Medications for Panic Disorder and Generalized Anxiety Disorder During Pregnancy

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Objective: Approximately 30% of women experience some type of anxiety disorder during their lifetime. In addition, some evidence exists that anxiety disorders can affect pregnancy outcomes. This article reviews the literature on the course of generalized anxiety disorder (GAD) and panic disorder during pregnancy and the postpartum period and presents guidelines for management.

Data Sources and Study Selection: An English language electronic search of relevant studies using PubMed (January 1, 1985–January 2004) was performed using the search terms *anxiety and pregnancy*, *maternal mental illness*, *panic and pregnancy*, *psychotropic medications in pregnancy*, and *treatment options in pregnancy.* Review articles and primary pharmacologic treatment articles were selected for discussion.

Data Extraction and Synthesis: Despite the extensive use of psychotropic drugs such as antidepressants during pregnancy, there is a scarcity of information regarding the effect of such exposure on the developing fetus. Review articles and primary pharmacologic treatment trials were analyzed and incorporated into the review based on adequate methodology, completeness of data, and information on pregnancy outcome.

Conclusion: It is important that physicians understand the course of these disorders during pregnancy and available treatments so they appropriately counsel women who are or intend to become pregnant. The goal of treatment during pregnancy and lactation is sufficient treatment for syndrome remission. To minimize the potential for neonatal withdrawal and maternal toxicity after delivery, vigilant monitoring of side effects is indicated. Also, if possible, nonpharmacologic treatment, such as cognitive-behavioral therapy, should be first-line treatment in pregnant women with GAD or panic disorder.

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MANAGING PANIC DISORDER AND GENERALIZED ANXIETY DISORDER DURING PREGNANCY

Pregnancy is a time of great emotional change for women, often producing increased stress and anxiety. Gonadal steroid levels have been reported with as much as a 100-fold variation in serum estrogen levels and a 1000-fold change in serum progesterone levels during pregnancy.[1] These changes can exacerbate such emotional difficulties.

Psychological factors may also have an important role to play in the development of anxiety disorders at this time. Often the expectant mother has concerns over the health of the child, the change in lifestyle likely to occur in her own life after the birth of the child, her own ability to be a good mother, and finances. There are also instances where the pregnancy is unexpected or unwanted, which may further increase stress and anxiety. For some women, pregnancy may bring to mind painful events in their lives with their own parents.

Although it is obvious that pregnancy alone may produce states of anxiety, the question has been raised as to what happens to preexisting anxiety disorders during this period. Most of the literature in this area has focused on the effect of pregnancy on preexisting panic disorder and obsessive-compulsive disorder to the exclusion of other anxiety disorders such as generalized anxiety disorder (GAD). Although childbirth may lead to the onset of panic disorder in some cases, research of the effect of pregnancy on preexisting panic disorder has revealed mixed results. In one retrospective review[2] of 49 women with panic disorder, only 20% described an improvement in their symptoms during pregnancy, while 54% remained the same, 20% worsened, and 2% had a mixed course. Cohen et al.[3] reported that women with milder panic symptoms may experience an improvement in symptoms during the pregnancy period but that in women with more severe symptoms, pregnancy may produce an exacerbation of panic disorder. Current evidence[3] suggests that pregnancy is not protective for panic symptoms and anxiety, and the postpartum period may be a time of particular vulnerability to exacerbations. In addition, evidence exists that anxiety disorders can affect pregnancy outcomes.[3]

DATA SOURCES AND STUDY SELECTION

This review provides an update on symptoms and diagnosis criteria for panic disorder and GAD and discusses the impact of untreated anxiety disorders on pregnancy as well as potential adverse effects of medication treatment, the pathophysiology of anxiety, and a treatment guideline for the prenatal care provider.

An English-language electronic search of relevant studies using PubMed (January 1, 1985–January 2004) was performed using the search terms *anxiety and pregnancy*, *maternal mental illness*, *panic and pregnancy*, *psychotropic medications in pregnancy*, and *treatment options in pregnancy.* Review articles and primary pharmacologic treatment articles were selected for discussion.

