

AMERICAN ACADEMY OF PEDIATRICS

Committee on Drugs

Use of Psychoactive Medication During Pregnancy and Possible Effects on the Fetus and Newborn

ABSTRACT. Psychoactive drugs are those psychotherapeutic drugs used to modify emotions and behavior in the treatment of psychiatric illnesses. This statement will limit its scope to drug selection guidelines for those psychoactive agents used during pregnancy for prevention or treatment of the following common psychiatric disorders: schizophrenia, major depression, bipolar disorder, panic disorder, and obsessive-compulsive disorder. The statement assumes that pharmacologic therapy is needed to manage the psychiatric disorder. This decision requires thoughtful psychiatric and obstetric advice.

ABBREVIATION. FDA, Food and Drug Administration.

The primary literature on use of these drugs during pregnancy has been extensively reviewed in the past decade.¹⁻¹³ The serious consequences to the mother and fetus of not using these drugs during pregnancy also have been addressed.^{4,6,8,11,13} The Food and Drug Administration (FDA) classifies drugs for teratogenic risk as shown in Table 1.^{14,15} Friedman et al¹⁶ and the Public Affairs Committee of the Teratology Society¹⁷ have challenged these "Use-in-Pregnancy Ratings." These authors believe that the ratings do not provide sufficient useful therapeutic guidance to physicians and that the default assignment of agents to FDA category C is misleading to many practitioners who consider this rating to indicate some degree of risk (ie, more risk than that of category B) rather than a lack of information from studies in humans. They recommend FDA ratings be replaced by narrative statements that summarize and interpret available data regarding hazards of developmental toxicity and provide estimates of teratogenic risk. The Committee on Drugs is encouraged to note that an FDA subcommittee is actively working on this issue assisted by the Office of Research on Women's Health of the National Institutes of Health.¹⁸

Estimates of risk for drugs used during pregnancy are derived largely from case reports or retrospective cohort epidemiologic studies. These types of studies are often biased or flawed because of possible reporting bias and the many confounding variables, such as nutritional and health status; maternal age; use of alcohol, tobacco, or illicit drugs; environmental tox-

ins; history of miscarriages and stillbirths; genetic history; use of multiple drugs including nonprescription drugs; gestational age at time of drug exposure; compliance; total dose; and the effects of the psychiatric illness or other illnesses present. Our knowledge will remain limited because prospective, randomized, and well-controlled investigational studies on the risks of exposure to psychoactive drugs during pregnancy are neither feasible nor ethical.¹⁹ When psychoactive drugs are medically indicated during pregnancy, this exposure could provide an opportunity to conduct prospectively controlled comparisons of the fetal effects of these drugs to carefully matched controls. Recent prospective, well-controlled epidemiologic studies have lessened, to some extent, the concerns that lithium and fluoxetine are teratogenic.²⁰⁻²² Guidelines published in 1996²³ for the use of anticonvulsants during pregnancy are available.

With these limitations in mind, this statement provides literature-based guidelines to assist physicians with appropriate drug selection for women who contemplate pregnancy or are pregnant and who have psychiatric disorders that require drug treatment. Information about the effects of those drugs on the fetus and newborn is also provided. Detailed advice regarding drug selection is provided in the accompanying tables. The determination of which drug treatment to use entails the following: 1) physician and informed patient (family) risk-benefit analysis; 2) an assessment of risk for the fetus and the breastfed newborn²⁴; 3) consideration of skip-generation or first filial (F1) generation risk (eg, epidemiologic evidence of the development of vaginal cancer in the offspring of a mother exposed to diethylstilbestrol²⁵); and 4) the family medical history, especially a history of psychoactive drug treatment that was effective.

