# The Effect of Sertraline Add-On to Brief Dynamic Psychotherapy for the Treatment of Postpartum Depression: A Randomized, Double-Blind, Placebo-Controlled Study

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**ABSTRACT**

***Objective:*** The efficacy of antidepressants in the treatment of mild-to-moderate postpartum depression and the possible advantage of the combination of an antidepressant and psychotherapy have not been adequately studied. We hypothesized that psychotherapy and concurrent antidepressant treatment would be more effective than psychotherapy alone in the treatment of postpartum depression.

***Method:*** Women diagnosed with mild-to-moderate severity postpartum depression according to *DSM-IV-TR* criteria were enrolled in an 8-week, randomized, double-blind, placebo-controlled study. Participants received 12 sessions of focused brief dynamic psychotherapy (BDP) concurrently with 8-week sertraline or placebo treatment, followed by a 4-week open phase. Primary outcomes were depression scores measured by the Montgomery-Asberg Depression Rating Scale (MADRS) and remission rates. The study was conducted in a referral center from May 2008 to September 2010.

***Results:*** Forty of 42 women randomized into the study entered the intent-to-treat analysis. A significant time effect for the MADRS was observed ($F_{4,35} = 21.3$, $P < .0001$); however, no time-by-group effect was found for any outcome measure. Response rates were 70% and 55% for the drug and placebo groups, respectively, and remission rates were 65% and 50%, respectively, with no significant difference between groups.

***Conclusion:*** While both treatment groups improved significantly, the results of the present study did not demonstrate a significant benefit for sertraline over placebo as an add-on treatment to focused BDP in mild-to-moderate postpartum depression. Because of the study's small sample, the results cannot be viewed as definitive, and a much larger study is needed to confirm these results. Furthermore, the promising potential of focused BDP as an intervention in this population should be studied under controlled conditions.

***Trial Registration:*** clinicaltrials.gov Identifier: NCT01028482

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As many as 15% of postpartum women experience clinically significant depression[1,2] and anxiety[3,4] mood symptoms during the postpartum period. According to the *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition, Text Revision (*DSM-IV-TR*), women experiencing postpartum depression must meet criteria for an episode of major depression, with an onset within the first month postpartum. Untreated postpartum depression causes significant emotional distress, as well as negative effects on the child's well-being and development[5]; however, only a few clinical studies have systematically assessed the effectiveness of various pharmacologic and psychological interventions in its treatment.

Several controlled studies have shown the efficacy of various psychotherapeutic methods, such as cognitive,[6,7] dynamic,[7] and interpersonal psychotherapy[8] in the treatment of mild-to-moderate postpartum depression. Both a Cochrane meta-analysis[9] and a recent meta-analysis by Cuijpers et al[10] of randomized controlled trials of treatment for postpartum depression conclude that both psychosocial and psychological interventions are effective in decreasing depression and have a moderate positive effect in the treatment of postpartum depression. Furthermore, Dimidjian and Goodman[11] conclude that, while there is considerable support for the use of psychotherapy as a stand-alone intervention for postpartum depression, there is no evidence base to inform the relative value of psychotherapy versus pharmacotherapy for postpartum depression.

Studies of antidepressant medications in the treatment of postpartum depression are also very scarce, and 2 recent reviews of this subject[12,13] resulted in only 9 acceptable studies, of which only 4 were randomized[6,14–16] and only 2 were placebo controlled.[6,16] While the nonrandomized studies show a benefit for antidepressant use in postpartum depression, their generalizability is limited due to design weaknesses. Of the randomized studies, Misri et al[14] compared paroxetine treatment with paroxetine plus cognitive-behavioral therapy (CBT), showing a good response rate for both groups, but no advantage to the CBT add-on treatment group. Wisner et al[15] compared nortriptyline with sertraline, again with good response but without between-group differences. Appleby et al[6] studied 4 groups; fluoxetine plus 1 session of CBT, fluoxetine plus 6 sessions of CBT, placebo plus 1 session of CBT, and placebo plus 6 sessions of CBT. All groups showed a significant improvement after 12 weeks. Fluoxetine was superior to placebo (effect size = 2.4), and 6-session CBT was superior to 1-session CBT. However, the combination of drug plus CBT was not significantly better then CBT alone. In this study, fluoxetine could not be proved to be better then CBT. Yonkers et al[16] treated women with postpartum depression for 8 weeks with either paroxetine or placebo without concomitant psychotherapy. No significant advantage was seen for the paroxetine-treated group in the

