0					None	None
		AEs – Maternal – Serious, Cardiovascular	0					None	None
		AEs – Maternal – Discontinuation due to AEs	0					None	None
		AEs – Fetal/Child – Serious, Any	0					None	None
		AEs – Fetal/Child – Serious, Spontaneous abortion or elective or induced abortion	0					None	None
		AEs – Fetal/Child – Serious, Stillbirth or fetal death	0					None	None
		AEs – Fetal/Child – Serious, Neonatal or infant death	0					None	None
		AEs – Fetal/Child – Serious, Preterm birth	0					None	None
		AEs – Fetal/Child – Serious, Low birth weight	1 (2)	Moderate	Consistent	Precise	Indirect	Moderate	No increased risk of small for gestational age
		AEs – Fetal/Child – Serious, Congenital anomalies	1 (2)	Moderate	Consistent	Precise	Indirect	Moderate	Increased major and cardiovascular anomalies
		AEs – Fetal/Child – Serious, Perinatal complications	1 (2)	Moderate	Consistent	Precise	Indirect	Moderate	Increased neonatal convulsions and respiratory distress
		AEs – Fetal/Child – Serious, Neurodevelopmental/Behavioral/Social	1 (1)	Moderate	N/A	Imprecise	Indirect	Insufficient	None
		AEs – Fetal/Child – Discontinuation due to AEs	0					None	None
Serotonin and norepinephrine reuptake inhibitors (SNRIs)	Venlafaxine	AEs – Maternal – Serious, Any	0					None	None
		AEs – Maternal – Serious, Cardiovascular	0					None	None
		AEs – Maternal – Discontinuation due to AEs	0					None	None
		AEs – Fetal/Child – Serious, Any	0					None	None
		AEs – Fetal/Child – Serious, Spontaneous abortion or elective or induced abortion	0					None	None
		AEs – Fetal/Child – Serious, Stillbirth or fetal death	0					None	None
		AEs – Fetal/Child – Serious, Neonatal or infant death	0					None	None
		AEs – Fetal/Child – Serious, Preterm birth	1 (2)	Moderate	Consistent	Precise	Indirect	Moderate	Increased preterm birth
		AEs – Fetal/Child – Serious, Low birth weight	0					None	None
		AEs – Fetal/Child – Serious, Congenital anomalies	0					None	None
		AEs – Fetal/Child – Serious, Perinatal complications	0					None	None

Class	Drug	Outcome	N SRs (N Studies)	RoB	Consistency	Precision	Directness	SoE	Conclusions
		AEs – Fetal/Child – Serious, Neurodevelopmental/Behavioral/Social	0					None	None
		AEs – Fetal/Child – Discontinuation due to AEs	0					None	None
Beta blockers	Any	AEs – Maternal – Serious, Any	0					None	None
		AEs – Maternal – Serious, Cardiovascular	0					None	None
		AEs – Maternal – Discontinuation due to AEs	1 (9)	Moderate	Consistent	Precise	Indirect	Low	No increased risk
		AEs – Fetal/Child – Serious, Any	0					None	None
		AEs – Fetal/Child – Serious, Spontaneous abortion or elective or induced abortion	0					None	None
		AEs – Fetal/Child – Serious, Stillbirth or fetal death	0					None	None
		AEs – Fetal/Child – Serious, Neonatal or infant death	0					None	None
		AEs – Fetal/Child – Serious, Preterm birth	1 (4)	Moderate	Consistent	Precise	Indirect	Moderate	No increased risk
		AEs – Fetal/Child – Serious, Low birth weight	0					None	None
		AEs – Fetal/Child – Serious, Congenital anomalies	1 (1–5*)	Low to moderate	Consistent	Precise	Indirect	Moderate	Increased cardiovascular anomalies, cleft lip/palate, and neural tube defects
		AEs – Fetal/Child – Serious, Perinatal complications	1 (1)	Moderate	N/A	Precise	Indirect	Insufficient	None
		AEs – Fetal/Child – Serious, Neurodevelopmental/Behavioral/Social	0					None	None
		AEs – Fetal/Child – Discontinuation due to AEs	0					None	None
Calcium channel blockers	Any	AEs – Maternal – Serious, Any	0					None	None
		AEs – Maternal – Serious, Cardiovascular	0					None	None
		AEs – Maternal – Discontinuation due to AEs	1 (2)	Moderate	Consistent	Imprecise	Indirect	Low	No increased risk
		AEs – Fetal/Child – Serious, Any	0					None	None
		AEs – Fetal/Child – Serious, Spontaneous abortion or elective or induced abortion	1 (5)	Moderate	Consistent	Imprecise	Indirect	Low	No increased risk
		AEs – Fetal/Child – Serious, Stillbirth or fetal death	1 (5)	Moderate	Consistent	Imprecise	Indirect	Low	No increased risk
		AEs – Fetal/Child – Serious, Neonatal or infant death	1 (5)	Moderate	Consistent	Imprecise	Indirect	Low	No increased risk
		AEs – Fetal/Child – Serious, Preterm birth	1 (4)	Moderate	Consistent	Precise	Indirect	Low	No increased risk
		AEs – Fetal/Child – Serious, Low birth weight	0					None	None
		AEs – Fetal/Child – Serious, Congenital anomalies	0					None	None
		AEs – Fetal/Child – Serious, Perinatal complications	1 (1-3*)	Low to moderate	Consistent	Precise	Indirect	Moderate	No increased risk of NICU admission, neonatal respiratory distress syndrome
		AEs – Fetal/Child – Serious, Neurodevelopmental/Behavioral/Social	0					None	None
		AEs – Fetal/Child – Discontinuation due to AEs	0					None	None
Calcium channel blockers	Nifedipine	AEs – Maternal – Serious, Any	0					None	None

Class	Drug	Outcome	N SRs (N Studies)	RoB	Consistency	Precision	Directness	SoE	Conclusions
		AEs – Maternal – Serious, Cardiovascular	0					None	None
		AEs – Maternal – Discontinuation due to AEs	0					None	None
		AEs – Fetal/Child – Serious, Any	0					None	None
		AEs – Fetal/Child – Serious, Spontaneous abortion or elective or induced abortion	0					None	None
		AEs – Fetal/Child – Serious, Stillbirth or fetal death	0					None	None
		AEs – Fetal/Child – Serious, Neonatal or infant death	1 (2)	Moderate	Consistent	Precise	Indirect	Moderate	No increased risk
		AEs – Fetal/Child – Serious, Preterm birth	1 (2)	Moderate	Consistent	Imprecise	Indirect	Low	No increased risk
		AEs – Fetal/Child – Serious, Low birth weight	0					None	None
		AEs – Fetal/Child – Serious, Congenital anomalies	0					None	None
		AEs – Fetal/Child – Serious, Perinatal complications	0					None	None
		AEs – Fetal/Child – Serious, Neurodevelopmental/Behavioral/Social	0					None	None
		AEs – Fetal/Child – Discontinuation due to AEs	0					None	None
Anti-epileptics	Valproate	AEs – Maternal – Serious, Any	0					None	None
		AEs – Maternal – Serious, Cardiovascular	0					None	None
		AEs – Maternal – Discontinuation due to AEs	0					None	None
		AEs – Fetal/Child – Serious, Any	0					None	None
		AEs – Fetal/Child – Serious, Spontaneous abortion or elective or induced abortion	1 (96)	Low to moderate	Consistent	Precise	Indirect	Moderate	Increased spontaneous abortion
		AEs – Fetal/Child – Serious, Stillbirth or fetal death	1 (96)	Low to moderate	Consistent	Precise	Indirect	Moderate	Increased fetal death
		AEs – Fetal/Child – Serious, Neonatal or infant death	0					None	None
		AEs – Fetal/Child – Serious, Preterm birth	1 (96)	Low to moderate	Consistent	Precise	Indirect	Moderate	No increased risk
		AEs – Fetal/Child – Serious, Low birth weight	0					None	None
		AEs – Fetal/Child – Serious, Congenital anomalies	2 (96)	Low to moderate	Consistent	Precise	Indirect	Moderate	Increased major anomalies, hypospadias, cleft lip/palate, club foot, neural tube defects
		AEs – Fetal/Child – Serious, Perinatal complications	0					None	None
		AEs – Fetal/Child – Serious, Neurodevelopmental/Behavioral/Social	1 (96)	Low to moderate	Consistent	Precise	Indirect	Moderate	Increased cognitive delay, autism/dyspraxia, psychomotor developmental delay, language delay
		AEs – Fetal/Child – Discontinuation due to AEs	0					None	None
Anti-epileptics	Topiramate	AEs – Maternal – Serious, Any	0					None	None

Class	Drug	Outcome	N SRs (N Studies)	RoB	Consistency	Precision	Directness	SoE	Conclusions
		AEs – Maternal – Serious, Cardiovascular	0					None	None
		AEs – Maternal – Discontinuation due to AEs	0					None	None
		AEs – Fetal/Child – Serious, Any	1 (96)	Low to moderate	Consistent	Precise	Indirect	Moderate	Increased fetal growth restriction
		AEs – Fetal/Child – Serious, Spontaneous abortion or elective or induced abortion	1 (96)	Low to moderate	Consistent	Precise	Indirect	Moderate	Increased spontaneous abortion
		AEs – Fetal/Child – Serious, Stillbirth or fetal death	1 (96)	Low to moderate	Consistent	Precise	Indirect	Moderate	Increased fetal death
		AEs – Fetal/Child – Serious, Neonatal or infant death	0					None	None
		AEs – Fetal/Child – Serious, Preterm birth	1 (96)	Low to moderate	Consistent	Precise	Indirect	Moderate	No increased risk
		AEs – Fetal/Child – Serious, Low birth weight	0					None	None
		AEs – Fetal/Child – Serious, Congenital anomalies	1 (96)	Low to moderate	Consistent	Precise	Indirect	Moderate	Increased major anomalies and cleft lip/palate
		AEs – Fetal/Child – Serious, Perinatal complications	0					None	None
		AEs – Fetal/Child – Serious, Neurodevelopmental/Behavioral/Social	1 (96)	Low to moderate	Consistent	Imprecise	Indirect	Low	No increased risk of cognitive or developmental delays
		AEs – Fetal/Child – Discontinuation due to AEs	0					None	None
Anti-epileptics	Gabapentin	AEs – Maternal – Serious, Any	0					None	None
		AEs – Maternal – Serious, Cardiovascular	0					None	None
		AEs – Maternal – Discontinuation due to AEs	0					None	None
		AEs – Fetal/Child – Serious, Any	1 (96)	Low to moderate	Consistent	Imprecise	Indirect	Low	No increased risk of fetal growth restriction
		AEs – Fetal/Child – Serious, Spontaneous abortion or elective or induced abortion	0					None	None
		AEs – Fetal/Child – Serious, Stillbirth or fetal death	0					None	None
		AEs – Fetal/Child – Serious, Neonatal or infant death	0						
		AEs – Fetal/Child – Serious, Preterm birth	1 (96)	Low to moderate	Consistent	Precise	Indirect	Low	No increased risk
		AEs – Fetal/Child – Serious, Low birth weight	0					None	None
		AEs – Fetal/Child – Serious, Congenital anomalies	1 (96)	Low to moderate	Inconsistent	Imprecise	Indirect	Low	Increased cardiovascular anomalies and hypospadias, but not cleft lip/palate or club foot
		AEs – Fetal/Child – Serious, Perinatal complications	0					None	None
		AEs – Fetal/Child – Serious, Neurodevelopmental/Behavioral/Social	1 (96)	Low to moderate	Inconsistent	Precise	Indirect	Low	Increased psychomotor developmental delay, but not cognitive developmental delays
		AEs – Fetal/Child – Discontinuation due to AEs	0					None	None

Class	Drug	Outcome	N SRs (N Studies)	RoB	Consistency	Precision	Directness	SoE	Conclusions
Anti-epileptics	Carbamazepine	AEs – Maternal – Serious, Any	0					None	None
		AEs – Maternal – Serious, Cardiovascular	0					None	None
		AEs – Maternal – Discontinuation due to AEs	0					None	None
		AEs – Fetal/Child – Serious, Any	0					None	None
		AEs – Fetal/Child – Serious, Spontaneous abortion or elective or induced abortion	1 (96)	Low to moderate	Consistent	Precise	Indirect	Low	No increased risk
		AEs – Fetal/Child – Serious, Stillbirth or fetal death	1 (96)	Low to moderate	Consistent	Precise	Indirect	Low	No increased risk
		AEs – Fetal/Child – Serious, Neonatal or infant death	0					None	None
		AEs – Fetal/Child – Serious, Preterm birth	1 (96)	Low to moderate	Consistent	Precise	Indirect	Low	No increased risk
		AEs – Fetal/Child – Serious, Low birth weight	0					None	None
		AEs – Fetal/Child – Serious, Congenital anomalies	1 (96)	Low to moderate	Consistent	Precise	Indirect	Moderate	Increased major and minor anomalies
		AEs – Fetal/Child – Serious, Perinatal complications	0					None	None
		AEs – Fetal/Child – Serious, Neurodevelopmental/Behavioral/Social	1 (96)	Low to moderate	Consistent	Precise	Indirect	Moderate	No increased risk
		AEs – Fetal/Child – Discontinuation due to AEs	0					None	None
Anti-epileptics	Lamotrigine	AEs – Maternal – Serious, Any	0					None	None
		AEs – Maternal – Serious, Cardiovascular	0					None	None
		AEs – Maternal – Discontinuation due to AEs	0					None	None
		AEs – Fetal/Child – Serious, Any	1 (96)	Low to moderate	Consistent	Precise	Indirect	Moderate	No increased risk
		AEs – Fetal/Child – Serious, Spontaneous abortion or elective or induced abortion	1 (96)	Low to moderate	Consistent	Precise	Indirect	Moderate	No increased risk
		AEs – Fetal/Child – Serious, Stillbirth or fetal death	1 (96)	Low to moderate	Consistent	Precise	Indirect	Moderate	No increased risk
		AEs – Fetal/Child – Serious, Neonatal or infant death	0					None	None
		AEs – Fetal/Child – Serious, Preterm birth	1 (96)	Low to moderate	Consistent	Precise	Indirect	Moderate	No increased risk
		AEs – Fetal/Child – Serious, Low birth weight	0					None	None
		AEs – Fetal/Child – Serious, Congenital anomalies	1 (96)	Low to moderate	Consistent	Precise	Indirect	Moderate	No increased risk
		AEs – Fetal/Child – Serious, Perinatal complications	0					None	None

Class	Drug	Outcome	N SRs (N Studies)	RoB	Consistency	Precision	Directness	SoE	Conclusions
		AEs – Fetal/Child – Serious, Neurodevelopmental/Behavioral/Social	1 (96)	Low to moderate	Consistent	Precise	Indirect	Moderate	Increased autism/dyspraxia, but no increased risk of cognitive or psychomotor developmental delays, language delay, for attention deficit hyperactivity disorder
		AEs – Fetal/Child – Discontinuation due to AEs	0					None	None
Benzodiazepines	Any	AEs – Maternal – Serious, Any	0					None	None
		AEs – Maternal – Serious, Cardiovascular	0					None	None
		AEs – Maternal – Discontinuation due to AEs	0					None	None
		AEs – Fetal/Child – Serious, Any	0					None	None
		AEs – Fetal/Child – Serious, Spontaneous abortion or elective or induced abortion	0					None	None
		AEs – Fetal/Child – Serious, Stillbirth or fetal death	0					None	None
		AEs – Fetal/Child – Serious, Neonatal or infant death	0					None	None
		AEs – Fetal/Child – Serious, Preterm birth	0					None	None
		AEs – Fetal/Child – Serious, Low birth weight	0					None	None
		AEs – Fetal/Child – Serious, Congenital anomalies	1 (6-9*)	Moderate	Consistent	Precise	Indirect	Low	Increased major congenital anomalies and oral cleft
		AEs – Fetal/Child – Serious, Perinatal complications	0					None	None
		AEs – Fetal/Child – Serious, Neurodevelopmental	0					None	None
		AEs – Fetal/Child – Discontinuation due to AEs	0					None	None
Analgesics/ Antipyretics	Acetaminophen	AEs – Maternal – Serious, Any	0					None	None
		AEs – Maternal – Serious, Cardiovascular	0					None	None
		AEs – Maternal – Discontinuation due to AEs	0					None	None
		AEs – Fetal/Child – Serious, Any	0					None	None
		AEs – Fetal/Child – Serious, Spontaneous abortion or elective or induced abortion	0					None	None
		AEs – Fetal/Child – Serious, Stillbirth or fetal death	0					None	None
		AEs – Fetal/Child – Serious, Neonatal or infant death	0					None	None
		AEs – Fetal/Child – Serious, Preterm birth	0					None	None
		AEs – Fetal/Child – Serious, Low birth weight	0					None	None
		AEs – Fetal/Child – Serious, Congenital anomalies	0					None	None
		AEs – Fetal/Child – Serious, Perinatal complications	0					None	None
		AEs – Fetal/Child – Serious, Neurodevelopmental/Behavioral/Social	1 (4-6*)	Moderate	Inconsistent	Precise	Indirect	Low	Increased attention deficit hyperactivity disorder, hyperactivity symptoms, autism spectrum disorder, and conduct disorder
		AEs – Fetal/Child – Discontinuation due to AEs	0					None	None

