ORIGINAL ARTICLE

Risk of Death in Elderly Users of Conventional vs. Atypical Antipsychotic Medications

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ABSTRACT

BACKGROUND

Recently, the Food and Drug Administration (FDA) issued an advisory stating that atypical antipsychotic medications increase mortality among elderly patients. However, the advisory did not apply to conventional antipsychotic medications; the risk of death with these older agents is not known.

METHODS

We conducted a retrospective cohort study involving 22,890 patients 65 years of age or older who had drug insurance benefits in Pennsylvania and who began receiving a conventional or atypical antipsychotic medication between 1994 and 2003. Analyses of mortality rates and Cox proportional-hazards models were used to compare the risk of death within 180 days, less than 40 days, 40 to 79 days, and 80 to 180 days after the initiation of therapy with an antipsychotic medication. We controlled for potential confounding variables with the use of traditional multivariate Cox models, propensity-score adjustments, and an instrumental-variable analysis.

RESULTS

Conventional antipsychotic medications were associated with a significantly higher adjusted risk of death than were atypical antipsychotic medications at all intervals studied (≤180 days: relative risk, 1.37; 95 percent confidence interval, 1.27 to 1.49; <40 days: relative risk, 1.56; 95 percent confidence interval, 1.37 to 1.78; 40 to 79 days: relative risk, 1.37; 95 percent confidence interval, 1.19 to 1.59; and 80 to 180 days: relative risk, 1.27; 95 percent confidence interval, 1.14 to 1.41) and in all subgroups defined according to the presence or absence of dementia or nursing home residency. The greatest increases in risk occurred soon after therapy was initiated and with higher dosages of conventional antipsychotic medications. Increased risks associated with conventional as compared with atypical antipsychotic medications persisted in confirmatory analyses performed with the use of propensity-score adjustment and instrumental-variable estimation.

CONCLUSIONS

If confirmed, these results suggest that conventional antipsychotic medications are at least as likely as atypical agents to increase the risk of death among elderly persons and that conventional drugs should not be used to replace atypical agents discontinued in response to the FDA warning.

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Antipsychotic medications are disproportionately used among elderly persons and are prescribed for more than a quarter of Medicare beneficiaries in nursing homes.[1-3] The conditions for which these agents are prescribed include dementia, delirium, psychosis, agitation, and affective disorders, with many of the prescriptions being written for indications that have not been approved by the Food and Drug Administration (FDA).[4] In addition to increasing use, there have been rapid shifts from first-generation conventional agents (e.g., phenothiazines and butyrophenones) to heavily marketed second-generation atypical agents (e.g., aripiprazole [Abilify], clozapine [Clozaril], olanzapine [Zyprexa], quetiapine [Seroquel], risperidone [Risperdal], and ziprasidone [Geodon]).[5]

In a Public Health Advisory issued in April 2005, the FDA warned that the use of atypical antipsychotic medications nearly doubled the risk of death, as compared with the risk with placebo, in 17 short-term, randomized, controlled trials involving elderly persons with dementia.[6] "Black box" warnings describing this risk and advising that the atypical antipsychotic medications were not approved for use in elderly patients with dementia were added to the labels of all such agents. The advisory did not extend to conventional antipsychotic medications, although the FDA noted that the risk associated with these agents is an important issue for future study.[6,7]

In the absence of data regarding the risk of death posed by conventional antipsychotic medications, there is mounting concern that clinicians may simply switch elderly patients to these older agents,[8] particularly since their replacement by the newer drugs occurred so rapidly and recently.[5] Mainly on the basis of extrapolations from studies involving younger populations, some investigators have suggested that conventional antipsychotic medications could, in theory, pose risks equal to or greater than those associated with the newer drugs in older populations.[9-12]

We sought to define the risk of death in the short term among elderly patients who were beginning therapy with conventional antipsychotic medications, as compared with the risk among those beginning treatment with atypical antipsychotic agents. We also examined whether the risk of death differed according to the dosage of conventional antipsychotic medications, the presence or absence of dementia, and whether or not the patient resided in a nursing home. The underlying reasons for using both types of drugs (e.g., to treat dementia or delirium) may themselves be risk factors for death. Therefore, we restricted our analysis to patients who were given an antipsychotic medication. In addition, we restricted the analysis to new users in order to guard against selection bias among those already using antipsychotic medications from early emergence of symptoms, drug intolerance, or treatment failure.[13] To control for potential differences in the characteristics of patients who were prescribed different antipsychotic medications, we used traditional multivariate and propensity-score–adjusted Cox proportional-hazards models[14] as well as instrumental-variable estimation,[15-17] with a given physician's preference for prescribing conventional as compared with atypical antipsychotic medications as the instrument.[18] In sensitivity analyses,[19] we examined the degree to which a hypothetical confounder would have to be related to the use of a conventional antipsychotic medication and to mortality to cause a spurious increase in the apparent risk associated with conventional agents if none truly existed.

