

## IMIPRAMINE PLUS COGNITIVE-BEHAVIORAL THERAPY FOR SCHOOL REFUSAL

*To the Editor:*

A double-blind, randomized study by Bernstein et al. (2000) demonstrated that imipramine plus cognitive-behavioral therapy is significantly more efficacious than placebo plus cognitive-behavioral therapy in improving school attendance and decreasing symptoms of depression in school-refusing adolescents with comorbid anxiety and depression. We read this study with great interest and wish to raise some questions.

The authors did not provide information about how many subjects were initially assessed, how many subjects were excluded, and the reasons for exclusion. Information on the response rate and the participation rate has implications for generalizability and future research. The selection of patients for randomized controlled trials has been a controversial issue. In this context, the Consolidated Standards of Reporting Trials (CONSORT) guidelines state that all patients assessed for a trial should be accounted for and that the report should be accompanied by a diagram that explains what happened to all the patients involved in the trial (Begg et al., 1996).

Random allocation to intervention groups remains the only method of ensuring that groups being compared are on an equivalent footing at the outset of the study, thus eliminating allocation and confounding biases. In this paper there are baseline differences between the groups (Table 1) in severity of symptoms which do not appear solely by chance. In the absence of adequate information on method of randomization, the possibility of allocation bias arises.

The dropout rate was approximately 25%, which is relatively high; a dropout rate of more than 20% can have a significant impact on results. Although the authors try to justify the fact that there was no significant difference in the number of dropouts between the groups, it is possible to keep the purpose of randomization intact only if they carried out an intent-to-treat analysis.

Imipramine causes marked anticholinergic side effects, which can make investigators easily unblind. We question, therefore, whether investigators really were blind. It has been found that trials that are not double-blind yield larger estimates of treatment effect than trials in which the authors specify double-blinding (Schulz, 2000; Schulz et al., 1995).

Finally, the authors failed to communicate precision of effect size. With a sufficiently large sample size, even very small effects become highly statistically significant.

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*Dr. Bernstein et al. reply:*

We believe the questions raised by Dr. Jainer about randomization, blinding, dropout rate, data analysis, and effect size can be answered largely with information presented in the report, which is underscored below. This investigation was designed to evaluate combined treatments for severely ill school-refusing adolescents with comorbid anxiety disorders and major depression. Telephone screening was used to evaluate basic inclusion and exclusion criteria. On the basis of screening results, potential participants were scheduled for outpatient evaluation. The majority of subjects who qualified for participation on the basis of outpatient assessment agreed to participate.

Subjects were randomly assigned to one of two conditions (imipramine plus cognitive-behavioral therapy [CBT] or placebo plus CBT) with blocking on gender and whether there was a week of school vacation during the 8-week treatment (Bernstein et al., 2000b). Safeguards (not described in the report) helped preserve the blind. The randomization code was established in advance of initiating the study and was stored in the pharmacy and also in a sealed envelope in a locked research file. Identical-appearing active medication and placebo were prepared by a drug company and dispensed from the pharmacy in coded containers.

All study staff were blind to condition except the child and adolescent psychiatrist who monitored imipramine levels, which were drawn on all subjects including those randomized to placebo (Bernstein et al., 2000b). This psychiatrist recommended increasing a participant's imipramine dose if the blood level was sub-

therapeutic and decreasing it if the level was high. To help maintain the blind, increases or decreases in dosage were also suggested for randomly selected participants receiving placebo.

The dropout rate of 25.4% was partially explained by the fact that we were studying severely ill, anxious-depressed school refusers. In addition, close to half of the subjects were from lower socioeconomic status families with limited support and resources (e.g., transportation). There were no significant differences between dropouts and completers with regard to demographics and baseline severity of symptoms (Bernstein et al., 2000b), suggesting that results are generalizable to the entire randomized sample. Our noncompletion rate of 25% is not out of line with pediatric treatment studies. Silverman and colleagues (1999) describe dropout rates of 20% to 27% in four published studies of CBT for youths with anxiety disorders (two conditions per study). Dr. Jainer recommends intent-to-treat analyses because of a high dropout rate. In fact, the statistical analysis section states, "All randomized subjects were included in analyses based on intent to treat" (Bernstein et al., 2000b, p. 279).

To preserve the blind and decrease the likelihood of expectancy bias, a child and adolescent psychiatrist who had no previous contact with participants or their data performed all endpoint ratings. Baseline clinician ratings were completed by a different child and adolescent psychiatrist, who later did medication management appointments. The bachelor-level project coordinator administered clinician ratings at weeks 2, 4, and 6. Raters received comprehensive training before administering outcome measures. Intraclass correlation coefficients among raters were 0.85 to 0.99 for total scores on clinician rating scales. Our study was abstracted with commentary in *Evidence-Based Mental Health* (March, 2000) and found to meet criteria for a randomized clinical trial with concealed allocation and blinded patients and outcome evaluators.

