Pharmacologic Treatment of Postpartum Women With New-Onset Major Depressive Disorder: A Randomized Controlled Trial With Paroxetine

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Objective: Approximately 6% to 8% of postpartum women suffer from major depressive disorder (MDD), but only a few controlled trials have investigated the efficacy of pharmacologic treatments. The current study determined the relative efficacy of paroxetine compared to placebo in the treatment of acute postpartum MDD.

Method: This was an 8-week, multicenter, parallel, placebo-controlled trial of paroxetine for treatment of postpartum depression. Subjects were eligible if they had an onset of DSM-IV MDD after, but within 3 months of, delivery and had a minimum score of 16 on the 17-item Hamilton Rating Scale for Depression (HAM-D-17) at intake. Seventy women were randomly assigned to either immediate-release paroxetine or matching placebo, and 31 completed the trial. Subjects were reassessed with the HAM-D-17, the Inventory of Depressive Symptomatology–Self-Report (IDS-SR) form and the Clinical Global Impressions (CGI) scales. The study was conducted between 1997 and 2004.

Results: Both groups improved over time and did not differ significantly on the HAM-D-17 or IDS-SR at follow-up. However, greater improvement in overall mean ± SD clinical severity was found for the paroxetine (Clinical Global Impressions-Severity of Illness [CGI-S] score = 1.8 ± 1.4) compared with the control group (CGI-S score = 3.1 ± 1.4; p = .05). The paroxetine group also had a significantly higher rate of remission, compared to the placebo group (37% vs. 15%, odds ratio = 3.5, 95% CI = 1.1 to 11.5). The rate of adverse effects did not differ significantly between groups.

Conclusion: Study results were limited by lower than expected enrollment and higher than anticipated attrition. Nonetheless, paroxetine treatment was associated with a significantly higher rate of remission among women with postpartum onset of MDD.

(J Clin Psychiatry 2008;69:659–665)

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This study was supported by a Collaborative Research Trial, Investigator-Initiated grant from GlaxoSmithKline to Drs. Yonkers and Cohen and by National Institute of Mental Health grant MH01648 to Dr. Yonkers.

Dr. Yonkers has received grant/research support from Wyeth and Eli Lilly and honoraria from Berlex. Dr. Cohen has received grant/research support from Forest, Eli Lilly, Wyeth-Ayerst, GlaxoSmithKline, AstraZeneca, and Sepracor; serves as a consultant and/or advisor to Eli Lilly, Wyeth-Ayerst, GlaxoSmithKline, Ortho-McNeil, Novartis, Janssen, and JDS; and serves on the speakers bureaus for Eli Lilly, Pfizer, GlaxoSmithKline, Wyeth-Ayerst, Forest, AstraZeneca, Janssen, and Berlex. Drs. Heath and Lin and Ms. Howell report no financial or other relationship relevant to the subject of this article.

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Approximately 6% to 8% of postpartum women suffer from major depressive disorder (MDD).[1–3] Despite the high rates of MDD in recently delivered women, only a handful of controlled trials have investigated the efficacy of pharmacologic treatments.[4–7] An earlier study showed that fluoxetine was more effective than placebo and as effective as counseling for treatment of women who were postpartum and depressed.[4] While this outcome suggests that medications effective for nonreproductive-related MDD will be equally useful for postpartum MDD, some of these women were already depressed during pregnancy and did not have incident illness after parturition, a feature that distinguishes postpartum depression from other depressive disorders. It is possible that the acute onset of postpartum depression modifies treatment responsiveness or that women with an acute illness have high rates of spontaneous remission.[2,8] Hence, the purpose of the current study was to determine whether paroxetine is more effective than placebo in

treating symptoms of acute MDD with onset during the 4 weeks postdelivery.

METHOD

This was a multicenter, parallel, placebo-controlled trial of paroxetine for the treatment of MDD commencing in the immediate postpartum period. Participating sites included the Yale University School of Medicine/Bridgeport Hospital in New Haven, Conn.; the University of Texas Southwestern Medical Center in Dallas, Tex.; and Massachusetts General Hospital in Boston. The study was conducted between 1997 and 2004 and prior to general requirements for clinical trial database registration. The study was approved by each institutional review board and was conducted in accord with the principals outlined in the Declaration of Helsinki. Participants were recruited by advertisement or referral from obstetric care providers. Services were available in English and Spanish, and all participants provided verbal and written informed consent.

