Mood Disorders During Pregnancy and Lactation: Defining Issues of Exposure and Treatment

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ABSTRACT

Epidemiologic studies have consistently demonstrated a greater incidence of depressive disorders and anxiety among women. Many women experience these conditions during the reproductive years. The dramatic expanse of literature focusing on the use of medications often has failed to pay homage to the potential impact of the disorders. When considering the extant human and laboratory data on mental illness and stress during pregnancy and the postpartum period, it is evident that some degree of exposure (be it treatment or illness) always occurs. The primary goal of the risk-benefit assessment for the treatment of mental illness during these periods is to assist patients and their families in choosing the path of potential exposure that possesses the least risk for them. Once this decision is made, the goal is to limit the number of exposures for the fetus/neonate.

CNS Spectrums *2001;6(2):150-166*

INTRODUCTION

Social scientists, politicians, and theologians continue to debate whether life begins at birth or conception. Although this debate is outside the purview of the present discussion, it is clear that parenting behaviors begin not only before a child's birth but, in many species, even before conception. Germane to this issue is the seminal role of early childhood experiences in shaping subsequent patterns of adult behavior. Considering the high prevalence of mental illness in the childbearing years, it is likely that the clinician will face the challenge of treatment planning during a patient's pregnancy and lactation. Unfortunately, many proposed models for the treatment of pregnant women do not include potentially pertinent data on the impact of stress and untreated mental illness during fetal and neonatal development.

In our previous review, we detailed the facets of the risk-benefit assessment for women during pregnancy and lactation, with emphasis on the unrealistic perception that the ideal pregnancy and childbirth experience represents the norm.[1] The current article expands the components of the risk-benefit assessment by including laboratory animal data on the impact of perinatal maternal stress on offspring development. Such an expansion emphasizes the issues of fetal and neonatal exposure to purposefully underscore that "exposure always occurs, be it to treatment or illness." Second, rather than provide yet another review of the data on medications, this article will address many of the clinical steps in monitoring this population with a view to minimizing the infants' overall exposure.

Exposure in these populations has not been formally defined. In the current report, we define the following pathways of exposure: (1) direct exposure to the neuroendocrine alterations associated with mental illness/stress via umbilical circulation, amniotic fluid, or alterations in breast milk content; (2) indirect exposure through its impact on prenatal behaviors or the psychosocial milieu in which the neonate develops (eg, nurturing); (3) direct exposure to somatic treatments by the appearance of such agents in fetal circulation, amniotic fluid, and breast milk; and (4) indirect exposure to somatic treatments by altering the neurochemical environment to which the fetus or neonate is exposed (see figure).

Dissection of the diagram in the figure, with the inclusion of both human and animal data, provides the basis for the clinical decision as to which path of exposure is best for the patient and her family.

PSYCHIATRIC DISORDERS DURING PREGNANCY AND THE POSTPARTUM PERIOD

Do women suffer from mental illness during pregnancy? Despite clinical "lore" or the attribution of many symptoms as normal sequelae of pregnancy, recent data indicate that pregnancy does not confer any protection against mental illness. The incidence and severity of depression during pregnancy have been shown to vary significantly.[2-7] Up to 70% of pregnant women reported depressive symptoms, with 10% to 16% of women fulfilling diagnostic criteria for a major depressive episode during pregnancy.[8-11] These rates of major depression in pregnancy are similar to those in nongravid women.[12] Data on the course of bipolar disorder remain obscure; however, a lithium discontinuation study indicated that a very high proportion of women experienced relapse during pregnancy.[13] Psychiatric disorders with a psychotic component—schizophrenia, schizoaffective

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Disclosures: This work is supported by the National Institute of Mental Health Grant R01 MH-56420A02 (to Dr. Stowe).

disorder, etc—generally appear to worsen during pregnancy.[14] The data on anxiety disorders remain sparse and nonconclusive. One group reported that a significant percentage of women (>25%) with obsessive-compulsive disorder experienced illness onset during pregnancy. In contrast, the severity and frequency of panic attacks purportedly decrease during pregnancy; however, another study did not confirm such improvement.[15]

The precise incidence of psychiatric illness during pregnancy remains obscure for a variety of reasons: (1) the overlap of symptoms between normal sequelae of pregnancy and those of major depression (eg, fatigue, alterations in appetite and weight); (2) the reliance on retrospective reports in the majority of nondepression studies; and (3) limited inclusion/assessment of medical disorders that could contribute to psychiatric symptoms (eg, anemia, gestational diabetes, and thyroid dysfunction such as autoimmune thyroiditis).[16]

In contrast to pregnancy, the impact of childbirth on mental illness has been documented for centuries. Hippocrates and other ancient scholars suggested that puerperal mood disorders were the result of diverse physiologic and psychologic change following childbirth. In a widely cited landmark investigation by Kendler and colleagues,[17] a pronounced increase in both general and psychotic psychiatric hospitalizations for postpartum women was clearly demonstrated. Another group found that up to 12.5% of all psychiatric hospital admissions of women occur during the first postpartum year.[18] Despite the long-standing recognition and subsequent inclusion as a modifier in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition,[19] the etiology of puerperal mental illness remains obscure.

Currently, most investigators group postpartum psychiatric disturbances into three categories: maternity blues, postpartum depression, and postpartum psychosis. Maternity blues is a relatively mild emotional disturbance affecting 50% to 85% of postpartum women.[20-24] This transient condition is characterized by mood lability, depression, increased sensitivity to criticism, and despondency, which develop and resolve in the first 2 weeks postpartum. Because of its transient nature, this condition requires little intervention. However, approximately 20% of women with maternity blues will go on to develop major depression in the first postpartum year.[25,26] Postpartum depression, a major depressive episode during the puerperium, affects between 10% and 22% of adult women, and up to 26% of adolescent mothers, before the infant's first birthday.[27,28] For many of these women, it will be their first episode of major depression with symptom onset typically occurring within the first 6–12 weeks postpartum.[29] Although depression and anxiety are historically viewed as postpartum events, there is mounting evidence that their occurrence during pregnancy actually may herald the onset of postpartum illness.[30] The most severe category of postpartum mental illness is postpartum psychosis (PPS). PPS is a relatively rare condition, occurring in 1 or 2 of every 1,000 live births, with onset typically in the first 6 weeks postpartum.[31] This is a severe psychiatric disorder, typically with acute onset of overt psychotic symptoms, and represents a true psychiatric emergency. A majority of these psychoses appear to be primary mood disorders with psychotic features.[31]