mean change for depression; however, a higher remission rate was observed for the treatment group. In conclusion, most studies of the pharmacologic treatment of postpartum depression are limited by their design, which usually lacks sufficient power and a placebo-control group. Furthermore, data comparing pharmacotherapy and psychotherapy or regarding the efficacy of the combination of these 2 modalities are virtually lacking.

We report a randomized, double-blind, placebo-controlled study assessing the possible advantage of treatment with the antidepressant sertraline as an add-on treatment in women suffering from mild-to-moderate postpartum depression concurrently undergoing focused brief dynamic psychotherapy (BDP). Our hypothesis was that, in this population of women with nonsevere postpartum depression who were treated concurrently with expert, focused BDP treatment with an antidepressant would not prove to be more effective than placebo.

- Sertraline as an adjunctive treatment to psychotherapy may confer no added advantage over brief dynamic psychotherapy alone in women suffering from mild-to-moderate postpartum depression.
- When treating women suffering from moderate postpartum depression, clinicians should consider an initial intervention with brief dynamic psychotherapy alone before initiating antidepressant treatment.
- If treatment with a selective serotonin reuptake inhibitor is initiated for postpartum depression, a relatively high dose may be warranted for clinical efficacy.

Clinical Points

## METHOD

### Study Overview and Eligibility Criteria

The study was a single-center (Tel Aviv Sourasky Medical Center, Israel), 8-week, randomized, double-blind, placebo-controlled trial of sertraline treatment concurrent with time-limited, focused BDP, for women suffering from a first episode of mild-to-moderate postpartum depression. Patients were referred from maternity wards or from baby care centers. A power analysis performed a priori, based on a conservative 5-point between-group difference in the Montgomery-Asberg Depression Rating Scale (MADRS)[17] score (a small expected difference because of the limitation to moderate depression and concomitant psychotherapy), with $\alpha = .05$ and power of 0.80 resulted in 22 patients in each group (total N = 44).

Patient inclusion criteria were age 18–45 years; criteria met during the screen and baseline visits for current major depressive disorder according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM–IV*), as assessed by the Structured Clinical Interview for *DSM-IV* Axis I disorders[18]; and onset of the depressive episode starting within 2 months of parturition. Exclusion criteria were MADRS score ≥ 30, suicidal ideation (MADRS item 10 score ≥ 5), psychotic symptoms, bipolar disorder; length of current episode longer than 6 months, current treatment with antidepressants, 2 failed adequate trials of antidepressants; and major physical illness or alcoholism or drug use.

After a complete description of the study, including the procedure and possible side effects, the subjects gave their informed consent to participate. The study (06-301) was approved by the Institutional Review Board and was registered on ClinicalTrials.gov (Identifier: NCT01028482).

### Study Procedures

The institution's pharmacy-generated random patient serial numbers with active versus placebo ratio of 1:1 were issued to the researchers and randomly assigned to eligible patients by the psychiatrist after the informed consent was signed. The psychiatrist who interviewed and managed the patients (M.L.) is a certified senior psychiatrist who is very familiar with both the clinical condition of postpartum depression and its pharmacotherapy. All *DSM-IV-TR* diagnoses were discussed with another psychiatrist (the primary investigator, M.B.), and during the trial, consultation was encouraged in ambiguous cases. The managing psychiatrist was blinded to the treatment condition and made all of the clinical decisions regarding protocol continuation or termination; however, in relevant cases, and in order to maintain the blind, consultation with another psychiatrist (M.B.) was encouraged. The managing psychiatrist was also asked at the end of the full protocol to document her assessment of whether the patient received active or placebo pills, and indeed, was unable to correctly guess this factor in every instance.

