Mortality Risk in Patients With Schizophrenia Participating in Premarketing Atypical Antipsychotic Clinical Trials

Arif Khan, M.D.; Kelly Schwartz, M.S.; Chelsea Stern; Nick Redding, M.S.; Russell L. Kolts, Ph.D.; Walter A. Brown, M.D.; and Donald S. Robinson, M.D.

Objectives: Given the concern that mortality rates may be increased in geriatric patients exposed to atypical antipsychotic agents, we assessed mortality rates for adult patients with schizophrenia assigned to an investigational antipsychotic (olanzapine, quetiapine, risperidone, or ziprasidone), a control antipsychotic (haloperidol or chlorpromazine), or placebo in preapproval clinical development programs to assess relative risk with atypical antipsychotics as compared to typical antipsychotics or placebo.

Method: We reviewed safety data (from clinical trials conducted from approximately 1982 to 2002) for 16,791 adult patients with schizophrenia (DSM-III or DSM-IV criteria) in U.S. Food and Drug Administration (FDA) Summary Basis of Approval (SBA) reports for 6 antipsychotic drugs. Mortality rates were calculated for each treatment group (investigational agent, active control, or placebo) on the basis of patient exposure years (PEY) and gross mortality. We compared the differences in mortality rates between placebo and investigational agents, active controls, and all antipsychotic drugs combined using odds ratios.

Results: By PEY analysis, the mortality rate for patients assigned to placebo treatment was significantly higher ($p < .05$) than for either the investigational antipsychotic (OR = 0.23, 95% CI = 0.13 to 0.45) or the active control group (OR = 0.19, 95% CI = 0.08 to 0.45). Although rates based on gross mortality were also higher with placebo treatment, statistical significance was only seen when comparing patients assigned to placebo with those assigned to the active control antipsychotic group (OR = 0.35, 95% CI = 0.15 to 0.82).

Conclusions: Despite reported excess mortality with antipsychotic use in elderly patients with dementia, SBA data did not reveal a similar increased risk of antipsychotics in adult patients with schizophrenia. However, methodological limitations of the FDA SBA reports may affect the generalizability of these findings.

(J Clin Psychiatry 2007;68:1828–1833)

Received Dec. 20, 2006; accepted Mar. 12, 2007. *From the Northwest Clinical Research Center, Bellevue, Wash. (Dr. Khan, Mss. Schwartz and Stern, and Mr. Redding); the Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, N.C. (Dr. Khan); Department of Psychology, Eastern Washington University, Cheney, Wash. (Dr. Kolts); Department of Psychiatry, Brown Medical School, Providence, R.I., and Department of Psychiatry, Tufts University School of Medicine, Boston, Mass. (Dr. Brown); and Worldwide Drug Development, Burlington, Vt. (Dr. Robinson).*

The Northwest Clinical Research Center in Bellevue, Wash., supported this research from private funds. No support was provided by any pharmaceutical companies or other funding agencies.

Dr. Khan, principal investigator of over 200 trials sponsored by more than 40 pharmaceutical companies, has done no consulting or speaking on their behalf. Ms. Schwartz, Ms. Stern, and Mr. Redding have been employees of the Northwest Clinical Research Center. Dr. Kolts has had no support from either pharmaceutical companies or other agencies and is a full-time employee of Eastern Washington University. Dr. Brown is the cofounder and President of Clinical Research Centers International, a company that develops and manages clinical trials sites overseas. These sites carry out research sponsored by drug companies. Dr. Robinson is a consultant to the pharmaceutical industry and has published extensively on clinical methodology and drug development in psychopharmacology.

Corresponding author and reprints: Arif Khan, M.D., 1900 116th Ave. N.E., Bellevue, WA 98004 (e-mail: akhan@nwcrc.net).