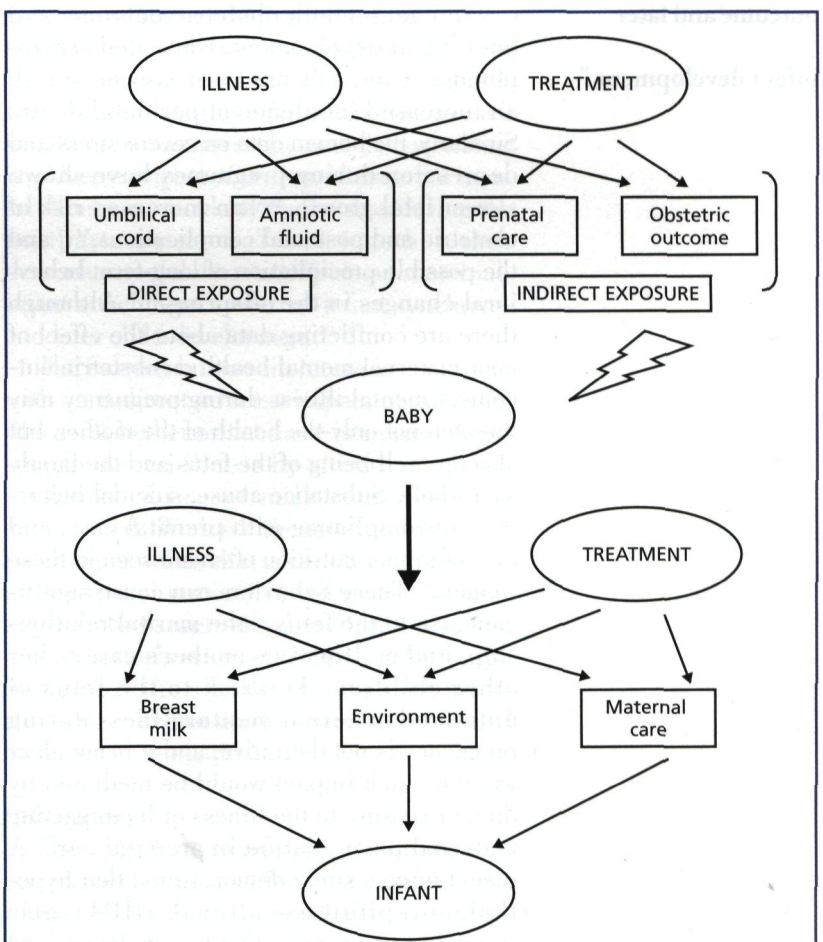

FIGURE. Pathway of potential exposure.

Stowe ZN, Calhoun K, Ramsey C, et al. *CNS Spectrums.* Vol 6, No 2. 2001.

In summary, the voluminous neuroendocrine and psychosocial events of pregnancy and childbirth do not protect women from the onset of psychiatric illness, nor does there appear to be definitive evidence that the course of preexisting illness improves. In the exposure model proposed, these data underscore the likelihood that a significant number of women will have illness during pregnancy and postpartum.

"Several human investigations have demonstrated that untreated maternal mental illness during pregnancy may have a deleterious impact on both obstetric outcome and later infant development."

IMPACT OF STRESS AND UNTREATED MENTAL ILLNESS DURING PREGNANCY

Clinical

Fetal and child development clearly does not occur in a neuroendocrine, psychologic, or sociologic vacuum. Considering the results of early-life stress research, it is not clear whether any degree of protection is afforded the fetus or neonate from alterations in these spheres. Several human investigations have demonstrated that untreated maternal mental illness during pregnancy may have a deleterious impact on both obstetric outcome and later infant development. Untreated schizophrenia historically has been associated with an increased incidence of perinatal death. Similarly, the human data on severe stress and depression during pregnancy have shown slower fetal growth,[32,33] an increased risk of obstetric and postnatal complications,[34-37] and the possible precipitation of long-term behavioral changes in the offspring.[38,39] Although there are conflicting data about the effect of poor maternal mental health on obstetric outcome,[40] mental illness during pregnancy may threaten not only the health of the mother, but also the well being of the fetus and the family as a whole. Substance abuse, suicidal behavior, noncompliance with prenatal care, and lack of proper nutrition often are seen in these women.[41] These behaviors can cause significant risk to the fetus,[37] the marital relationship, and multiparous mother's care of her other children. The risk to the fetus of untreated maternal mental illness during pregnancy is not definitive, and it is not clear whether such impact would be mediated by direct exposure to the illness or by impacting maternal participation in prenatal care. A recent human study demonstrated that hypothalamic-pituitary-adrenal (HPA) axis response to a noxious stimulus, as determined by infant salivary cortisol, may be determined by the level of stress via delivery method.[42] These data support the animal data that fetal and neonatal stress can establish the response of the HPA axis.[43] These human data also support our contention that the *in utero* environment can be modulated by both direct and indirect pathways during pregnancy.

Laboratory

A long line of animal research has shown the effects of prenatal stress on the developing offspring. Consistent with the limited human database, animal studies suggest that stress during pregnancy can adversely impact offspring growth,[44,45] learning ability,[46-48] and the attainment of other developmental milestones.[49]

Further evidence of a direct exposure to the illness via neurobiologic alterations in the offspring is apparent in the laboratory investigations of stress during pregnancy. Briefly, the offspring of pregnant rats exposed to an uncontrollable stressor demonstrate alterations in the HPA axis. These alterations include: (1) increased basal concentrations of plasma corticosterone and adrenocorticotrophic hormone (ACTH)[50-52]; (2) repeated brief exposures to prenatal stress, which increase the expression of corticotropin-releasing factor (CRF) mRNA in the paraventricular nucleus of the fetal hypothalamus, while sustained stress exposure induces neuronal apoptosis[53]; (3) persistence into adulthood of exaggerated corticosterone responses to subsequent mild stressors[49,54-56]; and (4) a phase advance in the circadian rhythm of corticosterone secretion.[57]

The mechanism by which maternal stress during pregnancy activates the HPA axis in the offspring is not clear. Placental passage of maternal corticosterone during prenatal stress exposure may be the means by which stress exposure during pregnancy impacts the offspring. For example, eradicating maternal corticosterone via bilateral adrenalectomy prior to stress exposure obviates the impact of prenatal stress on offspring hippocampal glucocorticoid receptors.[58] However, evidence of an indirect exposure also exists. A study reporting that neonatal adoption reverses the impact of prenatal stress on hippocampal glucocorticoid receptors suggests that the effect may be mediated through changes in postnatal maternal care.[59] Consistent with the latter hypothesis, there is evidence from experimental studies in rats that stress during pregnancy adversely impacts postnatal efforts at maternal care.[60,61]

There has been little study of the impact of prenatal stress on primate HPA axis activity. In one study, prenatally stressed juvenile rhesus monkeys exhibited increases in basal and stress-responsive ACTH and cortisol.[62] Another study, in which the administration of ACTH to pregnant rhesus monkeys produced developmental changes similar to those of other stress paradigms during pregnancy, lends additional credence to the theory that HPA axis hyperactivation underlies the long-term sequelae of prenatal stress.[63]

The impact of prenatal maternal stress is not limited to the HPA axis. Prenatally stressed rats and primates exhibit alteration in the plasma concentrations of norepinephrine (NE), dopamine (DA), and their metabolites,[56,64-66] consistent with increases in turnover of these catecholamines. Furthermore, prenatal stress is associated with alterations in the distribution and density of both NE receptors[67] and DA receptors.[68] Like the catecholamines, prenatal stress potentiates long-term alterations in serotonergic activity. Plasma and central nervous system (CNS) concentrations of serotonin (5-hydroxytryptophan [5-HT]) and its metabolites are decreased in prenatally stressed animals.[56,69,70] 5-HT receptor profiles in the hippocampus[69,71] and behavioral responses to 5-HT challenge[71,72] are altered in adult rats subjected to prenatal stress. These changes in serotonergic function may in part be programmed by increased glucocorticoid exposure during pregnancy.[73]

