Prevention of Recurrent Postpartum Depression: A Randomized Clinical Trial

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Background: Women who have suffered one episode of postpartum-onset major depression (PPMD) comprise a high-risk group for subsequent episodes. We conducted a double-blind, randomized clinical trial to test the efficacy of nortriptyline in the prevention of recurrent PPMD.

Method: Nondepressed women who had at least one past episode of PPMD (Research Diagnostic Criteria) were recruited during pregnancy. Subjects were randomly assigned to nortriptyline or placebo. Treatment began immediately postpartum. Each subject was assessed for 20 sequential weeks with the Hamilton Rating Scale for Depression and Research Diagnostic Criteria for recurrence of major depression.

Results: No difference was found in the rate of recurrence in women treated with nortriptyline compared with those treated with placebo. Of 26 subjects who took nortriptyline preventively, 6 (0.23, 95% exact confidence interval [CI] = 0.09 to 0.44) suffered recurrences. Of 25 subjects who took placebo, 6 (0.24, 95% exact CI = 0.09 to 0.45) suffered recurrence (Fisher exact p = 1.00).

Conclusion: Nortriptyline did not confer additional preventive efficacy beyond that of placebo. The rate of recurrence of PPMD (one fourth of women) was unacceptably high.

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The postpartum period is frequently associated with the onset of mood disorder. Kendell and colleagues[1] found a dramatic rise in the rate of psychiatric admission in the first 3 months after childbirth. Of 120 women admitted within 90 days of giving birth, 87% received diagnoses of mood disorders, most commonly major depression.

Women who have suffered one episode of postpartum-onset major depression (PPMD) comprise a high-risk group for subsequent episodes. Davidson and Robertson[2] followed 35 women after an initial episode of PPMD. Six subjects developed 8 more episodes of PPMD. The risk of subsequent PPMD in this sample was 1 in 3 to 4. Women with both PPMD and other depressive episodes are likely be at highest risk for recurrence, as is the case for women with bipolar disorder.[3]

PPMD is a model of psychiatric illness that provides an ideal opportunity for prevention because its onset is preceded by a clear marker (giving birth), the period of risk for illness onset is well defined, and a high-risk sample of mothers is identifiable. The theoretical framework of this project was that administration of an antidepressant shown to treat depression, when given to asymptomatic women during the postpartum period, will prevent episodes. Several lines of evidence supported this concept. Promising data from open trials[4,5] showed that administration of lithium postnatally prevented recurrent affective psychoses. Recurrent unipolar depression was prevented by the maintenance continuation of antidepressants following resolution of an acute episode.[6–8] Presence of the drug during a period of high risk (immediately following an acute episode) prevented recurrence. Therefore, presence of an antidepressant drug during the postpartum period might prevent recurrence of PPMD.

Our open preventive postpartum antidepressant trial[9] provided encouraging results. We offered 2 options for management of the postpartum period (monitoring alone and immediate postpartum antidepressant treatment plus monitoring). Only 1 (6.7%) of 15 women who chose antidepressant treatment at birth suffered a recurrence. Of women who were monitored without medication, 5 (62.5%) of 8 suffered a recurrence (p = .01; Fisher exact test).

To systematically pursue these promising data, we conducted a double-blind, randomized, 20-week clinical trial of the efficacy of nortriptyline in the prevention of recur-

rent PPMD. The hypotheses were that (1) the rate of recurrence of PPMD would be less in the nortriptyline-treated women compared with the placebo-treated women, (2) the time to recurrence would be longer in the nortriptyline-treated women compared with the placebo-treated women, (3) women who remained nondepressed (did not fit criteria for the diagnosis of major depression) during the clinical trial would have fewer depressive symptoms with nortriptyline compared with placebo, and (4) the rate of recurrence would be greater among women who have PPMD and other major depressive episodes compared with women who have only episodes of PPMD. We followed these mothers for the remaining 32 weeks of the first postpartum year to evaluate the adequacy of the length of preventive treatment.

Ethics required consideration of the question, how long can the study continue before we make an interim assessment of whether nortriptyline is as effective as we demonstrated in our preliminary study[9]? The results presented here are the outcome of this planned interim analysis after half the subjects completed the 20-week trial.

SUBJECTS AND METHOD

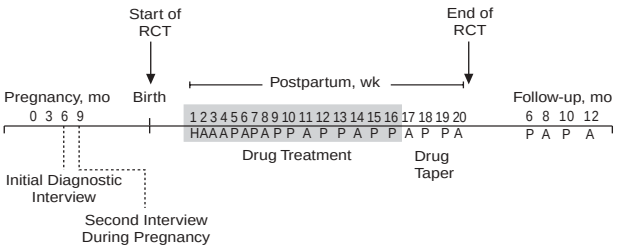
Overview of Project Plan

The project consisted of several phases that spanned 15 months (Figure 1). Pregnant subjects were recruited, and the initial diagnostic interview, the Schedule for Affective Disorders and Schizophrenia (SADS),[10] was performed. A second interview was scheduled between 32 and 36 weeks to be certain that the subject had not developed major depression since the initial interview at which time subjects were given the SADS (Change Version) and the 17-item Hamilton Rating Scale for Depression (HAM-D).[11] The subjects were randomly assigned to nortriptyline or placebo.

