Comparative Mortality Risk in Adult Patients With Schizophrenia, Depression, Bipolar Disorder, Anxiety Disorders, and Attention-Deficit/Hyperactivity Disorder Participating in Psychopharmacology Clinical Trials

Arif Khan, MD; James Faucett, MS; Shaneta Morrison, AA; Walter A. Brown, MD

IMPORTANCE There is concern that increased mortality risk among patients with psychiatric illness may be worsened by psychopharmacological agents.

OBJECTIVES To assess mortality risk among adult patients with a diagnosis of schizophrenia, depression, bipolar disorder, anxiety disorders, or attention-deficit/hyperactivity disorder participating in clinical trials conducted by pharmaceutical companies for US Food and Drug Administration (FDA) approval to market and to evaluate if psychopharmacological agents worsen this risk.

DATA SOURCES The FDA Summary Basis of Approval (SBA) reports of new drug applications and supplemental applications for 28 psychopharmacological agents approved between 1990 and 2011.

STUDY SELECTION The FDA SBA reports detailing exposure data from acute placebo-controlled trials and safety extension studies including 92,542 patients from 47 adult drug approval programs for treatment of schizophrenia, depression, bipolar disorder, anxiety disorders, or attention-deficit/hyperactivity disorder and SBA reports on combination and maintenance therapy programs for treatments of bipolar disorder.

DATA EXTRACTION AND SYNTHESIS We reviewed and synthesized mortality data from SBA reports that combined mortality rates across the clinical trials, including information on patient exposure years (PEY) for active treatments and placebo for individual indications.

MAIN OUTCOMES AND MEASURES Overall mortality rate per 100,000 PEY in relation to the psychiatric diagnosis of the patients participating in psychopharmacology clinical trials. Also, the overall mortality rates using PEY technique among patients assigned to psychopharmacological agents or placebo were evaluated.

RESULTS Overall, mortality risk was high and significantly associated with psychiatric diagnosis ($\chi^2 = 1760; P < .001$). Compared with the general adult population, patients with schizophrenia had the highest mortality risk (3.8-fold increase), followed by patients with depression (3.15-fold increase) and bipolar disorder (3.0-fold increase). The mortality risk was not increased when patients were assigned to psychotropic agents rather than placebo except for heterocyclic antidepressants. Suicide accounted for 109 of all 265 deaths (41.1%).

CONCLUSIONS AND RELEVANCE These data suggest that increased mortality rates reported in population studies are detectable among adult patients with psychiatric illnesses participating in psychopharmacological trials. Furthermore, 3- to 4-month exposure to modern psychotropic agents, such as atypical antipsychotic agents, selective serotonin reuptake inhibitors, and selective serotonin-norepinephrine reuptake inhibitors does not worsen this risk. Given the inherent limitations of the FDA SBA reports, further research is needed to support firm conclusions.

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Based on the observation more than 75 years ago that patients in mental asylums had high mortality rates, \(^{1-3}\) several retrospective population studies have been conducted. As shown in Table 1, \(^{4-16}\) which reviews these studies, increased mortality risk is associated with schizophrenia and major mood disorders but not anxiety disorders. Furthermore, the increased mortality risk is more pronounced when the follow-up time is shorter (eg, 10 years) and dissipates if the follow-up period is 20 years or longer.

The increase in mortality risk is due to natural causes\(^{11,12,15,17-19}\) as well as suicide.\(^{20-23}\) Speculation regarding the risk of increased mortality due to natural causes relates it to poor self-care; poor hygiene; substance abuse, including excessive smoking; and the simple inability to get good medical care.

Several investigators have raised the possibility that modern pharmacotherapy may worsen the already increased mortality risk for patients with severe psychiatric illness. The possibilities include increased risk of cardiovascular disorders,\(^{24,25}\) suicide,\(^{26-28}\) sudden death due to cardiac conduction defects, and metabolic disorders leading to increased mortality risk.\(^{24,29-32}\)

We undertook this study to find out whether an alternate method of inquiry would confirm previous reports of increased mortality risk in psychiatric patients and to assess whether pharmacotherapy worsens this risk compared with placebo. We accessed public domain data from the US Food and Drug Administration (FDA) archives that are available as part of drug development programs by pharmaceutical companies under the Freedom of Information Act (FOIA).\(^{33}\)

These public domain data are potentially useful for answering these questions. Pharmaceutical companies are required to provide all the clinical investigation data to the FDA, and FDA scientists and physicians conduct independent safety and efficacy analysis, regardless of the analysis by the pharmaceutical companies.