Patients with schizophrenia have an estimated 20% reduction in life expectancy,[1] in part due to an increased mortality risk that is twice as high as that of the general population.[2–4] This higher mortality risk comes from an increase in both unnatural causes such as suicide and natural causes such as heart and lung disease. Additionally, respiratory diseases, diabetes, and cardiovascular diseases are 2 to 3.4 times more frequent in patients with schizophrenia than in the general population, all of which may indirectly contribute to increases in mortality risk.[5–7] Poor diet, smoking, and excess alcohol consumption may also contribute to the observation of higher mortality rates in schizophrenic patients.[8]

There is evidence that antipsychotic medications may increase mortality risk for sudden cardiac death and other adverse cardiac effects.[9–12] Certain typical antipsychotics, especially thioridazine, prolong cardiac conduction with resulting fatalities.[13] For newer atypical antipsychotics, risk factors include significant weight gain, metabolic syndrome, and new onset diabetes.[5] Regarding suicide and suicide attempts, previous reports[14,15] have noted that rates do not differ between patients receiving an antipsychotic compared with those receiving placebo treatment in antipsychotic clinical trial programs.

Recent evidence suggests that geriatric patients with neurodegenerative disorders treated with antipsychotics have an increased mortality rate.[16] This increase in mortality is seen with both older (typical) antipsychotics[17] and newer (atypical) antipsychotic agents.[16] This mortality assessment among elderly patients with neurodegenerative disorders is one of the first controlled trials comparing an antipsychotic and placebo. Much of the previous research was relatively uncontrolled.

Given the minimal research regarding mortality rates in schizophrenia comparing conditions such as placebo, active comparator, and investigational antipsychotic, we were left with 3 hypotheses to consider. In adult patients with schizophrenia, placebo patients may have higher mortality rates compared to antipsychotic, placebo patients may have lower mortality rates compared to antipsychotic, or there may be no difference in mortality rates between placebo and antipsychotic.

The finding regarding geriatric patients with neurodegenerative disorders suggests that the mortality rate may be higher with antipsychotics compared to placebo. Hence, for our analysis, we hypothesized that mortality rates would be higher among adult patients with schizophrenia assigned to both active control and investigational antipsychotics compared with patients assigned to placebo treatment.

We accessed U.S. Food and Drug Administration (FDA) Summary Basis of Approval (SBA) reports to calculate the mortality rates for adult patients with schizophrenia assigned to an investigational antipsychotic, an active control, or placebo in order to detect any statistical differences in mortality risk among treatment groups. We also investigated whether the causes of death differed between the 3 treatment assignments (investigational antipsychotics, active control antipsychotics, and placebo).

METHOD

Background

The FDA generates an SBA dossier on a new drug and indication for each New Drug Application. The reports are compiled by the FDA staff, which includes physicians, chemists, pharmacologists, toxicologists, and pharmacists, each reviewing different aspects of the new drug application. The senior physician signs off on the completed report, which incorporates portions of the information in the product labeling. SBAs are available publicly through the Department of Freedom of Information.

The SBA reports, which contain both preclinical and clinical data reviews and average 200 pages in length, consist of research data from several thousand patients exposed to the study drug. All participants detailed in these SBA reports voluntarily participate in a clinical trial and are treated with the study drug (investigational, active control, or placebo) depending on clinical trial design.

Sections of the SBA reports commonly include an overview of the clinical program, efficacy data, safety findings, dosing recommendations, information for use in special populations, and recommendations for approval. The safety section, averaging 30 to 60 pages in length, contains summaries (typically tabular) of serious adverse events including deaths, common adverse events, and discontinuation rates, as well as hematology, serum chemistry, and urinalysis tests. The reports provide patient numbers and occasionally patient exposure years (PEY) for each treatment. SBAs do not detail each serious adverse event (including deaths); rather, they tally total numbers of adverse events.