The first group was started on 25 mg of sertraline (Unipharm, Tel Aviv) for 1 week, followed by 50 mg for 3 more weeks. After 4 weeks, the psychiatrist was allowed to either continue the same dose or increase the dose to 100 mg for the next 4 weeks. The increase in dosage was initiated if the MADRS score at 4 weeks failed to show at least a 20% improvement or if there was no improvement on the Clinical Global Impressions scale (CGI).[19] The second group received dummy pills daily, identical in appearance to the active pills, according to the same protocol as the active group. At the end of the 8-week randomized period, patients who reached remission openly continued on the same regimen, while those who did not reach remission continued regular care as needed according to clinical assessment. All patients also received 12 weekly sessions of focused BDP concurrent with the pharmacologic treatment starting on the first week.

After the baseline visit, patients were seen every 2 weeks, for a total of 4 postbaseline visits until the end of the 8-week randomization phase of the study. A final visit was performed at the end of week 12, when psychotherapy ended. Subjects who were unable to tolerate the study medications or who stopped psychotherapy were withdrawn. A pill count was



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conducted to monitor compliance. Protocol violation was defined as < 80% compliance by pill count.

### Brief Dynamic Psychotherapy

Brief dynamic psychotherapy is a psychotherapeutic intervention commonly used in our unit for postpartum depression with good results. In one of the few large studies in this area, Cooper et al[7] compared psychodynamic therapy to CBT and nondirective counseling, and only the psychodynamic arm was found to be superior to the control group in reducing depression scores.

The psychotherapeutic technique applied was derived from Malan's focused BDP[20] and from the literature specifying BDP's distinctive techniques.[21–24] The principle of this treatment is a time-limited intervention in which the primary objective is to enhance the patient's insights regarding repetitive conflicts. The use of BDP is especially appropriate in the circumstance of childbirth, as it is consistent with the usually cited indications for BDP, which include high motivation for change, a circumscribed problem, evidence of at least 1 good relationship in the past, and the capacity for self-reflection or "psychological mindedness."[22] In treatment, a "focus" conflict for treatment is identified, in line with Balint and Balint's[25] notion of a focus in dynamic therapy. This focus connects the patient's presenting problem with past difficulties and with the current transferential relationship with the therapist.

In the initial phase of treatment (sessions 1–2), the clinician performs an in-depth clinical interview focused on collecting information regarding factors such as the patient's course of life, coping style, and defense mechanisms. Possible primary problem areas that were activated by childbirth, disturbing the patient's mental equilibrium, are identified. In sessions 3 and 4, the identified issues (focus) are thoroughly addressed. Recurrent themes (eg, of loss or separation), attributed meanings and consistent patterns of relationships, feelings, and behaviors are identified and clarified, and specific patterns of internal object relationships are formulated. In sessions 5 and 6, psychotherapist and patient identify such reoccurring themes and patterns as reflecting the central conflict behind childbirth. The consequences of childbirth are addressed, discussed, and worked through in relation to the conflictual past experiences and patterns identified. During sessions 7 through 9, the therapy focuses on interpreting interpersonal relations in general and on the therapeutic relationship specifically. During sessions 10 and 11, the course of the psychotherapy and its major benefits to the patient are discussed as well as ways to maintain these benefits after therapy is terminated. In the last session, termination of treatment and related issues are discussed.

Five therapists, all experienced clinical psychologists, participated in the study. The patients were assigned to the therapists at random. All therapists were well trained in brief Malan-derived psychodynamic psychotherapy and participated in weekly group and individual monitoring and supervision meetings by 2 independent senior supervising psychologists. In these supervisions, adherence to the protocol was monitored, and the therapists raised problematic issues that were consequently discussed and resolved. In addition, the senior psychologists examined the patients' files each week and gave relevant feedback to the therapists.

### Assessment Tools

A demographic questionnaire was administered before the study. The following symptom rating scales were completed at baseline and on every follow-up visit (weeks 0, 2, 4, 6, 8, and 12): the MADRS,[17] Cronbach α = 0.82; Edinburgh Postnatal Depression Scale (EPDS),[26] Cronbach α = 0.753; Mental Health Inventory (MHI),[27] Cronbach α = 0.85; CGI-Severity of illness (CGI-S) and Improvement (CGI-I) scales[19]; and the UKU Side Effect Rating Scale.[28] Unfortunately, treatment expectancy was not routinely performed before treatment was commenced and thus these data are lacking.