All clinical trial participants are required to undergo prospective psychiatric diagnostic evaluation based on structured interviews, such as the Structured Clinical Interview for DSM-IV Axis I Disorders\(^{34}\) and the Mini-International Neuropsychiatric Interview.\(^{35}\) In addition to these structured diagnostic procedures, clinical trial participants need to be in good health without significant unstable medical illnesses or co-morbid conditions.

The US government via the FDA requires that clinical trial participants are to be followed up for at least 30 days after clinical trial participation to identify any untoward serious outcomes. All the approval programs require a placebo control arm in several studies to help evaluate the safety and efficacy of the individual psychotropic agents.

The FDA scientists and physicians compile individual Summary Basis of Approval (SBA) reports that provide much more detailed information than is available in the product labels, such as those provided by the Physicians’ Desk Reference,\(^{36}\) but there was considerable heterogeneity in the number of psychiatric patients included in the studies as well as the reported SMRs at follow-up. To minimize this variability in the SMRs, we therefore weighted the reported SMR for each evaluation by the total number of psychiatric patients that were included and reported the mean overall SMR for each row total.

### Table 1. Standardized Mortality Ratios (SMRs) From Published Studies Evaluating All-Cause Mortality in Adult Patients With Schizophrenia, Bipolar Disorder, Depression, and Anxiety Disorders Compared With Population Controls

<table>
<thead>
<tr>
<th>Duration of Follow-up by Diagnosis, y</th>
<th>Evaluations, No. (^{a})</th>
<th>Patients, No.</th>
<th>Actual Deaths, No. (%)</th>
<th>SMR(^{b,c})</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Schizophrenia</strong> (^{d})</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10</td>
<td>3</td>
<td>11,429</td>
<td>2155 (18.9)</td>
<td>2.60</td>
</tr>
<tr>
<td>10-20</td>
<td>1</td>
<td>99</td>
<td>39 (39.4)</td>
<td>2.83</td>
</tr>
<tr>
<td>&gt;20</td>
<td>3</td>
<td>6722</td>
<td>4811 (71.6)</td>
<td>1.32</td>
</tr>
<tr>
<td><strong>Depression</strong> (^{e})</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10</td>
<td>3</td>
<td>39,715</td>
<td>9153 (23.0)</td>
<td>2.02</td>
</tr>
<tr>
<td>10-20</td>
<td>3</td>
<td>1606</td>
<td>607 (37.8)</td>
<td>1.28</td>
</tr>
<tr>
<td>&gt;20</td>
<td>3</td>
<td>523</td>
<td>340 (65.0)</td>
<td>1.59</td>
</tr>
<tr>
<td><strong>Bipolar disorder</strong> (^{f})</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10</td>
<td>3</td>
<td>16,191</td>
<td>3506 (21.7)</td>
<td>2.57</td>
</tr>
<tr>
<td>10-20</td>
<td>2</td>
<td>389</td>
<td>123 (31.6)</td>
<td>1.45</td>
</tr>
<tr>
<td>&gt;20</td>
<td>2</td>
<td>320</td>
<td>212 (66.2)</td>
<td>1.49</td>
</tr>
<tr>
<td><strong>Anxiety disorders</strong> (^{g})</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10</td>
<td>1</td>
<td>82</td>
<td>4 (4.9)</td>
<td>0.90</td>
</tr>
<tr>
<td>10-20</td>
<td>2</td>
<td>1288</td>
<td>283 (220)</td>
<td>1.07</td>
</tr>
<tr>
<td>&gt;20</td>
<td>1</td>
<td>113</td>
<td>31 (27.4)</td>
<td>1.88</td>
</tr>
</tbody>
</table>

\(^{a}\) Several individual studies reported mortality outcomes for more than 1 psychiatric indication. The number of evaluations represents the number of studies that reported an SMR for the specified indication during the specified follow-up period.

\(^{b}\) Each of the identified studies calculated and reported the SMR by retrospectively identifying a cohort of psychiatric patients and following medical and death records over a period of time. The mortality risk in the psychiatric patients was then compared with that in a matched cohort control or with those in the general population to create a ratio between observed deaths in the psychiatric patients and what would be expected in the population or matched control cohort.

