Suicide Risk During Antidepressant Treatment

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Objective: In March 2004 the U.S. Food and Drug Administration (FDA) warned physicians and patients regarding increased risk of suicide with 10 newer antidepressant drugs. Available data leave considerable uncertainty regarding actual risk of suicide attempt and death by suicide during antidepressant treatment. The authors used population-based data to evaluate the risk of suicide death and serious suicide attempt in relation to initiation of antidepressant treatment.

Method: Computerized health plan records were used to identify 65,103 patients with 82,285 episodes of antidepressant treatment between Jan. 1, 1992, and June 30, 2003. Death by suicide was identified by using state and national death certificate data. Serious suicide attempt (suicide attempt leading to hospitalization) was identified by using hospital discharge data.

Results: In the 6 months after the index prescription of antidepressant treatment, 31 suicide deaths (40 per 100,000 treatment episodes) and 76 serious suicide attempts (93 per 100,000) were identified in the study group. The risk of suicide attempt was 314 per 100,000 in children and adolescents, compared to 78 per 100,000 in adults. The risk of death by suicide was not significantly higher in the month after starting medication than in subsequent months. The risk of suicide attempt was highest in the month before starting antidepressant treatment and declined progressively after starting medication. When the 10 newer antidepressants included in the FDA advisory were compared to older drugs, an increase in risk after starting treatment was seen only for the older drugs.

Conclusions: The risk of suicide during acute-phase antidepressant treatment is approximately one in 3,000 treatment episodes, and risk of serious suicide attempt is approximately one in 1,000. Available data do not indicate a significant increase in risk of suicide or serious suicide attempt after starting treatment with newer antidepressant drugs.

In March 2004, the U.S. Food and Drug Administration (FDA) issued a public health advisory regarding worsening depression and suicidality in pediatric and adult patients being treated with 10 newer antidepressants (bupropion, citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, escitalopram, and venlafaxine) (1). The March 2004 advisory recommended close observation for the emergence of suicidality in all patients treated with antidepressants, especially at the time of treatment initiation or dose increase. The FDA warning prompted reports in the medical (2, 3) and lay (4, 5) press that antidepressants could worsen depression or increase the risk of suicide in adults as well as adolescents.

The United Kingdom Committee on Safety of Medicines first raised concerns about suicide risk in early 2003 after reports of self-harm and potentially suicidal behavior in adolescents treated with paroxetine (6). Subsequent reanalyses of clinical trial data indicated higher rates of "possibly suicide-related events" in adolescents treated with several newer antidepressants (7). After reviewing these data in February 2004, the FDA advisory committee commissioned a reevaluation and reanalysis of data from all pediatric antidepressant trials. That meta-analysis found a significantly higher risk of suicidal behavior in adolescents treated with newer antidepressants than in those who received placebo, and the FDA advisory committee recommended a "black box" warning regarding risk of antidepressant use in adolescents. A requirement for a "black box" warning for all antidepressants was issued in October 2004.

The March 2004 FDA advisory acknowledged that the available data did not indicate any increased risk in adults treated with antidepressants (8). Absent such data, the March 2004 FDA warning was based on traditional clinical wisdom that early activating effects of antidepressants may transiently increase suicide risk (9) and on the compelling personal accounts by family members of suicide victims (8, 10). The most recent reanalysis of clinical trial data and the most recent advisory committee recommendation did not consider risk in adults.

Before the current controversy, two meta-analyses of data from adult clinical trials found no difference between antidepressant drugs and placebo in risk of suicide during short-term treatment (11, 12). Ironically, those meta-analyses were motivated by ethical concerns about suicide risk in study subjects who were randomly assigned to receive