Class	Drug	Outcome	N SRs (N Studies)	RoB	Consistency	Precision	Directness	SoE	Conclusions
NSAIDs	Any	AEs – Maternal – Serious, Any	0					None	None
		AEs – Maternal – Serious, Cardiovascular	1 (4)	Moderate	Consistent	Precise	Indirect	Moderate	No increased risk of postpartum hypertension
		AEs – Maternal – Discontinuation due to AEs	0					None	None
		AEs – Fetal/Child – Serious, Any	0					None	None
		AEs – Fetal/Child – Serious, Spontaneous abortion or elective or induced abortion	0					None	None
		AEs – Fetal/Child – Serious, Stillbirth or fetal death	0					None	None
		AEs – Fetal/Child – Serious, Neonatal or infant death	0					None	None
		AEs – Fetal/Child – Serious, Preterm birth	0					None	None
		AEs – Fetal/Child – Serious, Low birth weight	0					None	None
		AEs – Fetal/Child – Serious, Congenital anomalies	0					None	None
		AEs – Fetal/Child – Serious, Perinatal complications	0					None	None
		AEs – Fetal/Child – Serious, Neurodevelopmental/Behavioral/Social	0					None	None
		AEs – Fetal/Child – Discontinuation due to AEs	0					None	None
NSAIDs	Indomethacin	AEs – Maternal – Serious, Any	0					None	None
		AEs – Maternal – Serious, Cardiovascular	0					None	None
		AEs – Maternal – Discontinuation due to AEs	0					None	None
		AEs – Fetal/Child – Serious, Any	0					None	None
		AEs – Fetal/Child – Serious, Spontaneous abortion or elective or induced abortion	0					None	None
		AEs – Fetal/Child – Serious, Stillbirth or fetal death	0					None	None
		AEs – Fetal/Child – Serious, Neonatal or infant death	1 (15)	Unclear	Consistent	Precise	Indirect	Low	No increased risk of neonatal death
		AEs – Fetal/Child – Serious, Preterm birth	0					None	None
		AEs – Fetal/Child – Serious, Low birth weight	0					None	None
		AEs – Fetal/Child – Serious, Congenital anomalies	1 (17)	Unclear	Consistent	Precise	Indirect	Low	No increased risk of patent ductus arteriosus
		AEs – Fetal/Child – Serious, Perinatal complications	1 (9-18)	Unclear	Consistent	Precise	Indirect	Low	Increased risk of periventricular leukomalacia, Grade III-IV intraventrucular hemorrhage, and necrotizing enterocolitis
		AEs – Fetal/Child – Serious, Neurodevelopmental/Behavioral/Social	0					None	None
		AEs – Fetal/Child – Discontinuation due to AEs	0					None	None
NSAIDs	Low-dose aspirin	AEs – Maternal – Serious, Any	1 (3)	Low	Consistent	Precise	Indirect	Moderate	No increased risk of hospitalization

Class	Drug	Outcome	N SRs (N Studies)	RoB	Consistency	Precision	Directness	SoE	Conclusions
		AEs – Maternal – Serious, Cardiovascular	0					None	None
		AEs – Maternal – Discontinuation due to AEs	0					None	None
		AEs – Fetal/Child – Serious, Any	0					None	None
		AEs – Fetal/Child – Serious, Spontaneous abortion or elective or induced abortion	3 (3-28)	Low to moderate	Consistent	Precise	Indirect	Low	No increased risk of spontaneous abortion
		AEs – Fetal/Child – Serious, Stillbirth or fetal death	3 (3-28)	Low to moderate	Consistent	Precise	Indirect	Low	No increased risk of stillbirth, perinatal mortality
		AEs – Fetal/Child – Serious, Neonatal or infant death	3 (3-28)	Low to moderate	Consistent	Precise	Indirect	Low	No increased risk of infant death
		AEs – Fetal/Child – Serious, Preterm birth	4 (9)	Low to moderate	Consistent	Precise	Indirect	Low	No increased risk
		AEs – Fetal/Child – Serious, Low birth weight	2 (8)	Low to moderate	Inconsistent	Precise	Indirect	Low	No increased risk
		AEs – Fetal/Child – Serious, Congenital anomalies	0					None	
		AEs – Fetal/Child – Serious, Perinatal complications	1 (8-15)	Low to moderate	Inconsistent	Precise	Indirect	Low	No increased risk of NICU admission, intraventricular hemorrhage, other neonatal bleed
		AEs – Fetal/Child – Serious, Neurodevelopmental/Behavioral/Social	1 (1)	Low	N/A	Imprecise	Indirect	Low	No increased risk of gross motor, fine motor, language, hearing, speech, etc.
		AEs – Fetal/Child – Discontinuation due to AEs	0					None	None
Antiemetics: 5HT3 Antagonists	Ondansetron	AEs – Maternal – Serious, Any	0					None	None
		AEs – Maternal – Serious, Cardiovascular	0					None	None
		AEs – Maternal – Discontinuation due to AEs	0					None	None
		AEs – Fetal/Child – Serious, Any	0					None	None
		AEs – Fetal/Child – Serious, Spontaneous abortion or elective or induced abortion	0					None	None
		AEs – Fetal/Child – Serious, Stillbirth or fetal death	0					None	None
		AEs – Fetal/Child – Serious, Neonatal or infant death	0					None	None
		AEs – Fetal/Child – Serious, Preterm birth	0					None	None
		AEs – Fetal/Child – Serious, Low birth weight	0					None	None
		AEs – Fetal/Child – Serious, Congenital anomalies	2 (16)	Moderate	Consistent	Precise	Indirect	Moderate	Increased risk of cardiovascular anomalies, orofacial clefts, diaphragmatic hernia, and respiratory system anomalies
		AEs – Fetal/Child – Serious, Perinatal complications	0					None	None
		AEs – Fetal/Child – Serious, Neurodevelopmental/Behavioral/Social	0					None	None
		AEs – Fetal/Child – Discontinuation due to AEs	0					None	None
Antihistamines	Any	AEs – Maternal – Serious, Any	0					None	None

Class	Drug	Outcome	N SRs (N Studies)	RoB	Consistency	Precision	Directness	SoE	Conclusions
		AEs – Maternal – Serious, Cardiovascular	0					None	None
		AEs – Maternal – Discontinuation due to AEs	0					None	None
		AEs – Fetal/Child – Serious, Any	0					None	None
		AEs – Fetal/Child – Serious, Spontaneous abortion or elective or induced abortion	1 (8-13)	Low	Consistent	Precise	Indirect	Moderate	No increased risk of spontaneous abortion
		AEs – Fetal/Child – Serious, Stillbirth or fetal death	1 (8-13)	Low	Consistent	Precise	Indirect	Moderate	No increased risk of stillbirth
		AEs – Fetal/Child – Serious, Neonatal or infant death	0					None	None
		AEs – Fetal/Child – Serious, Preterm birth	1 (9)	Low	Consistent	Precise	Indirect	Moderate	No increased risk
		AEs – Fetal/Child – Serious, Low birth weight	1 (3)	Low	Consistent	Precise	Indirect	Moderate	No increased risk
		AEs – Fetal/Child – Serious, Congenital anomalies	2 (43)	Low	Consistent	Precise	Indirect	Moderate	No increased risk of major congenital anomalies
		AEs – Fetal/Child – Serious, Perinatal complications	0					None	None
		AEs – Fetal/Child – Serious, Neurodevelopmental/Behavioral/Social	0					None	None
Corticosteroids	Prednisolone	AEs – Maternal – Serious, Any	0					None	None
		AEs – Maternal – Serious, Cardiovascular	0					None	None
		AEs – Maternal – Discontinuation due to AEs	0					None	None
		AEs – Fetal/Child – Serious, Any	0					None	None
		AEs – Fetal/Child – Serious, Spontaneous abortion or elective or induced abortion	0					None	None
		AEs – Fetal/Child – Serious, Stillbirth or fetal death	0					None	None
		AEs – Fetal/Child – Serious, Neonatal or infant death	0					None	None
		AEs – Fetal/Child – Serious, Preterm birth	0					None	None
		AEs – Fetal/Child – Serious, Low birth weight	0					None	None
		AEs – Fetal/Child – Serious, Congenital anomalies	1 (4-6)	Unclear	Inconsistent	Precise	Indirect	Low	Increased oral clefts, but no increased risk of major anomalies
		AEs – Fetal/Child – Serious, Perinatal complications	0					None	None
		AEs – Fetal/Child – Serious, Neurodevelopmental/Behavioral/Social	0					None	None
Triptans	Any	AEs – Maternal – Serious, Any	0					None	None
		AEs – Maternal – Serious, Cardiovascular	0					None	None
		AEs – Maternal – Discontinuation due to AEs	0					None	None
		AEs – Fetal/Child – Serious, Any	0					None	None
		AEs – Fetal/Child – Serious, Spontaneous abortion or elective or induced abortion	1 (2)	Unclear	Consistent	Precise	Direct	Moderate	No increased risk of spontaneous abortion
		AEs – Fetal/Child – Serious, Stillbirth or fetal death	0					None	None
		AEs – Fetal/Child – Serious, Neonatal or infant death	0					None	None
		AEs – Fetal/Child – Serious, Preterm birth	1 (3)	Unclear	Inconsistent	Imprecise	Direct	Low	No increased risk
		AEs – Fetal/Child – Serious, Low birth weight	0					None	None

Class	Drug	Outcome	N SRs (N Studies)	RoB	Consistency	Precision	Directness	SoE	Conclusions
		AEs – Fetal/Child – Serious, Congenital anomalies	1 (3)	Unclear	Consistent	Precise	Direct	Moderate	No increased risk of major anomalies
		AEs – Fetal/Child – Serious, Perinatal complications	0					None	None
		AEs – Fetal/Child – Serious, Neurodevelopmental/Behavioral/Social	0					None	None
Antipsychotics	Any	AEs – Maternal – Serious, Any	0					None	None
		AEs – Maternal – Serious, Cardiovascular	0					None	None
		AEs – Maternal – Discontinuation due to AEs	0					None	None
		AEs – Fetal/Child – Serious, Any	0					None	None
		AEs – Fetal/Child – Serious, Spontaneous abortion or elective or induced abortion	2 (7)	Moderate	Inconsistent	Precise	Indirect	Low	No increased risk of spontaneous abortion
		AEs – Fetal/Child – Serious, Stillbirth or fetal death	2 (7)	Moderate	Inconsistent	Precise	Indirect	Low	No increased risk of stillbirth
		AEs – Fetal/Child – Serious, Neonatal or infant death	0					None	None
		AEs – Fetal/Child – Serious, Preterm birth	2 (7)	Moderate	Consistent	Precise	Indirect	Moderate	Increased preterm birth
		AEs – Fetal/Child – Serious, Low birth weight	2 (3)	Moderate	Consistent	Precise	Indirect	Moderate	Increased risk of birth weight, small for gestational age
		AEs – Fetal/Child – Serious, Congenital anomalies	2 (4-7)	Moderate	Inconsistent	Precise	Indirect	Low	Increased major and cardiovascular anomalies
		AEs – Fetal/Child – Serious, Perinatal complications	0					None	None
		AEs – Fetal/Child – Serious, Neurodevelopmental/Behavioral/Social	0					None	None
Intravenous magnesium	Magnesium	AEs – Maternal – Serious, Any	1 (4-5)	Unclear	Unclear	Precise	Indirect	Low	Increased respiratory depression/other respiratory problems, but no increased risk of respiratory arrest or death
		AEs – Maternal – Serious, Cardiovascular	1 (4-5)	Unclear	Unclear	Imprecise	Indirect	Low	Increased hypotension, tachycardia, but no increased risk of increased cardiac arrest or death
		AEs – Maternal – Discontinuation due to AEs	1 (5)	Unclear	Unclear	Precise	Indirect	Low	Increased discontinuation due to AEs
		AEs – Fetal/Child – Serious, Any	0					None	None
		AEs – Fetal/Child – Serious, Spontaneous abortion or elective or induced abortion	0					None	None
		AEs – Fetal/Child – Serious, Stillbirth or fetal death	0					None	None
		AEs – Fetal/Child – Serious, Neonatal or infant death	0					None	None
		AEs – Fetal/Child – Serious, Preterm birth	0					None	None
		AEs – Fetal/Child – Serious, Low birth weight	0					None	None
		AEs – Fetal/Child – Serious, Congenital anomalies	0					None	None
		AEs – Fetal/Child – Serious, Perinatal complications	0					None	None
		AEs – Fetal/Child – Serious, Neurodevelopmental/Behavioral/Social	0					None	None

Class	Drug	Outcome	N SRs (N Studies)	RoB	Consistency	Precision	Directness	SoE	Conclusions
Oral magnesium	Magnesium	AEs – Maternal – Serious, Any	1 (1-5)	Low to moderate	Inconsistent	Precise	Indirect	Low	No increased risk of hospitalization or eclampsia
		AEs – Maternal – Serious, Cardiovascular	0					None	None
		AEs – Maternal – Discontinuation due to AEs	0					None	None
		AEs – Fetal/Child – Serious, Any	0					None	None
		AEs – Fetal/Child – Serious, Spontaneous abortion or elective or induced abortion	1 (6)	Low to moderate	Consistent	Precise	Indirect	Low	No increased risk of spontaneous abortion
		AEs – Fetal/Child – Serious, Stillbirth or fetal death	1 (4)	Low to moderate	Consistent	Precise	Indirect	Low	No increased risk of stillbirth
		AEs – Fetal/Child – Serious, Neonatal or infant death	1 (4)	Low to moderate	Consistent	Precise	Indirect	Low	Increased neonatal death
		AEs – Fetal/Child – Serious, Preterm birth	0					None	None
		AEs – Fetal/Child – Serious, Low birth weight	1 (5)	Low to moderate	Consistent	Precise	Indirect	Low	No increased risk of NICU admission
		AEs – Fetal/Child – Serious, Congenital anomalies	0					None	None
		AEs – Fetal/Child – Serious, Perinatal complications	1 (3)	Low to moderate	Consistent	Precise	Indirect	Low	No increased risk of NICU admission
		AEs – Fetal/Child – Serious, Neurodevelopmental/Behavioral/Social	0					None	None

Abbreviations: AE = adverse effect, NICU = neonatal intensive care unit, NSAID = nonsteroidal antiinflammatory drug

Excluded Studies

Primary Studies

The 355 excluded articles, along with reasons for exclusion, are summarized in Table B-38. The most common reasons for exclusion were that the articles were not primary studies, were not focused on primary headache, or participants were not pregnant (or attempting to be pregnant), postpartum, or breastfeeding.

Table B-38. Excluded primary studies with reasons for exclusion

No.	PMID or Other Identifier	First Author Last Name	Title	Journal	Reason for Exclusion
1	30574176	Afridi	Current concepts in migraine and their relevance to pregnancy	*Obstet Med*	Narrative review
2	20464586	Airola	Non-pharmacological management of migraine during pregnancy	*Neurol Sci*	Narrative review
3	108093518 (CINAHL)	Albrecht	Is triptan therapy as safe option for acute migraine in pregnancy	*Evidence-Based Practice*	Narrative review
4	15108609	Allais	[Migraine during pregnancy and lactation: treatment of the acute attack and non-pharmacological prophylactic strategies]	*Minerva Med*	Narrative review
5	30835003	Allais	Acupuncture treatment of migraine, nausea, and vomiting in pregnancy	*Neurol Sci*	Narrative review
6	15549555	Allais	Picotamide in migraine aura prevention: a pilot study	*Neurol Sci*	Participants not pregnant (or attempting to be pregnant), postpartum, or breastfeeding
7	28759918	Alrasheed	Special Considerations for Primary and Secondary Stroke Prevention in Women	*Semin Neurol*	Participants did not have primary headache or there were no primary headache-specific data
8	25797654	Alsaad	First trimester exposure to topiramate and the risk of oral clefts in the offspring: A systematic review and meta-analysis	*Reprod Toxicol*	SR
9	30020646	Altabakhi	Acetaminophen/Aspirin/Caffeine	*StatPearls*	Narrative review
10	212950	Aminoff	Neurological disorders and pregnancy	*Am J Obstet Gynecol*	Narrative review
11	25776823	Amundsen	Pharmacological treatment of migraine during pregnancy and breastfeeding	*Nat Rev Neurol*	Narrative review
12	27624901	Amundsen	Use of antimigraine medications and information needs during pregnancy and breastfeeding: a cross-sectional study among 401 Norwegian women	*Eur J Clin Pharmacol*	Only addresses predictors/distribution of intervention use
13	30819714	Amundsen	Risk perception, beliefs about medicines and medical adherence among pregnant and breastfeeding women with migraine: findings from a cross-sectional study in Norway	*BMJ Open*	Only addresses predictors/distribution of intervention use

No.	PMID or Other Identifier	First Author Last Name	Title	Journal	Reason for Exclusion
14	29873961	Andrade	Valproate in Pregnancy: Recent Research and Regulatory Responses	*J Clin Psychiatry*	Participants did not have primary headache or there were no primary headache-specific data
15	16478288	Ashkenazi	Hormone-related headache: pathophysiology and treatment	*CNS Drugs*	Narrative review
16	10487510	Aube	Migraine in pregnancy	*Neurology*	Narrative review
17	30091332	Ayer	[Headaches in pregnancy : management in the emergency department]	*Rev Med Suisse*	Narrative review
18	27137420	Balon	Should women of childbearing potential be prescribed valproate? a call to action	*J Clin Psychiatry*	Narrative review
19	17097212	Banhidy	Pregnancy complications and delivery outcomes in pregnant women with severe migraine	*Eur J Obstet Gynecol Reprod Biol*	No intervention of interest
20	12073705	Barnett	Migraine in women	*Practitioner*	Narrative review
21	26996986	Bateman	Persistent opioid use following cesarean delivery: patterns and predictors among opioid-naive women	*Am J Obstet Gynecol*	No intervention of interest
22	25877672	Becker	Acute Migraine Treatment in Adults	*Headache*	Narrative review
23	26252584	Becker	Acute Migraine Treatment	*Continuum (Minneap Minn)*	SR
24	22270537	Bendtsen	Reference programme: diagnosis and treatment of headache disorders and facial pain. Danish Headache Society, 2nd Edition, 2012	*J Headache Pain*	Guideline
25	22612391	Berard	Dihydroergotamine (DHE) use during gestation and the risk of adverse pregnancy outcomes	*Headache*	Participants did not have primary headache or there were no primary headache-specific data
26	21243447	Bigal	Migraine chronification	*Curr Neurol Neurosci Rep*	No intervention of interest
27	31242344	Black	Medication Use and Pain Management in Pregnancy: A Critical Review	*Pain Pract*	SR
28	10637811	Block	[Neurologic diseases and pregnancy]	*Nervenarzt*	Participants did not have primary headache or there were no primary headache-specific data
29	23406160	Blumenfeld	Expert consensus recommendations for the performance of peripheral nerve blocks for headaches--a narrative review	*Headache*	Participants not pregnant (or attempting to be pregnant), postpartum, or breastfeeding
30	104249214 (CINAHL)	Blumenfeld	Expert Consensus Recommendations for the Performance of Peripheral Nerve Blocks for Headaches - A Narrative Review	*Headache: The Journal of Head & Face Pain*	Participants not pregnant (or attempting to be pregnant), postpartum, or breastfeeding
31	28974300	Bolz	The Treatment of Illnesses Arising in Pregnancy	*Dtsch Arztebl Int*	Narrative review
32	27050859	Bordini	Recommendations for the treatment of migraine attacks - a Brazilian consensus	*Arq Neuropsiquiatr*	Participants not pregnant (or attempting to be pregnant), postpartum, or breastfeeding