\(^{c}\) There was considerable heterogeneity in the number of psychiatric patients included in the studies as well as the reported SMRs at follow-up. To minimize this variability in the SMRs, we therefore weighted the reported SMR for each evaluation by the total number of psychiatric patients that were included and reported the mean overall SMR for each row total.

\(^{d}\) References 7, 9-11, 13, 15, 16.

\(^{e}\) References 4-6, 8-10, 12, 14, 16.

\(^{f}\) References 4, 6, 9, 10, 12, 14, 16.

\(^{g}\) References 8-10, 12.
these are abbreviated compared with the full data set, which includes 3000 to 50 000 clinical participants in individual development programs for psychotropic agents conducted by pharmaceutical companies.

Given the nature of the FDA SBA reports, we considered that we could evaluate mortality risk among patients with psychiatric illnesses in relation to diagnosis and exposure to psychotropic agents. We hypothesized that the increased mortality risk seen in population studies would also be evident among clinical trial participants, although the patients in clinical trials may be medically more stable than the clinical populations with similar psychiatric diagnoses. We also hypothesized that mortality risk is not significantly increased by short- to medium-term exposure to modern psychotropic agents.

Methods

As part of the FOIA, data submitted to the US FDA in support of a new drug application are available in the public domain. During the process of approving a new drug for a new indication, the physicians, scientists, and statisticians at the FDA conduct a detailed and independent review of all preclinical and clinical trial data.

The FDA staff also conducts supplemental approval for sponsors seeking an additional indication for an already approved agent, also making these data available in the public domain. For example, paroxetine was initially approved for depression but had 4 other supplemental indications added later: generalized anxiety disorder (GAD), social anxiety disorder (SAD), posttraumatic stress disorder (PTSD), and obsessive-compulsive disorder (OCD). The data are compiled into SBA reports and are available at the FDA website (www.fda.gov) or by written request through the FOIA.

The FDA SBA reports include data from preclinical experiments and clinical trial data, primarily focusing on the “registration trials” designed to establish efficacy, although they also include all available data for safety. The individual SBA reports vary considerably in quality and level of detail.

We accessed the FDA SBA reports for agents approved to treat schizophrenia, attention-deficit/hyperactivity disorder (ADHD), bipolar disorder, depression, and anxiety disorders including panic disorder, SAD, GAD, OCD, and PTSD between 1990 and 2011. Specifically, we reviewed the clinical trial reports and the safety subsection of medical reviews for each drug, tabulating mortality and suicide data as well as the number of patients and extent of patient exposure, defined as patient exposure years (PEY).

SBA Reports Obtained for the Study

We set 1990 as the cutoff date owing to the lower quality of data reporting and the heterogeneous nature of SBA reports before that time. Because several agents were approved for more than 1 indication, we reviewed the approval history for the new drug as well as available supplemental SBAs for agents approved for multiple indications.

To identify the medications approved for treatment of these disorders, we accessed the National Institute of Mental Health website, which provides an alphabetical updated list of each medication approved for treatment of schizophrenia, depression, bipolar disorder, anxiety disorders, and ADHD.

For the indication of schizophrenia, we obtained the SBA reports of several atypical antipsychotic agents approved in the United States since 1990: risperidone, olanzapine, quetiapine, quetiapine extended release (XR), ziprasidone, aripiprazole, paliperidone, iloperidone, asenapine, and lurasidone. Data for typical antipsychotic agents, such as haloperidol, were not targeted because they were approved before 1990. When the older psychotropic agents were included in the clinical trials, we included these data.

Supplemental approval for treatment of different phases of bipolar 1 disorder was granted for several of the atypical antipsychotic agents after they were approved for treatment of schizophrenia. We obtained the supplemental approval reports for atypical antipsychotic agents used for acute antimanic monotherapy (olanzapine, ziprasidone, risperidone, quetiapine, aripiprazole, and asenapine) and acute antimanic adjunctive therapy (olanzapine, risperidone, and quetiapine). Finally, we obtained 2 available supplemental approval reports for maintenance treatment of bipolar I disorder (olanzapine for monotherapy, quetiapine for adjunctive therapy).

For depression and the anxiety disorders, we again targeted all the agents approved for at least 1 of these indications since 1990; these agents included clonazepam, sertraline, fluoxetine, venlafaxine, venlafaxine XR, nefazodone, mirtazapine, paroxetine, paroxetine controlled release (CR), citalopram, escitalopram, duloxetine, desvenlafaxine, trazodone XR, and vilazodone.