Like the HPA axis and neurotransmitter systems, the immune system in offspring may be adversely impacted by prenatal stress. Decreases in natural killer cell activity[74] and the proliferative response to mitogen exposure[74,75] in adult rats exposed to prenatal stress demonstrate that cellular immunity may be impaired well into adulthood.[76]

Animal research also indicates that prenatal stress can induce persistent behavioral aberrations. In particular, adult rats that were exposed to prenatal stress continue to exhibit anxiety-like behaviors manifested by defensiveness and decreased exploration in novel situations,[77-81] depression-like behaviors,[82] and exaggerated "emotional" responses to stress.[83-85] Primate studies also have demonstrated decreased exploratory behavior in prenatally stressed offspring.[86,87]

Although a direct correlation between stress models in laboratory animals and mental illness in humans is difficult to establish, these animal data emphasize the potential effects of NE alterations associated with stress and mental illness. Most data suggest that the long-term neurobiologic sequelae of prenatal maternal stress are mediated via alterations in the developing HPA axis. Although it remains unclear whether the transplacental passage of maternal glucocorticoids or the impact of inadequate postnatal care is responsible for the changes in offspring HPA-axis function, the ultimate clinical import of these data is the same.

"Most data suggest that the long-term neurobiologic sequelae of prenatal maternal stress are mediated via alterations in the developing HPA axis."

IMPACT OF UNTREATED MENTAL ILLNESS DURING THE POSTPARTUM PERIOD

Clinical

The historic emphasis in psychiatry has not been exclusively on child development, but rather on the formative processes that unfold in the context of parent-child interaction. The impact of parent-child interaction (particularly the mother-child dyad) has been the key to our attempts to understand the developing human psyche. Consistent with the dynamic importance of these findings has been a wealth of human investigations demonstrating an adverse impact of untreated maternal mental illness, particularly depression during the postpartum period. Taken together, they demonstrate deleterious effects on maternal-infant attachment, maternal-infant synchrony, and later child development.[88-93]

The current human literature is consistent with an indirect adverse impact of maternal illness. Whether or not there is a direct exposure to mental illness by alteration of constituents of breast milk remains to be determined. We have demonstrated in preliminary studies that alterations in breast milk cortisol concentrations were present when mothers were depressed, but resolved when mothers were euthymic.[94] Although intriguing, the significance of such alterations is unknown and, to date, unconfirmed by larger investigations.

Laboratory

The large human postpartum database is complemented by a variety of animal investigations. A potential confound of the rodent literature is that the CNS of the newborn rat pup is developmentally homologous to a 24-week human fetus.[95] Therefore, much of these data may be applicable to stress during pregnancy.

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A model applicable to our understanding of the consequences of interruption of the maternal-infant interaction is neonatal handling of rat pups as the initial stressor. In this paradigm, infant rats or mice are removed from their cages (usually on a daily basis for a prescribed interval prior to weaning) and handled briefly by laboratory personnel, then returned to the dam. Neonatal handling of rodents decreases anxiety-like behaviors and biological responsivity to stress (eg, secretion of CRF). Handled pups are resistant to stress or aging decrements in learning ability[96,97] and exhibit increased exploratory behavior in novel environments.[83,98] In fact, anxiety-like behaviors induced by prenatal stress can be obviated by infant handling.[83]

Neonatal handling studies obviously provide an excellent example of how subtle environmental variations can impact the development of biologic systems. First, these studies emphasize the role of physical contact. Several investigators have noted that neonatal handling of rodent pups stimulates maternal care. Handled pups are more frequently groomed and licked by their mothers.[99-103] Thus, it may follow that the neurobiological and behavioral changes induced by neonatal handling of rodents are mediated indirectly through the changes induced in maternal care.

In contrast, maternal deprivation protocols potentially represent models with greater similarity to untreated maternal mental illness. In these models, rat pups are separated from their mother for a prescribed interval (or repeated intervals) prior to weaning. In addition to being deprived of maternal care during the separation period, the pups typically experience persistently deranged maternal behavior after the reunion.[104] Behaviorally, maternal separation in the rat potentiates changes homologous to both depression and anxiety.[100] Maternal separation induces acute changes in HPA-axis activity, as indicated by increases in serum corticosterone[105,106] and ACTH concentrations.[107] The impact of separation on CRF secretion appears to be dependent on the age of the pup during the separation.[105]

The maternal separation paradigm has been extended to explore two rat strains: one bred for susceptibility to the inescapable shock ("learned helplessness") paradigm, and the other bred for resistance to inescapable shock.[108] When exposed to maternal deprivation followed by a subsequent stressor, their HPA-axis stress responses were markedly dissimilar. The stress-susceptible group exhibited an increased ACTH (but normal cortisol) response to stress on postnatal day 21, a pattern similar to the HPA-axis changes associated with posttraumatic stress disorder (PTSD).[109-111] The stress-resistant line did not demonstrate the exaggerated ACTH response to stress. This study provides an excellent example of the potential relative genetic and epigenetic contributions to the susceptibility for illness.

Initial confirmation that the impact of maternal separation is mediated by aberrant or absent maternal care, rather than simply by deprivation of food, has been demonstrated.[112] Neither food supplementation nor contact with a sedated/nonlactating mother reversed the impact of the separation. In contrast, providing surrogate maternal care (eg, stroking the anogenital region with a warm brush) reversed the effects of maternal separation upon CRF_2 receptor mRNA expression in the hypothalamus. These findings suggest that alterations in maternal care underlie the biologic changes induced by maternal separation in the rat neonate.

Maternal separation paradigms also have been used in studies of nonhuman primates. Scrutiny of the primate social deprivation model has been quite intensive, and the magnitude of social deprivation in these models extends well beyond the loss of mother-infant interaction. These animals are deprived of an entire range of social interaction when removed not only from their mothers, but also from the social group as a whole. Therefore, findings from such research may not be directly homologous to the study of interrupted maternal parenting.[113] Investigations that are limited to maternal separation have found similar effects. Other studies have modified the manner of separation from the infant's mother. A 24-hour separation study placed infants into one of three conditions: (1) total isolation; (2) remaining with the mother; or (3) physical separation from the mother while the mother is still in the infant's visual field.[114] In this study, the totally isolated infants were least likely to vocalize, but had the highest plasma cortisol concentrations; there were no detectable differences in the behavioral measures or cortisol concentrations of the other two groups. A similar study, in which infants were either totally isolated, left with their mother, or placed in

an adjacent cage with the mother in full view, demonstrated elevations in plasma cortisol and cerebrospinal fluid (CSF) catecholamine metabolites (eg, 3-methoxy-4-hydroxyphenylglycol, homovanillic acid), which were greatest in the total isolates and at an intermediate level in those separated but able to see their mother.[115] Interestingly, the infants in view of their mother exhibited the most frequent vocalizations, whereas those remaining with their mother had the least.

Although maternal and social separation paradigms interfere with the quality of parenting and reliably induce neurobiological and behavioral alterations in both rodent and primate species, they depend on an experimental intervention (ie, separation) that is disparate from normal human experience. The homology of the research protocol can be improved by modulating a naturalistic stressor that does not directly stress the infant but instead challenges the ability of the parent to meet the demands of providing adequate care.

