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First, we compared the rate of suicidal events in those withdrawn from fluoxetine to those withdrawn from an SSRI with a shorter half-life (i.e., citalopram, escitalopram, fluvoxamine, paroxetine, or sertraline). There was no difference in the rate of suicidal events in those withdrawn from fluoxetine relative to those withdrawn from an SSRI with a shorter half-life, although there was a trend in the hypothesized direction (9/99 [9.1%] vs. 39/235 [16.6%]; χ^2=3.19, df=1, p=0.07).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events, and our results are ambiguous with respect to the effect of the half-life of a drug from which a patient is withdrawn.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

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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).

TABLE 1. Serious Adverse Events With Four Atypical Antipsychotics[a]

Event	Treatment Group (randomly assigned)				Total
	Aripiprazole (N=64)	Olanzapine (N=54)	Quetiapine (N=65)	Risperidone (N=50)	
Medical hospitalization					
Cardiovascular event	3	1	3	2	9
Cerebrovascular event	0	0	1	0	1
Pneumonia	0	3	6	0	9
Seizure	0	0	2	0	2
Infection	1	0	2	0	3
Other	7[b]	4[c]	10[d]	4[e]	25
Total	11	8	24	6	49
Psychiatric hospitalization					
Worsening of psychiatric condition	4	4	5	1	14
Suicidal event	0	0	1	0	1
Total	4	4	6	1	15
Emergency room visit	0	1	3	1	5
Death	1	3	2	0	6
Other	1	1	2	0	4
Total	17	17	37	8	79

[a] Data show the number of serious adverse events.
[b] Data represent patients with altered mental status (N=2), anemia (N=1), chronic obstructive pulmonary disease (N=1), hemiarthroplasty (N=1), mastectomy (N=1), and orchiectomy (N=1).
[c] Data represent patients with a fall (N=1), gastroesophageal reflux disorder (N=1), gastrointestinal bleeding (N=1), and placement in advanced care facility (N=1).
[d] Data represent patients with acute cholecystitis (N=1), appendectomy (N=1), a fall (N=1), a fracture requiring surgical repair (N=1), gastroenteritis (N=1), a laceration (N=1), liver failure (N=1), renal failure (N=1), small bowel obstruction (N=1), and syncope (N=1).
[e] Data represent patients with chronic obstructive pulmonary disease (N=1), encephalopathy (N=1), hemiarthroplasty (N=1), and renal failure (N=1).

A multivariate logistic regression analysis for all serious adverse events was performed, covarying for age, prior antipsychotic treatment, and medical burden. The overall difference in the proportion of serious adverse events among the four drug groups remained similar in all analyses. Likewise, differences in length of treatment did not seem to be responsible for differential rates of serious adverse events, since there was no significant difference between quetiapine and other drugs regarding the duration the subjects continued to take their randomly assigned medication.

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Dr. Jeste reports that AstraZeneca, Bristol-Myers Squibb, Eli Lilly, and Janssen donated quetiapine, aripiprazole, olanzapine, and risperidone, respectively, for this NIMH-funded study.

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