Antidepressants and the Risk of Suicidal Behaviors

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In 1991 the US Food and Drug Administration (FDA) held a public meeting to address widespread concerns that a recently marketed selective serotonin reuptake inhibitor (SSRI) antidepressant, fluoxetine (Prozac), was causing severe suicidal behaviors. Dozens of attendees related personal experiences that described such behavior in relatives and friends shortly after they had started taking fluoxetine for depression.1

Subsequently, a meta-analysis of clinical trial data pooled from 17 double-blind studies conducted by Eli Lilly & Co, the marketer of fluoxetine, concluded that “data from these trials do not show that fluoxetine is associated with an increased risk of suicidal acts. . . .”2 The authors of 2 formal epidemiological studies on the relation of fluoxetine and suicidal behavior concluded that the findings indicated that the risk of such behavior in fluoxetine users was not materially different from that among users of certain other commonly prescribed antidepressants.3,4

More recently questions about the safety of paroxetine, another SSRI, in relation to suicidal behavior have been the subject of public broadcast programs such as Panorama in the United Kingdom, which highlighted a possible increased risk in young people.

The UK Committee on Safety of Medicines issued an interim report of an

Context The relation between use of antidepressants, especially selective serotonin reuptake inhibitors (SSRIs), and suicidal ideation and behaviors has received considerable public attention recently. The use of such drugs among teenagers has been of particular concern.

Objective To estimate the relative risks (RRs) of nonfatal suicidal behavior in patients starting treatment with 1 of 3 antidepressant drugs compared with patients starting treatment with dothiepin.

Design and Setting Matched case-control study of patients treated in UK general practices using the UK General Practice Research Database for 1993-1999.

Participants The base population included 159810 users of the 4 antidepressant drugs. Participants could have used only 1 of these antidepressants and had to have received at least 1 prescription for the study antidepressant within 90 days before their index date (the date of suicidal behavior or ideation for cases and the same date for matched controls).

Main Outcome Measures Frequency of first-time exposure to amitriptyline, fluoxetine, paroxetine, and dothiepin of patients with a recorded diagnosis of first-time nonfatal suicidal behavior or suicide compared with comparable patients who did not exhibit suicidal behavior.

Results After controlling for age, sex, calendar time, and time from first antidepressant prescription to the onset of suicidal behavior, the relative risks for newly diagnosed nonfatal suicidal behavior in 555 cases and 2062 controls were 0.83 (95% confidence interval, [CI] 0.61-1.13) for amitriptyline, 1.16 (95% CI, 0.90-1.50) for fluoxetine, and 1.29 (95% CI, 0.97-1.70) for paroxetine compared with those using dothiepin. The RR for suicidal behavior among patients first prescribed an antidepressant within 1 to 9 days before their index date was 4.07 (95% CI, 2.89-5.74) compared with patients who were first prescribed an antidepressant 90 days or more before their index date. Time since first antidepressant prescription was not, however, a confounder of the relation between specific antidepressants and suicidal behavior since its relation to suicidal behavior was not materially different among users of the 4 study drugs. Similarly for fatal suicide, the RR among patients who were first prescribed an antidepressant within 1 to 9 days before their index date was 38.0 (95% CI, 6.2-231) compared with those who were first prescribed an antidepressant 90 days or more before their index date. There were no significant associations between the use of a particular study antidepressant and the risk of suicide.

Conclusions The risk of suicidal behavior after starting antidepressant treatment is similar among users of amitriptyline, fluoxetine, and paroxetine compared with the risk among users of dothiepin. The risk of suicidal behavior is increased in the first month after starting antidepressants, especially during the first 1 to 9 days. A possible small increase in risk (bordering statistical significance) among those starting the newest antidepressant, paroxetine, is of a magnitude that could readily be due to uncontrolled confounding by severity of depression. Based on limited information, we also conclude that there is no substantial difference in effect of the 4 drugs on people aged 10 to 19 years.

