Overview

The Use of SSRIs in Depressive Disorders Specific to Women

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The prevalence of depressive disorders in women is twice that in men,[1,2] with lifetime prevalence rates of major depressive disorder in women estimated to be as high as 21%. In contrast, childhood rates of depression are similar in boys and girls, with differences in rates beginning around 10 years of age and persisting until middle age.[1] The impact of reproductive events including the menstrual cycle, pregnancy, postpartum, perimenopause, and menopause on the incidence of depression has been considered in the literature as one of many possible explanations for the differential rates of depression between genders.

The articles in this supplement will address depressive disorders unique to women and approaches to their appropriate evaluation and management. Table 1 summarizes the number of studies and cases reported involving the use of the different selective serotonin reuptake inhibitors (SSRIs) in women with depressive disorders during particular reproductive life phases. These studies and case reports were identified by searching MEDLINE for the terms *PMDD*, *pregnancy and depression*, *postpartum depression*, *lactation and SSRIs*, *perimenopause and depression*, and *menopause and depression.* Tables 2 through 4 list the published studies and their design for depressive situations unique to women. Although beyond the scope of this supplement, it is worth noting that gender may influence response to antidepressants. Several studies have reported that women may have a more robust response to SSRIs or monoamine oxidase inhibitors than to tricyclic antidepressants (TCAs) and may respond less well to TCAs compared with men.[3–9] Gender-specific response rates to different classes of antidepressants may further be influenced by reproductive status.[7] One study observed that premenopausal women with chronic depression responded significantly better to an SSRI compared with a TCA, whereas postmenopausal women responded similarly to both.[5] Certainly, more research is needed in this interesting area.

PREMENSTRUAL DYSPHORIC DISORDER

Premenstrual dysphoric disorder (PMDD) refers to a constellation of relatively severe symptoms that start after ovulation (the luteal phase of the cycle) and disappear within the first day or 2 of menses. In contrast to the milder premenstrual syndrome (PMS) reported by 20% to 40% of American women,[10] PMDD is associated with functional impairment and is found in only 2% to 10% of women.[11–13] Symptoms of PMDD include depressed mood, anxiety, affective lability, and/or persistent anger or irritability that occur at least during the last week of the luteal phase and cease after the onset of menstruation. The symptoms and associated functional impairment should be confirmed prospectively by at least 2 months of daily ratings. This step is critical, as up to 40% of women seeking treatment for PMDD do not, by prospective evaluation, have symptoms that are directly linked to the late luteal phase of their menstrual cycle.[14,15]

The efficacy of SSRIs in the treatment of premenstrual dysphoric disorder is one of the most replicated psychiatric findings. Table 2 cites the studies reporting the use of particular SSRIs for the treatment of PMS and PMDD, and some of these studies are reviewed further in the article by Elias Eriksson, Ph.D., and colleagues. Each of these medications has been successfully used at standard antidepressant dosage ranges, mostly throughout the cycle (continuous dosing). Preliminary data support the efficacy of luteal phase–only dosing with some of the SSRIs, including sertraline, fluoxetine, paroxetine, and citalopram.[16–23] Some data also support comparable efficacy of luteal and continuous treatment with fluoxetine[24] and citalopram[16] in women who suffer from PMDD.

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Table 1. Studies Assessing the Use of Selective Serotonin Reuptake Inhibitors in Women

	Citalopram		Fluoxetine		Fluvoxamine		Paroxetine		Sertraline	
Time of Assessment	No. of Studies	Total N	No. of Studies	Total N	No. of Studies	Total N	No. of Studies	Total N	No. of Studies	Total N
PMDD[a]	2	81	16	811	2	30	3	97	11	974
During pregnancy	2	376	15	2515	2	92	7	299	5	195
Postpartum depression	0	0	2	91	1	6	0	0	1	21
Breastfeeding	4	12	10	118	4	8	6	54	10	108
Perimenopause/ postmenopause	0	5	4	965	0	5	1	30	0	5

[a]Premenstrual dysphoric disorder (PMDD) is defined as premenstrual syndrome or luteal phase dysphoric disorder.

