Six-Month Outcomes From a Randomized Trial Augmenting Serotonin Reuptake Inhibitors With Exposure and Response Prevention or Risperidone in Adults With Obsessive-Compulsive Disorder

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ABSTRACT

Objective: To compare outcomes after 6-month maintenance treatment of adults diagnosed with obsessive-compulsive disorder (OCD) based on DSM-IV criteria who responded to acute treatment with serotonin reuptake inhibitors (SRIs) augmented by exposure and response prevention (EX/RP) or risperidone.

Method: A randomized trial was conducted at 2 academic sites from January 2007 through December 2012. In the acute phase, 100 patients on therapeutic SRI dose with at least moderate OCD severity were randomized to 8 weeks of EX/RP, risperidone, or pill placebo. Responders entered the 6-month maintenance phase, continuing the augmentation strategy they received acutely (n = 30 EX/RP, n = 8 risperidone). Independent evaluations were conducted every month. The main outcome was the Yale-Brown Obsessive Compulsive Scale (Y-BOCS).

Results: Intent-to-treat analyses indicated that, after 6-month maintenance treatment, EX/RP yielded OCD outcomes that were superior to risperidone (Y-BOCS = 10.95 vs 18.70; t<sub>40</sub> = 2.76, P = .009); more patients randomized to EX/RP met response criteria (Y-BOCS decrease ≥ 25%: 70% vs 20%; P < .001) and achieved minimal symtoms (Y-BOCS ≤ 12: 50% vs 5%; P < .001). During maintenance, OCD severity decreased slightly in both conditions (Y-BOCS decrease = 2.2 points, P = .020). Lower Y-BOCS at entry to maintenance was associated with more improvement in both conditions (r<sub>38</sub> = 0.57, P < .001).

Conclusions: OCD patients taking SRIs who responded acutely to antipsychotics alone, because both groups received EX/RP, the study could not ascertian the long-term effects of augmenting SRIs with antipsychotics alone. To compare the long-term effects of EX/RP versus risperidone augmentation, we analyzed data from a trial that randomized 100 OCD adults receiving SRIs to EX/RP,
While serotonin reuptake inhibitors (SRIs) are the only medications approved by the US Food and Drug Administration to treat obsessive-compulsive disorder (OCD), many SRI-treated patients remain quite symptomatic. For partial SRI responders, practice guidelines recommend adding either exposure and response prevention (EX/RP) or antipsychotics (eg, risperidone). The results of this study strongly support augmenting SRIs with EX/RP rather than with risperidone in adults with OCD. The results also suggest that extending EX/RP beyond the 17 acute treatment sessions (up to 30 sessions) helps many patients maintain their gains.

risperidone, or pill placebo. After 8 weeks of acute treatment, EX/RP was superior to both risperidone and pill placebo. Responders then continued to receive their assigned treatment for an additional 6 months. We hypothesized that after the 6-month maintenance phase, patients randomized to EX/RP would have a superior OCD outcome to those randomized to risperidone.

**METHOD**

**Setting**

Data came from a randomized controlled trial conducted at 2 academic outpatient clinics in Philadelphia, Pennsylvania, and New York, New York. Study details appear elsewhere. Enrollment began in January 2007; data collection ended in December 2012. Each site’s institutional review board approved the study. Participants provided written informed consent prior to entry. The study was registered on ClinicalTrials.gov (identifier: NCT00389493).

**Participants**

Eligible participants were adults (18–70 years) with a principal diagnosis of OCD (≥ 1 year), who were receiving an SRI at a stable dose for at least 12 weeks and yet remained symptomatic (Yale-Brown Obsessive Compulsive Scale [Y-BOCS] score ≥ 16). Exclusion criteria included bipolar and psychotic disorders, substance abuse or dependence in the past 3 months, prominent suicidal ideation, a 17-item Hamilton Depression Rating Scale (HDRS) score indicating severe depression (> 25), or hoarding as the only OCD symptom. Other Axis I diagnoses were permitted if OCD was the most severe and impairing. Patients were excluded if they had previously received risperidone (≥ 0.5 mg/d for 8 weeks) or EX/RP (≥ 8 sessions over 2 months) while taking an SRI (as described above) or were receiving their first SRI with no response, as practice guidelines recommend switching to another SRI in such cases. Trained clinicians determined eligibility. Trained raters with expertise in OCD and related disorders confirmed psychiatric diagnoses prior to study entry using the Structured Clinical Interview for DSM-IV. Treatment history was confirmed with the referring clinician and/or chart review.