Inclusion/Exclusion Criteria

Women were eligible if they were at least 16 years of age, met DSM-IV diagnostic criteria for MDD with an onset in the 3 months postdelivery, were within 9 months of delivery at intake, and had a score on the 17-item Hamilton Rating Scale for Depression (HAM-D-17)[9] of at least 16 at the initial visit. Women who were breastfeeding were allowed to participate. Subjects were excluded if they had an onset of MDD prior to delivery; suffered from current (within the last 6 months) alcohol or drug abuse or dependence; showed evidence of current psychotic symptoms; had a lifetime diagnosis of schizophrenia, bipolar disorder, or schizoaffective disorder; were receiving treatment (pharmacotherapy or psychotherapy) for a psychiatric disorder; had suicidal ideation with intent; were currently pregnant; were unwilling to be randomly assigned to either placebo or active medication; or were unable to attend treatment visits at a participating site.

Study Procedures

Women were screened either by phone or in person. Potentially eligible women were seen for a baseline assessment. Those who continued to be eligible were randomly assigned to paroxetine or placebo and then assessed again at weeks 1, 2, 3, 4, 6, and for a final visit, at week 8 (± 7 days). At the request of the Yale Institutional Review Board members, who were concerned about the possible untoward effects of maternal depression on the mother's offspring, women at the Yale and Bridgeport sites were seen for additional administrative visits during weeks 5 and 7. At the baseline visit, subjects were administered the Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition (SCID-I/P)[10] and the HAM-D-17 and were assigned a Clinical Global Impressions-Severity of Illness (CGI-S) score.[11] Subjects also completed the Inventory of Depressive Symptomatology–Self-Report version (IDS-SR),[12] the Social Adjustment Scale,[13] and the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36).[14] Data from the latter 2 measures will be presented separately. Blood for laboratory testing was obtained only if necessary to rule out other conditions that might confound reports of depressive symptoms. All subjects provided urine to show a negative pregnancy test prior to enrollment; this status was rechecked at any subsequent point when unprotected sexual intercourse was reported. At each follow-up visit, the HAM-D-17, IDS-SR, CGI-Improvement (CGI-I), and CGI-S scales were repeated by a blinded rater.

Randomization and Pill Administration

Subjects were randomly assigned to take identical capsules of either paroxetine or placebo. Random assignment was predetermined with a computer-generated schedule in blocked sets of 4 and was stratified by site. A study statistician was responsible for random assignment, and remaining study staff were blind to group assignment. After random assignment, subjects were instructed to take 1 capsule (10 mg of immediate-release paroxetine or identical placebo) daily for the first and second week; this dosage was increased to 2 capsules during the third and fourth weeks of the study unless side effects limited an increase. Further increments to 30 mg and then 40 mg were encouraged if improvement was less than 30% compared to baseline by week 4 and week 6, respectively. Pill counts were conducted at each follow-up visit, and those who took less than 80% of the prescribed pills were designated as noncompliant for that visit and were counseled regarding compliance.

Statistical Methods

Our original goal was to recruit 120 women. In a sample of 120 women, with a difference in the HAM-D-17 of 3 points and a standard deviation of 5, a 2-tailed test and a significance level of .05 would have had greater than 80% chance of finding a significant difference between groups, if one existed. Instead, we recruited a sample of 70 women. The difference between groups in the HAM-D-17 scores was 3, with a standard deviation of 8, for power of .53.