Data Extraction

By request to the FDA (Freedom of Information Staff, 5600 Fishers Lane, HFI-35 Rockville, MD 20857; www.fda.gov),[18] we accessed available public domain data on 25,550 patients with schizophrenia (DSM-III or DSM-IV criteria) who participated in antipsychotic clinical trials evaluating aripiprazole (approval letter dated 11/15/02), clozapine (approval letter dated 11/04/88), olanzapine (approval letter dated 9/30/96), quetiapine (approval letter dated 9/26/97), risperidone (approval letter dated 7/2/99), and ziprasidone (approval letter dated 2/5/01). We extracted information on mortality from the safety sections in each SBA report to assess fatalities for each treatment condition—investigational drug, active comparator, or placebo. The investigational drug group included 6 atypical antipsychotics (in 1 trial risperidone served as the active control and for this analysis was included in the investigational agent category). The active control treatment condition comprised haloperidol and chlorpromazine.

Duration of exposure differs among treatment conditions in part due to high discontinuation rates for patients with schizophrenia. The patient samples in these analyses (intention-to-treat) comprised adults (18 years of age and older) with schizophrenia. Unfortunately, the clozapine SBA lacked information regarding the number of patients in the placebo and active control groups and data regarding patient exposure years (PEY = the cumulative time in years of patients exposed to study drug) and the clozapine data were therefore excluded from the analyses. Similarly, aripiprazole was excluded from mortality analyses because the SBA did not distinguish among patients with schizophrenia, bipolar disorder, and dementia disorders. We tabulated deaths occurring within 30 days of study drug, and when available, the patient's age, cause of death, gender, and treatment assignment.

The olanzapine SBA contained PEY data for a smaller patient sample than the total number of patients given for gross mortality rates. Fortunately, the SBA report listed the number of deaths for this subset and we elected to use the patient numbers and death rates provided as PEY data.

Table 1. Mortality Rates, Mean Age at Death, and Percent Male Deaths for Patients With Adult Schizophrenia Assigned to an Investigational Antipsychotic, Placebo, or an Active Control During Clinical Trials Evaluating 6 Antipsychotics

Drug Trial	N	Mean Age at Death, y	Percentage of Male Deaths	No. of Deaths (%)	PEY	PEY Rate
Section A. Trials in which the SBA reports provided sufficient information for analysis						
Olanzapine						
Investigational drug	2,500	66.0	88.9	20 (0.8)	1,122.2	1,782/100,000
Placebo	236	NR	NR	2 (0.8)	27.1	7,380/100,000
Active comparator[a]	810	NR	NR	3 (0.4)	193.0	1,554/100,000
Total	3,546	…	…	25 (0.7)	1,342.3	1,862/100,000
Quetiapine						
Investigational drug	2,523	65.9	69.2	13 (0.5)	1,103.2	1,178/100,000
Placebo	206	NR	NR	0 (0.0)	14.6	0/100,000
Active comparator[a,b]	420	47.5	50.0	2 (0.5)	51.7	3,868/100,000
Blinded treatment	NR	NR	NR	1	NR	…
Total	3,149	…	…	16 (0.5)	1,169.5	1,368/100,000
Risperidone						
Investigational drug[c]	3,033	47.7	66.7	20 (0.7)	1,054.4	1,897/100,000
Placebo	195	NR	NR	0 (0.0)	15	0/100,000
Active comparator[a]	621	35.0	100	2 (0.3)	71	2,817/100,000
Total	3,849	…	…	22 (0.6)	1,140.4	1,929/100,000
Ziprasidone						
Investigational drug	4,571	44.5	69.8	50 (1.1)	1,732.6	2,886/100,000
Placebo	605	NR	NR	10 (1.7)	91.8	10,893/100,000
Active comparator[a,c]	1,071	NR	NR	3 (0.3)	298.6	1,005/100,000
Total	6,247	…	…	63 (1.0)	2,123.0	2,967/100,000
All antipsychotic trials						
Investigational drug	12,627	53.8	72.7	103 (0.8)	5,012.4	2,055/100,000
Placebo	1,242	…	…	12 (1.0)	148.5	8,081/100,000
Active comparator	2,922	…	…	10 (0.3)	614.3	1,628/100,000
Total	16,791	…	…	126 (0.8)	5,775.2	2,182/100,000
Section B: Trials in which the SBA reports did not contain sufficient information for analysis						
Aripiprazole						
Investigational drug	4,710	69.9	49.2	61 (1.3)	2,656.3	2,296/100,000
Placebo	928	NR	NR	0 (0.0)	85.8	0/100,000
Active comparator[d]	673	38.5	100	2 (0.3)	340.2	588/100,000
Blinded treatment	NR	NR	NR	13	NR	…
Total	6,311	…	…	76	3,082.3	2,044/100,000
Clozapine						
Investigational drug	1,742	47.6	28.6	9 (0.5)	NR	…
Placebo	NR	NR	NR	NR	NR	…
Active comparator[a,b]	NR	NR	NR	NR	NR	…