FIGURE 1. Risk of Suicide Death During the First 6 Months After Initial Antidepressant Prescription, by Patients' Sex and Age[a]
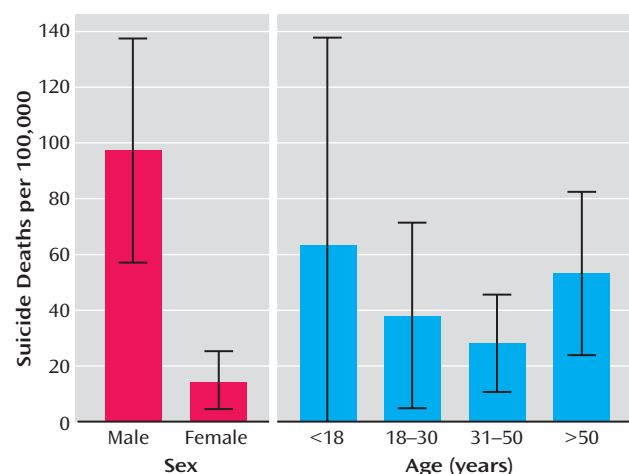
[a] Bars indicate 95% confidence intervals.

placebo. Because clinical trials typically exclude those at high risk for suicide, some writers have questioned whether suicide risk in clinical trial populations underestimates true risk in those treated for depression (13, 14).

Jick and colleagues (15) used data from a United Kingdom general practice network to examine risk of suicide attempt and completed suicide after starting antidepressant treatment. Risk was four times higher in the 9 days after an initial prescription than in the subsequent 80 days, but no data were presented regarding risk of suicide attempt before starting treatment. The authors suggested that the increased risk after starting treatment reflected more severe depression early in treatment rather than a medication-induced increase in risk. Risk did not vary significantly across the four antidepressants examined (amitriptyline, dothiepin, fluoxetine, and paroxetine).

In this study, we used computerized records from a large prepaid health plan in the United States to address three questions: 1) What is the risk of death by suicide and serious suicide attempt (i.e., suicide attempt leading to hospitalization) during acute-phase antidepressant treatment? 2) Is there an increased risk of death by suicide or serious suicide attempt during the month after starting an antidepressant? 3) Are the drugs included in the FDA warning associated with higher risk of death by suicide or serious suicide attempt than are older antidepressants?

Method

Setting

Group Health Cooperative (GHC) is a mixed-model prepaid health plan serving approximately 500,000 members in the states of Washington and Idaho. The GHC membership is demographically similar to the area population (16). During the study period, approximately 10% of members were enrolled through Medicare (for elderly and disabled persons) and an additional 7% through low-income insurance programs (Medicaid and Basic Health Plan). At GHC, the majority of antidepressant treatment is prescribed by primary care physicians. Specialty mental health care is available without referral, and medication management visits to psychiatrists or psychiatric nurse practitioners are covered at parity with general medical visits. From 1992 to 2002, overall mortality due to suicide in the GHC population was approximately 17 per 100,000. The GHC Human Subjects Review Committee approved all study procedures and granted a waiver of consent for use of administrative data.

Data Sources

Data were extracted from four computerized record systems. Computerized pharmacy records include data on date, drug dispensed, and prescribing physician for all prescriptions filled at GHC pharmacies. Previous research indicates that GHC members fill more than 95% of antidepressant prescriptions at GHC pharmacies (17). Outpatient visit registration data include all billing or encounter diagnoses for visits covered by GHC. Hospital discharge data include all recorded diagnoses for all hospital admissions (medical and psychiatric) to GHC and non-GHC facilities. Mortality records are created annually by linking GHC membership rolls to state and national death certificate data. This database tracks date and cause of death for all persons ever enrolled in GHC, regardless of continued enrollment.

We identified all episodes of antidepressant treatment that met the following criteria: 1) outpatient antidepressant prescription filled between Jan. 1, 1992, and June 30, 2003, 2) no antidepressant prescription filled in the previous 180 days (i.e., the index prescription was the first prescription in a new episode of treatment), and 3) visit diagnosis of unipolar major depressive disorder (ICD-9 codes 296.2, 296.3), dysthymia (ICD-9 code 300.04), or depressive disorder not otherwise specified (ICD-9 code 311) during the 30 days before or 30 days after the index prescription.

To ensure correct identification of new treatment episodes, the sample was further limited to persons enrolled in the health plan during the 6 months before the index prescription. Mean duration of enrollment before the index prescription was 8.9 years (SD=6.5).

