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THE TREATMENT OF SSRI-RESISTANT DEPRESSION IN ADOLESCENTS (TORDIA): IN SEARCH OF THE BEST NEXT STEP

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The Treatment of SSRI-Resistant Depression in Adolescents study (TORDIA) was designed to inform clinicians as to the best next step in the treatment after a depressed adolescent has not responded to an adequate trial with a selective serotonin re-uptake inhibitor (SSRI).^[1] In this six-site study, conducted from 2000 to 2006, 334 treatment-resistant adolescents with major depressive disorder (MDD) were randomized to one of the four treatment strategies in a two-by-two balanced factorial design: (a) switch to another SSRI; (b) switch to venlafaxine; (c) switch to another SSRI and add cognitive behavioral therapy (CBT); or (d) switch to venlafaxine and add CBT. The SSRI switch options were fluoxetine, and for the first half of the trial ($n = 181$), paroxetine. Because of the concerns about the safety and efficacy of paroxetine, citalopram was used instead during the second half of the trial ($n = 153$). All enrolled youth had not responded to an “adequate trial” with an SSRI, defined as treatment for at least 8 weeks, with the last 4 weeks at a dosage that was the equivalent of 40 mg of fluoxetine. This communication focuses on acute treatment, which was 12 weeks in duration.

The failed SSRI was cross-tapered over the first 2 weeks, and by 6 weeks, the study medication was titrated to 20 mg for all SSRI's and to 150 mg for venlafaxine; at that point, nonresponders could have their dosage increased to 40 and 225 mg, respectively. CBT sessions were weekly, and used a modification of the Treatment for Adolescent Depression Study (TADS) manual that matched each participant to a subset of CBT modules on the basis of a cross-site conference call.^[1, 2] The outcomes with respect to acute treatment response and suicidal events as well as the predictors and moderators of those outcomes are described. This review concludes by placing the findings of TORDIA in context, discussing clinical implications, and offering recommendations for further research.

SAMPLE

The sample was mostly female (70%), white (82%), and of middle income (median income \$61,000). Participants had moderate-to-severe depression, often with co-morbid psychiatric disorders (52%). More than half had a duration of depression for two years or greater. Nearly six in ten entered the study with clinically significant suicidal ideation.

RESPONSE

Response at 12 weeks was defined as a Clinical Global Impressions, Improvement subscale (CGI-I) 2, corresponding to “much” or “very much” improved, a 50% improvement from baseline in the Children’s Depression Rating Scale, Revised (CDRS-R), and a CDRS-R <40. The addition of CBT to either medication strategy resulted in a better response rate than either medication mono-therapy (54.8% vs. 40.5%, $P = .009$, Number Needed to Treat [NNT]=7), whereas similar results were found in those switched to venlafaxine and to another SSRI, whether or not they also received CBT (48.2% vs. 47.0%).^[1] Treatment with venlafaxine resulted in more cardiovascular side effects, although these were rarely of clinical importance.

PREDICTORS AND MODERATORS OF RESPONSE

Poorer response, across treatments, was predicted by greater severity of self-rated depression, hopelessness, suicidal ideation, a history of nonsuicidal self-injury, and family conflict.^[3] CBT continued to be associated with an increased likelihood of a response, even after controlling for the most salient adverse predictors of response. SSRI’s were superior to venlafaxine in those participants with higher self-reported depression. The combination of CBT and medication was superior to medication alone for those with multiple co-morbidities, particularly anxiety or ADHD. Participants with a history of abuse showed a lower response rate to combination treatment than to medication monotherapy.^[3] Those who received pharmacological treatment for sleep difficulties showed a poorer response rate than did those who did not receive medication for sleep.^[1] Participants whose self-reported drug and alcohol use was high at baseline and remained so, or whose substance use accelerated during the trial, showed a poorer response rate compared to those whose drug and alcohol use either remained or became low.

