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The Use of Psychotropic Medications During Pregnancy and Lactation

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INTRODUCTION

Many women with various psychiatric disorders taking different psychotropic drugs will become pregnant by intention or by accident. This chapter deals with the use of psychotropic medications during pregnancy (especially the first trimester), the perinatal period, and lactation and nursing. Each of the four major classes of psychotropics—anxiolytics, antidepressants, antipsychotics, and mood stabilizers—are reviewed as to their appropriate use and especially their potential deleterious affects on mother and child during these critical stages.

No psychotropic drug has been proved safe for use during pregnancy,[1] although some agents may be potentially more

hazardous to the fetus than others. Psychotropic drugs should be used in pregnancy only when the risk to the mother and fetus of not using medications outweighs the risk of drug treatment. By this standard, psychotropic medication should be considered if the pregnant patient shows inability to care for herself or obtain proper prenatal care; is dangerous to herself or others because of severe depression or impaired reality testing, as seen in psychoses; or manifests disorganization of thought, perception, and behavior unresponsive to nonbiologic interventions.[2] There is an increasing emphasis on the high risk to both mother and fetus of untreated psychiatric illness during pregnancy, relative to the prior emphasis on possible teratogenic effects of psychotropic medications.[3,4,5]

Surprisingly, surveys indicate between 50% and 80% of pregnant women have taken prescription drugs and up to 35% of these women used a psychotropic drug for one reason or another.[6] The major concern of using medications in pregnancy, especially during the first trimester, is the risk of teratogenesis or mutogenesis to the fetus during its critical period of organ formation. The interval between 2 and 8 weeks in human gestation is the most sensitive period with respect to congenital malformations. Almost all of the major organ systems are laid down during critical discrete stages by the end of the first 2 months.[7,8,9] After the first trimester, teratogenic drugs rarely produce gross structural malformations but can affect the growth and functional development of the fetus' various organ systems, especially the central nervous system and the special sensory system.[7] The overall incidence of major congenital malformations is around 2% to 3%, perhaps 2% to 7%, of all live births, and the incidence of minor malformations may be as high as 9%.[10] Of increasing concern is behavioral teratogenicity, with deleterious long-term behavioral and cognitive changes in offspring exposed to drugs during their prenatal development and perhaps during nursing.[1] In laboratory animals, such exposure has been associated with long-lasting behavioral and learning disabilities.[1,7] Such human psychoteratogenicity might be expressed as disturbed psychomotor activity, abnormal learning capacity, or other subtle cognitive deficits and mood disturbances.[1] Long-term systematic follow-up of exposed children is needed.

All psychotropic drug classes cross the placenta, as do most other drugs,[1,9] and can reach concentrations in fetal plasma and tissues that equal or exceed those attained in maternal plasma.[7] Risk assessments in humans must be preceded by reliable animal experiments, but substantial species differences with respect to the embryotoxicity of particular drugs cloud the picture.[7] Many human studies are anecdotal and poorly controlled, and large prospective epidemiologic studies are needed. In the meantime, prenatal drug exposure should be kept to a minimum, with the lowest effective dose employed. If a patient is

planning a pregnancy and she is psychiatrically stable, a gradual reduction of psychotropic medication and consultation with a psychiatrist are generally called for. The management of a newly discovered pregnant patient already on psychotropic drugs is discussed later.

During the prenatal period and delivery, direct toxic effects of the maternal psychotropic drugs on the fetus and newborn include potentially reversible effects that may be exaggerated by the immature fetal and neonatal metabolism. Metabolic liver enzymes are not fully developed, and the immature central nervous system may be more sensitive to medication.[1] Also, long-term prenatal administration of a variety of drugs, including several classes of psychotropics, narcotics, and drugs of abuse, may lead to fetal dependence and ultimately to neonatal withdrawal symptoms when the drug exposure abruptly ceases at birth.[1] Generally, the mother's labor process does not seem to be significantly affected by psychotropic medications when these are indicated and used properly.[9]

All psychotropic medications administered to lactating women can be found in varying concentrations in their breast milk.[9] Direct toxic effects have occasionally occurred in breast-fed newborns,[11] and there is ongoing concern for potential behavioral teratogenesis. Whether a mother on psychotropic medications should nurse depends not only on the specific drug taken but also on the clinician's attitude toward the importance of breast-feeding. Recommendations range from the admonition that breast-feeding for patients on psychotropic medications is contraindicated to permissiveness.[12] Regardless, if a mother chooses to nurse while receiving psychotropic medications that are necessary, the infant should be closely observed for signs of drug effects.

BENZODIAZEPINES

The evidence for the teratogenic potential of benzodiazepines is conflicting and controversial. Some studies have suggested an increase of major congenital malformations, especially cleft lip/cleft palate, associated with maternal benzodiazepine use during the first trimester.[13] Diazepam (e.g. Valium) is the major suspect in causing such oral clefts in offspring, whereas chlordiazepoxide (e.g. Librium) was generally exonerated as a teratogen in a review of several large studies.[8] Another large but possibly biased study found that maternal first trimester use of tranquilizers (most commonly diazepam) was associated with inguinal hernia, cardiac defects, and pyloric stenosis.[14] There are few data on the teratogenic potential of the short-acting

benzodiazepines.[15] To the contrary, Rosenberg and colleagues found no evidence that maternal exposure to diazepam was associated with increased risk of cleft lip/cleft palate versus other fetal malformations.[16] However, the use of other malformations rather than normal births as a control group clouds the issue. In a prospective study of 276 women delivering live newborns and who were exposed to alprazolam (e.g. Xanax) during their first trimester, the rate of congenital anomalies was 4.7%.[17] This was not thought to be dissimilar to the anomaly rate in the general population. Although the authors believed there was no increased incidence or pattern of any specific abnormality, there were two cases each of cleft palate and pyloric stenosis. The spontaneous abortion rate of 13% was not thought to be excessive and was not dose-related. Albeit somewhat reassuring, the authors warn this sample size was insufficient for statistical reliability in ruling out alprazolam's possible teratogenicity.

A retrospective review of the Michigan Medicaid files of 104,000 pregnant women delivering babies between 1980 and 1983 found 80 women who received 10 or more benzodiezepine prescriptions during their pregnancy.[18] Seventy-three percent had received benzodiazepines during the first trimester. There were also high rates of polysubstance and alcohol abuse, along with serious medical disorders, such as hypertension, diabetes, and asthma, among these 80 index patients. Two infants with congenital abnormalities died at birth and the 6 of 64 surviving children had evidence of neurologic and other congenital anomalies. Interestingly, no cases of oral cleft were reported. Although a 13% teratogenicity rate among offspring of women heavily exposed to benzodiazepines during their pregnancy is clearly excessive, the authors believed other factors like polysubstance and alcohol use may explain such rates. That the large majority of exposed infants were born without overt consequences is somewhat reassuring. In summary, although benzodiazepines have not been scientifically established as a cause of oral clefts or other congenital malformations in prenatally exposed infants, their use should be avoided during pregnancy[16]—especially diazepam during the first trimester. Benzodiazepines are rarely an absolute necessity during a first trimester; if needed, a short-acting agent such as lorazepam (e.g. Ativan) makes sense.

For a woman planning a future pregnancy, gradual benzodiezepine withdrawal should be employed, as outlined elsewhere in these volumes. In most newly discovered pregnant patients on relatively small doses of benzodiazepines for brief periods, withdrawal can be hastened and usually completed over several days under close supervision. More gradual withdrawal will be necessary for those pregnant women on higher dosages for longer periods of time to prevent serious maternal and possibly fetal

complications. Maternal use of benzodiazepines during the latter trimesters and the perinatal period may result in several types of neonatal complications. The floppy infant syndrome has been described following either moderate benzodiazepine usage during the last trimester of pregnancy or a single large dose given just prior to delivery.[15] The following symptoms, sometimes lasting several weeks, were found in the neonates: hypotonia (floppy appearance of the muscles); lethargy; sucking difficulty; feeble cry; hypothermia; and, in some cases, low APGAR (adaptability, partnership, growth, affection, and resolve) scores and respiratory depression, especially in infants whose mothers received high doses of diazepam (>30 mg) during labor.[19] Short-acting benzodiazepines (e.g. lorazepam) may be safer; however, the less complicated metabolism is also prolonged in the newborn, and cases of neonatal sedation and respiratory depression have been reported.[20] Benzodiazepine withdrawal syndromes have been described in neonates exposed to *in utero* benzodiazepines during the last several months of pregnancy.[21,22,23] Such symptoms include tremor, restlessness, hypertonia, irritability, hyperreflexia, and diarrhea/vomiting. Because of slow neonatal metabolism, actual withdrawal symptoms may not appear before several days to several weeks in some cases. To avoid a neonatal abstinence syndrome, it seems reasonable to gradually withdraw benzodiazepines from the mother during her last months of pregnancy,[8] or even sooner if possible.