**Study Procedures**

During the acute phase, 100 adults with OCD on a stable SRI dose were randomized to augmentation by EX/RP (n = 40), risperidone (n = 40), or pill placebo (n = 20) (Figure 1). Patients randomized to EX/RP saw a study therapist for 2 planning/introductory sessions and 15 twice-weekly 90-minute EX/RP sessions and met with a study psychiatrist for SRI maintenance at weeks 0, 4, and 8. Those randomized to risperidone or pill placebo met with a study psychiatrist at weeks 0, 1, 2, 3, 4, 6, and 8.

Responders at week 8 (Y-BOCS score decrease ≥ 25%) were eligible to enter the 6-month maintenance phase; nonresponders were referred for open treatment. During maintenance, responders continued their SRI at the same dose (meeting monthly with their study psychiatrist) and the augmentation strategy to which they were originally assigned (EX/RP with their study therapist or risperidone). For EX/RP patients, maintenance sessions included exposures, ritual prevention (following standard procedures), and instruction in relapse prevention. The length and frequency of maintenance EX/RP sessions depended upon the patient’s OCD severity. Patients who achieved minimal symptoms at the end of the acute phase (Y-BOCS score ≤ 12) received 4 weekly 45-minute sessions followed by 45-minute sessions every other week for the duration of the maintenance phase. The remaining patients received 90-minute EX/RP sessions twice-weekly until they achieved minimal symptoms (Y-BOCS score ≤ 12) or had received 15 additional 90-minute EX/RP sessions. Subsequently, patients received 4 weekly 45-minute sessions followed by one 45-minute session every other week until the end of the maintenance phase. Risperidone patients received ongoing risperidone, with the intent of maintaining the same dose used during the acute phase. Consistent with clinical practice, however, medication decreases for side effects and increases for OCD symptom exacerbations were allowed if the dose stayed between 0.5 and 4.0 mg/d, reflecting doses used in prior risperidone augmentation studies in OCD.

**Assessments**

Sociodemographic features and treatment history were assessed at baseline. Independent evaluators (IEs), blind to treatment, evaluated patients every 4 weeks during the acute (weeks 0, 4, 8) and maintenance phases (weeks 12, 16, 20, 24, 28, 32). The IE training included reviewing tapes of senior IEs conducting evaluations, rerating these tapes with a goal of achieving at least 90% agreement with the original ratings, and observing at least 2 live evaluations by senior IEs. In addition, IEs conducted at least 2 evaluations with the senior IE in the room, with the goal of achieving at least 90% agreement with the senior IE. During the study, IEs audiotaped their assessments, and these were sent to the IE supervisor (J.D.H.) for review. Independent evaluators at each site conducted ongoing reliability meetings for the Y-BOCS in which all the IEs rated the audiotaped assessments. Ratings were compared afterward and any divergences were resolved. In addition, IEs from both sites met with the IE
supervisor in person or by conference call twice per year, and taped interviews from each site were formally rated by all IEs to assess interrater and cross-site reliability, and any points of divergence were resolved. Intraclass correlations (ICCs) between IEs were extremely high (eg, Y-BOCS ICC = 0.99; 95% CI, 0.97–1.00).

Independent evaluators administered the Y-BOCS to assess OCD severity, the 17-item HDRS to assess depressive severity, and the Brown Assessment of Beliefs Scale (BABS) to assess degree of insight about the main OCD belief. Every 4 weeks, patients also completed the Quality of Life Enjoyment and Satisfaction Questionnaire—Short Form (QLESQ), the Social Adjustment Scale—Self-Report (SAS-SR), and the Obsessive-Compulsive Inventory-Revised (OCI-R).

