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Pharmacological Treatment of Postpartum Women with New Onset Major Depressive Disorder: A Randomized Controlled Trial with Paroxetine

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Abstract

Objective—Approximately 6–8% of postpartum women suffer from major depressive disorder (MDD) but only a few controlled trials have investigated the efficacy of pharmacological 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, multi-center, parallel, placebo-controlled trial of paroxetine for treatment of postpartum depression. Subjects were eligible if they had an onset of MDD after, but within 3 months of delivery and had a minimum score of 16 on the 17-item Hamilton Rating Scale for Depression ($HRS\text{-}D_{17}$) 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 $HRS\text{-}D_{17}$, the Inventory of Depressive Symptomatology-Self Report (IDS-SR) form and the Clinical Global Impression (CGI) Scales.

Results—Both groups improved over time and did not differ significantly on $HRS\text{-}D_{17}$ or the IDS-SR at follow-up. However, greater improvement in overall clinical severity was found for the paroxetine (CGI-S =1.8 ±1.4) compared with the control group (CGI-S=3.1 ± 1.4; p=0.05). The paroxetine group also had a significantly higher rate of remission, compared to the placebo group (37% vs 15%; OR=3.5; 95% CI = 1.1–11.5). The rate of adverse effects did not differ significantly between groups.

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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.

Keywords

postpartum depression; depressive episode; paroxetine; postnatal

Introduction

Approximately 6–8% 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 pharmacological treatments [4–7]. An earlier study showed that fluoxetine was more effective than placebo, and equally therapeutic as counseling for treatment of women who were postpartum and depressed [4]. While this suggests that medications effective for non-reproductive related MDD will be equally useful for postpartum MDD, some 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 four weeks post delivery.

Materials and Methods

This was a multi-center, 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 (YUSM)/Bridgeport Hospital (BH), University of Texas Southwestern Medical Center (UTSW), and Massachusetts General Hospital (MGH). The study was conducted between 1997 and 2004 and prior to the 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 obstetrical 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 diagnostic criteria for MDD with an onset in the three months post-delivery, were within nine months of delivery at intake and had a score on the 17-item Hamilton Rating Scale for Depression ($HRS\text{-}D_{17}$) [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 randomized 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 randomized 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 her offspring, women at the Yale and Bridgeport sites were seen for administrative visits during weeks 5 and 7. At the baseline visit, subjects were administered the Structured Clinical Interview for DSM-IV (SCID) [10], the HRS-D_{17} and were assigned a Clinical Global Impression (CGI) severity score [11]. Subjects also completed the Inventory of Depressive Symptomatology (IDS-SR) [12], the Social Adjustment Scale [13] and the SF-36 Health Status Survey [14]. Data from the latter two 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 was rechecked at any subsequent point when unprotected sexual intercourse was reported. At each follow up visit, the HRS-D, IDS-SR and CGI improvement and severity scales were repeated by a blinded rater.

Randomization and Pill Administration

Subjects were randomized to take identical capsules of either paroxetine or placebo. Randomization was pre-determined 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 randomization, subjects were instructed to take 1 capsule (10 mg of immediate release paroxetine or similar appearing placebo) daily for the first and second week; this was increased to two capsules during the third and fourth weeks of the study unless side effects limited an increase. Further increments to 30 mgs and then 40 mgs 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 non-compliant for that visit and were counseled regarding compliance.

Statistical Methods

Demographic, baseline clinical characteristics and adverse effects among study participants in each of the two groups were compared by analysis of variance for continuous measures, chi-square test for categorical measures, and Fisher's exact test for cell sizes that were less than 5. In order to test our primary hypothesis, that paroxetine is 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 HRS-D_{17}, IDS-SR and CGI-S. The linear 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, HRS-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, HRS-D_{17} or CGI-S, the interaction term was not included in the final analytic models. Additional analyses used logistic regression to estimate the likelihood of post treatment differences between groups in rates of remission, defined as a HRS-D_{17} score of 8 or less, and response, defined as a CGI-Improvement 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 according to the HRS-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 between 7 and 8 weeks of treatment. Subject characteristics are described in Table 1. At baseline, there were no significant differences in age, race/ethnicity, education, likelihood of breastfeeding at intake, concurrent psychiatric condition or suicidal thoughts between treatment groups. Active and placebo groups differed significantly on baseline IDS-SR scores (38.6 ± 8.4 vs 42.8 ± 8.4; t= −2.07, p=0.042) but did not differ significantly on baseline HRS-D_{17} or CGI-Severity scores.

Pill Compliance

Pill counts revealed that among women assigned to paroxetine, 7 (28%) were non-compliant (took less than 80% of prescribed pills) at one visit and 4 (16%) were non-compliant at two 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 two visits. Among subjects assigned to placebo, 10 (40%) were non-compliant on one visit, 3 (12%) were non-compliant during at least two visits and one was non-compliant on four occasions.

