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Concepts for selection and utilization of psychiatric medications in pregnancy

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Abstract

Psychiatric illness may develop or relapse during pregnancy, and understanding best practices is paramount. In 2017, the British Association for Psychopharmacology (BAP) consensus guidance on the use of psychotropic medication preconception, in pregnancy, and postpartum was released. The BAP guidelines provide concise evidence and additional insight and flexibility for use of psychiatric medication. Key takeaways of these guidelines are highlighted serving as a concise reference for practitioners. Additionally, practice points, such as recommendations for rapid tranquilization and the role of long-acting injectable antipsychotic medications as well as additional insights to the growing body of literature associated with psychiatric medications in pregnancy since 2017 are summarized. Providers are strongly encouraged to stay up to date to provide optimal care for pregnant patients and their babies.

Keywords: antidepressant, antipsychotic, depression, mood disorder, mood stabilizer, peripartum, pregnancy, psychotropic, schizophrenia

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Introduction

Psychiatric illness may develop or relapse during pregnancy, affecting approximately 500 000 pregnancies each year.[1,2] A high prevalence of psychiatric illness of 14% was reported during the second trimester of pregnancy with a low percentage (5.5%) receiving treatment.[3] Uncertainty of best practices may lead to medication discontinuation without consideration of the risks to mother and child associated with the underlying psychiatric illness (Table 1). On the other hand, medications may be initiated or added based on the psychiatric diagnosis without consideration of pregnancy status. Baseline risk of congenital malformation for all pregnancies range from 3% to 6% with medication exposure thought to account for less than 1% of all birth defects. Environmental issues (eg, maternal conditions, such as poor nutrition or infection) account for around 10% and genetics-related congenital malformations account for 15% to 25% of all birth defects.[4]

The British Association for Psychopharmacology (BAP) 2017 consensus guidance provides concise evidence and additional leeway for use of psychiatric medication. As an example of this flexibility, Ebstein's anomaly associated with lithium exposure is now thought to be more likely associated with maternal psychiatric diagnosis.[5] Unfortunately, pregnancy is not protective against psychiatric illness, and poor psychiatric health care during pregnancy is strongly predictive of continued postnatal psychiatric illness.[5] Furthermore, a recent study revealed 0.04% of women aged 20 to 35 years who die by suicide do so during pregnancy.[6] All

Take Home Points:

1. Preconception planning is paramount, and detailed education and discussion with mom to be and/or caregiver should occur while encouraging patient input prior to making treatment decisions with thorough documentation. Nonpharmacologic treatment options such as psychoeducation should be considered.
2. Medication monotherapy at higher doses is preferred over polypharmacy, and the lowest possible dose of a medication should be used. Optimizing current agents is preferred over switching to a different agent so that fetal medication exposure is limited.
3. No currently available antidepressants or antipsychotics are absolutely contraindicated in pregnancy. Selective serotonin reuptake inhibitors are first-line treatments for depression. Lamotrigine and lithium are acceptable in pregnancy with an appropriate risk-benefit analysis, and valproic acid derivatives should generally be avoided in women of childbearing age.
4. Patients should be encouraged to enroll in the National Pregnancy Registry by calling 1-866-961-2388 or emailing the registry at registry@partners.org. Adverse effects during pregnancy should be reported to the Food and Drug Administration MedWatch program.

pregnant patients should be assessed for risk of suicide and infanticide at each appointment. Suicidality or psychosis should be considered psychiatric emergencies requiring prompt intervention.[1,7]

Patient-Centered Care

AK, a 22-year-old, pregnant (21 weeks and 3 days) woman, along with her partner, present for an outpatient psychiatric appointment with the chief complaint: "I need help, my meds are off." The partner confirms that AK has been demonstrating symptoms of psychosis, making odd statements, and ruminating about them. AK has not been taking medicine for 3 weeks since discovering the pregnancy. During the appointment, AK is calm and cooperative and mood is depressed with flat affect and soft speech. Auditory hallucinations are reported as "hearing 2 to 3 voices, mumbling." AK is paranoid, reporting "they're after me," but denies suicidal or homicidal ideation. Most recent medications included quetiapine 400 mg by mouth at bedtime, citalopram 30 mg by mouth daily, and trazodone 50 mg at bedtime. Past history includes schizophrenia, major depressive disorder (MDD), multiple inpatient hospitalizations, and 2 overdose attempts. Domestic violence and childhood emotional, physical, and sexual trauma are endorsed. Family history includes an uncle who died by suicide, father with alcohol use disorder, and mother with untreated depression. Social substance use was denied, she spent time in foster care, "aging out," and was previously homeless, but now lives with her boyfriend and father of the baby. Vital signs and laboratory results were unremarkable: urine drug screen (UDS) was negative; urine pregnancy test was positive. Brief Psychiatric Rating Scale score was 42.

Individuals living with mental illness may be able to discontinue medications preconception or during pregnancy for mild illness. In practice, this decision is patient-specific and should be made after careful consideration of all potential risks and benefits.[7,8]

TABLE 1: Risk analysis for psychotropic medications in pregnancy[2,5,7,8,12,16–18,26,27]

	Bipolar Disorder	Major Depression	Schizophrenia
Risk of untreated disorder to baby	Microencephaly Neonatal hypoglycemia Low birth weight Preterm delivery Decreased fetal growth Postnatal complications Increased infant crying Increased NICU admission	Low birth weight Preterm delivery Decreased fetal growth Increased postnatal complications Increased infant crying Increased NICU admission possible (data conflicting) Attention deficit hyperactivity disorder symptoms Autism (possible) Conduct disorder Emotional problems Impaired cognitive function	Stillbirth Congenital malformations Low birth weight Small for gestational age Preterm labor Placental abnormalities Antenatal hemorrhage Postnatal/neonatal death
Risk of untreated disorder to mother (obstetric and other)	Increased relapse Increased risk of suicidality Increased risk of psychosis Preterm delivery Cesarean section Instrumental delivery Nonspontaneous start to delivery	Preterm delivery Increased major depressive disorder relapse Increased postpartum depression rates Preeclampsia Poor engagement with infant Possibly increased Cesarean sections (conflicting)	Increased relapse Delivery complications

NICU = neonatal intensive care unit.

Pregnancy is reported as a key reason for discontinuing antidepressant and antipsychotic medication with a goal of avoiding fetal exposure.[9,10] Cited rationale for medication discontinuation includes fear of harm to the baby; pressure from family; symptoms of psychiatric illness, such as paranoid thinking; or poor ability to follow up.[1,7] Untreated psychiatric diagnosis may result in both obstetric (eg, preterm delivery, prolonged labor, fetal distress) and neonatal (eg, decreased developmental scores, congenital malformations, small for gestational age, neonatal intensive care unit admission) difficulties.[2] Additionally, untreated or inadequately treated maternal psychiatric illness could result in poor adherence with prenatal care; poor maternal self-care and nutrition; increased use of substances, such as alcohol and tobacco; unsupervised use of herbals or prescription medication; poor mother-infant bonding, and poor infant care.[2]

However, when the risk-versus-benefit analysis is considered for discontinuing psychiatric medications during pregnancy, the risk of untreated illness must be considered alongside the risk associated with medication continuation. Advising medication discontinuation often exchanges the fetal risk of medication exposure for fetal and maternal risks of untreated psychiatric illness.[5] Often, in research studies that evaluate the risk of psychiatric medications, healthy controls are compared to medicated psychiatric patients with no control for the psychiatric illness itself as a confounder.[5] Highlighting this effect, a meta-analysis including 23 studies found only 6 attempted to control for depression severity.[10] Antidepressant medications do not seem to confer neonatal risk to the degree previously thought when women are matched based on the severity of depression, lending credence to the theory of depression potentially being a stronger risk factor than the psychiatric medications, and this theory could be extrapolated to other psychiatric diagnoses.[5,7,11]

Data regarding the risks and benefits of psychiatric medications in the perinatal period have many weaknesses, especially multiple confounding factors. Therefore, expert opinion recommends avoiding definitive statements about risks and benefits when speaking with patients.[5] Along with standard education parameters, providers may utilize information in Tables 1 through 4 to inform patients and caregivers about the risks associated with untreated psychiatric illness and the potential risks of medication(s). This information may also be used for a risk-benefit analysis as part of preconception planning with a goal to initiate preferred agents in women of childbearing age in case of pregnancy. Multidisciplinary management is a best practice recommended to facilitate care, and the entire education session should be documented along with patient understanding. For patients who are adamant about discontinuing psychiatric medications, support should be provided as patients are likely to stop drug therapy on their own if not assisted.[8,9] It is important to educate patients that symptomatic relapse may occur if medications are discontinued.[12] Considerations should be given to the disorder being treated, severity of disease, course and most recent episode, number of episodes, response to medication, medication dose, and evidence supporting length of therapy as these factors contribute to the likelihood of symptom relapse occurring.