Two outcomes were examined. Suicide attempt with hospitalization was defined as a hospital admission associated with any diagnosis of suicide attempt (ICD-9 codes E950 to E959) during the period beginning 90 days before the index prescription and ending 180 days after. Hospitalization data were available through Dec. 31, 2003. Suicide death was defined as any death certificate diagnosis of suicide attempt (ICD-9 codes E950 to E959 or ICD-10 codes X60 to X84 and Y87) during the period beginning on the day of the index prescription and ending 180 days after. Death certificate data were available through Dec. 31, 2002. Any individual could contribute more than one treatment episode to the sample.

Data Analysis

Rates for suicide attempt were calculated by using the complete sample of new treatment episodes. Because mortality data were available only through Dec. 31, 2002, rates for suicide death were limited to those episodes with an initial prescription date on or before June 30, 2002. Samples for calculation of month-by-month rates were further limited as follows: 1) Rates of suicide death in any month included all patients alive at the start of that month, and 2) rates of suicide attempt included all persons alive at the beginning of the month and enrolled in the health plan throughout the month. To account for multiple observations per person, comparisons of rates between patient groups or across months were performed by using repeated-measures logistic models implemented through generalized estimating equations.

FIGURE 2. Risk of Suicide Attempt During the First 6 Months After Initial Antidepressant Prescription, by Patients' Sex and Age[a]

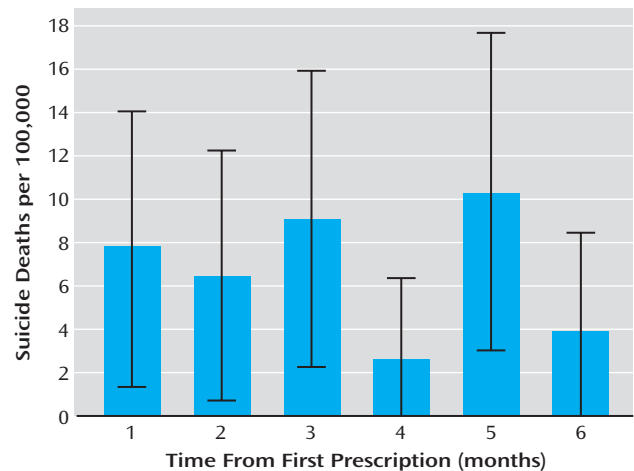[a] Bars indicate 95% confidence intervals.

FIGURE 3. Rates of Suicide Death During the First 6 Months After Initial Antidepressant Prescription[a]
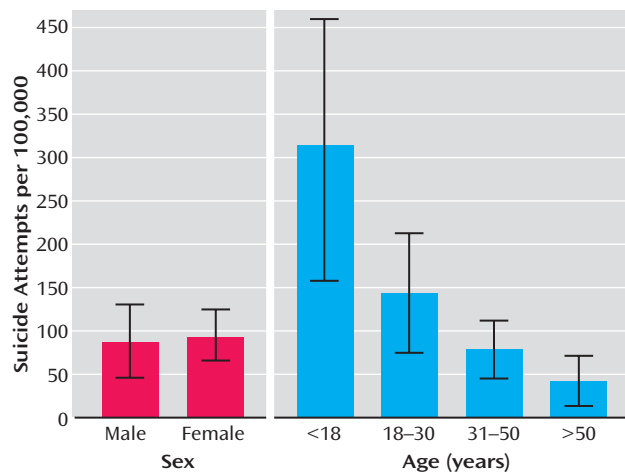
[a] Bars indicate 95% confidence intervals.

Role of Funder

The funder (National Institute of Mental Health) had no role in study design, data collection, data analysis and interpretation, or preparation of this report.

Results

Using the procedures described in the Method section, we identified 82,285 episodes of antidepressant treatment among 65,103 health plan members during the 10.5-year study period. A total of 9,520 members contributed two treatment episodes to the sample, and 1,916 members contributed more than two episodes. A total of 69.5% (N= 45,247) of the subjects were female. Age at time of the index prescription ranged from 5 to 105 years (mean=44 years [SD=18]). A total of 5,107 episodes (6.2%) were among patients age 17 years or younger.