The goal in these studies is to increase the work of parenting while permitting adequate nutrition for both mother and offspring. A suitable model has been implemented in primate research, utilizing three foraging conditions: (1) low foraging demand (LFD); (2) high foraging demand (HFD); and (3) variable foraging demand (VFD). In the LFD condition, food is readily available and requires no maternal effort for procurement. By contrast, HFD mothers are required to perform a task, such as digging through wood chip bedding, to obtain food. In the VFD condition, the requirements for food procurement are unpredictable. In this paradigm, the HFD condition serves not only as a comparator state but also as a nutritional control.

Infants raised by mothers in the VFD condition exhibit behavioral alterations suggestive of insecure attachment that are homologous to anxiety in humans.[116-119] As adults, primates raised under VFD conditions exhibit elevated CSF and CRF, lower cortisol, and increased somatostatin in comparison to both the HFD and LFD groups.[120,121]

This finding is strikingly similar to the HPA-axis activity reported for patients with PTSD.[109-111] Additional studies using the VFD paradigm are needed to investigate HPA-feedback mechanisms, hippocampal structure profiles, and immune system function.

Summary

Although a direct model of human maternal behavior during both pregnancy and postpartum cannot be provided in the laboratory, it is clear that both prenatal and postnatal maternal stress modulates a variety of NE and neurotransmitter systems in the offspring. The similarities between laboratory data and human data emphasize the historical axiom that "healthy mothers make healthy babies." These data, both human and laboratory, must be weighed against the burgeoning database on psychotropic medications during pregnancy and lactation.

THE USE OF PSYCHOTROPIC MEDICATIONS DURING PREGNANCY AND LACTATION

The current literature on the use of psychotropic medications during pregnancy and lactation reveals a cadre of methodological problems. The most prominent potential confound is the definition of an appropriate control group for comparison. It is unlikely that the "ideal study" will ever be conducted because pregnant or lactating women without illness do not take psychotropic medications. As such, all outcome studies are subject to the confound of illness effects that may be misinterpreted as medication effects. The decision of whether or not to use psychotropic medications during pregnancy and/or lactation carries complicated clinical, ethical, and potentially legal ramifications, regardless of the decision. To date, the Food and Drug Administration has not approved any psychotropic medication for use during pregnancy or lactation. A recent study of sleep deprivation[122] and the long-standing case data on the use of electroconvulsive therapy[123] may be viable alternatives to psychotropic medications. The extent of exposure for these options has not been well studied.

The literature on the use of antidepressants and mood stabilizers during pregnancy has been steadily expanding. In a comprehensive meta-analysis, Altshuler and colleagues[124] concluded that the risk of psychotropic medications during pregnancy falls into three categories: (1) somatic teratogenicity and organ malformation; (2) neonatal toxicity, including neonatal withdrawal symptomatology; and (3) long-term neurobehavioral and developmental teratogenesis. The use of psychotropic medications during pregnancy has been reviewed by several groups.[123-133] Similarly, the impact of

"The current literature on the use of psychotropic medications during pregnancy and lactation reveals a cadre of methodological problems."

maternal medications during lactation could be categorized as: (1) acute adverse effects on infants; (2) metabolic or interactive effects with medications or care takers, respectively; and (3) long-term neurodevelopmental effects. The excretion of psychotropic medications in breast milk has been reviewed.[134-136]

"Antidepressants have been in use for almost four decades, and there are no confirmed birth defects related to antidepressant use during pregnancy."

Pregnancy-Management Issues

Antidepressants have been in use for almost four decades, and there are no confirmed birth defects related to antidepressant use during pregnancy. The burgeoning data on obstetric outcome following the use of selective serotonin reuptake inhibitors (SSRIs) during pregnancy have been derived from large pharmaceutical company case series,[137,138] birth registries,[139] retrospective surveys,[140] and teratology or poison control centers,[141-143] all of which have failed to confirm an adverse effect. This data set is complemented by the landmark study of Nulman and colleagues[140] in 1998, which did not demonstrate adverse neurodevelopmental effects of fluoxetine (n=55) or tricyclic antidepressants (TCAs) (n=80). Neurodevelopmental studies on other antidepressants remain limited to clinical impression.

The initial phase of pregnancy management begins prior to conception. The majority of pregnancies occur before institution of prenatal care (eg, inadvertent conception); therefore, the clinician would be advised to consider nongravid women of reproductive potential as future pregnant patients when choosing a treatment option. Once women learn they are pregnant (typically at >5 weeks' gestation), exposure to the medication has already occurred. Considering the exposure model proposed, changing to a second medication would increase the number of fetal exposures, for which there are no reproductive safety data. Similarly, clinical prudence about stopping medication is warranted. Should the patient relapse, the fetus would be exposed to both the medication and the illness. The management of daily medication represents an intriguing clinical question. Previous studies with TCAs have demonstrated decreased maternal serum concentrations in later pregnancy.[124,144] A recent study found increased depressive symptoms in later pregnancy in women treated with SSRIs, which responded to a higher maternal dose.[145] Hence, ongoing symptom assessment and serum monitoring (when indicated) are warranted because such relapse would provide exposure to both medication and illness.

It is assumed that all antidepressants cross the placenta, although formal study is sparse. Preliminary data indicate that the SSRIs cross the placenta and that significant differences in the placental passage of antidepressants exist.[146] Additional studies also have shown detectable concentrations of SSRIs in amniotic fluid.[145] These data confirm that the fetus is always exposed to the medication, but it is not clear whether such exposure accounts for the purported withdrawal symptoms reported with TCAs, such as fetal tachycardia, tachypnea, cyanosis, irritability, hypertonia, clonus, and spasm.[147-150] There are only three case reports of potential neonatal toxicity or withdrawal associated with fluoxetine,[151] paroxetine,[152] and sertraline.[153] No long-term adverse effects were noted in these infants, and no clear treatment intervention (if indicated) has been proposed.

The management of bipolar disorder during pregnancy has received considerable attention, but far less investigation.[135] Unlike efficacious antidepressants, the number of clinically efficacious medications for bipolar disorder is limited. Notably, all mood stabilizers are teratogenic, regardless of the stage of pregnancy in which they are used. Lithium carbonate remains one of the cornerstones of treatment for both phases of bipolar disorder. The association with cardiac malformations and first-trimester lithium exposure is well documented.[154,155] Cohen and colleagues[156] completed an extensive survey of the available information and found an increase in the relative risk ratio of cardiac malformations of 1.2 to 7.7 and an overall increase in the relative risk for congenital malformations of 1.5 to 3.0 for in utero lithium exposure. The neonate may be at risk for lithium toxicity at serum concentrations lower than maternal concentrations, and the clinician should avoid nonsteroidal anti-inflammatory drugs in both the mother and infant during the early postpartum period. Symptoms of toxicity include flaccidity, lethargy, and poor sucking reflexes that may persist for more than 7 days.[157]

Several anticonvulsants have been effective in the treatment of bipolar disorder, all of which are known teratogens.[158,159] The risk of spina bifida associated with fetal exposure to carbamazepine is 1% (relative risk is about 13.7%).[160] Similarly, valproic acid is a known