The randomized clinical trial (RCT) phase began immediately postpartum. We delivered the study drug to the subject in the maternity hospital immediately after birth. The subject was assessed weekly for 20 weeks. During weeks 17 through 20, nortriptyline or placebo was tapered and discontinued. Since the period of risk is 3 months (about 13 weeks), we administered nortriptyline or placebo through the first 17 weeks postpartum to cover this time frame. The follow-up phase began immediately after the RCT with assessments every 2 months and maintenance of double-blind conditions.

We selected nortriptyline for the following reasons: nortriptyline has lower anticholinergic effects compared with other tricyclic antidepressants (TCAs), and a relationship between serum concentration and therapeutic effect exists. It is also the only drug for which data to support use during breastfeeding were available[12] at the inception of the study. We selected a placebo-treated group as the control for the RCT to separate the effects of prophylactic nortriptyline treatment from those of pill administration. The remainder of the protocol, which included education and mood-symptom monitoring consistent with good clinical practice, was identical in the nortriptyline and placebo groups.

Figure 1. Clinical Trial Design: Nortriptyline Versus Placebo[a]



[a]Abbreviations: A = in-person interview, H = home visit, P = phone interview, RCT = randomized controlled trial.

The primary study staff (nurse, mood symptom rater, coordinator [K.S.P.], and principal investigator [K.L.W.]) were blind to medication assignment. The medication monitoring function (nurse) was separate from (and blind to) the mood-symptom monitoring. Nonblinded staff included the coinvestigator (J.M.P.), statistician (B.H.H.), medical monitor (R.L.F.), and study pharmacist.

Subjects

Subjects with the following characteristics were included: ≤ 35 weeks' gestation, aged 21 to 45 years, and at least one past episode of PPMD with onset of symptoms within the first 3 months after a live birth. At least one past episode of PPMD must have begun within 5 years prior to study enrollment.

We distinguished the episode of PPMD from the "baby blues," a transient mood syndrome that begins on day 3 or 4 and lifts by 2 weeks postbirth.[13] We carefully defined the requirements for the past episode of PPMD, which had to fit Research Diagnostic Criteria (RDC)[14] for definite major depression. Instead of the SADS-Lifetime, which rates symptoms as present or absent, we used the scaled depression symptoms of the SADS-Part I (items 234–352) to retrospectively establish severity for the past episode of PPMD. This meticulous exploration of symptoms prompted recall and allowed a detailed description of the past episode. This procedure also allowed derivation of a HAM-D score for the past episode of PPMD,[15] which had to be ≥ 15 for eligibility.

Subjects must have been nondepressed since the conception of the index pregnancy. Remission was defined as not meeting RDC for probable major depression. These criteria excluded women with chronic depression. Subjects who were exposed to an antidepressant after the first trimester of pregnancy were excluded. Subjects were excluded if they met criteria for any other Axis I diagnosis

(except generalized anxiety or panic disorder) or antisocial or borderline personality disorder. Subjects with past episodes of psychosis or bipolar disorder were excluded. Women who chose to continue psychotherapy or use other psychotropic medications were also excluded.

All subjects had laboratory assessments, blood pressure, and electrocardiogram results in the normal range prior to randomization. Side effects were assessed with the Asberg Side Effects Scale[16] weekly by the nurse. Approval was obtained from the institutional review board, and written informed consent was obtained from all participants.

Drug Administration

Subjects were randomly assigned by strata (past PPMD only or PPMD plus other episodes of major depression). The goal was for the subject to take the first dose of study drug as soon as possible after birth (optimally within 24 hours). Thereafter, the nortriptyline or placebo was given as a single bedtime dose of 3 capsules. The capsules contained pure nortriptyline or no drug in identical tablets. For the first postpartum week, the dose was increased daily as follows: 20, 30, 40, 50, 50, 60, and 70 mg/day and continued at 75 mg/day through day 21. The serum drug level from day 14 was used to determine the dose from day 22 forward. Serum drug levels were obtained at weeks 2, 3, 4, 6, 8, 11, 14, and 17.

The nonblinded medical monitor used the serum drug levels and side effects data to adjust the dosage so the nortriptyline level was 50 to 150 ng/mL, with the optimal level defined as 80 to 120 ng/mL. A level:dose ratio was used to calculate the dose needed to achieve the desired serum level range. The level:dose ratio was constant across time and served as a measure of compliance.[17]

Starting at week 17, the study drug dose was tapered at a rate of 33% per week. The medication phase of the study terminated at week 20 postpartum. The blind was continued until the end of the entire study for staff.