Demographic characteristics, baseline clinical characteristics, and adverse effects among study participants in each of the 2 groups were compared by analysis of variance for continuous measures, χ^2 test for categorical measures, and Fisher exact test for cell sizes that were less than 5. In order to test our primary hypothesis, that paroxetine would be superior to placebo in the treatment of an episode of postpartum MDD, we used a linear mixed-effects model with dependent variables that included the HAM-D-17, IDS-SR, and CGI-S scores. The linear

Table 1. Demographic Characteristics and Baseline Scores of the Sample, by Random Assignment[a]

Characteristic	Active (N = 35)	Placebo (N = 35)	Test Statistic	df	p[b]
Age, mean ± SD, y	26.1 ± 6.5	25.9 ± 6.5	t = 0.11	64	.910
Race, N (%)			Fisher Exact	NA	.894
White	18 (51.4)	16 (45.7)			
Black	5 (14.3)	4 (11.4)			
Hispanic	11 (31.4)	14 (40.0)			
Other	1 (2.9)	1 (2.9)			
Site, N (%)			Fisher Exact	NA	.891
MGH	4 (11.4)	5 (14.3)			
UTSW	10 (28.6)	11 (31.4)			
YUSM/BH	21 (60.0)	19 (54.3)			
Education, N (%), y[c]			$\chi^2 = 1.405$	1	.2359
≤ 12	11 (37.9)	15 (53.6)			
> 12	18 (62.1)	13 (46.4)			
Breastfeeding, N (%),[d]	11 (42.3)	12 (38.7)	$\chi^2 = 0.669$	1	.414
Current comorbid condition, N (%)[e]			$\chi^2 = 0.584$	1	.442
Yes	8 (22.9)	10 (28.6)			
No	27 (77.1)	25 (71.4)			
Current suicidal thoughts/attempt, N (%)[f,g]			$\chi^2 = 1.812$	2	.404
Neither	19 (54.3)	20 (60.6)			
Feel life empty	9 (25.7)	10 (30.3)			
Suicidal ideation	7 (20.0)	3 (9.1)			
HAM-D-17 score, mean ± SD	23.6 ± 4.7	24.7 ± 5.0	t = –0.98	68	.330
IDS-SR score, mean ± SD	38.6 ± 8.4	42.8 ± 8.4	t = –2.07	66	.042
CGI-S score, mean ± SD	4.2 ± 1.0	4.5 ± 0.9	t = –1.58	68	.120

[a]Table values are mean ± SD for continuous variables and N (%) for categorical variables.
[b]p Value is for t test (continuous variables) or for χ^2 test or Fisher exact test (categorical variables).
[c]Data were missing for 6 and 7 subjects in the active and placebo groups, respectively.
[d]Data were missing for 9 and 4 subjects in the active and placebo groups, respectively.
[e]Comorbid psychiatric conditions included agoraphobia, alcohol abuse, OCD, panic disorder, PTSD, dysthymic disorder, generalized anxiety disorder, and social phobia.
[f]As identified on the Inventory of Depressive Symptomatology–Self-Report.
[g]Data were missing for 2 subjects in the placebo group.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-D-17 = 17-item Hamilton Rating Scale for Depression, IDS-SR = Inventory of Depressive Symptomatology–Self-Report, MGH = Massachusetts General Hospital, NA = not applicable, OCD = obsessive-compulsive disorder, PTSD = posttraumatic stress disorder, UTSW = University of Texas Southwestern Medical Center, YUSM/BH = Yale University School of Medicine/Bridgeport Hospital.

mixed-effects model can accommodate repeatedly measured outcomes over time as well as missing observations. In the analysis, response over time (0, 1, 2, …, 8 weeks) for IDS-SR, HAM-D-17, and CGI-S were examined separately. The fixed covariates included treatment group, time in weeks, and their interaction; random effects for subjects were included to accommodate within-subject correlations. Since the time-by-group interaction was not significant for the IDS-SR, HAM-D-17, or CGI-S scores, the interaction term was not included in the final analytic models. Additional analyses used logistic regression to estimate the likelihood of posttreatment differences between groups in rates of *remission*, defined as a HAM-D-17 score of 8 or less, and *response*, defined as a CGI-I scale score of 1 or 2. These models included site and randomization status. Finally, we used logistic regression to investigate predictors of remission. The initial model included site, treatment group, lifetime comorbidity, education, race/ethnicity, suicidality at baseline, and initial severity of illness according to the HAM-D-17. The final model included site and treatment group; other covariates were retained if the parameter estimate was changed by at least 10%.