As mentioned earlier, the possibility of behavioral teratogenesis is of increasing concern. Laegreid and coworkers believed they identified a syndrome, *benzodiazepine embryofetopathy,* related to *in utero* benzodiazepine exposure[24]; it resembled, to some extent the fetal alcohol syndrome. These investigators believed that such exposure could precipitate delayed minor motor and mental development and later perceptual disorders, hyperactivity, and learning disability in such children. A more recent study by this group failed to confirm their previous findings of teratogenesis and benzodiazpine-exposed infants; rather, they found mainly sedation and withdrawal in these newborns.[25] Also, of the 64 surviving babies followed in the previously cited Michigan Medicaid Study,[18] none had mental retardation, and excluding the 6 babies born with teratogenic abnormalities, none had the developmental changes originally described by Laegreid and coworkers. In addition, Hartz and associates studied 1870 children prenatally exposed to meprobamate (Miltown, Equanil) or chlordiazepoxide and found neither major congenital malformations nor gross evidence that these drugs caused higher manifestations of brain damage, as judged by mental and motor scores at 8 months and 4 years.[26] Finally, a case has been reported of a possible fatal synergism of two drugs occasionally used in pregnant women. Kargas and colleagues reported the unexpected stillbirth of a term infant with no apparent abnormalities less than 8 hours after the mother had ingested a combination of the antihistamine diphenhydramine (e.g. Benadryl) and the

benzodiazepine hypnotic temazepam (e.g. Restoril).[27] Further investigation with laboratory rabbits revealed an 81% perinatal mortality rate with a drug combination versus a 0% incidence of stillborn fetuses in animals that received one or the other drug singly. Caution!

Benzodiazepines are excreted in breast milk in varying amounts, and there are case reports that nursing infants of mothers taking diazepam or chlordiazepoxide suffering lethargy, weight loss,[28] and floppy infant syndrome.[15] There was also concern that physiologic jaundice and hyperbilirubinemia may be prolonged in infants receiving benzodiazepines perinatally or through breast milk because these drugs are eventually metabolized by conjugation with glucuronic acid competing with the same mechanism for eliminating free bilirubin.[8,11] Several careful reviews strongly recommended avoiding the use of benzodiazepines in nursing women or, if benzodiazepines are needed, to forgo nursing.[8,11,15]

Buspirone (BuSpar) is a nonbenzodiazepine anxiolytic without the sedative, dependency, or withdrawal problems associated with the benzodiazepines. However, buspirone lacks antipanic affects and its antianxiety properties are often delayed several weeks.[29] A Medline literature search (1966 to the present) failed to identify any citations regarding the use of buspirone during pregnancy in humans.[30] This was confirmed as well by communication with Bristol Myers Squibb, the makers of Buspar. No fertility impairment or fetal damage was observed in reproduction studies performed in rats and rabbits at buspirone doses of approximately 30 times the maximum recommended human dose.[30] However, one report noted an increased number of stillbirths and prolonged development in rat offspring at the highest dose of buspirone.[31] Again, animal studies are not always predictive of human response.

ANTIDEPRESSANTS

Since the last update of this chapter, the or selective serotonin reuptake inhibitors (SSRIs) have essentially become first-line agents in the treatment of depression. With improved safety records, better tolerability, and excellent efficacy, they have become the new standard in treatment. As well, other antidepressants such as buproprion (Wellbutrin SR [sustained-release]), venlafaxine (Effexor XR [extended-release]), nefazodone (Serzone), and mirtazipine (Remeron) have been shown to have excellent efficacy in the treatment of depression. We explore each of the medications individually, given the enormous usage of

such in the depressed patient. To be as comprehensive as possible, we also once again include data concerning the heterocyclic antidepressants still used especially in psychiatric circles for the treatment of depression.

Fluoxetine

Fluoxetine (Prozac) is the first SSRI launched in the United States and is among the world's most frequently prescribed medications for depression. In humans, the safety of fluoxetine during pregnancy has been evaluated in prospective and retrospective studies and surveys that encompassing over 2000 women.[32] As well, Eli Lilly maintains a worldwide Pharmacovigilence Safety Data Base, which includes information from all fluoxetine-exposed pregnancies reported to Eli Lilly & Company and its affiliates. Eli Lilly was kind enough to provide us with a review of this database as of April 9, 1996; let us examine this first.

First trimester exposure has occurred within the clinical trial setting. There were 45 prospectively identified pregnancies with available outcomes (37 fluoxetine, 8 placebo). Spontaneous abortions occurred in 9 women exposed to fluoxetine (24.3%) and in 2 women (25%) exposed to placebo. Of the remaining pregnancies with outcomes (28 fluoxetine, 6 placebo), 1 fluoxetine-exposed pregnancy (3.6%) and 1 placebo-exposed pregnancy (16.7%) resulted in a major malformation. The major malformation of fluoxetine-exposed pregnancy was a hepatoblastoma that was subsequently excised. No malformations were noted with the remaining pregnancies, and no premature births were reported in either group.[33]

There have also been 759 prospectively identified, spontaneously reported, first trimester–exposed pregnancies with available outcomes. Daily doses range from 10 to 80 mg of fluoxetine. Spontaneous abortions occurred in 101 (13.3%)[33] of these pregnancies compared with a 15% historical rate of spontaneous abortion.[34] Of the remaining 658 pregnancies with outcome, 23 (3.5%) resulted in major malformations.[33] The malformations included abnormal wall disruption/gastroschisis in 1 term birth and pyloric stenosis in another.[33] No one major malformation stood out, and the major malformation rate is consistent with the expected 2% to 7% rate observed in the general population, although these numbers are subject to argument.[35,36]

There were 426 retrospectively reported pregnancies. Of these, 89 were abnormal but failed to show a recurring pattern of abnormality or an increase in frequency of a particular condition.[33]

The Data Base also contained 123 prospectively identified pregnancy (including 3 twin pairs) exposed to fluoxetine in all three trimesters.[33] Only 3.2% of infants experienced a major or postperinatal malformation, and only 9.7% experienced neonatal complications such as irritability, sepsis, transient tachypnea, and atrial septal defect.

Multiple independent studies have been conducted concerning fluoxetine in pregnancy. Pastuszak and coworkers conducted a controlled, prospective study of 128 women exposed to fluoxetine in the first trimester.[37] They were compared with two matched groups of women exposed during the first trimester to either nonteratogens or tricyclic antidepressants (TCAs). Owing to the limited number of TCA exposures, the findings were divided into comparisons between 128 fluoxetine cases and 128 aged-matched, nonteratogen controls (NTCs) and comparisons among 74 fluoxetine cases, 74 aged-matched TCA cases, and 74 age-matched NTCs. The study found no differences in rates of major birth defects when the live births exposed to fluoxetine were compared with the NTC live births or when a small fluoxetine group was compared with both of its controls. There were no statistically significant differences in pregnancy outcomes, maternal weight gain during pregnancy, gestational age delivery, birth weight, or forceps deliveries when the fluoxetine groups are compared with controls. Although the miscarriage rate was slightly higher than that with TCAs, the rate of the fluoxetine group was 13.5% (TCA, 12.2%) but is still lower than that in the historical controls.[34,35,37]

A review of the Michigan Medicaid Claim Data Base consisting of 104 pregnancies exposed to fluoxetine found a rate of major malformation of 2%. This is consistent with the expected 2% to 7% rate observed in the general population.[34,35,38]

As for development, Nulman and associates demonstrated no difference in cognitive language and behavioral development between children exposed to antidepressant drugs *in utero* and those who were not.[39] This prospective, controlled study compared women who received fluoxetine or TCAs during pregnancy with a control group. The control group consisted of 84 women not exposed to any known teratogens. There were 40 first trimester exposures to TCAs, 2 first and second trimester exposures, 2 first and third trimester exposures, and 36 exposures for the entire duration of pregnancy. There were 37 first trimester exposures to fluoxetine and 18 exposures throughout all pregnancy. Neurodevelopment was determined in children born to these females by assessing global IQ and language development when the children were between 16 and 86 months of age. No differences in mean global IQ scores were found in the groups. The evaluation scores for language development were

also similar for all these groups. In addition, there were no significant differences found in scores of activity level, arousal functions, behavioral problems, or distractibility of mood.[39]

In sum, all the studies show fluoxetine to be a safe medication during pregnancy. Nonetheless, it should be used only when absolutely needed. The authors believe it is still prudent to stop fluoxetine in stable patients 6 weeks prior to conception to allow a reasonable amount of washout time, with immediate discontinuation of fluoxetine in the newly discovered stable pregnant patient.

However, when severe depression occurs in the face of pregnancy, fluoxetine is an excellent choice for treatment. Multiple studies have shown that fluoxetine is indeed excreted into breast milk. Some reports of infantile crying, watery stools, sleep disturbance, and vomiting have now been noted. In one such case, the symptoms abated after change to conventional formula at 6 weeks. Three weeks later, the infant was rechallenged while the mother continued to take 20 mg of fluoxetine. The colic returned in 24 hours.[40]

Yoshida and colleagues summarized data in four cases of mothers who breast-fed their infants while taking fluoxetine. They were assessed using the Baley Scales of Infant Development, and none of the infants showed any neurologic abnormality and they did showed normal development.[41] Taddio and associates estimate that approximately 10% of the maternal doses are ingested by the breast-fed infant. They concluded that fluoxetine therapy for breast-feeding mothers appears to be justifiable.[42] The risk-benefit scenario needs to be explored in each individual case.