No.	PMID or Other Identifier	First Author Last Name	Title	Journal	Reason for Exclusion
33	18325295	Brandes	Headache related to pregnancy: management of migraine and migraine headache in pregnancy	*Curr Treat Options Neurol*	Narrative review
34	22868545	Brandes	Migraine in women	*Continuum (Minneap Minn)*	Participants not pregnant (or attempting to be pregnant), postpartum, or breastfeeding
35	26635276	Brin	Pregnancy outcomes following exposure to onabotulinumtoxinA.	*Pharmacoepidemiology and drug safety*	Participants did not have primary headache or there were no primary headache-specific data
36	29270933	Broner	Migraine in Women	*Semin Neurol*	Narrative review
37	CN-00440883 (Cochrane)	Brown Jr	A comparative study of butoconazole vs. miconazole	*Journal of reproductive medicine for the obstetrician and gynecologist*	Participants did not have primary headache or there were no primary headache-specific data
38	24001268	Browne	Maternal butalbital use and selected defects in the national birth defects prevention study	*Headache*	Participants did not have primary headache or there were no primary headache-specific data
39	30470274	Burch	Headache in Pregnancy and the Puerperium	*Neurol Clin*	Narrative review
40	22814005	Burdan	Prenatal tolerability of acetaminophen and other over-the-counter non-selective cyclooxygenase inhibitors	*Pharmacol Rep*	Participants did not have primary headache or there were no primary headache-specific data
41	29595872	Bushman	Headaches Through a Woman's Life	*Obstet Gynecol Surv*	SR
42	28980122	Calhoun	Migraine Treatment in Pregnancy and Lactation	*Curr Pain Headache Rep*	Narrative review
43	20425207	Calhoun	Treatment of cluster headache in pregnancy and lactation	*Curr Pain Headache Rep*	Narrative review
44	16999965	Campos	Intracerebral hemorrhage in postpartum cerebral angiopathy associated with the use of isometheptene	*Int J Gynaecol Obstet*	Participants did not have primary headache or there were no primary headache-specific data
45	22113510	Cardona	Early postpartum headache: case discussions	*Semin Neurol*	Narrative review
46	22993393	Carville	Diagnosis and management of headaches in young people and adults: summary of NICE guidance	*Bmj*	Participants not pregnant (or attempting to be pregnant), postpartum, or breastfeeding
47	20662551	Cassina	Migraine therapy during pregnancy and lactation	*Expert Opin Drug Saf*	SR
48	3632373	Chen	Migraine and other diseases in women of reproductive age. The influence of smoking on observed associations	*Arch Neurol*	Only addresses predictors/distribution of intervention use
49	NCT03951649 (ClinicalTrials.gov)	ClinicalTrials.gov	Acute Headache Treatment in Pregnancy: Occipital Nerve Block vs PO Acetaminophen With Caffeine	-	Study not yet recruiting
50	NCT00632606 (ClinicalTrials.gov)	ClinicalTrials.gov	MgSO4 vs Metoclopramide for Headache in Pregnant Women	-	Study withdrawn

No.	PMID or Other Identifier	First Author Last Name	Title	Journal	Reason for Exclusion
51	NCT01821807 (ClinicalTrials.gov)	ClinicalTrials.gov	Comparison of Two Spinal Needles Regarding Postdural Puncture Headache	-	Participants did not have primary headache or there were no primary headache-specific data
52	NCT02219269 (ClinicalTrials.gov)	ClinicalTrials.gov	A Complex Contraception Registry	-	Participants not pregnant (or attempting to be pregnant), postpartum, or breastfeeding
53	NCT02962427 (ClinicalTrials.gov)	ClinicalTrials.gov	Treatment of Post-dural Puncture Headache in Postpartum Patients: Sphenopalatine Ganglion Block to Epidural Blood Patch.	-	Participants did not have primary headache or there were no primary headache-specific data
54	NCT03185130 (ClinicalTrials.gov)	ClinicalTrials.gov	Intravenous Fluids in Benign Headaches Trail	-	Participants not pregnant (or attempting to be pregnant), postpartum, or breastfeeding
55	NCT02549300 (ClinicalTrials.gov)	ClinicalTrials.gov	The Effects of Connective Tissue Massage and Lifestyle Modifications in Adolescents Tension Type Headache	-	Participants not pregnant (or attempting to be pregnant), postpartum, or breastfeeding
56	NCT04148846 (ClinicalTrials.gov)	ClinicalTrials.gov	Sphenopalatine Blockade Versus Clinical Treatment	-	Participants did not have primary headache or there were no primary headache-specific data
57	NCT02017444 (ClinicalTrials.gov)	ClinicalTrials.gov	Safety and Effectiveness of 11b-Hydroxysteroid Dehydrogenase Type 1 Inhibitor (AZD4017) to Treat Idiopathic Intracranial Hypertension.	-	Participants not pregnant (or attempting to be pregnant), postpartum, or breastfeeding
58	NCT03389945 (ClinicalTrials.gov)	ClinicalTrials.gov	Different Spinal Needles Sizes and Dural Puncture Epidural For Labor Analgesia	-	Participants did not have primary headache or there were no primary headache-specific data
59	NCT03831659 (ClinicalTrials.gov)	ClinicalTrials.gov	Migraine and Infertility	-	Participants not pregnant (or attempting to be pregnant), postpartum, or breastfeeding
60	NCT01803984 (ClinicalTrials.gov)	ClinicalTrials.gov	MIBRAIN - Migraine and the Brain: Consequences, Causes, and Vascular Interaction	-	Participants not pregnant (or attempting to be pregnant), postpartum, or breastfeeding
61	NCT03606707 (ClinicalTrials.gov)	ClinicalTrials.gov	Efficacy of Fluoroscopic Guided Atlantoaxial Joint Injection on Head and Neck Pain and Sleep Quality in RA Patients	-	Participants did not have primary headache or there were no primary headache-specific data
62	NCT03767803 (ClinicalTrials.gov)	ClinicalTrials.gov	Collection of Whole Blood Samples for the Evaluation of Preeclampsia (Pre-E) Biomarkers From Pregnant Women	-	Participants did not have primary headache or there were no primary headache-specific data
63	NCT02122419 (ClinicalTrials.gov)	ClinicalTrials.gov	The Effect of Patient Position on Postdural Puncture Headache	-	Participants did not have primary headache or there were no primary headache-specific data
64	NCT02999919 (ClinicalTrials.gov)	ClinicalTrials.gov	Body Mass Index and Post-dural Puncture Headache	-	Participants did not have primary headache or there were no primary headache-specific data
65	NCT01194661	ClinicalTrials.gov	Neural Dynamics and Connectivity in Response Inhibition and Traumatic Brain Injury	-	Participants did not have primary headache or there were no primary headache-specific data
66	30290741	Coad	Acute medical problems in pregnancy	*Br J Hosp Med (Lond)*	No intervention of interest

No.	PMID or Other Identifier	First Author Last Name	Title	Journal	Reason for Exclusion
67	11412202	Cohen	A new interest in an old remedy for headache and backache for our obstetric patients: a sphenopalatine ganglion block	*Anaesthesia*	Participants did not have primary headache or there were no primary headache-specific data
68	1540370	Cohen	Grand mal seizure in a postpartum patient following intravenous infusion of caffeine sodium benzoate to treat persistent headache	*J Clin Anesth*	Participants did not have primary headache or there were no primary headache-specific data
69	0	Collin-Lavesque	Infant Exposure to Methylphenidate and Duloxetine during Lactation	*Breastfeeding Medicine*	Participants did not have primary headache or there were no primary headache-specific data
70	23857445	Coluzzi	Chronic pain management in pregnancy and lactation	*Minerva Anestesiol*	Narrative review
71	16266607	Conner	Clinical Inquiries. What are the best therapies for acute migraine in pregnancy?	*J Fam Pract*	Narrative review
72	16670039	Conner	Clinical inquiries. How can you prevent migraines during pregnancy?	*J Fam Pract*	Narrative review
73	20930632	Contag	Contemporary management of migrainous disorders in pregnancy	*Curr Opin Obstet Gynecol*	Narrative review
74	19597515	Contag	Migraine during pregnancy: is it more than a headache?	*Nat Rev Neurol*	Narrative review
75	2871927	Dalessio	Classification and treatment of headache during pregnancy	*Clin Neuropharmacol*	Narrative review
76	No PubMed ID	Damase-Michel	What do pregnant women know about non-steroidal anti-inflammatory drugs?	*Pharmacoepidemiology and Drug Safety*	Participants did not have primary headache or there were no primary headache-specific data
77	6440873	Damasio	Drug management of adult vascular headaches (migraine and cluster headache): Part II--Prevention and attacks	*Iowa Med*	Participants not pregnant (or attempting to be pregnant), postpartum, or breastfeeding
78	25217187	Davanzo	Breastfeeding and migraine drugs	*Eur J Clin Pharmacol*	SR
79	2134841	Day	Migraine and other vascular headaches. An overview of diagnosis and management	*Aust Fam Physician*	Narrative review
80	23446156	de Wit	[Neonatal abstinence syndrome after maternal use of tramadol]	*Ned Tijdschr Geneeskd*	Participants did not have primary headache or there were no primary headache-specific data
81	No PubMed ID	Deck	Congenital malformations in infants exposed to antiepileptic medications in utero at Boston Medical Center from 2003 to 2010	*Epilepsy and Behavior*	Participants did not have primary headache or there were no primary headache-specific data
82	11251702	Demirkaya	Efficacy of intravenous magnesium sulfate in the treatment of acute migraine attacks	*Headache*	Participants did not have primary headache or there were no primary headache-specific data
83	28561915	Deneris	Migraines in Women: Current Evidence for Management of Episodic and Chronic Migraines	*J Midwifery Womens Health*	Narrative review
84	22419343	Derry	Caffeine as an analgesic adjuvant for acute pain in adults	*Cochrane Database Syst Rev*	Participants not pregnant (or attempting to be pregnant), postpartum, or breastfeeding
85	25502052	Derry	Caffeine as an analgesic adjuvant for acute pain in adults	*Cochrane Database Syst Rev*	Participants not pregnant (or attempting to be pregnant), postpartum, or breastfeeding

No.	PMID or Other Identifier	First Author Last Name	Title	Journal	Reason for Exclusion
86	21530095	Dhillon	A new horizon into the pathobiology, etiology and treatment of migraine	*Med Hypotheses*	Narrative review
87	4821163	Diamond	The diagnosis and treatment of headache	*Med Trial Tech Q*	Narrative review
88	0	Diamond	Headache treatment during lactation	*Consultant*	Participants not pregnant (or attempting to be pregnant), postpartum, or breastfeeding
89	18336060	Diav-Citrin	Pregnancy outcome after in utero exposure to valproate : evidence of dose relationship in teratogenic effect	*CNS Drugs*	Participants did not have primary headache or there were no primary headache-specific data
90	11772289	Diener	Advances in pharmacological treatment of migraine	*Expert Opin Investig Drugs*	Narrative review
91	23563877	Digre	Headaches during pregnancy	*Clin Obstet Gynecol*	Narrative review
92	22518165	Dixit	Headache in pregnancy: a nuisance or a new sense?	*Obstet Gynecol Int*	Narrative review
93	20553334	Dodick	Transcranial magnetic stimulation for migraine: a safety review	*Headache*	SR
94	19022842	Duncan	Diagnosis and management of headache in adults: summary of SIGN guideline	*Bmj*	Participants not pregnant (or attempting to be pregnant), postpartum, or breastfeeding
95	20547518	Duong	Safety of triptans for migraine headaches during pregnancy and breastfeeding	*Can Fam Physician*	Narrative review
96	30074315	Ehi	Migraine management in pregnancy	*Clin Exp Obstet Gynecol*	Narrative review
97	27030834	Ekusheva	[Current approaches to treatment of migraine during pregnancy]	*Zh Nevrol Psikhiatr Im S S Korsakova*	Narrative review
98	23643373	Elder	Acupuncture and migraine prophylaxis, probiotics and C. Difficile-associated diarrhea, preventive group counseling and postpartum depression, black cohosh and menopausal symptoms, deep needling electroacupuncture and trigeminal neuralgia	*Explore (NY)*	Narrative review
99	10838359	Eldridge	Monitoring birth outcomes in the Sumatriptan Pregnancy Registry	*Prim Care Update Ob Gyns*	Participants did not have primary headache or there were no primary headache-specific data
100	CN-01803902	Euctr	A Multicenter Study Evaluating the Efficacy and Safety of BOTOX¬Æ (Botulinum Toxin Type A) Purified Neurotoxin Complex as Headache Prophylaxis in Migraine Patients with 15 or More Headache Days per 4-Week Period in a 24-Week, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Phase Followed by a 32-Week Open-Label Extension Phase	*Http://www.who.int/trialsearch/trial2.aspx?Trialid=euctr2005-004637-17-de*	Participants not pregnant (or attempting to be pregnant), postpartum, or breastfeeding
101	18349309	Evans	Use of 5-HT1 agonists in pregnancy	*Ann Pharmacother*	SR

No.	PMID or Other Identifier	First Author Last Name	Title	Journal	Reason for Exclusion
102	18806984	Evers	[Alternatives to beta blockers in preventive migraine treatment]	*Nervenarzt*	Narrative review
103	29728203	Faubion	Migraine Throughout the Female Reproductive Life Cycle	*Mayo Clin Proc*	Narrative review
104	6629764	Featherstone	Fetal demise in a migraine patient on propranolol	*Headache*	Participants did not have primary headache or there were no primary headache-specific data
105	23350149	Fedorets	[Headache in pregnant women]	*Lik Sprava*	Narrative review
106	8336286	Feller	Headaches during pregnancy: diagnosis and management	*J Perinat Neonatal Nurs*	Narrative review
107	7551126	Ferrari	Acute treatment of migraine attacks	*Curr Opin Neurol*	Narrative review
108	25822385	Flake	Practical selection of antiemetics in the ambulatory setting	*Am Fam Physician*	No intervention of interest
109	26614723	Forde	Managing Chronic Headache Disorders	*Med Clin North Am*	Participants not pregnant (or attempting to be pregnant), postpartum, or breastfeeding
110	24934057	Forderreuther	[Treatment of migraine in pregnancy, in patients with comorbidities and in elderly people]	*MMW Fortschr Med*	Narrative review
111	15330843	Fox	Revised estimates for probability of successful outcome of pregnancy after sumatriptan exposure	*Headache*	Narrative review
112	12005279	Fox	Evidence-based assessment of pregnancy outcome after sumatriptan exposure	*Headache*	Narrative review
113	15962998	Fox	Migraine during pregnancy: options for therapy	*CNS Drugs*	Narrative review
114	106081110 (CINAHL)	Fox	Revised estimates for probability of successful outcome of pregnancy after sumatriptan exposure...Headache. 2001 Apr;41(4):351-6	*Headache: The Journal of Head & Face Pain*	Participants did not have primary headache or there were no primary headache-specific data
115	11135036	Fox	Sumatriptan and pregnancy outcome	*Headache*	Participants did not have primary headache or there were no primary headache-specific data
116	15330822	Friedman	Local inflammation as a mediator of migraine and tension-type headache	*Headache*	Participants not pregnant (or attempting to be pregnant), postpartum, or breastfeeding
117	1319244	Fullerton	Sumatriptan: a selective 5-hydroxytryptamine receptor agonist for the acute treatment of migraine	*Ann Pharmacother*	Participants not pregnant (or attempting to be pregnant), postpartum, or breastfeeding
118	24475654	Gaul	[Aspirin for migraine in pregnancy. This recommendation seems questionable]	*MMW Fortschr Med*	Narrative review
119	15316764	Gendolla	[Difficult decisions: headache treatment in pregnancy and childhood]	*Schmerz*	Narrative review
120	24571806	Gentile	Risks of neurobehavioral teratogenicity associated with prenatal exposure to valproate monotherapy: a systematic review with regulatory repercussions	*CNS Spectr*	Participants did not have primary headache or there were no primary headache-specific data

No.	PMID or Other Identifier	First Author Last Name	Title	Journal	Reason for Exclusion
121	21302868	Gilmore	Treatment of acute migraine headache	*Am Fam Physician*	Narrative review
122	9421548	Gilmore	Medication use during pregnancy for neurologic conditions	*Neurol Clin*	Participants did not have primary headache or there were no primary headache-specific data
123	19125883	Giraud	Cluster headache during pregnancy: case report and literature review	*Headache*	No intervention of interest
124	15095535	Gladstone	Migraine in special populations. Treatment strategies for children and adolescents, pregnant women, and the elderly	*Postgrad Med*	Participants not pregnant (or attempting to be pregnant), postpartum, or breastfeeding
125	18583683	Goadsby	Migraine in pregnancy	*Bmj*	Narrative review
126	20104718	Gobel	[Migraine therapy in general practice 2006]	*MMW Fortschr Med*	Participants not pregnant (or attempting to be pregnant), postpartum, or breastfeeding
127	14579489	Gobel	[Treatment of migraine: analgetic plus antiemetic or tryptan]	*MMW Fortschr Med*	Participants not pregnant (or attempting to be pregnant), postpartum, or breastfeeding
128	6133267	Golightly	Pindolol: a review of its pharmacology, pharmacokinetics, clinical uses, and adverse effects	*Pharmacotherapy*	Narrative review
129	31047730	Gonzalez-Garcia	Headache: pregnancy and breastfeeding Recommendations of the Spanish Society of Neurology's Headache Study Group	*Neurologia*	Guideline
130	109666935 (CINAHL)	Govindappagari	Peripheral nerve blocks in pregnant patients with headache	*Obstetrics & Gynecology*	No intervention of interest
131	24986563	Grant	Transnasal topical sphenopalatine ganglion block to treat tension headache in a pregnant patient	*Int J Obstet Anesth*	Participants did not have primary headache or there were no primary headache-specific data
132	16647669	Graves	Management of migraine headaches	*J Midwifery Womens Health*	Narrative review
133	22724387	Green	Utilization of topiramate during pregnancy and risk of birth defects	*Headache*	No intervention of interest
134	28101987	Grossman	Delivery Outcomes of Patients with Acute Migraine in Pregnancy: A Retrospective Study	*Headache*	No intervention of interest
135	CN-00979620 (Cochrane)	Guerreiro da Silva	Corrigendum to Acupuncture for tension-type headache in pregnancy: a prospective, randomized, controlled study	*European journal of integrative medicine*	Erratum
136	11387882	Gutierrez Moctezuma	[Migraine in pregnancy]	*Ginecol Obstet Mex*	Narrative review
137	909023	Habib	Effects on the neonate of propranolol administered during pregnancy.	*The Journal of pediatrics*	Participants did not have primary headache or there were no primary headache-specific data
138	17160116	Hagen	[Treatment of migraine during pregnancy and breast feeding]	*Tidsskr Nor Laegeforen*	Narrative review

