The Use of Paroxetine and Cognitive-Behavioral Therapy in Postpartum Depression and Anxiety: A Randomized Controlled Trial

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Background: Approximately 10% to 16% of women experience a major depressive episode after childbirth. A significant proportion of these women also suffer from comorbid anxiety disorders. The purpose of this study was to evaluate whether the addition of cognitive-behavioral therapy (CBT) to standard antidepressant therapy offers additional benefits in the treatment of postpartum depression with comorbid anxiety disorders.

Method: Thirty-five women referred to a tertiary care hospital outpatient program with a DSM-IV diagnosis of postpartum depression with comorbid anxiety disorder were randomly assigned to 1 of 2 treatment groups—paroxetine-only monotherapy group (N = 16) or paroxetine plus 12 sessions of CBT combination therapy group (N = 19)—for a 12-week trial. Progress was monitored by a psychiatrist blinded to treatment group, using the Hamilton Rating Scale for Depression, Hamilton Rating Scale for Anxiety, Yale-Brown Obsessive Compulsive Scale, Clinical Global Impressions scale, and Edinburgh Postnatal Depression Scale. Data were analyzed using 2-tailed statistical tests at an alpha level of .05. The study was conducted from April 1, 2002, to June 30, 2003.

Results: Both treatment groups showed a highly significant improvement ($p < .01$) in mood and anxiety symptoms. Groups did not differ significantly in week of recovery, dose of paroxetine at remission, or measures of depression, anxiety, and obsessive-compulsive symptoms at outcome.

Conclusion: Antidepressant monotherapy and combination therapy with antidepressants and CBT were both efficacious in reducing depression and anxiety symptoms. However, in this sample of acutely depressed/anxious postpartum women, there were no additional benefits from combining the 2 treatment modalities. Further research into the efficacy of combination therapy in the treatment of moderate-to-severe depression with comorbid disorders in postpartum women is recommended.

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The postpartum period is considered a time of increased risk for the onset of mood and anxiety disorders.[1] Research indicates that approximately 10% to 16% of women experience a major depressive episode in the first few months after childbirth.[1–3] Although depression is the maternal psychiatric illness that receives the most attention in the literature, the postpartum period also represents a time of heightened vulnerability to recurring anxiety disorders, such as panic disorder and obsessive-compulsive disorder.[4–6] Among the anxiety disorders that may manifest in the postpartum period, the obsessive-compulsive symptoms are the most challenging to treat in a clinical setting.

Pharmacologic therapy is a common modality of treatment for depression and/or anxiety during the postnatal period. The clinical effectiveness of the therapy is dependent on the extent to which patients adhere to the prescribed course of treatment.[7] A number of factors have been shown to influence patients' compliance including attitudes toward the illness, the prescribed medication, and the side effects profile.[8] Ensuring compliance in pharmacologic treatment is even more complex in the management of postpartum psychiatric disorders.

Psychological interventions represent an alternative to pharmacotherapy. The efficacy of psychotherapy in the treatment of postpartum depression has been demonstrated in a few well-controlled research trials.[9–12] How-

ever, research on the clinical effectiveness of combined pharmacologic and psychological intervention for postpartum depression is sparse. Only 1 published study has examined the effects of combining antidepressants (fluoxetine) with psychotherapy (cognitive-behavioral therapy) for postpartum depression. Although both cognitive-behavioral therapy (CBT) and fluoxetine alone were effective in improving maternal mood, there was little evidence for an additive effect when CBT was combined with pharmacologic treatment.[13]

There is currently no published research known to the authors comparing the use of paroxetine monotherapy versus combination therapy of paroxetine and CBT for the treatment of postpartum depression and comorbid anxiety disorders. Comorbidity, in this study, is defined as the presence of coexisting or additional disorders with reference to an initial diagnosis. Paroxetine, a selective serotonin reuptake inhibitor (SSRI), has been used worldwide for the treatment of depression and accompanying anxiety disorder spectrum, specifically panic disorder and obsessive-compulsive disorder.[14] Levels of paroxetine secreted into the breast milk appear to be low, and paroxetine is frequently used to treat postpartum disorders.[15]

This study examined whether the addition of CBT to paroxetine yielded additional benefits. We hypothesized that the patients receiving both paroxetine and CBT would achieve remission of depression and anxiety symptoms earlier than those receiving monotherapy with paroxetine and that the dose of paroxetine required to achieve remission would be lower in the combination therapy group.