Sertraline (Zoloft)

Sertraline was a second SSRI available to patients in the United States. It is an effective and safe medication for the treatment of depression. Limited human data for sertraline do not appear to support a teratogenic risk, and case reports have described the effects of *in utero* exposure to sertraline. When they occurred, effects such as insomnia, agitation, nystagamus, and hypotonia generally abated within 72 hours of delivery with no sequelae. Pregnancy outcomes in the relative risk for major malformation were not significantly different from outcomes in the general population.[43]

There have been several case reports on pregnancy outcomes. Altshuler and coworkers reported on a 28-year-old female with a

history of recurrent depression who received sertraline 100 mg/day and nortriptyline 125 mg/day throughout pregnancy and gave birth to a healthy male baby at term.[44]

Kent and Laidlaw reported suspected withdrawal symptoms in a newborn following the use of 200 mg/day of sertraline throughout pregnancy. Delivered healthy, after 1 day, the baby began to show symptoms of agitation, restlessness, poor feeding, constant crying, insomnia, and enhanced startle response. The symptoms lasted for 48 hours and subsided over the next few days.[45]

Oca and Donn reported a case of an infant girl born at 35 weeks' gestation to a mother prescribed sertraline 50 mg/day for 2 weeks prior to delivery. The baby received bag and mask ventilation with 100% O_2 for 15 seconds after delivery with APGAR scores of 5 and 8 at 1 and 5 minutes, respectively. The baby was noted to have hypotonia, horizontal nystagamus with an intermittent rotary component in both eyes. Muscular tone improved rapidly; the nystagamus continued for 24 hours, but resolved by 72 hours. Because hypotonia and nystagamus have been seen in adults on sertraline, in this case the symptoms were attributable to sertraline.[46]

Wilton and colleagues conducted a retrospective review in England to determine the maternal proportion of congenital anomalies of women exposed to newly marketed drugs during the first trimester of pregnancy. Twenty-eight babies were born to mothers taking sertraline and 2 had documented congenital anomalies; however, the mothers were also receiving other medications. The 2.5% proportion of congenital abnormalities within the study was similar to the overall estimations made by the Office for National Statistics.[47]

Kulin and coworkers in a prospective, controlled cohort reported in pregnancy outcomes following fetal exposure to fluvoxamine (Luvox), paroxetine (Paxil), and sertraline (Zoloft) in 267 women. The group exposed to SSRIs was matched to controls who were randomly selected from the total group of women counseled and followed by the Motherrsk Program after exposure to nonteratogenic agents. Of these, 147 females use sertraline. In sum, the pregnancy outcome did not differ between the groups, with similar rates of malformations and spontaneous and elective abortions and similar mean birth weight and gestational age. The authors concluded that fluvoxamine, paroxetine, and sertraline do not appear to increase teratogenic risk when used at recommended doses.[48]

Chambers and associates prospectively evaluated 112 pregnant women receiving sertraline and compared their outcomes with those of a control group of 191 women ascertained for nonteratogenic exposure. Major anomaly rates did not differ significantly —3.8% for sertraline and 1.9% for the control group. Some of the sertraline group anomalies included bilateral choanal atresia, valvular pulmonic stenosis with atrial septal aneurysm, and unilateral clubfoot. The frequency of minor abnormalities was similar in both groups, although there was a higher rate of spontaneous abortion in the sertraline group (16.7% versus 10.9%). Infants who were exposed to sertraline in the third trimester were more often premature, had transition problems, or were admitted to a special care nursery. The authors concluded sertraline was not a structural teratogen but may increase the risk of neonatal complications if taken late in pregnancy.[49]

Pfizer generously granted these authors access to their Early Alert Safety Database, which identified 29 cases of adverse outcomes in babies of mothers treated with sertraline. These are cases entered from the time of market introduction through April 30, 1996. The adverse events included spontaneous abortions, abnormal uterine movements, preterm labor, abnormal fetal death, hypotonia, oligohydramnios, cystic hygroma, VATER (vertebral defects, imperforate anus, tracheoesophageal fistula, and radial and renal dysplasia) syndrome, small brain with dilated ventricles, hand malformation, achondroplasia, laryngomalacia, Ebstein's anomaly, mitral valve collapse, and pulmonic stenosis of the right lung.[50] It is notable here that there is no pattern or emergence of a single, fairly common teratogenic anomaly in pregnant patients taking sertraline. The authors believe, therefore, that, like fluoxetine, sertraline is a viable medication to be taken when needed in pregnancy. Again, when a stable patient wishes to become pregnant a 4-week washout period is advisable before conception and a 2- to 4-week downward titration is prudent before delivery.

Several studies have examined sertraline in breast-fed infants and breast-feeding mothers. Studies and reports that have analyzed infant and maternal plasma in milk:plasma ratios have shown that sertraline or its metabolite *N*-desmethylsertraline can be detected in infant plasma, although most cases have shown low or undetectable levels. The majority of the case reports found no or mild adverse effects in infants whose mothers were receiving sertraline therapy during breastfeeding. Although the reports and the data look reasonably good, problems can arise, as mentioned earlier. Caution is advised.[43,51]

Paroxetine

Another popular and effective SSRI, paroxetine was launched after fluoxetine and sertraline in the United States. It appears that the profile for paroxetine is essentially equal to that of fluoxetine and sertraline. The Kulin and coworkers' study also included 97 women who were exposed to paroxetine. The investigators indicated that the pregnancy outcome among women who took an SSRI throughout pregnancy did not differ from those who took the drug during the first trimester.[48]

A 1999 study by Ericson and associates from the Swedish Medical Birth Registry included 118 women on paroxetine.[52] A total of 21 infants were born with a congenital malformation without a clustering of any major or unusual type of congenital abnormality noted.

An observational cohort study in the United Kingdom, conducted by Prescription Event Monitoring (PEM), reports 138 pregnancies during the time from March 1991 through March 1992 in which mothers were treated with paroxetine. Exposure to paroxetine was likely in 63 of the pregnancies. Of the 42 live births, no congenital abnormalities were reported. There were 8 spontaneous abortions.[47,53,54]

As of March 2000, GlaxoSmithKline had received over 1100 reports of patients treated with paroxetine during pregnancy, most of which had received Paxil during the first trimester. Many of the reports stated the normal outcome, with a pattern of congenital abnormalities similar to that reported in the general population, and there was no unexpected clustering of abnormalities among the reports.[55]

GlaxoSmithKline has received reports of convulsions, muscle tone disturbances, excitability, tremor, jitteriness, somnolence, and/or respiratory distress in neonates born of mothers receiving paroxetine in the third trimester.[55] Geola and colleagues reported symptoms of hunger, jitteriness, mild hypertension, and diarrhea in a female infant born to a mother who took 10 mg/day of paroxetine throughout pregnancy.[56] The symptoms appeared 48 hours postdelivery and resolved in 2 days.

It is reasonable to assess paroxetine similarly to sertraline and fluoxetine using essentially the same parameters for pregnancy. Once again, approximately a 4-week washout before the estimated date of confinement is recommended.

Paroxetine is excreted into breast milk, as confirmed by Misri and coworkers[57] and Stowe and associates.[58] Ohman and colleagues investigated excretion of paroxetine into human breast milk in 7 women who were genotyped as extensive

metabolizers of cytochrome P450 2D6. Mothers took doses from 10 to 40 mg/day. Paroxetine levels in breast milk varied between serum trough and peak times, although these changes were not as great as changes in serum levels. This suggests that the nursing mother who is not breast-feeding at night could reduce infant exposure by doing so at night. The mothers did not report any adverse events in the infants, and the infants thrived normally through the treatment period.[59] Certainly, Paroxetine is a viable choice to use in depressed breast-feeding women, but once again, the risk/benefit ratio is to be considered and caution used.

Citalopram

Citalopram (Celexa), the SSRI most recently released in the United States, is another excellent and clean addition to the armamentarium against depression. Because of its more recent release, there is less literature on citalopram. However, Wisner and coworkers, in 1999, reviewed data from four studies and, as noted, did not find any increased risk for major birth defects in SSRIs and TCAs.[60] Citalopram was not included in that study; however, Ericson and associates did report on citalopram's use in pregnancy because 375 patients used citalopram.[52] As reported, it was found that use of antidepressants such as citalopram did not increase the risk of infant mortality, presence of congenital defects, or low birth weight. Clearly, more study is needed, and because citalopram continues to produce effective results, more in general will need to be learned about its use in pregnancy. A Medline search provided no literature concerning its use in lactating women.

Fluvoxamine

Fluvoxamine (Luvox) is approved for use in Europe for obsessive-compulsive disorder (OCD) and depression but is approved for use in the United States only for OCD. Nonetheless, it has been used regularly "off label" for depression. It too was included in the Kulin and coworkers' study, in which 26 women used fluvoxamine.[48] Again, the studies revealed that fluvoxamine, paroxetine, and sertraline do not appear to increase the teratogenic risk when used in their recommended doses.

Solvay Pharmaceuticals, the makers of Luvox, have received approximately 70 case reports of use during pregnancy.[61] Of these, at least 30 pregnancies resulted in normal births. The outcome of 14 pregnancies is unknown. There were 8 elective abortions and 8 spontaneous abortions. One elective abortion was performed after genetic abnormalities were detected in

amniocentesis, and 1 miscarried fetus revealed a Turner syndrome. Two neonates were born with transposition of the great vessels, 1 with tetralogy of Fallot, 1 with enlarged abdominal organs, and 1 with polydactyly. One neonate experienced liver dysfunction and jaundice at birth, and 2 others had uncomplicated neonatal jaundice. There was 1 ectopic pregnancy, and 1 premature birth with hypoglycemia, apnea, and bradycardia.