Case Outcome

In this case, AK and her partner were educated about the risks of quetiapine and citalopram during pregnancy; untreated schizophrenia and depression (Table 1); the baby's exposure to these medications; and that the majority of the baby's central nervous system, heart, and upper and lower limbs have developed.[5,13] From 21 weeks forward, the central nervous system, eyes, teeth, palate, genitalia, and ears continue to develop. Major abnormalities generally occur in the first 8 weeks of development, whereas minor abnormalities occur between weeks 9 through 40.[2,13] The patient's psychiatric health, personal well-being, and ability to care for herself and her child were discussed. AK verbalized that she is better able to care for herself and her child if she continues psychiatric medications that have worked well in the past. Based on expert opinion and consideration of patient factors, both quetiapine 400 mg by mouth at bedtime and citalopram 20 mg by mouth daily were started with plans to titrate as tolerated and return for a follow-up appointment in 2 weeks. Trazodone was not continued as it is often best to discontinue adjunct medications if possible to limit exposures.[7] Whereas the medication regimen does not fully align with guideline-based recommendations because 2 medications were initiated instead of 1, the multidisciplinary team fully evaluated the patient-specific risks and benefits and chose these medications as the initial course of treatment. AK was educated about sleep hygiene and behavioral therapy. It is rational but not guideline based to consider over-the-counter doxylamine 12.5 to 25 mg and pyridoxine 50 mg by mouth at bedtime as needed for sleep because it is approved for nausea and vomiting and has safety data to support use during pregnancy.[14] Use may be extrapolated in clinical practice for sedation and potentially anxiety (similar to hydroxyzine) because doxylamine is a histaminic H1 antagonist. AK was reminded to take a prenatal vitamin daily, which she agreed to do. The patient was also encouraged to enroll in the National Pregnancy Registry.

Treatment Strategies

TM, a 32-year-old, pregnant (34 weeks and 1 day) patient was voluntarily admitted to the inpatient psychiatric unit with suicidal thoughts for "a while." TM reports, "an attempt about 2 months ago by overdosing on zolpidem but vomiting the pills." Following that event, psychiatric care was sought, and lithium, which was initially held due to first trimester pregnancy, was restarted when TM was 22 weeks pregnant.[5,7] TM has been experiencing depression off and on for the past

2 years since the birth of her first child with a history of MDD prior to giving birth. Hopelessness, inability to work, loss of interest, low energy and motivation, and feelings of isolation have escalated over the past few months. These features contributed to daily suicidal thoughts, but TM has resisted acting on them because of her other child and current pregnancy. TM reports laying on the couch for hours each day and that caring for her child is difficult. Over the last 3 days, she is hearing music playing with no source for the sound. Current medications include fluoxetine 60 mg by mouth daily (adherent), lithium 300 mg by mouth twice daily (often forgets), zolpidem 5 mg by mouth at bedtime as needed (not using), and a prenatal vitamin (adherent). TM has taken fluoxetine since first being diagnosed with depression and stated it previously worked well. TM states lithium works when taken consistently. Psychiatric history includes depression and postpartum depression with psychosis. Family history is positive for a mother with depression. Socially, all substances are denied, lives with her husband and son, and works as a stay-at-home parent since the birth of her first child. Past medical history is positive for diabetes and hypertension, both at goal without medication. Vital signs, urinalysis, UDS, and electrocardiogram (ECG) were unremarkable; labs were notable for the following: glucose = 98 mg/dL, creatinine clearance = 100 mL/min, A1c 5.2%, and lithium concentration = 0.2 mmol/L. A urine pregnancy test was positive. The multidisciplinary team requested input whether to continue current pharmacotherapy or introduce new medications to achieve therapeutic response. Patient Health Questionaire-9 score was 14.

In mild-to-moderate illness, psychotherapy may often be considered first line, but in moderate-to-severe or recurrent illness, pharmacotherapy should be considered.[7,8,15] Relatively limited data regarding the efficacy of psychiatric medications during pregnancy exists; therefore, in practice, it is usually necessary to extrapolate and generalize efficacy evidence from studies in nonperinatal populations. Data commonly used to estimate the risk associated with medications in pregnancy include animal studies, case reports, case-control studies, prospective cohort studies, historical cohort studies, and voluntary reporting systems. Difficulty with the available data lies in the value of historical reports and noncontrolled studies as birth defects can occur by chance and recall bias may be a concern.

Optimally, shared decision making should occur prior to pregnancy as part of preconception planning.[2,5,7] These discussions early on can help determine pharmacologic therapy. For example, a patient of childbearing age should generally not be prescribed valproic acid (VPA) due to strong associations with teratogenicity.[2,5,7,8,17] If VPA is necessary, oral contraceptives with little potential for nonadherence, such as intrauterine devices, should be considered along with folic acid. Nonpharmacologic treatment options, such as psychotherapy, should be implemented when appropriate. Nonpharmacologic options should be considered for appropriateness to potentially help avoid medication use or assist with reducing medication burden.

The selection of medication to minimize the risk of illness should be based on disease-specific guidelines and efficacy evidence, history of past efficacy with medications, prior exposure during pregnancy, and available reproductive safety information. Medications with fewer metabolites, higher protein binding, and fewer interactions with other medications are generally preferred if possible.[2,5] It is recommended to use the lowest possible dose, but a single medication at a higher dose is preferred over multiple medications to limit overall neonatal exposure.[5,7] If a mother is already prescribed a medication, and the baby has been exposed, efforts should be made to optimize the current medication before utilizing a switch or augmentation strategy.[2,5,7,16] Potential benefits of psychiatric medications, such as treatment response, remission, and prevention of relapse should be part of patient education. Patients should be advised regarding what may occur if treatments are stopped abruptly (eg, potential decompensation and withdrawal) and to seek assistance with discontinuation if desired. It is crucial to conduct a literature review prior to making recommendations for medication use in pregnancy as this information is constantly evolving, and both mother and baby are affected by therapeutic recommendations.