METHODS

SOURCES OF DATA

The Pharmaceutical Assistance Contract for the Elderly

Information from the Pennsylvania Pharmaceutical Assistance Contract for the Elderly (PACE), a large state prescription-benefits program for the elderly in the United States, was available from January 1, 1994, through December 31, 2003.[20] PACE has no deductibles or maximum annual benefit and charges a modest copayment of $6 for each prescription. The income ceiling for eligibility is $14,000 per year for single persons and $17,200 per year for couples, resulting in a recipient population of both indigent and near-poor elderly persons. These generous benefits and requirements for financial need result in essentially no out-of-pocket (i.e., out-of-system) medication use.

Pennsylvania Medicare

Medicare data included both Part A (covering hospitalizations and nursing home stays) and Part B (covering outpatient services and procedures) for all PACE enrollees from January 1, 1994, through December 31, 2003. Medicare data on mortality were drawn from the Death Master File, which undergoes extensive verification and weekly updates by the Social Security Administration.[21]

We assembled data for all filled prescriptions, procedures, physician encounters, hospitalizations, and long-term care into a relational database. All traceable, person-specific identifying factors were transformed into anonymous, coded study numbers to protect subjects' privacy. The study was approved by the institutional review board of Brigham and Women's Hospital.

STUDY POPULATION

All subjects were 65 years of age or older and filled a first recorded (index) prescription for an oral antipsychotic medication between January 1, 1994, and December 31, 2003. To ensure a uniform six-month eligibility period before the index prescription for antipsychotic medication was filled, all study subjects were required to have used at least one medical service (e.g., a physician visit, procedure, or hospitalization) and filled at least one prescription, both within the six months before the index date and in the time period preceding the six months before the index date.

ANTIPSYCHOTIC MEDICATIONS

Atypical antipsychotic agents included aripiprazole (Abilify), clozapine (Clozaril), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), and ziprasidone (Geodon). Other antipsychotic medications were considered to be conventional agents, including acetophenazine (Tindal), chlorpromazine (Thorazine), fluphenazine (Prolixin, Permitil), mesoridazine (Serentil), perphenazine (Trilafon), thioridazine (Mellaril), trifluoperazine (Stelazine), triflupromazine (Vesprin), chlorprothixene (Taractan), haloperidol (Haldol), loxapine (Loxitane), molindone (Moban), pimozide (Orap), and thiothixene (Navane).[22]

OTHER VARIABLES

We defined the characteristics of the patients during the six months before each subject's index date according to demographic data (age, sex, and race), coexisting illnesses, and use of health care. To define clinical conditions that may have been associated with a higher or lower risk of death in the short term, we used the diagnostic codes of the *International Classification of Diseases, 9th Revision, Clinical Modification*,[23] the procedure codes of *Physicians' Current Procedural Terminology*,[24] and diagnosis-related group hospital-discharge codes,[25] and we assessed medication use. For example, arrhythmias were defined according to the presence of ventricular arrhythmias and diagnoses of other cardiac arrhythmias and the use of an antiarrhythmia medication. Similarly, diabetes was defined according to previous diagnoses plus the use of medications for the treatment of diabetes. Other conditions included cerebrovascular disease (e.g., both cerebral hemorrhagic and ischemic events), congestive heart failure, myocardial infarction, other evidence of ischemic heart disease (e.g., angina, percutaneous transluminal coronary angioplasty, coronary-artery bypass grafting, or use of nitroglycerin), other cardiovascular conditions (e.g., valvular disease, aneurysms, or peripheral vascular disease), cancer, human immunodeficiency virus (HIV) infection, dementia, delirium, mood disorders, psychotic disorders, and other psychiatric disorders. The use of health care services that were potentially predictive of a higher or lower risk of death in the short term were also assessed; these included hospitalizations, nursing home stays, the use of other psychiatric medications, and the total number of medications used (excluding antipsychotic agents and drugs used to define covariables).[26]

Statistical Analysis

We calculated distributions of demographic and clinical characteristics and use of medications among subjects receiving conventional and atypical antipsychotic agents and then plotted mortality rates during the first 180 days after the initiation of therapy with a drug from either class. A 180-day follow-up period was chosen on the basis of the duration of trials in the FDA's reanalysis (which ranged from 4 to 26 weeks, with a modal duration of 10 weeks).[6] Unadjusted and multivariate Cox proportional-hazards models (controlled for calendar year and all variables listed above) were constructed for deaths occurring within 180 days after the initiation of therapy. Models of death within less than 40 days, 40 to 79 days, and 80 to 180 days were also constructed after a visual inspection of plots of death rates revealed roughly proportional hazards among users of conventional and atypical antipsychotic medications within these intervals. Adjusted models were analyzed separately in subgroups defined according to the presence or absence of dementia and nursing home residency. We also investigated whether a dose–response relationship existed in adjusted models by separating users of conventional antipsychotic medications into subgroups made up of those taking the median daily dose or less and those taking more than the median daily dose.