[a]Haloperidol used as the active comparator.
[b]Chlorpromazine used as an active comparator.
[c]Risperidone was used in ziprasidone trials as an active comparator. Two deaths among 426 patients (196.4 PEY) were added to the risperidone data and removed from the active comparator group for ziprasidone.
[d]Haloperidol, olanzapine, and risperidone used as active comparators.
Abbreviations: NR = information not reported in the U.S. Food and Drug Administration SBA reports, PEY = patient exposure years, SBA = Summary Basis of Approval.
Symbol: … = data missing, excluded from analysis.

We examined risk based on both PEY and gross numbers, although we believe PEY risk is the more valid method of assessment because it takes into account both the number of subjects and duration of exposure to treatment condition. The underlying assumption is that cumulative exposure to drug is the preferred measure for rare events such as deaths, suicides, and seizures. For more common adverse events such as headaches or nausea, PEY analysis is not usually included in the risk analysis.

Statistical Analysis

We calculated 2 mortality rates with this patient sample (listed in Table 1, Section A). First, we calculated the mortality rate based on gross numbers. We divided number of deaths by total number of patients for each treatment condition for the 6 antipsychotic clinical trials. Mortality risk was also assessed using total exposure to drug in patient years on the basis of available PEY data. This method of analysis is calculated as risk per 100,000 patient years of drug exposure. To obtain PEY mortality risk, we divided the number of deaths by total drug exposure in patient years for each treatment condition (investigational antipsychotic, placebo, or active control).

In addition, we recorded the age and gender of the patient who died and treatment assignment at the time of death (Table 1, Section A). There was considerable variability in FDA SBA reports about cause of death among

Table 2. Odds Ratio Results for Mortality Risks in Antipsychotic Clinical Trials of Patients With Adult Schizophrenia[a]

	Adjusted for PEY				Unadjusted for PEY			
Treatment Condition	PEY	No. of Deaths	OR	95% CI	N	No. of Deaths	OR	95% CI
Comparison 1								
Investigational	5,012	103	0.23*	0.13 to 0.45	12,627	103	0.84	0.46 to 1.54
Placebo	149	12			1,242	12		
Comparison 2								
Active comparator	614	10	0.19*	0.08 to 0.45	2,922	10	0.35*	0.15 to 0.82
Placebo	149	12			1,242	12		
Comparison 3								
All drugs	5,626	113	0.23*	0.13 to 0.43	15,549	113	0.75	0.41 to 1.37
Placebo	149	12			1,242	12		

[a]Aripiprazole and clozapine were not included in this analysis.
*Significant at level of $p < .05$.
Abbreviation: PEY = patient exposure years.

patients assigned to various treatment arms. A majority of deaths (85%) occurring on investigational antipsychotics had a reported cause while cause of death was typically absent for patients assigned to placebo (75%), and the active comparator group (58%).

We calculated odds ratios to determine if significant differences in mortality rates based on PEY data existed among the 3 treatment groups (investigational antipsychotic, control antipsychotic [haloperidol and chlorpromazine], or placebo; Table 2) by combining data in each treatment condition across all antipsychotic clinical trials. We also assessed differences in mortality rates based on gross patient numbers.

Table 3 presents the ranked ordered causes of death for the investigational treatment arm of all the antipsychotic clinical trials, the only treatment condition for which causes are reported for the majority of cases in the condition. Because of the discrepancies in reporting between the investigational and control groups, we could not accurately compare causes of death across treatment conditions.