METHOD

Following approval from the University of British Columbia Research Ethics Board and St. Paul's Hospital Research Ethics Board, subjects were recruited from outpatient referrals to the Reproductive Mental Health Program at St. Paul's Hospital and BC Women's Hospital in Vancouver, B.C., between April 2002 and April 2003.

Subjects were invited to enroll in the study if they exhibited symptoms of postpartum mood and anxiety disorder. Diagnosis was confirmed by the psychiatrist, using the *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition (DSM-IV)[16] criteria for depressive and anxiety disorders within 6 months of giving birth. The 21-item Hamilton Rating Scale for Depression (HAM-D),[17] the 14-item Hamilton Rating Scale for Anxiety (HAM-A),[18] and the Edinburgh Postnatal Depression Scale (EPDS)[19] were used as additional screening tools. Subjects met the inclusion criteria if they scored ≥ 18 on the HAM-D, ≥ 20 on the HAM-A, and ≥ 12 on the EPDS; were between 18 and 40 years of age; were able to understand English and provide written consent; had delivered a healthy baby close to term (37–42 weeks) with a minimum birth weight of 2.5 kg; were nonsmokers; and were willing to use adequate contraception to avoid pregnancy while participating in the study. Women were excluded if they were psychotic, suicidal, abusing substances, receiving psychotherapy or other psychotropic medications, or could not be prescribed paroxetine for medical reasons.

After providing written informed consent, patients were randomly allocated, using computer-generated random numbers, to 1 of 2 treatment groups to receive either paroxetine or a combination of paroxetine and CBT. Subjects in both groups were required to return for weekly clinical assessments in weeks 1 through 6, week 8, and week 12, for a total of 8 clinical visits. At the baseline clinical visit, a psychiatrist blinded to the subject treatment group assessed maternal mood and anxiety. The following instruments were used: HAM-A, HAM-D, Yale-Brown Obsessive Compulsive Scale (YBOCS),[20] and Clinical Global Impressions scale (CGI).[21] At the baseline visit, a self-rating scale of EPDS was administered to the subjects. At weekly clinical visits, subjects were monitored for medication compliance and adverse events. Patients' progress was evaluated by the psychiatrist investigator, who administered the HAM-A, HAM-D, YBOCS, and CGI at each clinical visit. Subjects were asked to complete the EPDS once more at the final visit at week 12.

Patients in the paroxetine monotherapy group were prescribed paroxetine by the psychiatrist investigator at the first clinical visit. The initial dose in this study was 10 mg. We implemented an individually tailored, flexible-dose regimen, whereby the daily dose was titrated uniformly across the 2 groups, up to a maximum of 50 mg. The week at which the patient remitted was noted. Remission was defined as a reduction of HAM-D and HAM-A scores to ≤ 7.

Patients in the paroxetine and CBT combination therapy group followed the same protocol as the one outlined for pharmacologic treatment. In addition, they received a 1-hour individual CBT session every week for 12 weeks. Cognitive-behavioral therapy was delivered by a registered psychologist who followed a treatment manual developed specifically for women with postpartum depression and anxiety. The study manual was tailored, from CBT manuals, for depression, anxiety disorder, and eating disorders.[22–24] The CBT sessions focused on the interrelationships between thoughts, affect, behavior, physical reactions, and environment; provided general education about the interrelationships between each of these domains; and included strategies that target positive change in each.