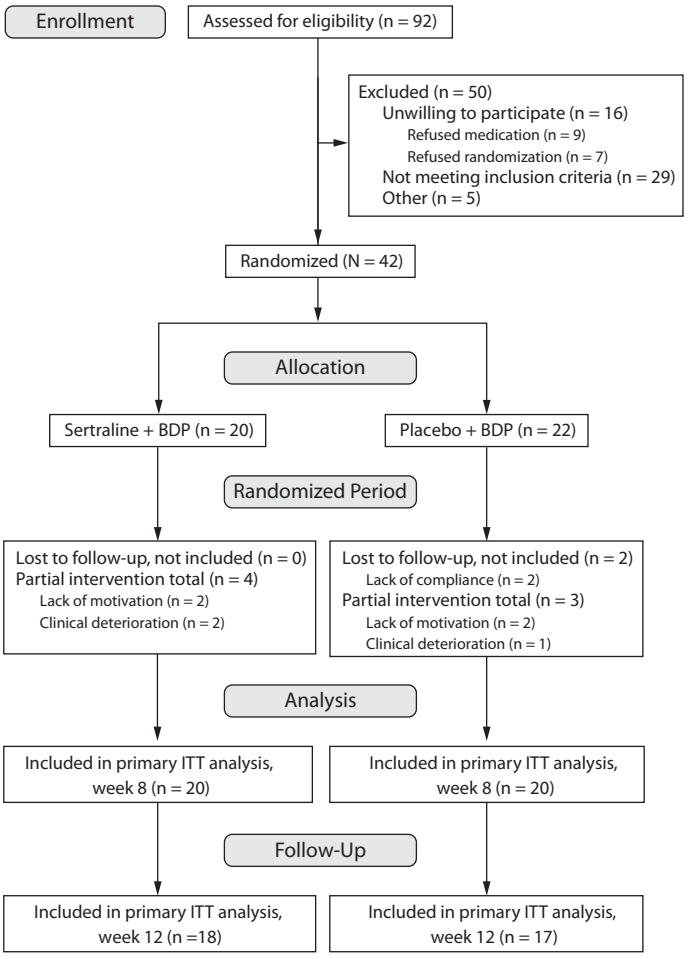
### Statistical Analysis

The primary outcome measure for the present study was defined as continuous change in MADRS and EPDS score severity ratings during the 8-week randomization phase. The study data set was defined using the intent-to-treat approach, consisting of all patients randomly assigned to treatment except for 2 patients who were randomized but never started the protocol. The last-observation-carried-forward approach was used in defining severity of depression at the endpoint for patients who prematurely discontinued the trial. A hierarchical linear model using the Proc Mix procedure on the SAS 9.2 for Windows (SAS Institute Inc, Cary, North Carolina) was also used to recheck the data with respect to missing data. Secondary outcome measures included (1) continuous change in MADRS and EPDS score severity ratings including the open phase of the study (week 12), (2) the proportion of patients meeting response and remission status at week 8 (response was defined as a > 50% reduction in MADRS or EPDS scores during treatment and remission as a final score of < 10 on the MADRS scale or < 7 on the EPDS), and (3) other secondary rating scales such as the CGI-I, CGI-S, and MHI. The Student *t* test was employed for the comparison of independent samples and the $\chi^2$ test for categorical data. Analysis of variance (ANOVA) was employed for the comparison of continuous outcomes with group as the between-subject variable and time point as the within-subject variable. All tests were conducted as 2-tailed, and α was set at .05 for all tests.

## RESULTS

Ninety-two women were assessed for the study, of whom 50 either were not willing to participate or were found unsuitable for the protocol (Figure 1). There was no difference on any of the epidemiologic parameters between women assessed for the study who did not meet the study inclusion and exclusion criteria (n = 50) and those who were recruited (n = 42).

**Figure 1. Patient Flowchart**




Abbreviations: BDP = brief dynamic psychotherapy, ITT = intent-to-treat.

