Paroxetine CR Augmentation for Posttraumatic Stress Disorder Refractory to Prolonged Exposure Therapy

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Objective: Little is known about the efficacy of "next step" strategies for patients with posttraumatic stress disorder (PTSD) who remain symptomatic despite treatment. This study prospectively examines the relative efficacy of augmentation of continued prolonged exposure therapy (PE) with paroxetine CR versus placebo for individuals remaining symptomatic despite a course of PE.

Method: Adult outpatients meeting DSM-IV criteria for PTSD were recruited from February 2003 to September 2005 at 4 academic centers. Phase I consisted of 8 sessions of individual PE over a 4- to 6-week period. Participants who remained symptomatic, defined as a score of ≥ 6 on the Short PTSD Rating Interview (SPRINT) and a Clinical Global Impressions-Severity of Illness scale (CGI-S) score ≥ 3, were randomly assigned to the addition of paroxetine CR or matched placebo to an additional 5 sessions of PE (Phase II).

Results: Consistent with prior studies, the 44 Phase I completers improved significantly with initial PE (SPRINT: paired $t = 7.6$, $df = 41$, $p < .0001$; CGI-S: paired $t = 6.37$, $df = 41$, $p < .0001$). Counter to our hypothesis, however, we found no additive benefit of augmentation of continued PE with paroxetine CR compared to pill placebo for the 23 randomly assigned patients, with relatively minimal further gains overall in Phase II.

Conclusion: Although replication with larger samples is needed before definitive conclusions can be drawn, our data do not support the addition of paroxetine CR compared with placebo to continued PE for individuals with PTSD who remain symptomatic after initial PE, suggesting that the development of novel treatment approaches for PTSD refractory to PE is needed.

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Posttraumatic stress disorder (PTSD) is common in the general population, with a lifetime prevalence of about 8% and a 12-month prevalence of 3.5% in the United States.[1,2] PTSD is associated with marked symptomatic distress as well as significant impairment, dysfunction, and reduction in overall quality of life.[3] Both pharmacotherapy with selective serotonin reuptake inhibitors (SSRIs), including paroxetine,[4–6] and psychosocial interventions such as prolonged exposure therapy (PE), a form of cognitive-behavioral therapy (CBT), have demonstrated efficacy for PTSD and may be considered first-line interventions.[7–12] Although these interventions can be helpful, many patients remain symptomatic despite initial treatment. There are few data available to guide practice regarding the efficacy of "next step" strategies for patients remaining symptomatic despite treatment. In this study we examine the relative efficacy of augmentation of continued PE with the SSRI paroxetine CR compared

to placebo for patients remaining symptomatic despite a brief and intensive course of PE, as developed by Foa and colleagues.[8,13]

We hypothesized that individuals who remained symptomatic after 8 sessions of PE would derive greater benefit from the addition of the SSRI paroxetine CR than the addition of placebo to an additional 5 sessions of PE administered once every 2 weeks.

METHOD

Adult outpatients meeting DSM-IV criteria for PTSD were recruited to 4 academic centers (Duke University Medical Center; Massachusetts General Hospital; University of California San Diego; University of Pennsylvania) from February 2003 to September 2005 through advertisement and clinical referral for participation in a 2-phase treatment trial. The initial phase (Phase I) consisted of eight 90- to 120-minute sessions over a 4- to 6-week period of individual PE. Participants who completed a minimum of 7 sessions of PE but remained symptomatic, defined as a score greater than or equal to 6 on the Short PTSD Rating Interview (SPRINT)[7] and a Clinical Global Impressions-Severity of Illness scale (CGI-S)[14] score greater than or equal to 3 as assessed by an independent evaluator at random assignment, were randomly assigned 1:1 to the addition of pharmacotherapy with paroxetine CR or placebo as augmentation to an additional 5 sessions of PE provided once every 2 weeks (Phase II). Random assignment was blocked on the basis of a CGI-S score of equal to 3 or greater than 3. The primary outcome measure was the clinician-rated SPRINT. The SPRINT is a well-validated, 10-item, clinician-administered questionnaire assessing the core symptoms of PTSD.[15] SPRINT responses for items 1 through 8 range from a score of 0 ("not at all") to 4 ("very much") and are summed, yielding a total score range of 0 to 32. The SPRINT is sensitive to change with treatment[15] and has been found to perform comparably to the longer Clinician-Administered PTSD Scale for DSM-IV.[16]