Post Treatment Results

Mean scores on all three symptom scales for paroxetine and placebo groups by visit are shown in Table 2. Both groups showed significant improvement over time according to all three clinical measures. While subjects in the paroxetine group showed numerically lower scores and greater improvement than did the placebo group, this 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 lower than in the placebo group; p=0.047. 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 (LOCF) data set, occurred in 31% of subjects given placebo and 43% of those assigned to paroxetine, but this was not significantly different (OR 1.04; 95% CI= 0.33–3.26; p=0.94). On the other hand, 15% of subjects who received placebo and 37% of those who took paroxetine achieved remission (HRS-$D_{17} \leq 8$) by week 8, which differed significantly between groups (OR=3.5; 95% CI = 1.1–11.5; p=0.04). Given the high rate of drop out, we explored additional models to assess the robustness of the remission results. These models first assumed that all drop-outs were remitters and then that they were all non-remitters. In both models, treatment with paroxetine remained significantly better than placebo (OR= 76.6 (df=1); p<0.001 and OR=1.4 (df=1); p=0.03, 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 breastfeeding, which was not significantly different. In a model that evaluated predictors of remission, being non-Hispanic White vs Hispanic or Black, and not having a comorbid psychiatric condition were predictors of remission (see Table 3).

The average dose at endpoint achieved by women randomized to paroxetine was 21.1 ±10.7 mgs per day with a range of 10–50 mgs per day. Subjects assigned to paroxetine and deemed responders (CGI-I=1 or 2) took an average dose of 22.9 ± 12.1 mgs daily at endpoint and those who did not respond took an average dose of 19.4 ± 9.0 mgs daily at endpoint. The dose did not differ significantly between groups (t=−0.96 (df=1), p=0.34). The average dose

for subjects randomized to placebo was 2 capsules per day, which would have been 19.1 ± 9.3 mgs per day (range 10–40 mgs/day) if the pills had contained active medication. Responders took what would have been an average dose of 22.8 ± 8.9 mgs daily while non-responders took what would have been an average of 15 ± 8.2 mgs daily, a difference that was statistically significant (t=−2.64 (df=1), p=0.013).

Adverse Events and Withdrawals

Table 4 lists adverse events that occurred in at least five percent of subjects randomized to paroxetine and the corresponding rate for subjects assigned to placebo. Decreased appetite, dizziness and dry mouth occurred at a non-significantly higher rate in the paroxetine group; nausea and headache occurred at a non-significantly higher rate in subjects randomized to placebo. The rates for diarrhea and somnolence were the same in both groups. Participants had no suicide attempts, nor attempts to harm offspring.

Subjects withdrew from active treatment for the following reasons: one due to an adverse event (nausea), six due to lack of efficacy, including one subject who was psychiatrically hospitalized, six who were lost to follow-up, five who felt well and no longer desired treatment, one who became pregnant and one who was non-compliant. In subjects randomized to placebo, four left the study because of perceived adverse events (rash, nausea, diarrhea, headache), seven discontinued because of lack of efficacy, including one subject who required hospitalization, nine were lost to follow up, two felt improved and no longer desired treatment, and one subject moved.

Discussion

This study compared the efficacy of standard antidepressant treatment and placebo in a group of subjects who suffered 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 randomized to paroxetine compared to those assigned to placebo. However, statistically significant differences between groups were not found for IDS-SR scores over time, for the $HRS\text{-}D_{17}$ nor for response rates by the end of the study. 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 pharmacological treatment. Clearly, the limited sample size and high attrition rate complicate the interpretation of our uneven findings.

Prior published randomized clinical trials found 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 its relative value as an augmenting agent vs 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 suggesting a higher rate of remission among paroxetine treated women, if confirmed, would extend the results from this 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 Caucasian 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 Caucasian 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=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. Others workers find that concurrent anxiety disorders decrease the likelihood of response to antidepressant treatment [19]. While women with either a current substance use disorder or a lifetime psychotic disorder were excluded, subjects may have had a previous substance use disorder, a previous anxiety disorder or a current anxiety disorder. As can be seen in Table 1, lifetime comorbid illness was evenly distributed among the two groups so the results are not biased by lifetime psychiatric comorbidity.

This study had a number of limitations. First, the sample size was only 70 women, yielding limited power. Our original goal was to recruit 120 women. In a sample of 120 women, with a difference in the HRS-D_{17} of 3 points and a standard deviation of 5, a two-tailed test and a significance level of 0.05 would have had greater than 80% chance of finding a significant difference between groups, if one existed. Instead, the difference between our smaller sample of HRS-D_{17} scores was 3 with a standard deviation of 8 for power of .53.

There are a number of unique features that make recruitment difficult in this population. Others note and we concur that media advertising for participation in a postpartum depression is less successful than referrals from obstetrical providers [20]. Our study primarily relied on clinician referral and this can be inefficient depending up rates of detection and a clinician's willingness to refer a woman to a placebo-controlled trial. Although many women with postpartum depression are very symptomatic, they are also burdened with the care of a new baby and may be limited in the time they are willing to devote to self care and depression treatment, even after they are referred. Moreover, many women believe that depression after delivery is simply part of the usual course of postpartum events and do not follow up with a referral because they think that they will spontaneously improve. Our study had the additional burden that participation was limited to women who had an onset of illness after delivery. This decreased the potential pool of women who were depressed and postpartum by about one-half since many women who are found to depressed after parturition actually had an onset during pregnancy [2]. Further reducing the number of eligible women was the reluctance on the part of many women to take an antidepressant while they were breastfeeding.