Panic Disorder

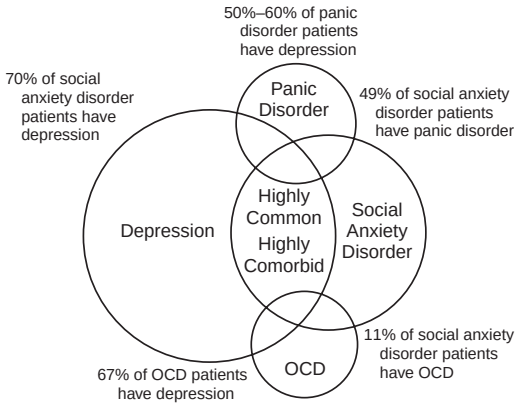
Panic disorder is distinguished by sudden and persistent unreasonable fear that may be brought on by the presence or anticipation of a specific object or situation. Panic disorder is more common in adult women than men, and the onset of this disorder is typically during the mid-20s, which coincides with the peak childbearing years. The prevalence of panic disorder in the general adult population is approximately 5%; the prevalence during pregnancy has not been accurately documented in the literature due to a lack of longitudinal and epidemiologic studies.

Among the most common conditions comorbid with panic disorder is depression, with up to two thirds of panic patients experiencing major depression at some point during their lifetime (Figure 1). The presence of comorbid depression may complicate treatment and increase the overall severity of the patient's distress, and the presence of panic attacks in patients with major depression is associated with an increased risk of suicide.

Generalized Anxiety Disorder

Anxiety disorders are the most prevalent of all psychiatric disorders, especially among women, 30% of whom have an anxiety disorder at some time during their lives.[5] Sixty-five percent of patients with current GAD report comorbid disorders (most commonly depression, panic disorder, and agoraphobia). Generalized anxiety disorder tends to be a chronic and disabling condition with lifetime comorbidity as high as 90%.[6] The goals of pharmacotherapy for GAD include treatment of the symptoms of worry, anxiety, tension, somatic distress, and autonomic arousal. The presence of a psychiatric disorder does not exclude the potential coexistence of other medical and obstetrical conditions. Therefore, evaluation for mood and anxiety disorders in pregnancy should involve an appropriate physical examination with optional laboratory testing, such as a complete blood count and thyroid, renal, and liver function tests (especially if treatment appears to be ineffective). We also recommend sending a urine toxicology screen (if history or collateral information warrants), given the high comorbidity between psychiatric disorders and drug and alcohol use. In addition, the woman should be evaluated for use of herbal medication and over-the-counter remedies that may precipitate or exacerbate anxiety disorders.

Figure 1. Comorbidity of Anxiety and Depression[a]



[a]Based on Hirschfeld.[4]
Abbreviation: OCD = obsessive-compulsive disorder.

Comorbidity

Ninety-one percent of patients with panic disorder and 84% of those with agoraphobia have at least 1 other psychiatric disorder.[5] According to DSM-IV-TR, 50% to 65% of persons with panic disorder have comorbid major depressive disorder. About one third of persons with both disorders have major depressive disorder before the onset of panic disorder; about two thirds first experience panic disorder during or after the onset of major depression.[5]

Additional anxiety disorders also commonly occur in persons with panic disorder and agoraphobia. Fifteen percent to 30% of persons with panic disorders also have social phobia, 2% to 30% have specific phobia, 15% to 30% have GAD, 2% to 10% have posttraumatic stress disorder, and up to 30% have obsessive-compulsive disorder.[5] Other common comorbid conditions are hypochondriasis, personality disorder, and substance-related disorders (Figure 1).

Pathophysiology

Several neuroanatomic areas (including the amygdala, locus ceruleus, and hippocampus) and a number of neurotransmitters (including norepinephrine, serotonin, and GABA [γ-aminobutyric acid]) have been the focus of research into the pathophysiology of panic disorder and GAD. Other lines of research have focused on the brainstem as the neural trigger for panic attacks, suggesting that patients may inherit brainstem loci that are hyper-

excitable (accounting for sensitivity to lactate, increased carbon dioxide levels, and yohimbine in provoking panic attacks in experimental situations). The prefrontal cortex, an area of the higher brain involved with learning and complex emotions, has been viewed as a neuroanatomical substrate for phobic avoidance in panic disorder.[7]

This biological system has many similarities to the cognitive model of panic disorder, which suggests that panic symptoms result from errors in cognitive appraisal, leading to increased levels of anxiety, arousal, and somatic complaints that result in a vicious cycle of anxiety symptoms.[7]

Table 1. Medications Used for Treatment of Generalized Anxiety Disorder and Panic Disorder

Agent	Initial Dose, mg/d	Target Dose, mg/d
Citalopram	10	20–60
Clomipramine	25	25–250
Fluoxetine	10	20–80
Fluvoxamine	25	50–300
Paroxetine	10	20–60
Sertraline	25	50–200
Venlafaxine XR (extended release)	37.5	75–300
Paroxetine CR (controlled release)	12.5	25–50
Mirtazapine	15	30–45
Escitalopram	10	20

DATA EXTRACTION AND SYNTHESIS

Review articles and primary pharmacologic treatment trials were analyzed and incorporated into the review based on adequate methodology, completeness of data, and information on pregnancy outcome.