None of the currently available antidepressants is absolutely contraindicated in pregnancy (Table 2). Patient-specific factors must be considered in therapy selection and treatment adjustment during pregnancy. Most guidelines recommend selective serotonin reuptake inhibitors (SSRIs) as first-line pharmacologic treatments for depression because they have the largest evidence for reproductive safety.[2,5,7,18,19]

Sertraline is currently considered the most preferred agent during pregnancy.[2,5,7,17–20] Citalopram is considered a preferred agent, and fluoxetine is nonpreferred, but continuation is acceptable.[18,19] Paroxetine has conflicting evidence for use.[2,5,7,16] Of the tricyclic antidepressants (TCAs), amitriptyline, clomipramine, desipramine, imipramine, and nortriptyline have sufficient evidence to support use and are considered to have the fewest adverse effects.[7,19] Most evidence related to adverse effects is associated with clomipramine and includes preterm birth, low birthweight, hypoglycemia, respiratory diagnoses, low Apgar score, jaundice, and cardiac malformations.[5,18] TCA exposure effects are considered to be "not significantly different" when compared with SSRIs or other antidepressants besides monoamine oxidase inhibitors (MAOIs).[5] MAOIs should be avoided during pregnancy predominantly because of the association with fetal growth restriction and hypertensive crisis.[2,5,7,16,19] Serotonin and norepinephrine reuptake inhibitors, such as duloxetine and venlafaxine, also have limited information and are not considered preferred agents.[8] Other commonly used agents,

TABLE 2: Evidence for commonly used antidepressant medications in pregnancy[2,5,7,8,12,16-24,29,30,32-39]

Medication	Recommendation	Note or concern
Bupropion	Not a preferred agent, not recommended for use	Increased risk in congenital abnormalities has not been observed; possible cardiac malformations Possible association with spontaneous abortion, cardiac malformations, and attention deficit hyperactivity disorder No major defects reported in 113 cases of use
Citalopram	Considered a preferred agent	Previous reports of use associated with anencephaly, omphalocele, and craniosynostosis Increased odds of neural tube defects Reports of 8 major anomalies in a group of 184 cases
Duloxetine	Not a preferred agent; caution continuation/consider change	Possibly associated with an increased risk of postpartum hemorrhage (RR = 1.53), increased risk of cardiac malformations (RR = 1.29), increased risk of congenital malformations (RR = 1.11), small for gestational age (RR = 1.14)
Escitalopram	May be considered and continued	Case series of 7 pregnant women taking 10 to 20 mg/day, all babies carried to full term with no major malformations; mild withdrawal in one baby who was also exposed to 2 benzodiazepines, paroxetine, alcohol, and cigarettes. Low birth weight in 1 baby (5.29 pounds), but otherwise healthy
Fluoxetine	Nonpreferred but may be continued	Considered to have extensive data compared with other agents May accumulate in neonate due to long half-life Risks of cardiac malformations no longer significant after adjustment for depression-associated confounders (BAP 2017) versus increased odds of isolated ventricular septal defects RANZCP recommends avoiding use (2021)
Fluvoxamine	Not recommended; change if possible	Limited data Cohort study of 267 women, 26 exposed infants to fluvoxamine and reported it does not appear to increase teratogenic risk
Mirtazapine	Not a preferred agent	Possible association with patent ductus arteriosus and midline facial defects; reports of spontaneous abortion, conflicting evidence related to preterm delivery along with reports of healthy infant births
Monoamine oxidase inhibitors	Not recommended	Fetal growth restriction Hypertensive crisis
Paroxetine	May be considered for use, conflicting data exists	Possibly associated with cardiac malformations (FDA 2015) Risks of cardiac malformations no longer significant after adjustment for depression-associated confounders (BAP 2017) RANZCP recommends avoiding use (2021) Monitor for decreased efficacy in pregnancy due to PK changes
Selective serotonin reuptake inhibitors	See individual agents	Anencephaly, craniosynostosis, omphalocele, congenital cardiac defects, jitteriness, respiratory distress, transient tachypnea, weak cry, poor tone, neonatal intensive care admission rate increased, persistent pulmonary hypertension of the newborn, withdrawal symptoms, possible effect on gestational age, possible effect on Apgar scores
Sertraline	Preferred first-line agent, may be continued	Previously thought to be associated with omphalocele, septal defects
Trazodone	Not a preferred agent	Outcomes similar to unexposed pregnancy
Tricyclic antidepressants	Acceptable agents: amitriptyline, clomipramine, imipramine, and nortriptyline (other agents considered to be lacking data).	Fetal tachycardia, neonatal tachypnea, tachycardia, cyanosis, irritability, hypertonia, clonus, spasm, transient withdrawal symptoms, preterm birth, low birthweight, hypoglycemia, respiratory diagnoses, low Apgar score, jaundice, and cardiac malformations
Venlafaxine	Not a preferred agent; may be continued	Monitor for decreased efficacy in pregnancy due to pharmacokinetic changes RANZCP recommends avoiding use (2021)
Vilazodone	Considered a nonpreferred agent; limited data	Case report of patient taking 40 mg throughout and prior to pregnancy; baby delivered at 39 weeks + 3 days with jaundice, which resolved without treatment
Vortioxetine	Considered a nonpreferred agent; limited data	Case series of 17 pregnancies exposed during the first trimester for which follow-up was obtained resulting in 11 pregnancies with 12 births with no malformations, 4 pregnancy losses, and 2 terminations. Two women reportedly used medication throughout pregnancy.

BAP = British Association for Psychopharmacology; PK = pharmacokinetic; RANZCP = Royal Australian and New Zealand College of Psychiatrists; RR = relative risk.

such as bupropion, mirtazapine, and trazodone, have limited data. Bupropion is not considered a first-line agent during pregnancy due to possible associations with spontaneous abortion or cardiac malformations though there are conflicting reports highlighting no risk.[5,21–24] Clinically, bupropion may be considered for depressed women who have failed nonpharmacologic smoking cessation attempts as well as nicotine replacement therapy or who have failed other agents and cannot be switched.[5]

In clinical practice, when psychotic symptoms (such as hearing music, muffled talking, or paranoid thoughts) are present, an antipsychotic agent as adjunct therapy may be considered for MDD or postpartum depression, similar to treatment of bipolar disorder.[7,19] Data related to antipsychotic medication use in pregnancy comes from data with patients diagnosed with schizophrenia, bipolar disorder, and depression.[5,25] Reinitiating lithium as adjunctive therapy could be considered for treatment-resistant depression associated with pregnancy though this is more commonly recommended for bipolar disorder or postpartum depression with psychosis. Evidence is lacking regarding use of adjunct agents for MDD in pregnancy, but in clinical practice, selection of adjunct agents is similar for those who are not pregnant (eg, antidepressant with alternative mechanism of action, antipsychotic medications, or lithium to target remaining complaints or symptoms). Another consideration includes increasing the dose of lithium to account for possible pharmacokinetic changes in pregnancy if the patient has been adherent and the medication was reported to have been working previously.[5,7,19,26]

Case Outcome

Becausee TM has continual suicidal thoughts, intent, a plan, and means, she is considered high risk and appropriate for inpatient admission to ensure a safe environment.[16] Because the patient had a positive response to fluoxetine in the past, is 34 weeks pregnant, and the baby has already been exposed to fluoxetine, a first-line intervention will be to optimize fluoxetine dosing by increasing to fluoxetine 80 mg by mouth daily.[2,5,7] In the case of poor response to an increased dose of fluoxetine, another antidepressant could be considered. It would be pertinent to speak with TM regarding all past medication trials to determine what previously worked well. Selecting a medication with a history of positive response should be initiated to provide efficacy and limit subsequent drug exposures for the baby. If auditory hallucinations continue with antidepressant treatment, an antipsychotic could be considered. Risks and benefits of lithium were discussed with TM, and rationale was provided for discontinuation though it may be an alternative option (Table 4). Because TM was nonadherent to lithium, exposure to the baby was limited and would not warrant further use and titration at this time. When comparing lithium to initiating another agent with less fetal risk, such as a different antidepressant or adjunctive antipsychotic, the latter may be preferred.[7,15] Recommendations for lithium use during pregnancy generally are to gradually taper until discontinuation prior to conception when possible for mild or infrequent episodes.[5] For moderate illness or risk of relapse, it is still recommended to taper lithium until discontinuation prior to conception and avoid lithium in the first trimester if possible.[5,7,26] Lithium, along with folic acid, may be restarted in the second trimester if needed, which occurred in this case. For severe illness, lithium may be continued for the duration of pregnancy with clear and complete patient education.[2,5,7] Fetal ECG monitoring and anatomical evaluations are recommended for babies exposed to lithium in the first trimester.[2,7] It is also recommended to discontinue lithium 48 to 72 hours prior to expected delivery or to reduce dose prior to the onset of delivery to assist in preventing possible lithium toxicity in the infant.[2,5,7,26,27] The medication may be restarted at a prepregnancy dose immediately following delivery for relapse prevention if the patient does not wish to breastfeed.[5,7,26,27] Because TM is at 34 weeks and likely to deliver her baby in the next 6 weeks, lithium could be continued or discontinued based on available literature. In this case, the multidisciplinary team decided that the continued use of lithium should be avoided and rationale for use would be reevaluated later. The patient was also instructed not to take zolpidem. A safety plan with clear instructions for what to do during periods of suicidal thoughts was developed with the patient prior to discharge with weekly obstetric follow-up and psychiatric follow-up in 2 weeks. Patients should be educated about all potential medication risks (Tables 2 through 4).[5,8,12,16–24,26–53]