No.	PMID or Other Identifier	First Author Last Name	Title	Journal	Reason for Exclusion
139	20407056	Haghshenas	High-flow oxygen for cluster headache	*Jama*	Participants not pregnant (or attempting to be pregnant), postpartum, or breastfeeding
140	12068456	Hainline	Migraine and other headache conditions	*Adv Neurol*	Narrative review
141	7990784	Hainline	Headache	*Neurol Clin*	Narrative review
142	30403400	Hamilton	Migraine Treatment in Pregnant Women Presenting to Acute Care: A Retrospective Observational Study	*Headache*	Only addresses predictors/distribution of intervention use
143	29292614	Hammerman	[PSYCHO-MEDICAL ASPECTS OF PRIMARY HEADACHES]	*Harefuah*	Narrative review
144	19910	Hardebo	Reduced sensitivity to alpha- and beta-adrenergic receptor agonists of intra- and extracranial vessels during pregnancy. Relevance to migraine	*Acta Neurol Scand Suppl*	Narrative review
145	28705177	Harris	Patterns and predictors of analgesic use in pregnancy: a longitudinal drug utilization study with special focus on women with migraine	*BMC Pregnancy Childbirth*	Only addresses predictors/distribution of intervention use
146	24708567	Hashmi	Low-pressure headache presenting in early pregnancy with dramatic response to glucocorticoids: a case report.	*Journal of medical case reports*	Participants did not have primary headache or there were no primary headache-specific data
147	No PubMed ID	Hernandez-Diaz	Comparative safety of antiepileptic drugs during pregnancy	*Neurology*	Participants did not have primary headache or there were no primary headache-specific data
148	15316107	Hilaire	Treatment of migraine headaches with sumatriptan in pregnancy	*Ann Pharmacother*	SR
149	20518610	Hill	Teratogenic effects of antiepileptic drugs	*Expert Rev Neurother*	Narrative review
150	202428	Hopkins	Neurological disorders	*Clin Obstet Gynaecol*	Narrative review
151	9679377	Horne	Treating headaches. A conceptual framework	*Aust Fam Physician*	Participants not pregnant (or attempting to be pregnant), postpartum, or breastfeeding
152	23154716	Hoshiyama	Postpartum migraines: a long-term prospective study	*Intern Med*	Only addresses predictors/distribution of intervention use
153	23983844	Hosley	Acute neurological issues in pregnancy and the peripartum	*Neurohospitalist*	Narrative review
154	29250761	Hsu	Medical Treatment Guidelines for Acute Migraine Attacks	*Acta Neurol Taiwan*	Participants not pregnant (or attempting to be pregnant), postpartum, or breastfeeding
155	28752512	Huang	Medical Treatment Guidelines for Preventive Treatment of Migraine	*Acta Neurol Taiwan*	Participants not pregnant (or attempting to be pregnant), postpartum, or breastfeeding
156	3574535	Huisjes	[Drugs in migraine]	*Ned Tijdschr Geneeskd*	No intervention of interest
157	27807736	Hultzsch	[Analgesic drugs during pregnancy]	*Schmerz*	Narrative review

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158	18645165	Hunt	Topiramate in pregnancy: preliminary experience from the UK Epilepsy and Pregnancy Register	*Neurology*	Participants did not have primary headache or there were no primary headache-specific data
159	16111449	Hunt	Safety of antiepileptic drugs during pregnancy	*Expert Opin Drug Saf*	Participants did not have primary headache or there were no primary headache-specific data
160	23465038	Hutchinson	Use of common migraine treatments in breast-feeding women: a summary of recommendations	*Headache*	SR
161	CN-01754801 (Cochrane)	Jahanfar	Modifications of maternal caffeine intake for improving pregnancy outcome	*Cochrane database of systematic reviews (Online)*	Participants did not have primary headache or there were no primary headache-specific data
162	20025128	Janszky	[Role of zonisamid in treating epilepsy, Parkinson disorders and other neurological diseases]	*Ideggyogy Sz*	Narrative review
163	29371217	Jarvis	Managing migraine in pregnancy	*Bmj*	Narrative review
164	15172516	Johnson	Headache in women	*Prim Care*	Narrative review
165	19170693	Jurgens	Treatment of cluster headache in pregnancy and lactation	*Cephalalgia*	Narrative review
166	27154242	Kallen	Ongoing Pharmacological Management of Chronic Pain in Pregnancy	*Drugs*	Narrative review
167	19810997	Kanner	Valproate: a practical review of its uses in neurological and psychiatric disorders	*Expert Rev Neurother*	Narrative review
168	15557546	Kaplan	Reproductive health effects and teratogenicity of antiepileptic drugs	*Neurology*	Narrative review
169	31089104	Karpova	[Migraine in women: clinical and therapeutical aspects]	*Zh Nevrol Psikhiatr Im S S Korsakova*	Narrative review
170	23972191	Kennis	Diagnosis and management of headaches in young people and adults: NICE guideline	*Br J Gen Pract*	Participants not pregnant (or attempting to be pregnant), postpartum, or breastfeeding
171	23516693	Kevat	Neurological diseases in pregnancy	*J R Coll Physicians Edinb*	Narrative review
172	3804145	Kromer	[Drug treatment of pain. 4: Headache and migraine, drug interactions, contra-indications, use of analgesics in pregnancy and lactation]	*Fortschr Med*	Narrative review
173	20415949	Kuczkowski	The potential dangers of caffeine in pregnancy	*Acta Anaesthesiol Scand*	No intervention of interest
174	20456148	Kurth	Commentary: Triptan use during pregnancy: a safe choice?	*Headache*	Narrative review
175	21442333	Kvisvik	Headache and migraine during pregnancy and puerperium: the MIGRA-study	*J Headache Pain*	No intervention of interest
176	2867457	Lance	The pharmacotherapy of migraine	*Med J Aust*	Narrative review

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177	5912494	Lance	Some clinical aspects of migraine. A prospective survey of 500 patients	*Arch Neurol*	Participants did not have primary headache or there were no primary headache-specific data
178	15172517	Landy	Challenging or difficult headache patients	*Prim Care*	Narrative review
179	10194980	Landy	Divalproex sodium--review of prophylactic migraine efficacy, safety and dosage, with recommendations	*Tenn Med*	Narrative review
180	104982660 (CINAHL)	Landy	[Commentary on] Chen HM, Chen SF, Chen YH, Lin HC. Increased risk of adverse pregnancy outcomes for women with migraines: A nationwide population-based study. Cephalalgia. 2010; 30:433-438	*Headache: The Journal of Head & Face Pain*	No intervention of interest
181	23246266	Lanteri-Minet	[Guidelines for the diagnosis and management of migraine in adults and children]	*Rev Neurol (Paris)*	Guideline
182	6366275	Laska	Caffeine as an analgesic adjuvant	*Jama*	Narrative review
183	16628532	Lay	Special considerations in the treatment of migraine in women	*Semin Neurol*	Participants not pregnant (or attempting to be pregnant), postpartum, or breastfeeding
184	9075493	Lewis	Tramadol: a new centrally acting analgesic	*Am J Health Syst Pharm*	Narrative review
185	2872511	Lindhout	In-utero exposure to valproate and neural tube defects.	*Lancet (London, England)*	Participants did not have primary headache or there were no primary headache-specific data
186	108080885 (CINAHL)	Lloyd	Acupuncture during pregnancy for daily frontal headaches	*Journal of the Acupuncture Association of Chartered Physiotherapists*	Unable to retrieve article
187	108113640 (CINAHL)	Lock	Acupuncture and physiotherapy for chronic tension-type headache in a pregnant patient	*Journal of the Acupuncture Association of Chartered Physiotherapists*	Unable to retrieve article
188	17940921	Loder	Migraine in pregnancy	*Semin Neurol*	Narrative review
189	12467489	Loder	Safety of sumatriptan in pregnancy: a review of the data so far	*CNS Drugs*	SR
190	16792985	Lopez	[Safety of antimigraine drugs during pregnancy]	*Med Clin (Barc)*	Narrative review
191	11800529	Lowe	Drugs in pregnancy. Anticonvulsants and drugs for neurological disease	*Best Pract Res Clin Obstet Gynaecol*	Narrative review
192	26865183	Lucas	The Pharmacology of Indomethacin	*Headache*	Narrative review
193	19728967	Lucas	Medication use in the treatment of migraine during pregnancy and lactation	*Curr Pain Headache Rep*	Narrative review

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194	31241597	Lucas	Migraine and Other Headache Disorders: ACOG Clinical Updates In Women's Health Care Primary and Preventive Care Review Summary Volume XVIII, Number 4	*Obstet Gynecol*	Guideline
195	24867839	MacGregor	Migraine in pregnancy and lactation	*Neurol Sci*	Narrative review
196	24492815	Macgregor	Headache in pregnancy	*Continuum (Minneap Minn)*	Narrative review
197	22840792	MacGregor	Headache in pregnancy	*Neurol Clin*	Narrative review
198	17407673	MacGregor	Migraine in pregnancy and lactation: a clinical review	*J Fam Plann Reprod Health Care*	SR
199	No PubMed ID	Magee	The safety of calcium channel blockers in human pregnancy: A prospective, multicenter cohort study	*American Journal of Obstetrics and Gynecology*	Participants did not have primary headache or there were no primary headache-specific data
200	27300484	Maggioni	Triptans or Not? This Is the Question. Management of Migraine Attacks During Pregnancy	*Headache*	Narrative review
201	9399007	Maggioni	Headache during pregnancy	*Cephalalgia*	No intervention of interest
202	12061464	Mannix	Women and headache: a treatment approach based on life stages	*Cleve Clin J Med*	Narrative review
203	25644494	Marchenko	Pregnancy outcome following prenatal exposure to triptan medications: a meta-analysis	*Headache*	SR
204	11934341	Marcus	Pregnancy and chronic headache	*Expert Opin Pharmacother*	Narrative review
205	10358852	Marcus	Focus on primary care diagnosis and management of headache in women	*Obstet Gynecol Surv*	Narrative review
206	17288886	Marcus	Headache in pregnancy	*Curr Treat Options Neurol*	Narrative review
207	12828878	Marcus	Headache in pregnancy	*Curr Pain Headache Rep*	Narrative review
208	18345969	Marcus	Managing headache during pregnancy and lactation	*Expert Rev Neurother*	Narrative review
209	11252843	Marcus	Management of headache in women	*J Gend Specif Med*	Participants not pregnant (or attempting to be pregnant), postpartum, or breastfeeding
210	No PubMed ID	Margulis	Use of topiramate in pregnancy and risk of oral clefts	*American Journal of Obstetrics and Gynecology*	Participants did not have primary headache or there were no primary headache-specific data
211	25096056	Marmura	Safety of topiramate for treating migraines	*Expert Opin Drug Saf*	Narrative review
212	22012659	Marmura	Use of dopamine antagonists in treatment of migraine	*Curr Treat Options Neurol*	Narrative review
213	15725852	Martin	Approach to the pregnant patient with headache	*Clin Obstet Gynecol*	Narrative review
214	927751	Massey	Migraine during pregnancy	*Obstet Gynecol Surv*	Narrative review
215	11961994	Matharu	Understanding migraine in women	*Practitioner*	Narrative review

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216	25649095	Mehta	Headaches in the pregnant patient	*R I Med J (2013)*	Narrative review
217	18332840	Menon	Headache and pregnancy	*Neurologist*	Narrative review
218	15423706	Merritt	The diagnosis and management of patients with chronic recurrent headache	*New Orleans Med Surg J*	Participants did not have primary headache or there were no primary headache-specific data
219	26305473	Migliore	Prenatal Paracetamol Exposure and Wheezing in Childhood: Causation or Confounding?	*PLoS One*	Participants did not have primary headache or there were no primary headache-specific data
220	8525351	Miles	Treatment of migraine during pregnancy and lactation	*S D J Med*	Participants did not have primary headache or there were no primary headache-specific data
221	4914209	Miller	Propoxyphene hydrochloride. A critical review	*Jama*	Narrative review
222	42893	Milton-Thompson	Anti-nauseant drugs	*Practitioner*	Narrative review
223	24692316	Mines	Topiramate use in pregnancy and the birth prevalence of oral clefts	*Pharmacoepidemiol Drug Saf*	Participants did not have primary headache or there were no primary headache-specific data
224	21535375	Moloney	Migraine headaches: diagnosis and management	*J Midwifery Womens Health*	Narrative review
225	10703023	Moloney	Caring for the woman with migraine headaches	*Nurse Pract*	Narrative review
226	16361610	Morgan	Botulinum toxin A during pregnancy: a survey of treating physicians.	*Journal of neurology, neurosurgery, and psychiatry*	Participants did not have primary headache or there were no primary headache-specific data
227	12534326	Nappi	Tolerability of the triptans: clinical implications	*Drug Saf*	Narrative review
228	21465113	Nappi	Headaches during pregnancy	*Curr Pain Headache Rep*	No intervention of interest
229	29563831	Negro	Serotonin receptor agonists in the acute treatment of migraine: a review on their therapeutic potential	*J Pain Res*	Narrative review
230	29052046	Negro	Headache and pregnancy: a systematic review	*J Headache Pain*	SR
231	20132339	Nezvalova-Henriksen	Triptan exposure during pregnancy and the risk of major congenital malformations and adverse pregnancy outcomes: results from the Norwegian Mother and Child Cohort Study	*Headache*	Duplicate
232	No PubMed ID	Nezvalova-Henriksen	Effects of ibuprofen, diclofenac, naproxen, and piroxicam on the course of pregnancy and pregnancy outcome: A prospective cohort study	*BJOG: An International Journal of Obstetrics and Gynaecology*	Participants did not have primary headache or there were no primary headache-specific data
233	19911464	Nezvalova-Henriksen	Maternal characteristics and migraine pharmacotherapy during pregnancy: cross-sectional analysis of data from a large cohort study	*Cephalalgia*	Only addresses predictors/distribution of intervention use

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234	19895705	Nino-Maldonado	Efficacy and tolerability of intravenous methylergonovine in migraine female patients attending the emergency department: a pilot open-label study	*Head Face Med*	No intervention of interest
235	8459173	None listed	[Diagnosis and therapy in patients with headache (discussion)]	*Nihon Naika Gakkai Zasshi*	Narrative review
236	24662840	None listed	In brief: warning against use of valproate for migraine prevention during pregnancy	*Med Lett Drugs Ther*	Narrative review
237	30681655	None listed	Fremanezumab (Ajovy) and galcanezumab (Emgality) for migraine prevention	*Med Lett Drugs Ther*	Narrative review
238	30000371	None listed	Dichloralphenazone	*Drugs and Lactation Database (LactMed)*	Narrative review
239	21304447	None listed	Drugs for migraine	*Treat Guidel Med Lett*	Narrative review
240	25964975	None listed	Triptans during pregnancy	*Prescrire Int*	Narrative review
241	28170366	None listed	Drugs for migraine	*Med Lett Drugs Ther*	Narrative review
242	25802922	None listed	Prevention of migraine attacks. First-choice treatments	*Prescrire Int*	Narrative review
243	26768660	None listed	Errata...Marchenko, A, Etwel F, Olutunfese O,et al. Pregnancy Outcome Following Prenatal Exposure to Triptan Medications: A Meta-Analysis. Headache 2015;55:490-501	*Headache: The Journal of Head & Face Pain*	SR
244	18686655	None listed	[Treatment guidelines for preventive treatment of migraine]	*Acta Neurol Taiwan*	Guideline
245	107171571 (CINAHL)	None listed	Early pregnancy sumatriptan exposure	*Nurses' Drug Alert*	Unable to retrieve article
246	108081307 (CINAHL)	None listed	NICE develops its first clinical guideline on headaches	*Guidelines in Practice*	Unable to retrieve article
247	30000045	None listed	Ibuprofen	*Drugs and Lactation Database (LactMed)*	Participants did not have primary headache or there were no primary headache-specific data
248	30000253	None listed	Acetaminophen	*Drugs and Lactation Database (LactMed)*	Participants did not have primary headache or there were no primary headache-specific data
249	29913472	None listed	Erenumab (Aimovig) for migraine prevention	*Med Lett Drugs Ther*	Participants not pregnant (or attempting to be pregnant), postpartum, or breastfeeding
250	18220021	None listed	[Treatment guidelines for acute migraine attacks]	*Acta Neurol Taiwan*	Participants not pregnant (or attempting to be pregnant), postpartum, or breastfeeding
251	25964974	None listed	Migraine and pregnancy. Choice of treatment	*Prescrire Int*	Only addresses predictors/distribution of intervention use

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252	15863557	None listed	Topiramate (topamax) for prevention of migraine	*Obstet Gynecol*	Participants not pregnant (or attempting to be pregnant), postpartum, or breastfeeding
253	25964970	None listed	Triptans: beware of vasoconstrictive effects	*Prescrire Int*	Participants did not have primary headache or there were no primary headache-specific data
254	No PubMed ID	Nordeng	Medication safety in pregnancy ‚Äì Results from the MoBa study	*Norsk Epidemiologi*	Narrative review
255	26638119	Noruzzadeh	Memantine for Prophylactic Treatment of Migraine Without Aura: A Randomized Double-Blind Placebo-Controlled Study	*Headache*	Participants not pregnant (or attempting to be pregnant), postpartum, or breastfeeding
256	28473606	O'Neal	Headaches complicating pregnancy and the postpartum period	*Pract Neurol*	Narrative review
257	11251709	Olesen	Sumatriptan: what do we know about fetal risks?	*Headache*	Participants did not have primary headache or there were no primary headache-specific data
258	17598713	Ostendorf	[Acupuncture for pregnancy support]	*Versicherungs medizin*	Narrative review
259	30291521	Parikh	Unique Populations with Episodic Migraine: Pregnant and Lactating Women	*Curr Pain Headache Rep*	Narrative review
260	20309829	Pascual-Gomez	[Migraine and gestation: a complex relationship]	*Rev Neurol*	Narrative review
261	10563361	Pastore	Risk of stillbirth from medications, illnesses and medical procedures	*Paediatr Perinat Epidemiol*	Participants did not have primary headache or there were no primary headache-specific data
262	8610754	Paulson	Headaches in women, including women who are pregnant	*Am J Obstet Gynecol*	Narrative review
263	22828113	Pearce	Headache and neurological disease in pregnancy	*Clin Obstet Gynecol*	Narrative review
264	30477838	Peng	Utilization of complementary and alternative medicine and conventional medicine for headache or migraine during pregnancy: A cross-sectional survey of 1,835 pregnant women	*Complement Ther Med*	Only addresses predictors/distribution of intervention use
265	10904600	Pfaffenrath	[Migraine therapy in pregnancy. Paracetamol leads in acute therapy]	*MMW Fortschr Med*	Narrative review
266	9825951	Pfaffenrath	Migraine in pregnancy: what are the safest treatment options?	*Drug Saf*	Narrative review
267	18747391	Pfeffer	Migraine: the pill and pregnancy	*West J Med*	Only addresses predictors/distribution of intervention use
268	9644438	Pintz	Prescribing medication in pregnancy	*Lippincotts Prim Care Pract*	Narrative review
269	17724970	Pollmann	[Acute headaches--when to treat immediately, when to wait]	*MMW Fortschr Med*	Narrative review
270	22683887	Pringsheim	Canadian Headache Society guideline for migraine prophylaxis	*Can J Neurol Sci*	SR and guideline
271	6425308	Proctor	Biofeedback pain control	*Hosp Pract (Off Ed)*	Narrative review

