References

1. Brent DA, Emslie GJ, Clarke GN, Asarnow J, Spirito A, Ritz L, Vitiello B, Iyengar S, Birmaher B, Ryan ND, Zelazny J, Onorato M, Kennard B, Mayes TL, DeBar LL, McCracken JT, Strober M, Suddath R, Leonard H, Porta G, Keller MB: Predictors of spontaneous and systematically assessed suicidal adverse events in the Treatment of SSRI-Resistant Depression in Adolescents (TORDIA) study. Am J Psychiatry 2009; 166:418–426
2. Weissman MM: Teenaged, depressed, and treatment resistant: What predicts self-harm? Am J Psychiatry 2009; 166:385–387
3. Foley DL, Goldston DB, Costello EJ, Angold A: Proximal psychiatric risk factors for suicidality in youth: the Great Smoky Mountain Study. Arch Gen Psychiatry 2006; 63:1017–1024

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Dr. Cooney has served on the speaker's bureau for Eli Lilly, GlaxoSmithKline, and Pfizer; and he has served on an advisory panel for Servier. Dr. Moore reports no competing interests.

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TORDIA: Unique Opportunity to Explore Half-Life Theory

TO THE EDITOR: Dr. Brent et al. (1) provided excellent detail about self-harm events during the Treatment of SSRI-Resistant Depression in Adolescents (TORDIA) trial. The authors observed that venlafaxine is associated with greater risk of self-harm in adolescents with higher than median suicidal ideation when compared with SSRI treatment. These results are consistent with theory and analysis put forth by myself (2) and others (3) indicating that risks of suicidal ideation/behavior in adolescent antidepressant trials correlate significantly with antidepressant half-life. I would like to request that the authors take advantage of TORDIA's unique data (randomizing to four antidepressants of substantially different half-life) by presenting rates, by individual antidepressant, of self-harm and suicidal adverse events in the total sample and among those participants with higher baseline suicidal ideation.

The antidepressant half-life theory predicts that a general pattern would be observed, i.e., venlafaxine would likely have the numerically highest event rates, paroxetine the next highest, etc. To maximize sample size, I would suggest combining participants receiving a specific antidepressant alone with participants receiving that antidepressant plus cognitive behavior therapy. However, caveats definitely exist. First, with only four medications, any relationship will almost certainly not reach statistical significance, even if suicidality risks rank in perfect register with the medication half-lives (unfortunately reported most consistently for adults, not adolescents). Second, while the Food and Drug Administration (FDA) meta-analysis found that fluoxetine had one of the lowest rates of suicidal ideation/behavior, its rates were similar to those for citalopram (4). For both these reasons, it would be interesting to also compare the rate of self-harm and suicidal adverse events of the combined participants receiving venlafaxine and paroxetine with the combined participants receiving citalopram and fluoxetine. Last, TORDIA might show a different pattern of risk by half-life because, in the FDA meta-analysis (4, p. 122–123), the rate of suicidal events with fluoxetine and citalopram peaked earlier in treatment than with paroxetine, and the TORDIA trial has the highest rates of self-harm early in treatment.

Despite these potential limitations, it is important to our patients that psychiatry continues to investigate whether a small but genuine increased risk of suicidal behavior exists early in antidepressant treatment and, if so, the ultimate biological mechanisms by which such risk occurs (and might be prevented). Exploring the antidepressant half-life theory in the TORDIA sample would be one important contribution.