RESULTS

Patient Characteristics

Seventy women qualified for the study, and 31 completed study treatment. Subject characteristics are described in Table 1. At baseline, treatment groups did not differ significantly on age, race/ethnicity, education, likelihood of breastfeeding at intake, lifetime comorbidity, current comorbidity, or suicidal thoughts. Of the women in the active treatment group, 47% had either a current or past comorbid psychiatric disorder. Eight women assigned to active treatment had at least 1 additional diagnosis, including 3 subjects with agoraphobia, 1 with alcohol abuse, 1 with obsessive-compulsive disorder (OCD), 1 with panic disorder, 3 with posttraumatic stress disorder (PTSD), and 1 with dysthymic disorder. In the placebo group, 10 subjects had at least 1 additional diagnosis, including 2 with agoraphobia, 1 with OCD, 5 with panic disorder, 2 with PTSD, 2 with generalized anxiety disorder, and 1 with social phobia. Active and placebo groups differed significantly on baseline mean ± SD IDS-SR scores (38.6 ± 8.4 vs. 42.8 ± 8.4; t = –2.07, p = .042) but did not differ significantly on baseline HAM-D-17 or CGI-S scores.

Table 2. Symptom Scores at Each Visit

	Number of Patients		IDS-SR		HAM-D-17		CGI-S	
Visit	Active	Placebo	Active	Placebo	Active	Placebo	Active	Placebo
Baseline	35	35	38.6 ± 8.4	42.8 ± 8.4	23.6 ± 4.7	24.7 ± 5.0	4.2 ± 1.0	4.5 ± 0.9
Week 1	26	23	27.2 ± 8.3	33.5 ± 14.1	16.3 ± 5.6	20.0 ± 7.7	3.4 ± 1.2	3.8 ± 1.1
Week 2	28	24	25.2 ± 11.1	30.2 ± 12.9	15.9 ± 6.4	16.6 ± 7.2	3.2 ± 1.3	3.7 ± 1.4
Week 3	25	20	22.6 ± 10.5	30.6 ± 14.8	13.6 ± 6.5	16.7 ± 7.3	2.9 ± 1.2	3.6 ± 1.2
Week 4	22	12	20.9 ± 9.8	29.4 ± 11.1	13.5 ± 7.1	17.8 ± 9.1	2.6 ± 1.2	3.3 ± 1.4
Week 5[a]	26	16	19.5 ± 14.1	19.9 ± 9.5	12.6 ± 9.1	11.1 ± 5.3	2.3 ± 1.6	2.5 ± 1.0
Final[b]	17	14	14.0 ± 11.6	22.6 ± 14.1	8.6 ± 7.5	13.3 ± 7.7	1.8 ± 1.4	3.1 ± 1.4
Main (group) effect[c]			–4.98 (p = .019)		–1.62 (p = .22)		–0.48 (p = .047)	
Time slope			–3.49 (p < .0001)		–1.95 (p < .0001)		–0.32 (p < .0001)	

[a]Week 5 occurred between 5 and 6 weeks after baseline.
[b]Final week visit occurred between 7 and 8 weeks after baseline.
[c]The group effect was significant for the IDS-SR at baseline, but the group-by-time interaction was not significant, suggesting that the baseline difference was carried forward to end point.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-D-17 = 17-item Hamilton Rating Scale for Depression, IDS-SR = Inventory of Depressive Symptomatology–Self-Report.

Pill Compliance

Pill counts revealed that, among women assigned to paroxetine, 7 were noncompliant (took less than 80% of prescribed pills) at 1 visit, and 4 were noncompliant at 2 visits. One subject assigned to active treatment was discontinued due to ongoing lack of compliance; of the remaining subjects, no others fell below the 80% compliance rate at more than 2 visits. Among subjects assigned to placebo, 10 were noncompliant at 1 visit, 3 were noncompliant during at least 2 visits, and 1 was noncompliant on 4 occasions.