In reviewing the SBA reports of agents approved for ADHD, we identified 5 agents approved for treatment of the disorder in adults since 1990. We were able to obtain SBA reports for atomoxetine, methylphenidate (osmotic CR oral delivery system), and dextemethylphenidate. The supplemental SBA reports for lisdexamfetamine and mixed amphetamine salts XR were unavailable because they were not completed by the FDA.

Organization of Data

One of us (J.F.) went through individual FDA SBA reports to collect and collate all the mortality data. These included both initial and supplemental SBA reports. We initially evaluated 50 separate SBA reports, as shown in Table 2, but we collated the data for only 47; the 3 excluded reports did not provide mortality risk rates based on duration of exposure, including only data for the total number of participants and the number who died. Thus, we could not include data from approvals for lurasidone (schizophrenia), paroxetine CR (depression), and sertraline (panic disorder) because exposure durations were not reported for these programs.

The mortality data were obtained from the safety sections of the SBA reports, by the diagnosis, by the specific approved indication, by the individual drug, and by cause of death. Demographic features, such as age and sex of the decedent, and other ancillary information were also collated when available.

For schizophrenia, depression, anxiety disorders, and ADHD, all included trials were monotherapy trials for acute treatment of the disorder or safety extension studies of mono-
therapy treatment. We did not target or include supplemental approvals of combination therapy treatments for depression because of the treatment-resistant population. We also did not target maintenance approval programs for schizophrenia or depression because of the lack of adequate patient exposure from a homogenously designed, controlled, and conducted group of trials. There were no adjunctive therapy or maintenance trials for treatments of ADHD or anxiety in adults.

Most SBA reports for schizophrenia, depression, and anxiety reported all available PEY for patients assigned to investigational agents and treatment controls, including placebo controls. Four SBA reports (on duloxetine for depression and duloxetine, paroxetine CR, and escitalopram for anxiety) did not include PEY for patients assigned to placebo. Thus, we included only PEY and mortality data associated with investigational agents for these 4 programs.

In contrast, the design and conduct of bipolar mood disorder trials was comparatively heterogeneous. Specifically, there were 5 study design models. One of these was a double-blind, placebo-controlled design using either a parallel or relapse prevention method.

Three design models did not include placebo controls; these were prospective double-blind trials comparing a mood stabilizer combined with either an atypical antipsychotic agent or a placebo and using either a parallel method or a relapse prevention method. The fifth design consisted of open-label treatment. Furthermore, although all of the patients had a diagnosis of bipolar I disorder, not all of the entry requirements were uniform. In some trials the patients were purely manic, in some they were either purely manic or in a mixed episode of depression and mania, and in the relapse prevention trials several patients were depressed. Given this heterogeneity, unbalanced cells, and a lack of a true placebo control from most trials, these data were considered to be not as reliable and were primarily included for overall mortality risk estimates, including suicide risk. Thus, a more descriptive method of analysis for suicide risk based on individual treatment assignment was considered.

We were able to include PEY and mortality data for investigational and control treatments for all bipolar mood disorder approval programs. We estimated PEY for the control arms of the olanzapine, ziprasidone, and quetiapine acute mania programs based on the reported exposure of the drug arms in the acute 3-week trials. All PEY for investigational treatments and controls were specifically detailed in the SBA reports for all the other programs.

### Statistical Analysis

To test the hypothesis of different overall mortality rates based on diagnostic indication, we first established the total mortality rates per 100 000 PEY inclusive of patients assigned to investigational agents, comparators, and placebo. This was done by dividing the mortality count for each indication by the corresponding PEY totals and multiplying the outcome by 100 000. After establishing the mortality or suicide rate per 100 000 PEY, we conducted a χ² analysis to evaluate differences in mortality rates based on indication. We also conducted a separate post hoc analysis using Bonferroni correction for multiple comparisons to evaluate any specific differences between schizophrenia, acute mania, and depression.

Odds ratios were used to evaluate the significance of any difference in mortality rates (per 100 000 PEY) between active medication and placebo. Because the SBA reports frequently detail data from the active comparator trial arms separately from those for the investigational agents, we also compared mortality rates between the comparator and placebo arms.