Definition of Recurrence

During the RCT, the HAM-D and Bech-Rafaelsen Mania Scale (BRMS)[18] were given weekly. When a subject reported symptoms of depression, she was evaluated twice within a 7-day period. If the subject met RDC for definite major depression and had a HAM-D severity score ≥ 15 on both occasions, she was evaluated by the principal investigator and a board-certified psychiatrist not affiliated with the study. If both evaluators diagnosed major depression, the subject was identified as having a recurrence. A similar procedure was used to assess for emergent mania according to RDC and a score of 10 or greater on the BRMS.

Data Analyses

Subjects who took at least one dose of study drug and completed any assessments were included in analyses. Primary outcomes were recurrence, time to recurrence, and HAM-D scores during the 17-week trial. Power statements for proportion recurring were done with exact binomial probabilities. StatXact3 software (Cytel Software, Cambridge, Mass.) was used for these analyses.

The proportion of subjects who suffered recurrences in each treatment group was compared with the Fisher exact test. The time to recurrence was assessed with exact log-rank tests. Data from subjects who withdrew from the study were censored at the week they withdrew. Analyses of serial HAM-D scores for the women who did not become depressed during the 17-week trial were conducted with random effects regression. Random effects regression was done with the noncompliers both included and removed from the analysis the first week their serum nortriptyline levels were < 50 ng/mL. Number of weeks from birth was modeled as a continuous variable with backward stepping procedures with drug status; linear, quadratic, and cubic time measures; and the interactions of time measures and drug status. The effect of previous depression (in addition to PPMD) and the interaction of drug status and previous depression were assessed with exact log-rank statistics. We tested the effect of previous non-postpartum major depression on time to recurrence and as a main effect in the serial random effects regression for HAM-D scores.

RESULTS

Subject Disposition

We interviewed 121 women eligible for the protocol, and 56 participated. No significant demographic differences were found between the groups of women randomly assigned to nortriptyline or placebo. The mean ± SD HAM-D score for the previous episode of PPMD was 28.0 ± 5.7 (range, 17–40), and the mean HAM-D score at 9 months of the index pregnancy was 4.0 ± 2.5 (range, 2–12). Of the 56 subjects, 4 declined to take the study drug after randomization. One subject (randomly assigned to nortriptyline) developed mania in the first postpartum week.

Data for the clinical trial are derived from 51 subjects: 26 who received nortriptyline and 25 who received placebo. Four subjects withdrew from the protocol. Three subjects assigned to placebo withdrew because of side effects, personal reasons, and pregnancy at 4, 10, and 14 weeks, respectively. One subject assigned to nortriptyline was lost to follow-up at week 14. There was no difference in time to withdrawal of subjects in the nortriptyline or placebo groups (exact Savage test = 0.05, p = .91, df = 1).

Nortriptyline was well tolerated by the subjects. Only 1 symptom (constipation) was reported significantly more frequently and at higher levels of severity in subjects who took nortriptyline compared with those who took placebo (78% vs. 22%; Fisher exact p ≤ .00).

Treatment Outcome

The mean ± SD time from birth to first dose was 10.6 ± 5.7 hours (range, 1–22 hours). The mean serum drug level for the nortriptyline-treated women across the study period was 83 ng/mL.

We found no difference in the rate of recurrence in women treated preventively with nortriptyline compared with those treated with placebo (Fisher exact p = 1.00). Of the sample of 51 women, there were 12 recurrences in the 17-week preventive treatment period. Of 26 subjects who took nortriptyline, 6 (0.23, 95% exact confidence interval [CI] = 0.09 to 0.44) suffered recurrences. Of 25 subjects who took placebo, 6 (0.24, 95% exact CI = 0.09 to 0.45) suffered recurrences.

The time to postpartum recurrence ranged from 1 to 16 weeks. Five recurrences occurred within the first 2 weeks, and the remaining 7 were spaced across weeks 6 to 16. Of the 5 early recurrences, 3 subjects were randomly assigned to nortriptyline and 2 to placebo. As depicted in Figure 2, the time to recurrence did not differ between the nortriptyline and placebo treatments (exact log-rank ≤ 0.00, exact p = .83). There was also no difference in time to recurrence between nortriptyline and placebo when stratified by presence of non-postpartum depressive episodes (exact log-rank ≤ 0.00, exact p = .83).

Five subjects who took nortriptyline were defined as noncompliant (serum nortriptyline level < 50 ng/mL). Censoring of these subjects at the time of noncompliance did not change the results of the recurrence analysis (exact log-rank < 0.00, p = .83).