BENEFITS AND RISKS OF DRUG TREATMENT

Because of the potential for teratogenesis and other adverse events in the fetus or newborn, varying degrees of concern exist when any drug is prescribed during pregnancy. Avoidance of pregnancy and avoidance of drug therapy during pregnancy are commonly suggested strategies to prevent fetal drug exposure. However, these strategies are often not possible. It frequently becomes necessary to contemplate pharmacotherapy following counseling of a pregnant woman who has a serious psychiatric illness, because the benefit of appropriate psychoactive drug treatment has been clearly established.²⁶

Drug treatment is indicated if psychotherapy is inadequate or inappropriate for the patient's severity of

The recommendations in this statement do not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

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TABLE 1. FDA Use-in-Pregnancy Ratings

Category	Interpretation
A	Controlled studies show no risk. Adequate, well-controlled studies in pregnant women have failed to demonstrate risk to the fetus.
B	No evidence of risk in humans. Either animal findings show risk, but human findings do not, or if no adequate human studies have been done, animal findings are negative.
C	Risk cannot be ruled out. Human studies are lacking, and animal studies are either positive for fetal risk or lacking as well. However, potential benefits may justify the potential risk.
D	Positive evidence of risk. Investigational or postmarketing data show risk to the fetus. Nevertheless, potential benefits may outweigh the potential risk.
X	Contraindicated in pregnancy. Studies in animals or humans, or investigational or postmarketing reports have shown fetal risk that clearly outweighs any possible benefit to the patient.

illness. Once a decision to offer pharmacotherapy is made, important factors in drug selection for the mother include efficacy of the drugs available, the anticipated response of the individual patient, and the overall toxicity profile of the drug for the mother and fetus.

Potential adverse effects for the fetus and the ne-

onate include: 1) structural malformations, 2) acute neonatal effects including intoxication and neonatal abstinence syndromes, 3) intrauterine fetal death, 4) altered fetal growth, and 5) neurobehavioral teratogenicity. Neurobehavioral teratogenicity encompasses long-term central nervous system defects that result in delayed behavioral maturation, impaired problem solving, and impaired learning.²⁷ Physical malformations do not necessarily accompany the functional deficits. Chronic in utero exposure to drugs may result in intoxication or tolerance postnatally.²⁸ Neonatal drug withdrawal symptoms may occur when drug exposure ceases at birth.²⁹ Specific and supportive therapy may be required if the newborn displays signs of continued drug effects or withdrawal. Long-term developmental and neurologic follow-up is appropriate, including consideration for referral to centers for national databases (eg, Teratology Information Services and Motherisk Program).

GENERAL DOSING RECOMMENDATIONS

Before it is possible to predict potential adverse events based on pharmacokinetic data, considerable pharmacokinetic studies will be required in infants and children. Adverse drug events are often linked to the pharmacokinetic variations in maternal, placental, fetal, or neonatal drug absorption, distribu-

