Infant Safety With Antipsychotic Therapy in Breast-Feeding: A Systematic Review

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Background: A relatively high number of women may suffer from psychotic symptoms at postpartum onset. Such symptoms may have devastating effects not only on the mothers but also on the later infant's well being. Children born to mothers with psychosis are at increased risk of physiologic, psychological, and personality development disturbance, whereas children born to mothers with bipolar disorder are at increased risk of early-onset psychiatric disorders. Hence, clinicians should consider it imperative to prevent or manage effectively psychotic and affective relapses in new mothers.

Objectives: To analyze the literature for information about the safety of first- and secondgeneration antipsychotics for breast-fed infants in order to individuate the safest treatment option for women who need such medications during puerperium.

Data Sources: A computerized search was carried out on MEDLINE/PubMed/TOXNET (1950–January 2008). The following key words were used: *breast-feeding*, *lactation*, *puerperium*, *psychotropic drugs*, *atypical antipsychotics*, *typical antipsychotics*, and *neuroleptics*.

Conclusions: No conclusions can be drawn about the risk/benefit profile of the majority of antipsychotic medications in breast-feeding Hence, when clinicians are forced to start antipsychotic treatment in drug-naive patients, the choice of the safest option should be based on the general effectiveness profile of each agent, with 2 possible exceptions: clozapine (the drug should be considered contraindicated during breastfeeding because of its liability of inducing potential life-threatening events in the infant), and olanzapine (the drug seems to be associated with an increased risk of inducing extrapyramidal reactions in the breast-fed babies). Conversely, in patients who need to continue antipsychotic therapy during breast-feeding, it is suitable to maintain the previous pharmacologic regimen, if known as effective.

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Postpartum psychosis is a severe and relatively frequent maternal psychiatric disorder, as it may occur in 1–2 per 1000 women; this risk, however, rises to 1:7 for women with a history of previous postpartum psychotic episodes.¹ The onset of the disorder usually occurs within the first 4 weeks after parturition, but over 50% of symptoms are clinically manifest within the first 3 days.^{2,3}

Puerperal psychosis is not a specific nosologic entity, as the disorder could represent both the onset/relapse of schizophrenia-spectrum disorders during puerperium (cumulative incidence: 0.07%) and acute bipolar episodes, either manic or depressive (cumulative incidence: 0.03%).⁴⁻⁷ Indeed, clinical manifestations of postpartum psychosis depend on the underlying maternal psychiatric disorder. Symptoms that are more frequently reported with affective postpartum psychosis and that may have a specific genetic susceptibility⁸ are grandiose delusions, confused ideation, and grossly disorganized behavior, any of which represent a dramatic change from the mothers' previous functioning.9 Manic episode is usually considered the most frequent acute psychotic event at postpartum onset, as it affects up to 35% of women with a history of bipolar disorder.¹⁰ When postpartum psychosis represents a puerperal onset/relapse of schizophrenia-spectrum disorder, symptoms often include paranoid delusions and denial of pregnancy.¹¹ However, women with positive symptoms seem to show a better parental outcome than mothers with marked negative symptoms,¹² and this difference may be due to the different response of the different symptomatologic patterns to antipsychotic therapy.

The cognitive disorganization that occurs with postpartum psychosis may result in a mother's neglect of her infant's need and unsafe practices.^{13,14} Moreover, psychotic symptoms at postpartum onset may have other devastating effects on the infants, depending on the specific underlying maternal disorder. In fact, children born to mothers with schizophrenia or schizoaffective disorders are at increased risk of developing physiologic, psychological, and personality development disturbances, including neurologic abnormalities, anxious and psychosomatic symptoms, social behavior problems, and widespread mental disturbance, in adulthood.¹⁵⁻¹⁸ Infants born to women with bipolar disorder show a compromised quality of their attachment to their mothers as well as a generalized impairment to regulate their own emotions adaptively during the first 18 months of age.¹⁹ Later in life, such children may also show deficits in executive functioning and selective deficits in spatial memory and attention in comparison with children of well mothers.²⁰ Moreover, children born to mothers with bipolar disorder are at significantly increased risk for developing a wide range of severe psychiatric disorders, such as attention-deficit/hyperactivity disorder, major depression or dysthymia, and bipolar disorder, and accompanying dysfunction in adolescence and early adulthood.^{21,22}