References

1. Brent DA, Emslie GJ, Clarke GN, Asarnow J, Spirito A, Ritz L, Vitiello B, Iyengar S, Birmaher B, Ryan ND, Zelazny J, Onorato M, Kennard B, Mayes TL, DeBar LL, McCracken JT, Strober M, Suddath R, Leonard H, Porta G, Keller MB: Predictors of spontaneous and systematically assessed suicidal adverse events in the Treatment of SSRI-Resistant Depression in Adolescents (TORDIA) study. Am J Psychiatry 2009; 166:418–426
2. Smith EG: Association between antidepressant half-life and the risk of suicidal ideation or behavior among children and adolescents: confirmatory analysis and research implications. J Affec Disorders 2009; 114:143–148
3. Weiss JJ, Gorman JM. Antidepressant adherence and suicide risk in depressed youth. Am J Psychiatry 2005; 162:1756–1762
4. Hammad TA: Relationship Between Psychotropic Drugs and Pediatric Suicidality. Silver Spring, Md, FDA Psychopharmacologic Drugs Advisory Committee, 2004. www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4065b1-10-TAB08-Hammads-Review.pdf (accessed October 2006)

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Dr. Brent, Ms. Porta, and Dr. Emslie Reply

TO THE EDITOR: We thank Drs. Moore and Cooney for sounding a note of caution about generalizing from our finding that the use of benzodiazepines was associated with an increased risk of suicidal events and self-injury (1). Their concerns—that the number of participants who received benzodiazepines was small (N=10) and those who received benzodiazepine may have been treated for symptoms that also increased the risk for suicidal events—are valid. We did adjust for baseline differences between those who received benzodiazepines and those who did not, and our findings persisted. Nevertheless, we recognize the importance of being circumspect about drawing strong inferences from these findings. Perhaps it is useful to restate the concerns that we articulated in the Discussion: "The relationship between the use of benzodiazepines and the occurrence of self-harm events must be interpreted cautiously because of the small number involved, the heavy representation of just one site, and non-random assignment" (1, p. 424). As per our conclusion, we simply suggested "the need to re-evaluate the risk and benefits of…anti-

anxiety agents in treatment-resistant depressed adolescents at high suicidal risk" (1, p. 424).

We also appreciate the positive observations offered by Dr. Smith about our study (1, 2). He articulates the hypothesis that suicidal events are more likely to occur with the use of antidepressants with shorter half-lives, such as paroxetine, sertraline, and citalopram, than with an SSRI with a longer half-life, such as fluoxetine. As per Dr. Smith's suggestion, we examined our data in the TORDIA study to test this hypothesis.

First, we compared the rate of suicidal events in those withdrawn from fluoxetine to those withdrawn from an SSRI with a shorter half-life (i.e., citalopram, escitalopram, fluvoxamine, paroxetine, or sertraline). There was no difference in the rate of suicidal events in those withdrawn from fluoxetine relative to those withdrawn from an SSRI with a shorter half-life, although there was a trend in the hypothesized direction (9/99 [9.1%] vs. 39/235 [16.6%]; χ^2=3.19, df=1, p=0.07).

Second, we compared the rate of suicidal events as a function of the medication to which the participants were assigned in TORDIA. There was no difference in the rate of suicidal events among subjects assigned to treatment with paroxetine (3/50 [6.0%]), citalopram (4/34 [11.8%]), fluoxetine (14/84 [16.7%]), or venlafaxine extended release (27/166 [16.3%]) (Fisher's exact test, p=0.27). Even among those participants switched from shorter half-life SSRIs, there was no difference in the rate of events among those switched to paroxetine (2/24 [8.3%]), citalopram (0/7 [0.0%]), fluoxetine (14/84 [16.7%]), or venlafaxine (23/120 [19.3%]) (Fisher's exact test, p=0.48).

This conclusion is consistent with findings from the Treatment of Adolescent Depression Study (TADS), which found a higher rate of suicidal events in subjects treated with fluoxetine alone than in those treated with placebo (9.2% vs. 2.7%, p=0.04, odds ratio=3.7, 95% confidence interval, 1.0 to 13.7 [3]). Taken together, the findings from TORDIA and TADS do not support the view that a longer half-life in an antidepressant, as a treatment agent, confers protection against suicidal events, and our results are ambiguous with respect to the effect of the half-life of a drug from which a patient is withdrawn.