As for lactation, Golightly and Grant note that clinical experience has highlighted few problems, and antidepressants are generally classified as medications that can be used cautiously when mother and baby are monitored.[62] A case report from Wright and associates reported very little fluvoxamine accumulation in breast milk with a 200-mg/day dosage.[63] According to this report, if accumulation did occur, the baby would ingest only 0.5% of maternal intake, thus supporting the hypothesis that administration of fluvoxamine to nursing mothers poses little risk to the infant. Once again, the risk/benefit scenarios prevail.

Buproprion

Buproprion (Wellbutrin/Wellbutrin SR), an antidepressant of the aminoketone class, is a weak inhibitor of norepinephrine, serotonin, and dopamine.[64] There are no adequate and well-controlled studies in pregnant women. GlaxoSmithKline did provide the authors with pregnancy registry data.[65] As of August 31, 2000, 236 pregnancies involving exposure to buproprion have been prospectively registered. Of these, 97 were pending delivery, 51 cases were lost to follow-up, and 90 outcomes were obtained, with 2 sets of twins. Of the 90 outcomes, 66 involved first trimester exposure, 19 involved second trimester exposure, and 5 involved third trimester exposure. Of the 66 first trimester–exposed deliveries, there were 57 infants without birth defects, 7 spontaneous abortions, 1 termination, and 1 infant with a birth defect of bilateral clubfeet. The outcome for all 19 births that involved second trimester exposure as well as for the 5 third trimester exposures resulted in no birth defects. Although this is promising, it is far too small a sample to reach any definitive conclusions in the risk of teratogenesis with buproprion.

Experience in the uses of buproprion during lactation is limited. Briggs and colleagues reported on studies that showed a lactating mother receiving 100 mg of buproprion immediate-release (IR) three times a day did excrete buproprion and metabolites into breast milk.[66] Once again, caution is the word.

Mirtazapine

Mirtazapine (Remeron) belongs to the piperazine-azepine class. It acts as an antagonist at central presynaptic alpha-adrenergic inhibitory auto receptors and hetero receptors. It is a potent antagonist of 5-HT2 and 5-HT3 receptors and a potent antagonist of H1 receptors with moderate peripheral $alpha_1$ antagonismPrecious little is known with regards to use in pregnancy and no literature was found by Organon, the makers of the medication, concerning lactation.[67] Simhandl and coworkers reported on the use of mirtazapine during pregnancy in a 28-year-old female with depression. She was entered into a study and counseled on the need for contraception, and she received intravenous mirtazapine and then oral medication up to 45 mg/day for 6 months. At the last visit, 1 week after the intake of the last dose of mirtazapine, she was found to be pregnant. Last menstrual bleeding was 26 days before the last dose of mirtazapine. In the 39th week, she gave birth to a healthy baby girl—no adverse events or defects were noted in the newborn.[68]

Saks, in the *Archives of Women's Mental Health,* 2001, reported on seven cases of the use of mirtazapine in depressed, anxious patients who were also experiencing hyperemesis gravidarum.[69] Because mirtazapine blocks the 5-HT3 receptor postsynaptically, like ondansetron (Zofran), there is reason to believe mirtazapine may be of great use in treating not only depression and anxiety in pregnancy but also nausea and the more severe condition, hyperemesis gravidarum. In the review, five patients were treated as outpatients. Two patients were begun on mirtazapine as inpatients already on a transparenteral nutrition. All patients demonstrated improvement of depressed mood and reduced nausea and vomiting. All seen babies were born at term, each with APGARs of 7 or 8 at 1 minute, 9 at 5 minutes. This is indeed promising, and mirtazapine may prove a valuable asset for cases such as these, although further studies are needed and warranted.

Venlafaxine (Effexor/Effexor XR)

Venlafaxine (Effexor/Effexor XR) is a new, novel antidepressant that inhibits serotonin and norepinephrine uptake potently and is a weak inhibitor of dopamine.[70] Since the release of the XR variety, venlafaxine has become a very well tolerated and extremely effective medication in the depressed and anxious patient. During the clinical trials of both the IR and the SR forms of venlafaxine, a total of 20 pregnancies occurred.[71] With respect to IR, there were 5 full term births of healthy, normal-weight babies. Fetal exposure to venlafaxine was estimated to range from 10 to 60 days. There were 1 ectopic pregnancy and 3

spontaneous abortions. One patient was lost to follow-up, and there were 4 elective terminations. Of the XR patients, 2 had elective abortions, 2 were lost to follow-up, and no further information was available on the other 2. Einarson and associates published a recent article in the *American Journal of Psychiatry* (2001) concerning the results of a multicenter, prospective study to determine whether use of venlafaxine in pregnancy is associated with an increase in risk for major malformations above the baseline rate of approximately 1% to 3%, although as noted, this number varies from 1% to 3% to up to 2% to 7%.[72] Mothers suffering from depression taking SSRIs (fluvoxamine, sertraline, fluoxetine, paroxetine) or other nonteratogenic medications, both matched for age, smoking, and alcohol abuse, served as control groups. The results were 120 live births, 18 spontaneous abortions, 2 therapeutic abortions, and 2 major malformations—hypospadias and neural tube defects with clubfoot. In all cases, venlafaxine exposure occurred during the first trimester. The authors of this study concluded that "the results in 150 females exposed to venlafaxine during pregnancy in the first trimester do not suggest that there is a greater risk for major malformations above the baseline rate." Postmarketing adverse events have been reported with no obvious pattern or trend with respect to the type of congenital abnormalities that had been noted. There have been reports of "discontinuation syndromes in infants, along with reports of first trimester spontaneous abortions and delivery of normal health infants."[71] There are not enough data yet to draw obvious conclusions, but it does appear to be encouraging.

Studies have been published regarding breast-feeding. Ilett and colleagues conducted two studies to essentially determine milk:plasma ratio of venlafaxine and *O*-desmethylvenlafaxine (ODV), its metabolite. The results suggest both venlafaxine and ODV are concentrated in breast milk. It was noted that the dose of medication ingested by the infant might be as high as 9.2% of maternal intake in one study and 6.4% in the second. Therefore, exposed infants need to be carefully monitored, and although no adverse events were reported, it appears especially important to take caution with preterm and young neonates in whom hepatic drug metabolism may be low.[73] Through postmarketing adverse experience reporting, Wyeth, the makers of venlafaxine have received reports of adverse effects including agitation, colicky babies, drowsiness and dyspepsia, increased startle, jitteriness, sleeplessness, and seizure in infants coincident with venlafaxine use by their mothers.[74] Caution as usual is advised.

Nefazodone

Nefazodone (Serzone) is a synthetically derived phenylpiperazine antidepressant. The mechanism of action appears to be

inhibition of neuronal uptake of serotonin and norepinephrine. It recently received a black box warning from the U.S. Food and Drug Administraiton (FDA) concerning liver toxicity.[75] There are no adequate and well-controlled studies in pregnant women. Mackay and coworkers, in 1999, discussed the results of a noninterventional cohort study that examined the safety of nefazodone in general practice in England. Information garnered revealed nefazodone to have been used in 38 first trimester pregnancies. Two premature births were seen at 27 and 31 weeks; 2 babies had renal abnormalities, 1 with a dilated renal pelvis with grade 2 vesicoureteric reflux and the second with a congenital hydronephrosis. One term baby had low-birth-weight. Obviously, more study is needed.[76] Little was available regarding nefazodone use in breast-feeding. Given the potential for liver toxicity, extreme caution is to be used with serious thought given to stoppage of nefazodone or change to another agent if absolutely needed.

Tricyclic Antidepressants and Monoamine Oxidase Inhibitors

There is no significant evidence that heterocyclic antidepressants are teratogenic in humans[8,77,78] although their safety has not been proved. Earlier case reports indicated a possible association between fetal limb-reduction deformities in the first trimester use of heterocyclic antidepressants such as imipramine (e.g. Tofranil).[79] However, birth defects surveillance groups were subsequently unable to detect antenatal exposure to heterocyclic antidepressants among infants born with limb-reduction deformities.[80] In a prospective study comparing pregnant women exposed during their first trimester to fluoxetine, to heterocyclic antidepressants, and to nonteratogens, for example, acetaminophen penicillins, there was no difference in the rates of major congenital malformations among the three groups.[4] These rates also did not exceed those expected in the general population. Although not reaching statistical significance, there was a tendency, as noted before, for a slightly higher percentage of spontaneous abortion and neonatal complications in both the fluoxetine and the heterocyclic antidepressant–exposed groups compared with the NTCs. The methodology and sample size of the study pose limits on such conclusions, and further studies are needed; several were discussed earlier in this chapter.

Both direct toxic effects and withdrawal syndromes in neonates have occasionally been reported with a maternal use of heterocyclic antidepressants during the latter trimesters and during the perinatal period. There have been isolated case reports of neonatal urinary retention association with the maternal use of nortriptyline (Aventyl, Pamelor)[81] and a small left colon syndrome, a functional intestinal obstruction in the neonate, associated with the maternal use of doxepin (Sinequan, Adapin)

(phenothiazines and antiparkinsonian agents were also used during the pregnancy.)[82] Both toxic effects were probably secondary to the anticholinergic properties of these psychotropics that accumulated in the infant prior to delivery. Neonatal distress (or due to withdrawal?) has occasionally been described following birth to mothers who used various heterocyclic antidepressants during pregnancy (i.e. desipramine).[83,84,85] Symptoms in the newborn included respiratory distress, cyanosis, tachycardia, irritability, sweating, tremor, muscle spasms and clonus, feeding difficulties, and even convulsions. Generally though, heterocyclic antidepressants are relatively safe to use during pregnancy when truly indicated.[8] Given a lower side effect profile, the secondary and mean group (i.e. desipramine) seems a reasonable choice in this class. Conversely, in newly discovered pregnant patients on heterocyclics or who are psychiatrically stable, gradual withdrawal should be attempted to avoid even remote teratogenic potential. Abrupt discontinuation is to be avoided, but by decreasing the heterocyclic dosage by 25 to 50 mg daily, withdrawal can usually be accomplished in under a week during the first trimester. During the last trimester, the literature suggests an antidepressant washout period for the fetus[8] to lower the risk of any direct toxic effects or withdrawal syndromes. A more gradual withdrawal (decrements of 25 mg every 3 to 4 days) seems reasonable during this period before delivery and in psychiatrically stable women planning future pregnancy.