A number of our subjects were very symptomatic, making it difficult to retain them in a placebo-controlled study. Two subjects, one from each group were psychiatrically hospitalized at the beginning, but after enrollment into the study. There was low threshold for removing women from the protocol if they were not responding due to concern about subjects' capacity to care for their infants as well as themselves. This led to removal for non-response in 17% of women from the paroxetine group and 20% of the placebo group. Mother-child interactions for all subjects were continuously assessed by study staff whom were mindful of the small but serious risk of harm to a child. A further six and nine 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] and comparator studies such as that of Misri et al [21] and Wisner et al [22] to offset the risk of 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 randomized to paroxetine, remitted. The remission rates are somewhat less than that found by others for MDD in general [23] and for the treatment specifically of postpartum MDD [21, 22]. This may reflect the severity of illness among women in our cohort 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 two postpartum depression studies did not have a placebo-control group.

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

Summary

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 pharmacological treatment during the immediate postpartum period.

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Table 1

Description and Baseline Scores of the Sample, by Randomization Status [a]

Characteristic	Randomized: Active (N = 35)	Randomized: Placebo (N = 35)	Test Statistic	df	p[b]
Age (years)	26.1 ± 6.5	25.9 ± 6.5	t=0.11	64	0.910
Race, # (%)			Fisher Exact		0.894
White	18 (52.9)	16 (47.1)			
Black	5 (55.6)	4 (44.4)			
Hispanic	11 (44.0)	14 (56.0)			
Others	1 (50.0)	1 (50.0)			
Site, # (%)			Fisher Exact		0.891
MGH	4 (44.4)	5 (55.6)			
UT	10 (47.6)	11 (52.4)			
Yale	21 (52.5)	19 (47.5)			
Education, # (%)			χ^2=1.405	1	0.2359
≤12 years	11 (42.3)	15 (57.7)			
>12 years	18 (58.1)	13 (41.9)			
Breastfeeding (Y) [c]	11 (47.8)	12 (52.2)	χ^2 =0.669	1	0.414
Comorbid condition[d], # (%)			χ^2=0.842	1	0.359
Yes	15 (46.9)	17 (53.1)			
No	17 (58.6)	12 (41.4)			
Current suicidal thought/Attempt [e], # (%)			χ^2=1.812	2	0.404
Neither	19 (48.7)	20 (51.3)			
Feel life empty	9 (47.4)	10 (52.6)			
Suicide ideation	7 (70.0)	3 (30.0)			
HRS-D17[f]	23.6 ± 4.7	24.7 ± 5.0	t=−0.98	68	0.330
IDS-SR[g]	38.6 ± 8.4	42.8 ± 8.4	t=−2.07	66	0.042
CGI-Severity	4.2± 1.0	4.5 ± 0.9	t=−1.58	68	0.120

[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 for Fisher exact test (categorical variables).

[c] Data were missing from 4 women in the placebo group and 9 women in the active group

[d] Comorbid psychiatric conditions included lifetime alcohol abuse, alcohol dependence, drug abuse, drug dependence, anxiety disorder.

[e] As identified on the Inventory of Depressive Symptomatology (Self-Report).

[f] Hamilton Rating Scale for Depression (17 item version).

[g] Inventory of Depressive Symptomatology (Self-Report).

Table 2

Symptom Scores at Each Visit

Visit	Number of Patients		IDS-SR		HRS-D		CGI-S	
	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			−4.98(p=0.019)		−1.62(p=0.22)		−0.48(p=0.047)	
Time Slope			−3.49(p<0.0001)		−1.95(p<0.0001)		−0.32(p<0.0001)	

[a] Week 5 occurred between 5 & 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 endpoint

Table 3

Factors Associated with Remission[#]

Outcome measure	Odds Ratio	95% Confidence Interval		P value
Paroxetine vs Placebo	3.24	0.68	15.31	0.14
MGH vs Yale	0.12	0.005	2.75	0.19
UT vs Yale	0.16	0.02	1.18	0.07
Initial HRS-D_{17}	0.81	0.65	0.99	0.04
White/non-Hispanic vs Hispanic or non-White	29.5	2.78	313.6	0.005
Comorbid Illness	0.14	0.03	0.76	0.02

[#]Remission was operationalized as achieving an HRS-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.

Table 4

Reported Adverse Events, # (%)

Effect	Active N (%)	Placebo N (%)	P value
Decreased Appetite	3 (8)	2 (6)	>0.99
Diarrhea	4 (11)	4 (11)	>0.99
Dizziness	6 (17)	3 (8)	0.48
Dry Mouth	4 (11)	0	0.11
Headache	9 (25)	13 (37)	0.30
Nausea	5 (14)	6 (17)	0.74
Somnolence drowsiness	5 (14)	5 (14)	>0.99

Differences in the distributions for adverse effects in the two groups were tested by Chi Square unless cell sizes were less than 5 and then Fisher's exact test was used.