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272	1337766	Prusinski	[Sumatriptan and its use in treatment of migraine and cluster headaches]	*Neurol Neurochir Pol*	Narrative review
273	29802634	Raggi	Behavioral Approaches for Primary Headaches: Recent Advances	*Headache*	SR
274	18368683	Rana-Martinez	[Migraine in females]	*Rev Neurol*	Narrative review
275	9356103	Rathmell	Management of nonobstetric pain during pregnancy and lactation	*Anesth Analg*	Narrative review
276	30880363	Rau	Other Preventive Anti-Migraine Treatments: ACE Inhibitors, ARBs, Calcium Channel Blockers, Serotonin Antagonists, and NMDA Receptor Antagonists	*Curr Treat Options Neurol*	Narrative review
277	No PubMed ID	Ravishankar	Guidelines on the diagnosis and the current management of headache and related disorders	*Annals of Indian Academy of Neurology*	Participants not pregnant (or attempting to be pregnant), postpartum, or breastfeeding
278	3752178	Rayburn	Drug prescribing for chronic medical disorders during pregnancy: an overview	*Am J Obstet Gynecol*	Narrative review
279	4147459	Regli	[Treatment of vascular headaches]	*Dtsch Med Wochenschr*	Narrative review
280	10649172	Reiff-Eldridge	Monitoring pregnancy outcomes after prenatal drug exposure through prospective pregnancy registries: a pharmaceutical company commitment	*Am J Obstet Gynecol*	Participants did not have primary headache or there were no primary headache-specific data
281	3143135	Reik	Headaches in pregnancy	*Semin Neurol*	Narrative review
282	18045126	Reynolds	Valproate and neuroendocrine changes in relation to women treated for epilepsy and bipolar disorder: a review	*Curr Med Chem*	Participants did not have primary headache or there were no primary headache-specific data
283	8039469	Richens	Safety of lamotrigine	*Epilepsia*	Narrative review
284	30074551	Robbins	Headache in Pregnancy	*Continuum (Minneap Minn)*	Narrative review
285	23921799	Roberto	Triptans and serious adverse vascular events: data mining of the FDA Adverse Effect Reporting System database	*Cephalalgia*	Participants did not have primary headache or there were no primary headache-specific data
286	20352590	Robertson	Management of migraine headache in the emergency department	*Semin Neurol*	Participants not pregnant (or attempting to be pregnant), postpartum, or breastfeeding
287	8003593	Roquer	[Treatment of migraine]	*Aten Primaria*	Narrative review
288	18973735	Rosen	Psychological issues in the evaluation and treatment of tension-type headache	*Curr Pain Headache Rep*	Participants not pregnant (or attempting to be pregnant), postpartum, or breastfeeding
289	23054980	Rosen	Psychological issues in the evaluation and treatment of tension-type headache	*Curr Pain Headache Rep*	Participants not pregnant (or attempting to be pregnant), postpartum, or breastfeeding
290	7091205	Rosene	Cerebral ischemia associated with parenteral terbutaline use in pregnant migraine patients	*Am J Obstet Gynecol*	No intervention of interest

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291	22482825	Rozen	Female cluster headache in the United States of America: what are the gender differences? Results from the United States Cluster Headache Survey	*J Neurol Sci*	No intervention of interest
292	25890621	Rubin	Migraines in women	*Dis Mon*	Narrative review
293	105348935 (CINAHL)	Rubin	Case studies. Good medication choices for pregnancy	*NHF Head Lines*	Participants not pregnant (or attempting to be pregnant), postpartum, or breastfeeding
294	28132364	Sacco	Migraine in pregnancy	*J Headache Pain*	Narrative review
295	20177448	Sachdeva	Drug use in pregnancy; a point to ponder!	*Indian J Pharm Sci*	Participants did not have primary headache or there were no primary headache-specific data
296	30522137	Sader	Headache in Pregnancy, the Puerperium, and menopause	*Semin Neurol*	Narrative review
297	17545337	Sadler	Complementary, holistic, and integrative medicine: butterbur	*Pediatr Rev*	Narrative review
298	20649650	Saper	A practice guide for continuous opioid therapy for refractory daily headache: patient selection, physician requirements, and treatment monitoring	*Headache*	Participants not pregnant (or attempting to be pregnant), postpartum, or breastfeeding
299	104567436 (CINAHL)	Sarchielli	Italian guidelines for primary headaches: 2012 revised version	*Journal of Headache & Pain*	Guideline
300	25834672	Schoen	Headache in pregnancy: an approach to emergency department evaluation and management	*West J Emerg Med*	Narrative review
301	18325296	Schurks	Update on the prophylaxis of migraine	*Curr Treat Options Neurol*	Participants not pregnant (or attempting to be pregnant), postpartum, or breastfeeding
302	4725480	Selbach	[Caffeine, coffee, headache and migraine]	*Med Klin*	Narrative review
303	30880281	Shaheen	Prescribed analgesics in pregnancy and risk of childhood asthma	*The European respiratory journal*	Participants did not have primary headache or there were no primary headache-specific data
304	15017339	Shehata	Neurological disorders in pregnancy	*Curr Opin Obstet Gynecol*	Narrative review
305	29224452	Silberstein	Migraine and women	*Postgrad Med*	Narrative review
306	7716087	Silberstein	Migraine and women. The link between headache and hormones	*Postgrad Med*	Narrative review
307	11371755	Silberstein	Headache and female hormones: what you need to know	*Curr Opin Neurol*	Narrative review
308	27902848	Silberstein	Topiramate in Migraine Prevention: A 2016 Perspective	*Headache*	Narrative review
309	15474764	Silberstein	Headaches in pregnancy	*Neurol Clin*	Narrative review
310	9058407	Silberstein	Migraine and pregnancy	*11903523*	Narrative review
311	12457199	Silberstein	MIGRAINE AND PREGNANCY	*J sogc*	Narrative review
312	16362655	Silberstein	Headaches in pregnancy	*J Headache Pain*	Narrative review

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313	7904984	Silberstein	Headaches and women: treatment of the pregnant and lactating migraineur	*Headache*	Narrative review
314	9793694	Silberstein	Methysergide	*Cephalalgia*	Participants not pregnant (or attempting to be pregnant), postpartum, or breastfeeding
315	CN-01006941 (Cochrane)	Silva	Acupuncture for tension-type headache in pregnancy: a prospective, randomized, controlled study	*Journal of alternative and complementary medicine (new york, N.Y.)*	Duplicate
316	29736103	Skarica	Effectiveness of Manual Treatment on Pregnancy Symptoms: Usefulness of Manual Treatment in Treating Pregnancy Symptoms	*Med Arch*	Participants did not have primary headache or there were no primary headache-specific data
317	25835347	Skeik	Postpartum reversible cerebral vasoconstriction syndrome: review and analysis of the current data	*Vasc Med*	Participants did not have primary headache or there were no primary headache-specific data
318	18223456	Soldin	Triptans in pregnancy	*Ther Drug Monit*	Narrative review
319	6440302	Spector	Migraine	*Surv Ophthalmol*	No intervention of interest
320	25488459	Suetterlin	Diagnosis and management of headache	*Br J Hosp Med (Lond)*	Participants not pregnant (or attempting to be pregnant), postpartum, or breastfeeding
321	19545260	Taylor	Headache prevention with complementary and alternative medicine	*Headache*	Participants not pregnant (or attempting to be pregnant), postpartum, or breastfeeding
322	No PubMed ID	Tennis	Topiramate use during pregnancy and major congenital malformations in multiple populations	*Birth Defects Research Part A - Clinical and Molecular Teratology*	Participants did not have primary headache or there were no primary headache-specific data
323	25881682	Tepper	Pregnancy and lactation--migraine management	*Headache*	Narrative review
324	No PubMed ID	Tepper	Onabotulinum A (Botox)	*Headache*	Narrative review
325	24400754	Tepper	Should butalbital ever be given, much less to a pregnant woman?	*Headache*	Narrative review
326	16097850	Tietjen	The risk of stroke in patients with migraine and implications for migraine management	*CNS Drugs*	Participants not pregnant (or attempting to be pregnant), postpartum, or breastfeeding
327	21198577	Tobin	Treatment of migraine with occipital nerve blocks using only corticosteroids	*Headache*	Participants did not have primary headache or there were no primary headache-specific data
328	29855724	Todd	Women and Migraine: the Role of Hormones	*Curr Neurol Neurosci Rep*	Narrative review
329	2202585	Todd	Naproxen. A reappraisal of its pharmacology, and therapeutic use in rheumatic diseases and pain states	*Drugs*	Participants did not have primary headache or there were no primary headache-specific data
330	22805351	Tomson	Teratogenic effects of antiepileptic drugs	*Lancet Neurol*	Participants did not have primary headache or there were no primary headache-specific data
331	20464584	Torelli	Clinical review of headache in pregnancy	*Neurol Sci*	Narrative review

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332	6146972	Turner	Beta-blocking drugs in migraine	*Postgrad Med J*	Participants not pregnant (or attempting to be pregnant), postpartum, or breastfeeding
333	1889976	Uknis	Review article: migraine and pregnancy	*Headache*	No intervention of interest
334	No PubMed ID	Urbaczek	Migraines during pregnancy treated with acupuncture - A case report	*Revista Internacional de Acupuntura*	Unable to retrieve article
335	23461556	Vajda	Associations between particular types of fetal malformation and antiepileptic drug exposure in utero	*Acta Neurol Scand*	Participants did not have primary headache or there were no primary headache-specific data
336	26711274	VanderPluym	Cluster Headache: Special Considerations for Treatment of Female Patients of Reproductive Age and Pediatric Patients	*Curr Neurol Neurosci Rep*	Narrative review
337	30109437	Vatzaki	Latest clinical recommendations on valproate use for migraine prophylaxis in women of childbearing age: overview from European Medicines Agency and European Headache Federation	*J Headache Pain*	SR and guideline
338	30684032	Veronese	Magnesium and health outcomes: an umbrella review of systematic reviews and meta-analyses of observational and intervention studies	*Eur J Nutr*	Only addresses predictors/distribution of intervention use
339	29446070	Vgontzas	A Hospital Based Retrospective Study of Acute Postpartum Headache	*Headache*	No intervention of interest
340	30225735	Vikelis	Sustained onabotulinumtoxinA therapeutic benefits in patients with chronic migraine over 3 years of treatment	*J Headache Pain*	Participants not pregnant (or attempting to be pregnant), postpartum, or breastfeeding
341	11889417	Von Wald	Headache during pregnancy	*Obstet Gynecol Surv*	Narrative review
342	26049338	Vsc	[Migraines in pregnant patients: how safe are triptans?]	*MMW Fortschr Med*	Narrative review
343	634879	Wainscott	The outcome of pregnancy in women suffering from migraine	*Postgrad Med J*	Participants not pregnant (or attempting to be pregnant), postpartum, or breastfeeding
344	1288557	Wall	Breastfeeding and migraine headaches	*J Hum Lact*	Only addresses predictors/distribution of intervention use
345	27888528	Warnock	Hormone-Related Migraine Headaches and Mood Disorders: Treatment with Estrogen Stabilization	*Pharmacotherapy*	Narrative review
346	24291939	Watanabe	[Management of chronic migraine in Japan]	*Rinsho Shinkeigaku*	Participants not pregnant (or attempting to be pregnant), postpartum, or breastfeeding
347	27993305	Weinstock	Postpartum Headaches	*Ann Emerg Med*	Narrative review
348	8291477	Welch	Migraine and pregnancy	*Adv Neurol*	Narrative review

No.	PMID or Other Identifier	First Author Last Name	Title	Journal	Reason for Exclusion
349	27002079	Wells	Managing Migraine During Pregnancy and Lactation	*Curr Neurol Neurosci Rep*	Narrative review
350	22550159	Williams	An update in the treatment of neurologic disorders during pregnancy--focus on migraines and seizures	*J Pharm Pract*	Narrative review
351	8866921	WojnaB-Horton	Distribution and excretion of sumatriptan in human milk	*Br J Clin Pharmacol*	Participants did not have primary headache or there were no primary headache-specific data
352	26554750	Wood	Prenatal triptan exposure and parent-reported early childhood neurodevelopmental outcomes: an application of propensity score calibration to adjust for unmeasured confounding by migraine severity	*Pharmacoepidemiol Drug Saf*	Participants did not have primary headache or there were no primary headache-specific data
353	23968886	Worthington	Canadian Headache Society Guideline: acute drug therapy for migraine headache	*Can J Neurol Sci*	SR and guideline
354	30403278	Yilmaz	Headache in challenging and special circumstances: Pregnancy and lactation	*Agri*	Narrative review
355	No PubMed ID	Yusta Izquierdo	A 32-year old woman with recurrent hemicranial headache that gets worse during pregnancy	*Medicine (Spain)*	Unable to retrieve article

Abbreviations: PMID = PubMed identifier, SR = systematic review.

SRs

The 347 excluded articles, along with reasons for exclusion, are listed in Table B-39. The most common reasons for exclusion were that the articles were SRs that did not meet our minim criteria, there were no interventions of interest, or there was no information about adverse effects.

Table B-39. Excluded systematic reviews with reasons for exclusion

No.	PMID or Other Identifier	First Author Last Name	Title	Journal	Reason for Exclusion
1	24504933	Abalos	Antihypertensive drug therapy for mild to moderate hypertension during pregnancy	*Cochrane Database Syst Rev*	Older version of another review
2	17253478	Abalos	Antihypertensive drug therapy for mild to moderate hypertension during pregnancy	*Cochrane Database Syst Rev*	Older version of another review
3	15266543	Adab	Common antiepileptic drugs in pregnancy in women with epilepsy	*Cochrane Database Syst Rev*	Duplicate
4	26678040	Adab	Common antiepileptic drugs in pregnancy in women with epilepsy	*Cochrane Database of Systematic Reviews*	Review withdrawn
5	22942331	Adams	Safety of pain therapy during pregnancy and lactation in patients with inflammatory arthritis: a systematic literature review	*J Rheumatol Suppl*	SR, but did not meet minimum criteria
6	11717636	Aghajafari	Multiple courses of antenatal corticosteroids: a systematic review and meta-analysis	*Am J Obstet Gynecol*	SR, but did not meet minimum criteria
7	17266890	Aguilera	[Low dose of aspirin during pregnancy]	*Med Clin (Barc)*	Narrative review only
8	25797654	Alsaad	First trimester exposure to topiramate and the risk of oral clefts in the offspring: A systematic review and meta-analysis	*Reprod Toxicol*	No information about adverse effects
9	8615404	Altshuler	Pharmacologic management of psychiatric illness during pregnancy: dilemmas and guidelines	*Am J Psychiatry*	Narrative review only
10	25881578	Amer	Safety of Popular Herbal Supplements in Lactating Women	*J Hum Lact*	Narrative review only
11	17980183	Amin	Metaanalysis of the effect of antenatal indomethacin on neonatal outcomes	*Am J Obstet Gynecol*	No intervention of interest
12	25732401	Aminoshariae	Acetaminophen: old drug, new issues	*J Endod*	Narrative review only
13	31577868	Andrade	Gestational Exposure to Benzodiazepines, 2: The Risk of Congenital Malformations Examined Through the Prism of Compatibility Intervals	*J Clin Psychiatry*	Narrative review only
14	32044579	Antza	The flipside of hydralazine in pregnancy: A systematic review and meta-analysis	*Pregnancy Hypertens*	No intervention of interest
15	2605908	Areia	Low-moleculaB-weight heparin plus aspirin versus aspirin alone in pregnant women with hereditary thrombophilia to improve live birth rate: meta-analysis of randomized controlled trials	*Archives of gynecology and obstetrics*	No information about adverse effects
16	24443652	Arrowsmith	Drugs acting on the pregnant uterus	*Obstet Gynaecol Reprod Med*	Narrative review only
17	17512048	Askie	Antiplatelet agents for prevention of pre-eclampsia: a meta-analysis of individual patient data	*Lancet*	No intervention of interest
18	29039130	Atallah	Aspirin for Prevention of Preeclampsia	*Drugs*	Narrative review only