Data were analyzed on an intention-to-treat basis. Any subject with at least 1 postbaseline assessment was included in the analysis of change and the last observation was carried forward for noncompleters. A paired t test was used to analyze changes in the mean scores of treatment groups between the baseline and final visits. An indepen-

Table 1. Characteristics of Women Who Declined to Participate in the Study, Withdrew From the Study, and Completed the Study[a]

Characteristic	Declined (N = 5)[b]	Withdrew (N = 3)	Completed (N = 32)
Age, mean (SD), y	32.00 (2.55)	27.67 (4.93)	30.34 (4.84)
Marital status			
Married	5 (100)	3 (100)	31 (96.9)
Employment status			
Working	2 (40.0)	2 (66.7)	12 (37.5)
Education level			
Did not complete high school	…	1 (33.3)	2 (6.3)
Completed high school	2 (40.0)	2 (66.7)	16 (50.0)
Some postsecondary	…	0	2 (6.3)
Completed postsecondary	…	0	12 (37.5)
Ethnicity			
White	2 (40.0)	1 (33.3)	21 (65.6)
South Asian	1 (20.0)	0	5 (15.6)
First Nations	…	1 (33.3)	2 (6.3)
Mexican	…	0	1 (3.1)
Spanish	…	0	1 (3.1)
Indo-Canadian	1 (20.0)	0	1 (3.1)
Italian	…	0	1 (3.1)
South American	…	1 (33.3)	0
Number of children			
1	2 (40.0)	1 (33.3)	19 (59.4)
2	3 (60.0)	0	10 (31.3)
3	0	1 (33.3)	3 (9.4)
4	0	1 (33.3)	0
DSM-IV diagnosis			
Depression only	1 (20.0)	0	1 (3.1)
Depression + anxiety	2 (40.0)	2 (66.7)	10 (31.3)
Depression + anxiety + obsessions only	1 (20.0)	0	11 (34.4)
Depression + anxiety + OCD	…	1 (33.3)	10 (31.3)

[a]All values are N (%) unless otherwise stated.
[b]Data for some categories not available for women who declined to participate.
Abbreviation: OCD = obsessive-compulsive disorder, … = no data available.

Table 2. Characteristics of Women in the Paroxetine and Combination Treatment Groups[a]

Characteristic	Paroxetine Monotherapy (N = 16)	Paroxetine + CBT Combination Therapy (N = 19)
Age, mean (SD), y	30.81 (3.31)	29.52 (5.85)
Marital status		
Married	16 (100)	18 (94.7)
Employment status		
Working	6 (37.5)	8 (42.1)
Education level		
Did not complete high school	1 (6.3)	2 (10.5)
Completed high school	10 (62.5)	8 (42.1)
Some postsecondary	0	2 (10.5)
Completed postsecondary	5 (31.3)	7 (36.8)
Ethnicity		
White	9 (56.3)	13 (68.4)
South Asian	2 (12.5)	3 (15.8)
First Nations	3 (18.8)	0
Mexican	1 (6.3)	0
Spanish	0	1 (5.3)
Indo-Canadian	1 (6.3)	0
Italian	0	1 (5.3)
South American	0	1 (5.3)
Number of children		
1	9 (56.3)	11 (57.9)
2	4 (25.0)	6 (31.6)
3	3 (18.8)	1 (5.3)
4	0	1 (5.3)
DSM-IV diagnosis		
Depression only	1 (6.3)	0
Depression + anxiety	5 (31.3)	7 (36.8)
Depression + anxiety + obsessions only	7 (43.8)	4 (21.1)
Depression + anxiety + OCD	3 (18.8)	8 (42.1)

[a]All values are N (%) unless otherwise stated.
Abbreviations: CBT = cognitive-behavioral therapy, OCD = obsessive-compulsive disorder.

dent samples t test was used to evaluate differences in baseline and outcome measures between treatment groups. Additionally, the 4 psychiatric measures (HAM-A, HAM-D, EPDS, and YBOCS) were analyzed separately by analysis of variance (ANOVA) with repeated measures over time. For categorical variables, a χ^2 test was employed. All statistical tests were 2-tailed and used an α level of .05. All analyses were performed using SPSS program package for Windows, version 11.5 (Chicago, Ill.).