Despite such evidence, mentally ill mothers who wish to breast-feed their babies are often reluctant to seek treatment for puerperal psychiatric disorders: the fear of adverse events for the suckling infant plays a central role in such maternal considerations. However, recent information suggests an increased risk for deterioration of psychiatric symptoms and/or daily life functioning in mentally ill mothers after delivery due to drug discontinuation, even in remitted patients.²³

Given this background, clinicians should consider it imperative to prevent or manage effectively psychotic and affective symptoms in new mothers, taking into consideration the mother's commitment to breast-feeding.^{24,25} The improved neurologic tolerability of second-generation antipsychotics (SGAs) compared with first-generation antipsychotics (FGAs) led clinicians to increase the prescription of these agents in both schizophrenia and bipolar disorder, despite an increased risk of inducing metabolic adverse events, such as weight gain and dysregulation, in people with either glycemic or lipidic metabolisms.^{26–29}

On the other hand, FGAs continue to represent one of the most utilized classes of psychotropic agents in both disorders.^{30,31} Recently, it was also suggested that depot antipsychotics may be taken into consideration for the long-term control of mood episodes in bipolar patients who have relapsed due to medication nonadherence or who have failed to respond to standard therapies with lithium and/or anticonvulsants.³²

Hence, the aim of this article is to evaluate the risk/ benefit profile of FGAs and SGAs used during breastfeeding in order to individuate the safest treatment option for women who need antipsychotic medications during puerperium and wish to breast-feed their infants.

DATA SOURCES

A computerized search was carried out on MEDLINE/ PubMed/TOXNET covering the period between 1950 and January 2008. The following key words were used: *breastfeeding*, *lactation*, *puerperium*, *psychotropic drugs*, *atypical antipsychotics*, *typical antipsychotics*, and *neuroleptics*. A separate search was also conducted to complete the safety profile of each antipsychotic medication. Finally, resulting articles were cross-referenced for other relevant articles not identified in the initial search.

RESULTS

Atypical Antipsychotics

Aripiprazole. Aripiprazole is excreted in the milk of rodents. It is not known whether the drug or its metabolites are also excreted in human milk.³³ A single clinical observation reported failure of lactation in a woman treated with aripiprazole during pregnancy.³⁴

Clozapine. Despite the fact that clozapine was the atypical antipsychotic first introduced to market, data on its use during breast-feeding (Table 1) are anecdotal. Relatively high concentrations of the medication were found in breast milk in a case report.³⁵ On this occasion, however, the mother did not breast-feed her baby. Further, Dev and Krupp³⁶ reported 4 cases of babies breast-fed by mothers receiving clozapine therapy. Unwanted events were recorded in 2 of these infants. One case of neurodevelopmental delay in an infant breast-fed by a mother who continued medication during puerperium was also reported by Mendhekar³⁷; this baby, however, was also exposed to clozapine during the fetal life.

Olanzapine. There are a total of 26 cases of breast-feeding during maternal use of olanzapine reported in the Eli Lilly pharmacovigilance database up to September 30, 2001 (Annamaria Desiati, Eli Lilly Italia, written communication, December 2006, and Goldstein et al.³⁸). The length of exposure to the drug via maternal milk ranged from 1 day to 8 months. Sporadic cases of unwanted reactions were recorded in the Eli Lilly database as well as in other single case reports.³⁹

The first study describing the amount of excretion of olanzapine into breast milk was performed by Croke et al.⁴⁰ The levels of the drug in the mother's serum and milk and in the infant's serum were determined by high-performance liquid chromatography (HPLC).⁴¹ The authors found that the infant's exposure to the drug through breast milk was relatively low. The detection limits of the used methodology, however, were not specified. The relative infant dose (as percentage of weight-adjusted maternal dose) ranged from 0.66% to 2.66%.

