Suicide Attempts and Nonsuicidal Self-Injury in the Treatment of Resistant Depression in Adolescents: Findings from the TORDIA Study

Joan Rosenbaum Asarnow, Ph.D., Giovanna Porta, M.S., Anthony Spirito, Ph.D., Graham Emslie, M.D., Greg Clarke, Ph.D., Karen Dineen Wagner, M.D., Ph.D., Benedetto Vitiello, M.D., Martin Keller, M.D., Boris Birmaher, M.D., James McCracken, M.D., Taryn Mayes, M.S., Michele Berk, Ph.D., David A. Brent, M.D.

Objective: To evaluate the clinical and prognostic significance of suicide attempts (SAs) and nonsuicidal self-injury (NSSI) in adolescents with treatment-resistant depression. **Method:** Depressed adolescents who did not improve with an adequate SSRI trial (N = 334) were randomized to a medication switch (SSRI or venlafaxine), with or without cognitive-behavioral therapy. NSSI and SAs were assessed at baseline and throughout the 24-week treatment period. **Results:** Of the youths, 47.4% reported a history of self-injurious behavior at baseline: 23.9% NSSI alone, 14% NSSI+SAs, and 9.5% SAs alone. The 24-week incidence rates of SAs and NSSI were 7% and 11%, respectively; these rates were highest among youths with NSSI+SAs at baseline. NSSI history predicted both incident SAs (hazard ratio [HR]= 5.28, 95% confidence interval [CI] = 1.80–15.47, z = 3.04, p = .002) and incident NSSI (HR = 7.31, z = 4.19, 95% CI = 2.88–18.54, $p < .001$) through week 24, and was a stronger predictor of future attempts than a history of SAs (HR = 1.92, 95% CI = 0.81–4.52, z = 2.29, p = .13). In the most parsimonious model predicting time to incident SAs, baseline NSSI history and hopelessness were significant predictors, adjusting for treatment effects. Parallel analyses predicting time to incident NSSI through week 24 identified baseline NSSI history and physical and/or sexual abuse history as significant predictors. **Conclusions:** NSSI is a common problem among youths with treatment-resistant depression and is a significant predictor of future SAs and NSSI, underscoring the critical need for strategies that target the prevention of both NSSI and suicidal behavior. Clinical Trial Registration Information—Treatment of SSRI-Resistant Depression in Adolescents (TORDIA). URL: http://www.clinicaltrials.gov. Unique Identifier: NCT00018902. J. Am. Acad. Child Adolesc. Psychiatry, 2011;50(8):772–781. **Key Words:** suicide, nonsuicidal self-injury, depression, adolescents, self-injurious behavior

Suicidal behavior and nonsuicidal self-injury (NSSI) are major public health problems. Suicide is the third leading cause of death among youth 10 to 24 years of age, and national surveillance data indicate an annual suicide attempt (SA) rate of approximately 6.3% among high school students.[1] NSSI, defined as deliberate self-harm without suicidal intent (e.g., cutting, burning), is at least as common as suicidal behavior, although rates vary across studies, underscoring the impact of sampling and methodological factors.[2,3] The significance of NSSI as a treatment target in clinical samples is underscored by surveys of mental health providers indicating that NSSI is a more frequent problem than SAs among their patients.[4]

Despite increasing recognition of NSSI, its prognostic significance with respect to depression response and suicidal behavior is not well understood.[5-7] This article reports secondary analyses examining NSSI and SAs cross-sectionally and lon-

This article is discussed in an editorial by Dr. Paul Wilkinson on page 741.

gitudinally in the Treatment of Selective Serotonin Reuptake Inhibitors (SSRI)–Resistant Depression in Adolescents (TORDIA) study, a large multi-site study of chronically depressed adolescents. Given the links between depression and suicidal behavior, as well as emerging data indicating that depression is associated with NSSI, this sample of youths with severe and treatment-resistant depression offers a unique opportunity to examine patterns of SAs and NSSI in a high-need clinical sample.