RESULTS

During the 12-month recruitment period, 40 women were found to meet the eligibility criteria and were approached to participate in the study. Four women declined to participate, and 1 participated in the baseline visit but was subsequently withdrawn from the study due to an allergic reaction (rash) to the medication. Of the 35 remaining women who enrolled in the study, 32 (91.4%) completed the study. Two patients in the paroxetine and CBT combination group withdrew: 1 after visit 2 due to noncompliance with medications and the other after visit 4 because of inability to comply with CBT protocol. One patient in the paroxetine monotherapy group had to withdraw because of suicidal ideation and was hospitalized after visit 5. None of these 3 patients had responded to treatment prior to withdrawing.

The characteristics of women who declined to participate, who withdrew from the study, and who completed the study are shown in Table 1. The groups did not differ significantly in age, marital status, employment status, education level, ethnicity, or number of children. Chi square analysis revealed no significant differences in diagnosis between the groups.

The characteristics of the 2 treatment groups are shown in Table 2. There were no significant differences between treatment groups on any demographic or clinical variables.

Table 3 presents the baseline and final mean scores on the HAM-D, HAM-A, EPDS, YBOCS, and CGI. No significant differences were observed between the 2 groups on any of the baseline measures.

Table 3. Mean Test Scores at Baseline and Final Assessment and Differences Between Treatment Groups

	Paroxetine Monotherapy		Paroxetine + CBT Combination Therapy				
Assessment	N	Mean (SD)	N	Mean (SD)	t	df	p
HAM-D baseline	16	22.06 (3.38)	19	21.16 (2.03)	0.98	33	.34
HAM-D final	16	4.50 (4.27)	19	6.00 (7.09)	–0.74	33	.47
HAM-A baseline	16	20.31 (6.58)	19	21.32 (8.22)	–0.39	33	.70
HAM-A final	16	6.06 (5.92)	19	6.68 (7.54)	–0.27	33	.79
EPDS baseline	13	18.15 (6.45)	15	18.87 (4.42)	–0.35	26	.73
EPDS final	14	9.71 (5.17)	14	8.64 (5.51)	0.53	26	.60
YBOCS baseline	16	7.12 (6.80)	19	12.37 (10.24)	–1.75	33	.09
YBOCS final	16	2.13 (4.92)	19	3.26 (5.91)	–0.61	33	.55
CGI-Severity of Illness baseline	16	4.19 (0.83)	19	4.37 (0.60)	–0.75	33	.46
CGI-Severity of Illness final	16	1.44 (0.63)	19	1.78 (1.22)	–1.01	33	.32

Abbreviations: CGI = Clinical Global Impressions scale, EPDS = Edinburgh Postnatal Depression Scale, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression, YBOCS = Yale-Brown Obsessive Compulsive Scale.

Table 4. Response Rates of the 2 Groups at Final Visit

	Paroxetine Monotherapy (N = 16)		Paroxetine + CBT Combination Therapy (N = 19)		χ^2	
Measure	N	%	N	%	(df = 1)	p
HAM-D						
Responder (≥ 50% score reduction)	14	87.5	15	78.9	0.45	.50
HAM-A						
Responder (≥ 50% score reduction)	12	75.0	16	84.2	0.46	.50
EPDS[a]						
Responder (≥ 50% score reduction)	8	61.5	7	58.3	0.28	.87
YBOCS[b]						
Responder (≥ 60% score reduction)	8	80.0	11	78.6	0.01	.93
CGI (1 = normal, not at all ill)						
Depression (based on HAM-D)	12	75.0	12	63.2	1.13	.23
Anxiety (based on HAM-A)	12	75.0	11	57.9	0.57	.45
Obsessions and/or OCD (based on YBOCS)[b]	8	80.0	10	71.4	0.45	.50