Eligible participants were men or women aged 18 years and older with a primary diagnosis of DSM-IV PTSD diagnosed by structured clinical interview by trained study investigators using the Mini-International Neuropsychiatric Interview (MINI).[17] Excluded were those with lifetime psychosis, schizophrenia, mental retardation, organic mental disorders, or bipolar disorder and those who in the past 6 months exhibited obsessive-compulsive disorder, eating disorders, cutting or other significant self-injurious behavior, alcohol/substance abuse disorders (other than nicotine), or current serious unstable medical illness. Also excluded were individuals with current compensation or legal actions related to the effects of the trauma, those with an ongoing relationship with their assailant (in the case of assault-related PTSD), those with a history of hypersensitivity or poor response to paroxetine IR or paroxetine CR, and pregnant or lactating women or those of childbearing age who were not using contraception. Sleep aids (trazodone, zolpidem, and zaleplon) were allowed, as long as the therapy had been initiated at least 2 months prior to random assignment and had been maintained at a constant dose for 4 weeks or longer prior to random assignment, with the dose held constant through the study. Use of other psychotropic medication during the course of treatment was prohibited. All participants provided written informed consent prior to participation. Participants were reimbursed $20 per visit (excluding the screening visit) for their time and effort in completing evaluations. The institutional review boards at each site approved identical study procedures.

Prolonged exposure therapy (PE) is an empirically supported, trauma-focused CBT[8,13] with large effects for PTSD across multiple studies.[10,18] A standard protocol developed by Foa was used[13,18] All therapists received certification in PE, including a 2-day training (by E.F. and colleagues) and completed 2 supervised and approved training cases prior to study participation.

In Phase II, participants were randomly assigned to paroxetine CR or matched pill placebo, which was initiated at 12.5 mg/day and flexibly titrated on the basis of efficacy and tolerability to a maximum of 62.5 mg/day for 10 weeks. Randomly assigned patients received medication management by a study psychiatrist during 10- to 20-minute sessions weekly for the first 2 weeks and once every 2 weeks thereafter. Primary efficacy evaluations were performed by a rater blind to treatment assignment at baseline, at the conclusion of intensive PE treatment (randomization week), and at weeks 4, 8, and 10 of randomized pharmacotherapy (Phase II). Safety assessments performed at each visit included reporting of adverse events and measurement of vital signs.

Statistical Methods

This pilot study was designed to generate effect sizes, which were calculated along with traditional statistical testing. Primary analyses were of the intent-to-treat (ITT) sample, defined as those with at least 1 postrandomization assessment, with the last observation carried forward. The Fisher exact test was used for the assessment of categorical variables such as gender and remission. Paired t tests were employed for examination of change in Phase I, and nonpaired t tests were used to examine group differences in continuous variables in Phase II. All tests were 2-sided, and α was set at 0.05.

RESULTS

Open Prolonged Exposure Therapy (Phase I)

Seventy-eight individuals signed informed consent, and 68 met study criteria and went on to receive at least 1

Table 1. Characteristics at Phase II Baseline for Intent-to-Treat Sample (N = 23)[a]

Characteristic	Paroxetine CR (N = 9)	Placebo (N = 14)
Age, mean ± SD, y	47.8 ± 11.4	44.2 ± 15.9
Sex, %		
Female	44	64
Race/ethnicity, %		
White	71	78
Index trauma, %		
Physical and/or sexual abuse	89	57
Exposure to war	0	14
Physical accident and/or medical trauma	11	29
Comorbidity, %		
At least 1 mood or anxiety disorder	89	79
Major depressive disorder	33	64

[a]There were no significant differences between groups.

Table 2. Treatment Response for Intent-to-Treat Sample (N = 23)[a]

Measure	Paroxetine CR (N = 9) Mean ± SD	Placebo (N = 14) Mean ± SD	t (df)
Severity at random assignment			
CGI-S	4.11 ± 1.05	4.00 ± 0.82	–0.28 (20)
SPRINT	16.11 ± 8.99	17.00 ± 7.65	–0.25 (21)
Phase II improvement[b]			
SPRINT reduction	2.33 ± 5.24	4.57 ± 7.24	–0.80 (21)
CGI-S reduction	0.78 ± 1.30	1.00 ± 0.82	–0.49 (20)
CGI-I score	2.33 ± 1.22	2.08 ± 0.95	–0.55 (20)

[a]There were no significant differences between groups.
[b]Data are missing for 1 patient in the placebo group for the CGI-S reduction and the CGI-I score.
Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, PTSD = posttraumatic stress disorder, SPRINT = Short PTSD Rating Interview.

session of PE. Of this group, the mean ± SD age was 41.75 ± 13.32 years (data missing for 1 patient), and 65% were female (N = 44). The sample was 59% (N = 40) white, 29% (N = 20) black, 6% (N = 4) Hispanic, and 4% (N = 3) Asian, with 1% (N = 1) identifying as *other*. Twenty-four participants (35%) began PE but dropped out prior to completion of Phase I. Reasons for treatment discontinuation included difficulty scheduling/coming to sessions (N = 6), loss to follow-up or unknown reason (N = 11), loss of interest (N = 1), noncompliance with protocol (N = 2), car accident (N = 1), and worsening symptoms (N = 2).