**Table 1. Baseline Demographic and Clinical Characteristics of Patients With Postpartum Depression**

| | Placebo (n = 20) | | Drug (n = 20) | | Statistic | |
|---|---|---|---|---|---|---|
| Variable | n | % | n | % | $\chi^2$ | *P* Value |
| Married/cohabitating | 20 | 100 | 19 | 95 | 1.03 | .31 |
| Education | | | | | 5.09 | .08 |
| No high school education | 0 | 0 | 2 | 10 | | |
| High school education | 7 | 35 | 2 | 10 | | |
| College/university degree | 13 | 65 | 16 | 80 | | |
| Income | | | | | 4.35 | .11 |
| High | 4 | 20 | 7 | 35 | | |
| Average | 7 | 35 | 10 | 50 | | |
| Low | 9 | 45 | 3 | 15 | | |
| Anxiety diagnosis | 4 | 20 | 5 | 25 | 0.14 | .705 |
| Past depression | 5 | 25 | 4 | 20 | 0.14 | .705 |
| History of depression in family | 9 | 45 | 6 | 30 | 1.12 | .57 |
| In vitro fertilization treatment | 1 | 5 | 2 | 10 | 0.36 | .55 |
| Mood change 2 weeks after birth | 17 | 85 | 14 | 70 | 1.80 | .41 |
| Currently breastfeeding | 12 | 60 | 11 | 55 | 0.02 | .89 |
| Currently taking oral contraceptives | 4 | 20 | 5 | 25 | 1.24 | .54 |
| Calm baby temperament | 13 | 65 | 14 | 70 | 0.15 | .70 |
| Healthy baby | 18 | 90 | 17 | 85 | 2.36 | .31 |
| | Mean | SD | Mean | SD | *t* | *P* |
| Pregnancies, n | 1.55 | 0.69 | 2.25 | 1.25 | 2.19 | .04 |
| Number of current birth | 1.15 | 0.49 | 1.8 | 0.89 | 2.51 | .01 |
| Elapsed time since birth, wk | 15.47 | 11.47 | 13.4 | 8.83 | 0.64 | .53 |

Forty-two women were randomly assigned to pharmacologic treatment, 22 to placebo, and 20 to active medication. Two patients (4.8%) dropped out of the study after baseline assessment and were not included in the analysis. All the rest (n = 40) were included in the ITT analysis. Table 1 shows the baseline demographic and clinical data for these patients. A nonsignificant trend was found for education level, and significantly higher past pregnancy number was also found for the active drug group (but not past psychiatric history). Of the 40 participants, 33 women completed the full 8-week trial: 17 (52%) taking placebo and 16 (48%) taking active sertraline (data not shown).

Seven patients discontinued medication between weeks 4 and 8, 3 (43%) from the placebo and 4 (57%) from the active group. Discontinuation was due to lack of motivation (n = 4: placebo group, n = 2; sertraline group, n = 2) and clinical deterioration (n = 3: placebo group, n = 1; sertraline group, n = 2). We found no differences in mean baseline MADRS scores between the full completers (n = 33) and partial completers (n = 7). A total of 8 patients had their dose escalated to 100 mg after weeks 4, 3 from the placebo group and 5 from the active group. The mean ± SD dose for the sertraline group was 65.0 ± 23.5 mg at 4 weeks and 67.5 ± 24.5 mg at 8 weeks and for the placebo group was 60.0 ± 20.5 mg at 4 weeks and 62.5 ± 21.5 mg at 8 weeks (*P* = not significant [NS]). Of the partial completers, all 7 remained on 50 mg of sertraline therapy, while in 30% of the full completers, the dose was increased to 100 mg at 4 weeks. The compliance for psychotherapy was good: in the sertraline group, 92% of the psychotherapy sessions were attended compared to 87% in the placebo group (*P* = NS).

Adverse events for patients who received placebo versus active medication were similar (Table 2). The major serious adverse event reported during the study was a hypomanic switch observed in 2 women from the active drug group. This switch occurred in both patients during week 8 of the randomized phase, one of whom was taking 50 mg and the other 100 mg of sertraline.