Using computerized records, we identified 31 suicide deaths (40 per 100,000 treatment episodes) and 76 suicide attempts leading to hospitalization (93 per 100,000 treatment episodes) during the 6-month follow-up period. There were 73 suicide attempts leading to hospitalization during the 3 months before the index prescription. Demographic correlates of suicide death and suicide attempt are shown in Figure 1 and Figure 2. In a repeated-measures logistic model with adjustment for year of treatment, the probability of suicide death was significantly higher in male subjects (odds ratio=6.6, 95% confidence interval [CI]=2.9–14.7), but it did not vary significantly across age categories. The probability of suicide attempt did not vary significantly between male and female subjects but was strongly related to younger age ($z=3.18$, $p<0.001$). Absolute rates were 314 per 100,000 in children and adolescents (95% CI=160–468), compared to 78 per 100,000 in adults (95% CI=58–98).

The risk of suicide death was relatively stable during the 6 months after initiation of antidepressant treatment (Figure 3), but the confidence intervals for the risk estimates were wide, reflecting the small number of events. In a repeated-measures logistic model with adjustment for age, sex, and year of treatment, the risk of suicide death in the first month of treatment was not significantly higher than in subsequent months (odds ratio=1.2, 95% CI=0.5–2.9). The number of suicide deaths in adolescents (N=3) was too small to support analysis of time trends.

As shown in Figure 4, the risk of serious suicide attempt was higher in the month after starting treatment than in the subsequent 5 months (odds ratio=2.4, 95% CI=1.6–3.8). The highest risk, however, was seen in the month before starting treatment. Although the total number of events in adolescents was much smaller (N=17), the pattern of risk over time (Figure 4) was generally similar to that in adults, with the highest risk in the month before starting treatment, a sharp decline immediately after starting treatment, and a gradual decline over the next 6 months. Analyses for Figure 4 were repeated after excluding subjects with any record of previous suicide attempt, after excluding those with any record of previous antidepressant treatment, and after excluding those whose antidepressants were switched during the current treatment episode. In all three cases, the results were essentially identical to those in the main sample: risk was highest in the month before starting medication, fell by more than one-half in the month after starting medication, and declined progressively after that.

The months immediately before and after the index prescription were further subdivided into 7-day periods. As shown in Figure 5, the higher rate of suicide attempts during the month before starting treatment was primarily attributable to increased risk in the 7 days before the index prescription. Suicide attempts during the first month of

FIGURE 4. Rates of Suicide Attempts During the 3 Months Before and the 6 Months After Initial Antidepressant Prescription[a]
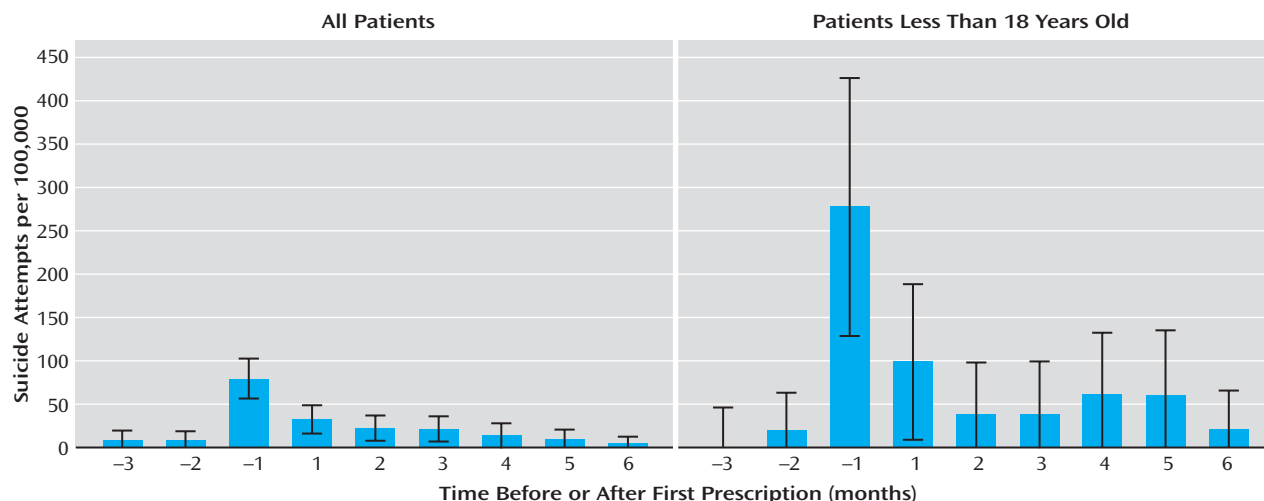
[a] Bars indicate 95% confidence intervals.