Such results were replicated by Gardiner et al.⁴² Olanzapine concentration in plasma and milk was calculated by HPLC: the detection limits were approximately $1 \mu g/L$

Study							
inuy	Z	Maternal Dose After Parturition	Evaluation Timing After Parturition	Breast Milk Levels	Infant Serum Levels	Milk-to-Plasma Ratio	Frequency and Clinical Description of Adverse Events
Clozapine							
Barnas et al (1994) ³⁵ Dev and Krupp (1995) ³⁶ Mendhekar (2007) ³⁷	- 4 -	100 mg/d NA 100 mg/d	1 wk NA NA	115.6 ng/mL NA NA	NA NA NA	2.79 NA NA	Mother did not breast-feed Agranulocytosis (N = 1) lethargy (N = 1) Delayed speech acquisition
Olanzapine							
Goldstein et al (2002) ³⁸ and Desiati (2006) ^a	26	7.1 mg/d (mean)	NA	NA	NA	NA	Jaundice and sedation (N = 1) Shaking, poor sucking, and lethargy resolved after formula switch (N = 1) Protruding tongue (N = 1) Dianer rash, diarrhea, and sleen disorder (N = 1)
Kirchheiner et al. (2000) ³⁹	1	10 mg/d	6 wk	NA	Below the detection limits (2 ng/mL)	NA	Temporary motor development delay
Croke et al (2002) ⁴⁰ Gardiner et al (2003) ⁴²	5	2.5–10 mg/d 5–20 mg/d	NA 2.4 mo (mean)	< 1–21 ng/mL 2–33 ng/mL	NA Below the detection limits (1 ng/m1)	0.2 - 0.84 0.1 - 0.6	No No
Friedman and Rosenthal (2003) ⁴³	1	5 mg/d	NA	NA	NA	NA	No
Ambresin et al (2004) ⁴⁴	-	20 mg/d	After 14 d and during successive 10 d	0–27.5 ng/mL	NA	NA	Mother did not breast-feed
Quetiapine							
Balke (2001) ⁴⁵ Sennälä (2004) ⁴⁶		50 mg/d 25–200 mg/d	NA 6 wk	NA NA	NA NA	NA NA	No No
Ritz $(2005)^{47}$	1	200 mg/d	NA	NA	NA	NA	No
Gentile $(2006)^{48}$		400 mg/d	NA	NA P 1 1 1	NA	NA	No
Kruninger et al (2007)	-	400 mg/d	NA	Below the detection limits (NA)	NA	NA	No
Lee et al (2004) ⁵⁰	1	200 mg/d	3 wk	13 ng/mL (mean)	NA	NA	No
Rampono et al (2007) ⁵¹ Misri et al (2006) ⁵²	1	400 mg/d 25–400 mg/d	3 mo 6.5–17.5 wk	≤ 170 ng/mL 0-264 ng/mL	1.4 ng/mL NA	0.29 NA	No Mildly delayed mental performance $(N=1)^{\rm b}$ Slight mental and physical delays $(N=1)^{\rm b}$
Risperidone							
Ratnayake and Libretto (2002) ⁵³	-	6 mg/d	NA	NA	NA	NA	No
Hill et al $(2000)^{54}$ llett et al $(2004)^{55}$	1 2	6 mg/d 1.5-4 mg/d	1 wk 0–3, 3 mo	≤ 50 ng/mL° ≤ 15 ng/mL°	NA Below the detection	0.66° 0.39 (9-hydroxy-	Mother did not breast-feed No (1 mother did not breast-feed)
Aichhorn et al (2005) ⁵⁶	1	2 mg/d	2 wk	≤14 ng/mL°	0.1 ng/mL (9-hydroxy- risperidone)	0.21-0.31	No
Haloperidol							
Ohkubo et al (1992) ⁵⁷ Stewart et al (1980) ⁵⁸ Whalley et al (1981) ⁵⁹ Yoshida et al (1988) ⁶⁰	0 1 1 3	3-6 mg/d 2-20 mg/d 10 mg/d 1-40 mg/day	NA 5 wk 20 d 1–18 wk	4.7–32 ng/mL ≤ 5 ng/mL ≤ 40 ng/mL ≤ 988 ng/mL	NA NA NA ≤ 8 ng/mL	NA NA ≤ 0.58 ≤ 8.0	NA No No
							(continued)