For these comparisons, if the active comparator in mania or schizophrenia trials was an atypical antipsychotic, we included the mortality and exposure data with the investigational atypical antipsychotic agents. Adequate data were also available from comparators used during clinical trials of schizophrenia (haloperidol, 898 PEY) and depression (tricyclic antidepressants, 1593 PEY) to evaluate the profiles of these agents compared with placebo.
We conducted 2 ancillary analyses to better characterize the suicide risk observed during the approval programs. First, we calculated overall suicide rates per 100 000 PEY for each indication inclusive of patients assigned to investigative agents, placebo, and active comparators. Additional odds ratios were used to evaluate the suicide risk in patients assigned to modern psychopharmacological agents and first-generation agents relative to placebo. Because the data from the bipolar disorder trials were heterogeneous and did not include sufficient data for controls, analysis of suicide risk was limited to descriptive evaluations.

Finally, we tried to evaluate if any of the anxiety disorders may have primarily contributed to overall mortality rates. We therefore calculated mortality rates individually for GAD and SAD, OCD, PTSD, and panic attacks.

**Results**

As shown in Table 2, we reviewed the FDA SBA reports for 46 new drug approvals between 1990 and 2011. Of these 46 drug approval reports, 43 met our criteria for evaluation because they used the PEY method of assessment.

As shown in Table 3, 92 542 patients with psychiatric illnesses participated in the 43 psychopharmacology clinical trial programs. The total exposure period for psychotropic agents was 23 711 years and total exposure period for placebo was 2183 years.

As shown in Table 4, the age and sex distributions in this sample of patients reflects general community prevalence. Suicide was by far the most common cause of death, accounting for 109 of all 265 deaths (41.1%).

Based on the PEY method of analysis, as shown in Figure 1, the overall mortality risk was associated with psychiatric diagnosis ($\chi^2 = 1760; P < .001$). The mortality risk for patients with schizophrenia was 1249 per 100 000 PEY (95% CI, 1029-1469), followed by that for patients with major depression (1045 per 100 000 PEY; 95% CI, 844-1246) and bipolar disorder (1000 per 100 000 PEY; 95% CI, 654-1346).

The mortality risk for patients with anxiety disorders (222 per 100 000 PEY; 95% CI, 28-416) was comparable to that for the general US adult population aged 20 to 65 years in the year 2000 (331 per 100 000 PEY). No deaths occurred in the 3 programs that included adult patients with ADHD.

Finally, we tried to evaluate whether mortality risk differed among the 5 anxiety spectrum disorders. Because of the limited number of mortality observations across disorders, it was not possible to conduct a statistical evaluation. Overall, except in patients with PTSD, the mortality rates were homogeneously low: patients with OCD, 1 death in 580 exposure years (172 per 100 000 PEY); panic disorder, 0 deaths in 735 exposure years; PTSD, 2 deaths in 239 exposure years (837 per 100 000 PEY); GAD and SAD, 2 deaths in 575 exposure years (348 per 100 000 PEY).

The overall mortality was lower among patients with schizophrenia assigned to antipsychotic agents (both haloperidol and modern atypical antipsychotics) compared with patients with schizophrenia assigned to placebo (Figure 2). Similarly, in patients with bipolar disorder, the overall mortality risk was also lower among those assigned to atypical antipsychotic agents, mood stabilizers, or a combination of both than among those assigned to placebo (Figure 2). On the other hand, in patients with depression or anxiety disorders, the
The aim of the study was to evaluate if mortality risk was increased among patients with various psychiatric illnesses participating in clinical psychopharmacological trials and whether overall mortality risk was similar between those assigned to modern antidepressants (selective serotonin reuptake inhibitors [SSRIs], selective serotonin-norepinephrine reuptake inhibitors [SNRIs], and related compounds) and those assigned to placebo.

In patients with depression, the overall mortality risk was significantly higher among those assigned to heterocyclic (eg, tricyclic and tetracyclic) antidepressants than among those assigned to placebo (Figure 2). There were 29 total deaths during the 1567 PEY for patients assigned to heterocyclic antidepressants, for a mortality risk of 1851 per 100,000 PEY (95% CI, 1214-2488). Suicide was the most common cause of death in these patients (16 of 29; 55.2%).