An overview indicated that heterocyclic drug concentrations in milk were comparable with those in maternal serum or plasma.[86] However, nursing infants typically receive well under 1 mg of the drug daily through the mother's milk, which generally produces little evident toxicity.[85,86] A case report suggests that such toxic effects as lethargy and respiratory depression may occasionally be produced in some infants, despite ingestion of relatively small quantities of the antidepressant.[87] Most reviews recommend caution and close infant monitoring if heterocyclic antidepressants are to be given to a breast-feeding mother.[9,11]

Monoamine oxidase inhibitors (MAOIs) are to be avoided during pregnancy because they are teratogenic in animals[9] and possibly in humans[15] and pose a potentially lethal reaction at the time of delivery if the mother requires anesthesia, memperidine (Demerol), or other contraindicated drugs.

ANTIPSYCHOTICS

Dramatic developments have occurred in the antipsychotic drug arena with the development of the "atypical" antipsychotics.

Five atypical antipsychotics are now available: risperidone, olanzapine, quetiapine, ziprasidone, and clozapine. Clozapine (Clozaril) is still essentially used only in the management of severely ill schizophrenic patients who failed to respond to standard antipsychotic drug treatment. The other four agents, however, have become first-line agents and essentially standard in the treatment of psychotic disorders. Olanzapine (Zyprexa), which is quite similar in chemical structure to clozapine, does have significant experience in the pregnant patient. Eli Lilly, the manufacturer of Zyprexa, provided data tracked within their Clinitrace System. The reporting period dates from January 1, 1983, through September 30, 2000. During this period, there were 126 prospectively identified pregnancies with a pregnancy outcome. Of these 126 cases, 30 elective terminations without abnormalities were reported. Of the 96 remaining cases, there were 69 normal births, 1 major malformation, 12 spontaneous abortions, 2 ectopic pregnancies, 2 premature births, 3 stillbirths, and 7 cases of perinatal complications. This leaves a 73% normal birth rate, a 12.6% spontaneous abortion rate, a premature birth risk rate of 2.1% compared with controls of 10.3%, and only a 1% risk of congenital abnormalities versus a control of 3.8%. Based on this, olanzapine does not appear to be associated with major malformations or a disproportionately high risk of birth complications. However, these numbers are still relatively small. Retrospectively, 69 reports of exposure to olanzapine were identified with 67 final cases with an outcome. Once again, these retrospectively reported abnormal cases fail to show a pattern of abnormalities or an increase of a particularly rare condition. This does suggest that olanzapine does not increase the risk of malformation.[88]

Three published case reports involve olanzapine exposure during pregnancy. The first case, reported by Dickson and Dawson in the *Canadian Journal of Psychiatry* in 1988, involved a 41-year-old woman with a schizoaffective disorder, treated with 12.5 mg/day of Zyprexa. She terminated her pregnancy and no fetal abnormalities were found.[89]

The second case was reported by Kirchheimer and associates in *Pharmacopsychiatry* in the year 2000. Olanzapine was initiated at week 18 of gestation and continued through delivery and initiation of breast-feeding. The baby was delivered on time without complications. Olanzapine serum concentrations that were monitored the day after delivery were reported as follows: 33.4 ng/mL (mother) and 11.3 ng/mL (newborn). Levels were again drawn following nursing and the newborn serum concentration level at 6 weeks was less than 2 ng/mL. The child has developed normally through the 15-month pediatric visit.[90]

The third case involved a 40-year-old obese schizophrenic who was on 20 mg/day of olanzapine prior to pregnancy. One month after becoming pregnant, her dose was reduced to 15 mg/day because of sedation. She had a weight gain of 79 pounds, 36

pounds in the first trimester. Medical complications thus ensued including hypertension, gestational diabetes, preeclampsia, substantial proteinuria and elevated liver function tests. She delivered a female infant at 30 weeks via cesarean section weighing 4 pounds, 11 ounces, with APGARs of 7 at 1 minute and 9 at 5 minutes. Although the obstetric team did not attribute her difficulties to olanzapine, the contribution of the medication could not be excluded.[91] There were 20 case reports of women exposed to olanzapine while breast-feeding. Sixteen noted no adverse affects. There are 4 case reports of problems including a jaundiced and sleepy-appearing baby, shakiness, poor sucking, and lethargy. In 1 case, the infant experienced a protruding tongue, which resolved, and another case in which a 9-month-old developed rash, diarrhea, and sleeping problems 1 day after breast-feeding. The outcome of this case is unknown.[91] Clearly, further study is warranted and more cases will accumulate. It appears that olanzapine may be safe enough to use in pregnancy, but only if there is a large benefit/risk ratio. These numbers are still too small, however, and certainly we are not yet ready to absolutely recommend usage during pregnancy and breast-feeding.

Risperidone is a frequently used atypical antipsychotic that is also extremely effective in both psychotic disorder and bipolar disorder. Janssen provided a literature search and identified one citation with respect to use during pregnancy. Mackay and colleagues conducted a noninterventional, observational, postmarketing cohort study for the purpose of examining the safety of risperidone in a large patient population treated in a general practice setting.[92] Seven thousand, six hundred and eighty-four patients were involved. Nine patients were found to be taking risperidone, 1 mother with twins. There were 7 live births and 3 early therapeutic terminations. Further review determined there were no abnormalities reported among the live births. Trixler and Tenyi published an article regarding antipsychotic uses in pregnancy in which they reported that the safety of risperidone has not been established.[93] One citation was also found with respect to nursing mothers. Hill and coworkers discussed a case report of a 21-year-old female with a 2-year history of bipolar disorder.[94] After delivery, multiple symptoms returned and breast-feeding was stopped as she was placed on risperidone, titrated to 6 mg/day. After 1 week on the 6-mg dosage, seven serial samples of plasma and six serial samples of breast milk were drawn over a 24-hour period and tested for risperidone and 9-hydroxyrisperidone levels. The researchers concluded that the nursing infant would receive 0.84% of the maternal dose of risperidone and another 3.46% from 9-hydroxyrisperidone. The authors concluded that the recommendation to stop breast-feeding was conservative but justified.

The cases are far too small to recommend risperidone at this point in pregnancy. We also cannot yet recommend its use in breast-feeding mothers. Once again, the risk/benefit scenario as outlined in the package insert applies.

Another antipsychotic, ziprasidone (Geodon) has been approved for treatment of schizophrenia. This compound is known to potentially increase the risk of QT interval prolongation, which is one reason why it took a relatively long time to come to market. In correspondence with Pfizer, a computerized literature search in February 2002 failed to identify any relevant references regarding the use of ziprasidone in pregnancy and lactation.[95] As outlined in the package insert, ziprasidone demonstrated developmental toxicity, including possible teratogenic effects, at doses similar to human therapeutic doses in pregnant rabbits. Most common were ventricular septal defects, other cardiovascular abnormalities, and kidney alterations. This was observed at doses of 30 mg/kg/day which exceeds the maximum recommended human dose of 200 mg/day for 3 days. There was also an increase in the number of pups born dead and a decrease in postnatal survival through the first 4 days of lactation among the offspring of female rats treated with doses of 10 mg/kg/day or 0.5 times the maximum recommended human dose. Offspring developmental delays in neural behavioral functional impairment were observed at doses of 5 mg/kg/day or 0.2 times the maximum recommended human dose. At this time, there are not enough data to draw conclusions with ziprasidone—therefore, in both the pregnant and the breast-feeding patient, ziprasidone is not recommended. It should be used in pregnancy only if the potential benefit justifies the risk.[96]

AstraZeneca's medication zuetiapine (Seroquel) is a drug belonging to the dibenzothiazepine class and is approved for use in the treatment of schizophrenia. In correspondence, AstraZeneca stated it is policy to provide adverse event information, including information on drug use during pregnancy, primarily from the prescribing information and the published literature for marketed products. AstraZeneca does not provide specific adverse event information from the Safety Database because of the inherent limitation of spontaneous reports. Such limitations include adverse event recognition, underreporting, biases, estimation of patient exposure, report quality, and lack of established causality of the events.[97]

Quetiapine is a category C drug via the FDA, indicating that evidence of embryo/fetal toxicity was found in animal models. There has been no evidence, however, of teratogenicity in rats or rabbits when dosed at 0.6/1.8 times the maximum human dose during the period of organogenesis. Patients who are on quetiapine are advised neither to breast-feed nor to use during pregnancy. Once again, the use of quetiapine should be undertaken only if the patient benefit justifies the potential risk.[98] A

MEDLINE/PUBMED search revealed no information concerning use of quetiapine during pregnancy and lactation.