Impact of Untreated Anxiety Disorder in Pregnancy

There are few data regarding the long-term risk to the fetus of untreated psychiatric illness during pregnancy. Overall, the clinical and laboratory data indicate that untreated maternal anxiety during pregnancy can cause lower infant birth weight, lower gestational age, altered Apgar scores, and impairment of fetal hemodynamics and fetal movement.[3] In one study, anxiety symptoms early in pregnancy were associated with a 3-fold increase in preeclampsia.[8] Rizzardo et al.[8] reported an association between anxiety symptoms and premature rupture of the membranes, cervical dyskinesia, and incidence of cesarean section. Panic attacks during pregnancy can cause placental abruption, fetal distress, decreased nutrition, and use of potentially harmful substances for self-medication.[9] Agoraphobia in addition to panic disorder is assumed to also impair prenatal care and adversely affect the outcome of pregnancy, although it has not been directly investigated.

Pharmacokinetics During Pregnancy

Each of the 4 generally recognized phases of the pharmacokinetic sequence (absorption, distribution, metabolism, and elimination) is affected by pregnancy.[10] Several factors serve to increase the absorption of orally administered medications during gestation. Decreases in the rate of gastric emptying and intestinal motility lengthen the transit time of oral medications and thus increase the time for absorption across the intestinal mucosa. Both plasma volume and extracellular fluid volume increase dramatically. In addition, increase in body fat during pregnancy further increases the volume of distribution for psychotropic medications, which are almost uniformly highly lipophilic compounds.

Rates of drug metabolism during pregnancy are also affected by other mechanisms. First, tissue delivery of medication is increased during pregnancy by an up to 50% increase in cardiac output, but a smaller percentage of this heightened cardiac output is delivered to the liver as more blood is diverted to the uterus and other organs. Second, pregnancy is associated with numerous changes in the activity of various hepatic and extrahepatic enzymes. The activity of the hepatic cytochrome P450 (CYP) 3A4 enzyme is increased during gestation, but that of CYPIA2 is decreased. Many CYP enzymes are also present in placental tissue, although the activity of the placental enzymes appears to be considerably lower than that of their maternal hepatic counterparts. Finally, drug elimination during pregnancy is affected by increase in renal blood flow and glomerular filtration rate.[10]

Treatment of Anxiety During Pregnancy

Given the fact that psychotropic drugs readily cross the placenta and could have important implications for the developing fetus, it is necessary to balance the possible effects of medication against the potential effects on both the mother and fetus if the anxiety disorder is left untreated.

Despite the widespread use of psychotropic drugs such as antidepressants (selective serotonin reuptake inhibitors [SSRIs] and serotonin norepinephrine reuptake inhibitors [SNRIs]) during pregnancy (Table 1), there is a paucity of information regarding the effects of such exposure on the developing fetus. Drugs should be prescribed when the risks of depression for the mother and fetus outweigh the risks of drug exposure. To date, published retrospective and prospective reports on SSRI use during gestation currently consist of 1241 fluoxetine exposures and 364 citalopram, 309 paroxetine, 225 sertraline, and 80 fluvoxamine exposures. No published reports regarding prenatal exposure to the new enantiomeric compounds duloxetine and escitalopram are currently available. Collectively, these data provide no

evidence that prenatal SSRI exposure is associated with an increased incidence of congenital malformation.[1,11–13]

From a review of the literature, it is clear that the issue of psychotropic drugs during pregnancy is far from resolved, and no conclusive evidence exists for or against use of these medications in the pregnant patient. Animal studies indicate that serotonin reuptake inhibitors are not teratogenic,[14] but these studies cannot be directly extrapolated to humans. In addition, varying sample sizes and multiple drug exposures further complicate interpretation of human studies.[15]