In patients with schizophrenia, depression, or anxiety disorders, suicide rates were lower in those assigned to either antipsychotic agents or modern antidepressants (SSRIs, SNRIs, or related compounds) than in those assigned to placebo (Figure 3). The suicide outcomes from the various models of bipolar I disorder trials are shown in Table 5. There were 13 suicide deaths in the 3070 PEY of the respective drug arms of these trials, with none occurring in the 131 PEY for placebo. Specifically, the duration of exposure to placebo was only 4% of that for psychotropic agents. Thus, we were unable to conduct any meaningful statistical tests to compare suicide risk between these treatment groups.

Discussion

The aim of the study was to evaluate if mortality risk was increased among patients with various psychiatric illnesses participating in clinical psychopharmacological trials and whether

Table 4. Mortality Data From Clinical Trials in FDA Drug Approval Programs for Psychopharmacological Agents Used to Treat Psychiatric Disorders

<table>
<thead>
<tr>
<th>Mortality Data</th>
<th>Schizophrenia Programs (n = 9)</th>
<th>Depression Programs (n = 12)</th>
<th>Bipolar Disorder Programs (n = 11)</th>
<th>Anxiety Disorder Programs (n = 12)</th>
<th>ADHD Programs (n = 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total deaths, No. (% of patients)</td>
<td>17 (14.8)</td>
<td>34 (36.6)</td>
<td>1 (.03)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Drug arms</td>
<td>115 (0.4)</td>
<td>93 (0.3)</td>
<td>29 (0.3)</td>
<td>4 (0.05)</td>
<td>0</td>
</tr>
<tr>
<td>Placebo arms</td>
<td>9 (0.3)</td>
<td>11 (0.2)</td>
<td>3 (0.2)</td>
<td>1 (0.03)</td>
<td>0</td>
</tr>
<tr>
<td>Total suicides, No. (% of total deaths)</td>
<td>46 (40.0)</td>
<td>39 (41.9)</td>
<td>13 (45)</td>
<td>2 (50.0)</td>
<td>0</td>
</tr>
<tr>
<td>Drug arms</td>
<td>12 (22.2)</td>
<td>6 (54.5)</td>
<td>0</td>
<td>1 (100)</td>
<td>0</td>
</tr>
<tr>
<td>Placebo arms</td>
<td>7 (14.3)</td>
<td>2 (3.09)</td>
<td>9 (19.7)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Deaths in patients aged ≥65 years, No. (% of total deaths)</td>
<td>18 (15.7)</td>
<td>2 (2.2)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sudden death</td>
<td>15 (13.0)</td>
<td>5 (5.4)</td>
<td>4 (11.8)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cardiovascular causes</td>
<td>14 (12.2)</td>
<td>24 (21.9)</td>
<td>5 (17.2)</td>
<td>1 (25.0)</td>
<td>0</td>
</tr>
<tr>
<td>External causes</td>
<td>11 (9.6)</td>
<td>1 (1.1)</td>
<td>5 (17.2)</td>
<td>1 (25.0)</td>
<td>0</td>
</tr>
<tr>
<td>Neoplasm</td>
<td>1 (0.9)</td>
<td>8 (8.6)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory illness or infection</td>
<td>15 (13.0)</td>
<td>5 (5.4)</td>
<td>4 (11.8)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Suicide</td>
<td>18 (15.7)</td>
<td>2 (2.2)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; FDA, Food and Drug Administration.

* Reported totals represent deaths that occurred in the investigative and control arms and in addition were specified by the reviewers to correspond with reported patient exposure years.

* Total deaths as a percentage of patients enrolled were calculated from the raw number of patients and did not factor in duration of patient exposure.

* Refer to Table 5 for full details of patient exposure and suicide rate in the several designs of trials for treatment of bipolar disorder.

* Reported totals represent deaths that occurred in the investigative agent and active control treatment arms with details specified by the reviewers. Deaths in the placebo arms were not included because these data were not consistently available.
Mortality in Psychopharmacology Clinical Trials