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Table 1 (continued). Atvnical and Tvnical Antinsvchotics and Breast-Feeding	al and	Tvnical Antinsvcl	hotics and Breast-Fe	eedinø			
		Maternal Dose	Evaluation Timing	Breast Milk	Infant Serum	Milk-to-Plasma	Frequency and Clinical Description
Study	z	Atter Parturition	After Parturition	Levels	Levels	Katio	01 Adverse Events
Flupenthixol							
Matheson and Skjaeraasen (1988) ⁶¹	-	8 mg/d	d 6,7	≤ 2.2 ng/mL	NA	≤ 2.20	No
Zuclopenthixol							
Matheson and Skjaeraasen (1988) ⁶¹	1	24 mg/d	d 2,3,4,8	≤44 ng/mL	NA	≤ 1.62	No
Chlorpromazine							
Yoshida et al (1998) ⁶⁰	9	50-600 mg/d	1-18 wk	≤ 501 ng/mL	$\leq 0.7 \text{ ng/mL}$	≤ 4.5	No
Kris and Carmichael (1957) ⁶²	8	50-150 mg/d	NA	NA	NA	NA	No
Ayd (1964) ⁶³	9	NA	NA	NA	NA	NA	No
Blacker et al (1962) ⁶⁴	1	1500 mg/d	22 d	≤ 290 ng/mL	NA	0.38	No
Wiles et al $(1978)^{65}$	4	NA	NA	≤ 98 ng/mL	NA	0.4–1.88	1 case of drowsiness and lethargy (2 mothers did not breast-feed)
Trifluoperazine							
Yoshida et al (1998) ⁶⁰	9	5-10 mg/d	1–8 wk	Below the detection limits	Below the detection limits	NA	No
^a Annamaria Desiati, Eli Lilly Italia, written communication, December 2006. ^b Baby was also exposed to paroxetine. ^c Risperidone plus 9-hydroxyrisperidone. Abheviation: NA = not available	alia, wr xetine. peridon	itten communication e.	n, December 2006.				

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for both plasma and milk. The authors concluded that exposure to olanzapine through maternal milk might be considered relatively safe for healthy-term infants. In this study, the relative infant dose ranged between 0.93% and 1.19%.

A single clinical observation⁴³ also failed in demonstrating iatrogenic adverse events in an infant whose mother (diagnosed with perinatal delusional disorder) breast-fed during a psychopharmacologic regimen.

The most recent case report⁴⁴ on olanzapine in breast milk confirmed that olanzapine is excreted into breast milk in relatively small amounts, as calculated by gas chromatography methodology. The baby was bottle-fed. Table 1 summarizes available data on olanzapine during breast-feeding.

Quetiapine. Reviewed information (see Table 1) seems to suggest a relatively favorable risk/benefit profile of quetiapine for breast-fed infants, although, on some occasions, their mothers took concomitant psychotropic medications.^{45–49}

The first report⁵⁰ describing the pattern of quetiapine excretion into breast milk was published quite recently. In this study, the relative infant dose was relatively low, as it ranged from 0.09% to 0.43% of the weight-adjusted maternal dose. Analogous results emerged from a successive case report, in which the relative infant dose was 0.09% of the weight-adjusted maternal dose; quetiapine concentration in the infant's plasma was estimated at approximately 6% of the maternal drug concentration.⁵¹

In a recent case series study,⁵² however, 33% of the infants exposed to quetiapine through maternal milk showed signs of slight or mild neurodevelopmental delay as assessed by the Bayley Scales of Infant Development, although dosages of quetiapine less than 75 mg/day were unlikely to determine detectable levels of the compound in breast milk. Notably, such babies were also exposed to other psychotropic medications.

Risperidone. A case report⁵³ described no risperidone-induced unwanted reactions in an infant whose mother continued antipsychotic therapy during lactation.

The first published study⁵⁴ evaluating the amount of risperidone and its metabolite transferred into breast milk suggested that the infant would receive 0.84% of the weight-adjusted maternal dose of risperidone and an additional 3.46% from its metabolite (as risperidone equivalents).

Further, the transfer of risperidone and 9-hydroxyrisperidone into human milk was investigated in 2 breast-feeding women and in a third woman who experienced risperidone-induced galactorrhea.⁵⁵ In this study, the relative infant doses (as risperidone equivalents) ranged from 2.3% to 4.7% of the maternal weightadjusted maternal dose. The infants showed neither unwanted reactions nor neurodevelopmental problems. Reassuring results were also reported by Aichhorn et al.⁵⁶ Data on risperidone and breast-feeding are shown in Table 1.