Women who did not fit criteria for PPMD did not have fewer depressive symptoms in the nortriptyline group compared with the placebo group. The model that emerged of 39 women with 638 observations of serial HAM-D scores contained significant time effects and time-by-drug status interactions. With these interactions in the model, the effect of drug status was not significant (β = 2.08, 95% CI = –0.57 to 4.74, p = .13).

During the final 32 weeks of the protocol, 6 subjects suffered recurrences. Following the end of the drug taper at week 20, 1 woman who took nortriptyline had a recurrence of depression. Between weeks 20 and 28, 4 subjects developed depression (3 who had taken nortriptyline and 1 who took placebo). At 52 weeks postpartum, 1 woman who had been taking placebo had a recurrence.

We monitored the adequacy of the blind. Except for the nurse who monitored side effects (κ = 0.47, p = .01), none of the other personnel were more successful than chance at identifying the drug assignment (κ from –0.02 to 0.18).

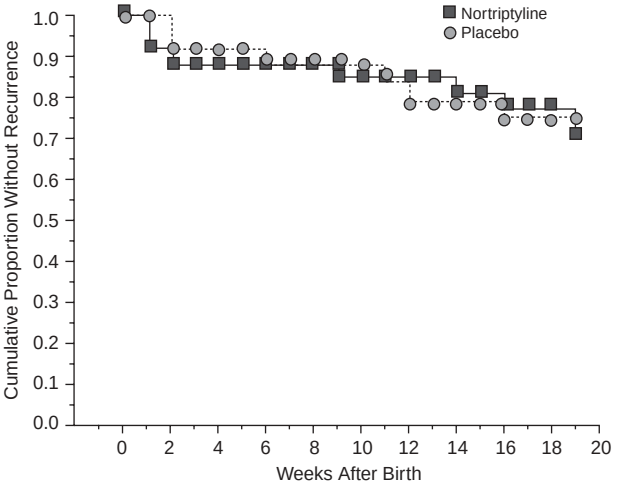
COMMENT

We found that the rate of recurrence of PPMD was unacceptably high, with one fourth of women developing depression, similar to Davidson and Robertson's risk estimate.[2] Contrary to our hypothesis, nortriptyline did not confer additional preventive efficacy beyond that of placebo. Women who have had PPMD alone or PPMD plus other depressive episodes had the same risk for postpartum recurrence. We planned an interim analysis of the data because the difference in recurrence rates between preventively treated (0.07) compared with monitored (0.63) subjects was large in our preliminary study.[9] If these rates had been replicated in our RCT, enrolling the entire sample would have been unethical because the sample size (N = 104) was based on conservative recurrence estimates (0.39 in the placebo group and 0.13 in the nortriptyline group).

However, the recurrence rates of the 2 groups were so similar that there was essentially no likelihood that true differences exist. There is less than a 2 in 100 chance that the true rate of recurrence with nortriptyline treatment is 0.09 with recurrence in the placebo group of 0.24 (a 15% difference). Alternatively, there is a 9 in 100 chance that the recurrence rate in women treated with placebo is 15% higher (estimated at 0.38) than the observed rate in women treated with nortriptyline (0.23). The equivalence of the HAM-D scores in both treatment groups supports our conclusion that postpartum nortriptyline treatment confers no additional preventive efficacy beyond that of placebo for PPMD. We concluded that our original hypotheses had been adequately tested and stand as a completed negative study.

Why does nortriptyline treatment fail to protect against development of major depression in the postpartum period? The differences between the findings of this RCT and our pilot study[9] warrant consideration. In the pilot study, each subject received the medication to which she had responded for past episodes. Perhaps this individual tailor-

Figure 2. Proportion of Women With Postpartum Depression



ing of pharmacotherapy yielded a more effective preventive strategy than our single-drug–constrained RCT.

The bias inherent in our nonblind pilot trial probably contributed to the difference in recurrence risk compared with the RCT. The separation of the side effect reviews from the primary outcome assessments was an important methodological advance in our RCT. The nurse who evaluated side effects was able to guess the drug assignment consistently better than chance, unlike staff blind to side effects.

Five of our 12 subjects who suffered recurrences became depressed within the first 2 weeks postpartum. We are continuing our investigations with a selective serotonin reuptake inhibitor (SSRI). An SSRI was chosen because minimal initial dose titration is required. SSRIs (but not TCAs) directly alter the activity of neurosteroidogenic enzymes in the brain, which may be an important mechanism related to response.[19] For PPMD, treatment response to a TCA may be less robust than to an SSRI.[20]

What should the clinician recommend to a pregnant woman who has had PPMD? Because of the risk for recurrence in this population, the minimum standard of care should be monitoring for PPMD with treatment upon recurrence. If pharmacologic prevention is instituted, the drug to which the subject has previously responded or an SSRI is a reasonable choice.

Drug name: nortriptyline (Pamelor and others).

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