Odds ratios were calculated by using mortality rates (per 100 000 patient exposure years) for patients assigned to active treatment or control arms based on suicide and exposure data from Food and Drug Administration Summary Basis of Approval reports. Suicide rates are not included for attention-deficit/hyperactivity disorder (ADHD) because no suicides occurred during the ADHD clinical trials. Atypical antipsychotic agents for schizophrenia included olanzapine, ziprasidone, risperidone, quetiapine, aripiprazole, asenapine, quetiapine sustained release, paliperidone, and iloperidone. Agents approved for bipolar disorder included atypical antipsychotic agents olanzapine, ziprasidone, risperidone, quetiapine, aripiprazole, and asenapine; mood stabilizers lithium carbonate, divalproex sodium, and carbamazepine; and combinations of atypical antipsychotic agents and mood stabilizers. Serotonergic antidepressants included selective serotonin reuptake inhibitors (SSRIs) (sertraline, paroxetine, paroxetine controlled release (CR), citalopram, and escitalopram), selective serotonin-norepinephrine reuptake inhibitors (SNRIs; venlafaxine, venlafaxine extended release (XR), duloxetine, and desvenlafaxine), and SSRIs plus nefazodone, trazodone, or vilazodone. Heterocyclic antidepressant agents included imipramine, amitriptyline, maprotiline, and mirtazapine. Anti-anxiety agents included fluoxetine, paroxetine, clonazepam, venlafaxine XR, and paroxetine CR.

Figure 2. Relationship Between Psychotropic Agents and Overall Mortality Risk Compared With Overall Mortality Risk With Placebo

Figure 3. Relationship Between Psychotropic Agents and Suicide Risk Compared With Suicide Risk With Placebo

It was related to specific psychiatric diagnosis, as seen in population follow-up studies. We also wanted to evaluate if short- or medium-term exposure to modern psychotropic agents led to a further increase in mortality risk.

Although we hypothesized that mortality risk would be associated with psychiatric diagnosis, even in short- to medium-duration psychopharmacology clinical trials, the magnitude of the relationship between psychiatric diagnosis and mortality risk was very large (Figure 1), contrary to expectations. Furthermore, this mortality risk pattern was almost identical to that seen in retrospective population studies as shown in Table 1.

The mortality risk for the participants in short- to medium-term psychopharmacology clinical trials compared with the general adult population was 3.8-fold higher in adult patients with schizophrenia, 3.15-fold higher in those with depression, and 3.0-fold higher in those with bipolar mood disorder. It is important to note that these clinical trial participants were relatively medically stable, had a prospective psychiatric diagnosis based on structured interviews by trained clinicians, had minimal comorbid substance abuse, and were given close medical attention.

Thus, mortality risk is associated with specific psychiatric diagnoses and detectable within relatively short durations of observation, even among relatively physically healthy patients. Interestingly, even when suicide deaths are excluded, the natural cause mortality rates in adult patients with schizophrenia, bipolar mood disorder, or depression still exceeded those in the general adult population.

Moreover, contrary to expectations, the mortality risk is not increased with short- and medium-term exposure to modern psychotropic agents, such as atypical antipsychotics or antidepressants. Although this finding replicates our findings in an earlier study of schizophrenic patients in premarketing trials, based on a portion of the current database, such a phenomenon has not previously been noted for patients with depression or bipolar disorder who participate in premarketing trials. These data suggest that exposure to these modern psychotropic agents for up to 3 or 4 months does not increase mortality risk.

The rate of suicide, the most common cause of death among these trial participants, was not increased by either atypical antipsychotic agents in patients with schizophrenia or antidepressants, such as SSRIs and SNRIs, in those with depression or anxiety spectrum disorders. The suicide risk associated with psychotropic agents compared with placebo could not be evaluated meaningfully for the trials including patients with bipolar mood disorders, as shown in Table 5.
Abbreviations: NA, not available; PEY, patient exposure years.

Nonsurprisingly, exposure to tricyclic and heterocyclic antidepressants was associated with increased mortality risk among adult patients with depression, a finding seen by earlier investigators.26 Furthermore, these agents also increased suicide risk among adult patients with depression, a finding seen by earlier investigators.26 Thus, caution is warranted in the use of these agents in clinical trials. However, the data are insufficient to conclude that these concerns can be extended to clinical practice because many other factors may play a role in this setting.

Because of the abbreviated and variable form of FDA SBA reports, we could not assess premorbid history, age and sex of the clinical participant, family history, course of illness, or details of any autopsy reports. Furthermore, deaths occurring among clinical trial participants exposed to placebo or active comparators were infrequent and difficult to interpret.

It is important to note that the aim of these FDA SBA reports was to evaluate mortality risk but rather to evaluate the safety and efficacy of a variety of psychotropic agents, so results should be viewed with caution.