TABLE 2. Treatment of Schizophrenia During Pregnancy

Generic Name Trade Name	Relative Potency*	Remarks
Risperidone Risperdal	1 (High)	Neonatal effects: Signs at delivery associated with exposure to the low-potency group include tachycardia, gastrointestinal dysfunction, sedation, and hypotension. Depending on the extent of exposure, these reactions seldom persist for more than a few days. ⁴⁸
Fluphenazine Permatil Prolixin	2	
Olanzapine Zyprexa	†	Extrapyramidal signs that are associated with large maternal doses of high-potency antipsychotics include hyperactivity, hyperactive deep tendon reflexes, motor restlessness, and abnormal movements. ²⁸ These may persist for several months. Additional signs reflecting extrapyramidal activity include tremors, posturing and flapping of the hands, increased muscle tone, unusually vigorous rooting and sucking, arching of the back, and shrill crying.
Haloperidol Haldol	2	Teratogenic effects: Haloperidol, perphenazine, thiothixene and trifluoperazine do not have a known teratogenic action based on either animal data or limited surveillance data in humans. The lower potency agents, particularly chlorpromazine, have been cited as being teratogenic by some authors ⁴⁹ ; however, surveillance data do not support this finding for chlorpromazine, prochlorperazine, triflupromazine ⁵⁰ or thioridazine. ⁵¹ Most antipsychotic agents are not known to cause structural birth defects. Studies in animals suggest that neurobehavioral abnormalities occur. ^{2,52-56} Studies in humans ^{50,57} found no evidence of behavioral, emotional, or cognitive abnormalities, but some confounding variables were not controlled. ⁵
Pimozide Orap	2	
Thiothixene Navane	5	Guidelines: Despite the potential for drug-induced extrapyramidal reactions (usually self-limited) in the neonate, high-potency antipsychotic agents (ie, fluphenazine, haloperidol, perphenazine, thiothixene, and trifluoperazine) are preferred to minimize maternal anticholinergic, hypotensive, and antihistaminergic effects. data on the chlorprothixene, clozapine, loxapine, mesoridazine, molindone, olanzapine, pimozide, and risperidone are too limited to provide a recommendation. Long-action (depot) preparations of the high-potency group (fluphenazine enanthate, fluphenazine decanoate, and haloperidol decanoate) should be avoided in order to limit the duration of any possible toxic effect in the neonate. Withdrawal does not seem to be a serious problem with any of these agents in the mother or fetus.
Trifluoperazine Stealzine	5	
Perphenazine Trilafon	10	Guidelines: Despite the potential for drug-induced extrapyramidal reactions (usually self-limited) in the neonate, high-potency antipsychotic agents (ie, fluphenazine, haloperidol, perphenazine, thiothixene, and trifluoperazine) are preferred to minimize maternal anticholinergic, hypotensive, and antihistaminergic effects. data on the chlorprothixene, clozapine, loxapine, mesoridazine, molindone, olanzapine, pimozide, and risperidone are too limited to provide a recommendation. Long-action (depot) preparations of the high-potency group (fluphenazine enanthate, fluphenazine decanoate, and haloperidol decanoate) should be avoided in order to limit the duration of any possible toxic effect in the neonate. Withdrawal does not seem to be a serious problem with any of these agents in the mother or fetus.
Molindone Moban	10	
Loxapine Loxitane	15	Guidelines: Despite the potential for drug-induced extrapyramidal reactions (usually self-limited) in the neonate, high-potency antipsychotic agents (ie, fluphenazine, haloperidol, perphenazine, thiothixene, and trifluoperazine) are preferred to minimize maternal anticholinergic, hypotensive, and antihistaminergic effects. data on the chlorprothixene, clozapine, loxapine, mesoridazine, molindone, olanzapine, pimozide, and risperidone are too limited to provide a recommendation. Long-action (depot) preparations of the high-potency group (fluphenazine enanthate, fluphenazine decanoate, and haloperidol decanoate) should be avoided in order to limit the duration of any possible toxic effect in the neonate. Withdrawal does not seem to be a serious problem with any of these agents in the mother or fetus.
Prochlorperazine Compazine	15	
Triflupromazine Vesprin	25	Guidelines: Despite the potential for drug-induced extrapyramidal reactions (usually self-limited) in the neonate, high-potency antipsychotic agents (ie, fluphenazine, haloperidol, perphenazine, thiothixene, and trifluoperazine) are preferred to minimize maternal anticholinergic, hypotensive, and antihistaminergic effects. data on the chlorprothixene, clozapine, loxapine, mesoridazine, molindone, olanzapine, pimozide, and risperidone are too limited to provide a recommendation. Long-action (depot) preparations of the high-potency group (fluphenazine enanthate, fluphenazine decanoate, and haloperidol decanoate) should be avoided in order to limit the duration of any possible toxic effect in the neonate. Withdrawal does not seem to be a serious problem with any of these agents in the mother or fetus.
Chlorprothixene Taractan	50	
Mesoridazine Serentil	50	Guidelines: Despite the potential for drug-induced extrapyramidal reactions (usually self-limited) in the neonate, high-potency antipsychotic agents (ie, fluphenazine, haloperidol, perphenazine, thiothixene, and trifluoperazine) are preferred to minimize maternal anticholinergic, hypotensive, and antihistaminergic effects. data on the chlorprothixene, clozapine, loxapine, mesoridazine, molindone, olanzapine, pimozide, and risperidone are too limited to provide a recommendation. Long-action (depot) preparations of the high-potency group (fluphenazine enanthate, fluphenazine decanoate, and haloperidol decanoate) should be avoided in order to limit the duration of any possible toxic effect in the neonate. Withdrawal does not seem to be a serious problem with any of these agents in the mother or fetus.
Clozapine Clozaril	75	
Chlorpromazine Thorazine	100	Guidelines: Despite the potential for drug-induced extrapyramidal reactions (usually self-limited) in the neonate, high-potency antipsychotic agents (ie, fluphenazine, haloperidol, perphenazine, thiothixene, and trifluoperazine) are preferred to minimize maternal anticholinergic, hypotensive, and antihistaminergic effects. data on the chlorprothixene, clozapine, loxapine, mesoridazine, molindone, olanzapine, pimozide, and risperidone are too limited to provide a recommendation. Long-action (depot) preparations of the high-potency group (fluphenazine enanthate, fluphenazine decanoate, and haloperidol decanoate) should be avoided in order to limit the duration of any possible toxic effect in the neonate. Withdrawal does not seem to be a serious problem with any of these agents in the mother or fetus.
Thioridazine Mellaril	100 (Low)	