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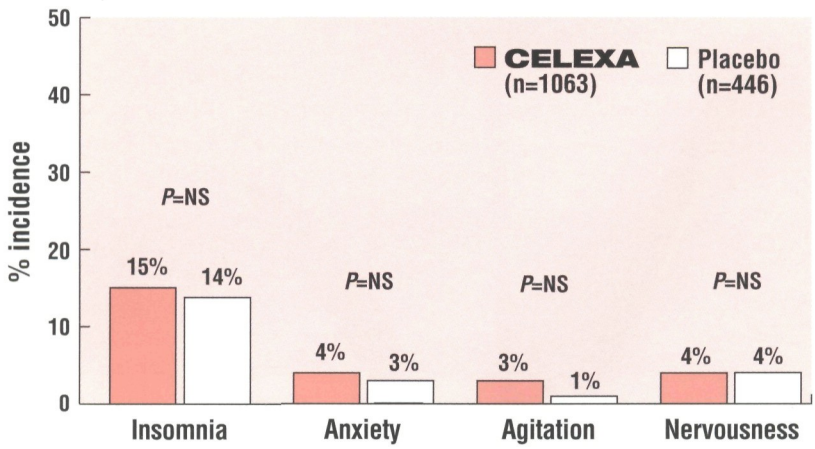

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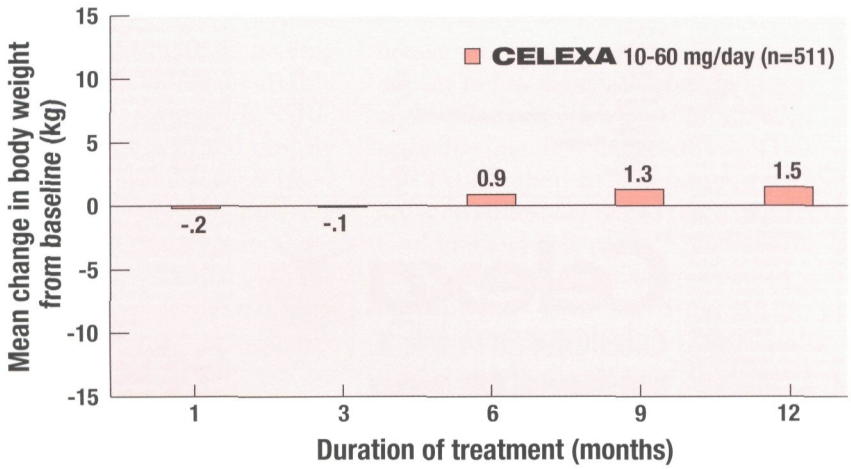

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References: **1.** Data on file, Forest Laboratories, Inc. **2.** Flicker C, Tsay J-Y. Citalopram treatment of depression with anxiety. Poster presented at the 38th Annual Meeting, New Clinical Drug Evaluation Unit, 1998; Boca Raton, Florida.

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Celexa is contraindicated in patients with a hypersensitivity to citalopram or any of the inactive ingredients in Celexa. **WARNINGS Potential for Interaction with Monoamine Oxidase Inhibitors In patients receiving serotonin reuptake inhibitor drugs in combination with a monoamine oxidase inhibitor (MAOI), there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued SSRI treatment and have been started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Furthermore, limited animal data on the effects of combined use of SSRI's and MAOI's suggest that these drugs may act synergistically to elevate blood pressure and evoke behavioral excitation. Therefore, it is recommended that Celexa should not be used in combination with an MAOI, or within 14 days of discontinuing treatment with an MAOI. Similarly, at least 14 days should be allowed after stopping Celexa before starting an MAOI. PRECAUTIONS General** Hyponatremia Several cases of hyponatremia and SIADH (syndrome of inappropriate antidiuretic hormone secretion) have been reported in association with Celexa treatment. All patients with these events have recovered with discontinuation of Celexa and/or medical intervention. Activation of Mania/Hypomania In placebo-controlled trials of Celexa,some of which included patients with bipolar disorder, activation of mania/hypomania was reported in 0.2% of 1063 patients treated with Celexa and in none of the 446 patients treated with placebo. Activation of mania/hypomania has also been reported in a small proportion of patients with major affective disorders treated with other marketed antidepressants. As with all antidepressants, Celexa should be used cautiously in patients with a history of mania. Seizures Although anticonvulsant effects of citalopram have been observed in animal studies, Celexa has not been systematically evaluated in patients with a seizure disorder. These patients were excluded from clinical studies during the product's premarketing testing. In clinical trials of Celexa, seizures occurred in 0.3% of patients treated with Celexa (a rate of one patient per 98 years of exposure) and 0.5% of patients treated with placebo (a rate of one patient per 50 years of exposure). Like other antidepressants, Celexa should be introduced with care in patients with a history of seizure disorder. Suicide The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Close supervision of high-risk patients should accompany initial drug therapy. Prescriptions for Celexa should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. Interference With Cognitive and Motor Performance In studies in normal volunteers, Celexa in doses of 40 mg/day did not produce impairment of intellectual function or psychomotor performance. Because any psychoactive drug may impair judgement, thinking, or motor skills, however, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that Celexa therapy does not affect their ability to engage in such activities. Use in Patients With Concomitant Illness Clinical experience with Celexa in patients with certain concomitant systemic illnesses is limited. Caution is advisable in using Celexa in patients with diseases or conditions that produce altered metabolism or hemodynamic responses. Celexa has not been systematically evaluated in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were generally excluded from clinical studies during the product's premarketing testing. However, the electrocardiograms of 1116 patients who received Celexa in clinical trials were evaluated, and the data indicate that Celexa is not associated with the development of clinically significant ECG abnormalities. In subjects with hepatic impairment, citalopram clearance was decreased and plasma concentrations were increased. The use of Celexa in hepatically impaired patients should be approached with caution and a lower maximum dosage is recommended. Because citalopram is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. Until adequate numbers of patients with severe renal impairment have been evaluated during chronic treatment with Celexa, however, it should be used with caution in such patients. **Drug Interactions** CNS Drugs – Given the primary CNS effects of citalopram, caution should be used when it is taken in combination with other centrally acting drugs. Alcohol – Although citalopram did not potentiate the cognitive and motor effects of alcohol in a clinical trial, as with other psychotropic medications, the use of alcohol by depressed patients taking Celexa is not recommended. Monoamine Oxidase Inhibitors (MAOI's) – See CONTRAINDICATIONS and WARNINGS. Cimetidine – In subjects who had received 21 days of 40 mg/day Celexa, combined administration of 400 mg/day cimetidine for 8 days resulted in an increase in citalopram AUC and C_{max} of 43% and 39%, respectively. The clinical significance of these findings is unknown. Digoxin – In subjects who had received 21 days of 40 mg/day Celexa, combined administration of Celexa and digoxin (single dose of 1 mg) did not significantly affect the pharmacokinetics of either citalopram or digoxin. Lithium – Coadministration of Celexa (40 mg/day for 10 days) and lithium (30 mmol/day for 5 days) had no significant effect on the pharmacokinetics of citalopram or lithium. Nevertheless, plasma lithium levels should be monitored with appropriate adjustment to the lithium dose in accordance with standard clinical practice. Because lithium may enhance the serotonergic effects of citalopram, caution should be exercised when Celexa and lithium are coadministered. Sumatriptan - There have been rare postmarketing reports describing patients with weakness, hyperreflexia, and incoordination following the use of a selective serotonin reuptake inhibitor (SSRI) and sumatriptan. If concomitant treatment with sumatriptan and an SSRI (eg, fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram) is clinically warranted, appropriate observation of the patient is advised. Warfarin – Administration of 40 mg/day Celexa for 21 days did not affect the pharmacokinetics of warfarin, a CYP3A4 substrate. Prothrombin time was increased by 5%, the clinical significance of which is unknown. Carbamazepine – Combined administration of Celexa (40 mg/day for 14 days) and carbamazepine (titrated to 400 mg/day for 35 days) did not significantly affect the pharmacokinetics of carbamazepine, a CYP3A4 substrate. Although trough citalopram plasma levels were unaffected, given the enzyme-inducing properties of carbamazepine, the possibility that carbamazepine might increase the clearance of citalopram should be considered if the two drugs are coadministered. CYP3A4 and CYP2C19 Inhibitors – *In vitro* studies indicated that CYP3A4 and CYP2C19 are the primary enzymes involved in the metabolism of citalopram. As data are not available from clinical pharmacokinetic studies, the possibility that the clearance of citalopram will be decreased when citalopram is administered with a potent inhibitor of CYP3A4 (eg, ketoconazole, itraconazole, fluconazole, or erythromycin) or a potent inhibitor of CYP2C19 (eg, omeprazole) should be considered. Metoprolol – Administration of 40 mg/day Celexa for 22 days resulted in a two-fold increase in the plasma levels of the beta-adrenergic blocker metoprolol. Increased metoprolol plasma levels have been associated with decreased cardioselectivity. Coadministration of Celexa and metoprolol had no clinically significant effects on blood pressure or heart rate. Imipramine and Other Tricyclic Antidepressants (TCA's) - *In vitro* studies suggest that citalopram is a relatively weak inhibitor of CYP2D6. Coadministration of Celexa (40 mg/day for 10 days) with the tricyclic antidepressant imipramine (single dose of 100 mg), a substrate for CYP2D6, did not significantly affect the plasma concentrations of imipramine or citalopram. However, the concentration of the imipramine metabolite desipramine was increased by approximately 50%. The clinical significance of the desipramine change is unknown. Nevertheless, caution is indicated in the coadministration of TCA's with Celexa. Electroconvulsive Therapy (ECT) – There are no clinical studies of the combined use of electroconvulsive therapy (ECT) and Celexa. **Pregnancy** Pregnancy Category C - There are no adequate and well-controlled studies in pregnant women; therefore, citalopram should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Labor and Delivery** The effect of Celexa on labor and delivery in humans is unknown. **Nursing Mothers** As has been found to occur with many other drugs, citalopram is excreted in human breast milk. The decision whether to continue or discontinue either nursing or Celexa therapy should take into account the risks of citalopram exposure for the infant and the benefits of Celexa treatment for the mother. **Pediatric Use** Safety and effectiveness in pediatric patients have not been established. **Geriatric Use** Of 4422 patients in clinical studies of Celexa, 1357 were 60 and over, 1034 were 65 and over, and 457 were 75 and over. No overall differences in safety or effectiveness were observed between these subjects