Posttreatment Results

Mean ± SD scores on all 3 symptom scales for paroxetine and placebo groups by visit are shown in Table 2. Both groups showed significant improvement over time according to all 3 clinical measures. While subjects in the paroxetine group showed numerically lower scores and greater improvement than did the placebo group, this difference only achieved significance for the CGI-S. There was no significant difference between groups for the CGI-S at baseline, but the estimate for mean improvement over time in the paroxetine group was 0.48 points lower than in the placebo group (p = .047). The IDS-SR scores differed between groups at baseline, and the interaction of treatment group by time was not significant, suggesting that the baseline difference carried over to subsequent time points. Response (CGI-I = 1 or 2) by week 8 in a last-observation-carried-forward data set occurred in 11 (32%) of subjects given placebo and in 15 (43%) of those assigned to paroxetine, but this difference was not significant (odds ratio [OR] = 1.04, 95% CI = 0.33 to 3.26, p = .94). On the other hand, 5 (14%) of subjects who received placebo and 13 (37%) of those who took paroxetine achieved remission (HAM-D-17 ≤ 8) by week 8, which differed significantly between groups (OR = 3.5, 95% CI = 1.1 to 11.5, p = .04). Given the high rate of dropout, we explored additional models to assess the robustness of the remission results.

Table 3. Factors Associated With Remission[a]

Outcome Measure	Odds Ratio	95% CI	p Value
Paroxetine vs placebo	3.24	0.68 to 15.31	.14
MGH vs YUSM/BH	0.12	0.005 to 2.75	.19
UTSW vs YUSM/BH	0.16	0.02 to 1.18	.07
Initial HAM-D-17 score	0.81	0.65 to 0.99	.04
White/non-Hispanic vs Hispanic or nonwhite	29.5	2.78 to 313.6	.005
Comorbid illness	0.14	0.03 to 0.76	.02

[a]Remission was operationalized as achieving a HAM-D-17 score of ≤ 8. Logistic regression was used to determine remission (Y/N). Site and treatment were included in the models, and additional covariates were retained in the model if they changed the parameter estimate by 10% or more.
Abbreviations: HAM-D-17 = 17-item Hamilton Rating Scale for Depression, MGH = Massachusetts General Hospital, UTSW = University of Texas Southwestern Medical Center, YUSM/BH = Yale University School of Medicine/Bridgeport Hospital.

These models first assumed that all dropouts were remitters and then that they were all nonremitters. In both models, treatment with paroxetine remained significantly better than treatment with placebo (OR = 76.6, df = 1, p < .001 and OR = 1.4, df = 1, p = .03, respectively), suggesting that our estimate for an effect of active treatment on remission is likely to be significant, even considering attrition.

Of those who remitted, 29.4% and 21.7% were or were not breastfeeding, respectively, which was not a significantly different percentage. In a model that evaluated predictors of remission, being non-Hispanic white versus Hispanic or black and not having a comorbid psychiatric condition were predictors of remission (Table 3).

The mean ± SD dose at end point achieved by women randomly assigned to paroxetine was 21.1 ± 10.7 mg/day, with a range of 10 to 50 mg/day. Subjects assigned to paroxetine and deemed responders (CGI-I score = 1 or 2) took a mean ± SD dose of 22.9 ± 12.1 mg daily at end point, and those who did not respond took a mean ± SD dose of 19.4 ± 9.0 mg daily at end point. The dose did not

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differ significantly between groups (t = –0.96, df = 1, p = .34). The mean dose for subjects randomly assigned to placebo was 2 capsules per day, which would have been a mean ± SD dose of 19.1 ± 9.3 mg/day (range, 10–40 mg/day) if the pills had contained active medication. Responders took what would have been a mean ± SD dose of 22.8 ± 8.9 mg daily, while nonresponders took what would have been a mean ± SD dose of 15 ± 8.2 mg daily, a difference that was statistically significant (t = –2.64, df = 1, p = .013).