Compared with our knowledge of adolescent suicidal behavior, less is known about correlates and predictors of NSSI in adolescents, in part because efforts to clearly distinguish between self-injurious behavior with and without suicidal intent have been relatively recent. Extant research indicates that youths with a history of NSSI have elevated rates of depressed/anxious symptoms, conduct problems, substance use, symptoms of borderline personality disorder, dissociative symptoms, stress, and histories of abuse/violence.[2,8,9] NSSI also appears to be associated with elevated rates of SAs and to predict future suicide and SAs in adults.[2,10-13] The question of whether NSSI predicts future suicide/SAs in adolescents requires evaluation.

In a previous report, focusing on acute treatment outcomes at 12 weeks in the TORDIA study sample, we found relatively high incidence rates of suicidal adverse events (new-onset or increased suicidal ideation or an attempt, present in 11.3% of youths). However, the rate of new-onset SAs was only 5%, and NSSI was present in 9% of the sample, during these 12 weeks.[14] Although predictors of suicidal events included drug and alcohol use, family conflict, and higher levels of intake suicidal ideation, the strongest predictor of incident NSSI was a previous history of NSSI; it was found that NSSI history was not a significant predictor of suicidal events during the 12-week acute treatment period.[14] Other predictors of NSSI through week 12 were self-reported suicidal ideation, history of abuse, and history of suicide attempts. We now extend these results to examine the progression of self-injurious behavior (SA and NSSI) over an additional 12 weeks of continuation treatment for a total of 24 weeks or 6 months. Specific aims of this article are as follows: 1) to describe NSSI and SA outcomes through the 24-week treatment period; 2) to compare rates of incident NSSI and SAs among youths with baseline histories of NSSI, SAs, and both NSSI and SAs; 3) to explore other predictors of SAs and NSSI over the 24-week treatment/follow-up period; and 4) to present new analyses of correlates of NSSI and SA histories at the initial/baseline evaluation. Based on prior literature indicating that suicide attempts are predicted by prior suicide attempts[15] and emerging literature indicating that prior NSSI predicts future NSSI,[14] we predicted that SAs and NSSI during the 24-week treatment period would be predicted by baseline histories of self-injurious behavior of the same type. We hypothesized that the strongest predictors of SAs would be depression, hopelessness, and suicidal ideation, whereas NSSI was predicted to be more strongly associated with abuse histories and substance use, problems often associated with personality disorders.[12,13] Given prior research indicating that NSSI and suicidal behavior are associated forms of self-injurious behavior, we predicted a significant association between baseline histories of NSSI and SAs.[12,14]

METHOD

Detailed descriptions of participants, assessments, treatments and outcomes are available elsewhere.[14,16,17] Therefore, we focus here on participant characteristics, measures, and procedures relevant to the outcomes of SAs and NSSI. The study was reviewed by each site's local institutional review board. All subjects gave informed assent/consent (as appropriate), and parents gave informed consent.

Participants

Participants were adolescents 12 to 18 years of age, with moderate to severe *DSM-IV*[18] major depressive disorder (MDD) and clinically significant depression (Child Depression Rating Scale—Revised (CDRS-R)[19] total score ≥40 and a Clinical Global Impression—Severity (CGI-S) Subscale ≥4 (moderate or greater severity)[20] despite being in active treatment with an SSRI for ≥8 weeks (Table 1). The sample was 69.7% female, with a mean age of 15.9 years. Exclusion criteria were bipolar spectrum disorder, psychosis, pervasive developmental disorder or autism, eating disorders, substance abuse or dependence, or hypertension.

Randomization

Subjects were randomly assigned to one of four conditions: change to another SSRI, change to venlafaxine, change to another SSRI plus CBT, or change to venlafaxine plus CBT. Subjects were assigned to treatment using a variation of Efron's biased coin toss,[21] balancing both across and within sites with respect to incom-