No.	PMID or Other Identifier	First Author Last Name	Title	Journal	Reason for Exclusion
19	10084341	Austin	Use of psychotropic medications in breast-feeding women: acute and prophylactic treatment	*Aust N Z J Psychiatry*	Narrative review only
20	9830392	Austin	Psychotropic medications in pregnant women: treatment dilemmas	*Med J Aust*	SR, but did not meet minimum criteria
21	26652709	Baber	The pharmacogenetics of opioid therapy in the management of postpartum pain: a systematic review	*Pharmacogenomics*	No information about adverse effects
22	24708875	Baldacchino	Neurobehavioral consequences of chronic intrauterine opioid exposure in infants and preschool children: a systematic review and meta-analysis	*BMC Psychiatry*	SR, but did not meet minimum criteria
23	20000869	Banach	Long-term developmental outcome of children of women with epilepsy, unexposed or exposed prenatally to antiepileptic drugs: a meta-analysis of cohort studies	*Drug Saf*	SR, but did not meet minimum criteria
24	29341895	Bauer	Prenatal paracetamol exposure and child neurodevelopment: A review	*Horm Behav*	SR, but did not meet minimum criteria
25	12044345	Beardmore	Excretion of antihypertensive medication into human breast milk: a systematic review	*Hypertens Pregnancy*	No information about adverse effects
26	26252584	Becker	Acute Migraine Treatment	*Continuum (Minneap Minn)*	Narrative review only
27	8205012	Beilin	Aspirin and pre-eclampsia	*Bmj*	Narrative review only
28	17397101	Bellantuono	Serotonin reuptake inhibitors in pregnancy and the risk of major malformations: a systematic review	*Hum Psychopharmacol*	No intervention of interest
29	25784291	Bellantuono	The safety of serotonin-noradrenaline reuptake inhibitors (SNRIs) in pregnancy and breastfeeding: a comprehensive review	*Hum Psychopharmacol*	SR, but did not meet minimum criteria
30	No PubMed ID	Berg	Effects of Opioid Agonist Treatment for Pregnant Opioid Dependent Women	*NIPH Systematic Reviews: Executive Summaries*	No intervention of interest
31	29320133	Berg	NIPH Systematic Reviews: Executive Summaries	*Effects of Opioid Agonist Treatment for Pregnant Opioid Dependent Women*	Unable to retrieve article
32	26731178	Bergeron	Prevention of Preeclampsia with Aspirin in Multiple Gestations: A Systematic Review and Meta-analysis	*Am J Perinatol*	SR, but did not meet minimum criteria
33	25833188	Berhan	Should magnesium sulfate be administered to women with mild pre-eclampsia? A systematic review of published reports on eclampsia	*J Obstet Gynaecol Res*	SR, but did not meet minimum criteria
34	25515299	Bjorn	Use of inhaled and oral corticosteroids in pregnancy and the risk of malformations or miscarriage	*Basic Clin Pharmacol Toxicol*	SR, but did not meet minimum criteria
35	31242344	Black	Medication Use and Pain Management in Pregnancy: A Critical Review	*Pain Practice*	SR, but did not meet minimum criteria
36	27168518	Boelig	Interventions for treating hyperemesis gravidarum	*Cochrane Database Syst Rev*	No information about adverse effects
37	28614956	Boelig	Interventions for treating hyperemesis gravidarum: a Cochrane systematic review and meta-analysis	*J Matern Fetal Neonatal Med*	No information about adverse effects
38	25150272	Brogly	Prenatal buprenorphine versus methadone exposure and neonatal outcomes: systematic review and meta-analysis	*Am J Epidemiol*	No intervention of interest

No.	PMID or Other Identifier	First Author Last Name	Title	Journal	Reason for Exclusion
39	25354543	Bromley	Treatment for epilepsy in pregnancy: neurodevelopmental outcomes in the child	*Cochrane Database Syst Rev*	No information about adverse effects
40	19863482	Broy	Gestational exposure to antidepressants and the risk of spontaneous abortion: a review	*Curr Drug Deliv*	SR, but did not meet minimum criteria
41	25845914	Bruning	Antidepressants during pregnancy and postpartum hemorrhage: a systematic review	*Eur J Obstet Gynecol Reprod Biol*	SR, but did not meet minimum criteria
42	20664402	Bujold	Prevention of preeclampsia and intrauterine growth restriction with aspirin started in early pregnancy: a meta-analysis	*Obstetrics and gynecology*	SR, but did not meet minimum criteria
43	29595872	Bushman	Headaches Through a Woman's Life	*Obstet Gynecol Surv*	Not a review
44	29187414	Cairns	Postpartum management of hypertensive disorders of pregnancy: a systematic review	*BMJ Open*	No information about adverse effects
45	27054939	Carstairs	Ondansetron Use in Pregnancy and Birth Defects: A Systematic Review	*Obstet Gynecol*	SR, but did not meet minimum criteria
46	20662551	Cassina	Migraine therapy during pregnancy and lactation	*Expert Opin Drug Saf*	SR, but did not meet minimum criteria
47	10576835	Cates	Benzodiazepine use in pregnancy and major malformations or oral clefts. Pooled results are sensitive to zero transformation used	*Bmj*	Not a review
48	21130227	Chatillon	[Antepartum depression: prevalence, diagnosis and treatment]	*Encephale*	SR, but did not meet minimum criteria
49	25429049	Cheelo	Paracetamol exposure in pregnancy and early childhood and development of childhood asthma: a systematic review and meta-analysis	*Arch Dis Child*	No information about adverse effects
50	28646257	Chen	Effect of epilepsy in pregnancy on fetal growth restriction: a systematic review and meta-analysis	*Arch Gynecol Obstet*	No information about adverse effects
51	24323370	Chin	Re-analysis of safety data supporting doxylamine use for nausea and vomiting of pregnancy	*Am J Perinatol*	No intervention of interest
52	25674710	Cluver	Interventions for helping to turn term breech babies to head first presentation when using external cephalic version	*Cochrane Database Syst Rev*	No intervention of interest
53	22258940	Cluver	Interventions for helping to turn term breech babies to head first presentation when using external cephalic version	*Cochrane Database Syst Rev*	No intervention of interest
54	25674710	Cluver	Interventions for helping to turn term breech babies to head first presentation when using external cephalic version	*Cochrane Database Syst Rev*	Duplicate
55	8031346	Cohen	A reevaluation of risk of in utero exposure to lithium	*Jama*	Narrative review only
56	31129438	Cole	A systematic review of the safety and effectiveness of repetitive transcranial magnetic stimulation in the treatment of peripartum depression	*J Psychiatr Res*	SR, but did not meet minimum criteria
57	No PubMed ID	Costa	Eslicarbazepine acetate exposure in pregnant women with epilepsy	*Seizure*	No intervention of interest
58	19622997	Costantine	Effects of antenatal exposure to magnesium sulfate on neuroprotection and mortality in preterm infants: a meta-analysis	*Obstet Gynecol*	Narrative review only
59	25639010	Costoloni	[Mood stabilisers and pregnancy outcomes - a review]	*Psychiatr Pol*	Narrative review only

No.	PMID or Other Identifier	First Author Last Name	Title	Journal	Reason for Exclusion
60	29487964	Crettenand	[Use of antiepileptic drugs during breastfeeding : What do we tell the mother?]	*Nervenarzt*	SR, but did not meet minimum criteria
61	7631713	Crowley	Antenatal corticosteroid therapy: a meta-analysis of the randomized trials, 1972 to 1994	*Am J Obstet Gynecol*	SR, but did not meet minimum criteria
62	26142898	Crowther	Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes	*Cochrane Database Syst Rev*	No intervention of interest
63	29725376	Cui	Low-dose aspirin at </=16 weeks of gestation for preventing preeclampsia and its maternal and neonatal adverse outcomes: A systematic review and meta-analysis	*Exp Ther Med*	SR, but did not meet minimum criteria
64	26520624	Dalili	Lamotrigine effects on breastfed infants	*Acta Med Iran*	SR, but did not meet minimum criteria
65	31273431	Dathe	Risk estimation of fetal adverse effects after short-term second trimester exposure to non-steroidal anti-inflammatory drugs: a literature review	*Eur J Clin Pharmacol*	Narrative review only
66	25217187	Davanzo	Breastfeeding and migraine drugs	*Eur J Clin Pharmacol*	Narrative review only
67	20958101	Davanzo	Antidepressant drugs and breastfeeding: a review of the literature	*Breastfeed Med*	SR, but did not meet minimum criteria
68	23985170	Davanzo	Antiepileptic drugs and breastfeeding	*Italian Journal of Pediatrics*	SR, but did not meet minimum criteria
69	8760737	de Craen	Analgesic efficacy and safety of paracetamol-codeine combinations versus paracetamol alone: a systematic review	*Bmj*	Participants not pregnant (or attempting to be pregnant), postpartum, or breastfeeding
70	27398292	de Jong	The Risk of Specific Congenital Anomalies in Relation to Newer Antiepileptic Drugs: A Literature Review	*Drugs Real World Outcomes*	SR, but did not meet minimum criteria
71	28486556	Deshmukh	Antenatal corticosteroids for neonates born before 25 Weeks-A systematic review and meta-analysis	*PLoS One*	No information about adverse effects
72	23136875	Dideriksen	First trimester in utero exposure to methylphenidate	*Basic Clin Pharmacol Toxicol*	No intervention of interest
73	23884904	Dodd	Antithrombotic therapy for improving maternal or infant health outcomes in women considered at risk of placental dysfunction	*Cochrane Database Syst Rev*	No intervention of interest
74	20553334	Dodick	Transcranial magnetic stimulation for migraine: a safety review	*Headache*	Narrative review only
75	28029463	Doret	[Tocolysis for preterm labor without premature preterm rupture of membranes]	*J Gynecol Obstet Biol Reprod (Paris)*	No intervention of interest
76	21128087	Doucet	Interventions for the prevention and treatment of postpartum psychosis: a systematic review	*Arch Womens Ment Health*	No information about adverse effects
77	19461430	Doyle	Antenatal magnesium sulfate and neurologic outcome in preterm infants: a systematic review	*Obstet Gynecol*	SR, but did not meet minimum criteria
78	21718553	Duckitt	Recurrent miscarriage	*BMJ Clin Evid*	Narrative review only
79	19450314	Duckitt	Recurrent miscarriage	*BMJ Clin Evid*	Older version of another review
80	29030992	Duffy	Inadequate safety reporting in pre-eclampsia trials: a systematic evaluation	*Bjog*	SR, but did not meet minimum criteria
81	21718554	Duley	Pre-eclampsia, eclampsia, and hypertension	*BMJ Clin Evid*	Narrative review only

No.	PMID or Other Identifier	First Author Last Name	Title	Journal	Reason for Exclusion
82	CD000025 (Cochrane)	Duley	Magnesium sulphate and other anticonvulsants for women with pre,Äêeclampsia	*Cochrane Database of Systematic Reviews*	No intervention of interest
83	14583911	Duley	Magnesium sulphate versus phenytoin for eclampsia	*Cochrane Database Syst Rev*	No intervention of interest
84	11279786	Duley	Magnesium sulphate versus lytic cocktail for eclampsia	*Cochrane Database Syst Rev*	No intervention of interest
85	20824833	Duley	Magnesium sulphate versus lytic cocktail for eclampsia	*Cochrane Database Syst Rev*	No intervention of interest
86	21069663	Duley	Magnesium sulphate and other anticonvulsants for women with pre-eclampsia	*Cochrane Database Syst Rev*	No intervention of interest
87	23900968	Duley	Drugs for treatment of very high blood pressure during pregnancy	*Cochrane Database Syst Rev*	No information about adverse effects
88	CD004659 (Cochrane)	Duley	Antiplatelet agents for preventing pre,Äêeclampsia and its complications	*Cochrane Database of Systematic Reviews*	No information about adverse effects
89	19445808	Duley	Pre-eclampsia, eclampsia, and hypertension	*BMJ Clin Evid*	Older version of another review
90	12804383	Duley	Magnesium sulphate and other anticonvulsants for women with pre-eclampsia	*Cochrane Database Syst Rev*	Older version of another review
91	16855969	Duley	Drugs for treatment of very high blood pressure during pregnancy	*Cochrane Database Syst Rev*	Older version of another review
92	14974075	Duley	Antiplatelet agents for preventing pre-eclampsia and its complications	*Cochrane Database Syst Rev*	Older version of another review
93	10796090	Duley	Anticonvulsants for women with pre-eclampsia	*Cochrane Database Syst Rev*	Older version of another review
94	20687086	Duley	Alternative magnesium sulphate regimens for women with pre-eclampsia and eclampsia	*Cochrane Database Syst Rev*	Older version of another review
95	26115649	Durst	Pregnancy in Women With Solid-Organ Transplants: A Review	*Obstet Gynecol Surv*	No intervention of interest
96	16529525	Eberhard-Gran	Use of psychotropic medications in treating mood disorders during lactation : practical recommendations	*CNS Drugs*	SR, but did not meet minimum criteria
97	15742359	Einarson	Newer antidepressants in pregnancy and rates of major malformations: a meta-analysis of prospective comparative studies	*Pharmacoepidemiol Drug Saf*	SR, but did not meet minimum criteria
98	24360293	Eltonsy	Beta2-agonists use during pregnancy and perinatal outcomes: a systematic review	*Respir Med*	SR, but did not meet minimum criteria
99	25536446	Ennis	Pregnancy exposure to olanzapine, quetiapine, risperidone, aripiprazole and risk of congenital malformations. A systematic review	*Basic Clin Pharmacol Toxicol*	SR, but did not meet minimum criteria
100	26854889	Etwel	When positive studies of novel therapies are subsequently nullified: cumulative meta-analyses in preeclampsia	*Clin Invest Med*	Not a review
101	24678814	Etwel	The fetal safety of cetirizine: an observational cohort study and meta-analysis	*J Obstet Gynaecol*	No intervention of interest
102	18349309	Evans	Use of 5-HT1 agonists in pregnancy	*Ann Pharmacother*	Narrative review only
103	21338428	Eyers	Paracetamol in pregnancy and the risk of wheezing in offspring: a systematic review and meta-analysis	*Clin Exp Allergy*	SR, but did not meet minimum criteria
104	28237129	Fan	Prenatal paracetamol use and asthma in childhood: A systematic review and meta-analysis	*Allergol Immunopathol (Madr)*	SR, but did not meet minimum criteria

No.	PMID or Other Identifier	First Author Last Name	Title	Journal	Reason for Exclusion
105	11094241	Ferrer	Management of mild chronic hypertension during pregnancy: a review	*Obstet Gynecol*	No information about adverse effects
106	19454064	Festin	Nausea and vomiting in early pregnancy	*BMJ Clin Evid*	Not a review
107	24646807	Festin	Nausea and vomiting in early pregnancy	*BMJ Clin Evid*	Narrative review only
108	21726485	Festin	Nausea and vomiting in early pregnancy	*BMJ Clin Evid*	Older version of another review
109	24832366	Firoz	Oral antihypertensive therapy for severe hypertension in pregnancy and postpartum: a systematic review	*Bjog*	SR, but did not meet minimum criteria
110	26105410	Firoz	PP088. Oral antihypertensive therapy for severe hypertension in pregnancy	*Pregnancy Hypertens*	SR, but did not meet minimum criteria
111	31648376	Fitton	In utero exposure to antidepressant medication and neonatal and child outcomes: a systematic review	*Acta Psychiatr Scand*	SR, but did not meet minimum criteria
112	20060203	Fleet	Non-axial administration of fentanyl in childbirth: a review of the efficacy and safety of fentanyl for mother and neonate	*Midwifery*	No intervention of interest
113	24903678	Flenady	Oxytocin receptor antagonists for inhibiting preterm labour	*Cochrane Database Syst Rev*	No intervention of interest
114	32421208	Foong	Oral galactagogues (natural therapies or drugs) for increasing breast milk production in mothers of non‚Äêhospitalised term infants	*Cochrane Database of Systematic Reviews*	No information about adverse effects
115	31623458	Fornaro	Lithium Exposure During Pregnancy and the Postpartum Period: A Systematic Review and Meta-Analysis of Safety and Efficacy Outcomes	*Am J Psychiatry*	SR, but did not meet minimum criteria
116	19736267	Fortinguerra	Psychotropic drug use during breastfeeding: a review of the evidence	*Pediatrics*	SR, but did not meet minimum criteria
117	14756581	Fried	Malformation rates in children of women with untreated epilepsy: a meta-analysis	*Drug Saf*	Participants not pregnant (or attempting to be pregnant), postpartum, or breastfeeding
118	21034180	Galbally	Mood stabilizers in pregnancy: a systematic review	*Aust N Z J Psychiatry*	SR, but did not meet minimum criteria
119	22972143	Garrison	Magnesium for skeletal muscle cramps	*Cochrane Database Syst Rev*	No information about adverse effects
120	12076417	Gates	Prophylaxis for venous thromboembolic disease in pregnancy and the early postnatal period	*Cochrane Database Syst Rev*	No information about adverse effects
121	24571806	Gentile	Risks of neurobehavioral teratogenicity associated with prenatal exposure to valproate monotherapy: a systematic review with regulatory repercussions	*CNS Spectr*	Narrative review only
122	17407365	Gentile	Serotonin reuptake inhibitoB-induced perinatal complications	*Paediatr Drugs*	No intervention of interest
123	25189088	Gentile	Pregnancy exposure to second-generation antipsychotics and the risk of gestational diabetes	*Expert Opin Drug Saf*	SR, but did not meet minimum criteria
124	20583298	Gentile	Neurodevelopmental effects of prenatal exposure to psychotropic medications	*Depress Anxiety*	SR, but did not meet minimum criteria
125	20414166	Gentile	On categorizing gestational, birth, and neonatal complications following late pregnancy exposure to antidepressants: the prenatal antidepressant exposure syndrome	*CNS Spectr*	SR, but did not meet minimum criteria
126	18787227	Gentile	Antipsychotic therapy during early and late pregnancy. A systematic review	*Schizophr Bull*	SR, but did not meet minimum criteria

No.	PMID or Other Identifier	First Author Last Name	Title	Journal	Reason for Exclusion
127	18370569	Gentile	Infant safety with antipsychotic therapy in breast-feeding: a systematic review	*J Clin Psychiatry*	SR, but did not meet minimum criteria
128	27866497	Gentile	Neurodevelopmental outcomes in infants exposed in utero to antipsychotics: a systematic review of published data	*CNS Spectr*	SR, but did not meet minimum criteria
129	31026107	Gentile	Schizophrenia and motherhood	*Psychiatry Clin Neurosci*	SR, but did not meet minimum criteria
130	15150376	Gentile	Clinical utilization of atypical antipsychotics in pregnancy and lactation	*Ann Pharmacother*	SR, but did not meet minimum criteria
131	27283340	Gerosa	Challenges and treatment options for rheumatoid arthritis during pregnancy	*Expert Opin Pharmacother*	Narrative review only
132	25307228	Gilboa	Antihistamines and birth defects: a systematic review of the literature	*Expert Opin Drug Saf*	Narrative review only
133	25436639	Gillon	Hypertensive disorders of pregnancy: a systematic review of international clinical practice guidelines	*PLoS One*	Narrative review only
134	31317955	Gimenez	Adverse outcomes during pregnancy and major congenital malformations in infants of patients with bipolar and schizoaffective disorders treated with antiepileptic drugs: A systematic review	*Psychiatr Pol*	SR, but did not meet minimum criteria
135	23946962	Glacy	AHRQ Comparative Effectiveness Reviews	*Treatments for Seasonal Allergic Rhinitis*	Unable to retrieve article
136	10917399	Goldstein DJ	Olanzapine-exposed pregnancies and lactation: early experience	*J Clin Psychopharmacol*	Not a review
137	24518915	Gordon	Magnesium sulphate for the management of preeclampsia and eclampsia in low and middle income countries: a systematic review of tested dosing regimens	*J Obstet Gynaecol Can*	No intervention of interest
138	26105485	Gordon	PP164. Magnesium sulphate for prevention and treatment of eclampsia in low and middle income countries: Systematic review of tested regimens	*Pregnancy Hypertens*	No intervention of interest
139	30654621	Gou	Association of maternal prenatal acetaminophen use with the risk of attention deficit/hyperactivity disorder in offspring: A meta-analysis	*Aust N Z J Psychiatry*	SR, but did not meet minimum criteria
140	24259987	Gregersen	Safety of bronchodilators and corticosteroids for asthma during pregnancy: what we know and what we need to do better	*J Asthma Allergy*	Narrative review only
141	12709924	Griessham mer	Acquired thrombophilia in pregnancy: essential thrombocythemia	*Semin Thromb Hemost*	Narrative review only
142	31294935	Grigoriadis	Benzodiazepine Use During Pregnancy Alone or in Combination With an Antidepressant and Congenital Malformations: Systematic Review and Meta-Analysis	*J Clin Psychiatry*	SR, but did not meet minimum criteria
143	32148076	Grigoriadis	Pregnancy and Delivery Outcomes Following Benzodiazepine Exposure: A Systematic Review and Meta-analysis	*Can J Psychiatry*	SR, but did not meet minimum criteria
144	23528915	Groeneveld	Preconceptional low-dose aspirin for the prevention of hypertensive pregnancy complications and preterm delivery after IVF: a meta-analysis with individual patient data	*Hum Reprod*	Not a review