Adverse Events and Withdrawals

Table 4 lists adverse events that occurred in at least 5% of subjects randomly assigned to paroxetine and the corresponding rate for subjects assigned to placebo. Decreased appetite, dizziness, and dry mouth occurred at a nonsignificantly higher rate in the paroxetine group; nausea and headache occurred at a nonsignificantly higher rate in subjects randomly assigned to placebo. The rates for diarrhea and somnolence were the same in both groups. Participants made no suicide attempts or attempts to harm offspring.

Subjects withdrew from active treatment for the following reasons: 1 due to an adverse event (nausea), 6 due to lack of efficacy, including 1 subject who was psychiatrically hospitalized, 6 who were lost to follow-up, 5 who felt well and no longer desired treatment, 1 who became pregnant, and 1 who was noncompliant. In subjects randomly assigned to placebo, 4 left the study because of perceived adverse events (rash, nausea, diarrhea, headache), 7 discontinued because of lack of efficacy, including 1 subject who required hospitalization, 9 were lost to follow-up, 2 felt improved and no longer desired treatment, and 1 subject moved.

Table 4. Adverse Events Reported in at Least 5% of Subjects[a]

Event	Active (N = 35), N (%)	Placebo (N = 35), N (%)	p Value
Decreased appetite	3 (9)	2 (6)	> .99
Diarrhea	4 (11)	4 (11)	> .99
Dizziness	6 (17)	3 (9)	.48
Dry mouth	4 (11)	0	.11
Headache	9 (26)	13 (37)	.30
Nausea	5 (14)	6 (17)	.74
Somnolence/drowsiness	5 (14)	5 (14)	> .99

[a]Differences in the distributions for adverse effects in the 2 groups were tested by χ^2 unless cell sizes were < 5, and then Fisher exact test was used.

DISCUSSION

This study compared the efficacy of standard antidepressant treatment and placebo in a group of subjects who experienced the onset of MDD within several months following parturition. It is important to assess the efficacy of antidepressant treatment relative to placebo in this population, since acute onset of MDD may be associated with higher spontaneous remissions.[2,8] The results of our investigation show that improvement in the CGI-S scale was significantly greater, and the rate of remission was significantly higher, for subjects randomly assigned to paroxetine compared to those assigned to placebo. However, statistically significant differences between groups were not found for IDS-SR scores over time or for either the HAM-D-17 scores or response as defined as 50% improvement on the HAM-D-17. One possible interpretation of these results is that all women improved to some extent during the course of the study but that the greatest amount of improvement (remission) occurred among subjects who received pharmacologic treatment. Clearly, the limited sample size and high attrition rate complicate the interpretation of our uneven findings.

Prior published, randomized clinical trials found that β-estradiol[5] and fluoxetine[4] were more therapeutic than placebo for treatment of depression in postpartum women. In the first study, β-estradiol or placebo was given to postpartum women who had an onset of MDD within 3 months of parturition; however, some women received concurrent antidepressant therapy, and the relative value of β-estradiol as an augmenting agent versus monotherapy is not clear.[5] In the second study, fluoxetine was superior to treatment with pill placebo and equivalent to manualized psychotherapy in depressed, postpartum women.[4] Women in this study did not necessarily have an onset of depression after parturition. Our findings suggest a higher rate of remission among paroxetine-treated women than among women treated with placebo and, if confirmed, would extend the results from this earlier study by showing therapeutic response to paroxetine among women who specifically had a postpartum onset of illness.

An additional result from our trial was that women who were white and non-Hispanic were more likely to remit than black or Hispanic subjects. There is a small literature assessing the possible influence of subject race and ethnicity on treatment response.[15] One study found equivalent response rates among black and white subjects with depression who were treated in a primary care setting,[16] although a subsequent study found that blacks who were depressed and HIV positive had lower response rates to fluoxetine[17]; this same study found a higher rate of response to placebo among Hispanics compared to blacks and non-Hispanic whites.[17] A recent pooled analysis of depression and anxiety trials comparing paroxetine to placebo found that Hispanics had a lower response rate than blacks or non-Hispanic whites, particularly for remission (CGI-I score = 1).[18] More work is needed assessing the possible effect of race and ethnicity on response and remission of depression.