Treatment Nonadherence and Long-Acting Injectable Antipsychotics (LAIAs)

SG, a 29-year-old, pregnant (9 weeks and 6 days) patient was brought to the emergency department (ED) by police after being reported missing for days and found wandering around the airport dressed inappropriately for the season. Officers described SG as incoherent, fearful, disheveled, and confused. SG denied suicidal ideation but reported homicidal ideation toward her cousin, endorsed visual hallucinations of a snake and auditory hallucinations of her cousin talking to her boyfriend, being stalked by multiple people, and being unable to sleep for several days. Prior to transfer to the psychiatric unit, SG's phone was taken away, resulting in agitation; yelling, kicking, and striking at staff; and trying to elope. Her boyfriend, who was present in the ED, stated these outbursts occur frequently following similar, seemingly small requests. Haloperidol 5 mg intramuscular (IM) was given once after verbal de-escalation attempts failed and oral agents were refused.[54,55] SG takes medications off and on, which is

TABLE 3: Evidence for commonly used antipsychotic medications in pregnancy[5,8,12,16,18,19,31,40-51,53]

Medication	Recommendation	Note or concern
Antipsychotics	There are now more published safety data for second generation antipsychotics than first generation antipsychotics. Extrapyramidal and/or withdrawal symptoms, including agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder are reported in neonates who were exposed to antipsychotic drugs during the third trimester of pregnancy.	
First generation antipsychotics	Neuroleptic malignant syndrome Dyskinesia Extrapyramidal side effects Neonatal jaundice Postnatal intestinal obstruction	
Chlorpromazine	May be used	Likely not teratogenic Monitor infant for extrapyramidal syndrome (when used near delivery or late in pregnancy), jaundice, and/or hyper- or hyporeflexia
Haloperidol	Preferred if first generation antipsychotics is needed; most safety data	Possible limb malformations One case of persistent tongue thrusting and poor feeding Withdrawal syndrome
Perphenazine	Considered an alternative agent	Evidence ranges from no adverse effects to might have been caused by the medication Used as an antiemetic during labor without observable effects on the newborn
Second generation antipsychotics	Low birth weight Large for gestational age Increased therapeutic abortions Increased risk of metabolic disturbances (gestational diabetes, obesity, hypertension) Fetal growth abnormalities Preterm birth Congenital malformations Withdrawal symptoms such as agitation, feeding disorder, hypertonia, hypotonia, respiratory distress, somnolence, and tremor	
Aripiprazole	Alternative preferred; limited human data; weigh benefit versus risk for continuation	Transient neonatal cardiac rhythm effects possible Cohort study: 86 exposed to aripiprazole (30 in first trimester, 18 entire pregnancy) versus control group revealed possible low birth weight, intrauterine growth restriction. Two major malformations occurred (cardiac, esophageal), but benzodiazepines and selective serotonin reuptake inhibitors were used. Two cases of withdrawal with one exposed to methadone. Another review of first trimester exposures reported no increased risk of malformations.
Brexpiprazole	No published data Weigh risk versus benefit	May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure per package insert
Cariprazine	No published data Weigh risk versus benefit	May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure per package insert
Clozapine	Routine use not recommended but can be used If prior to conception, change to alternative if possible If fetus already exposed, weigh risk and benefit of changing agent May be continued in those who cannot tolerate a switch	Not linked with congenital malformations; data limited Third trimester use may cause extrapyramidal and/or withdrawal symptoms Possible effect on infant sleep, behavior, and development
Lumateperone	No published data Weigh risk versus benefit	May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure per package insert
Lurasidone	Limited data Weigh risk versus benefit	One case report with no reported congenital abnormalities present with C-section delivery at 40 + 5 weeks due to preeclampsia and concerning fetal heart tracing. Bupropion and folic acid were used during pregnancy. Therapy was interrupted from 20 to 24 weeks with only lurasidone being continued after 24 weeks.

TABLE 3: Evidence for commonly used antipsychotic medications in pregnancy[5,8,12,16,18,19,31,40-51,53] (continued)

Medication	Recommendation	Note or concern
		Drug concentrations were followed and dose increase required during second trimester. A 2018 study with 24 pregnancies exposed to lurasidone with no malformations or fetal demise reported. Neonatal outcomes were reportedly similar to other second generation antipsychotics and lamotrigine.
Olanzapine	A preferred agent Conflicting evidence for use Weigh benefit versus risk	Reports of no malformations One report of cleft lip, encephalocele, and aqueductal stenosis out of 60 exposed babies Possible altered glucose tolerance in mother Large for gestational age Recommended to keep dose low near term
Paliperidone	Alternative preferred; limited human data; weigh benefit versus risk of continuation	17 exposed pregnancies resulting in 14 births of 15 live infants and no major malformations, 2 spontaneous abortions, 1 elective abortion
Quetiapine	A preferred agent Most reproductive safety data	Quetiapine not associated with an increased risk of malformations in a 2015 systematic review
Risperidone	May be used Moderate reproductive safety data	Reports of no malformations 2007 prospective and retrospective reports of 713 pregnancies where structural anomalies (brain, lip, palate) and spontaneous abortions were reported consistent with background rates. Associated with an increased rate of overall and cardiac malformations in a 2016 cohort of 1566 risperidone exposed babies
Ziprasidone	Alternative preferred; limited human data; weigh benefit versus risk for continuation	Case report of mother delivering health infant after taking citalopram and ziprasidone throughout pregnancy Another case report of an infant with cleft palate

consistent with history. Lithium has not been taken in 2 months, aripiprazole was self-stopped almost 3 weeks ago, and her last appointment was missed. Past psychiatric history includes bipolar I, recurrent, severe with psychotic features for 10 years; a mother and grandmother with bipolar disorder, and her father died by suicide in 2018. SG denies substances currently, but reports THC use in the past and currently resides with her boyfriend of 9 years. Past medical history includes hypotension and headache. Vital signs, laboratory tests, and diagnostics (UDS and ECG) were unremarkable except glucose = 199 mg/dL, A1c = 6.6%, and urine pregnancy test positive. Young Mania Rating Scale score was 25.

Limited data is available regarding rapid tranquilization (RT) in pregnancy, but agents with short half-lives are preferred.[54,55] Three primary medications are recommended if nonpharmacologic strategies and oral agents are insufficient. When IM medications are needed, haloperidol, lorazepam, or promethazine are preferred, but none is considered first-line over the others.[54] These medications may be used alone or in combination with the lowest effective dose used.[56] Benzodiazepines used near delivery can result in floppy infant syndrome.[54] Benzodiazepines should not be utilized in pregnancy unless necessary for acute treatment of anxiety or agitation.[54,55]

Alternatively, antipsychotics for RT used near delivery may lead to extrapyramidal symptoms for the baby.[54] Studies report moderately increased risks for several adverse maternal and infant outcomes (Table 3) when pregnant patients exposed to oral antipsychotics are compared to nonpsychiatric, antipsychotic-unexposed pregnancies.[57–59] Conversely, studies report limited associations between antipsychotics and adverse outcomes for the infant or mother when they compared pregnant patients who have a psychiatric diagnosis that are either exposed or unexposed to oral antipsychotics.[25,55,60,61] It is also important to consider that patients prescribed oral antipsychotic medications during pregnancy are more likely to have additional risk factors such as diabetes, hypertension, obesity, alcohol use, tobacco use, or use of other medications when compared with those not taking antipsychotic medications during pregnancy.[25,55,60] When those confounders are controlled, few differences in adverse outcomes are found between medicated and nonmedicated psychiatric illnesses during pregnancy.