Table 2. Studies on the Use of Particular Selective Serotonin Reuptake Inhibitors for the Treatment of Premenstrual Syndrome/Premenstrual Dysphoric Disorder[a]

Drug/Study	N
Citalopram (total N = 81)	
Sundstrom and Backstrom, 1998 (O)[54]	12
Wikander et al, 1998 (DB)[16]	69
Fluoxetine (total N = 811)	
Stone et al, 1990 (DB)[55]	15
Stone et al, 1991 (DB)[56]	20
Menkes et al, 1992 (DB)[57]	16
Wood et al, 1992 (DB)[58]	8
Brandenburg et al, 1993 (O)[59]	10
Elks et al, 1993 (O)[60]	10
Menkes et al, 1993 (DB)[61]	21
Pearlstein and Stone, 1994 (O)[62]	64
Steiner et al, 1995 (DB)[24]	180
de la Gandara Martin, 1997 (O)[63]	20
Ozeren et al, 1997 (DB)[64]	35
Pearlstein et al, 1997 (SB)[65]	34
Steiner et al, 1997 (O)[66]	193
Steiner et al, 1997 (SB)[19]	48
Su et al, 1997 (DB)[67]	17
Diegoli et al, 1998 (DB)[68]	120
Fluvoxamine (total N = 30)	
Veeninga et al, 1990 (DB)[69]	20
Freeman et al, 1996 (O)[70]	10
Paroxetine (total N = 97)	
Eriksson et al, 1995 (DB)[71]	65
Yonkers et al, 1996 (O)[72]	14
Sundblad et al, 1997 (O)[22]	18
Sertraline (total N = 966)	
Freeman et al, 1996 (O)[73]	32
Yonkers et al, 1996 (DB)[74]	162
Halbreich and Smoller, 1997 (DB)[20]	15
Yonkers et al, 1997 (DB)[75]	200
Young et al, 1998 (DB)[23]	31
Culav-Sumic et al, 1999 (O)[76]	6
Freeman et al, 1999 (DB)[77]	31
Freeman et al, 1999 (DB)[18]	189
Jermain et al, 1999 (DB)[21]	57
Pearlstein et al, 2000 (SB)[78]	243

[a]Abbreviations: DB = double-blind, O = open, SB = single-blind.

Table 3. Studies Evaluating the Use of Selective Serotonin Reuptake Inhibitors During Pregnancy

Drug/Study	N	Focus of Study
Citalopram (total N = 376)		
Ericson et al, 1999[40]	375	Pregnancy outcome
Nordeng et al, 2001[79]	1	Withdrawal
Fluoxetine (total N = 2515)		
Shader, 1992[80]	610	Fetal development
Pastuszak et al, 1993[81]	128	Pregnancy outcome
Spencer, 1993[82]	1	Toxicity
Goldstein, 1995[83]	115	Neonatal complications
Chambers et al, 1996[35]	228	Birth outcome
Koren et al, 1998[84]	128	Pregnancy outcome
McElhatton et al, 1996[34]	96	Pregnancy/neonatal outcome
Goldstein et al, 1997[85]	796	Neonatal outcome
Johnson, 1997[86]	228	Birth outcome
Loebstein and Koren, 1997[36]	55	Pregnancy outcome/ neurodevelopment
Nulman et al, 1997[37]	55	Neurodevelopment
Mohan and Moore, 2000[87]	1	Neurodevelopment
Cohen et al, 2000[88]	64	Pregnancy outcome
Hostetter et al, 2000[89]	9	Dosing
Nordeng et al, 2001[79]	1	Fluoxetine withdrawal
Fluvoxamine (total N = 92)		
Kulin et al, 1998[39]	26	Pregnancy outcome
McElhatton et al, 1996[34]	66	Pregnancy/neonatal outcome
Paroxetine (total N = 299)		
Inman et al, 1993[90]	63	Prescription monitoring
Dahl et al, 1997[91]	1	Paroxetine withdrawal
Kulin et al, 1998[39]	97	Pregnancy outcome
Ericson et al, 1999[40]	122	Delivery outcome
Hostetter et al, 2000[89]	12	Dosing
Nordeng et al, 2001[79]	3	Paroxetine withdrawal
Nijhuis et al, 2001[92]	1	Paroxetine withdrawal
Sertraline (total N = 195)		
Kent and Laidlaw, 1995[93]	1	Congenital sertraline dependence
Kulin et al, 1998[39]	147	Pregnancy outcome
Ericson et al, 1999[40]	33	Delivery outcome
Oca and Donn, 1999[94]	1	Neonatal nystagmus
Hostetter et al, 2000[89]	13	Dosing