Typical Antipsychotics

Haloperidol. More than 15 years ago, Ohkubo et al.⁵⁷ published a simple method to estimate the amount of haloperidol excreted into human milk, but possible unwanted events in the infant were not investigated. Comments on infants' health were also unavailable in the report by Stewart et al.⁵⁸ However, reassuring information is available from a single case report.⁵⁹

In the study by Yoshida et al.,⁶⁰ the pharmacokinetics of 3 typical antipsychotics (including haloperidol) in breast milk was investigated by 2 methodologies: HPLC and enzyme immunoassay. Infants exposed to such medications through maternal milk were clinically and developmentally assessed at up to 30 months of age. The control subjects were 18 bottle-fed infants whose mentally ill mothers were also prescribed neuroleptic or mood-stabilizing drugs. There was no evidence of acute toxic effects. However, the comparison of the quality of neuro-development between exposed babies and unexposed, control infants was hindered by incomplete follow-up of the latter group (see Table 1 for the studies regarding haloperidol exposure through maternal milk).

Flupenthixol and zuclopenthixol. Only 1 case report is available for each medication, with no signs of unwanted reactions (see Table 1).⁶¹

Chlorpromazine. The study by Yoshida et al.⁶⁰ also reported data on chlorpromazine use in breast-feeding mothers. No adverse events were recorded in a small number of infants nursed by mothers who continued this antipsychotic medication. In 2 case series studies, infants exposed to chlorpromazine through the placenta and breast milk showed no signs of neurodevelopmental delay.^{62,63}

Analogous outcomes were reported by Blacker et al.⁶⁴ in a 22-day-old newborn whose mother was prescribed chlorpromazine for 18 days during puerperium, although the estimated daily dose ingested by the newborn was relatively high (3 mg/kg).

However, Wiles et al.⁶⁵ reported a case of drowsiness and lethargy in an infant whose mother showed relatively high chlorpromazine levels in breast milk. Table 1 shows reviewed information on nursing infants exposed to chlorpromazine.

Trifluoperazine. A small number of mother-infant pairs were investigated in the study by Yoshida et al.,⁶⁰ as Table 1 shows. The authors failed in demonstrating trifluoperazine-related adverse events in the breast-fed infants.

DISCUSSION

A significant number of mothers with psychotic symptoms at postpartum onset may require antipsychotic therapy treatment as a part of the overall pharmacologic management of the disorder. Indeed, in these vulnerable women, the well-known benefits of breast-feeding should be carefully balanced against the risk of sleep deprivation, disease aggravation, feeling of inadequacy about their ability to be mother, and increased risks of mental disturbance in their children. Regrettably, however, data on the use of SGAs and FGAs during breast-feeding show several limitations as well as safety concerns, as specified below.

Limitations

Studies on the safety of both SGAs and FGAs for the breast-fed infant are quantitatively insufficient, as the number of studies was below the theoretical threshold of 50 for all medications. Thus, the creation of a specific breast-fed infant safety index (Breastfed Infant-Neuroleptic Safety Index) analogous to that recently proposed for some modern antidepressants has been hindered.⁶⁶ The lack of long-term, prospective studies also makes information on the safety of antipsychotics for breast-fed infants qualitatively poor. Indeed, the vast majority of reviewed studies were single case reports or small case series studies. Moreover, some of the reports on the outcome of infants exposed to such psychotropic agents from breast milk were preliminary. Further, such data were often observational and, thus, could be blurred by either mother-related factors (such as the underlying maternal illness and/or other drug/environmental exposure), or infant-related factors (genetic differences in the competence of metabolizing drugs, maturation degree of infant's hepatic metabolism). Finally, additional, long-term, controlled studies are needed before confirming or excluding possible repercussions on later infants' neurodevelopment from exposure to all antipsychotics through maternal milk.