Dr. Jainer states that "Imipramine causes marked anticholinergic side effects, which can make investigators easily unblind." This comment applies to the psychiatrist doing medication checks. However, this person did not administer primary outcome measures at weeks 2, 4, 6, or endpoint. Posttreatment, subjects, mothers, fathers, and the psychiatrist doing medication management independently guessed treatment condition. Unfortunately, no guesses were obtained from the endpoint evaluator and project coordinator. Combining data from dropouts and completers, 66% (31/47) of subjects (greater than chance at  $p < .05$ ), 62.5% (30/48) of mothers (not significant), and 57.1% (8/14) of fathers (not significant) correctly guessed treatment condition (Bernstein et al., 2000a). The psychiatrist completing medication checks accurately guessed medication assignment in 79.5% (31/39) of participants (greater than chance at  $p < .001$ ). Logistic regression showed that weekly side effects were a strong predictor ( $p = .005$ ) of the psychiatrist's guess of condition assignment and weekly global improvement ratings ( $p = .06$ ) were a marginal predictor (Bernstein et al., 2000a).

These findings support the importance of blind independent evaluators for administration of outcome measures in clinical trials.

Effect sizes are reported as footnotes in Table 1 of the article (0.287 for improvement in school attendance and 0.333 for improvement in clinician-rated depression). These effect sizes are small to moderate. In summary, we believe our study provided a fair test of the stated hypotheses and demonstrated that imipramine plus CBT is more efficacious than placebo plus CBT in improving school attendance and depressive symptoms in school-refusing adolescents with comorbid anxiety and major depressive disorders.

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## WEB-BASED CBT FOR SELECTIVE MUTISM

To the Editor:

Selective mutism (SM) is a rare condition in which children speak in some situations but remain mute in others. Current evidence suggests that SM is a form of anxiety disorder (Anstendig, 1999). Cognitive-behavioral therapies (CBT) are effective in children with anxiety disorders (Kendall, 1994). Although treatment of children with SM has often been described as CBT, most treatments focus on behavior modification rather than cognitive restructuring. We report the successful application

of an Internet-based CBT program teaching cognitive strategies with a 7-year-old child with SM.

B.P.H. was in kindergarten when he was referred to a child and adolescent psychiatrist, who diagnosed SM and suggested medication. The family declined, and no further follow-up occurred. B.P.H. showed improvement the following year and started speaking to classmates but not to teachers. This prompted the referral to our center. There was no family history of SM or diagnosed mental disorders. B.P.H. was medically healthy and had no hearing deficits. Diagnostic assessment revealed SM, but no other Axis I disorder. B.P.H.'s mother completed a structured clinical diagnostic interview based on *DSM-IV* criteria to confirm diagnosis.

B.P.H.'s nonverbal reasoning, receptive language, spelling, and arithmetic skills were above average. There was no clinically discernible language disorder. Measures of anxiety, depression, global assessment of functioning, and a SM questionnaire were given before and after treatment.

The CBT program (adapted from the *Coping Bear Workbook*; Mendlowitz and Scapillato, 1996; Mendlowitz et al., 1999) is available from the authors ([daniel\\_fung@medscape.com](mailto:daniel_fung@medscape.com)). It includes a Web-based child workbook and notebook and a downloadable parent/teacher manual which focuses on psychoeducation. The approach teaches the child to recognize the signs of anxious arousal associated with speaking and to use appropriate anxiety management strategies.

Treatment consists of 14 individual, weekly 90-minute sessions (60 minutes with the child and 30 minutes with the parents). The program is divided into two segments, with the first eight sessions for training and the subsequent six for practice. Homework tasks are given weekly and submitted by the child via e-mail. Each session introduces new skills and concepts while reviewing what was previously taught. In the first segment, the child is taught the "CHAT Plan" (Check your body's feelings, Having bad thoughts, Attitudes and Actions that can help, Time for a reward). This is analogous to Kendall's FEAR Plan for anxiety, which uses an acronym to facilitate recall. The plan is introduced through stories about a shy mouse character called Meeky, who has symptoms that are similar to the child's.

The second segment is devoted to applying the CHAT Plan in increasingly difficult situations. The child is introduced to useful social skills to handle such situations. In session 8, a personal computer program called the "Meeky Soundpad" is introduced. This is based on an earlier idea (Kee et al., 2001) which allows the child to record short messages that can be replayed during the session, allowing the child to hear his or her voice and be desensitized to speaking in various situations.

B.P.H. initially hesitated in performing simple tasks, but he became more enthusiastic as his typing speed improved. B.P.H.

consistently completed the homework and e-mailed it to the therapist prior to his visit. In session 10, B.P.H. chose to record additional phrases during the session with the Meeky Soundpad. He read the session notes aloud and answered specific questions ("What does the CHAT Plan stand for?"). The next day, B.P.H. said his first words to his teacher and has been speaking in subsequent sessions.

The pre- and posttreatment ratings of anxiety by child, parent, and teacher showed an improving trend after CBT. Global improvement was also reported by all informants, and SM questionnaire scores improved in all environments.

Current practice favors the use of medication and behavioral techniques in persistent SM. The use of CBT in SM in this case resulted in improvement with relatively brief therapy. The use of Internet-based treatment has many advantages including wide dissemination, interactive sessions, and repetition of material by patients and families after the clinic session. As children often see the use of the computer as being enjoyable, treatment compliance is also improved. Web-based CBT should be used for older children of at least average intelligence with no learning or language disorders.

The central question raised by this case is whether the improvements are the result of the treatment or part of the natural course of children with SM. For further investigation, a controlled trial would be necessary. It is hoped that this case will provoke further research and generate more treatment alternatives for children with SM.

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