Table 3. Rank-Ordered Causes of Death in Investigational Groups of All 6 Antipsychotic Clinical Trials of Patients With Adult Schizophrenia

Cause of Death	No. of Deaths (%)
Suicide	48 (27.7)
Cardiovascular	31 (17.9)
Respiratory	29 (16.8)
Accident	10 (5.8)
Cancer	9 (5.2)
Sepsis	4 (2.3)
Asphyxia	4 (2.3)
Cachexia	2 (1.2)
Edema	2 (1.2)
Gastrointestinal	2 (1.2)
Renal failure	2 (1.2)
AIDS	1 (0.6)
Cerebrovascular	1 (0.6)
Embolism	1 (0.6)
Homicide	1 (0.6)
Not reported	26 (15.0)
Total	173 (100)

Abbreviation: AIDS = acquired immunodeficiency syndrome.

RESULTS

Demographic Information

The mean age at death and percentage of male deaths in the trials of the 6 antipsychotic agents are listed in Table 1. For the 4 trials used in the analysis of mortality rates, the SBA reports provided age and sex of the patient in 83 of 103 deaths (80.6%) among those patients assigned to an investigational antipsychotic. For these patients, mean age at death was 53.8 years and 72.7% were men. There was demographic information for 4 of 10 deaths (40.0%) in the active comparator group, and none for the 12 deaths reported in the placebo group.

Mortality Rate Based on PEY Data

When we examined PEY data, we calculated a mortality rate of 2182/100,000 exposure years among all patients participating in the 4 antipsychotic clinical trials examined. The mortality rate among patients treated with an investigational antipsychotic was 2055/100,000 exposure years (103 deaths/5012.4 exposure years). For patients assigned to placebo, the rate was 8081/100,000 exposure years (12 deaths/148.5 exposure years). Patients treated with an active control had a mortality rate of 1628/100,000 exposure years (10 deaths/614.3 exposure years).

The mortality rate for placebo was significantly higher ($p < .05$) than for either the investigational antipsychotic (OR = 0.23, 95% CI = 0.13 to 0.45) or the active control treatment condition (OR = 0.19, 95% CI = 0.08 to 0.45).

Mortality Rates Based on Gross Numbers

Among the 4 antipsychotic clinical trials evaluating 16,791 participants, 126 patients died. Of those who died, 103 received an investigational antipsychotic, 10 received an active control (haloperidol or chlorpromazine), and 12 were assigned to placebo.

The highest mortality rates (Table 1) occurred among patients participating in the aripiprazole (1.2%) and ziprasidone (1.0%) clinical trials, and the lowest in the quetiapine clinical trials with 0.5%. Odds ratios (Table 2) did not reveal statistically higher mortality risks among patients treated with an investigational antipsychotic (0.8%) compared to patients assigned to placebo (1.0%). However, a significant difference (OR = 0.35, 95% CI = 0.15 to 0.82; Table 2) emerged between those in the active control treatment condition (0.3%; haloperidol or chlorpromazine) compared to placebo (1.0%).

Causes of Death in Antipsychotic Clinical Trials

Table 3 lists all causes of death among those treated with investigational antipsychotics for each antipsychotic clinical trial, rank ordered by frequency. Across all antipsychotic clinical trials, the most frequent causes of death were suicide (28%), cardiovascular incidents (18%), and respiratory complications including pneumonia (17%). Acquired immunodeficiency syndrome (AIDS), cerebrovascular incident, embolism, and homicide were the least-cited causes of death, each accounting for less than 1%.

DISCUSSION

The aim of these analyses was to determine if mortality rates differed significantly among adult patients with schizophrenia assigned to an investigational (atypical) antipsychotic, an active control (typical antipsychotic), or placebo during 6 preapproval clinical development programs. We also evaluated the frequency of reported causes of death among these patients.