[a]3 patients in the monotherapy group and 7 in the combination group did not have complete EPDS scores.
[b]Rates were calculated only for those patients who scored > 7 on YBOCS at first and/or second visit. N = 10 for the monotherapy group and N = 14 for the combination group.
Abbreviations: CGI = Clinical Global Impressions scale, EPDS = Edinburgh Postnatal Depression Scale, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression, YBOCS = Yale-Brown Obsessive Compulsive Scale.

Results were analyzed for changes in the HAM-D, HAM-A, EPDS, YBOCS, and CGI between the baseline and final visits. Highly significant ($p < .01$) improvements on all 5 measures were evident in both treatment groups. Correlations between the HAM-D, HAM-A, EPDS, and CGI scores at final visit were statistically significant at the $p < .01$ level (values ranging from $r = 0.48$ to $r = 0.87$). YBOCS scores at final visit were not significantly correlated with the scores from any of the other outcome measures.

An independent t test revealed no significant differences between treatment groups in mean scores on the 5 outcome measures at the final visit. A repeated-measures univariate analysis of variance (ANOVA) was also used to examine group differences in psychiatric assessment scores over the 8 clinical visits. No significant group × assessment occasion interactions were observed.

Response rates are shown in Table 4. Chi square test was employed to evaluate whether there were any significant differences between groups in the percentage of responders; none of the differences were statistically significant.

The mean week of recovery, as well as the mean dose of paroxetine at the time of recovery, was evaluated. Although the combination paroxetine plus CBT group appeared to recover earlier than the paroxetine monotherapy group, differences were not statistically significant. Subjects receiving an antidepressant alone had a mean recovery time of 11.16 weeks, whereas in the combination therapy group, subjects achieved remission at a mean of 9.50 weeks. The mean dose required to achieve remission in the monotherapy group was 36.25 mg compared with 32.50 mg in the combination therapy group.

DISCUSSION

This study demonstrated that the 2 treatment modalities, i.e., administration of antidepressant alone and anti-

depressant plus CBT, were highly effective in the treatment of acute postpartum major depressive disorder with comorbid anxiety disorders.

Both treatments resulted in statistically significant improvements in maternal mood and anxiety symptoms between the baseline and final visits. The results also indicate that the combination therapy (antidepressant plus CBT) did not offer any additional advantage in treatment of major depressive disorder in the postpartum period. The addition of CBT did not yield any significant difference in the average dose of paroxetine required to achieve remission nor did it significantly shorten the length of treatment for the combination therapy group. Our findings that the combination therapy was not superior to antidepressant therapy alone are consistent with those of Appleby et al.[13]

This study did not attempt to assess the effectiveness of CBT alone in treating postpartum depression. Rather, the purpose of this study was to ascertain if combining CBT with antidepressant medication offered extra advantage. A few controlled studies[12,13,25] indicate that, in the short term, psychological interventions are as effective as drug therapy in treating mild postpartum depression. However, the efficacy of CBT without antidepressants for the treatment of moderate-to-severe postpartum depression and comorbid anxiety disorders remains unknown.

Although not statistically significant, the trends observed in this study merit discussion. The high percentage of women in our study (> 60%) suffering from comorbid obsessive thoughts and/or obsessive-compulsive disorder was an important observation, also consistent with the findings of other researchers.[5,26] This observation clearly demonstrates that women who receive a diagnosis of postpartum depression are a heterogeneous group of women.