Study psychiatrists assessed side effects at each visit using a modified version of the Systemic Assessment for Treatment-Emergent Events that included 26 items (each rated absent, mild, moderate, or severe). Vital signs and weight were measured at each visit; height was measured at baseline and used to calculate body mass index (kg/m²). Psychiatrists assessed tics using the Yale Global Tic Severity Scale at baseline, and extrapyramidal symptoms using the Simpson–Angus Scale and Barnes Akathisia Rating Scale at each visit, and the Abnormal Involuntary Movement Scale at weeks 0 and 8.

Details about the training of study staff and the reliability of assessments are provided elsewhere.

Data Analysis
While focusing on the maintenance phase, we included all randomized participants in our primary analyses, since those who entered maintenance did not constitute a randomized sample and therefore would render the results uninterpretable. Of the 20 placebo participants, only 3 were acute-phase responders, and 2 entered maintenance. Thus, the analyses focus on the 80 participants originally randomized to EX/RP or risperidone augmentation.

The primary outcome was the Y-BOCS, which was analyzed using linear mixed models (LMMs). Linear mixed models allow the inclusion of all subjects, irrespective of missing data. Importantly, LMMs are particularly suitable for analyzing maintenance trials such as ours because they produce accurate and unbiased results when data are missing due to patients being dropped because of nonresponse to treatment. Indeed, studies show that LMMs accurately estimate the results for the entire initial randomized sample, even when almost 90% of subjects are dropped from the study due to nonresponse to treatment, and even when sample sizes are very small.

Two separate LMMs were employed. To estimate the mean values at each assessment point, our first LMM used indicator variables to code each assessment point. This model freely estimates each mean value at each assessment without constraining it to fit any particular growth curve model. To estimate the slopes of Y-BOCS change, our second LMM used a linear piecewise growth curve model, allowing the slopes to change from the acute to the maintenance phase (see Figure 2). As preliminary analyses showed treatment site was unrelated to outcome (P values > .184), it was dropped from further analyses.

As secondary analyses, a Fisher exact test examined the proportion in each treatment group who met response criteria at the end of maintenance (Y-BOCS score decrease ≥ 25%) or excellent response criteria (Y-BOCS score ≤ 12), thereby using the criteria employed in prior studies to enable direct comparison for these analyses, the last available observation was used. The LMMs were used to examine outcomes from our secondary measures (SAS-SR, QLESQ, HDRS, BABS, and OCI-R). The significance level for all tests was α = .05.

RESULTS
Sample
As shown in Figure 1, of the 100 patients randomized, 44 patients were judged responders (Y-BOCS decrease ≥ 25%) at the end of the acute phase. Forty entered the maintenance phase (n = 30 EX/RP, n = 8 risperidone, n = 2 placebo), and 31 completed it (n = 28 EX/RP, n = 3 risperidone, n = 2 placebo). The reasons for dropout are detailed in Figure 1.

Demographic and clinical characteristics of the 30 EX/ RP and 8 risperidone patients who entered maintenance are presented in Table 1; the proportion who completed maintenance was significantly higher in EX/RP than in risperidone (P = .01). Of the risperidone patients, 4 continued on the same dose they were receiving at the end of the acute phase; 4 decreased their dose during maintenance to reduce side effects. The final mean risperidone dose of these 8 patients was 1.47 mg/d (SD = 0.91; range, 0.5–3.0). Twenty of the 30 EX/RP patients who entered maintenance received additional 90-minute sessions (mean = 10.30, SD = 4.64; range, 1–15); 7 received the maximum 15 sessions.

Primary Outcome: Y-BOCS
Y-BOCS over time. At the end of maintenance treatment, patients originally randomized to acute EX/RP augmentation had significantly lower mean Y-BOCS scores than those originally randomized to risperidone (Table 2; β = 7.75, t40 = 2.76, P = .009, d = 0.87). However, during maintenance, the groups did not significantly differ from one another with respect to change in Y-BOCS score (Figure 2; β = 0.12, t33 = 1.11, P = .276, for the treatment × time interaction during maintenance). During maintenance, both groups showed a small, statistically significant Y-BOCS improvement (β = −0.09, t26 = −2.47, P = .020, d = 0.24) of 2.2 points.