A significant time effect was observed for depression scores between baseline and end of treatment (8 weeks) on both the MADRS ratings ($F_{4,35} = 21.3$, $P < .0001$) and EPDS ($F_{4,35} = 6.8$, $P < .0001$). There was no group × time interaction effect for depression scores on either the MADRS ($F_{4,35} = 0.968$, $P = .437$) or EPDS ($F_{4,35} = 0.62$, $P = .651$) scores across the 8-week randomized phase. The change in MADRS scores from baseline to week 8 across the 2 treatment groups is



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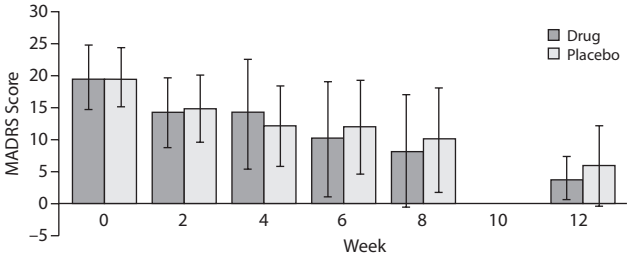
**Table 2. Clinical Variables Across Time Points for Patients With Postpartum Depression**

| | Baseline | | | | Week 8 | | | | | Week 12 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | BDP + Placebo (n = 20) | | BDP + Drug (n = 20) | | BDP + Placebo (n = 20) | | BDP + Drug (n = 20) | | Baseline to Week 8 | BDP + Placebo (n = 17) | | BDP + Drug (n = 18) | | Week 12 Between Groups |
| Assessment | Mean | SD | Mean | SD | Mean | SD | Mean | SD | $P$[a] | Mean | SD | Mean | SD | $P$[b] |
| MADRS score | 19.8 | 4.64 | 19.80 | 4.98 | 9.95 | 5.94 | 5.94 | 8.78 | .437 | 5.94 | 6.17 | 3.78 | 3.49 | .207 |
| EPDS score | 16.05 | 4.84 | 18.40 | 4.83 | 12.5 | 8.65 | 8.65 | 8.75 | .651 | 8.65 | 5.67 | 6.28 | 4.52 | .180 |
| CGI-S score | 3.80 | 0.62 | 3.70 | 0.66 | 2.30 | 1.82 | 1.82 | 1.41 | .470 | 1.82 | 0.96 | 1.72 | 1.02 | .763 |
| CGI-I score | 2.45 | 1.10 | 2.65 | 1.18 | 2.20 | .65 | .65 | 1.43 | .773 | .65 | 1.32 | 1.56 | 1.25 | .834 |
| UKU (total score) | 22.90 | 9.30 | 22.40 | 12.44 | 15.10 | 14.0 | 14.0 | 11.76 | .456 | 14.0 | 10.22 | 13.72 | 10.47 | .937 |
| MHI–Well-being score | 2.01 | 0.64 | 2.08 | 0.74 | 2.68 | 3.20 | 3.20 | 1.15 | .629 | 3.20 | 0.82 | 3.67 | 0.89 | .145 |
| MHI-Distress score | 3.83 | 0.86 | 4.16 | 0.77 | 3.02 | 2.69 | 2.69 | 1.16 | .493 | 2.69 | 0.78 | 2.30 | 0.63 | .140 |
| Lorazepam use at week 8, n (%)[c] | | | | | 10 (50) | | 13 (65) | | | | | | | |

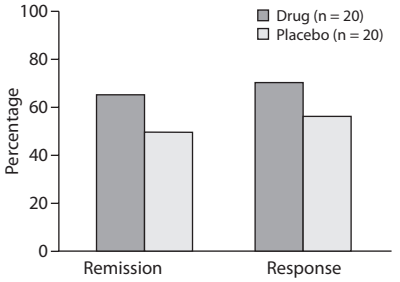
[a]ANOVA. [b]$t$ test. [c]The difference in lorazepam use at 8 weeks is not significant.
Abbreviations: ANOVA = analysis of variance, BDP = brief dynamic psychotherapy, CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, EPDS = Edinburgh Postnatal Depression Scale, MADRS = Montgomery-Asberg Depression Rating Scale, MHI = Mental Health Inventory, UKU = UKU Side Effects Rating Scale.