FIGURE 5. Rates of Suicide Attempts During the 4 Weeks Before and 4 Weeks After Initial Antidepressant Prescription[a]
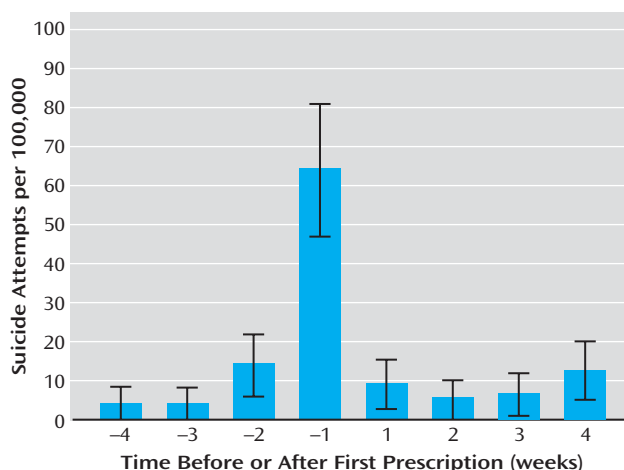
[a] Bars indicate 95% confidence intervals.

treatment were relatively evenly distributed throughout the month.

The final set of analyses compared risk during treatment with one of the 10 newer antidepressants included in the FDA warning (56,570 episodes) to that during treatment with other antidepressants (25,715 episodes). The category of other antidepressants included primarily tricyclic antidepressants (76%) and trazodone (21%). Risk of suicide death over 6 months was 34 per 100,000 for drugs included in the FDA warning, compared to 51 per 100,000 for other drugs. Risk of suicide attempt leading to hospitalization in the 6-month period was 76 per 100,000 among those using drugs included in the FDA warning, compared to 129 per 100,000 in those using other drugs. Older drugs were more often prescribed at the beginning of the study period, when the rates of hospitalization were generally higher. After adjustment for year of treatment in logistic regression models, the risk of suicide death and the risk of suicide attempt were not significantly lower in patients treated with newer drugs (odds ratio for suicide death=0.6, 95% CI=0.3–1.4; odds ratio for suicide attempt= 0.9, 95% CI=0.5–1.6). Month-by-month analyses of suicide attempt rates, however, revealed different patterns for newer and older drugs. Among those treated with newer antidepressants (Figure 6), risk was highest in the month before starting treatment, and risk in the first month of treatment was not significantly higher than in months 2–6 (odds ratio=1.6, 95% CI=0.9–3.1). Among those treated with older drugs (Figure 6), risk was highest in the first month of treatment, and risk in the first month of treatment was significantly higher than in months 2–6 (odds ratio=3.6, 95% CI=1.8 to 6.9).

Discussion

Risk of suicide death during acute-phase antidepressant treatment was approximately one in 3,000, and risk of suicide attempt leading to hospitalization was approximately one in 1,000. This rate of suicide death is similar to that reported in other community samples (18–20) and in pooled analyses from antidepressant clinical trials (11). This rate may appear low in comparison to the often cited statistic that 15%–20% of people with a depressive disorder die by suicide. As we (18) and others (20) have pointed out, that 15%–20% range, which is based on inpatient samples, significantly overestimates risk for the general population of patients treated for depression.