Using PEY analysis to calculate mortality rates, we observed that the placebo treatment condition had a significantly higher mortality rate (8081/100,000 exposure years) compared to either the investigational antipsychotic (2055/100,000 exposure years) or the active control (1628/100,000 exposure years) treatment conditions. On the basis of gross mortality rates (number of patients died/number of patients participating in the trials), odds ratio analysis also showed similar trends but the observed trends did not reach statistical significance for the difference between the placebo and investigational treatment conditions.

It is important to note that the PEY method of analysis is considered a more appropriate measure to analyze mortality risk, as it takes into account not just the number of patients exposed, but also the duration of exposure to each treatment assignment. For example, mean exposure was 4.8 months for investigational antipsychotics, 2.5 months for control antipsychotics, and 1.4 months for placebo, providing a better estimate of differential risk.

The increased mortality of geriatric patients treated with antipsychotics may not generalize to adult patients with schizophrenia. The mortality rate among the current sample of patients with schizophrenia assigned to antipsychotic treatment is similar to the mortality rates reported by other investigators from clinical and nonresearch samples. For example, the annual mortality rate for the general population in the United States for the last several years is about 850/100,000 population per year, and the mortality rate for patients with schizophrenia is estimated to be at least 2 times higher than that of the general population[1–4] (whether patients were receiving treatment is not apparent in these reports). Our results showing a mortality rate of 2055/100,000 exposure years for atypical antipsychotics, 1628/100,000 exposure years for typical antipsychotics, and 8081/100,000 exposure years for placebo are higher than these reports. This finding may be in part related to the detailed evaluations and follow-up that are part of clinical trials, and these rates may be much closer to the actual mortality risk with schizophrenia.

We also assessed whether causes of death unrelated to suicide may have contributed to increased mortality among patients with schizophrenia assigned to placebo. As shown in Table 3, we ascertained causes of death for a significant sample of patients that received investigational antipsychotics (85%). However, the sparse data for cause of death (placebo, 25%; active antipsychotic, 42%) do not permit comparison. This is an unfortunate limitation of the FDA SBA reports. The pattern of mortality risk among treatment conditions is a critical question that warrants investigation by pharmaceutical sponsors and the FDA, who have access to more detailed data and may be able to address this issue more thoroughly.

It is important to note that our results are consistent with previous literature. In these SBA data, the most frequent causes of death among patients with schizophrenia taking an investigational antipsychotic were suicide (28%), cardiovascular disease (18%), and respiratory complications including pneumonia (17%) (Table 3). In a study by Newman and Bland,[4] suicide accounted for 32% of all deaths, cardiovascular disease for 12%, and respiratory diseases for 9% among 3623 patients with schizophrenia. A meta-analysis by Harris and Barraclough[19] also cited these 3 causes of death as some of the most frequent causes of mortality among large samples of patients with schizophrenia.

These results cannot be regarded as conclusive regarding mortality patterns in antipsychotic trials for several reasons. SBA reports are not specifically designed to assess mortality rates and the data within the individual SBAs is not sufficient (i.e., duration of exposure and sample size) to detect potential differences. Additionally, treatment groups in SBAs are heterogeneous in that the placebo-controlled trials are typically short-term while exposure to investigational drug and active controls is of longer duration. This is due to most trials offering an extended phase of treatment for responders to investiga-

tional medication and active comparator, but not placebo. This increases the overall duration of exposure to investigational medication and active comparator relative to placebo.

Other limitations of SBA reports include inconsistencies in the manner of reporting patient information. Only 4 of the 6 atypical antipsychotic SBA reports listed in Table 1 contained sufficient specific information for this analysis of mortality rates. The aripiprazole data included patients with Alzheimer's disease and bipolar disorder, while the clozapine SBA lacked sufficient data on placebo and active control groups, as well as PEY data. The SBAs varied in providing detailed information about patient deaths, such as treatment assignment, age, and gender. In general, SBAs provided insufficient information on patient age or gender for deaths during placebo and comparator antipsychotic treatment conditions so that comparisons based on cause of death and demographic variables among treatment conditions were not possible.