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and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Most elderly patients treated with Celexa in clinical trials received daily doses between 20 and 40 mg. In two pharmacokinetic studies, citalopram AUC was increased by 23% and 30%, respectively, in elderly subjects as compared to younger subjects, and its half-life was increased by 30% and 50%, respectively. 20 mg/day is the recommended dose for most elderly patients. **ADVERSE REACTIONS** The premarketing development program for Celexa included citalopram exposures in patients and/or normal subjects from 3 different groups of studies: 429 normal subjects in clinical pharmacology/pharmacokinetic studies; 4422 exposures from patients in controlled and uncontrolled clinical trials, corresponding to approximately 1370 patient exposure years. There were, in addition, over 19,000 exposures from mostly open-label, European postmarketing studies. The conditions and duration of treatment with Celexa varied greatly and included (in overlapping categories) open-label and double-blind studies, inpatient and outpatient studies, fixed-dose and dose-titration studies, and short-term and long-term exposure. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, ECGs, and results of ophthalmologic examinations. Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and tabulations that follow, standard World Health Organization (WHO) terminology has been used to classify reported adverse events. The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. **Adverse Findings Observed in Short-term, Placebo-Controlled Trials** Adverse Events Associated With Discontinuation of Treatment Among 1063 depressed patients who received Celexa at doses ranging from 10 to 80 mg/day in placebo-controlled trials of up to 6 weeks in duration, 16% discontinued treatment due to an adverse event, as compared to 8% of 446 patients receiving placebo. The adverse events associated with discontinuation and considered drug-related (ie, associated with discontinuation in at least 1% of Celexa-treated patients and at a rate at least twice that of placebo) are shown in **TABLE 1**. It should be noted that one patient can report more than one reason for discontinuation and be counted more than once in this table.

TABLE 1.
Adverse Events Associated With Discontinuation of Treatment in Short-term, Placebo-Controlled Depression Trials

	Percentage of Patients Discontinuing Due to Adverse Event	
Body System/Adverse Event	**Celexa (N=1063)**	**Placebo (N=446)**
General		
Asthenia	1%	<1%
Gastrointestinal Disorders		
Nausea	4%	0%
Dry Mouth	1%	<1%
Vomiting	1%	0%
Central and Peripheral Nervous System Disorders		
Dizziness	2%	<1%
Psychiatric Disorders		
Insomnia	3%	1%
Somnolence	2%	1%
Agitation	1%	<1%

Well-tolerated SSRI therapy

Adverse Events Occurring at an Incidence of 2% or More Among Celexa-Treated Patients **TABLE 2** enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred among 1063 depressed patients who received Celexa at doses ranging from 10 to 80 mg/day in placebo-controlled trials of up to 6 weeks in duration. Events included are those occurring in 2% or more of patients treated with Celexa and for which the incidence in patients treated with Celexa was greater than the incidence in placebo-treated patients. The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the adverse event incidence rate in the population studied. The only commonly observed adverse event that occurred in Celexa patients with an incidence of 5% or greater and at least twice the incidence in placebo patients was ejaculation disorder (primarily ejaculatory delay) in male patients (see **TABLE 2**).

TABLE 2.
Treatment-Emergent Adverse Events:
Incidence in Placebo-Controlled Clinical Trials*

	Percentage of Patients Reporting Event	
Body System/Adverse Event	**Celexa (N=1063)**	**Placebo (N=446)**
Autonomic Nervous System Disorders		
Dry Mouth	20%	14%
Sweating Increased	11%	9%
Central & Peripheral Nervous System Disorders		
Tremor	8%	6%
Gastrointestinal Disorders		
Nausea	21%	14%
Diarrhea	8%	5%
Dyspepsia	5%	4%
Vomiting	4%	3%
Abdominal Pain	3%	2%
General		
Fatigue	5%	3%
Fever	2%	<1%
Musculoskeletal System Disorders		
Arthralgia	2%	1%
Myalgia	2%	1%
Psychiatric Disorders		
Somnolence	18%	10%
Insomnia	15%	14%
Anxiety	4%	3%
Anorexia	4%	2%
Agitation	3%	1%
Dysmenorrhea[1]	3%	2%
Libido Decreased	2%	<1%
Yawning	2%	<1%
Respiratory System Disorders		
Upper Respiratory Tract Infection	5%	4%
Rhinitis	5%	3%
Sinusitis	3%	<1%
Urogenital		
Ejaculation Disorder[2,3]	6%	1%
Impotence[3]	3%	<1%