Our data do not suggest increased risk of suicide death or serious suicide attempt during the first month of antidepressant treatment. Risk of suicide death appeared fairly constant throughout the first 6 months. In agreement with Jick and colleagues (15), we found a significantly higher risk of suicide attempt in the first week of antidepressant treatment than in subsequent weeks. Our

FIGURE 6. Rates of Suicide Attempts During the 3 Months Before and the 6 Months After Initial Prescription of Antidepressants That Were or Were Not Included in the March 2004 Advisory of the U.S. Food and Drug Administration (FDA)[a]

Newer Antidepressants
Included in March 2004 FDA Advisory

Older Antidepressants Not
Included in March 2004 FDA Advisory
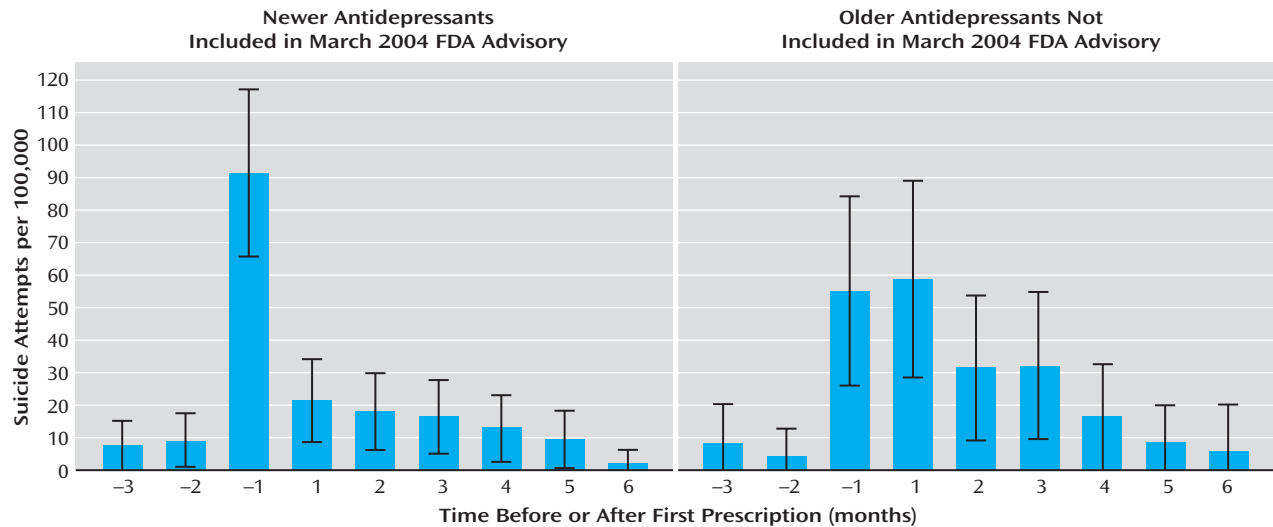
[a] Bars indicate 95% confidence intervals. The newer antidepressants included in the March 2004 advisory were bupropion, citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, escitalopram, and venlafaxine. The older antidepressants not included in the March 2004 advisory were primarily tricyclic antidepressants (76%) and trazodone (21%).

data supply two additional findings. First, we separated suicide attempts from suicide deaths. Although attempts were more common soon after initiation of antidepressant treatment, suicide deaths appeared relatively constant over the first 6 months of treatment. Second, we also examined risk of suicide attempt before treatment. We found that risk was highest in the month before the initial prescription, probably because of the fact that suicide attempt may prompt initiation of treatment. The patterns shown in Figure 4 and Figure 5 appear more consistent with a decline in risk after initiation of treatment than with a medication-induced increase. This trend in suicide attempts probably reflects improvement in depression rather than a specific effect of treatment on suicidality. The decline in suicide attempts shown in Figure 4 closely parallels the trend in depressive symptoms seen in patients who receive new antidepressant prescriptions (21).

Also in agreement with Jick and colleagues (15), we found no evidence of greater risk for the newer drugs included in the FDA advisory. Overall risk did not differ by drug class after adjustment for year of treatment. The results of the month-by-month comparison of newer and older drugs (Figure 6) certainly argue against any increase in risk specific to newer antidepressants. Only among those who used older antidepressant drugs (not included in the FDA warning) was the risk of suicide attempt in the first month of treatment as high as in the month before starting medication. This pattern may reflect the longer time necessary to reach a therapeutic dose with older antidepressants.

Our data certainly do not exclude the possibility that antidepressant drugs may precipitate increased suicidal ideation or suicide attempts in a subgroup of vulnerable individuals (22). If it occurs, however, such a phenomenon must be infrequent enough to be hidden by the general decline in risk of suicide attempts after starting antidepressant treatment.

