Impact of Physical and Sexual Abuse on Treatment Response in the Treatment of Resistant Depression in Adolescent Study (TORDIA)

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Objective: We previously reported that a history of abuse was associated with a poorer response to combination treatment in the Treatment of Resistant Depression in Adolescents study (TORDIA). We now report on the nature and correlates of abuse that might explain these findings. **Method:** Youth who did not benefit from an adequate selective serotonin re-uptake inhibitor (SSRI) trial (N = 334) were randomized to one of the following: an alternative SSRI; an alternative SSRI plus cognitive behavior therapy (CBT); venlafaxine; or venlafaxine plus CBT. Analyses examined the effect of history of abuse on response to the pharmacotherapy and combination therapy. **Results:** Those without a history of physical abuse (PA) or sexual abuse (SA) had a higher 12-week response rate to combination therapy compared with medication mono-therapy (62.8% versus 37.6%; odds ratio [OR] = 2.8, 95% confidence interval [CI] = 1.6-4.7, $p < .001$). Those with a history of SA had similar response rates to combination versus medication monotherapy (48.3% versus 42.3%; OR = 1.3, 95% CI = 0.4–3.7; $p = .66$), whereas those with history of PA had a much lower rate of response to combination therapy (18.4% versus 52.4%, OR = 0.1; 95% CI = 0.02–0.43). Even after adjusting for other clinical predictors, a history of PA moderated treatment outcome. **Conclusion:** These results should be considered within the limitations of a post hoc analysis, lack of detailed assessment of abuse and other forms of trauma, and neuropsychological status. Depressed patients with history of abuse, especially PA may require specialized clinical approaches. Further work is needed to understand by what mechanisms a history of abuse affects treatment response. J. Am. Acad. Child Adolesc. Psychiatry, 2011;50(3):293–301. Clinical Trial Registry Information: Treatment of SSRI-Resistant Depression in Adolescents (TORDIA); NCT00018902; http://www.clinicaltrials.gov. **Key Words:** depression, cognitive behavioral therapy, abuse, selective serotonin reuptake inhibitor

The relationship between a history of physical or sexual abuse and increased risk of adverse mental health outcomes, including depression is well established.[1,2] Moreover, childhood history of abuse may be associated with an earlier age of depression onset, more chronic course, and suicidal behavior.[3-6] However, there are few studies examining the association between history of abuse and response to treatment among depressed patients, particularly among adolescents.

In a study examining the efficacy of psychotherapy, pharmacotherapy, and combination therapy for chronic depression in adults, Nemeroff et al[7] found that participants with a history of child trauma (parental loss, abuse, or neglect) responded better to cognitive behavioral therapy

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(CBT), with or without the antidepressant nefazodone, compared with antidepressant alone, with a history of physical abuse most strongly accounting for this finding. Both a history of sexual abuse[8] and of either experiencing or witnessing actual or threatened serious injury[9] have been reported to result in a lower response to CBT in depressed adolescents. In the Treatment for Adolescents with Depression Study (TADS), a history of trauma flattened out expected differences among treatment groups, and in those with history of sexual abuse, there was a nonsignificant trend for a lower response to CBT only compared with the other treatments.[10]

In the Treatment of Resistant Depression in Adolescents study (TORDIA) study, we recently found that those with a history of physical or sexual abuse had a superior response to medication monotherapy compared with the combination of CBT and medication, which is the reverse of the pattern of response found among those without a history of abuse.[11,12] However, in reporting the moderation of treatment response by history of abuse, we did not examine or control for other possible confounding factors associated with a history of abuse that might influence treatment response, such as age of onset, chronicity, parental psychopathology, family discord, and poverty.[13-17]

The overarching aim of this secondary analysis of the TORDIA study is to unpack the previously reported relationship between a history of abuse and poorer response to combination treatment[12] by examining whether 1) the lower response to combination therapy was among those with history of physical abuse, sexual abuse, or both; and 2) this moderation effect is due to baseline differences in severity and comorbidity, other correlated family variables, treatment variation, or is best explained by history of abuse itself.

METHOD

Participants

All participants had clinically significant depression despite adequate, pretrial treatment with an SSRI at a dosage equivalent to 20 mg of fluoxetine for at least 4 weeks, with the final 4 weeks at a dosage equivalent to 40 mg of fluoxetine, unless this dose could not be tolerated. Significant depression was defined as a total score ≥40 on the Child Depression Rating Scale-Revised (CDRS-R)[18] and a score ≥4 on Clinical Global Impression–Severity (CGI-S).[19] The CDRS-R is a 17-item scale, which results in total scores ranging from 17 to 113, with a total score ≥40 indicating clinically significant depression.[20] The CGI-I is a measure of clinical improvement, as rated on a scale of 1 (very much improved) to 7 (very much worse).[19] Both the CDRS and CGI-I were completed by an independent evaluator (IE) blinded to treatment assignment.

Exclusion criteria were: completing two or more prior adequate SSRI trials; history of nonresponse to an adequate trial of venlafaxine; prior trial of CBT, with seven or more sessions; on medications with psychoactive properties, excluding some study-allowed medications at stable doses (≥6 weeks' duration); diagnoses of bipolar spectrum disorder, psychosis, autism, eating disorders, substance abuse or dependence; hypertension (diastolic blood pressure ≥90); and females who were pregnant, breast-feeding, or not reliably using contraception.

The study was approved by each site's local institutional review board; all participants gave informed assent and consent after they turned age 18, and parents gave informed consent.

Randomization and Treatment

Participants were randomly assigned to one of four treatments after the failed SSRI treatment: switching to a second SSRI; switching to venlafaxine; switching to a second SSRI combined with CBT; or switching to venlafaxine combined with CBT. Randomization was balanced both within and across sites on: incoming treatment medication, comorbid anxiety, chronic depression (duration ≥24 months), and suicidal ideation (Beck Depression Inventory [BDI] item 9 ≥2).[21]

CBT

Therapists who provided CBT had at least a master's degree in a mental health field, and had at least 1 year of prior experience in using this treatment modality. CBT drew upon the manuals that emphasize cognitive restructuring and behavior activation, emotion regulation, social skills, and problem solving for participants, and that also emphasize parent-child sessions to decrease criticism and to improve support, family communication, and problem solving.[11] The protocol consisted of 12 weekly sessions (60–90 minutes each) of CBT, three to six of which were to be family sessions. A median of nine CBT sessions were delivered across the treatment groups. Therapy audiotapes were reviewed using the Cognitive Therapy Rating Scale[22] by on-site supervisors, supervisors in Pittsburgh, and one external consultant, with a high proportion rated as acceptable (>93.9%).

Pharmacotherapy

Participants in the SSRI switch groups who were initially treated with citalopram, sertraline, or fluvox-