Our logistic model indicated that subjects who had a lifetime comorbid illness were less likely to respond than

those with no lifetime comorbidity. Other researchers have also found that concurrent anxiety disorders decrease the likelihood of response to antidepressant treatment.[19] As noted in the text, about one half of the women in our study had a concurrent psychiatric illness, which reflects the condition of patients in clinical practice and speaks to the morbidity of the cohort. However, lifetime and current comorbid illness was evenly distributed among the 2 groups, so it is not likely that comparisons between the 2 groups were biased by psychiatric comorbidity.

This study had a number of limitations. First, the sample size was only 70 women, yielding limited power (0.53) to find differences between groups, if they exist. There were also a number of unique features that made recruitment difficult in this population. Others note, and we concur, that media advertising for participation in a postpartum depression trial is not successful.[20] There are limited ways to reach out and recruit postpartum women. Our study primarily relied on clinician referral, and this method of recruitment can be inefficient. We found that many clinicians were reluctant to refer new mothers to a placebo-controlled trial, and often they would refer women after they had already started antidepressant treatment. A further difficulty was that many women did not follow up with a referral or told study staff that participation would be too burdensome. Moreover, many women believed that their depression was simply part of delivering a baby and thought that they would spontaneously improve.

An additional impediment to recruitment in our study was that we only offered participation to women who had an onset of depressive illness after delivery. This restriction decreased the potential pool of subjects, since many women who were evaluated for participation endorsed depression during, as opposed to after, pregnancy. In previous work, we found that about one half of women who were depressed postpartum actually had an onset after parturition.[2] Finally, many women were concerned about the possible effects of medication, passed through breastfeeding, on their babies. This reduced their likelihood of participating in an antidepressant treatment trial.

Retention in this study was also difficult. A number of our subjects were very symptomatic at the outset of the study. Two subjects, 1 from each group, were psychiatrically hospitalized at the beginning but after enrollment into the study. Since participants could be assigned to placebo rather than active treatment, there was a low threshold for removing women from the protocol if they were not responding. This concern was heightened, because subjects had to care for their infants as well as themselves. In the study, removal for nonresponse occurred in 17% of women from the paroxetine group and 20% of the placebo group. Mother-child interactions for all subjects were continually assessed by members of the study staff, who were mindful of the small but serious risk of harm to a child. A further 6 and 9 women were lost to follow-up in the active and placebo groups, respectively, which may have reflected lack of short-term efficacy. Future studies may need to consider alternative designs, including an active control such as employed by Appleby et al.[4] or a comparator group such as the ones employed by Misri et al.[21] and Wisner et al.[22] Such comparators offset the subjects' risk of receiving placebo and make the study more palatable to subjects and referring clinicians.

Among women assigned to placebo, 32% responded, and 15% achieved remission, while 43% of subjects given paroxetine responded, and 37% of all subjects randomly assigned to paroxetine, remitted. The remission rates are somewhat lower than those found by others for MDD in general[23] and for the treatment specifically of postpartum MDD.[21,22] This difference may reflect the severity of illness among women in our cohort or their comorbidity, rather than the study medication, since one of the referenced studies also employed paroxetine as the therapeutic agent.[21] It may also be a result of the study design. Randomized clinical trials that employ placebo controls tend to show lower remission and response rates,[24] and the other 2 postpartum depression studies did not have a placebo control group.

A third limitation to this study was that the human subjects' board mandated a difference in the visit schedule at the Yale and Bridgeport sites compared to the other sites. However, response did not differ as a result of the 2 extra visits subjects at the Yale and Bridgeport sites received.

CONCLUSION

The current trial finds that placebo-controlled trials are difficult to execute among women with postpartum onset of MDD. Nonetheless, this study showed that paroxetine treatment was associated with a significantly higher rate of remission for postpartum onset MDD. The results of this study may be of benefit to clinicians and patients who are weighing the risks and benefits of pharmacologic treatment during the immediate postpartum period.

Drug names: estradiol (Estrace, Menostar, and others), fluoxetine (Prozac and others), paroxetine (Paxil, Pexeva, 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.

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