In terms of treatment outcome, patients were considered to have achieved remission when their mood and anxiety symptoms had completely resolved. However, at the end of 12 weeks of acute treatment, 4 patients continued to suffer from mild-to-moderate obsessions and/or compulsions, as reflected on the YBOCS, despite the fact that their mood and anxiety symptoms had remitted. Three of these 4 women were in the combination therapy group. A possible explanation for the poor response of obsessional symptoms in the combination therapy group could be the high baseline YBOCS scores in this group, which reflect severity of the baseline symptoms. These findings have a clinical significance, as they suggest that there may be a subset of postpartum depressed women who require more specialized therapy to address obsessions and/or compulsions. In this study, CBT was designed for women with postpartum depression and anxiety. It is possible that a CBT program that targets OCD symptoms specifically would be more effective. Further research focusing specifically on OCD in postpartum women, and including more sophisticated measures beyond YBOCS, would provide valuable information on optimal treatments for this subgroup of patients.

The refusal rate in this study (10%) was lower than the rates reported in previous CBT studies. The differences in recruitment methods may explain this discrepancy. In past studies,[13,25] subjects were recruited by screening newly delivered mothers in the community. In contrast, recruitment for the present study took place in a tertiary care hospital outpatient program. The referring primary care physician, having already made a diagnosis of postpartum depression, sought further specialized treatment, thus reflecting the high morbidity of subjects. In fact, the mean HAM-D score at baseline in the present study was 21 to 22 (corresponding to an interpretation of moderate depression), whereas the mean HAM-D baseline scores in 2 previous CBT studies[13,25] that recruited via community screening ranged from 13 to 16, consistent with a diagnosis of mild depression. This may also explain why the attrition rate was low in the present study; the subjects enrolled displayed moderate-to-severe depressive symptoms and therefore were accepting of the pharmacologic treatment. Although common side effects of the paroxetine included sedation and nausea, no major adverse effects were reported. Also, over half of the mothers in our sample chose to breastfeed their infants, and the development and growth of the infants exposed to paroxetine through the breast milk are currently being assessed by the investigators.

Some limitations in the study should be noted. First, this study did not include a placebo or "no-treatment" control group. However, because of concerns regarding the adverse impact of untreated maternal depression on the infant, it would be unethical to include a no-treatment group in a study such as this. Second, although trends were in the expected direction, with the combination therapy group achieving remission faster and at lower doses of paroxetine than the monotherapy group, differences were not statistically significant. However, it is possible that differences would have been statistically significant had a larger sample been used. Further investigation into the efficacy of combination antidepressant plus CBT therapy, using a larger sample, is recommended. Third, all patients received weekly clinical visits with the investigating psychiatrist, which may be perceived by patients as supportive psychotherapy, and this may have had a confounding effect. However, these visits were strictly limited to evaluating their progress through the screening tools, and effort was made not to engage in any formal psychotherapy. Fourth, because of this particular population of patients (i.e., new mothers), some may have had practical difficulties adhering strictly to visits per the protocol, which in turn may have increased the mean week of recovery. However, allowances were made for 5 patients only. Finally, this study assessed changes in pa-

tients' mood and anxiety symptoms over a 12-week period. It is unclear whether or not remission will be sustained over a prolonged period. Patients in the present study will be followed up at 6 months of completing the study to evaluate whether remission beyond acute phase of treatment occurred.

Overall, the findings of this study have important clinical and economic implications. First, paroxetine is an effective antidepressant in the treatment of postpartum depression. Since the treatment outcome for both therapies is equivocal, the financial and time commitment required for CBT may not be warranted in the acute phase of treatment. Second, there is a high probability that women who suffer from major depressive disorder postpartum onset will also experience comorbid anxiety disorders, including obsessions and/or compulsions. Because these patients rarely self-disclose OCD symptoms, this diagnosis may be missed by the assessing clinician. Finally, when patients present with comorbid disorders, particularly obsessions and/or compulsions, specialized treatment to target this spectrum of symptoms is recommended.

Drug names: fluoxetine (Prozac and others), paroxetine (Paxil).

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