An observational study such as this one can neither clearly establish nor clearly refute a causal relationship between antidepressant use and risk of suicide. Decisively settling questions of causality would require randomized comparison of individual antidepressants to placebo in a sample large enough to measure differences in suicide attempts or suicide death. Pooled data from previous randomized trials indicate no difference in risk between patients exposed to antidepressants and those exposed to placebo (11, 12). Given the risk observed in our sample, a new study comparing any single drug to placebo would require more than 300,000 participants to detect a twofold difference in risk of suicide death during the first month of treatment. For a study of suicide death or serious suicide attempts, it will be necessary to rely on multiple sources of data, including both large observational studies and randomized trials.

The primary stimulus for recent concerns regarding an increase in suicide risk with antidepressants was the higher rate of "possibly suicide-related" events in adolescents enrolled in antidepressant clinical trials. Some writers questioned whether these events represented serious suicide attempts and whether such events accurately indicated risk of completed suicide (2). With this issue in mind, we limited our analyses to suicide attempts that led to hospitalization. We still found that suicide attempts and suicide deaths are quite distinct phenomena. Among men older than age 50 years, we observed 10 suicide deaths and three nonfatal suicide attempts that led to hospitalization.

Among women age 30 years or younger, this ratio was reversed: three suicide deaths and 28 nonfatal attempts that led to hospitalization. We urge caution in using data regarding suicidal ideation or suicide attempts to make predictions regarding risk of suicide death.

Adolescents constituted a small portion of our sample and accounted for three suicide deaths and 17 serious suicide attempts. Risk of serious suicide attempt in adolescents was four times as high as in adults, but the pattern over time was similar in the two groups (Figure 4). The October 2004 FDA advisory was based on a sample of 33 instances of "suicidal behavior," including 26 suicide attempts and no suicide deaths. Further research regarding risks of antidepressant treatment in this group is clearly needed. Our data contribute nothing to the debate regarding the efficacy or clinical appropriateness of antidepressant treatment for adolescents (23, 24).

Several limitations should be considered in interpreting these data. First, outpatient prescription records would misclassify the starting date for antidepressant treatment begun during hospitalization. In outpatient prescription records, the period of inpatient treatment (a period of low risk for suicide attempt) would be misclassified as preceding the index prescription rather than following it. The resulting bias would lead to underestimation of risk before treatment was started and overestimation of risk in the first month after starting treatment. Second, these data were drawn from a single health care system, and the findings might not generalize to the larger population if suicide risk was lower or if the intensity of follow-up care for depression was greater in the GHC population. Our estimates of suicide risk, however, are similar to those in other treated samples (11, 19, 20). The frequency of depression follow-up visits at GHC may be greater than in other U.S. health plans, but those differences are modest (21, 25). Third, we relied on death certificates for identification of suicide deaths, and those data may underestimate suicide rates by 10%–20% (26–28). In our previous research in the GHC population, broadening the definition of suicide to include all deaths due to injuries with "undetermined" causes increased rates by only 10% (18). Fourth, some writers have questioned whether suicidal ideation or suicide attempts during antidepressant treatment might be associated with medication lapses or discontinuation (29). Unfortunately, prescription refill data cannot date medication discontinuation with the precision necessary to study discontinuation reactions (30).

With respect to our three study questions, these data support the following conclusions: First, the rates of serious suicide attempt and suicide death during acute-phase antidepressant treatment are approximately 90 per 100,000 and 40 per 100,000, respectively. Second, available data do not indicate an increased risk of suicide or serious suicide attempt after starting antidepressant medication. Third, risk was not higher among those treated with newer antidepressants.

The March 2004 FDA warning advised closer monitoring of adolescents and adults who are beginning antidepressant treatment. As we (21, 31) and others (32) have pointed out, frequency of follow-up care after a new antidepressant prescription is often grossly insufficient. More systematic follow-up care significantly improves both adherence to treatment and clinical outcomes (33, 34). Closer monitoring of antidepressant treatment is clearly needed, but warnings regarding suicide precipitated by antidepressants may do more to discourage effective treatment than to improve the quality of follow-up care.

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