* Therapeutically equivalent oral dose (mg).⁵⁸

† In a study of patients suffering acute exacerbations of schizophrenic psychoses, doses of olanzapine between 7.5 and 17.5 mg/day were comparable in antipsychotic effect to haloperidol 10 to 20 mg/day.⁵⁹

TABLE 3. Treatment of Major Depression During Pregnancy

Drug Class Generic Name Trade Name	Remarks
Tricyclic antidepressants	Neonatal Effects: Signs in neonates exposed in utero to desipramine, imipramine, and nortriptyline include periodic apnea, cyanosis, tachypnea, irritability, seizures, feeding difficulties, heart failure, tachycardia, myoclonus, respiratory distress, and urinary retention. ⁶⁰⁻⁶³
Amitriptyline Elavil Endep	Teratogenicity: Tricyclics and fluoxetine do not have a known teratogenic effect in humans. ^{5,20} Miscarriages do not seem to be increased by fluoxetine. ⁶¹⁻⁶⁶ One birth defect (4 expected) among 100 patients occurred with exposure to trazodone. ⁷ Insufficient human data exist to ascertain the teratogenicity of bupropion, monoamine oxidase inhibitors, paroxetine, sertraline, or venlafaxine. Neurobehavioral abnormalities in animals have been cited. ^{2,67, 68} In utero exposure to various tricyclic antidepressant drugs or fluoxetine did not affect global IQ, language development, or behavioral development in preschool children. ⁵⁹
Amoxapine Asendin	
Clomipramine Anafranil	
Desipramine Norpramin Pertofrane	
Doxepin Sinequan	
Imipramine Janimine Tofranil	
Maprotiline Ludomil	
Nortriptyline Aventyl Pamelor	
Protriptyline Vivactil	
Trimipramine Surmontil	
Selective serotonin reuptake inhibitors	
Fluoxetine Prozac	
Fluvoxamine Luvox	
Paroxetine Paxil	
Sertraline Zoloft	
Venlafaxine Effexor	
Atypical antidepressants	
Bupropion Wellbutrin	
Mirtazapine Remeron	
Nafazodone Serzone	
Trazodone Desyrel	
Monoamine oxidase inhibitors	
Isocarboxazid Marplan	
Phenelzine Nardil	
Tranlycypromine Parnate	

tion, metabolism, and elimination.^{30,31} Some of these alterations are likely to increase or decrease the dose necessary for many drugs during pregnancy, thus increasing or decreasing the risk for fetal exposure. The change in dose can be complex depending on the trimester(s) of exposure. For example, to maintain serum levels within the therapeutic range, particularly in the third trimester, the dose of tricyclic antidepressant must be increased 1.6 times the mean dose required when the patients are not pregnant.³² In addition, some drugs tend to concentrate in the fetus, and their effects may be prolonged even after delivery.¹ It is advisable to monitor the effectiveness of treatment throughout pregnancy to achieve the lowest effective dose of any agent.