Adverse Reactions

Sertraline, fluvoxamine, and citalopram have the highest rates of gastrointestinal (GI) adverse effects. The most common GI complaints are nausea, diarrhea, and vomiting. Data indicate that the nausea and diarrhea are dose related and transient. Although most patients initially lose weight, up to one third of persons taking SSRIs will gain weight. Paroxetine has anticholinergic activity and is the SSRI most often associated with weight gain. The incidence of headache in SSRI trials is 18% to 20%. SSRIs often can cause trouble with sleeping or excessive somnolence. Fluoxetine is most likely to cause insomnia, for which reason it is often taken in the morning. Citalopram and paroxetine are more likely to cause somnolence than insomnia. Extrapyramidal symptoms are most closely associated with the use of fluoxetine, particularly at dosages in excess of 40 mg per day. SSRIs are rarely associated with platelet dysfunction or hyponatremia. Venlafaxine has generally been reported to be well tolerated. The most common adverse reactions are nausea, somnolence, dry mouth, dizziness, nervousness, constipation, asthenia, anxiety, anorexia, and blurred vision.

Abrupt discontinuation of venlafaxine or SSRIs (except fluoxetine) may produce a discontinuation syndrome consisting of nausea, somnolence, and insomnia. Antidepressants should be tapered gradually over 2 to 4 weeks (with the exception of fluoxetine, which has a long half-life). The most potentially worrisome adverse effect associated with venlafaxine is an increase in blood pressure in some persons, particularly those who are treated with more than 300 mg a day. An excellent review on SSRIs and the above adverse effects as well as uses is found in Masand and Gupta.[16]

Risk of Medications

Several areas of concern exist when using anxiolytic medication during pregnancy and the postpartum period including teratogenicity, perinatal syndromes, and neurobehavioral effects. Since all anxiolytics pass through the placenta with potential implications for the developing fetus, it is essential that the practitioner have an appreciation for the potential impact of each anxiolytic prescribed.

Teratogenicity

A medication is considered teratogenic when prenatal exposure significantly increases the risk of congenital deformities over the baseline, which is 2% in the United States.[9] The cause of most congenital malformations is unknown, and risk for teratogenicity occurs in the first 12 weeks of gestation. To date, no significant teratogenic effects of SSRIs have been identified in offspring of treated women. Most data regarding the newer antidepressants consist of analysis of women exposed to fluoxetine. The manufacturer's register contains 2000 cases of treated patients, with no cases of malformations following prenatal exposure. Citalopram has the next largest database of in utero exposure (N = 365) with no increased risk of teratogenicity.[17] Studies evaluating use in pregnancy of venlafaxine (N = 150) and mirtazapine also reported relative safety.[12] Prospective and retrospective studies documenting 500,000 births and 400 cases of first-trimester exposure to tricyclic antidepressants (TCAs) demonstrated no increased risk of congenital malformation.[1] The risk of using benzodiazepines during pregnancy remains unclear. A meta-analysis performed by Altshuler et al.[17] noted that the increased risk of cleft lip and palate associated with use of benzodiazepines was real, but small (less than 1%, compared with 0.06% in the general population).

Perinatal Syndromes

A few reports have discussed perinatal syndromes associated with the use of anxiolytics. Despite the fact that thousands of women have been exposed to SSRIs during pregnancy, only a few case reports of adverse events have been published. Two small case series, describing a total of 9 patients, reported withdrawal syndromes in infants exposed to SSRIs during the third trimester.[15] Symptoms included jitteriness, irritability, tremulousness, myoclonus, difficulty feeding and sleeping, hypotonia/hypertonia, hypothermia, tachypnea, and seizures. Two of the infants exposed to paroxetine were diagnosed with necrotizing enterocolitis. Infants may be particularly sensitive to paroxetine discontinuation because it has such a short half-life. Cohen et al.[18] examined 64 infants exposed to fluoxetine in utero and reported no difference in immediate neonatal outcome or birth weight between the first-trimester and the third-trimester exposed groups, although a higher frequency of special care nursery admissions took place for those infants exposed to late-trimester fluoxetine.