Exploratory analyses indicated that Y-BOCS change during maintenance was significantly related to Y-BOCS at entry to maintenance, with lower Y-BOCS associated with faster Y-BOCS decreases in both conditions (r18 = 0.57, P < .001). A post hoc cluster analysis of Y-BOCS slopes during maintenance, Y-BOCS severity at entry to maintenance, and amount of therapy received during maintenance suggested a complex relationship between amount of maintenance EX/RP treatment in minutes (summing 45- and 90-minute sessions) and maintenance outcome: those who improved the most during maintenance (Y-BOCS slope, mean = −0.20) had...
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Figure 1. Flowchart of Patients in Study

Table 1. Characteristics of Entrants to the Maintenance Phase

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Exposure and Response Prevention (n = 30)</th>
<th>Risperidone (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>34.47 (13.09)</td>
<td>42.25 (11.73)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>17 (57)</td>
<td>4 (50)</td>
</tr>
<tr>
<td>White, n (%)</td>
<td>28 (93)</td>
<td>8 (100)</td>
</tr>
<tr>
<td>Marital status, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>17 (57)</td>
<td>3 (38)</td>
</tr>
<tr>
<td>Married-partnered</td>
<td>11 (37)</td>
<td>3 (38)</td>
</tr>
<tr>
<td>Divorced-separated</td>
<td>2 (7)</td>
<td>2 (25)</td>
</tr>
<tr>
<td>Y-BOCS score, mean (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 0</td>
<td>27.50 (3.88)</td>
<td>24.13 (4.29)</td>
</tr>
<tr>
<td>Week 8</td>
<td>11.67 (5.36)</td>
<td>11.13 (6.71)</td>
</tr>
<tr>
<td>HDRS score, mean (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 0</td>
<td>6.87 (5.18)</td>
<td>10.00 (6.09)</td>
</tr>
<tr>
<td>Week 8</td>
<td>4.30 (3.71)</td>
<td>5.13 (3.23)</td>
</tr>
</tbody>
</table>

Abbreviations: HDRS = Hamilton Depression Rating Scale, Y-BOCS = Yale-Brown Obsessive Compulsive Scale.

minimal OCD symptoms at entry to maintenance (Y-BOCS score, mean = 8.60 [SD = 5.97]) and received a mean of 680 minutes (SD = 155) of maintenance treatment; those who improved less (Y-BOCS slope, mean = −0.05) had minimal OCD symptoms at entry (Y-BOCS score, mean = 8.67 [SD = 3.56]) but received less maintenance treatment than the former patients (mean = 255 minutes [SD = 203]); and those whose OCD symptoms did not change during maintenance (Y-BOCS slope, mean = 0) had the most OCD symptoms at entry to maintenance (Y-BOCS score, mean = 15.14 [SD = 3.18]) and received the most maintenance treatment (mean = 1,578 minutes [SD = 202]).

Response rates. By the end of maintenance treatment, significantly more patients originally randomized to EX/RP than to risperidone achieved response status (Y-BOCS score decrease ≥ 25%; 28 of 40 [70.0%] in EX/RP; 8 of 40 [20.0%] in risperidone; Fisher exact test, \( P < .001 \)), and significantly more patients randomized to EX/RP achieved minimal
Table 2. Outcomes Over Time From Augmenting Serotonin Reuptake Inhibitors

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Exposure and Response Prevention</th>
<th>Risperidone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 0</td>
<td>Week 8</td>
</tr>
<tr>
<td>Y-BOCS</td>
<td>27.18 (0.65)</td>
<td>13.17 (1.20)</td>
</tr>
<tr>
<td>SAS-SR</td>
<td>2.25 (0.07)</td>
<td>1.88 (0.07)</td>
</tr>
<tr>
<td>QESQ</td>
<td>57.83 (2.38)</td>
<td>70.64 (2.25)</td>
</tr>
<tr>
<td>HDRS</td>
<td>7.80 (0.91)</td>
<td>4.64 (0.78)</td>
</tr>
<tr>
<td>BABS</td>
<td>6.13 (0.68)</td>
<td>2.53 (0.57)</td>
</tr>
<tr>
<td>OCI-R</td>
<td>29.20 (1.92)</td>
<td>11.49 (0.95)</td>
</tr>
</tbody>
</table>

*Estimated mean (SE) values from linear mixed models (see text) using all patients randomized to exposure and ritual prevention (n = 40) and all randomized to risperidone (n = 40). Patients randomized to exposure and ritual prevention had significantly better week 32 scores than patients randomized to risperidone on the Y-BOCS and all secondary outcomes, except the BABS.

