

HPI: TZ is a 26-year-old married woman who suffers from bipolar disorder and is well maintained on mood-stabilizing medications. At a routine follow-up appointment, she tells you that she and her husband are considering starting a family.

She was first diagnosed with bipolar affective disorder when she presented with a manic episode at age 19. She was originally stabilized on a combination of an antipsychotic haloperidol and lithium. After taking lithium for 2 years her mood stabilizer was changed to valproic acid, as she was complaining of intolerable side effects. She has been hospitalized twice for manic episodes and treated as an outpatient for depression. She has never abused substances and does not use tobacco products. She has never been suicidal. She has a family history of bipolar disorder and major depression. She graduated from college and works as a dental hygienist. She lives in a rented apartment with her husband of 2 years, who works as a mechanic. She is taking prenatal vitamins and valproic acid 750 mg by mouth twice daily.

PE: Results of a recent annual physical with Chem 7, CBC, TFT, and UA were all within normal limits. Recent valproic acid level was 80 $\mu\text{g/mL}$ (reference range is 50–125 $\mu\text{g/mL}$).

MSE: She is well presented, her affect is of normal range, and her mood is euthymic. There is no evidence of psychosis and cognitive functions are intact.

Thought Questions

- What are your concerns about medications should this patient become pregnant?
- What other psychiatric medications can cause problems during pregnancy and during breast-feeding?
- What side effects of lithium may have proved intolerable?

Basic Science Review and Discussion

Care must be taken when prescribing **any medications** during pregnancy and while breast-feeding, but particular caution should be taken with psychiatric medications. The dangers to the fetus must be compared with the dangers of psychiatric illness, such as psychosis or depression. When a woman becomes pregnant her psychiatric medications and her mental state should be reviewed immediately, as the hormonal changes of pregnancy may cause changes in her psychiatric disorder.

Antipsychotic Agents Antipsychotic agents should be avoided in the first trimester, if possible. Although there is no conclusive evidence that these agents are teratogenic, low-potency agents such as chlorpromazine may increase the risk of fetal malformations. Low-potency agents may also cause hypotension. In general, if they are needed, high-potency agents such as haloperidol should be used. Breast-feeding is not contraindicated in those taking phenothiazines. Antiparkinsonian agents should not be prescribed routinely to those who are pregnant. There have been case reports of feeding difficulties, hypertonicity, and dystonic and parkinsonian movements in infants exposed to antipsychotic agents.

Antidepressants If possible, depressive symptoms in the first trimester should be treated with supportive measures and **psychoactive medications should be avoided**, but if severe depression develops, medications may be necessary, electroconvulsive therapy (ECT) may also be considered. Limb deformities have been reported with tricyclics, but the studies of teratogenesis remain inconclusive. Some agents such as amitriptyline, trimipramine, and trazadone have been reported to be associated with poor outcomes in animal studies. There is concern about the neurologic development of the fetus with the use of tricyclic agents in the second and third trimesters, and a withdrawal syndrome has been reported in neonates. The long-term effects of exposure to tricyclic antidepressants in breast milk are unknown and should be avoided, if possible. Monoamine oxidase inhibitors (MAOI) are contraindicated in pregnancy, as there have been reports of growth retardation in animal studies and these agents may exacerbate pregnancy-induced hypertension and affect placental perfusion. These agents are also contraindicated with the use of beta-mimetic agents in premature labor and opioids during labor itself. Selective serotonergic reuptake inhibitors (SSRI) are usually regarded as safe in pregnancy, but there is concern about possible behavioral teratogenicity. Fluoxetine may be associated with increased minor physical anomalies, but this remains controversial. There is less information about the safety of venlafaxine, nefazadone, and bupropion.

Mood Stabilizers Lithium should be avoided in the first trimester because of possible teratogenesis, namely Ebstein's anomaly (hypoplasia of the right ventricle and abnormalities of the tricuspid valve) which may occur in 1 in 1000 exposed. Lithium may cause neonatal goiter and impair vaginal delivery, as well as result in neurologic and

cardiovascular abnormalities in the neonate. Hence, it should be avoided in the first trimester and monitored closely during the rest of pregnancy because, if it must be used, the dramatic changes in fluid volume and renal function caused by pregnancy necessitate higher doses than in the nonpregnant state. After labor, rapid fluid loss may cause toxic effects, and lithium doses should be decreased 2 weeks before delivery and carefully monitored. The physician should look for evidence of toxic effects in the neonate. Lithium is secreted in breast milk, and neonatal renal function may lead to toxicity, with cyanosis, poor muscle tone, and cardiac abnormalities. It is therefore contraindicated during breast-feeding. Other agents, such as the anticonvulsants carbamazepine and valproic acid, have been reported to be associated with a tenfold increased risk (1% to 5%) of neural tube defects such as spina bifida. There are reports of cleft palates in those exposed to these drugs in the first

trimester. However, these agents may be safer than lithium in those who wish to breast-feed.

Benzodiazepines Diazepam crosses the placenta and has been reported to have a twofold increase in cleft lips and palate. The question of its teratogenesis remains unresolved; therefore it should be avoided in the first trimester. Occasional use in the second and third trimesters is not thought to have ill effects. Clonazepam may be used in the first trimester to control manic symptoms if antipsychotics cannot control symptoms. Impaired temperature regulation, apnea, low apgar scores, feeding difficulties, and hypotonicity have been reported in neonates exposed to benzodiazepines.

Miscellaneous Neonates may show withdrawal effects if the mother has been dependent on alcohol or opiates. Alcohol itself is a known teratogen and causes fetal alcohol syndrome.