Safety Concerns

SGAs. No human data are available on the safety of aripiprazole and ziprasidone during breast-feeding. Moreover, despite clozapine having been introduced to market more than 30 years ago, only 6 cases exist describing the outcome of infants breast-fed by mothers receiving clozapine therapy. In 3 of these cases, the babies showed unwanted events (ranging from hematologic complications to transient neurodevelopmental delay).^{36,37} No study investigated clozapine levels in the breast-fed infant; also, 1 investigation³⁵ reported that the milk-to-plasma (M/P) ratio* for clozapine was more than 2.5 and, thus, above the theoretical and controversial limit of concern of 1.0.⁶⁷

^{*}The M/P ratio represents the ratio of drug concentration in breast milk to drug concentrations in maternal plasma. Hence, an M/P ratio less than 1.0 should indicate that the drug transfer into breast milk is relatively low, the preferred situation.

Published reports and manufacturer's information describe only 41 babies exposed to olanzapine through maternal milk. Five cases of unwanted events were reported, although, on some occasions, olanzapine levels in the infant's serum were undetectable. Of note, 2 of these cases reported extrapyramidal reactions (Annamaria Desiati, Eli Lilly Italia, written communication, December 2006, and Goldstein et al³⁸). Among the 13 infants known to have been exposed to quetiapine through maternal milk, 2 cases of slight/mild transient neurodevelopmental delay were recorded.⁵² Only 3 infants exposed to risperidone through maternal milk have been investigated, and no adverse events were reported.

FGAs. There have been no reports of haloperidolinduced adverse reactions among the small number of infants with known exposure to the drug through maternal milk. Also, few data are available on chlorpromazine: overall, no more than 23 infants whose mothers continued chlorpromazine therapy during breast-feeding have been investigated, with 1 report of unwanted reactions (drowsiness and lethargy).⁶⁵ During breast-feeding, the 6 infants exposed to trifluoperazine, the 1 baby exposed to flupenthixol, and the 1 baby exposed to zuclopenthixol showed no unwanted reaction.

CONCLUSIONS

No conclusions can be drawn about the risk/benefit profile of use of the majority of antipsychotic medications (aripiprazole, quetiapine, risperidone, ziprasidone, chlorpromazine, flupenthixol, haloperidol, trifluoperazine, and zuclopenthixol) in mothers with severe and persistent mental disorders who wish to breast-feed their infants. Therefore, when clinicians deem it indispensable to start therapy with FGAs or SGAs in drug-naive women, the choice of the safest option should be based on the general effectiveness profile of each drug, with 2 possible exceptions: clozapine (until further information is published, the drug should be considered contraindicated during breast-feeding because of its liability of inducing potential life-threatening events in the infant, such as agranulocytosis) and olanzapine (the drug seems to be associated with an increased risk of inducing extrapyramidal reactions in the breast-fed babies).⁶⁸ Conversely, in patients who need to continue antipsychotic therapy during breast-feeding, it is suitable to maintain the previous pharmacologic regimen if known as effective. Indeed, breast-feeding is not a good period for attempting pharmacologic switches.

Nevertheless, when clinicians are forced to choose between the option of favoring breast-feeding and contemporarily withdrawing antipsychotic medication and the option of privileging psychopharmacologic regimen and discontinuing breast-feeding, the second option should be preferred.⁶⁹ However, in these patients the response to

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pharmacologic treatment should be carefully monitored in specific mother-baby units.⁷⁰ Joint admission to a psychiatric mother-baby unit could enable a mother to receive specific and optimal care for her mental impairment and contemporarily to obtain support in developing her maternal identity in order to prevent both attachment turmoil and mother-baby separation.⁷¹ In fact, it has been demonstrated that clinical and parenting outcomes are improved in the case of joint mother-baby admission.⁷²

In any case, in these vulnerable women, any psychopharmacologic intervention must be supported by specific psychosocial-educational programs, in order to improve social integration, reduce unhealthy lifestyles and behaviors, support a sound mother-child bonding, facilitate access to optimal medical care, and ensure maternal adherence to treatments.^{23,73}

Drug names: aripiprazole (Abilify), chlorpromazine (Thorazine, Sonazine, and others), clozapine (FazaClo, Clozaril, and others), haloperidol (Haldol and others), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa), paroxetine (Paxil, Pexeva, and others), quetiapine (Seroquel), risperidone (Risperdal), trifluoperazine (Stelazine and others).

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Women's Mental Health section. Please contact Marlene Freeman, M.D., at mfreeman@psychiatrist.com.