Abbreviations: BABS = Brown Assessment of Beliefs Scale, HDRS = Hamilton Depression Rating Scale, OCI-R = Obsessive-Compulsive Inventory-Revised, QLESQ = Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form, SAS-SR = Social Adjustment Scale—Self-Report, SE = standard error, Y-BOCS = Yale-Brown Obsessive Compulsive Scale.

**DISCUSSION**

This article describes 6-month outcomes after augmenting SRIs with EX/RP or risperidone in adults with OCD. Exposure and ritual prevention augmentation was superior to risperidone augmentation in reducing OCD and depression severity and improving quality of life and functioning not only after acute treatment but also at 6 months following acute treatment. By the end of maintenance, 50% of patients initially randomized to EX/RP augmentation achieved minimal OCD symptoms compared to 5% of those randomized to risperidone augmentation. These data support using EX/RP over antipsychotics for augmenting SRIs in OCD.

To our knowledge, this is the only study to systematically investigate the long-term outcome of augmenting SRIs with antipsychotics in OCD. Contrary to our expectations, few patients responded acutely to risperidone (9 of 40), and 8 agreed to enter maintenance. Although these 8 maintained their OCD gains as long as they were assessed, 5 did not complete maintenance due to intolerable side effects or increased depression. Thus, risperidone, albeit acutely efficacious for some, was not very effective over time in our sample. The 3 who completed maintenance were receiving risperidone doses (0.5, 0.75, and 1.0 mg/d) below the mean maximum dose during the acute (2.2 mg/d) or maintenance phases (1.5 mg/d). Low risperidone doses may increase long-term tolerability.

It is important to note that those who responded to augmenting SRIs with EX/RP were likely to maintain their gains (or slightly improve) for an additional 6 months with maintenance treatment. Thus, even though EX/RP treatment yielded very substantial acute improvement, there was no evidence of a tendency to regress or rebound during maintenance. This result is consistent with our data from a prior randomized trial in which patients responding to symptoms (Y-BOCS score ≤ 12: 20 of 40 [50.0%] in EX/RP; 2 of 40 [5.0%] in risperidone; Fisher exact test P < .001). However, of the 30 EX/RP and 8 risperidone responders who entered maintenance, the proportion who maintained their response status did not significantly differ by treatment (28 of 30 [93.3%] in EX/RP; 8 of 8 [100%] in risperidone; Fisher exact test, P = .619).

**Secondary Outcomes: Change in Secondary Measures Over Time**

At the end of maintenance treatment, patients originally randomized to EX/RP had significantly more improvement than patients randomized to risperidone on all secondary outcomes, including measures of depression, functioning, and quality of life (P values < .047, d values = 0.64–1.16), except the BABS, a measure of insight (P = .128; see Table 2). Notably, during maintenance, there were no group differences in the rates of change over time on any of the secondary outcomes (all P values > .207 for the treatment × time interactions). The slopes of improvement during maintenance for both treatment conditions were significant (small to medium in size) for all secondary outcomes (P values < .047, d values = 0.19–0.52), with the exception of the QLESQ (P = .183).
augmenting SRIs with EX/RP were followed for an additional 6 months. However, despite similar rates of acute response to EX/RP augmentation (80% in the current trial and 74% in the earlier trial), more patients in the current trial met response criteria after 6 months of maintenance (70% versus 41%) and achieved minimal symptoms (50% versus 24%). Differences in study designs may explain the disparity: patients in the current study received more frequent 45-minute maintenance sessions (twice monthly versus once monthly) and could also receive up to 15 additional 90-minute EX/RP sessions during maintenance if they did not achieve minimal OCD symptoms after the acute phase. This suggests that additional treatment may have helped some patients maintain their acute gains. Although the maintenance treatment in the current study is much more intensive (and hence more costly) than the maintenance treatment in the previous study, the superior 6-month outcomes observed in the current study may warrant the additional investment.