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expert working group on SSRIIs in September 2003. It described 2 areas of “continuing concern and scientific debate,” ie, suicidal behavior associated with treatment with SSRIIs and withdrawal reactions on stopping these drugs. It referred to prior warnings that “as with all antidepressants, suicidal thoughts may occur or increase in the early stages of treatment.” It added that “these issues have remained of public concern and recently this concern has focused on 1 SSRI, Seroxat (paroxetine).” Finally, it referred to clinical trials conducted by the manufacturer, which apparently led the working group to conclude that “paroxetine was contraindicated in patients under the age of 18 with major depressive disorder.” To our knowledge, the methods and results of these clinical trials, with 1 possible exception, have not been made public and we were unable to obtain further relevant documentation of the methods and results of these trials, from either the manufacturer of paroxetine or from the UK Medicines and Health Care Products Regulatory Agency. There has been controversy surrounding the possibility that the regulatory decision was influenced by selective reporting of favorable research results.

Most recently, on October 27, 2003, the FDA issued a talk paper on antidepressants and suicidal behavior in young people, emphasizing the continuing uncertainty surrounding this issue and calling for “additional data, analysis and a public discussion of available data.” Following a public meeting of the FDA Psychopharmacologic Advisory Committee and the Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committee on February 2, 2004, a Public Health Advisory was issued by the FDA in which the agency asked manufacturers of 10 different antidepressant drugs to include in their labeling a Warning section that recommends close observation of adult and pediatric patients treated with these agents for worsening depression or the emergence of suicidality.

The epidemiology of suicidal behavior in persons taking antidepressant drugs is not well documented by formal observational studies and much of the current debate is based on anecdotal experience. However, 2 major risk factors for such behavior have been convincingly demonstrated. First, a past episode of suicidal behavior is strongly associated with an increased risk for subsequent suicidal behavior. Second, persons who have been prescribed more than 1 antidepressant medication over time are substantially more likely to develop suicidal behavior than those who have taken only 1 antidepressant. This latter characteristic is likely to reflect more severe depression or depression that is resistant to prior therapy.

With consideration for these established strong risk factors in mind, we designed a case-control study to compare the risk of newly diagnosed suicidal behavior in recipients of amitriptyline, fluoxetine, or paroxetine with that in recipients of dothiepin. The study was based on the UK General Practice Research Database (GPRD), a highly accurate, detailed, and complete body of medical data encompassing more than 3 million people over a period of more than 10 years.

METHODS

Data Source

The UK GPRD has been described previously. Since 1987, more than 3 million residents in the United Kingdom have been enrolled with selected general practitioners who have agreed to provide data for research purposes to the GPRD. The general practitioners received 12 months of instruction on the standardized recording of medical information and they agreed to supply anonymized information to academic researchers on an ongoing basis. The information recorded includes patient characteristics, drugs dispensed, clinical diagnoses, notation of referrals to consultants, emergency department visits, hospitalizations, certain historical information, and other findings (eg, smoking status, blood pressure, height and weight). Referral letters from consultants and hospitalizations are kept in a manual file and are available to researchers (in anonymized form) upon request.

A modification of the Oxford Medical Information System (OXMIS) classification was used to enter medical diagnoses and a coded drug dictionary based on the Prescription Pricing Authority’s dictionary was used for recording prescriptions. Validation studies (examples of which are listed in Jick et al) have determined that information on patient referrals and hospitalizations available in the manual medical records in the general practitioners’ offices was recorded on the computer more than 90% of the time. Diagnostic codes for suicidal behavior, suicidal ideation, and suicide were recorded by general practitioners based on all available information.

The United Kingdom is an optimal setting for the development of a large computerized database derived from patient information held by general practitioners because the general practitioner’s record is the repository for virtually all medical information about each patient. All hospitalizations, emergency department visits, and referrals must be reported in writing to the general practitioner, and when patients are seen for medical reasons outside the general practice, it is required by the UK National Health Service that a written report on the details of the events be provided to the general practice with which a patient is registered. Causes of death, in particular, are routinely recorded. Thus, the general practitioner has a comprehensive record of a patient’s health care. An additional advantage of the computer systems used to generate information for the GPRD is that when a prescription is written by a general practitioner, the information is automatically entered into the computerized medical record, thereby ensuring that a complete listing of all outpatient medications is present on the computer.