To date, most evidence suggests first generation oral antipsychotics (FGAs) and second generation oral antipsychotics (SGAs) are not major teratogens. Available evidence reports no increased risk of stillbirth or spontaneous miscarriage though congenital malformations are reported.[18,61] Overall, there is little difference in fetal risks between FGAs

TABLE 4: Evidence for commonly used mood stabilizing medications in pregnancy[5,8,12,16,18,19,26,27,52]

Medication	Recommendation	Note or concern
Carbamazepine	Avoid if possible	Causes multiple serious fetal complications and adverse drug reactions Facial dysmorphism Fingernail hypoplasia Neural tube defects Cardiac abnormalities Growth retardation Spina-bifida
Lamotrigine	Preferred agent	Midline facial cleft reported in one registry Increased risk of recurrence during pregnancy because of declining concentrations with each trimester
Lithium	Consider maternal benefit versus fetal risk Avoid in first trimester if possible Preferred over Carbamazepine or Valproic acid in second and third trimesters	Teratogenic in first trimester Bradycardia Congenital malformations Cardiac arrhythmia (fetal and neonatal) Ebstein anomaly (1 in 400) Floppy infant syndrome Hypoglycemia Lithium toxicity Nephrogenic diabetes insipidus Premature birth Polyhydramnios Thyroid function changes (reversible)
Valproic Acid Derivatives	Avoid	Highest level of fetal anatomical and behavioral abnormalities, which may include Neural tube defects Craniofacial anomalies Spina-bifida Atrial septal defects Cleft palate Limb abnormalities Cardiovascular anomalies Neonatal hepatotoxicity Coagulopathies Hypoglycemia Withdrawal symptoms Fetal Valproate Syndrome Decreased IQ in school age children Increased risk of autism spectrum Varying degrees of cognitive impairment Developmental delays

and SGAs or between individual antipsychotics, but data for some individual antipsychotics, such as brexpiprazole, cariprazine, lurasidone, and lumateperone, are limited.[48–53] Oral antipsychotics can be utilized in pregnancy with quetiapine and haloperidol being preferred. Routine use of clozapine should be avoided if possible unless benefits outweigh risks.[18,19,31] In practice, however, patients prescribed clozapine have most likely failed multiple trials other antipsychotic agents and, therefore, must continue with treatment utilizing clozapine. Olanzapine has conflicting evidence for use (Table 3), and aripiprazole and risperidone have limited-to-moderate data (Table 3).

There is higher relapse potential among pregnant patients with severe illness who are medication nonadherent.[62,63] Currently, pregnancy is not a contraindication for using LAIAs.[64–66] Essentially, reported adverse effects from oral antipsychotics, when compared against the LAIA counterparts, are similar. Reinstein et al recommend a similar criterion be applied to determine appropriateness of LAIA, whether pregnant or not, such as medication nonadherence, especially when leading to hospitalizations; severe illness with extended hospitalizations associated with bipolar disorder; schizophrenia and schizoaffective disorder; previous decompensation during pregnancy; or substance use associated with poorly controlled illness.[67,68] LAIAs in pregnancy may be especially beneficial because first pass metabolism is avoided, which may limit fetal exposure to fluctuating plasma concentrations. Pharmacokinetic changes occurring in pregnancy (eg, increased body mass and blood volume) could make an LAIA with more frequent administrations appealing, so dosing can be adjusted as needed or discontinued if adverse effects occur. Alternatively, for patients who have difficulty keeping appointments, LAIAs with longer dosing intervals may be preferable. Patient-specific

TABLE 5: Long-acting injectable antipsychotics (LAIAs) and evidence to support use[65-70,74-83]

Medication	Summary of Evidence
Second Generation Antipsychotics	
Aripiprazole	Case 1: LAI aripiprazole continued throughout the duration of pregnancy (400 mg then 300 mg) for bipolar disorder. Obstetric visits from weeks 16 to 38 revealed no fetal malformations or development issues, and pregnancy progressed without complications. At birth (at 40 + 4 weeks) and for 5 months after no complications, malformations, or developmental abnormalities were reported.[66]
	Case 2: LAI aripiprazole continued throughout the duration of pregnancy (400 mg, then 300 mg) for schizophrenia. Delivered at 41 weeks with no neonatal or obstetric complications.[82]
Olanzapine	Case 1: LAI olanzapine 405 mg every 4 weeks initiated between weeks 23 and 24 gestation for psychosis. Induced vaginal delivery at 40 weeks' gestation, secondary to relapsing psychotic symptoms and hospitalization. No abnormalities reported and development reported as normal through 36 months of age.[83]
Paliperidone	Case 1: LAI paliperidone palmitate 156 mg (100 mg as base) for schizophrenia, administered IM every month, added haloperidol 5 mg PO daily at 28 weeks' gestation. Patient experienced a normal, healthy pregnancy with no abnormal findings at regular obstetric visits. C-section at 40 weeks with no complications and baby was without malformation or growth retardation through 4 months postpartum.[65]
	Case 2: LAI paliperidone palmitate 234 mg (150 mg as base), administered IM every month and continued throughout pregnancy. Excessive amniotic fluid was noted during pregnancy and club feet present upon C-section at 39 weeks. Mother used marijuana and alcohol throughout the pregnancy.[74]
	Case 3: LAI paliperidone palmitate 156 mg (100 mg as base), administered IM, decreased to 50 mg at 5 weeks. Delivered at 40 weeks with no malformations or issues noted. No abnormalities reported for the baby at 12 months of age. Mother also used venlafaxine, clonazepam, fluoxetine, lorazepam, alcohol, and cigarettes during pregnancy.[75]
	Case 4: LAI paliperidone palmitate 410 mg (263 mg as base), administered IM every 3 months. Presented to ER with stomach pain and was in labor. No issues with infant reported at 12 months. No prenatal care throughout pregnancy.[76]
Risperidone	Case 1: LAI risperidone 25 mg, injected every 2 weeks for schizophrenia. No abnormalities seen at regular obstetric visits, and baby was delivered at 36 weeks + 6 days after premature rupture of membranes. No congenital malformations or developmental abnormalities noted within first 8 months of life.[70]
	Case 2: LAI risperidone 50 mg every 2 weeks for bipolar disorder (+ oral risperidone, citalopram, benztropine). Induction at 35 weeks due to concerns for placental insufficiency and intrauterine growth restrictions. Infant with bilateral supernumerary digits (family trait, removed surgically). Baby reportedly meeting developmental milestones at 16 months of age.[77]
First Generation Antipsychotics	
Fluphenazine	Case 1: Fluphenazine decanoate 2 mL IM every 3 weeks for psychosis secondary to TBI delivered at 41 weeks. Minor extrapyramidal symptoms or withdrawal symptoms were reported 4 weeks after delivery. Mother reported the baby was healthy at a 20-month follow-up. The mother reportedly drank alcohol and smoked cigarettes throughout pregnancy.[78]
	Case 2: Fluphenazine decanoate 50 mg IM every 2 weeks beginning at week 14 of gestation and increased to 100 mg at 24 weeks. This was added to oral chlorpromazine 1200 mg/day, and electroconvulsive therapy was started at week 18. The baby was delivered at 39 weeks and was described as normal. At 3 weeks old, the baby developed choreiform, dystonic movements (upper limbs), hypertonicity, irritability, and jittery behavior. Treatment for fluphenazine withdrawal was started at that time and continued through 6 months of age. The mother reportedly smoked cigarettes during pregnancy.[79]
	Case 3: Fluphenazine enanthate injections throughout pregnancy for schizophrenia. The infant was born with cleft lip and palate, episodic rapid nystagmoid movements, imperforate anus, ocular hypertelorism with telecanthus, penoscrotal hypospadias, roving eye movements, rectourethral fistula, and poor ossification of frontal skull bone. The mother used doxylamine during the first trimester of pregnancy.[80]
Haloperidol	Case 1: Study with reported haloperidol use, but data grouped and reported by first and second generation antipsychotics and not individually.[81]

ER = emergency room; IM = intramuscular; PO = per os (by mouth).

factors and clinical judgment should be exercised when selecting the LAIA. Women who are taking antipsychotic medications during pregnancy should be monitored closely for gestational diabetes and hypertension.[67] Data for LAIAs during pregnancy are limited but summarized in Table 5.[65–70,74–83] In general, the antipsychotic effective in managing symptoms prior to pregnancy should be continued throughout pregnancy.[67] Considerations for medication selection in pregnancy

should be similar to that of nonpregnant patients (eg, affordability, efficacy, and tolerability).