SUICIDAL EVENTS

A suicidal event was defined as clinically significant new-onset or worsening suicidal ideation and/or a suicide attempt. For the first half of the study ($n = 181$ participants), the rating of suicidal events was based on spontaneous report, similar to most other FDA trials.^[4] After adverse publicity about SSRIs and concern about their association with suicidal events in adolescents,^[4] participants were monitored systematically for changes in suicidal ideation and behavior. The contrast between “spontaneous” and “systematic” reporting allowed for a natural experiment to compare the characteristics, prevalence, and correlates of spontaneous vs. systematically assessed events. Suicidal events were more frequently detected under circumstances of systematic assessment (20.8% vs. 8.8%, $P = .002$), although the rates of serious adverse events were similar under both methods of assessment (8.4% vs. 7.3%), as were the clinical correlates of suicidal events.^[5]

In TORDIA, the median time to a suicidal event was 3 weeks from intake. There were no differential effects of treatment on suicidal events, but under circumstances of high baseline suicidal ideation, the use of venlafaxine was associated with more self-harm (suicidal events or nonsuicidal self-injury) events (37.2% vs. 23.3%, $P = .05$). The strongest predictors of occurrence and time to suicidal events were high baseline suicidal ideation, adolescent-

reported parent—child conflict, and self-reported drug and alcohol use. Those who experienced suicidal events started and remained at high levels of depression and suicidal ideation, and thus, continued to be at increased risk for suicidal events throughout the trial. Those who experienced suicidal events were much less likely to respond to treatment (27.1% vs. 51.0%, $P = .002$), and consequently, there was substantial overlap between the predictors of these two inter-related outcomes.

TORDIA IN THE CONTEXT OF OTHER TRIALS OF DEPRESSION TREATMENT

Two other large studies of adolescent depression have compared medication monotherapy and the combination of medication and CBT. Like TORDIA, The Treatment of Adolescent Depression Study (TADS) found that combination treatment was superior to medication alone,^[2] whereas the United Kingdom-based Adolescent Depression Antidepressant and Psychotherapy Trial (ADAPT) did not find a difference between medication monotherapy and combination treatment.^[6] This negative finding in ADAPT may be because one entry criterion required that potential participants show no response to a brief psychosocial intervention. Also, ADAPT participants, compared to either those in TADS or TORDIA, had two additional characteristics that might reduce the incremental benefit of adding CBT to medication: they were more severely depressed and were younger than those in TADS or TORDIA.^[3, 7] Both TORDIA and TADS found that clinical severity, complexity, and chronicity predicted poorer outcome, and that socio-demographic advantage was associated with a better response to CBT, although there was less convergence on other variables that moderated CBT response.^[3, 7]

Combination treatment in TADS resulted in the most rapid decline in suicidal ideation, and the rate of events in combination treatment was intermediate between placebo and medication alone at 12 weeks, although not statistically different from medication alone.^[2, 8] In contrast, both the TORDIA and the ADAPT studies found no difference in the rate of suicidal events among treatments, perhaps because the proportion of seriously suicidal participants entering these studies was much higher than in TADS. Surprisingly, both ADAPT and TORDIA found a lower rate of nonsuicidal self-harm in the medication-only group. Given that the median time to a suicidal event in TORDIA was 3 weeks, it is unlikely that CBT as currently delivered could effectively protect against these early events.

Both TORDIA and the much larger and more complex Sequenced Treatment Alternatives to Relieve Depression study (STAR*D) targeted real-world samples of treatment-resistant individuals.^[9] While TORDIA focused only on the second treatment step, its results are entirely consistent with the STAR*D findings from multiple treatment steps with respect to predictors of events and response. Although not definitive, the findings of STAR*D suggest particular utility and tolerability of pharmacological augmentation strategies, which were not tested in TORDIA or in any other trial of adolescent depression.

Taken together, these studies suggest that most depressed people who are treatment-naïve will respond to a first intervention. What also emerges across these studies is that our current approach to treatments is hit or miss, with little ability to match patient to treatment.

Moreover, our treatments leave a substantial proportion of patients with residual or full-blown depressions, requiring subsequent intervention steps. However, in the face of nonresponse, persistence will eventually pay off, although the yield diminishes with each additional treatment step.