Base Population

The base population included all persons who filled at least 1 prescription for amitriptyline, fluoxetine, paroxetine, or dothiepin during the 1993-1999 years.
ANTIDEPRESSANTS AND RISK OF SUICIDAL BEHAVIORS

Data after 1999 were not included because of changes in computer software and diagnostic codes for nonfatal suicidal behavior that were implemented at various times in the late 1990s among participating practices, which precluded a direct application of the study design criteria to the later data.

We chose to study these 4 drugs because they were the most commonly prescribed antidepressants in the United Kingdom over the past decade and because they represent 2 distinct pharmacologic classes (tricyclic antidepressants and SSRIs). There were 159810 such persons—36165 people (22.6%) received amitriptyline; 46587 (29.2%), dothiepin; 49671 (31.1%), fluoxetine; and 35465 (22.2%), paroxetine. (Patients in the base population may have used more than 1 antidepressant, so these numbers total more than 100%.) There were 6976 persons aged 10 to 19 years, and 66% of the base population was female.

The mean number of study antidepressant prescriptions recorded over time was closely similar for each drug, varying from 4.6 to 4.8 per patient. However, the proportion of patients in the base population who received other antidepressant drug was substantially different among users of each drug. For users of amitriptyline and dothiepin, 2 tricyclic antidepressants, 19% and 20%, respectively, received at least one prescription for some other antidepressant either before or after their first prescription for the tricyclic antidepressant; for fluoxetine and paroxetine users it was 28% and 34%, respectively. This indicates that persons who received the 2 study SSRIs were almost 50% more likely than those who received the 2 study tricyclic antidepressants to have required a change in antidepressant treatment, consistent with findings in our earlier studies.3,4

Nonfatal Suicidal Behavior

Cases. Cases were those who (1) had a first-time recorded diagnosis of nonfatal suicidal ideation (OXMIS codes 3009B1, 3009BT, 3009BP, 3009CT) or attempted suicide (OXMIS codes 3009C, 9779A, 9779L, 9779NA) at age 10 through 69 years during the period 1993-1999, (2) had received at least 1 prescription for a study antidepressant within 90 days before their index date, ie, the date of the first diagnosis of suicidal behavior, and (3) had had at least 2 years of recorded history in the GPRD before their index date. To reduce likely confounding due to prior treatment failure with another antidepressant, we excluded those who had a recorded prescription for another antidepressant or who had recorded prescriptions for more than 1 study antidepressant prior to their index date. Also, to reduce heterogeneity in the study population due to disorders that may confer an altered risk of suicidal behavior compared with depression alone, we excluded patients with a recorded history of psychosis, panic disorders, phobias, obsessive-compulsive neurosis, manic-depressive disease, drug abuse, alcohol abuse, epilepsy, anorexia, bulimia, and attention-deficit disorder.

Controls. We identified control patients within the same base population from which the cases were drawn (ie, patients who had at least 1 recorded prescription for 1 of the 4 study drugs). For each case we identified up to 4 controls (ie, patients who did not develop suicidal behavior) matched by age (within 2 years), sex, and duration of recorded history in the GPRD (within 1 year). Controls were identified from the practices from which the cases were derived. Controls were assigned the same index date as the case to which they were matched. As we did for the cases, we required that the controls have at least 1 prescription for a study antidepressant recorded within 90 days before their index date. We applied all the same exclusions to the controls as to the cases.