ANTIDEPRESSANTS IN PREGNANCY

Concern exists regarding both the use and discontinuation of antidepressants in women during pregnancy. Discontinuing antidepressants is associated with high rates of relapse in nonpregnant patients with major depression,[25–28] especially in those patients with recurrent illness.[29] The state of pregnancy is not known to protect against major depressive disorder, and pregnant women who discontinue medication may be putting themselves at risk for relapse. Pilot data from 2 studies suggest that both the rate of restarting medications later in pregnancy (a proxy for relapse)[30] and the rate of relapse of major depression[31] are high in women who have discontinued medication at conception or early in pregnancy.

Table 4. Studies on the Use of Particular Selective Serotonin Reuptake Inhibitors for the Treatment of Postpartum Depression[a]

Drug/Study	N
Citalopram (none)	…
Fluoxetine (total N = 91)	
Roy et al, 1993 (O)[95]	4
Appleby et al, 1997 (DB)[42]	87
Fluvoxamine	
Suri et al, 2001 (SB)[44]	6
Paroxetine	…
Sertraline	
Stowe et al, 1995 (O)[43]	21

[a]Abbreviations: DB = double-blind, O = open, SB = single-blind.

Table 5. Studies Evaluating the Use of Selective Serotonin Reuptake Inhibitors in Breastfeeding Mothers

Drug/Study	N
Citalopram (total N = 12)	
Jensen et al, 1997[96]	1
Spigset et al, 1997[97]	3
Schmidt et al, 2000[98]	1
Rampono et al, 2000[99]	7
Fluoxetine (total N = 72)	
Isenberg, 1990[100]	1
Burch and Wells, 1992[101]	1
Lester et al, 1993[102]	1
Taddio et al, 1996[103]	11
Brent and Wisner, 1998[104]	1
Yoshida et al, 1998[105]	4
Chambers, 1996[35]	26
Kristensen et al, 1999[106]	14
Birnbaum et al, 1999[107]	13
Fluvoxamine (total N = 8)	
Wright et al, 1997[108]	1
Yoshida et al, 1997[109]	1
Piontek et al, 2001[110]	2
Hendrick et al, 2001[111]	4
Paroxetine (total N = 54)	
Spigset et al, 1996[112]	3
Ohman et al, 1999[113]	7
Stowe et al, 2000[114]	16
Hendrick et al, 2000[115]	1
Misri et al, 2000[116]	25
Birnbaum et al, 1999[107]	2
Sertraline (total N = 108)	
Altshuler et al, 1995[117]	1
Mammen et al, 1997[118]	3
Stowe et al, 1997[119]	26
Kristensen et al, 1998[120]	8
Wisner et al, 1998[121]	9
Epperson et al, 1997[122]	4
Birnbaum et al, 1999[107]	3
Dodd, 2000[123]	10
Hendrick et al, 2001[111]	30
Epperson et al, 2001[124]	14

Table 3 lists studies on the use of SSRIs during pregnancy and their impact on fetal outcome. Different facets of these studies are described in greater detail in several reviews on antidepressant use during pregnancy.[32,33] The outcomes of approximately 2750 infants whose mothers have taken SSRIs during pregnancy have been observed (2000 with fluoxetine, 300 with citalopram, 200 with sertraline, 200 with paroxetine, and 50 with fluvoxamine).[32,34–40] No study to date has reported an increased risk for teratogenicity in the population exposed to SSRIs in utero compared with individuals who have not had such exposure. Further, limited prospective data involving a small number of cases suggest that in utero exposure to SSRIs does not significantly affect neurobehavioral development in infancy or early childhood (V. Hendrick, M.D., unpublished observations, 2000).[36,37] Although these data suggest the relative safety of these medications, more studies are clearly needed. These issues are nicely reviewed in the article by Ruta Nonacs, M.D., Ph.D., and Lee S. Cohen, M.D., in this supplement.