On average, patients randomized to EX/RP and risperidone augmentation exhibited continued improvement during maintenance on most outcomes, but these gains were clinically small. Thus, outcome at the end of the maintenance phase primarily reflected successful maintenance of acute response, regardless of the treatment received. Indeed, lower OCD severity at entry to maintenance was associated with better outcome in both conditions.

The lack of treatment group differences in the rate of improvement during maintenance in the present study was initially surprising, given that 20 of 30 EX/RP patients received additional 90-minute treatment sessions during maintenance. However, those who received additional 90-minute sessions were not a random sample: patients received these 90-minute sessions until they either achieved minimal symptoms or had 15 sessions. In fact, a post hoc analysis suggested a complex relationship between maintenance outcome and amount of maintenance EX/RP treatment received (summing 45- and 90-minute sessions): those whose OCD improved the most during maintenance had minimal OCD symptoms at entry to maintenance and received some maintenance treatment; those who improved less had minimal OCD symptoms at entry but received less maintenance treatment than the former; and those whose OCD symptoms did not change during maintenance did not achieve minimal symptoms by the end of the acute phase, continued to receive 90-minute EX/RP sessions, and thus received the most maintenance treatment. These findings suggest that achieving minimal OCD severity with acute treatment and receiving some maintenance therapy were both important ingredients for maximizing EX/RP long-term outcome. However, our study was not designed to investigate this issue prospectively. Future studies should also develop cost-effective methods for delivering EX/RP and should examine what factors determine who will benefit most from maintenance therapy.

This study has several limitations. The first is sample size. For ethical considerations, nonresponders to acute treatment were referred for other treatments. Thus, only 8 risperidone patients entered the maintenance phase, which calls for caution in generalizing the long-term outcome of risperidone from these data. Nevertheless, studies show that LMM growth models in which almost 90% of cases are dropped for nonresponse still produce unbiased and accurate estimates of the actual population parameters for the entire initial randomized sample. A second limitation is that the maintenance phase lasted only 6 months. However, it is difficult to control all treatment that patients receive over an extended period of time, which is why studies with longer follow-up periods adopt naturalistic designs. Finally, patients receiving EX/RP were not blind to their treatment and had more clinician contact than those receiving risperidone. Yet, our prior study that compared EX/RP augmentation to a psychotherapy control suggests that blindness to therapy and clinician contact alone cannot explain the superiority of EX/RP.

In summary, OCD patients receiving SRIs who responded acutely to EX/RP or risperidone augmentation were likely to maintain their gains over 6 months with some continued treatment. However, many more EX/RP- than risperidone-treated patients responded acutely and thus entered the maintenance phase. As a result, augmenting SRIs with EX/RP yielded outcomes superior to risperidone 6 months later. It is important to note that, during the 8-week acute phase of treatment, of the 50 patients who received EX/RP augmentation, 30 were responders, whereas of the 50 who received risperidone, only 8 were responders. Taken together, the results of the acute and the maintenance treatment phases strongly support augmenting SRIs with EX/RP rather than with risperidone in adults with OCD. The data also suggest that ongoing EX/RP treatment can help many patients maintain their acute gains. Developing effective and cost-effective ways to deliver EX/RP to OCD patients will advance public health.

**Drug names:** clomipramine (Anafranil and others), risperidone (Risperdal and others).

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**Author contributions:** Drs Foa and Simpson had full access to all of the data in the study and take responsibility for the integrity of the data and, with Dr Rosenfield (the statistician), the accuracy of the data analysis. Drs Foa and Simpson made equal contributions. Conception and design: Drs Foa, Simpson, Liebowitz, Huppert, and Campeas. Acquisition of data: Drs Simpson, Huppert, Cahill, Maher, McLean, Bender, Williams, Van Meter, Rodriguez, Powers, Pinto, Hahn, and Campeas and Ms Vermes and Imms. Analysis and interpretation of data: Drs Foa, Simpson, Liebowitz, Huppert, Cahill, Rosenfield, Weaver, and Van Meter. Drafting of the manuscript: Drs Foa, Simpson, Rosenfeld, and McLean. All authors were involved in the critical revision of the manuscript for important intellectual content. All authors approved of the final version of the manuscript to be published.
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