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*Events reported by at least 2% of patients treated with Celexa are reported, except for the following events which had an incidence in placebo ≥ Celexa: headache, asthenia, dizziness, constipation, palpitation, vision abnormal, sleep disorder, nervousness, paryngitis, micturition disorder, back pain. [1]Denominator used was for females only (N=638 Celexa; N=252 placebo). [2]Primarily ejaculatory delay. [3]Denominator used was for males only (N=425 Celexa; N=194 placebo). Dose Dependency of Adverse Events The potential relationship between the dose of Celexa administered and the incidence of adverse events was examined in a fixed-dose study in depressed patients receiving placebo or Celexa 10, 20, 40, and 60 mg. Jonckheere's trend test revealed a positive dose response ($p<.05$) for the following adverse events: fatigue, impotence, insomnia, sweating increased, somnolence, and yawning. Male and Female Sexual Dysfunction With SSRI's Although changes in sexual desire, sexual performance and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that selective serotonin reuptake inhibitors (SSRIs) can cause such untoward sexual experiences. Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling, are likely to underestimate their actual incidence. The table below displays the incidence of sexual side effects reported by at least 2% of patients taking Celexa in a pool of placebo-controlled clinical trials in patients with depression.

Treatment	**Celexa (425 males)**	**Placebo (194 males)**
Abnormal Ejaculation (mostly ejaculatory delay)	6.1% (males only)	1% (males only)
Decreased Libido	3.8% (males only)	<1% (males only)
Impotence	2.8% (males only)	<1% (males only)

In female depressed patients receiving Celexa, the reported incidence of decreased libido and anorgasmia was 1.3% (n=638 females) and 1.1% (n=252 females), respectively. There are no adequately designed studies examining sexual dysfunction with citalopram treatment. Priapism has been reported with all SSRIs. While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRI's, physicians should routinely inquire about such possible side effects. Vital Sign Changes Celexa and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, and diastolic blood pressure) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses did not reveal any clinically important changes in vital signs associated with Celexa treatment. In addition, a comparison of supine and standing vital sign measures for Celexa and placebo treatments indicated that Celexa treatment is not associated with orthostatic changes. Weight Changes Patients treated with Celexa in controlled trials experienced a weight loss of about 0.5 kg compared to no change for placebo patients. Laboratory Changes Celexa and placebo groups were compared with respect to (1) mean change from baseline in various serum chemistry, hematology, and urinalysis variables and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in laboratory test parameters associated with Celexa treatment. ECG Changes Electrocardiograms from Celexa (N=802) and placebo (N=241) groups were compared with respect to (1) mean change from baseline in various ECG parameters and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. The only statistically significant drug-placebo difference observed was a decrease in heart rate for Celexa of 1.7 bpm compared to no change in heart rate for placebo. There were no observed differences in QT or other ECG intervals. **Other Events Observed During the Premarketing Evaluation of Celexa** Following is a list of WHO terms that reflect treatment-emergent adverse events, as defined in the introduction to the ADVERSE REACTIONS section, reported by patients treated with Celexa at multiple doses in a range of 10 to 80 mg/day during any phase of a trial within the premarketing database of 4422 patients. All reported events are included except those already listed in **TABLE 2** or elsewhere in labeling, those events for which a drug cause was remote, those event terms which were so general as to be uninformative, and those occurring in only one patient. It is important to emphasize that although the events reported occurred during treatment with Celexa, they were not necessarily caused by it. Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in less than 1/100 patients but at least 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. Cardiovascular – *Frequent:* tachycardia, postural hypotension, hypotension. *Infrequent:* hypertension, bradycardia, edema (extremities), angina pectoris, extrasystoles, cardiac failure, flushing, myocardial infarction, cerebrovascular accident, myocardial ischemia. *Rare:* transient ischemic attack, phlebitis, atrial fibrillation, cardiac arrest, bundle branch block. Central and Peripheral Nervous System Disorders – *Frequent:* paresthesia, migraine. *Infrequent:* hyperkinesia, vertigo, hypertonia, extrapyramidal disorder, leg cramps, involuntary muscle contractions, hypokinesia, neuralgia, dystonia, abnormal gait, hypesthesia, ataxia. *Rare:* abnormal coordination, hyperesthesia, ptosis, stupor. Endocrine Disorders – *Rare:* hypothyroidism, goiter, gynecomastia. Gastrointestinal Disorders – *Frequent:* saliva increased, flatulence. *Infrequent:* gastritis, gastroenteritis, stomatitis, eructation, hemorrhoids, dysphagia, teeth grinding, gingivitis, esophagitis. *Rare:* colitis, gastric ulcer, cholecystitis, cholelithiasis, duodenal ulcer, gastroesophageal reflux, glossitis, jaundice, diverticulitis, rectal hemorrhage, hiccups. General – *Infrequent:* hot flushes, rigors, alcohol intolerance, syncope, influenza-like symptoms. *Rare:* hayfever. Hemic and Lymphatic Disorders – *Infrequent:* purpura, anemia, epistaxis, leukocytosis, leucopenia, lymphadenopathy. *Rare:* pulmonary embolism, granulocytopenia, lymphocytosis, lymphopenia, hypochromic anemia, coagulation disorder, gingival bleeding. Metabolic and Nutritional Disorders – *Frequent:* decreased weight, increased weight. *Infrequent:* increased hepatic enzymes, thirst, dry eyes, increased alkaline phosphatase, abnormal glucose tolerance. *Rare:* bilirubinemia, hypokalemia, obesity, hypoglycemia, hepatitis, dehydration. Musculoskeletal System Disorders – *Infrequent:* arthritis, muscle weakness, skeletal pain. *Rare:* bursitis, osteoporosis. Psychiatric Disorders – *Frequent:* impaired concentration, amnesia, apathy, depression, increased appetite, aggravated depression, suicide attempt, confusion. *Infrequent:* increased libido, aggressive reaction, paroniria, drug dependence, depersonalization, hallucination, euphoria, psychotic depression, delusion, paranoid reaction, emotional lability, panic reaction, psychosis. *Rare:* catatonic reaction, melancholia. Reproductive Disorders/Female* – *Frequent:* amenorrhea. *Infrequent:* galactorrhea, breast pain, breast enlargement, vaginal hemorrhage. *% based on female subjects only: 2955 Respiratory System Disorders – *Frequent:* coughing. *Infrequent:* bronchitis, dyspnea, pneumonia. *Rare:* asthma, laryngitis, bronchospasm, pneumonitis, sputum increased. Skin and Appendages Disorders – *Frequent:* rash, pruritus. *Infrequent:* photosensitivity reaction, urticaria, acne, skin discoloration, eczema, alopecia, dermatitis, skin dry, psoriasis. *Rare:* hypertrichosis, decreased sweating, melanosis, keratitis, cellulitis, pruritus ani. Special Senses – *Frequent:* accommodation abnormal, taste perversion. *Infrequent:* tinnitus, conjunctivitis, eye pain. *Rare:* mydriasis, photophobia, diplopia, abnormal lacrimation, cataract, taste loss. Urinary System Disorders – *Frequent:* polyuria. *Infrequent:* micturition frequency, urinary incontinence, urinary retention, dysuria. *Rare:* facial edema, hematuria, oliguria, pyelonephritis, renal calculus, renal pain. **OVERDOSAGE Human Experience** Although there were no reports of fatal citalopram overdose in clinical trials involving overdoses of up to 2000 mg, postmarketing reports of drug overdoses involving citalopram have included 12 fatalities, 10 in combination with other drugs and/or alcohol and 2 with citalopram alone (3920 mg and 2800 mg), as well as nonfatal overdoses of up to 6000 mg. Symptoms most often accompanying citalopram overdose, alone or in combination with other drugs and/or alcohol, included dizziness, sweating, nausea, vomiting, tremor, somnolence, and sinus tachycardia. In more rare cases, observed symptoms included amnesia, confusion, coma, convulsions, hyperventilation, cyanosis, rhabdomyolysis, and ECG changes (including QTc prolongation, nodal rhythm, ventricular arrhythmia, and one possible case of Torsades de pointes).