The half-life hypothesis, whether related to a prescribed drug or one that is being discontinued, could be further investigated using large administrative data sets, meta-analyses of randomized trials, and prospective randomized trials. We regret that the TORDIA data set could not provide a definitive answer to Dr. Smith's thought-provoking question.

References

1. Brent DA, Emslie GJ, Clarke GN, Asarnow J, Spirito A, Ritz L, Vitiello B, Iyengar S, Birmaher B, Ryan ND, Zelazny J, Onorato M, Kennard B, Mayes TL, DeBar LL, McCracken JT, Strober M, Suddath R, Leonard H, Porta G, Keller MB: Predictors of spontaneous and systematically assessed suicidal adverse events in the Treatment of SSRI-Resistant Depression in Adolescents (TORDIA) study. Am J Psychiatry 2009; 166:418–426
2. Brent DA, Emslie G, Clarke G, Wagner KD, Asarnow JR, Keller M, Vitiello B, Ritz L, Iyengar S, Abebe K, Birmaher B, Ryan N, Kennard B, Hughes C, DeBar L, McCracken J, Strober M, Suddath R, Spirito A, Leonard H, Melhem N, Porta G, Onorato M, Zelazny J: Switching to another SSRI or to venlafaxine with or without cognitive behavioral therapy for adolescents with SSRI-resistant depression: the TORDIA randomized control trial. J Am Med Assoc 2008; 299:901–913
3. Emslie G, Kratochvil C, Vitiello B, Silva S, Mayes T, McNulty S, Weller E, Waslick B, Casat C, Walkup J, Pathak S, Rohde P, Posner K, March J: Treatment for Adolescents with Depression Study (TADS): safety results. J Am Acad Child Adolesc Psychiatry 2006; 45:1440–1445

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Discontinuation of Quetiapine From an NIMH-Funded Trial Due to Serious Adverse Events

TO THE EDITOR: We have been conducting a 5-year study, funded by the National Institute of Mental Health, to compare four commonly used atypical antipsychotics (aripiprazole, olanzapine, quetiapine, and risperidone) in middle-aged and older patients with psychotic symptoms for whom a treating clinician has recommended an atypical antipsychotic. In this Institutional Review Board-approved protocol, we use equipoise-stratified randomization (1), which allows the patients and their physicians to exclude up to two of these antipsychotic agents that are not acceptable to them. The treating physician chooses the dosage and duration of treatment. The detailed study design is described elsewhere (2). We report the results of an unplanned interim analysis recommended by our Data and Safety Monitoring Board, which led to the discontinuation of quetiapine from the study. It includes the first 294 of the proposed 450 subjects to be enrolled. Sixty-one subjects dropped out prior to data collection and were excluded from analysis. Diagnoses for the remaining 233 patients were as follows: schizophrenia (32%); bipolar disorder (11%); and psychosis associated with dementia (24%), with depression (11%), with posttraumatic stress disorder (16%), or not otherwise specified (6%).

There were 79 Food and Drug Administration-defined serious adverse events (3) that occurred in 57 of the 233 study subjects while they were taking their randomly assigned drugs (Table 1). Among the patients taking quetiapine, 38.5% had serious adverse events relative to 19.0% in other groups (χ^2=9.56, df=1, p=0.002), providing a relative risk of 2.0 (confidence interval=1.3–3.1). All pairwise differences involving quetiapine were significant. Using Mantel-Haenszel tests to account for the equipoise-stratified randomization and pooling the other drug groups, the quetiapine group exhibited higher rates of serious adverse events (χ^2=5.63, df=1, p=0.022). (Pairwise differences using Mantel-Haenszel analysis did not reach significance.) Of the serious adverse events with quetiapine, 29.7% (11/37) were rated as "probably" or "possibly" related to the medication. For other drugs, 21.1% (9/42) of the serious adverse events were rated as "probably" or "possibly" related to the medication. Of the individual types of medical serious adverse events, rates of pneumonia were higher with quetiapine than with other drugs combined (p=0.011, Fisher's exact).