Case Outcome

Because of SG's long-standing history of bipolar disorder with psychotic features and medication nonadherence, the decision to utilize an LAIA was made by the patient and multidisciplinary care team. SG's baby has been minimally exposed to aripiprazole (estimated 2 weeks or less), 1 dose of haloperidol, and no lithium. Therefore, any antipsychotic with evidence of previous effectiveness for the patient and safety data for pregnancy could be considered. The outpatient provider reported a history of good symptom control with LAI aripiprazole and paliperidone during times of adherence. Both paliperidone and aripiprazole are recommended as first-line monotherapy for bipolar mania according to the Canadian Network for Mood and Anxiety Treatments 2018; whereas, aripiprazole and risperidone are first-line options according to the National Institute for Health and Care Excellence and World Federation of Societies of Biological Psychiatry.[71–73] Although SG received aripiprazole 3 weeks prior to admission and haloperidol in the ED, paliperidone was selected for this patient due to published pregnancy data (Table 5),[65,66,69,70,74–82] history of previous personal use with positive outcomes, ability to access, and ease of initiation.[65–70,73–77] Both SG and her boyfriend received extensive medication education regarding the use of paliperidone in pregnancy. SG was started on oral paliperidone with dose titration to 6 mg over a 7-day hospitalization prior to discharge for outpatient LAIA administration. SG was referred to the obstetrician for pregnancy management and evaluation for potential gestational diabetes given her elevated A1c and observed hyperglycemia.

Conclusion

Whereas data regarding the safety of psychiatric medication during pregnancy is growing, efficacy data is still lacking in this population.[27] Preconception planning is paramount; utilization of medications with safety data in pregnancy should be considered for patients who wish to conceive. Special consideration should be given to all women of childbearing age whether they plan to conceive or not because unplanned pregnancy is possible. It is important for providers to encourage their patients to enroll in pregnancy registries for psychiatric medications. Additionally, providers are encouraged to publish evidence, at any level, related to pregnant patients diagnosed with a psychiatric illness whether or not they are receiving medication therapy. Drug safety during pregnancy does not correlate to safety during breastfeeding, and a separate risk-benefit analysis must be performed, but that is outside the scope of this manuscript. It is also important to remember the increased risk of suicidality in this population; therefore, objective monitoring should be conducted at each visit throughout pregnancy. Pregnant patients should be monitored more frequently than their nonpregnant counterparts, and drug concentrations, when appropriate, should be evaluated as there are numerous pharmacokinetic changes taking place during pregnancy. Because evidence is evolving, it is of utmost importance that healthcare providers review published medical literature before making practice decisions or educating patients. This article is intended to provide an overview and should not replace clinical judgment when caring for pregnant patients and their babies.

References

1. Rodriguez-Cabezas L, Clark C. Psychiatric emergencies in pregnancy and postpartum. Clin Obstet Gynecol. 2018;61(3):615-27. DOI: 10.1097/GRF.0000000000000377
2. ACOG practice bulletin: use of psychiatric medications during pregnancy and lactation. [Internet] 2008; 111(4):1001-20. Available from: http://www.aafp.org/afp/2008/0915/p772.html
3. Andersson L, Sundström-Poromaa I, Bixo M, Wulff M, Bondestam K, Åström M. Point prevalence of psychiatric disorders during the second trimester of pregnancy: a population-based study. Am J Obstetrics Gynecol. 2003;189(1):148-54. DOI: 10.1067/mob.2003.336
4. Brent RL. The role of the pediatrician in preventing congenital malformations. Pediatrics Rev. 2nd ed. 2011;32(10):411-22. DOI: 10.1542/pir.32.10.411
5. McAllister-Williams RH, Baldwin DS, Cantwell R. British Association for Psychopharmacology consensus guidance on the use of psychotropic medication preconception, in pregnancy and postpartum 2017. J Psychopharmacology 2017;31(5):519–52. Available from: https://www.bap.org.uk/pdfs/BAP_Guidelines-Perinatal.pdf
6. Khalifeh H, Hunt IM, Appleby L, Howard LM. Suicide in perinatal and non-perinatal women in contact with psychiatric services: 15 year findings from a UK national inquiry. Lancet Psychiatry. 2016;3(3):233-42. DOI: 10.1016/S2215-0366(16)00003-1
7. Bharadwaj B, Endumathi R, Parial S, Chandra PS. Management of psychiatric disorders during the perinatal period. Indian J Psychiatry. 2022;64(8):414. DOI: 10.4103/indianjpsychiatry.indianjpsychiatry_12_22
8. Malhi GS, Bell E, Bassett D, Boyce P, Bryant R, Hazell P, et al. The 2020 Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. Aust N Z J Psychiatry. 3rd ed. 2021;55(1):7-117. DOI: 10.1177/0004867420979353
9. Bayrampour H, Kapoor A, Bunka M, Ryan D. The risk of relapse of depression during pregnancy after discontinuation of antidepressants. J Clin Psychiatry. 2020;81(4). DOI: 10.4088/JCP.19r13134
10. Petersen I, Gilbert RE, Evans SJW, Man S-L, Nazareth I. Pregnancy as a major determinant for discontinuation of antidepressants. J Clin Psychiatry. 2011;72(7):979-85. DOI: 10.4088/JCP.10m06090blu
11. Ross LE, Grigoriadis S, Mamisashvili L, Vonderporten EH, Roerecke M, Rehm J, et al. Selected pregnancy and delivery outcomes after exposure to antidepressant medication: a systematic review and meta-analysis. JAMA Psychiatry. 2013;70(4):436-43. DOI: 10.1011/jamapsychiatry.2013.684
12. Niethe M, Whitfield K. Psychotropic medication use during pregnancy. J Pharm Pract Res. 2018;48(4):384-91. DOI: 10.1002/jppr.1483
13. Your pregnancy and childbirth: month to month. American College of Obstetricians and Gynecologists; 2021.
14. Koren G, Clark S, Hankins GDV, Caritis SN, Miodovnik M, Umans JG, et al. Effectiveness of delayed-release doxylamine and pyridoxine for nausea and vomiting of pregnancy: a randomized placebo controlled trial. Am J Obstetrics Gynecol. 2010;203(6):571.e1-7. DOI: 10.1016/j.ajog.2010.07.030
15. US Department of Veterans Affairs, US Department of Defense. VA/DoD clinical practice guideline for the management of major