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human teratogen, with a 1% to 2% risk of neural tube defects, as well as intrauterine growth retardation. Most literature on the teratogenic risk of these compounds is derived from studies of the treatment of epilepsy during pregnancy, limiting direct extrapolation to women with bipolar disorder.

In summary, the management of bipolar disorder during pregnancy requires careful assessment of the disorder and its severity. If possible, mood-stabilizing medications should be avoided during the first trimester. The guidelines suggested by Cohen and colleagues[156] emphasize the potentially favorable risk-benefit ratio of lithium use during pregnancy.

Lactation-Management Issues

The number of women planning to breastfeed is on the rise; recent estimates indicate that more than 50% of new mothers leaving the hospital plan to nurse.[161] The available data on antidepressant use, particularly SSRIs during breastfeeding, have accrued rapidly since the comprehensive review by Wisner and colleagues.[136] The new data comprise a diverse conglomeration of case reports, case series, and more extensive pharmacokinetic investigations. Although there remains disparity about the most accurate method for determining infant exposure, infant serum monitoring has emerged as the preferred standard over the milk/plasma ratio. The current literature and recent oral presentations at national meetings include approximately 150 nursing infant serum measures of the SSRIs citalopram,[162] fluoxetine,[163-166] fluvoxamine,[167] paroxetine,[168] and sertraline.[169-173] This represents the largest database for any class of medications in breastfeeding. Despite the burgeoning data, purported adverse effects are limited to two cases.[174,175]

There is no definitive consensus on the extent and frequency of monitoring the nursing infant exposed to antidepressants. Arguably, if the clinician does not have access to a research-quality laboratory, routine infant serum monitoring will be difficult to interpret. If the clinician has a high index of suspicion for adverse effects on the nursing infant, nursing should be suspended regardless of infant serum concentration levels. With respect to monitoring for nonantidepressants, such as anticonvulsants, no clear guidelines have been established. The conservative approach would be to monitor (more often than is recommended for adults taking the medication) the nursing infant (eg, liver enzyme levels, lymphocyte count, platelet counts), for any potential adverse effects.

The issue of antidepressant use during breastfeeding in women who had been on the medication at any point in pregnancy is straightforward using the exposure model. According to the model, the developing brain was exposed during pregnancy, and to avoid increasing the number of exposures, the same medication should be used. A comparison of the placental passage (40% to 70%) to the maximum possible dose (1% to 3%) in the nursing infant supports this treatment plan. It is important to emphasize the lack of any reproductive safety data on exposure to two medications, even from the same class.

The emphasis on breastfeeding may serve to encourage women with bipolar disorder to breastfeed. Carbamazepine and valproic acid appear in low concentrations in human milk, and both are considered compatible with breastfeeding. It is noteworthy that this rating was established by comparison with other anticonvulsants. An extensive review by Cauldron and colleagues[176] provides the clinician with extant information on mood stabilizers during breastfeeding. Like other psychotropic medications, mood-stabilizing medications are present in breast milk. Nursing infants can achieve serum lithium concentrations that are 40% to 50% of maternal levels.[177,178] Although there are no reports of toxic effects associated with lithium and nursing, the potential for such toxicity warrants close observation of the infant's hydration status. In contrast, the clinician may consider avoiding medications that increase the potential for liver toxicity in these infants, such as acetaminophen.

"The use of medications during pregnancy and lactation will continue to generate considerable debate, and it is doubtful that a final consensus will ever be reached."

SUMMARY

The use of medications during pregnancy and lactation will continue to generate considerable debate, and it is doubtful that a final consensus will ever be reached. The prospect of controlled studies with appropriate control groups is equally unlikely. Utilizing the exposure model discussed herein, inadvertent conception occurs while taking an efficacious medication, and thus the choice of medication has been made for both pregnancy and lactation. Although other treatment options may be more appealing or have a larger reproductive safety database, the second exposure to another treatment option or risk of relapse

with a novel treatment represent an unknown. For the woman seeking prepregnancy consultation, comprehensive risk-benefit assessment and the alternative treatment plan must take into account the patient's age. Extended treatment trials that may result in a delayed pregnancy may actually enhance the risk of maternal age to the pregnancy.

"In conclusion, the available human and animal data emphasize the potential adverse impact of untreated maternal mental illness in both pregnancy and the postpartum period on the developing offspring."

CONCLUSIONS

In conclusion, the available human and animal data emphasize the potential adverse impact of untreated maternal mental illness in both pregnancy and the postpartum period on the developing offspring. The exposure model serves as a complement to the comprehensive risk-benefit assessment encouraged in a previous review[1] and the decision model proposed by Wisner and colleagues.[133] These laboratory observations have tremendous implications for treatment planning in perinatal psychiatry. One goal, often deemed to be primary, is to minimize fetal/neonatal exposure to psychotropic medication. This is a laudable goal, but the finding that untreated maternal illness during pregnancy may have deleterious effects redefines the risk-benefit analysis in these patients. Presently, a reasonable treatment model is to respect the pathways of exposure and minimize the total number of exposures to which the fetus or neonate is subjected. As we await the completion of further neurodevelopmental outcome studies, which undoubtedly will suffer the confounds of previous investigations, the clinician should seek the path of least exposure.

Should future investigations demonstrate that untreated illness alters the constituents of umbilical cord blood, amniotic fluid, and breast milk, further clarification of the risk-benefit assessment will be warranted. The answer to the seminal research question of whether the treatment of mental illness during pregnancy and postpartum predisposes or protects the infant from future psychopathology remains obscure. Considering the relative strength of perceived parental warmth in predicting (and hopefully avoiding) adulthood major depression,[17] the maintenance of maternal mental health may be one of psychiatry's few opportunities to practice preventative medicine. CNS

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"One goal, often deemed to be primary, is to minimize fetal/neonatal exposure to psychotropic medication. This is a laudable goal, but the finding that untreated maternal illness during pregnancy may have deleterious effects redefines the risk-benefit analysis in these patients."

"As we await the completion of further neurodevelopmental outcome studies, which undoubtedly will suffer the confounds of previous investigations, the clinician should seek the path of least exposure."

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"Should future investigations demonstrate that untreated illness alters the constituents of umbilical cord blood, amniotic fluid, and breast milk, further clarification of the risk-benefit assessment will be warranted."

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