Clozapine (Clozaril), the first of the atypical antipsychotics, is still in use today, despite the onset of the aforementioned antipsychotics. It is associated with a 1% to 2% incidence of agranulocytosis, a potentially fatal blood disorder. Frequent monitoring of white blood cell counts continues to be required and is certainly required on a weekly basis for at least the first 6 months of treatment. Reproductive studies have been performed in animals at doses four times the human dose and have revealed no evidence of impaired fertility or harm to fetus owing to clozapine.[99] There have been at least 14 known women exposed to clozapine during gestation with no known adverse effects in the newborns.[100] As to the agranulocytosis, there is no reason to assume the 1% to 2% rate would not also be true for the exposed/newborn fetus. The standard caveat of using psychotropic medications in pregnancy only when the benefits to the mother and fetus outweigh the risks is especially germane with clozapine. Many clozapine responders have responded to no other antipsychotics, not even to newer atypical agents. Such patients have high relapse rates off clozapine, so the threat of harm to self and fetus is real. The decision to discontinue clozapine during the first trimester must be preceded by extensive discussion with patient, prospective father, and other family members.

The maternal use of clozapine during the latter trimester and perinatal period may result in direct toxic effects to the newborn. Clozapine does have significant sedative and anticholinergic side effects in adults, in addition to its propensity to cause orthostasis and seizures. Given the 1% to 2% incidence of agranulocytosis, women receiving clozapine should not breast-feed.

Evidence for the teratogenicity of the “more traditional” antipsychotic medications is conflicting and controversial. Many of the antipsychotics studied were used primarily as antiemetics or anxiolytics and were given in smaller doses and intermittently as opposed to their typical uses in treating psychoses. In a prospective study of 315 pregnant women exposed to phenothiazines during the first trimester, Rumeau-Rouquette and colleagues found more than twice the incidence of major congenital malformations in infants prenatally exposed to aliphatic phenothiazines, that is, chlorpromazine (e.g. Thorazine), but not to other phenothiazines when compared with nonexposed controls.[101] On the other hand, Kris reported no congenital malformations or other adverse effects with 52 children born to mothers maintained on chlorpromazine (between 50 and 150 mg/day) during pregnancy to prevent psychotic relapse.[102] Ayd’s extensive review of chlorpromazine usage during pregnancy and labor, as both an antiemetic and an antipsychotic, revealed a relatively benign profile.[103] Earlier isolated case reports of an

association between haloperidol (e.g. Haldol) and limb deformities were tainted because multiple drugs were involved.[104] Retrospective examination of 100 pregnant women given haloperidol (average of 1.2 mg/day) as an antiemetic revealed no increase in congenital malformation versus controls.[105] A retrospective investigation of 86 infants with limb deformities found no association with haloperidol use during pregnancy.[106] The large California Child Health & Development Project, involving over 19,000 births from 1959 through 1966, prospectively followed pregnant women treated during their first trimester with antiemetics, mostly phenothiazines, 80% of which were prochlorperazine (e.g. Compazine).[107] They found no increase in the rates of major congenital abnormalities or perinatal death in the phenothiazine-exposed group compared with controls. Edlund and Craig reanalyzed this data and discovered a possible increase in major birth defects in children whose mothers took phenothiazines during the 6th to 10th gestation week.[108] Overall, despite some conflicting studies, most reviews in the use of antipsychotic medications find no statistically significant increase in congenital malformation in exposed offspring.[2,9,77,103]

As with the atypical antipsychotics, use of traditional antipsychotics during the latter trimesters in the perinatal period may result in toxic effects to the newborn. Extrapyramidal syndromes, have been described in neonates whose mothers who took either chlorpromazine[84,109] or fluphenazine decanoate (Prolixin Decanoate)[110] during this period. Symptoms included parkinsonism with tremors and increased muscle tone with spasticity and rigidity, motor restlessness, and abnormal dyskinetic movements. Antiparkinsonian agents were useful in treating some of these infants. Desmond and associates found 19 of 22 infants exposed to phenothiazines *in utero* suffering from postnatal depression, with diminished movements, decreased crying, and difficulty with respiration and feeding lasting up to 5 days.[111] An “agitated” phase followed, sometimes lasting up to 7 months, with hyperactivity, excessive crying and sucking behaviors, hypertonicity, and vasomotor instability. There is also debate as to whether phenothiazine use by the mother can lead to increased bilirubin levels in newborn jaundice.[9] Despite haloperidol’s propensity to cause extrapyramidal syndrome, Ayd found that maternal use of haloperidol near term was not associated with neonatal depression or other effects in the newborn.[112]

Despite case reports of drowsiness in breast-fed infants of mothers taking chlorpromazine and a reports of neonatal galactorrhea associated with maternal use of chlorpromazine and the infrequently used thioridazine,[113] most reviews of traditional antipsychotics demonstrate a lack of significant side effects in breast-fed babies of mothers who took these agents.[11,15] The reviewers, however, recommend caution and close infant monitoring if use of the medications is necessary.

What needs to be considered, of course, is what is best for the patient, the fetus, and the patient's psychiatric symptoms. In looking closely at available data, cases in which psychotic symptoms are florid and disabling, haloperidol seems to be a reasonable choice. The data are beginning to also support the safety of zyprexa, but more study is needed. In general, newly discovered cases of pregnant patients on maintenance antipsychotics who are psychiatrically stable, gradual withdrawal should be attempted over several days to a week, depending on initial doses. Of course, when dealing with the disease entity that produces a high relapse rate when medications are stopped, prudence dictates very regular and frequent monitoring. One may see a grace period of weeks to months before symptoms return. This may allow avoidance of the antipsychotics during the first 10 weeks of pregnancy, which remains essentially the goal. However, at the first sign of decompensation, antipsychotics should be restarted. For psychiatrically stable women planning a future pregnancy, the previous protocol applies but on a more gradual reduction pattern. Much the same holds true as delivery nears. It is recommended that an antipsychotic washout period occur to lower direct toxic effects to the newborn. Gradual withdrawal over 10 days prior to the estimated date of conception seems reasonable (i.e. reduction by 10% of the doses per day).[8] It is essential to restart the medication shortly after delivery. The previously discussed washout periods and withdrawal of medication in stable pregnant patients would also pertain to clozapine and the atypical antipsychotics, with much attention of course being paid to psychiatric symptom redevelopment especially in the clozapine patient who is especially refractory.

As for behavioral teratogenesis, Sloane and coworkers found no differences in IQ scores at 4 years of age between children prenatally exposed to phenothiazines and control children.[114] Kris also commented on "normal" development of 52 children followed for up to 5 years after exposure to chlorpromazine.[102] Edlund and Craig caution that the following of these patients has generally been too short. In their critique of the California Study,[107] they found much of the increase in birth defects appeared in the 1- to 5-year follow-up period.Cogentin) should not be used prophylactically during pregnancy, especially in the first trimester. They should be reserved for treating emergent problems. In the Collaborative Perinatal Project, a possible association between exposure to anticholinergic medications in the first trimester and minor congenital abnormalities was found,[115] although no specific link was found with individual antiparkinsonian drugs. This project, however, did suggest a possible low-level association between maternal diphenhydramine use (Benadryl) and congenital abnormalities such as genitourinary malformation, eye and ear defects, inguinal hernia, and clubfoot.[115] There are conflicting studies concerning any associations between maternal first trimester diphenhydramine use and congenital oral clefts.[15] As for nursing infants, the

parkinsonian medications should be used with extreme caution, if at all.[15]

MOOD STABILIZERS

The use of lithium, carbamazapine, and valproic acid is widespread in the treatment of bipolar disorder. Recently, other anticonvulsants, such as lamotrigine, gabapentin, and topiramate have also been used to help with mood stabilization, although none of those is specifically approved for the treatment of bipolar disorder. We review each medications individually.

Lithium

Of all the psychotropic medications, lithium is one of the most problematic to use in pregnant and nursing women. Many investigators feel that the maternal use of lithium during the first trimester of pregnancy is associated with an increased incidence of congenital malformations, most especially cardiovascular anomalies.[12,15,116,117,118] Much of the original data supporting such a position came from the International Register of Lithium Babies—a joint effort begun in 1968 by Schou in Scandinavia and Weinstein and Goldfield in the United States, who followed babies born of mothers who took lithium during at least their first trimester.[12] When the project was terminated in 1979, 225 cases had been registered, 25 babies having congenital malformations for an 11% incidence of birth defects.[119] Especially significant was that 18 of the 25 infants born with defects had serious cardiovascular anomalies, an 8% incidence, suggesting that the risk of congenital heart disease in newborns exposed to lithium during the first trimester was approximately 8 times greater than that of an unexposed control group.[117] Ebstein's anomaly, a relatively rare defect of the tricuspid valve, was particularly overrepresented with 6 cases of the 18, a 2.7% incidence in "lithium babies" versus a normal incidence of 0.005% in the general population.[119,120] The severity of this anomaly variesl but the prognosis can be poor and less than one third survive through age 30 years.[120] London investigators have used echocardiography to detect fetal heart abnormalities in the middle trimester of pregnancy and suggest that screening be used before 20 weeks' gestation in pregnant women who have taken lithium during their pregnancies.[121] This might allow early preparations for diagnostic and possible treatment interventions. Despite Register Authorities' caveats (i.e. birth defects tend to be overreported in such registries), they concluded that lithium was "likely to be" teratogenic to the cardiovascular system and suggested that it not be used during the first trimester of pregnancy unless absolutely necessary.[12,119]

A recent cohort study reporting the outcome of pregnancies among women treated with lithium seems to support the conclusions of the Lithium Baby Register. Kallen and Tandberg studied 59 infants born to women treated with lithium in early pregnancy.[122] Four of these 59 (6.8%) infants had congenital heart disease compared with 2 of the 228 (0.9%) control infants of mothers with manic-depressive illness not treated with lithium. Although none of the 4 infants with congenital heart disease had Ebstein's anomaly, this represented an increased risk for cardiac malformations among the lithium-exposed newborns. For all congenital anomalies, there was a 3 times greater risk for lithium-exposed infants versus controls (12% versus 4%). Other studies suggest a more benign scenario. In a prospective cohort study of pregnancy outcome on 148 women treated with lithium during the first trimester, there was no statistically significant difference in major congenital anomalies between the lithium-exposed cohorts and the controls.[123] However, among the lithium-exposed group, there was 1 case of Ebstein's anomaly. In 4 case-control studies totaling 208 children born with Ebstein's anomaly, none of their mothers was treated with lithium during pregnancy.