No.	PMID or Other Identifier	First Author Last Name	Title	Journal	Reason for Exclusion
145	29469929	Grzeskowiak	Domperidone for increasing breast milk volume in mothers expressing breast milk for their preterm infants: a systematic review and meta-analysis	*Bjog*	No information about adverse effects
146	28333256	Gurney	Analgesia use during pregnancy and risk of cryptorchidism: a systematic review and meta-analysis	*Hum Reprod*	No information about adverse effects
147	14669141	Gutierrez-Alvarez	[Use of anticonvulsive drugs during pregnancy and the risk of malformations in the newborn: a meta-analysis]	*Rev Neurol*	Unable to retrieve article
148	16138282	Gutierrez-Alvarez	[The risk of defects in the neural tube caused by valproic acid and carbamazepine]	*Rev Neurol*	Unable to retrieve article
149	21463540	Haas	Preterm birth	*BMJ Clin Evid*	No information about adverse effects
150	14980290	Halliday	Use of steroids in the perinatal period	*Paediatr Respir Rev*	Narrative review only
151	19398681	Harden	Practice parameter update: management issues for women with epilepsy--focus on pregnancy (an evidence-based review): teratogenesis and perinatal outcomes: report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society	*Neurology*	Not a review
152	19398680	Harden	Practice parameter update: management issues for women with epilepsy--focus on pregnancy (an evidence-based review): vitamin K, folic acid, blood levels, and breastfeeding: report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society	*Neurology*	Not a review
153	28825316	Haskey	Mood stabilizers in pregnancy and child developmental outcomes: A systematic review	*Aust N Z J Psychiatry*	SR, but did not meet minimum criteria
154	No PubMed ID	Henderson	Low-Dose Aspirin for the Prevention of Morbidity and Mortality From Preeclampsia: A Systematic Evidence Review for the U.S. Preventive Services Task Force	*U.S. Preventive Services Task Force Evidence Syntheses, formerly Systematic Evidence Reviews*	Duplicate
155	15316107	Hilaire	Treatment of migraine headaches with sumatriptan in pregnancy	*The Annals of pharmacotherapy*	SR, but did not meet minimum criteria
156	No PubMed ID	Hobson	Melatonin for preventing pre-eclampsia	*Cochrane Database of Systematic Reviews*	Not a review
157	26400006	Hoover	Association Between Prenatal Acetaminophen Exposure and Future Risk of Attention Deficit/Hyperactivity Disorder in Children	*Ann Pharmacother*	SR, but did not meet minimum criteria
158	22771225	Hovdenak	Influence of mineral and vitamin supplements on pregnancy outcome	*Eur J Obstet Gynecol Reprod Biol*	Narrative review only
159	24094568	Huang	A meta-analysis of the relationship between antidepressant use in pregnancy and the risk of preterm birth and low birth weight	*Gen Hosp Psychiatry*	SR, but did not meet minimum criteria

No.	PMID or Other Identifier	First Author Last Name	Title	Journal	Reason for Exclusion
160	30030084	HubeB-Mollema	Exposure to antiepileptic drugs in pregnancy: The need for a family factor framework	*Epilepsy Behav*	No information about adverse effects
161	9744134	Hulse	Assessing the relationship between maternal opiate use and neonatal mortality	*Addiction*	Narrative review only
162	23465038	Hutchinson	Use of common migraine treatments in breast-feeding women: a summary of recommendations	*Headache*	Narrative review only
163	31551795	Imaz	Clinical Lactation Studies of Lithium: A Systematic Review	*Front Pharmacol*	SR, but did not meet minimum criteria
164	1829118	Imperiale	A meta-analysis of low-dose aspirin for the prevention of pregnancy-induced hypertensive disease	*Jama*	SR, but did not meet minimum criteria
165	26408639	Jackson	In utero exposure to valproate increases the risk of isolated cleft palate	*Arch Dis Child Fetal Neonatal Ed*	SR, but did not meet minimum criteria
166	21127116	Jentink	Intrauterine exposure to carbamazepine and specific congenital malformations: systematic review and case-control study	*Bmj*	SR, but did not meet minimum criteria
167	14583914	Jewell	Interventions for nausea and vomiting in early pregnancy	*Cochrane Database Syst Rev*	No information about adverse effects
168	11869567	Jewell	Interventions for nausea and vomiting in early pregnancy	*Cochrane Database Syst Rev*	Duplicate
169	10796155	Jewell	Interventions for nausea and vomiting in early pregnancy	*Cochrane Database Syst Rev*	Duplicate
170	23106923	Jones	Buprenorphine treatment of opioid-dependent pregnant women: a comprehensive review	*Addiction*	No intervention of interest
171	22084456	Kahan	Canadian guideline for safe and effective use of opioids for chronic noncancer pain: clinical summary for family physicians. Part 2: special populations	*Can Fam Physician*	Not a review
172	11394728	Kalis	Oxcarbazepine, an antiepileptic agent	*Clin Ther*	Narrative review only
173	10576836	Khan	Benzodiazepine use in pregnancy and major malformations or oral clefts. Quality of primary studies must influence inferences made from meta-analyses	*Bmj*	Not a review
174	9332996	Khan	Seizure prophylaxis in hypertensive pregnancies: a framework for making clinical decisions	*Br J Obstet Gynaecol*	Not a review
175	20180735	Khan	Safety concerns for the use of calcium channel blockers in pregnancy for the treatment of spontaneous preterm labour and hypertension: a systematic review and meta-regression analysis	*J Matern Fetal Neonatal Med*	SR, but did not meet minimum criteria
176	23724438	Klinger	Antipsychotic drugs and breastfeeding	*Pediatr Endocrinol Rev*	SR, but did not meet minimum criteria
177	28657488	Kong	The risks associated with the use of lamotrigine during pregnancy	*Int J Psychiatry Clin Pract*	Narrative review only
178	16638921	Koren	Nonsteroidal antiinflammatory drugs during third trimester and the risk of premature closure of the ductus arteriosus: a meta-analysis	*Ann Pharmacother*	SR, but did not meet minimum criteria
179	16639967	Koren	Major malformations with valproic acid	*Can Fam Physician*	SR, but did not meet minimum criteria
180	12852485	Kozer	Effects of aspirin consumption during pregnancy on pregnancy outcomes: meta-analysis	*Birth Defects Res B Dev Reprod Toxicol*	SR, but did not meet minimum criteria

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181	12501074	Kozer	Aspirin consumption during the first trimester of pregnancy and congenital anomalies: a meta-analysis	*Am J Obstet Gynecol*	SR, but did not meet minimum criteria
182	8998825	Kucera	[Is lithium a teratogen?]	*Cas Lek Cesk*	SR, but did not meet minimum criteria
183	19661763	Lanza di Scalea	Antidepressant medication use during breastfeeding	*Clin Obstet Gynecol*	SR, but did not meet minimum criteria
184	27852343	Larsen	Pregnancy and bipolar disorder: the risk of recurrence when discontinuing treatment with mood stabilisers: a systematic review	*Acta Neuropsychiatr*	No information about adverse effects
185	26435496	Lassen	First-Trimester Pregnancy Exposure to Venlafaxine or Duloxetine and Risk of Major Congenital Malformations: A Systematic Review	*Basic Clin Pharmacol Toxicol*	SR, but did not meet minimum criteria
186	15507273	Lassere	Treatment of antiphospholipid syndrome in pregnancy--a systematic review of randomized therapeutic trials	*Thromb Res*	SR, but did not meet minimum criteria
187	29754832	Lavecchia	Ondansetron in Pregnancy and the Risk of Congenital Malformations: A Systematic Review	*J Obstet Gynaecol Can*	SR, but did not meet minimum criteria
188	16034877	Lede	Uterine muscle relaxant drugs for threatened miscarriage	*Cochrane Database Syst Rev*	No intervention of interest
189	9141582	Leitich	A meta-analysis of low dose aspirin for the prevention of intrauterine growth retardation	*Br J Obstet Gynaecol*	SR, but did not meet minimum criteria
190	9681097	Lewis	Drug and environmental factors associated with adverse pregnancy outcomes. Part I: Antiepileptic drugs, contraceptives, smoking, and folate	*Ann Pharmacother*	Narrative review only
191	28562278	Lind	Maternal Use of Opioids During Pregnancy and Congenital Malformations: A Systematic Review	*Pediatrics*	SR, but did not meet minimum criteria
192	23141179	Liu	[Clinical efficacy and perinatal outcome of nifedipine for severe preeclampsia: meta-analysis]	*Zhonghua Fu Chan Ke Za Zhi*	Narrative review only
193	12467489	Loder	Safety of sumatriptan in pregnancy: a review of the data so far	*CNS Drugs*	Narrative review only
194	22370064	Lopez-Yarto	Do psychiatric medications, especially antidepressants, adversely impact maternal metabolic outcomes?	*J Affect Disord*	SR, but did not meet minimum criteria
195	27575940	Lourido-Cebreiro	The association between paracetamol and asthma is still under debate	*J Asthma*	SR, but did not meet minimum criteria
196	17407673	MacGregor	Migraine in pregnancy and lactation: a clinical review	*J Fam Plann Reprod Health Care*	SR, but did not meet minimum criteria
197	21975760	Mackeen	Tocolytics for preterm premature rupture of membranes	*Cochrane Database Syst Rev*	No intervention of interest
198	24578236	Mackeen	Tocolytics for preterm premature rupture of membranes	*Cochrane Database Syst Rev*	No intervention of interest
199	9326758	Macones	Evidence for magnesium sulfate as a tocolytic agent	*Obstet Gynecol Surv*	No intervention of interest
200	18998750	Madadi	Establishing causality of CNS depression in breastfed infants following maternal codeine use	*Paediatr Drugs*	SR, but did not meet minimum criteria
201	CD004351 (Cochrane)	Magee	Prevention and treatment of postpartum hypertension	*Cochrane Database of Systematic Reviews*	No information about adverse effects
202	11034777	Magee	Oral beta-blockers for mild to moderate hypertension during pregnancy	*Cochrane Database Syst Rev*	Older version of another review
203		Magee	Oral beta‚Äêblockers for mild to moderate hypertension during pregnancy	*Cochrane Database of Systematic Reviews*	Older version of another review

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204	14576246	Magee	Hydralazine for treatment of severe hypertension in pregnancy: meta-analysis	*Bmj*	SR, but did not meet minimum criteria
205	11687087	Makrides	Magnesium supplementation in pregnancy	*Cochrane Database Syst Rev*	Older version of another review
206	10796220	Makrides	Magnesium supplementation in pregnancy	*Cochrane Database Syst Rev*	Older version of another review
207	26530179	Marcellin	[Breast-feeding (part IV): Therapeutic uses, dietetic and addictions--guidelines for clinical practice]	*J Gynecol Obstet Biol Reprod (Paris)*	Narrative review only
208	20645675	Marinucci	Diazepam effects on non-syndromic cleft lip with or without palate: epidemiological studies, clinical findings, genes and extracellular matrix	*Expert Opin Drug Saf*	No intervention of interest
209	21794529	Martinez Lopez	[Systematic review: is the use of NSAIDs safe during pregnancy in women with rheumatic disease?]	*Reumatol Clin*	SR, but did not meet minimum criteria
210	30651174	Martinez-Paredes	Depression in Pregnancy	*Rev Colomb Psiquiatr*	Participants not pregnant (or attempting to be pregnant), postpartum, or breastfeeding
211	30170040	Masarwa	Prenatal exposure to selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors and risk for persistent pulmonary hypertension of the newborn: a systematic review, meta-analysis, and network meta-analysis	*Am J Obstet Gynecol*	SR, but did not meet minimum criteria
212	11934528	Matalon	The teratogenic effect of carbamazepine: a meta-analysis of 1255 exposures	*Reprod Toxicol*	SR, but did not meet minimum criteria
213	26348534	Matthews	Interventions for nausea and vomiting in early pregnancy	*Cochrane Database Syst Rev*	No intervention of interest
214	20824863	Matthews	Interventions for nausea and vomiting in early pregnancy	*Cochrane Database Syst Rev*	No information about adverse effects
215	24659261	Matthews	Interventions for nausea and vomiting in early pregnancy	*Cochrane Database Syst Rev*	No information about adverse effects
216	25618222	Mauri Llerda	The Spanish Society of Neurology's official clinical practice guidelines for epilepsy. Special considerations in epilepsy: comorbidities, women of childbearing age, and elderly patients	*Neurologia (Barcelona, Spain)*	SR, but did not meet minimum criteria
217	10230583	Mazzotta	Treating allergic rhinitis in pregnancy. Safety considerations	*Drug Saf*	No intervention of interest
218	20465753	McCauley-Elsom	Antipsychotics in pregnancy	*J Psychiatr Ment Health Nurs*	Narrative review only
219	22703834	McDonald	A systematic review of maternal and infant outcomes following magnesium sulfate for pre-eclampsia/eclampsia in real-world use	*Int J Gynaecol Obstet*	SR, but did not meet minimum criteria
220	17118042	McKenna	What over-the-counter preparations are pregnant women taking? A literature review	*J Adv Nurs*	No information about adverse effects
221	21982021	McKinlay	Repeat antenatal glucocorticoids for women at risk of preterm birth: a Cochrane Systematic Review	*Am J Obstet GynecolJ Clin Psychopharmacol*	No intervention of interest
222	27701665	McParlin	Treatments for Hyperemesis Gravidarum and Nausea and Vomiting in Pregnancy: A Systematic Review	*Jama*	No information about adverse effects

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223	18565732	Meador	Pregnancy outcomes in women with epilepsy: a systematic review and meta-analysis of published pregnancy registries and cohorts	*Epilepsy Res*	SR, but did not meet minimum criteria
224	27810551	Meher	Antiplatelet therapy before or after 16 weeks' gestation for preventing preeclampsia: an individual participant data meta-analysis	*Am J Obstet Gynecol*	SR, but did not meet minimum criteria
225	27704220	Mehta	A review of the safety of clozapine during pregnancy and lactation	*Arch Womens Ment Health*	SR, but did not meet minimum criteria
226	20550539	Merce Fernandez-Balsells	Prenatal dexamethasone use for the prevention of virilization in pregnancies at risk for classical congenital adrenal hyperplasia because of 21-hydroxylase (CYP21A2) deficiency: a systematic review and meta-analyses	*Clin Endocrinol (Oxf)*	SR, but did not meet minimum criteria
227	24366859	Minozzi	Maintenance agonist treatments for opiate-dependent pregnant women	*Cochrane Database Syst Rev*	No intervention of interest
228	CD006318 (Cochrane)	Minozzi	Maintenance agonist treatments for opiate‚Äêdependent pregnant women	*Cochrane Database of Systematic Reviews*	No intervention of interest
229	18425946	Minozzi	Maintenance agonist treatments for opiate dependent pregnant women	*Cochrane Database Syst Rev*	No intervention of interest
230	25211400	Molyneaux	Antidepressant treatment for postnatal depression	*Cochrane Database Syst Rev*	No intervention of interest
231	15969868	Montouris	Safety of the newer antiepileptic drug oxcarbazepine during pregnancy	*Curr Med Res Opin*	SR, but did not meet minimum criteria
232	15900008	Moses-Kolko	Neonatal signs after late in utero exposure to serotonin reuptake inhibitors: literature review and implications for clinical applications	*Jama*	SR, but did not meet minimum criteria
233	No PubMed ID	Munk-Olsen	Maternal and infant outcomes associated with lithium use in pregnancy: an international collaborative meta-analysis of six cohort studies	*The lancet. Psychiatry*	Narrative review only
234	24422733	Nakhai-Pour	Major malformations after first trimester exposure to aspirin and NSAIDs	*Expert Rev Clin Pharmacol*	SR, but did not meet minimum criteria
235	22903964	Namazy	Effects of asthma severity, exacerbations and oral corticosteroids on perinatal outcomes	*Eur Respir J*	SR, but did not meet minimum criteria
236	29024912	Navaratnam	How important is aspirin adherence when evaluating effectiveness of low-dose aspirin?	*Eur J Obstet Gynecol Reprod Biol*	No information about adverse effects
237	29052046	Negro	Headache and pregnancy: a systematic review	*J Headache Pain*	SR, but did not meet minimum criteria
238	25668040	Nensi	Effect of magnesium sulphate on fetal heart rate parameters: a systematic review	*J Obstet Gynaecol Can*	SR, but did not meet minimum criteria
239	31180257	Newmark	Risk-Benefit assessment of infant exposure to lithium through breast milk: a systematic review of the literature	*Int Rev Psychiatry*	SR, but did not meet minimum criteria
240	19330496	Nguyen	Teratogenesis associated with antibipolar agents	*Adv Ther*	Narrative review only
241	20591204	Nij Bijvank	Nicardipine for the treatment of severe hypertension in pregnancy: a review of the literature	*Obstet Gynecol Surv*	SR, but did not meet minimum criteria
242	19882796	None listed	Renal colic in adults: NSAIDs and morphine are effective for pain relief	*Prescrire Int*	Narrative review only
243	19536941	None listed	Sleep complaints: Whenever possible, avoid the use of sleeping pills	*Prescrire Int*	Narrative review only