depressive disorder. US Government Printing Office; 2022. Available from: https://www.healthquality.va.gov/.
16. Austin M-P, Highet N, Group EW. Mental health care in the perinatal period: Australian clinical practice guideline. Centre of Perinatal Excellence; 2017.
17. Norris MM. Use of Antidepressants during Pregnancy and Lactation. Ment Health Clin. 2013;3(2):58-60. DOI: 10.9740/mhc.n163520.
18. Briggs GG, Freeman RK, Yaffe SJ, Drugs in pregnancy and lactation, 12th ed. Lippincott Williams & Wilkins; 2021.
19. Larsen ER, Damkier P, Pedersen LH, Fenfer-Gron J, Mikkelsen RL, Nielsen RE, et al. Use of psychotropic drugs during pregnancy and breast-feeding. Acta Psychiatr Scand Suppl. 2015;(445):1-28. DOI:10.1111/acps.12479
20. Petersen JM, Esposito DB, Werler MM. Selective serotonin reuptake inhibitor use patterns among commercially insured US pregnancies (2005–2014). Arch Womens Ment Health. 2021;24(1):155-64. DOI: 10.1007/s00737-020-01027-x
21. Cole JA, Modell JG, Haight BR, Cosmatos IS, Stoler JM, Walker AM. Bupropion in pregnancy and the prevalence of congenital malformations. Pharmacoepidem. Drug Safe. 2007;16(5):474-84. DOI: 10.1002/pds.1296
22. Chun-Fai-Chan B, Koren G, Fayez I, Kalra S, Voyer-Lavigne S, Boshier A, et al. Pregnancy outcome of women exposed to bupropion during pregnancy: a prospective comparative study. Am J Obstet Gynecol 2005;192:932–6. PMID: 15746694.
23. Hendrick V, Suri R, Gitlin MJ, Ortiz-Portillo E. Bupropion use during pregnancy. Prim. Care Companion CNS Disord. 2017;19(5). DOI: 10.4088/PCC.17r02160
24. Figueroa R. Use of antidepressants during pregnancy and risk of attention-deficit/hyperactivity disorder in the offspring. J Dev Behav Pediatrics. 2010;31(8):641-8. DOI: 10.1097/DBP.0b013e3181e5ac93
25. Petersen I, McCrea RL, Sammon CJ, Osborn DPJ, Evans SJ, Cowen PJ, et al. Risks and benefits of psychotropic medication in pregnancy: cohort studies based on UK electronic primary care health records. Health Technol Assess. 2016;20(23):1-176. DOI: 10.3310/hta20230
26. Tillery EE, Tonet RL, Trahan CA. Oh baby! A review of mood stabilizers for bipolar disorder in the child-bearing woman. Ment Health Clin. 2013;3(2):61-70. DOI: 10.9740/mhc.n163522
27. Hedgepeth Kennedy ML. Medication management of bipolar disorder during the reproductive years. Ment Health Clin [Internet]. 2017;7(6):255-61. DOI: 10.9740/mhc.2017.11.255
28. MacQueen GM, Frey BN, Ismail Z, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: section 6. special populations: youth, women, and the elderly. Can J Psychiatry. 2016;61(9):588-603. DOI: 10.1177/0706743716659276
29. Anderson KN, Lind JN, Simeone RM, Bobo WV, Mitchell AA, Riehle-Colarusso T, et al. Maternal use of specific antidepressant medications during early pregnancy and the risk of selected birth defects. JAMA Psychiatry. 2020;77(12):1246-55. DOI: 10.1001/jamapsychiatry.2020.2453
30. Biffi A, Cantarutti A, Rea F, Locatelli A, Zanini R, Corrao G. Use of antidepressants during pregnancy and neonatal outcomes: an umbrella review of meta-analyses of observational studies. J Psychiatric Res. 2020;124(3):99-108. DOI: 10.1016/j.jpsychires.2020.02.023
31. Antipsychotic use during pregnancy and lactation: optimizing health for mother and newborn. Ment Health Clin. 2013;3(2):99-106. DOI: 10.9740/mhc.n164972
32. Ornoy A, Koren G. The effects of drugs used for the treatment of attention deficit hyperactivity disorder (ADHD) on pregnancy outcome and breast-feeding: a critical review. Curr Neuropharmacol. 2021;19(11):1794-804. DOI: 10.2174/1570159X18666201127164000
33. Einarson A, Choi J, Einarson TR, Koren G. Incidence of major malformations in infants following antidepressant exposure in pregnancy: results of a large prospective cohort study. Can J Psychiatry. 2009;54(4):242-6. DOI: 10.1177/070674370905400405
34. Louik C, Kerr S, Mitchell AA. First-trimester exposure to bupropion and risk of cardiac malformations. Pharmacoepidemiol Drug Saf. 2014;23(10):1066-75. DOI: 10.1002/pds.3661
35. Huybrechts KF, Bateman BT, Pawar A, Bessette LG, Mogun H, Levin R, et al. Maternal and fetal outcomes following exposure to duloxetine in pregnancy: cohort study. BMJ. 3rd ed. 2020;26:m237. DOI: 10.1136/bmj.m237
36. Bellantuono C, Bozzi F, Orsolini L. Safety of escitalopram in pregnancy: a case series. NDT. 2013;1333. DOI: 10.2147/NDT.S45951
37. Kulin NA, Pastuszak A, Sage SR, Schick-Boschetto B, Spivey G, Feldkamp M, et al. Pregnancy outcome following maternal use of the new selective serotonin reuptake inhibitors. JAMA. 1998;279(8):609. DOI: 10.1001/jama.279.8.609
38. Morrison CM. A case report of the use of vilazodone in pregnancy. Prim. Care Companion CNS Disord. 2014. DOI: 10.4088/PCC.13l01612
39. Shweiki S, Diav-Citrin O. Pregnancy outcome after first trimester exposure to vortioxetine: a case series. Birth Defects Res. 2021;113(6):511-5. DOI: 10.1002/bdr2.1864
40. Bellet F, Beyens M-N, Bernard N, Beghin D, Elefant E, Vial T. Exposure to aripiprazole during embryogenesis: a prospective multicenter cohort study. Pharmacoepidemiol Drug Saf. 7th ed. 2015;24(4):368-80. DOI: 10.1002/pds.3749
41. Ennis ZN, Damkier P. Pregnancy exposure to olanzapine, quetiapine, risperidone, aripiprazole and risk of congenital malformations. a systematic review. Basic Clin Pharmacol Toxicol. 3rd ed. 2015;116(4):315-20. DOI: 10.1111/bcpt.12372
42. Shao P, Ou J, Peng M, Zhao J, Chen J, Wu R. Effects of clozapine and other atypical antipsychotics on infants development who were exposed to as fetus: a post-hoc analysis. Plos One. 2015;10(4):e0123373. DOI: 10.1371/journal.pone.0123373
43. McKenna K, Koren G, Tetelbaum M, Wilton L, Shakir S, Diav-Citrin O, et al. Pregnancy outcome of women using atypical antipsychotic drugs. J Clin Psychiatry. 2005;66(4):444-9. DOI: 10.4088/JCP.v66n0406
44. Onken M, Mick I, Schaefer C. Paliperidone and pregnancy—an evaluation of the German Embryotox database. Arch Womens Ment Health. 2018;21(6):657-62. DOI: 10.1007/s00737-018-0828-z
45. Coppola D, Russo LJ, Kwarta RF Jr, Varughese R, Schmider J. Evaluating the postmarketing experience of risperidone use during pregnancy—pregnancy and neonatal outcomes. Drug Saf 2007;30:247–64. PMID: 17343431.
46. Werremeyer A. Ziprasidone and citalopram use in pregnancy and lactation in a woman with psychotic depression. Am J Psychiatry. 2009;166(11):1298. DOI: 10.1176/appi.ajp.2009.09060765
47. Peitl MV, Petrić D, Peitl V. Ziprasidone as a possible cause of cleft palate in a newborn. Psychiatr Danub. 2010;22(1):117-9. PMID: 20305605.
48. Product information. Rexulti. Otsuka Pharmaceutical Co.; 2015.
49. Product information. Vraylar. Allergan; 2017.
50. Product information. Caplyta. Intra-Cellular Therapies; 2019.
51. Product information. Latuda. Sunovion; 2017.
52. Kernizan N, Yancey A, Forinash A, Booth M, Bajwa A, Mathews K. Evaluation of mood stabilizers on neonatal outcomes during pregnancy. (Abstract). J Am Coll Clin Pharm 2019;2:563–71. DOI: 10.1002/jac5.1153
53. Montiel C, Newmark RL, Clark CT. Perinatal use of lurasidone for the treatment of bipolar disorder. Exp Clin Psychopharmacol. 2022;30(2):249-52. DOI: 10.1037/pha0000509
54. Chaudhry SK, Gordon-Elliott JS, Brody BD. The Cornell peripartum psychosis management tool: a case series and template. Psychosomatics. 2016;57(3):319-24. DOI: 10.1016/j.psym.2015.09.004
55. Patel MX, Sethi FN, Barnes TR, Dix R, Dratcu L, Fox B, et al. Joint BAP NAPICU evidence-based consensus guidelines for the