POSTPARTUM DEPRESSION

The optimal treatment for postpartum depression remains understudied despite the high incidence of the disorder (10%–20% of the population, depending on time of symptom onset). Prospective studies show that almost a quarter of mothers diagnosed with postpartum depression are still depressed at the child's first birthday.[41] Despite multiple medical contacts, this illness often remains either unidentified or untreated. Lack of diagnosis and treatment can lead to chronic maternal depression, decreased maternal interaction with her infant, and family dysfunction.

Table 4 summarizes the small literature reporting on the use of particular SSRIs for the treatment of postpartum depression. Despite their small number, these studies offer considerable optimism. One double-blind study found that fluoxetine and cognitive-behavioral therapy were effective treatments for major or minor depression presenting in the first 6 to 8 weeks postpartum.[42] Several open studies reported the efficacy of sertraline[43] or fluvoxamine[44] for treating postpartum depression. These studies are reviewed in greater detail in the article by D. Jeffrey Newport, M.D., and colleagues in this supplement.

One factor to be considered when deciding how to treat postpartum depression is whether or not the patient is breast-feeding her infant. Table 5 lists the studies reporting on the use of SSRIs in women who were breast-feeding their infants. Most antidepressants pass into breast milk, and the impact of these agents on the infant must be taken into account when choosing a medication. Several review articles on the use of antidepressants and other psychotropic medications in nursing women provide more detail on infant serum drug concentrations by drug class and neurobehavioral sequelae after exposure through breast milk.[45–48] The dilemmas associated with breastfeeding are reviewed in these articles, as well as in the article by Dr. Newport and colleagues in this supplement.

PERIMENOPAUSE

Perimenopause represents a time of great fluctuation in hormone levels, and menopause is associated with low

Table 6. Studies on the Use of Particular Selective Serotonin Reuptake Inhibitors in the Treatment of Perimenopausal/ Postmenopausal Women[a]

Drug/Study	N	Focus of Study
Citalopram (none)	…	…
Fluoxetine (total N = 965)		
Urban and Veldhuis, 1991 (O)[125]	7	Pulsatile prolactin release
Schneider et al, 1997 (DB)[126]	358	Fluoxetine + ERT vs fluoxetine
Amsterdam et al, 1999 (O)[127]	568	Fluoxetine + ERT vs fluoxetine
Bondi et al, 2000 (DB)[128]	32	Metabolic effects
Fluvoxamine (none)	…	…
Paroxetine		
Stearns et al, 2000 (O)[129]	30	Hot flashes in breast cancer survivors
Sertraline (none)	…	…

[a]Abbreviations: DB = double-blind, ERT = estrogen replacement therapy, O = open, SB = single-blind.

estrogen levels. Estradiol may have endogenous antidepressant properties, and there has been debate about whether the incidence of depressive symptoms or major depressive disorder increases in association with the drop in estradiol levels accompanying the transition. There is growing evidence that perimenopause may be a time of increased risk for depressive symptoms, both for women with a history of prior depression and for those without such a history,[49–51] and that estrogen replacement therapy may markedly ameliorate depressive symptoms.[52,53] The optimal approach to the treatment of depressive symptoms and depressive disorder in perimenopause remains controversial. The enclosed article by Natalie L. Rasgon, M.D., Ph.D., and colleagues adds to the literature on the efficacy of SSRIs in this population. Dr. Rasgon reviews the latest published data on treatment strategies and suggests hormonal strategies that may be reasonable as either a primary treatment and/or as an augmentation strategy with an SSRI. Table 6 lists studies reporting on the use of SSRIs in perimenopausal and postmenopausal women.

A surge of interest in the topics described in this supplement has resulted in an increase in the number of research studies currently being done in these areas. Research in the next decade will result in greater knowledge that will no doubt guide treatment.

Drug names: citalopram (Celexa), fluoxetine (Sarafem), fluvoxamine (Luvox), paroxetine (Paxil), sertraline (Zoloft).

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