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244	24720593	Nooij	The optimal treatment of severe hypertension in pregnancy: update of the role of nicardipine	*Curr Pharm Biotechnol*	Not a review
245	27199497	Noormohammadi	Buprenorphine Versus Methadone for Opioid Dependence in Pregnancy	*Ann Pharmacother*	No intervention of interest
246	12934124	Nordeng	[Use of antipsychotics during pregnancy and lactation]	*Tidsskr Nor Laegeforen*	SR, but did not meet minimum criteria
247	25527798	Nulman	The effects of the new antipsychotic medications on mothers and babies	*J Popul Ther Clin Pharmacol*	Narrative review only
248	27731292	O'Donnell	Treatments for hyperemesis gravidarum and nausea and vomiting in pregnancy: a systematic review and economic assessment	*Health Technol Assess*	No information about adverse effects
249	27891798	Oladapo	Authors' reply re: Clinical pharmacokinetic properties of magnesium sulphate in women with pre-eclampsia and eclampsia: a systematic review	*Bjog*	Not a review
250	25572308	Orsolini	Serotonin reuptake inhibitors and breastfeeding: a systematic review	*Hum Psychopharmacol*	SR, but did not meet minimum criteria
251	22483705	Oyebode	Psychotropics in pregnancy: safety and other considerations	*Pharmacol Ther*	SR, but did not meet minimum criteria
252	27568278	Pacchiarotti	Mood stabilizers and antipsychotics during breastfeeding: Focus on bipolar disorder	*Eur Neuropsychopharmacol*	SR, but did not meet minimum criteria
253	24071819	Paganelli	Retrospective analysis on the efficacy of corticosteroid prophylaxis prior to elective caesarean section to reduce neonatal respiratory complications at term of pregnancy: review of literature	*Arch Gynecol Obstet*	No intervention of interest
254	28434134	Pariente	Pregnancy Outcomes Following In Utero Exposure to Lamotrigine: A Systematic Review and Meta-Analysis	*CNS Drugs*	SR, but did not meet minimum criteria
255	10488364	Pattinson	A meta-analysis of the use of corticosteroids in pregnancies complicated by preterm premature rupture of membranes	*S Afr Med J*	SR, but did not meet minimum criteria
256	25475074	Paul	Use of domperidone as a galactagogue drug: a systematic review of the benefit-risk ratio	*J Hum Lact*	No intervention of interest
257	26695642	Pergialiotis	Propranolol and oxytocin versus oxytocin alone for induction and augmentation of labor: a meta-analysis of randomized trials	*Arch Gynecol Obstet*	No information about adverse effects
258	24211103	Pirie	Effects of monitoring strategies on seizures in pregnant women on lamotrigine: a meta-analysis	*Eur J Obstet Gynecol Reprod Biol*	No intervention of interest
259	29948232	Poels	Long-term neurodevelopmental consequences of intrauterine exposure to lithium and antipsychotics: a systematic review and meta-analysis	*Eur Child Adolesc Psychiatry*	SR, but did not meet minimum criteria
260	26485229	Pratt	Alternative regimens of magnesium sulfate for treatment of preeclampsia and eclampsia: a systematic review of non-randomized studies	*Acta Obstet Gynecol Scand*	SR, but did not meet minimum criteria
261	22683887	Pringsheim	Canadian Headache Society guideline for migraine prophylaxis	*Can J Neurol Sci*	Not a review
262	29802634	Raggi	Behavioral Approaches for Primary Headaches: Recent Advances	*Headache*	SR, but did not meet minimum criteria
263	31303443	Rajiv	Status epilepticus in pregnancy - Can we frame a uniform treatment protocol?	*Epilepsy Behav*	No information about adverse effects

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264	29692634	Ray-Griffith	Chronic pain during pregnancy: a review of the literature	*Int J Womens Health*	Not a review
265	27454720	Reichmann	Ondansetron Use in Pregnancy andOndansetron Use in Pregnancy and Birth Defects: A Systematic Review	*Obstet Gynecol*	Not a review
266	9361646	Rey	Report of the Canadian Hypertension Society Consensus Conference: 3. Pharmacologic treatment of hypertensive disorders in pregnancy	*Cmaj*	Not a review
267	26906184	Roberge	Low-Dose Aspirin in Early Gestation for Prevention of Preeclampsia and Small-foB-Gestational-Age Neonates: Meta-analysis of Large Randomized Trials	*Am J Perinatol*	Narrative review only
268	22495898	Roberge	Early administration of low-dose aspirin for the prevention of severe and mild preeclampsia: a systematic review and meta-analysis	*Am J Perinatol*	No information about adverse effects
269	29138036	Roberge	Aspirin for the prevention of preterm and term preeclampsia: systematic review and metaanalysis	*Am J Obstet Gynecol*	No information about adverse effects
270	23362106	Roberge	Prevention of perinatal death and adverse perinatal outcome using low-dose aspirin: a meta-analysis	*Ultrasound Obstet Gynecol*	SR, but did not meet minimum criteria
271	29305829	Roberge	Meta-analysis on the effect of aspirin use for prevention of preeclampsia on placental abruption and antepartum hemorrhage	*Am J Obstet Gynecol*	SR, but did not meet minimum criteria
272	27640943	Roberge	The role of aspirin dose on the prevention of preeclampsia and fetal growth restriction: systematic review and meta-analysis	*Am J Obstet Gynecol*	SR, but did not meet minimum criteria
273	22441437	Roberge	Early administration of low-dose aspirin for the prevention of preterm and term preeclampsia: a systematic review and meta-analysis	*Fetal Diagn Ther*	SR, but did not meet minimum criteria
274	23075483	Robinson	Treatment of schizophrenia in pregnancy and postpartum	*J Popul Ther Clin Pharmacol*	Narrative review only
275	32412703	Rommel	Long-Term Effects of Intrauterine Exposure to Antidepressants on Physical, Neurodevelopmental, and Psychiatric Outcomes: A Systematic Review	*J Clin Psychiatry*	SR, but did not meet minimum criteria
276	21641104	Rossi	Prevention of pre-eclampsia with low-dose aspirin or vitamins C and E in women at high or low risk: a systematic review with meta-analysis	*Eur J Obstet Gynecol Reprod Biol*	SR, but did not meet minimum criteria
277	16254678	Ruano	Prevention of preeclampsia with low-dose aspirin -- a systematic review and meta-analysis of the main randomized controlled trials	*Clinics (Sao Paulo)*	SR, but did not meet minimum criteria
278	15591613	Rubin	When breastfeeding mothers need CNS-acting drugs	*Can J Clin Pharmacol*	SR, but did not meet minimum criteria
279	28363609	Ryan	Maternal-Fetal Monitoring of Opioid-Exposed Pregnancies: Analysis of a Pilot Community-Based Protocol and Review of the Literature	*J Obstet Gynaecol Can*	Not a review
280	26516340	Saha	Postpartum women's use of medicines and breastfeeding practices: a systematic review	*International breastfeeding journal*	No information about adverse effects
281	21361848	Sanu	Hyperemesis gravidarum: pathogenesis and the use of antiemetic agents	*Expert Opin Pharmacother*	Narrative review only

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282	31425493	Schoretsanitis	Excretion of Antipsychotics Into the Amniotic Fluid, Umbilical Cord Blood, and Breast Milk: A Systematic Critical Review and Combined Analysis	*Ther Drug Monit*	No information about adverse effects
283	29083536	Scrandis	Bipolar Disorder in Pregnancy: A Review of Pregnancy Outcomes	*J Midwifery Womens Health*	SR, but did not meet minimum criteria
284	29588190	Seidler	Optimal aspirin dosing for preeclampsia prevention	*Am J Obstet Gynecol*	Not a review
285	9259911	Seto	Pregnancy outcome following first trimester exposure to antihistamines: meta-analysis	*Am J Perinatol*	SR, but did not meet minimum criteria
286	26448875	Shah	Pain Management in Pregnancy: Multimodal Approaches	*Pain Res Treat*	Narrative review only
287	26113232	Shekhar	Oral nifedipine versus intravenous labetalol for severe hypertension during pregnancy: a systematic review and meta-analysis	*Bjog*	No information about adverse effects
288	31809499	Shepherd	Antenatal magnesium sulphate and adverse neonatal outcomes: A systematic review and meta-analysis	*PLoS Med*	SR, but did not meet minimum criteria
289	27807847	Siristatidis	Aspirin for in vitro fertilisation	*Cochrane Database Syst Rev*	No intervention of interest
290	26631373	Smit	Mirtazapine in pregnancy and lactation - A systematic review	*Eur Neuropsychopharmacol*	SR, but did not meet minimum criteria
291	30173590	Sridharan	Interventions for treating hyperemesis gravidarum: a network meta-analysis of randomized clinical trials	*J Matern Fetal Neonatal Med*	No intervention of interest
292	30261764	Sridharan	Interventions for treating nausea and vomiting in pregnancy: a network meta-analysis and trial sequential analysis of randomized clinical trials	*Expert Rev Clin Pharmacol*	No information about adverse effects
293	29974489	Sridharan	Drugs for treating severe hypertension in pregnancy: a network meta-analysis and trial sequential analysis of randomized clinical trials	*Br J Clin Pharmacol*	SR, but did not meet minimum criteria
294	23112017	Tan	Does low-moleculaB-weight heparin improve live birth rates in pregnant women with thrombophilic disorders? A systematic review	*Singapore Med J*	No intervention of interest
295	31336231	Tanos	Review of migraine incidence and management in obstetrics and gynaecology	*Eur J Obstet Gynecol Reprod Biol*	No information about adverse effects
296	26044279	Tanoshima	Risks of congenital malformations in offspring exposed to valproic acid in utero: A systematic review and cumulative meta-analysis	*Clin Pharmacol Ther*	SR, but did not meet minimum criteria
297	19837868	Tegethoff	Effects of intrauterine exposure to synthetic glucocorticoids on fetal, newborn, and infant hypothalamic-pituitary-adrenal axis function in humans: a systematic review	*Endocr Rev*	SR, but did not meet minimum criteria
298	30111493	Tenorio	Oral antioxidant therapy for prevention and treatment of preeclampsia: Meta-analysis of randomized controlled trials	*Nutr Metab Cardiovasc Dis*	No intervention of interest
299	19434568	Ter Horst	[Antidepressants during pregnancy and lactation]	*Tijdschr Psychiatr*	SR, but did not meet minimum criteria
300	20919996	Thajam	Is neonatal abstinence syndrome related to the amount of opiate used?	*J Obstet Gynecol Neonatal Nurs*	SR, but did not meet minimum criteria

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301	No PubMed ID	Thibaut	WFSBP * and IAWMH ** Guidelines for the treatment of alcohol use disorders in pregnant women	*The world journal of biological psychiatry : the official journal of the World Federation of Societies of Biological Psychiatry*	No intervention of interest
302	28297592	Tosato	A Systematized Review of Atypical Antipsychotics in Pregnant Women: Balancing Between Risks of Untreated Illness and Risks of Drug-Related Adverse Effects	*J Clin Psychiatry*	SR, but did not meet minimum criteria
303	21654128	Trivedi	A meta-analysis of low-dose aspirin for prevention of preeclampsia	*J Postgrad Med*	SR, but did not meet minimum criteria
304	19698902	Tuccori	Safety concerns associated with the use of serotonin reuptake inhibitors and other serotonergic/noradrenergic antidepressants during pregnancy: a review	*Clin Ther*	SR, but did not meet minimum criteria
305	31479546	Turner	The impact of low-dose aspirin on adverse perinatal outcomes: a meta-analysis and meta-regression	*Ultrasound Obstet Gynecol*	SR, but did not meet minimum criteria
306	21034181	Udechuku	Antidepressants in pregnancy: a systematic review	*Aust N Z J Psychiatry*	SR, but did not meet minimum criteria
307	30624301	Uguz	Antipsychotic Use During Pregnancy and the Risk of Gestational Diabetes Mellitus: A Systematic Review	*J Clin Psychopharmacol*	Narrative review only
308	27028982	Uguz	Second-Generation Antipsychotics During the Lactation Period: A Comparative Systematic Review on Infant Safety	*J Clin Psychopharmacol*	Narrative review only
309	27297617	Uguz	Mood stabilizers during breastfeeding: a systematic review of the recent literature	*Bipolar Disord*	Narrative review only
310	31425466	Uguz	The Use of Antidepressant Medications During Pregnancy and the Risk of Neonatal Seizures: A Systematic Review	*J Clin Psychopharmacol*	Narrative review only
311	29596147	Uguz	Maternal Antidepressant Use During Pregnancy and the Risk of Attention-Deficit/Hyperactivity Disorder in Children: A Systematic Review of the Current Literature	*J Clin Psychopharmacol*	SR, but did not meet minimum criteria
312	27941417	Uguz	Is There Any Association Between Use of Antidepressants and Preeclampsia or Gestational Hypertension?: A Systematic Review of Current Studies	*J Clin Psychopharmacol*	SR, but did not meet minimum criteria
313	31416730	Valencia-Mendoza	Fatal reversible cerebral vasoconstriction syndrome: A systematic review of case series and case reports	*J Clin Neurosci*	Participants not pregnant (or attempting to be pregnant), postpartum, or breastfeeding
314	30109437	Vatzaki	Latest clinical recommendations on valproate use for migraine prophylaxis in women of childbearing age: overview from European Medicines Agency and European Headache Federation	*J Headache Pain*	Not a review
315	25102018	Verdurmen	The influence of corticosteroids on fetal heart rate variability: a systematic review of the literature	*Obstet Gynecol Surv*	No intervention of interest
316	26329145	Verrotti	Foetal safety of old and new antiepileptic drugs	*Expert Opin Drug Saf*	Narrative review only
317	26318519	Viale	Epilepsy in pregnancy and reproductive outcomes: a systematic review and meta-analysis	*Lancet*	SR, but did not meet minimum criteria

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318	31293454	VillamoB-Martinez	Cerebellar Hemorrhage in Preterm Infants: A Meta-Analysis on Risk Factors and Neurodevelopmental Outcome	*Front Physiol*	Narrative review only
319	28005135	Vitale	Psychopharmacotherapy in Pregnancy and Breastfeeding	*Obstet Gynecol Surv*	SR, but did not meet minimum criteria
320	18034353	Vlastarakos	Treating common ear problems in pregnancy: what is safe?	*Eur Arch Otorhinolaryngol*	Narrative review only
321	30421346	Wang	Advances in Epidemiological Methods and Utilisation of Large Databases: A Methodological Review of Observational Studies on Central Nervous System Drug Use in Pregnancy and Central Nervous System Outcomes in Children	*Drug Saf*	Only addresses predictors/distribution of intervention use
322	15369649	Waterman	Do commonly used oral antihypertensives alter fetal or neonatal heart rate characteristics? A systematic review	*Hypertens Pregnancy*	No information about adverse effects
323	CD004411 (Cochrane)	Webb	Antipsychotic drugs for non‚Äêaffective psychosis during pregnancy and postpartum	*Cochrane Database of Systematic Reviews*	No information about adverse effects
324	15106251	Webb	Antipsychotic drugs for non-affective psychosis during pregnancy and postpartum	*Cochrane Database Syst Rev*	Empty review, i.e., no included studies
325	15169695	Weissman	Pooled analysis of antidepressant levels in lactating mothers, breast milk, and nursing infants	*Am J Psychiatry*	SR, but did not meet minimum criteria
326	15507199	Wen	Risk of fetal exposure to tricyclic antidepressants	*J Obstet Gynaecol Can*	Review of animal studies
327	CD010527 (Cochrane)	Wilkinson	Melatonin for women in pregnancy for neuroprotection of the fetus	*Cochrane Database of Systematic Reviews*	No information about adverse effects
328	18246981	Wise	Treatment of narcolepsy and other hypersomnias of central origin	*Sleep*	SR, but did not meet minimum criteria
329	10517430	Wisner	Pharmacologic treatment of depression during pregnancy	*Jama*	SR, but did not meet minimum criteria
330	21501542	Wong	Substance use in pregnancy	*J Obstet Gynaecol Can*	Not a review
331	23968886	Worthington	Canadian Headache Society Guideline: acute drug therapy for migraine headache	*Can J Neurol Sci*	Not a review
332	20824872	Woudstra	Corticosteroids for HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome in pregnancy	*Cochrane Database of Systematic Reviews*	No information about adverse effects
333	16595080	Wu	Screening for thrombophilia in high-risk situations: systematic review and cost-effectiveness analysis. The Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS) study	*Health Technol Assess*	No information about adverse effects
334	No PubMed ID	Wu	The medical management of antiphospholipid syndrome in pregnancy: a meta-analysis	*Obstetrics and gynecology*	SR, but did not meet minimum criteria
335	12792553	Wunsch	Treatment of pain in pregnancy	*Clin J Pain*	SR, but did not meet minimum criteria
336	28216406	Xiao	The relationship between maternal corticosteroid use and orofacial clefts-a meta-analysis	*Reprod Toxicol*	SR, but did not meet minimum criteria
337	25833349	Xu	Low-Dose Aspirin for Preventing Preeclampsia and Its Complications: A Meta-Analysis	*J Clin Hypertens (Greenwich)*	SR, but did not meet minimum criteria

No.	PMID or Other Identifier	First Author Last Name	Title	Journal	Reason for Exclusion
338	26111687	Yao	[Early intervention with aspirin for preventing preeclampsia in high-risk women: a meta-analysis]	*Nan Fang Yi Ke Da Xue Xue Bao*	SR, but did not meet minimum criteria
339	10796091	Young	Antihistamines versus aspirin for itching in late pregnancy	*Cochrane Database Syst Rev*	No information about adverse effects
340	19445755	Young	Leg cramps	*BMJ Clin Evid*	Duplicate
341	25970567	Young	Leg cramps	*BMJ Clin Evid*	Duplicate
342	26735551	Zeng	Effects and Safety of Magnesium Sulfate on Neuroprotection: A Meta-analysis Based on PRISMA Guidelines	*Medicine (Baltimore)*	SR, but did not meet minimum criteria
343	26559249	Zhang	Antithrombotic Treatment for Recurrent Miscarriage: Bayesian Network Meta-Analysis and Systematic Review	*Medicine (Baltimore)*	SR, but did not meet minimum criteria
344	26262909	Zhou	Interventions for leg cramps in pregnancy	*Cochrane Database Syst Rev*	No intervention of interest
345	23806368	Zhou	Chinese herbal medicine in treatment of polyhydramnios:a meta-analysis and systematic review	*Chin Med Sci J*	SR, but did not meet minimum criteria
346	21144482	ZrouB-Hassen	[Safety of rheumatic disease drugs at childbearing age]	*Therapie*	Narrative review only
347	29747656	Zwink	Maternal drug use and the risk of anorectal malformations: systematic review and meta-analysis	*Orphanet J Rare Dis*	SR, but did not meet minimum criteria

Abbreviations: PMID = PubMed identifier, SR = systematic review.

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