Depending on severity of the disorder and opinion of the attending physician in consultation with other physicians (eg, psychiatrist, pediatrician, or obstetrician), it may be advisable to discontinue psychoactive drug(s) by tapering the dose, especially for anti-anxiety drugs, ~2 weeks before the estimated delivery date to minimize neonatal effects. However, cessation of drug treatment is usually inappropriate for patients with severe disease, and it may be associated with discontinuation syndromes or recurrence of signs and symptoms.

SCHIZOPHRENIA

Comments on the common fetal, neonatal, and teratogenic effects of antipsychotic drugs, and guide-

TABLE 4. Treatment of Bipolar Disorder During Pregnancy

Drug Class Generic Name Trade Name	Remarks
Mood stabilizing drugs Carbamazepine Tegretol Lithium carbonate Eskalith Lithane Lithobid Lithonate Lithotabs Lithium citrate Cibalith-S Valproic acid Depakene Divalproex sodium Depakote	<p>Fetal and neonatal effects: The use of lithium during the second and third trimesters occasionally causes fetal thyroid goiter. Exposure of the mother to toxic amounts of lithium has caused in the fetus and newborn: cyanosis, hypotonia, bradycardia, atrial flutter, hepatomegaly, T-wave inversion, cardiomegaly, gastrointestinal bleeding, diabetes insipidus, seizures, and shock (reviewed in reference 7). Most of these adverse reactions are self-limiting and resolve within 1 to 2 weeks after birth.</p> <p>Teratogenic effects: Lithium is reported to produce congenital cardiovascular malformations (especially Ebstein's anomaly) in the fetus when used in the first trimester.⁷¹ A recent reevaluation of this risk based on cohort and case control studies^{20,72} concludes that Ebstein's anomaly is rare and the risk is much lower than originally reported.²¹ Animal studies cited by Kerns¹ suggest that neurobehavioral abnormalities may be produced by lithium. The only study in humans could not confirm this increased risk⁷³; however, the design has been questioned.^{5,11}</p> <p>The fetal hydantoin syndrome consisting of facial dysmorphism, cleft lip and palate, cardiac defects, digital hypoplasia, and nail dysplasia was initially ascribed to the use of phenytoin during pregnancy. It is now recognized to occur with carbamazepine and valproic acid as well.^{74,75} NTDs also are associated with carbamazepine (incidence: ~1%)⁷⁶ and valproic acid (incidence: 1%–2%).⁷⁷ Carbamazepine can cause a transient and reversible deficiency in vitamin K-dependent clotting factors in the neonate that may lead to intracerebral hemorrhage.⁷⁸ This effect can be minimized by prescribing 10 to 20 mg of vitamin K orally at 36 weeks of gestation until delivery. Valproic acid has been associated with intrauterine growth retardation, hyperbilirubinemia, hepatotoxicity, skeletal dysplasia, and fetal/newborn distress.⁷</p> <p>Guidelines: Lithium has been the major antimanic agent used in bipolar disorder. Unfortunately, the use of lithium is ineffective or poorly tolerated in at least one third of patients, and it has the narrowest therapeutic index of any agent routinely prescribed in psychiatric practice.⁷⁹ Alternatively, a high-potency antipsychotic agent can be added or substituted if needed. Even though recent data suggest that the risk of Ebstein's anomaly from first trimester use of lithium is very low, cardiac ultrasonography is recommended at 18 to 20 weeks of gestation. Serum lithium concentrations should be monitored monthly in early pregnancy and weekly near delivery; however, lithium should be reinstated promptly after delivery to overcome postpartum depression. Avoidance of sodium depletion and avoidance of a low salt diet are recommended to prevent lithium toxicity.</p> <p>The USPHS recommends that all women of childbearing age in the United States who are capable of becoming pregnant should consume 400 μg (0.4 mg) of folic acid per day for the purpose of preventing spina bifida and other NTDs. USPHS guidelines also advise that higher risk women who are planning a pregnancy and have had a previous NTD-affected pregnancy consult with their physician and consider taking 4 mg folic acid daily. Women taking carbamazepine or valproic acid are at higher risk for spina bifida than the general population. There is no recommendation at the present time for higher risk women consuming carbamazepine and valproic acid who are planning a pregnancy. They may consult with their physician about using 4 mg of folic acid when they are planning to start a pregnancy. However, these women should follow the USPHS recommendation for all women and consume 400 μg of folic acid daily when they are not actively trying to start a pregnancy. MSAFP screening for neural tube defects before the 20th week of gestation with targeted sonography is advised to screen for NTDs, followed by amniocentesis for any elevated α-fetoprotein values.</p>