In summary, lithium seems to increase the risk of congenital malformations, particularly cardiovascular anomalies, but at a more modest teratogenic rate than originally predicted.[3] Whichever malformation rates are cited, the vast majority of lithium-exposed pregnancies result in normal births. There seems to be an increased trend toward therapeutic abortions among women exposed to lithium during pregnancy, perhaps owing to perceived teratogenic risk of lithium.[124,125] Given the previously discusses recent data suggesting a more moderate teratogenic risk, carrying the pregnancy to term is a viable option for women exposed to lithium during the first trimester.

Now the dilemma: The risk of untreated episodes of bipolar affective illness in pregnant patients may be substantial to both mother and fetus. In bipolar patients, significant rates of relapse and shorter intervals between episodes of emotional instability occur after lithium discontinuation.[125,126] In women who are psychiatrically stable on maintenance lithium and who wish to become pregnant (and after discussing the preceding pros and cons), some authors recommend that lithium be discontinued several months prior to attempt at conception[8]; others recommend stopping lithium at the beginning of the menstrual period on the first cycle during which the women wishes to conceive, thus allowing approximately 2 weeks for lithium clearance from her system.[117] The authors favor the latter, especially in women with a history of frequent bipolar episodes. Data suggest that psychiatric relapse may be delayed if lithium is gradually tapered (i.e. over 10 days)[3] rather than abruptly discontinued.[127]

Therefore, the patient and physician should consider tapering lithium 10 days prior to the patient's next expected menstrual period. In newly discovered pregnant patients on lithium and who are psychiatrically stable, abrupt discontinuation of lithium is appropriate, because there are no significant physiologic withdrawal symptoms as with the other psychotropic drugs, albeit some authors still recommend a gradual 10-day taper, given the relapse data.[3] If disabling psychiatric relapse occurs during the first trimester, a trial of alternate treatments (i.e. antipsychotics, antidepressants, perhaps electroconvulsive therapy should be considered. Lithium can always be restarted with follow-up echocardiography, as previously discussed.

Some preliminary data suggest that birth weight among lithium-exposed infants may be higher than that in controls despite identical gestational ages.[123] Another study found no such correlation as far as birth weights. However, they reported an association between maternal lithium therapy and premature delivery.[128] Further study is needed.

Lithium freely crosses the placenta and is present in nearly equal concentrations in maternal and fetal sera.[129] Maternal use of lithium during the latter trimester and especially during the perinatal period may result in direct toxic effects in the newborn, regardless of whether the mother's or infant's lithium levels are therapeutic or toxic.[22,78,84] A floppy baby syndrome has been described in which affected neonates showed lethargy, respiratory distress, cyanosis, hypotonia, hypothermia, low APGAR scores, and poor sucking reflexes.[22,116,130] Some of these newborns had transient cardiac dysfunction, including bradycardia, electrocardiogram abnormalities (T-wave inversion), and arrhythmias.[15] Neonates with lithium toxicity generally resolved within 2 weeks, reflecting ongoing, albeit prolonged, renal elimination of lithium in the newborn.[15] There are several reports of thyroid goiters in newborns whose mothers took lithium during pregnancy; some of the infants were euthyroid,[131,132] whereas others had transient hypothyroidism.[117,133] The thyroid abnormalities generally disappeared over several months. Because a large goiter in the newborn might complicate delivery, some researchers recommend fetal ultrasound monitoring for goiter during pregnancy, especially those in pregnant women with lithium-induced thyroid abnormalities themselves.[78]

Nephrogenic diabetes insipidus, which resolved within 3 months, has also been reported in neonates whose mothers took lithium near term.[133] At least two cases of polyhydramnios associated with maternal lithium therapy have been reported.[134,135] One of these infants also presented with the already described symptoms of lithium toxicity. In both cases, fetal nephrogenic diabetes insipidus was thought to contribute to excess amniotic fluid.

Despite few data on behavioral teratogenesis, Schou, following 60 lithium babies born without congenital abnormalities, found no differences in mother's reports of their children's physical or mental development at age 5 years compared with their nonexposed siblings.[132]

In women who are to remain on lithium during pregnancy, careful attention must be paid to their serum lithium levels. Because maternal glomerular filtration rate measured by creatinine clearance almost doubles during pregnancy, lithium is excreted more rapidly by the kidneys, resulting in lower serum levels and potentially increased risk for psychiatric relapse.[136] Higher lithium doses may well be required during pregnancy, and diuretics should be avoided. At delivery, there is an abrupt decrease in both glomerular filtration rate and lithium excretion to normal prepregnancy levels, resulting in higher serum levels and exposing both mother and newborn to potential lithium toxicity.[136] To avoid both maternal and neonatal lithium toxicity, reduction of lithium dosage is indicated as the woman nears term, although there are a variety of options as to the best method.[136,137] Discontinuing lithium 5 to 7 days before the expected date of delivery with resumption of the prepregnancy lithium dosage shortly after delivery seems most reasonable.[8]

The breast milk concentration of lithium is approximately half that in the maternal serum, and nursing infants can have serum lithium levels one third to one half of their mothers' levels.[138] Tunnessen and Hertz reported that a breast-fed infant with a serum lithium level of 0.6 mEq/L (mother's level was 1.5 mEq/L) who presented with signs of lithium toxicity including floppy baby syndrome and electrocardiogram changes that persisted until breast-feeding was stopped.[130] Otherwise, there has been a paucity of similar reports. Although Schou and colleagues adopted a more permissive view of lithium-treated mothers nursing their infants,[12,138] many authors still warn mothers on lithium against nursing their infants.[2,8,9,11]

Valproic Acid

Certainly valproic acid (Depakote) is now a cornerstone in the battle against bipolar disorder. Valproic acid has also been associated with significant malformations. Many studies as outlined by Iqbal and associates[139] have described an association between first trimester valproic acid therapy and the occurrence of spina bifida to the rate of 1% to 2%.[140] A *fetal valproate syndrome,* characterized by cardiovascular, craniofacial, urogenital, digital, and respiratory tract abnormalities and developmental delays have been observed.[141,142,143] As well, Lejeunie and coworkers have identified a craniosynostosis/metopic

suture synostosis in infants exposed to valproic acid.[144] There have also been reports of developmental delays by Ardinger and associates,[145] deficiencies of vitamin K_1–dependent clotting factors, thromobocytopenia, reduced platelet aggregation, and low fibrinogen levels in the pregnant patient taking valproic acid.[139] Thisted and Ebbesen discussed the increased risk of hypoglycemia in infants of mothers treated with valproic acid.[146]

Rodriguez-Pinilla and coworkers conducted a case-control study using data from the Spanish Collaborative Study of Congenital Malformations and the relationship between prenatal exposure to valproic acid and the presence of limb deformities in newborn infants. Of the total of malformed infants exposed to valproic acid, 36.8% presented with congenital limb defects of different types including overlapping digits, talipes, clubfoot, clinodactyly, arachnodactyly, hip dislocation, and pre- and post-axial polydactyly. Three of the infants had limb deficiencies, which were the following: case 1, hypoplasia of the left hand; case 2, unilateral forearm defect and a hypoplastic first metacarpal bone with the left hand; and case 3, short hands with hypoplastic first metacarpal bone, absent, and hypoplastic phalanges, retrognathia, facial asymmetry, hypospadias, teleangiectatic angioma in the skull, and hypotonia.[147]

Clearly, given the significant risks of anomalies with valproic acid, it needs to be avoided, especially within the first trimester of pregnancy, choosing an alternate agent, such as a neuroleptic. When it absolutely cannot be avoided, a reduction in the daily dose, with three or more equal doses, does seem reasonable to decrease infant risk.[148] As well, 4 mg of folic acid daily should be consumed by the mother to reduce the risk of neural tube defects. The supplements should be started before conception and continued until the 12th week of pregnancy. One must carefully monitor serum valproic acid levels, perform ultrasonography and fetal echocardiography at 16 to 18 weeks' gestation to detect malformation early, and check clotting parameters late in pregnancy[149] with the administration of oral vitamin K (10 to 20 mg/day) during the last month of pregnancy to protect against coagulopathies.[139]

As discussed and reviewed by Iqbal and associates,[139] there is evidence that valproate is excreted into breast milk in low concentrations ranging from 2% to 8% of maternal serum levels.[150,151] Case reports including thrombocytopenia and anemia with resolution 12 to 35 days after stoppage of breast-feeding[152] and potentially fatal hepatotoxicity[153,154] lead the authors to recommend very careful discussion regarding breast-feeding with all concerned parties.