clinical management of acute disturbance: de-escalation and rapid tranquillisation. J Psychopharmacol. 2018;32(6):601-40. DOI: 10.1177/0269881118776738
56. National Institute for Health and Care Excellence, Antenatal and postnatal mental health: clinical management and service guidance. NICE Clinical Guideline CG192. National Institute for Health and Care Excellence; 2014.
57. Ladavac AS, Dubin WR, Ning A, Stuckeman PA. Emergency management of agitation in pregnancy. Gen Hosp Psychiatry. 2007;29(1):39-41. DOI: 10.1016/j.genhosppsych.2006.09.003
58. Habermann F, Fritzsche J, Fuhlbrück F, Wacker E, Allignol A, Weber-Schoendorfer C, et al. Atypical antipsychotic drugs and pregnancy outcome: a prospective, cohort study. J Clin Psychopharmacol. 2013;33(4):453-62. DOI: 10.1097/JCP.0b013e318295fe12
59. Sadowski A, Todorow M, Yazdani Brojeni P, Koren G, Nulman I. Pregnancy outcomes following maternal exposure to second-generation antipsychotics given with other psychotropic drugs: a cohort study. Bmj Open. 2013;3(7):e003062. DOI: 10.1136/bmjopen-2013-003062
60. Bodén R, Lundgren M, Brandt L, Reutfors J, Kieler H. Antipsychotics during pregnancy. Arch Gen Psychiatry. 2012;69(7). DOI: 10.1001/archgenpsychiatry.2011.1870
61. Vigod SN, Gomes T, Wilton AS, Taylor VH, Ray JG. Antipsychotic drug use in pregnancy: high dimensional, propensity matched, population based cohort study. BMJ. 2015;350:h2298. DOI: 10.1136/bmj.h2298
62. Teodorescu A, Ifteni P, Moga MA, Burtea V, Bigiu N. Dilemma of treating schizophrenia during pregnancy: a case series and a review of literature. Bmc Psychiatry. 2017;17(1). DOI: 10.1186/s12888-017-1475-z
63. Taylor CL, Broadbent M, Khondoker M, Stewart RJ, Howard LM. Predictors of severe relapse in pregnant women with psychotic or bipolar disorders. J Psychiatr Res. 2018;104:100-7. DOI: 10.1016/j.psychires.2018.06.019
64. Ellfolk M, Leinonen MK, Gissler M, Kiuru-Kuhlefelt S, Saastamoinen L, Malm H. Second-generation antipsychotic use during pregnancy and risk of congenital malformations. Eur J Clin Pharmacol. 2021;77(11):1737-45. DOI: 10.1007/s00228-021-03169-y
65. Özdemir AK, Pak SC, Canan F, Geçici Ö, Kuloğlu M, Gücer MK. Paliperidone palmitate use in pregnancy in a woman with schizophrenia. Arch Women Ment Health. 2015;18(5):739-40. DOI: 10.1007/s00737-014-0496-6
66. Ballester-Gracia I, Pérez-Almarcha M, Galvez-Llompart A, Hernandez-Viadel M. Use of long-acting injectable aripiprazole before and through pregnancy in bipolar disorder: a case report. Bmc Pharmacol Toxicol. 2019;20(1). DOI: 10.1186/s40360-019-0330-x
67. Reinstein SA, Cosgrove J, Malekshahi T, Deligiannidis KM. Long-acting injectable antipsychotic use during pregnancy. J Clin Psychiatry. 2020;81(6). DOI: 10.4088/JCP.20ac13597
68. Nguyen T, Frayne J, Watson S, Lebedevs T, Teoh S, Galbally M. Long-acting injectable antipsychotic treatment during pregnancy: outcomes for women at a tertiary maternity hospital. Psychiatry Res. 2022;313(1):114614. DOI: 10.1016/j.psychres.2022.114614
69. O'Sullivan DL, Byatt N, Dossett EC. Long-acting injectable antipsychotic medications in pregnancy: a review. J Acad Consult Liaison Psychiatry. 2022;63(1):53-60. DOI: 10.1016/j.jaclp.2021.08.011
70. Kim S-W, Kim K-M, Kim J-M, Shin I-S, Shin H-Y, Yang S-J, et al. Use of long-acting injectable risperidone before and throughout pregnancy in schizophrenia. Prog Neuro Psychopharmacol Biological Psychiatry. 2007;31(2):543-5. DOI: 10.1016/j.pnpbp.2006.09.017
71. Yatham LN, Kennedy SH, Parikh SV, Schaffer A, Bond DJ, Frey BN, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. Dipolar Disord. 2018;20(2):97-170. DOI: 10.1111/bdi.12609
72. Grunze H, Vieta E, Goodwin GM, Bowden C, Licht RW, Azorin JM, et al. Members of the WFSBP Task Force on Bipolar Affective Disorders Working on this topic. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: acute and long-term treatment of mixed states in bipolar disorder. World J Biol Psychiatry 2018;19(1):2-58. DOI: 10.1080/15622975.2017.1384850
73. National Institute for Health and Care Excellence. Clinical guideline CG185. Bipolar disorder: assessment and management [cited 2020 Dec 12]. Available from: https://www.nice.org.uk/guidance/cg185
74. Binns R, O'Halloran SJ, Teoh S, Doherty K, Joyce DA. Placental transfer of paliperidone during treatment with depot formulation. J Clin Psychopharmacol 2017;37:474–5. PMID: 28486258.
75. Zamora Rodríguez FJ, Benítez Vega C, SánchezWaisen MR, et al. Use of paliperidone palmitate throughout a schizoaffective disorder patient's gestation period. Pharmacopsychiatry 2017;50:38-40. DOI: 10.1055/s-0042-110492
76. de Azevedo Avelar R, Corbal AL, Heitor MJ. A case report of pregnancy and paliperidone palmitate 3-monthly long-acting injection. Clin Case Rep 2020;8:2592-4. DOI: 10.1002/ccr3.3213
77. Clinebell K, Gannon J, Debrunner S, et al. Long-acting risperidone injections in a pregnant patient with bipolar disorder. Bipolar Disord 2017;19:606-7. DOI: 10.1111/bdi.12572
78. Cleary MF. Fluphenazine decanoate during pregnancy. Am J Psychiatry 1977;134:815-6. PMID: 869065.
79. O'Connor M, Johnson GH, James DI. Intrauterine effect of phenothiazines. Med J Aust 1981;1:416-7. PMID: 7254089.
80. Donaldson GL, Bury RG. Multiple congenital abnormalities in a newborn boy associated with maternal use of fluphenazine enanthate and other drugs during pregnancy. Acta Paediatr Scand. 1982;71(2):335-8. DOI: 10.1111/j.1651-2227.1982.tb09428.x
81. Nguyen T, Frayne J, Watson S, Lebedevs T, Teoh S, Galbally M. Long-acting injectable antipsychotic treatment during pregnancy: outcomes for women at a tertiary maternity hospital. Psychiatry Res. 2022;313(1):114614. DOI: 10.1016/j.psychres.2022.114614
82. Sole E, Ignacio Duran J, Lera S, Torres A, Andres S, Garriga M, et al. S206. Aripiprazole long-acting injectable in schizophrenia during pregnancy: a case report. Schizophrenia Bulletin. 2020;46(Supplement_1):S117. DOI: 10.1093/schbul/sbaa031.272
83. Manouilenko I, Öhman I, Georgieva J. Long-acting olanzapine injection during pregnancy and breastfeeding: a case report. Arch Womens Ment Health. 2018;21(5):587-9. DOI: 10.1007/s00737-018-0840-3