USPHS indicates US Public Health Service; NTD, neural tube defects; MSAFP, maternal serum α -fetoprotein.

lines for drug selection appear in Table 2. The continuum from lower to higher potency not only reflects the dose but also the differing adverse reaction profiles of these agents. Maternal side effects of the lower potency agents include sedation (antihistaminergic), gastrointestinal dysfunction, tachycardia (anticholinergic), hypotension (α -antiadrenergic), hyperprolactinemia, and, rarely, extrapyramidal reactions and cholestatic jaundice. Side effects of the higher potency agents consist of extrapyramidal reactions, such as acute dystonia, akathisia, parkinsonism, and tardive dyskinesia.

Newer agents include: 1) a low-potency antipsychotic agent, clozapine (Clozaril), which produces minimal extrapyramidal reactions in adult patients, but infrequently causes agranulocytosis (cumulative incidence: 0.8% at 12 months of treatment and 0.91% at 18 months of treatment³³); 2) a high-potency antipsychotic agent, olanzapine (Zyprexa); and 3) risperidone (Risperdal), a high-potency agent pharmacologically similar to haloperidol. The use of these newer agents is increasing rapidly; however, almost no systematic studies in pregnant women are available.

TABLE 5. Treatment and Prevention of Panic Disorder During Pregnancy

Drug Class Generic Name Trade Name	Remarks
Treatment and prevention: Benzodiazepine agonists Alprazolam Xanax Clonazepam Klonopin Diazepam Valium Lorazepam Ativan	Neonatal effects: The major neonatal side effects of benzodiazepines include sedation and dependence with withdrawal signs. A benzodiazepine-induced "floppy infant syndrome" characterized by muscular hypotonia, low Apgar scores, hypothermia, impaired response to cold, and neurologic depression can occur at the time of delivery in benzodiazepine-dependent neonates, even with the lower doses used to treat anxiety disorders. Withdrawal signs include hypertonia, hyperreflexia, restlessness, irritability, seizures, abnormal sleep patterns, inconsolable crying, tremors or jerking of the extremities, bradycardia, cyanosis, chewing movements, and abdominal distention. These signs can appear shortly after delivery to 3 weeks after birth and last up to several months depending on the degree of dependence and the pharmacokinetic profile of the benzodiazepine. Diazepam has a long-acting metabolite, dimethyldiazepam, whose mean elimination half-life is 73 (30–100) hours in adults. Of the benzodiazepines with no or weakly active, short-lived metabolites, clonazepam has the longest mean elimination half-life of 23 (18–50) hours in adults.
Prevention only: selective serotonin reuptake inhibitor Fluoxetine Prozac Tricyclic antidepressant Imipramine Janimine Tofranil Monoamine oxidase inhibitor Phenelzine Nardil	Teratogenic effects: Tricyclics and fluoxetine do not have known teratogenic effects in the human. ^{5,7,22} Insufficient human data exist to ascertain the teratogenicity of monoamine oxidase inhibitors. The belief that diazepam causes congenital malformations, especially cleft lip/palate, is controversial. ⁷ No congenital defects in humans have been attributed to lorazepam or alprazolam. ⁷⁹ The data based on the conclusion for alprazolam have been contested, ¹¹ but the authors state that the risk for oral cleft remains small. A limited surveillance study revealed 3 major birth defects (0.8 expected) in 19 pregnant women exposed to clonazepam ⁸⁰ ; therefore, targeted sonography for anomaly screening is recommended at 18 to 20 weeks of gestation. Animal studies have suggested that neurobehavioral teratogenicity occurs with some of the benzodiazepines. ^{81–84} In humans, the findings were mixed, no motor or cognitive deficits were observed in children at 8 months of age, and no effects on IQ were observed at 4 years of age. ⁸⁵ Conversely, delayed motor development and mental retardation were reported in 7 of 8 children with in utero exposure to various benzodiazepines. ⁸⁶ Guidelines: From the viewpoint of the fetus, fluoxetine is recommended for preventive therapy for panic disorder during pregnancy. When a benzodiazepine is indicated for treatment of an acute panic disorder in the pregnant patient, alprazolam or lorazepam is preferred during pregnancy to longer-acting diazepam and clonazepam. No birth defects have been linked to alprazolam, lorazepam, or fluoxetine. Lorazepam is preferred over alprazolam for preventive therapy, because it has a somewhat longer duration of action, it lacks active metabolites, and it does not seem to be associated with an immediate and as severe a withdrawal syndrome in the neonate compared with alprazolam. However, withdrawal reactions may be more severe but less protracted compared with the longer acting benzodiazepines, clonazepam, and diazepam.