Exposure

By design, each patient was currently or recently exposed to 1 and only 1 of the 4 study antidepressants, defined as having at least 1 recorded prescription within 90 days before their index date. Before we analyzed the data, we decided to compare the risk of suicidal behavior among patients who used amitriptyline, fluoxetine, or paroxetine to that among users of dothiepin (reference exposure) because dothiepin was the tricyclic antidepressant drug most frequently prescribed during the period we studied. (Dothiepin is not currently licensed for marketing in the United States and is distinct from the antidepressant drug doxepin, which is currently available in the United States.) Using information on the number of pills prescribed and the instructions for use of the last antidepressant prescription before the index date, we also estimated the relative risk of suicidal behavior among patients whose last antidepressant prescription was calculated to end before their index date (those who “stopped”) compared with those whose last antidepressant prescription before their index date was calculated to end on or after their index date. In addition, for each person, we calculated the time interval in days from the date of the first recorded prescription for the antidepressant to the index date and analyzed the association between this interval and the risk of suicidal behavior.

Suicide

We also identified all patients aged 10 through 69 years in the base population who committed suicide in 1993-1999, who received at least 1 prescription for 1 of the 4 study drugs within 90 days before their index date and who had at least 2 years of follow-up in the GPRD before their index date. The same exclusions were applied to these suicide cases as to the nonfatal suicidal behavior cases. We matched up to 10 controls to each case by age (within 2 years) and sex. Controls received at least 1 prescription for 1 of the 4 study drugs within 90 days before their index date and had at least 2 years of follow-up in the GPRD before their index date. The same exclusions were applied to the controls as to the cases.

Analysis

We used conditional logistic regression13 to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for asso-
cations between exposure to the various study antidepressants and nonfatal suicidality and, separately, suicide itself, using dothiepin as the reference exposure. We studied the effect of time since the first antidepressant prescription on the relative risk of suicidality (with 90 days or longer as the reference category). Also we evaluated the effect of stopping antidepressant treatment among cases and controls who started more than 30 days before their index date. We examined the possibility of effect measure modification by the use of multiplicative interaction terms and likelihood ratio testing. In addition, we evaluated smoking and body mass index (BMI) as potential confounders of the associations between suicidality, and antidepressant treatment. We also carried out separate analyses among 10- through 19-year-old patients. We used SAS version 8.02 (SAS Institute Inc, Cary, NC) for all analyses. P < .05 was considered statistically significant.

RESULTS
Nonfatal Suicidal Behavior
After exclusions, the study included 555 cases with a first-time episode of nonfatal suicidal behavior or ideation and 2062 controls. Cases of nonfatal suicidal behavior were predominantly female (65.4%). Most cases (75.3%) were under 30 years of age. About 80% of cases who attempted suicide were recorded as having been hospitalized or evaluated in an emergency department, and an additional 5% were referred to a psychiatric specialist but were not hospitalized or seen in an emergency department. By contrast, approximately 30% of patients who had only suicidal ideation were hospitalized or evaluated in an emergency department while 55% were referred to a specialist but not hospitalized or seen in an emergency department.

When we evaluated the possible effects of the 4 antidepressant drugs on suicidal behavior, we discovered that the time since starting the antidepressant was strongly associated with the outcome. Compared with patients who had started taking a study antidepressant more than 90 days before developing nonfatal suicidal behavior, those who had started taking their study antidepressant within 1 to 9 days before their index date were more than 4 times as likely to have a first nonfatal suicidal episode (adjusted OR, 4.07); those who had received a first prescription 10 through 29 days before their index date were almost 3 times as likely to develop a nonfatal suicidal behavior (adjusted OR, 2.88); those who had received their first prescription 30 to 89 days before their index date were one and one half times as likely (OR, 1.53; Table 2). This association was increasingly prominent with increasing age (P = .025 for trend). However, there was no modification of the effect of time since starting antidepressant treatment by sex or antidepressant drug.

The adjusted OR estimates comparing amitriptyline, fluoxetine, and paroxetine each with dothiepin as the reference group were 0.83, 1.16, and 1.29, respectively (Table 3). All of the 95% confidence intervals included 1 although the OR comparing paroxetine...
and dothiepin bordered on statistical significance. We found no evidence of effect modification by age or sex. Among 10-through 19-year-olds, the ORs of nonfatal suicidal behaviors 10 through 19 years (vs users of dothiepin, adjusted for time since starting antidepressant therapy) were 0.9 (95% CI, 0.3-2.8) for amitriptyline users, 1.3 (95% CI, 0.6-3.0) for fluoxetine users, and 1.7 (95% CI, 0.7-4.1) for paroxetine users.