Although effective as a class against anxiety, TCA exposure in the third trimester can be more problematic. Case reports have described an association between late-trimester exposure and abnormalities in perinatal adaptation, including irritability, jitteriness, and seizures.[15] Anticholinergic side effects of bowel obstruction and urinary retention also have been described.[15]

Table 2. Treatment Guidelines for Panic Disorder and Generalized Anxiety Disorder During Pregnancy[a]

Nonpharmacologic treatment such as cognitive-behavioral therapy or interpersonal psychotherapy should be employed whenever possible
Benzodiazepines may cause physiological dependence and withdrawal in the newborn, so they should be avoided if alternative treatments are available. Given the first-trimester risk of benzodiazepine-associated oral cleft, the use of SSRIs is preferable
If medication is required, pregnant women should be prescribed the lowest effective dosage for the minimum amount of time
Keeping dosages low close to the time of delivery may also minimize withdrawal and adverse effects in the newborn. A balance between treatment efficacy and potential withdrawal syndrome should be considered
The SSRIs are the first-line treatment for anxiety disorders because of data supporting their efficacy, their minimal need for dose titration, and their overall favorable side effect profile
Newer antidepressants, such as venlafaxine XR and mirtazapine, are options for patients unresponsive to, or intolerant of, SSRIs
Abrupt discontinuation of antipanic medication is not recommended; taper of the medication with adjunctive cognitive-behavioral therapy may be pursued in an effort to minimize fetal exposure if necessary
Women who have avoided medications during pregnancy should consider resumption postpartum, because the postpartum period is a time of high risk for relapse. The clinician should give the patient as much information as possible to facilitate the decision-making process

[a]Based on Cohen and Rosenbaum[12] and Altshuler et al.[17]
Abbreviations: SSRIs = selective serotonin reuptake inhibitors, XR = extended release.

Data regarding third-trimester benzodiazepine use demonstrate genuine risk. The most prominent effects upon the newborn infant include sedation and withdrawal symptoms. A "floppy baby" syndrome has been described, characterized by low Apgar scores, hypothermia, muscular hypotonia, and sluggish response to cold temperature.[19] Symptoms thought to be associated with benzodiazepine withdrawal include hypertonia, hyperreflexia, excessive crying, tremors, bradycardia, restlessness, irritability, seizures, abnormal sleep patterns, and cyanosis.[11] These effects have been seen for several months after birth and vary depending upon the amount and length of in utero exposure. Evidence of a withdrawal syndrome associated with benzodiazepine use is considerably more substantial than that resulting from exposure to SSRIs.[18]

Neurobehavioral Effects

Neurobehavioral sequelae include long-term abnormalities in children who were exposed to psychotropics in utero. However, the data regarding neurobehavioral functions, including IQ, in children with histories of in utero exposure to fluoxetine fail to show adverse effects. The possibility that benzodiazepine exposure may lead to long-term effects on infants has been evaluated with mixed results. Laegreid et al.[20] reported deviant motor development at 6 months and 10 months for benzodiazepine-exposed children. At 18 months, however, exposed children tested nearly normal. In a similar study on children up to 18 months of age, benzodiazepine-exposed children demonstrated delays in mental development quotients and social, hearing, and speech subscales.[12,17] In contrast, other studies have not demonstrated a negative impact upon neurobehavioral development after exposure to benzodiazepines in utero.[12,17] While studies of neurobehavioral effects in children exposed to benzodiazepines in utero show mixed results, it should be noted that those reporting negative outcomes were limited in their sample size compared with those that failed to find adverse outcome. Little research has been conducted into the effect of prenatal SSRI exposure on postnatal behavioral development. Nulman et al.[21] assessed the effect of prenatal exposure to fluoxetine on postnatal development. The mean global IQ score for children who were exposed to fluoxetine was 117, and 114 in the control group. The language scores were similar in all groups. There were no significant differences in temperament, mood, distractibility, activity level, arousability, or behavioral problems.

CONCLUSION

When the decision is made to use a psychotropic medication, the goal is to maximize efficacy so that the offspring exposure to maternal mental illness can most reliably be eliminated while avoiding offspring exposure to multiple medications. The most important factor in choosing a medication is, therefore, treatment history. If a patient has a history of a positive response to a particular medication, a novel agent should not be started during pregnancy or lactation.

It is impossible to provide a complete list of all the risks for any given psychotropic medication, but the evidence for adverse effects and organizational effects of each medication should be reviewed. It is equally important to discuss with the patient the risks of the untreated illness to both the mother and the infant. Finally, it is important to document that other treatment modalities have been attempted or considered.

It is highly recommended that the primary care provider discuss the medication and potential interactions with the patient's obstetrician and pediatrician (if applicable) and with the patient's family (Table 2).

Drug names: citalopram (Celexa and others), clomipramine (Anafranil and others), duloxetine (Cymbalta), escitalopram (Lexapro), fluoxetine (Prozac and others), mirtazapine (Remeron), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft), venlafaxine (Effexor).

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