Teenaged, Depressed, and Treatment Resistant: What Predicts Self-Harm?

Self-harm affects thousands of depressed teenagers each year. A careful meta-analysis of pediatric antidepressant trials by the Food and Drug Administration (FDA) showed a higher rate of spontaneously reported suicidal behaviors in adolescents randomly assigned to antidepressants versus placebo. The publicity about this relationship and the subsequent FDA black box warning was followed by a decrease in antidepressant use (1) and a possible increase in adolescent suicides. Whether the increase is real and sustained is still unclear (2–4). Data that can identify who is at risk for an increase in reported self-harm with medication are difficult to find. Standardized systematic assessment of suicidal events in adolescent trials have only recently been developed (5), and adolescents with a history of self-harm behaviors, the ones with greatest risk, have usually been excluded from clinical trials.

Brent and his associates tackled these issues directly in the Treatment of SSRI-Resistant Depression in Adolescents (TORDIA) trial (6) and produced a report full of pearls for psychiatrists and families who must confront this problem. Treatment-resistant depressed adolescents (N=334) who had not responded to a previous 12-week trial of an SSRI antidepressant were switched to either another SSRI or venlafaxine with and without cognitive behavioral therapy (CBT). Over 60% of the adolescents had clinically significant suicidal ideation at entry into the trial. Many developed suicidal behaviors early in treatment. In the report featured in this issue (7), the authors attempt to identify the predictors of self-harm adverse events during the course of the trial.

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Because the tools for systematic identification improved while the trial was still in progress, the authors could capitalize on a natural experiment to find out how best to detect suicidal behavior during the course of treatment. Adverse events were assessed by spontaneous report for the first 181 adolescents and by systematic weekly assessments for the last 153, which permitted comparison of the two strategies. Second, the self-harm events they recorded not only included suicidal thoughts and behavior but also nonsuicidal self-injury events. These are defined as self-injurious behaviors such as cutting/burning/skin scratching resulting in physical damage with no explicit or implicit intent to die but rather to gain relief from negative emotion or obtain social reinforcement. As the authors note, except for one unpublished FDA report that suggested a trend toward an increased risk of nonsuicidal self-injury with antidepressants versus placebo, the occurrence of nonsuicidal self-injury has not been examined in pediatric trials (8).

Nonsuicidal self-injury is alarmingly prevalent in adolescents (13%–23% lifetime prevalence) and may be increasing (9). A recent paper by Hilt et al. (10) found that only 21% of adolescents received medical treatment as a result of self-injury. Nonsuicidal self-injury prevalence was associated with poor communication with peers and an increase in rumination.

The two different methods of obtaining the information—spontaneous reporting early in the trial and systematic monitoring later in the trial—and the inclusion of nonsuicidal self-injury yielded information on adverse events in the TORDIA study that might have otherwise been lost. Systematic monitoring as contrasted with spontaneous

reports yielded considerably higher rates of suicidal (20.8% versus 8.8%) and nonsuicidal self-injury (17.6% versus 2.2%) adverse events. However, the rate of the most serious adverse events—those that led to hospitalization or were life threatening, disabling, or resulted in death—was not significantly different (8.4% versus 7.3%). These major events almost always bring medical attention, and thus we would expect them to be detected even without special efforts. It is tempting to conclude that the additional less serious events detected by systematic monitoring are not clinically important, since their detection did not decrease the rate of the most life-threatening events, but the pearl here is the value of systematic monitoring for early detection. Systematic monitoring provides more opportunities than we have had before for early intervention with high-risk adolescents, before events become serious. We need now to develop and test new psychotherapeutic and psychopharmacological strategies to react to these events in vulnerable patients.

For example, a previous history of either suicidal or nonsuicidal self-injury events were early predictors of a recurrence of suicidal behavior within 2–3 weeks of treatment entrance. Severity of suicidal ideation, family conflicts, and drug and alcohol use were also predictors. Poor peer communication, suggested by Hilt as a moderator of nonsuicidal self-injury, was not assessed in this study. The Behavior Questionnaire used in TORDIA limited the assessment of conflict to parent/child. The addition of a few questions on adolescent conflict with peers may reveal possibilities for intervention, especially for nonsuicidal self-injury and maybe for other suicidal behaviors in at-risk adolescents.

The study also yields some preliminary insight on the effects of different pharmacological interventions. None of the antidepressant drugs increased suicidal behavior significantly more than others across the whole study. However, venlafaxine compared to SSRIs was associated with a higher rate of self-harm in adolescents with a previous history of suicidal ideation (37.2% versus 23.3%). It is of interest that the Psychopharmacologic Drug Advisory Committee (PDAC) of the FDA, in a meta-analysis of 24 short-term placebo-controlled trials, found a suggestion that the mixed serotonin-norepinephrine reuptake inhibitor (SNRI) drug class that includes venlafaxine had a slight effect on increasing suicidality in patients under 25 years (11).

Adjunctive use of benzodiazepines, even in a small sample, markedly increased the rate of both suicidal and nonsuicidal self-injury (40% versus 8.3%). Why one site was overly represented (80% of the cases) is a puzzle that requires a closer look at the patient recruitment and characteristics at that site. The possible association of benzodiazepines with increased risk taking should be investigated further in these patients.

CBT was associated with earlier onset of nonsuicidal self-injury events, which the authors attribute to better monitoring and increased contact because of the therapeutic visits, but it may also be that CBT did not address the problems in peer communications associated with nonsuicidal self-injury.

Now that this elegantly designed trial has been completed, a thorough review of the clinical cases to glean even more data on these issues would be appropriate. Adolescent self-harm is a serious, prevalent problem. Do antidepressants increase or protect against self-harm, and in whom? This study, by including rather than excluding treatment-resistant adolescents with suicidal and nonsuicidal self-harm histories, has boldly taken on this issue. The authors have shown that systematic monitoring of suicidal events may uncover risky situations in depressed adolescents and that nonsuicidal self-harm should also be monitored. A history of these behaviors is an early predictor of a repeated event in 2–3 weeks. Adolescents with a history of adverse events, who are in conflict with family and peers, and using drugs or alcohol require special attention. Venlafaxine and benzodiazepines should be monitored closely in adolescents with a previous history of suicidal thinking because of the evidence for increased risk in these children. Studies such as TORDIA can provide other evidence for guidelines for the use of antidepressants in high-risk adolescents so that treatments are not withheld

for the majority who might benefit but are used more cautiously in those who are at higher risk for suicide and injury.

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