In order to examine an important potential withdrawal symptom after an antidepressant is stopped, we evaluated the association between stopping an antidepressant and nonfatal suicidal behaviors. Among patients who started taking their antidepressant 30 days or more before their index date, we found no evidence for an increased risk of nonfatal suicidal behaviors among patients whose last antidepressant prescription was estimated to end before their index date (ie, those who “stopped”; Table 4) vs those whose antidepressant prescription continued up to or beyond their index date.

**Suicide**

There were 17 patients who committed suicide, who received only 1 of the study drugs within 90 days before the index date and who had no prior documented suicidal behavior. In contrast to nonfatal suicidal behavior cases, the majority of suicide cases were males: 13 (76%), and 4 (24%) were females. None of these suicides occurred in patients aged 10 through 19 years. Nine cases (53%) were aged 20 to 39 years and 8 (47%) were aged 40 to 69 years. Three cases and 37 controls received amitriptyline, 7 cases and 52 controls received dothiepin, 4 cases and 36 controls received fluoxetine, and 3 cases and 32 controls received paroxetine. Adjusted for time since starting antidepressant treatment and using dothiepin as the reference group, there were no significant associations between the specific antidepressant drugs and the risk of suicide.

Time since starting antidepressant therapy, however, was strongly associated with the outcome (Table 5). Patients who started antidepressant treatment within 1 to 9 days before their index date were 38 times more likely to commit suicide than those who started treatment 90 days or more before their index date.

### Table 3. Relation Between Study Antidepressants and Nonfatal Suicidal Behaviors

<table>
<thead>
<tr>
<th>Antidepressant</th>
<th>Cases (n = 555)</th>
<th>Controls (n = 2062)</th>
<th>Odds Ratio (95% Confidence Interval)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dothiepin</td>
<td>167 (30.1)</td>
<td>707 (34.3)</td>
<td>1.00</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>77 (13.9)</td>
<td>367 (17.8)</td>
<td>0.83 (0.61-1.13)</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>176 (31.7)</td>
<td>588 (28.5)</td>
<td>1.16 (0.90-1.50)</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>135 (24.3)</td>
<td>400 (19.4)</td>
<td>1.29 (0.97-1.70)</td>
</tr>
</tbody>
</table>

*Odds ratios and 95% confidence intervals are estimated from a conditional logistic regression model conditional on the matching factors (age, sex, index date) and duration of recorded history in the UK General Practice Research Database before the index date and adjusted for antidepressant drug.

### Table 4. Relation Between Stopping Antidepressant Treatment and Nonfatal Suicidal Behaviors Among Subjects Who Started Antidepressant 30 Days or More Before Their Index Date, Stratified by Time Since Starting Antidepressant

<table>
<thead>
<tr>
<th>Variables</th>
<th>Cases (n = 372)</th>
<th>Controls (n = 544)</th>
<th>Odds Ratio (95% Confidence Interval)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥90 Days since starting Continued</td>
<td>166 (44.8)</td>
<td>343 (69.2)</td>
<td>1.00</td>
</tr>
<tr>
<td>Stopped</td>
<td>56 (25.2)</td>
<td>153 (30.9)</td>
<td>0.71 (0.48-1.04)</td>
</tr>
<tr>
<td>30-89 Days since starting Continued</td>
<td>85 (56.7)</td>
<td>79 (53.4)</td>
<td>1.00</td>
</tr>
<tr>
<td>Stopped</td>
<td>65 (43.3)</td>
<td>69 (46.6)</td>
<td>0.91 (0.52-1.59)</td>
</tr>
</tbody>
</table>

*Odds ratios and 95% confidence intervals are estimated from a conditional logistic regression model conditional on the matching factors (age, sex, index date, and duration of recorded history in the UK General Practice Research Database before the index date) and adjusted for antidepressant drug.