DEPRESSION

The principal drugs used to treat major depression are listed in Table 3. Comments on their neonatal and possible teratogenic effects and guidelines for drug selection are included in the table.

The frequency of seizures is increased in pregnant women receiving maprotiline compared with other tricyclic antidepressants. Because equally effective drugs for depression are available, maprotiline should be avoided during pregnancy, particularly in patients with hypertension and seizure disorders.³⁴

Monoamine oxidase inhibitors are not frequently recommended or used in pregnancy, because they can exacerbate hypertension, and their drug and food interaction profile is extensive and often complicates treatment. No maternal or fetal adverse complications were noted in 2 women taking phenelzine throughout pregnancy.^{35,36}

Unlike the tricyclics, fluoxetine therapy does not result in maternal sedative, anticholinergic, hypotensive actions, and cardiotoxicity. Compared with tricyclics, serious acute reactions are less likely after large doses. Common side effects include nausea, somnolence, insomnia, sexual dysfunction, headache, tremor, dyspepsia, abdominal pain, and nervousness.

BIPOLAR DISORDER

Mood stabilizing drugs used to treat the manic phase of bipolar disorder include lithium, carbamazepine, and valproic acid. Benzodiazepines with weakly active, short-lived, or inactive metabolites (eg, alprazolam and lorazepam) are also given occasionally in conjunction with antipsychotic agents to control agitation. Carbamazepine and valproic acid are used alone or in combination with lithium for maintenance therapy in patients who do not respond adequately to lithium.

The principal mood stabilizing drugs and comments on their major fetal and teratogenic effects and guidelines for drug selection are listed in Table 4. If an antipsychotic, antidepressant, or benzodiazepine drug needs to be added to the regimen for management of bipolar disorder, see the guidelines section in Tables 2, 3, and 5, respectively.

PANIC DISORDER

Most patients with panic disorder can be managed by cognitive behavioral techniques except when anxiety is sufficiently severe to produce social dysfunction, depression, and suicidal ideation.³⁷ The treatment of choice for panic disorder is an antidepressant; however, benzodiazepines may be used in the initial stages of treatment for an acute attack