In conclusion, on the basis of our analysis, we did not detect a signal suggesting an increased mortality rate with antipsychotic use (both investigational drugs as well as active controls) compared with the placebo treatment condition during preapproval development programs of antipsychotic drugs. The increased mortality risk in elderly dementia patients treated with antipsychotic drugs may not extend to adult patients with schizophrenia. Although these results offer only crude estimates of mortality rates, they are the best available in light of the large sample sizes based on the SBAs offered by this FDA database. Efforts to improve the quality of safety monitoring and continued vigilance are warranted to better assess mortality rates associated with newer antipsychotic agents.

Drug names: aripiprazole (Abilify), chlorpromazine (Thorazine, Sonazine, and others), clozapine (FazaClo, Clozaril, and others), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

REFERENCES

1. Felker B, Yazel JJ, Short D. Mortality and medical comorbidity among psychiatric patients: a review. Psychiatr Serv 1996;47:1356–1363
2. Amaddeo F, Bisoffi G, Bonizzato P, et al. Mortality among patients with psychiatric illness: a ten year case register study in an area with a community-based system of care. Br J Psychiatry 1995;166:783–788
3. Allebeck P. Schizophrenia: a life-shortening disease. Schizophr Bull 1989;15:81–89
4. Newman SC, Bland RC. Mortality in a cohort of patients with schizophrenia: a record linkage study. Can J Psychiatry 1991;36:239–245
5. Casey DE. Metabolic issues and cardiovascular disease in patients with psychiatric disorders. Am J Med 2005;118(suppl 2):15S–22S
6. Ösby U, Correia N, Brandt L, et al. Mortality and causes of death in schizophrenia in Stockholm county. Schizophr Res 2000;45:21–28
7. Enger C, Weatherby L, Reynolds RF, et al. Serious cardiovascular events and mortality among patients with schizophrenia. J Nerv Ment Dis 2004;192:19–27
8. Stark C, MacLeod M, Hall D, et al. Mortality after discharge from long-term psychiatric care in Scotland, 1977–94: a retrospective cohort study. BMC Public Health 2003;3:30
9. Straus SM, Bleumink GS, Dieleman JP, et al. Antipsychotics and the risk of sudden cardiac death. Arch Intern Med 2004;164:1293–1297
10. Merrill DB, Dec GW, Goff DC. Adverse cardiac effects associated with clozapine. J Clin Psychopharmacol 2005;25:32–41
11. Fayek M, Kingsbury SJ, Zada J, et al. Cardiac effects of antipsychotic medications. Psychiatr Serv 2001;52:607–609
12. Chong SA, Mythily, Mahendran R. Cardiac effects of psychotropic drugs. Ann Acad Med Singapore 2001;30:625–631
13. Brannon MD, Riggs JJ, Hageman WE, et al. A comparison of the cardiovascular effects of haloperidol, thioridazine and chlorpromazine HCL. Arch Int Pharmacodyn Ther 1980;244:48–57
14. Khan A, Khan SR, Leventhal RM, et al. Symptom reduction and suicide risk among patients treated with placebo in antipsychotic clinical trials: an analysis of the Food and Drug Administration database. Am J Psychiatry 2001;158:1449–1454
15. Khan A, Schwartz K. Suicide risk and symptom reduction in patients assigned to placebo in duloxetine and escitalopram clinical trials: analysis of the FDA Summary Basis of Approval reports. Ann Clin Psychiatry 2007;19:31–36
16. Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. JAMA 2005;294:1934–1943
17. Wang PS, Schneeweiss S, Avorn J, et al. Risk of death in elderly users of conventional vs atypical antipsychotic medications. N Engl J Med 2005;353:2335–2341
18. US Dept of Justice. Freedom of Information Act. Available at: http://www.usdoj.gov/oip/index.html. Accessibility verified July 3, 2007
19. Harris EC, Barraclough B. Excess mortality of mental disorder. Br J Psychiatry 1998;173:11–53