Carbamazepine

Carbamazepine (Tegretol) is now used as a frontline treatment of bipolar disorder, but there have been many reports of congenital abnormalities associated with the use of carbamazepine during pregnancy. Altshuler reviewed many articles and case reports in which there was first trimester exposure to carbamazepine. Malformations include a neural tube defect, developmental delays, craniofacial defects, fingernail hypoplasia, and behavioral changes.[155] Holmes and associates, in the *New England Journal of Medicine,* reported the following major malformations in infants exposed to carbamazepine: tetralogy of Fallot, esophageal atresia, vertebral abnormalities, multiple ventricular septal defects, and multiple terminal transverse limb defects.[156] Diav-Citrin completed a prospective study in which 210 women treated with carbamazepine in the first trimester were considered. The rate of anomalies was higher in the Carbamazepine-exposed group than in the general groups, although this study showed a lack of neural tube defects, which may reflect sample size limitation. The rate of congenital heart defects (2.9%) was relatively high versus controls. There was also a finding of reduced birth weight compared with controls.[157] Iqbal and associates,[139] in their seminal article, reviewed literature concerning the use of carbamazepine. All the following studies were cited in his seminal article. Hiilesmaa and colleagues reported a study of 133 epileptic pregnant females with matched controls that showed a 10-mm decrease in fetal head circumference in Carbamazepine-exposed infants and that catch-up growth was not observed by the age of 18 months.[158] Jones and coworkers observed craniofacial defects, fingernail hypoplasia, and developmental delay in eight children retrospectively ascertained to have been exposed to carbamazepine *in utero*.[159] It is clear that carbamazepine should be considered as a suspected human teratogen.[159] It causes major and minor congenital abnormalities and other adverse effects such as developmental problems, growth retardation, abnormal IQ, and bleeding disorders, secondary to coagulation problems, in the fetus and the newborn. Hence, carbamazepine should not be used by pregnant females, especially during the first trimester.[139]

Carbamazepine is detected in breast milk. Iqbal and associates cited two reports of hepatic toxicity[160,161] and seizure-like activity,[162] drowsiness, irritability, and refusal to feed in breast-fed 3-week-old and 10-week-old infants whose mothers were taking carbamazepine along with other drugs.[163] Iqbal and associates recommend measuring concentrations of carbamazepine and its epoxide metabolites in maternal plasma and breast milk and in infants' plasma if carbamazepine is continued during breast-feeding. If there are adverse reactions, nursing should be discontinued, at least temporarily. Neonatal acquisition via

nursing does not seem to be harmful for the neonate- and weighing the benefit of breast-feeding against potential risk, breast-feeding during maternal carbamazepine therapy is considered safe.[139]

Lamotrigine

Lamotrigine (Lamictal) is relatively new to psychiatric circles. It is approved for the treatment of seizures, but has gained reasonably widespread use for treatment of bipolar disorders. There are some case reports concerning use of lamotrigine in the pregnant patient, and GlaxoSmithKline does maintain a pregnancy registry program. Dominguez Salgado and associates reported on open-label results in 31 pregnant females with secondary generalized partial seizures receiving lamotrigine as monotherapy with the average dose being 200 to 400 mg/day. There was 1 seizure crisis in the first trimester without fetal consequences, and another patient had 2 spontaneous miscarriages in the first trimester. All were term deliveries, and no fetal malformations were observed in the newborns.[164] One-year follow-up completed in 23 newborns revealed proper development without any evidence of malformation at 0, 3, 6, and 12 months of age.[165]

Quattrini and colleagues described the case of a 32-year-old woman who experienced an uneventful pregnancy while receiving lamtrigine 200 mg/day, carbamazepine 1000 mg/day, and barbesaclone 200 mg/day.[166] This patient had three previous pregnancies, during which she received completely different medication combinations. Her first pregnancy led to the birth of an infant with severe malformations who subsequently died, and her two other pregnancies resulted in spontaneous abortion. There were no signs of any malformations or other diseases observed at delivery during the 39th week of this pregnancy. The weight, length, and head circumference of the child were all within the lower limits of normal growth age. Only during this fourth pregnancy did the patient receive folic acid for the duration of her pregnancy.

As of March 31, 2001, there were 537 prospectively registered pregnancies with 137 pending outcome. Of the remaining 400, 326 pregnancy reports had outcomes, and 74 reports were lost to follow-up. With lamotrigine monotherapy, there were 3 outcomes with major defects—esophageal malformation repaired by surgery, right clubfoot and cleft soft palate—out of 120 cases involving a first trimester monotherapy exposure. The remaining outcomes were all involved with polydrug therapy. The exposure group that had the highest proportion of major birth defects was the polytherapy group including lamotrigine with valproic acid.[167] Morrow and coworkers published data from an ongoing prospective observational registration and follow-up

study of pregnancy exposures to any antiepileptic drug in the United Kingdom since 1996. As of June 2001, over 1500 females registered, with outcome data currently available on 1060. Thirty-three percent of the females were prescribed folic acid preconceptually.[168] Among first trimester exposures with lamotrigine monotherapy, no major abnormalities were reported in 155 of 159 births and 17 of 18 pregnancy losses.[169] One must also be concerned here with the potential for severe skin rash development from lamotrigine owing to Stevens-Johnson Syndrome. Caution is of course advised.

Preliminary data do indicate that lamotrigine passes into human milk, based on studies by Rambeck and associates[170] and Ohman and colleagues[171] Because of the effects on an infant exposed to lamotrigine by this route are unknown, breast-feeding while taking lamotrigine is not recommended. Reports in the literature have estimated lamotrigine intake by infants during breast-feeding to be approximately 0.1 to 1 mg/kg/day.[172] As well, one must again remember the potential for the severe skin rash and Stevens-Johnson syndrome development, which can occur in anyone receiving lamotrigine.

The data are insufficient to recommend use of lamotrigine in pregnancy. However, the authors feel, if absolutely required, monotherapy is preferred with folic acid maintenance throughout the course of pregnancy.

Gabapentin

Another of the anticonvulsants, gabapentin (Neurontin) is being employed in bipolar disorder. Some women of childbearing age were included in trials with gabapentin. As of July 1994, nine of these women had become pregnant, four pregnancies were terminated by elective abortion, and five infants were born. The females who gave birth received doses of 600 to 1800 mg/day. Four infants were healthy at birth and continued to have normal development at ages ranging from 6 weeks to 3 years. The fifth had respiratory distress, pyloric stenosis, and inguinal hernia at birth but, as of July 1994, was developing normally at approximately 1 year of age. Each of the pregnancies had other anticonvulsants on board as well. An infant born 8/22/95 was identified as being exposed to gabapentin as a sole agent. The dosage reached 2400 mg/day, with gabapentin being stopped prior to conception. The baby was born in a healthy, normal manner.[173] The data are far too small to draw any conclusions.

Pfizer, the makers of gabapentin, was not aware of any published data on gabapentin in human breast milk. However, Parke-Davis has studied the secretion of gabapentin into breast milk. Five subjects completed the study in which they received 400

mg of gabapentin, which was followed by serial blood, urine, and breast milk sampling for 36 hours. Gabapentin was found in breast milk in almost the same amount as plasma (73%). Parke-Davis has conservatively estimated the exposure of an infant to abapentin from breast milk to be approximately 1.2 mg/kg/day for a 5-kg infant.[174] The effects exerted on the infant are unknown, and therefore gabapentin is not recommended for use in the breast-feeding patient.

Topiramate

Topiramate (Topimax) is another anticonvulsant medication gaining favor in the treatment of bipolar disorder. Hoyme and coworkers reported one case of minor abnormalities in an infant whose mother was on topiramate 700 mg twice daily throughout pregnancy. The mother had a history of intractable seizures that improved after a temporal lobectomy. She had been on topiramate for 3 years. The infant, at birth, was found to have prenatal-onset growth deficiency, generalized hirsutism, a third fontanelle, short nose with anteverted nares, blunt distal phalanges, and blunting of the nails. The anomalies are consisted with fetal anticonvulsant effects but can be secondary to antifolate effects, arene oxide metabolites, and vitamin K deficiency.[175] In correspondence with Ortho-McNeil, no other case reports were noted, making the data too small to make any conclusions.

Ohman and associates measured the plasma in milk concentration of Topiramate in three females with epilepsy treated with topiramate and in their offspring. Data were collected from one patient during both delivery and lactation, from one patient from delivery only, and from one patient during lactation. The concentration was quite similar in both maternal plasma and breast milk.[176] The consequences to the infant are unknown; therefore, the usage in breast-feeding mothers is not recommended.

In summary, psychotropic medication should be used with caution during pregnancy and nursing and only when the potential benefits outweigh the risks. There is also the high risk of untreated psychiatric illness during pregnancy to both mother and fetus. Because this has become such an important issue, it is highly recommended that close monitoring of patients who are pregnant, who intend to become pregnant, and who are nursing be followed. It is important to look individually at each case, each medication and class of medications, and the potential risk/benefit ratio before making an appropriate decision concerning the use of psychotropics during pregnancy and lactation.

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