There is considerable imbalance in treatment cells, active controls, and placebo control. For example, the placebo exposure duration is significantly shorter than that for psychotropic agents being evaluated (Table 3). Such imbalances are driven in part by ethical committee concerns about human subject protection and deprivation of active treatments.

In addition, we could not fully evaluate all the clinical trial data for a variety of reasons. First, the data included in the FDA SBA reports in general consist of data from the registration or “pivotal” trials. These are only a fraction of studies conducted, and unfortunately data from the others cannot be accessed via the FOIA as interpreted by the FDA.

Second, we somewhat underestimated the overall mortality risk ratio because we could not include data about several deaths that occurred in the screening phase before randomization. In essence, therefore, the FDA may have data on more than 20 000 patients for individual psychotropic agents, but the SBA reports in general include data on approximately 3000 to 5000 patients, with even fewer data in supplemental new drug applications.

Our results suggest that further detailed analysis of the clinical trial data by the FDA or the pharmaceutical companies is required before any firm conclusions can be drawn. Furthermore, it is desirable to acquire much longer-term data, such as a decade in duration, regarding potential mortality risk when exposed to psychotropic agents based on the findings from the population studies. To obtain definitive results, prospectively designed studies are required. Given the magnitude of excess mortality risk associated with some of the psychiatric diagnoses, such studies are essential both for evaluating mortality risk and for designing methods or treatments to reduce it.

In conclusion, the results from our analysis support retrospective findings from the population studies indicating that increased mortality risk is associated with schizophrenia, major depression, and bipolar mood disorder. Short- to medium-term (3-4 month) exposure to modern psychotropic agents, such as atypical antipsychotic agents, SSRIIs, and SNRIIs, is not associated with increased mortality risk among adult patients participating in psychopharmacology trials.

Table 5. Patients Enrolled, Duration of Patient Exposure, and Number of Suicides in 5 Design Models for Trials of Atypical Antipsychotic Agents

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Model</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients assigned, No.</td>
<td></td>
<td>2431</td>
<td>225</td>
<td>728</td>
<td>646</td>
<td>6261</td>
</tr>
<tr>
<td>Control arm</td>
<td></td>
<td>1699</td>
<td>136</td>
<td>600</td>
<td>680</td>
<td>NA</td>
</tr>
<tr>
<td>Duration of exposure, PEY</td>
<td></td>
<td>148</td>
<td>88</td>
<td>41</td>
<td>376</td>
<td>2364</td>
</tr>
<tr>
<td>Control arm</td>
<td></td>
<td>101 (placebo)</td>
<td>30 (placebo)</td>
<td>33 (placebo plus mood stabilizer)</td>
<td>282 (placebo plus mood stabilizer)</td>
<td>NA</td>
</tr>
<tr>
<td>Suicides, No.</td>
<td></td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Control arm</td>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>NA</td>
</tr>
<tr>
<td>Suicides/100 000 PEY</td>
<td></td>
<td>2027</td>
<td>1136</td>
<td>0</td>
<td>532</td>
<td>679</td>
</tr>
<tr>
<td>Active control arm</td>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>355</td>
<td>NA</td>
</tr>
<tr>
<td>Control arm</td>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>355</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: NA, not available; PEY, patient exposure years.

* Monotherapy or combination therapy for acute treatment of mania and/or mixed mania, relapse prevention in bipolar depression, mania, or mixed mania; and safety extension studies. The 5 models were defined as follows: model 1, double-blind, placebo-controlled phase of trials designed to evaluate monotherapy treatment with atypical antipsychotic agents for patients with a diagnosis of acute mania (sometimes inclusive of mixed mania); model 2, double-blind phase of trials designed to evaluate monotherapy relapse prevention with atypical antipsychotic agents for stabilized patients with a diagnosis of bipolar depression or acute mania; model 3, double-blind phase of trials designed to evaluate adjunctive therapy treatment with atypical antipsychotic agents plus a mood stabilizer for patients with a diagnosis of acute mania (sometimes inclusive of mixed mania), with a mood stabilizer plus placebo control arm; model 4, double-blind phase of trials designed to evaluate adjunctive therapy relapse prevention with atypical antipsychotic agents plus mood stabilizer for stabilized patients with a diagnosis of bipolar depression or acute mania, with a mood stabilizer plus placebo control arm; and model 5, open-label phase of each of the 4 models of trials just described.
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REFERENCES