**Figure 2. MADRS Score During Treatment With BDP Plus Sertraline (n = 20) and BDP Plus Placebo (n = 20)[a,b]**




[a]Endpoint scores determined by last observation carried forward in the intent-to-treat sample. [b]Group × time interaction at week 8: $F_{4,35} = 0.968$, $P = .437$.
Abbreviations: BDP = brief dynamic psychotherapy, MADRS = Montgomery-Asberg Depression Rating Scale.

**Figure 3. Remission and Response Rates Based on MADRS or EPDS Scores at the End of 8 Weeks of Treatment[a,b]**




[a]Data depict last observation carried forward for all patients randomly assigned. [b]Between-group differences are not significant.
Abbreviations: EPDS = Edinburgh Postnatal Depression Scale, MADRS = Montgomery-Asberg Depression Rating Scale.

shown in Figure 2. Other rating scales also do not show significant between-group differences and are shown in Table 2.

The overall response rate in the study according to the MADRS or EPDS ratings was 62.5%, with a response rate of 55.0% (n = 11) in the BDP + placebo group and 70.0% (n = 14) in the BDP + sertraline group (Figure 3). The difference between the groups was not significant ($\chi^2 = 0.96$, $P = .33$). The total remission rate was 67.5%, with a remission rate of 50.0% (n = 10) in the BDP + placebo group and 65.0% (n = 13) in the BDP + sertraline group. The difference between the groups was not significant ($\chi^2 = 0.92$, $P = .34$).

In order to check the possible effect of baseline depression severity on subjects' response to antidepressant treatment, we performed a post hoc analysis by dividing the sample into high and low MADRS scores (high subgroup baseline mean ± SD = 23.9 ± 2.1 and 23.7 ± 2.9 for the drug and placebo groups, respectively, and low subgroup baseline mean ± SD = 15.7 ± 3.2 and 16.6 ± 3.1 for the drug and placebo groups, respectively), using the median as a cutoff point. In the analysis of the high baseline group, no between-group difference was found at 8 weeks ($t = 1.05$, $P = .31$). A repeated-measures ANOVA performed for the high baseline group yielded a significant interaction ($F_{4,14} = 6.17$, $P = .004$); however, this interaction was secondary to a decrease in MADRS scores for the placebo group at week 4. The same pattern was observed for EPDS.

At the 12-week time point, 4 weeks into the open phase of the study, and by the end of psychotherapy, the mean MADRS scores continued to decrease in both groups (Table 2), still with no between-group difference ($t_{25} = -1.27$, $P = .21$). At this time point, the remission rates were 82% (14 of 17) for the BDP + placebo group and 94% (17 of 18) for the BDP + sertraline group.

## DISCUSSION

The question addressed in this study was whether treatment with the selective serotonin reuptake inhibitor (SSRI) sertraline (vs placebo) is beneficial as an add-on intervention to focused BDP in the treatment of women suffering from mild-to-moderate postpartum depression. Our study's main finding shows that, whereas both BDP with placebo and with sertraline demonstrate a very good clinical response, no added advantage could be demonstrated for the addition of active sertraline to BDP.

While postpartum depression may have a severe clinical presentation, including severe functional impairment and suicidal ideation, it often also presents as a milder form of major depression rather then a severe episode. In such cases, psychological issues that have started or been exacerbated subsequent to childbirth are often prominent and present as central issues causing distress to the patient. Based on several well-designed controlled studies that assessed the efficacy of various psychotherapeutic methods, such as cognitive,[6,7] dynamic,[7] and interpersonal psychotherapy,[8] in the treatment of moderate-severity postpartum depression, a number of recent reviews have concluded that there is considerable support for the use of psychotherapy as a viable treatment intervention for postpartum depression.[9–11] In line with this, in the present study, it can be seen that both treatment groups, including the group treated with focused BDP and placebo, improved significantly.