CLINICAL IMPLICATIONS

The clinician managing an adolescent patient with treatment-resistant depression should be persistent and communicate hope to the patient and family. For adolescents who have not responded to an SSRI, a switch to another SSRI is a reasonable next step, along with the addition of CBT. This combination is likely to be particularly beneficial for those depressed patients with additional co-morbid disorders and for those who do not have a history of maltreatment. Although the efficacy of venlafaxine was similar to that of the SSRI's, its use was associated with more side effects, and it did not perform as well as SSRI's under circumstances of higher self-reported depression and suicidal ideation. Systematic monitoring for suicidality should be implemented for depressed patients, with greater intensity of monitoring early in the treatment course. Suicidal events may be prevented by early interventions to promote reduction in drug and alcohol abuse, family conflict, and increase commitment to treatment and to a safety plan.^[5] Depressed patients with sleep difficulties represent a group at high-risk for nonresponse, and, ideally, should first be managed with nonpharmacological interventions. Since there are consistent data that the greater the duration of depression, the lower the response rate,^[4, 7] earlier detection and intervention are important public health measures that may reduce the incidence of treatment-resistant depression.

RESEARCH IMPLICATIONS

The TORDIA study demonstrated that highly suicidal individuals can be impaneled and managed in the context of clinical trials. Preparatory to this, we found it necessary to educate our Institution Review Boards (IRBs) as to the importance of studying high-risk populations in order to improve treatments, and to collaborate with these regulatory groups on the development of appropriate monitoring and rescue procedures.

The association of a history of abuse with a poorer response to CBT is consistent with previous work from our group,^[10] although different from reports in chronically depressed adults.^[11] It is unclear if this impact of abuse on outcome is due to continued ongoing family difficulties, or sequelae of the abuse that were not assessed or targeted in this study. Given the high rate of abuse among young depressed patients, it is of great public health importance to gain a better understanding of how adverse childhood experiences moderate treatment response and to use those findings to develop more effective treatments for this population. While adults with depression show increased activation in response to negative emotional stimuli, many depressed youth "shut down" when presented with similar probes.^[12, 13] Since CBT focuses in part on negative emotions, it may be less effective in abused patients and in other emotionally avoidant, depressed youth.

Future research to improve treatment outcomes in depressed adolescents should target domains associated with poorer response in this and other samples, namely, reduction of

drug and alcohol abuse, attenuation of family conflict, and nonpharmacological interventions to improve sleep and emotion regulation. Augmentation strategies should also be studied. However, advances in the development and personalization of treatment need to be informed by advances in assessment. Extant assessment batteries have identified nonspecific predictors of clinical response such as greater clinical severity, and the results of moderator analyses are not convergent. This may be because treatments target changes in regulatory mechanisms, rather than in symptoms per se, whereas most of our measures related to depression assess symptomatology. More direct assessment of important domains of mood, mood regulation, social interaction, and sleep through such approaches as Ecological Momentary Assessment (EMA), physiological measures of mood reactivity and regulation such as fMRI, and direct assessment of sleep quality through sleep actigraphy may lead to an improved ability to monitor the efficacy of treatment, match patient to treatment, and to develop treatments that result in faster and more complete response and remission rates than do our current methods of intervention.^[12, 14, 15]

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Biography

Dr. Brent is a Academic Chief, Child and Adolescent Psychiatry at Western Psychiatric Institute and Clinic. He holds the UPMC Endowed Chair in Suicide Studies, and is a Professor of Psychiatry, Pediatrics and Epidemiology, University of Pittsburgh School of Medicine. He co-founded and now directs Services for Teens at Risk (STAR), a Commonwealth of Pennsylvania-funded program for suicide prevention, education of professionals, and the treatment of at-risk youth and their families. Dr. Brent's program of research translates the findings of epidemiologic and family-genetic studies into viable, testable interventions for youth at risk for depression, and/or suicidal behavior. Having identified the roles of mood disorders, substance abuse, family history of suicide, impulsive aggression, and availability of firearms as risk factors for youth suicide, he and his group have consequently developed interventions for the prevention and treatment of depression and suicidal behavior. He directs an NIMH-funded T32 postdoctoral training grant that has trained many of the current leaders in child mental health research. Dr. Brent is a member of

the Institute of Medicine of the National Academy of Sciences, and most recently was co-awarded the Ruane Prize for Outstanding Achievement in Child and Adolescent Psychiatric Research (NARSAD).

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