Primary outcome data for the 44 Phase I completers demonstrated a significant mean ± SD reduction of 9.86 ± 8.40 points on the SPRINT (mean ± SD baseline score = 22.32 ± 4.84, paired $t = 7.6$, $df = 41$, $p < .0001$), and a mean ± SD drop of 1.48 ± 1.50 points on the CGI-S (mean ± SD baseline score = 4.79 ± 0.75, paired $t = 6.37$, $df = 41$, $p < .0001$; data are missing for 2 patients). Seventeen patients (38.6% of completers) met study criteria for remission (SPRINT score < 6) after Phase I treatment and were not eligible for random assignment, while 2 eligible patients refused random assignment.

Paroxetine CR Augmentation of Prolonged Exposure Therapy (Phase II)

Twenty-five individuals who remained symptomatic after completing Phase I were randomly assigned to paroxetine CR (N = 11) or placebo (N = 14). Two randomly assigned patients did not initiate medication. Thus, for all analyses and according to protocol, the ITT sample consisted of 23 participants, 9 randomly assigned to paroxetine CR and 14 assigned to placebo augmentation of PE. The randomly assigned sample had a mean ± SD age of 45.61 ± 14.11 years, was composed of 56% (N = 13) women, and was predominantly white (74%; N = 17), with 13% (N = 3) black, 4% (N = 1) Asian, 4% (N = 1) Hispanic, and 4% (N = 1) other. At least 1 additional mood or anxiety disorder was present for 84% (N = 21) of Phase II participants. No significant differences in any assessed baseline characteristics (Table 1) or in the proportion with a CGI-S score greater than 3 (i.e., greater than mild: 66.7% vs. 69.2%) were present for the paroxetine CR and placebo groups, respectively (Table 2).

Twenty participants (87%) completed Phase II, with study discontinuations by participants taking placebo due to dizziness and nausea (N = 1) and noncompliance (N = 1), and 1 study discontinuation by a participant taking paroxetine CR due to a serious adverse event with inpatient psychiatric hospitalization for suicidal ideation believed unrelated to study participation for a patient with a prior history of suicidal ideation. The mean ± SD end point dose was 45.8 ± 16.5 mg/day (median = 50 mg/day, range = 12.5–62.5 mg/day) for paroxetine CR and 44.8 ± 15.5 mg/day (median = 44.2 mg/day, range = 25–62.5 mg/day; data missing for 2 patients) for placebo. In both the paroxetine CR and placebo groups, all participants reported at least 1 side effect. The 3 most common side effects for the paroxetine CR and placebo groups, respectively, were concentration and memory difficulties (89% vs. 85%), sleep disturbance (89% vs. 85%), and drowsiness (67% vs. 77%).

Univariate ITT analyses including those with at least 1 assessment while taking medication revealed no significant difference between paroxetine CR and placebo augmentation of continued PE on the SPRINT, the CGI-S, or the Clinical Global Impressions-Improvement (CGI-I: see Table 2). Effect size analyses revealed differences favoring placebo that were small based on Cohen's standards[19] (Cohen d for SPRINT = 0.35, Cohen d for CGI-S = 0.20). Of note, however, rates of remission (defined a priori as a SPRINT score less than 6 at end point) in this highly comorbid and treatment-refractory cohort were low (placebo augmentation, 14% [N = 2] vs. paroxetine CR aug-

mentation, 33% [N = 3]; Fisher exact test p = .343). A follow-up multiple regression analysis of Phase II end point SPRINT score, adjusting for possible confounding by age, sex, site, presence of current major depression, and Phase II randomization SPRINT score similarly revealed no significant association of paroxetine CR compared with placebo augmentation with Phase II end point (β [SE] = 2.11 [3.69], t = 0.57, p = not significant), with only SPRINT score at random assignment predictive of end point score in the model (β [SE] = 0.65 [0.26], t = 2.53, p = .025).