Case Conclusion TZ was encouraged to plan her pregnancy carefully in close coordinated care with her obstetrician. She returns to visit you when she finds out she is pregnant. After careful discussion with both the patient and her husband, you decide to taper and discontinue the valproic acid and maintain her on low doses of haloperidol. During the second trimester, you restart the valproic acid at a lower dose and monitor her carefully throughout her pregnancy. She delivers a healthy baby boy, her medications are increased to her usual doses, and she is further carefully monitored for her high risk of postpartum relapse.

Thumbnail: Behavioral Science—Pharmacology of Lithium

Uses	Control of acute mania and prophylaxis of recurrent bipolar, unipolar disorder and schizoaffective disorder. It is used as an augmenting agent in schizophrenia.
Pharmacokinetics	Rapidly absorbed by oral route; complete within 6 to 8 hours. Peak plasma levels within 30 minutes to 2 hours. Not protein bound. Not metabolized; excreted unchanged by the kidney. Rates of clearance depend on renal function and follow sodium reabsorption in the proximal tubules. Increased sodium intake causes decreased reabsorption, and a sodium-restricted diet causes increased lithium reabsorption, leading to toxicity.
Therapeutic action	Exact mechanism of action remains unknown but is thought to influence sodium and calcium transfer across membranes, affecting neurotransmitter release and receptor activity; also acts via inhibiting cAMP second messenger systems. Stimulates Na and Mg-dependent ATPase. Increases uptake of tryptophan by serotonergic neurons.
Adverse effects	Early side effects: Nausea, vomiting and diarrhea, fine tremor, dry mouth, fatigue, drowsiness, nasal congestion, and metallic taste. Long term: Nephrogenic diabetes insipidus with polyuria and polydipsia due to distal tubule becoming resistant to ADH in approximately 9% to 20% of users. Hypothyroidism in approximately 5% of users; females more commonly affected than males. Edema and weight gain. Cardiac effects include T-wave flattening and arrhythmias. Neurologic effects include choreoathetosis, ataxia, dysarthria, tardive dyskinesia, and memory impairment. Acne and alopecia. Increased risk of Ebstein's anomaly in fetuses exposed in the first trimester of pregnancy. Reported hypotonicity and cyanosis in infants.
Drug interactions	Thiazides decrease lithium clearance by 30% to 50%. Low-salt diets, pregnancy, and diarrhea/vomiting/dehydration may increase levels. NSAIDs may also increase levels. Levels and risk of neurotoxicity may be increased by neuroleptics and carbamazepine. Levels of lithium decreased by theophylline, caffeine, antacids, acetazolamide, and osmotic diuretics.
Monitoring serum levels	Sampling should be drawn 12 hours after last dose to avoid peak levels. Such peaks and troughs are avoided with slow-release preparations. In acute disorders, serum levels should range between 0.8 and 1.2 mEq/L and maintenance, 0.6 to 0.8 mEq/L. In older persons keep at 0.5 mEq/L Toxic effects occur at levels greater than 2 mmol/L and may include tremor, ataxia, slurred speech, confusion, convulsions, coma, and death.

Key Points

- ▶ Care must be taken when prescribing any medications during pregnancy and while breast-feeding.
- ▶ Antipsychotic agents should be avoided in the first trimester if possible.
- ▶ If possible, treat depressive symptoms in the first trimester with supportive measures and avoid medications, but, if necessary, medications or ECT may be used.
- ▶ Lithium should be avoided in the first trimester because of possible teratogenesis and is contraindicated during breast-feeding.
- ▶ Diazepam has been reported to cause cleft lips and palate, and should be avoided in the first trimester.
- ▶ Neonates may show withdrawal effects if the mother has been dependent on alcohol or opiates.
- ▶ Lithium is an effective mood stabilizer but requires monitoring to minimize adverse effects.

Questions

1. Which of the following tests would you recommend to a patient taking lithium?
 - A. Urea, electrolytes, creatinine, thyroxine, TSH, and EKG monthly
 - B. Follow-up lithium levels weekly
 - C. EKG every 6 months
 - D. Urea, electrolytes, creatinine, thyroxine, TSH, EKG, and pregnancy tests at baseline, followed by lithium levels every 8 weeks, repeat chemistry, and TFTs twice a year and EKG annually
 - E. Urea, electrolytes, creatinine, thyroxine, TSH, EKG, and pregnancy tests at baseline, followed by lithium levels every 12 weeks, repeat chemistry and TFTs three times a year, and EKG twice a year
2. When discussing the possible side effects of valproic acid with the above patient and her husband which of the following do you warn her about?
 - A. Nausea, vomiting, weight and hair loss
 - B. Nausea, vomiting, weight gain, and hair growth
 - C. Nausea, vomiting, weight gain, hair loss, agitation, neural tube defects in fetuses
 - D. Nausea, vomiting, weight gain, hair loss, sedation, tremor, and neural tube defects in fetuses
 - E. Nausea, vomiting, weight gain, hair loss, sedation, thyroid abnormalities, and neural tube defects in fetuses
3. In general, when prescribing medications to a patient, which of the following does not affect the distribution of a drug?
 - A. Edema
 - B. Pregnancy
 - C. Hypoparathyroidism
 - D. Obesity
 - E. Age
4. Which of the following statements is correct?
 - A. The therapeutic window is the ratio between the lethal dose and the clinically effective dose.
 - B. The therapeutic index is the range of concentration of a drug in the serum in which the drug has a maximum clinical effect.
 - C. Efficacy is a measure of a drug's maximum effect.
 - D. Potency is a measure of a drug's ability to produce a desired effect.
 - E. There are no drugs used in psychiatry that have a therapeutic window.