### Table 5. Relation Between Time Since First Prescription and Suicide

<table>
<thead>
<tr>
<th>Time Since First Prescription, d</th>
<th>Cases (n = 17)</th>
<th>Controls (n = 157)</th>
<th>Odds Ratio (95% Confidence Interval)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥90</td>
<td>6 (35.3)</td>
<td>111 (70.7)</td>
<td>1.0</td>
</tr>
<tr>
<td>30-89</td>
<td>3 (17.7)</td>
<td>31 (19.8)</td>
<td>2.0 (0.4-8.9)</td>
</tr>
<tr>
<td>10-29</td>
<td>2 (11.8)</td>
<td>10 (6.4)</td>
<td>5.1 (0.7-34.7)</td>
</tr>
<tr>
<td>1-9</td>
<td>6 (35.3)</td>
<td>5 (3.2)</td>
<td>38.0 (6.2-231)</td>
</tr>
</tbody>
</table>

*Odds ratios and 95% confidence intervals are estimated from a conditional logistic regression model conditional on the matching factors (age, sex, and index date) and adjusted for antidepressant drug.

**COMMENT**

The primary objective of this observational study was to compare the risk of suicidal behavior among persons taking amitriptyline, fluoxetine, or paroxetine with that among persons taking dothiepin to determine whether such behavior is substantially more common after exposure to 1 or more medications than it is after taking dothiepin. Although the risk of suicidal behavior for patients starting to take paroxetine was not significantly higher than that for patients starting to take dothiepin, the difference approached statistical significance. The magnitude of the relative risk, 1.29 (95% CI, 0.97-1.70), however, is low enough that such a finding could easily be due to uncontrolled confounding by severity of depression. For example, if patients with more severe depression were more likely to be treated with the most recently marketed antidepressant among those we studied (ie, paroxetine), this in itself would lead to a higher risk of suicidal behavior among those starting this drug compared with those starting an older drug (ie, dothiepin, the reference exposure in our study).
We have documented that in our study population nonfatal suicidal behavior is 4 times more likely to occur within fewer than 10 days after receiving a first antidepressant prescription and almost 3 times more likely to occur within 10 through 29 days after a first antidepressant prescription than in more than 90 days after the first prescription. Of importance in relation to the main objective of this study, similar associations were present for all 4 of the study drugs and controlling for this finding in the analysis had minimal effect on the relative risk estimates comparing them. We think the most likely explanation for this finding is that antidepressant treatment may not be immediately effective, so there is a higher risk of suicidal behavior in patients newly diagnosed and treated than in those who have been treated for a longer time. It is also possible that this observation reflects patients starting to take an antidepressant drug when their depression, which naturally fluctuates over time, is at its worst and thereafter spontaneous improvement may be more likely. We cannot exclude what we think is a less likely possibility, namely that the drug itself “causes” depression to worsen rapidly, thus leading to suicidal behavior. Whatever the cause of this striking finding, the current study provides persuasive evidence that it occurs with a similar frequency in the recipients of the 4 antidepressants studied and that the timing of starting antidepressant therapy is an important factor that must be controlled in observational studies of suicidal behavior.

In addition, our study provides some evidence against the proposition that the risk of suicidal behavior is elevated after withdrawal of antidepressant treatment.

Given the careful control of potential confounding variables, including age, sex, calendar time, and duration of treatment prior to suicidal behavior, this study provides evidence that the risk of suicidal behavior is not substantially different among patients starting treatment with amitriptyline, fluoxetine, or paroxetine than among patients starting treatment with dothiepin. The available information on young people aged 10 through 19 years is limited, however, and some important difference in effect cannot be ruled out based on this study.

**REFERENCES**

1. US Food and Drug Administration Psychopharmacological Drugs Advisory Committee Meeting, No. 34; September 20, 1991; Rockville, Md.