DISCUSSION

Consistent with prior studies,[10,18] patients with PTSD improved significantly after completing 8 sessions of PE, with more than one third of participants reaching remission in this brief treatment phase. Counter to our hypothesis, however, we found no additive benefit of augmentation of continued PE with paroxetine CR compared to pill placebo; in fact, effect sizes were small and favored placebo. Attempts to draw conclusions regarding the relative efficacy of the interventions must be tempered by the relatively small sample size and power of this pilot study, and future research with larger samples is necessary to more definitively address this issue. For example, although remission rates did not significantly differ and were low for both groups, similar differences in proportions (i.e., 33% for paroxetine CR vs. 14% for placebo), if replicated in a larger study, might reach statistical significance. Further, there was no formal assessment of treatment compliance. Paroxetine CR dosing was flexible but achieved only moderate levels (mean = 46 mg/day) in this trial; it is unknown whether higher dosing would have resulted in greater treatment response. It should be noted, however, that the majority of improvement in PTSD symptomatology occurred during Phase I initial intensive PE, with relatively minimal further gains in Phase II overall despite low rates of study discontinuation in participants taking paroxetine CR (11%) and placebo (14%).

One possible contributor to the poor overall efficacy in Phase II may be the reduction in PE frequency and intensity that occurred concurrent with pharmacotherapy initiation: PE decreased from twice weekly to once every 2 weeks. While our study does not provide data regarding mechanism of action, and additional research examining this issue is needed, it is also possible that the antidepressant itself interfered with PE learning or retention. It has been proposed that medication use (and potentially awareness due to side effects) may provide an internal context that interferes with fear-extinction learning, similar to context-dependent learning effects in animal models and also that potentially reducing activation of fear memories during exposure therapy with medications may interfere with emotional processing and safety learning.[20–22]

In addition, the inclusion of only individuals who agreed to and completed an intensive 8-session course of PE yet did not achieve full response may have biased the sample toward those less likely to respond robustly to any additional intervention, including medication; nonetheless, this treatment-refractory clinical population is precisely the one for which additional effective intervention is needed.

The failure to find additional benefit for augmenting continued PE with SSRI pharmacotherapy stands in contrast to some reports of the potentially salutary effects of adding exposure-based CBT to pharmacotherapy.[23,24] One small study (N = 10) examined the addition of CBT to the SSRI sertraline compared to sertraline alone for Cambodian refugees with PTSD previously refractory to pharmacotherapy and found that combined therapy was suggestive of added benefit on the order of medium to large effect sizes.[23] Rothbaum and colleagues[24] recently reported a randomized, controlled trial of 10 twice-weekly sessions of PE augmentation of sertraline compared to continued sertraline alone for 65 individuals with PTSD who remained symptomatic after 10 weeks of open-label sertraline flexibly dosed to 200 mg/day. The addition of PE was associated with some benefit, but only in secondary analyses of a subgroup that had a partial response to medication and not those with an excellent pharmacotherapy response. Further, in contrast to the current study, which included all patients not remitted in Phase I, only those with some initial medication response (at least 20%) were eligible for random assignment to PE augmentation. In addition, Schnurr and colleagues[25] recently reported significantly greater response to PE than present-centered psychotherapy in 284 female veterans or active duty military with predominantly sexual trauma. However, this effect was not significant over time and at poststudy and 3-month follow-up represented small effect sizes (d = 0.29 and d = 0.24, respectively). It is worth noting that 73% to 76% of participants were taking a variety of psychiatric medications at baseline, and while change in dose or addition of new antidepressants occurred more commonly in the control group (29% vs. 15%) and did not impact outcomes, the impact of the presence or absence of psychiatric medication overall on therapy outcome was not reported.

Studies of initial combined CBT-based psychotherapy and pharmacotherapy are not currently available for PTSD, but data from another fear-based disorder, panic disorder, suggest some early benefit for combined treatment but a possible interference of medication with long-term efficacy of CBT for panic disorder.[26–29] Little to no benefit for initial simultaneous CBT and SSRI (over either treatment alone) was evident, however, in a trial of social anxiety disorder.[30] Empirically supported psychotherapies such as PE and SSRI antidepressants such as paroxetine each remain first-line clinical options for

patients with PTSD,[9–12] with initial treatment selection often based on factors such as treatment availability and patient preference.

There remains a paucity of data examining and supporting combined treatment for PTSD, particularly in the setting of PE partial or nonresponse. However, the significant morbidity and attendant distress and disability experienced by those with PTSD and the persistence of disorder in many despite standard treatments underscores the need for additional research with large, adequately powered studies to examine the individual and combined effects of CBT and pharmacotherapy for PTSD, ideally identifying patient-specific predictors of response to each. Nonetheless, although replication with larger samples is needed before definitive conclusions can be drawn, our findings of poor response to an SSRI for the significant proportion of individuals with PTSD refractory to initial intervention with PE suggest that the development of novel treatment approaches for patients refractory to initial PE is needed.

Drug names: paroxetine (Paxil, Pexeva, and others), zaleplon (Sonata), zolpidem (Ambien and others).

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