TABLE 6. Treatment of Obsessive-Compulsive Disorder During Pregnancy

Drug Class Generic Name Trade Name	Remarks
Antiobsessional agents Clomipramine Anafranil Fluoxetine Prozac Fluvoxamine Luvox Sertraline Zoloft	<p>Neonatal effects: Larger doses of clomipramine than those required for treatment of depression are needed for the treatment of obsessive-compulsive disorder. This possibility increases the potential for enhancing the typical side effects exhibited by the tricyclics. A withdrawal syndrome has been reported.⁸⁷⁻⁸⁹ This was manifested by lethargy, cyanosis, tachypnea, and respiratory acidosis within a few hours, jitteriness and tremors by the end of the first day, followed by intermittent hypotonia, tachypnea, and feeding problems. Full resolution of signs required 2 weeks. No long-term sequelae were noted at 5 months of age.⁹⁰</p> <p>Teratogenic effects: No congenital malformations have been reported for clomipramine⁸⁸ or fluoxetine.²² Neurobehavioral teratogenicity studies in humans have not been conducted. Insufficient data exist to ascertain the human teratogenicity of the other selective serotonin reuptake inhibitors.</p> <p>Guidelines: When behavioral therapy is inadequate and drug treatment is indicated, fluoxetine is recommended for the treatment of obsessive-compulsive disorder during pregnancy. Although the data are more limited, fluvoxamine, paroxetine, and sertraline are acceptable alternatives that seem to lack teratogenic effects.⁴³</p>

because antidepressants do not have an immediate clinical effect. Imipramine, phenelzine, or fluoxetine can be used for preventive therapy. Although alprazolam is the only benzodiazepine approved for treatment and prevention of panic disorder, lorazepam, clonazepam, and diazepam have similar efficacy.³⁸ Antidepressants, especially selective serotonin reuptake inhibitors, are preferred to benzodiazepines for preventive therapy.

The principal drugs used in the prevention and treatment of panic disorder and comments on their major neonatal and possible teratogenic effects, as well as guidelines for drug selection are listed in Table 5. See Table 3 for additional information on the tricyclics, the monoamine oxidase inhibitors, and the selective serotonin re-uptake inhibitors.

OBSESSIVE-COMPULSIVE DISORDER

Obsessive-compulsive disorder is now recognized as common, developing in 1% to 2% of the general population.^{39,40} Patients who are severely affected require both behavioral and pharmacologic therapy.⁴¹ Symptoms of both anxiety and depression are quite common and may require drug therapy.

The tricyclic with the most selective serotonergic re-uptake inhibitory action, clomipramine, and the selective serotonin re-uptake inhibitors, fluoxetine and fluvoxamine,⁴² are approved for patients with this disorder. Although the data are more limited, fluvoxamine, paroxetine and sertraline are acceptable alternatives that seem to lack teratogenic effects.⁴³

The antiobsessional agents used to manage obsessive-compulsive disorder and comments on their major neonatal and possible teratogenic effects, as well as guidelines for drug selection are listed in Table 6.

CONCLUSION

After counseling of the pregnant woman, severe psychiatric illness may compel drug treatment. To minimize the risk of fetal and neonatal toxicity, including an abstinence syndrome, the physician

should prescribe the lowest dosage that provides adequate control of the woman's illness. The neonate must be monitored for evidence of persistent drug effect or development of an abstinence syndrome. The Committee encourages long-term research on prospective studies of structural malformations and neurobehavioral teratogenicity.

The recommendations in this policy statement do not indicate an exclusive course of treatment or procedure to be followed. Variations, taking into account individual circumstances, may be appropriate.⁴⁴

OTHER RESOURCES

An on-line clinical automated teratology database, TERIS, is available by subscription from the Office of Teratology Information Services for a fee of \$1000 at the following Web site address: <http://weber.u.washington.edu/terisweb/teris/index.html>. Summaries in this database include timely data on teratogenicity, transplacental carcinogenesis, embryonic or fetal death, and fetal and perinatal pharmacologic effects of drugs and selected environmental agents. Another database is available from the National Library of Medicine at: <http://www.index.nlm.nih.gov/sitemap.html>. Additional references provided in *Teratogenic Effects of Drugs: A Resource for Clinicians*,⁴⁵ *Catalog of Teratogenic Agents*,⁴⁶ *Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risks*,⁷ and *Chemically Induced Birth Defects*⁴⁷ are also recommended.

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