In the design of this study, we did not include a waiting-list group or other form of control for psychotherapy for ethical reasons. Whereas this limitation does not allow us to conclude that focused BDP is an effective treatment on its own, the impressive remission rate in this well-defined postpartum depression population is very suggestive of a good response. Furthermore, the very low attrition rate from the study (less than 5%, compared to, eg, 26% in the Sequenced Treatment Alternatives to Relieve Depression study[29]) suggests that the therapeutic alliance achieved due to psychotherapy provided good support leading to high compliance.

Our inability to demonstrate a clinical benefit for the addition of sertraline to focused BDP may be related to the selected population of women suffering only from mild-to-moderate postpartum depression. Recently, a number of studies and reviews demonstrated the possible lack of efficacy of SSRIs in the treatment of mild-to-moderate major depression.[30,31] Fournier et al[30] concluded in their meta-analysis that the magnitude of benefit of antidepressant medication compared with placebo increases with severity of depression symptoms and may be minimal or nonexistent, on average, in patients with mild or moderate symptoms. This may very well apply to the observed results in the present study, as our cutoff criteria for the MADRS scale, established a priori to limit our study to patients with mild-to-moderate severity depression,[32] were comparable to those of the Hamilton Depression Rating Scale used in Fournier's meta-analysis. However, a secondary analysis looking at the effect of the drug on the more severely depressed patients in our cohort did not result in a between-group difference either.

Another possible explanation for the failure to observe a significant drug effect is a possible pharmacokinetic or pharmacodynamic interaction of sertraline with the unique hormonal phase characterizing postpartum depressed patients. There is a complex relationship between ovarian steroids and the serotonergic system.[33,34] While women may respond better than men to SSRIs,[35] it has been demonstrated that low estrogen levels may have a negative effect on the clinical efficacy of SSRIs.[36,37] The postpartum period is characterized by a short hypogonadal phase followed by some menstrual cycle and ovulatory irregularities, especially during lactation. Thus, it may be speculated that SSRIs such as sertraline are less effective as antidepressants during the postpartum period.

Nevertheless, a possible limitation of this study is the relatively low dose of sertraline used (50–100 mg) and the fact that dose increase to 100 mg was performed only at week 4 for an additional 4 weeks. Thus, in light of the previous discussion, the fact that all partial completers continued to take 50 mg, and the slight trend observed for improvement in the active medication group, it may be suggested that a relatively high dose of an SSRI may be warranted in the context of postpartum depression.

Another definite limitation of this study is its small sample size. This limitation is pronounced by the fact that the study is placebo-controlled and further compounded by the study's design, in which sertraline is used to augment psychotherapy. Placebo treatment is well known to have a considerable effect in depression studies, an effect that can obscure true drug effects.[38] This effect has been shown to be increasing in magnitude in the last decades. Interestingly, while in placebo-controlled trials a longer trial duration and lower baseline depression severity have been shown to decrease positive findings, sample size did not.[38] Nevertheless, because in the present study psychotherapy may have had a robust effect on depression scores, our study is probably not adequately powered to show any adjunctive drug effect, an effect that a much larger study may have been able to detect. To partially address this, we performed a power analysis using the between-group mean Δ found on the MADRS at the end of the study, at a power of 0.9, and found that a total sample size of 326 women would have been needed to show a significant difference between the groups. The calculated number needed to treat for remission at the end of 8 weeks of treatment was 7. Thus, while a type 2 error may be possible, the clinical significance of such a difference between the groups is probably minor.

In summary, while the results of our study demonstrate a very good clinical improvement in the treatment of mild-to-moderate postpartum depression with focused BDP, no significant added benefit was demonstrated for the addition of sertraline versus placebo to the treatment. Because of the small size of the present study, and the lack of a control group for psychotherapy, these results are not conclusive, and both the efficacy of BDP and adjunctive sertraline treatment should be studied in large-scale clinical studies. However, these results do give some support to the clinical perception[39] that, in mild-to-moderate postpartum depression, an initial intervention with focused BDP may be warranted before the initiation of antidepressant treatment.

***Drug names:*** fluoxetine (Prozac and others), lorazepam (Ativan and others), nortriptyline (Pamelor, Aventyl, and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others).



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