In confirmatory analyses, we used the Cox models again with propensity-score adjustments to balance independent risk factors for death between the groups of drug users.[14] Propensity scores were derived from predicted probabilities in logistic-regression models of the use of conventional as compared with atypical antipsychotic medications. The final nonparsimonious model contained all variables shown in Table 1 and strongly predicted the type of antipsychotic medication used (C statistic = 0.845). We then stratified Cox models of mortality across deciles of the propensity score.

We also used instrumental-variable analysis to provide estimates that would remain unbiased even if important confounding variables were not measured.[15-17] An instrumental variable is an observable factor related to treatment choice but unrelated to characteristics of patients or to outcomes. As in other recent work,[18] we used the prescribing physician's preference for conventional or atypical antipsychotic medications (as indicated by his or her most recent new prescription for an antipsychotic agent) as the instrument. We operationalized the instrumental variable as the choice of medication made by each prescribing physician for his or her most recent patient newly started on an antipsychotic medication before the index prescription was written. Using two-stage linear regression for the estimation of instrumental variables and additional adjustment for measured characteristics of the patients, we calculated the difference in the risk of death within 180 days between subjects receiving conventional antipsychotic medications and those receiving atypical agents. Finally, we performed a sensitivity analysis[19] to determine the degree to which a hypothetical confounder would have to be related to the use of a conventional antipsychotic medication as well as to mortality to cause a spurious increase in the apparent risk associated with the use of conventional antipsychotic agents if none truly existed.

RESULTS

Table 1 shows the characteristics of the 22,890 new users of conventional or atypical antipsychotic agents. The 9142 patients who began using conventional antipsychotic agents were slightly younger and more likely to be male and nonwhite than were the 13,748 who began using atypical antipsychotic drugs. New users of the conventional agents were less likely than new users of the atypical agents to have cerebrovascular disease, dementia, delirium, psychoses, or other psychiatric disorders but more likely to have congestive heart failure, ischemic heart disease other than myocardial infarction, or cancer. Users of conventional agents had lower rates of use of antidepressant agents and other psychotropic medications, a lower total number of drugs used, and lower rates of hospitalization and nursing home stays within the previous 180 days. In the first 180 days of use, 17.9 percent of patients who began using conventional antipsychotic medications died, as compared with 14.6 percent of those who began using atypical agents.

The relative risk of death among new users of conventional drugs, as compared with new users of atypical drugs, is shown in Table 2. The risk of death was significantly higher for conventional agents than for atypical agents in both unadjusted analyses of death within 180 days and in adjusted analyses in which we controlled for a large number of potential confounders. The greatest increase in the adjusted risk of death for conventional as compared with atypical antipsychotic medications occurred with higher doses (i.e., greater than the median) of conventional agents and during the first 40 days after the initiation of therapy. In analyses among subgroups defined by the presence or absence of dementia or residency in a nursing home, patients who began using conventional antipsychotic agents had a significantly higher risk of death within 180 days, in all subgroups studied, than did those who began using atypical agents (Table 2). Figure 1 shows mortality rates (in deaths per person-year) over the first 180 days after the beginning of therapy with antipsychotic medications. Consistent with our adjusted models of mortality during specific periods, we observed that the increased rates of death associated with conventional as compared with atypical antipsychotic agents were greatest soon after therapy was initiated; the rates of death then began converging in subsequent periods.

Confirmatory analyses with the use of propensity-score adjustments[14] yielded no substantive differences relative to traditional multivariate Cox analyses. For example, the hazard ratio for death within 180 days for conventional as compared with atypical antipsychotic medications in a Cox model with the use of deciles of propensity scores to balance covariables was 1.37 (95 percent confidence interval, 1.27 to 1.49). The hazard ratio remained stable and without trend (ranging between 1.17 and 1.58) across separate Cox analyses

performed within each decile of the propensity score.

In instrumental-variable analyses, conventional agents continued to be associated with a higher risk of death within 180 days than did atypical agents. The difference in risk of 0.073 (95 percent confidence interval, 0.020 to 0.126) meant that on average, for every 100 patients treated with a conventional antipsychotic drug instead of an atypical agent, there would be 7 additional deaths. Sensitivity analyses[19] revealed that very large relative risks — of 7 or more — would be needed, linking a hypothetical confounder to both the use of conventional agents and mortality, to explain fully the increased observed risk of death associated with the use of conventional agents, if no risk truly existed.

DISCUSSION

In this study of 22,890 elderly persons beginning therapy with antipsychotic medications, patients for whom conventional agents were prescribed had a 37 percent higher, dose-dependent risk of death in the short term than those for whom atypical agents were prescribed. To place this magnitude of risk in perspective, only cancer, congestive heart failure, and HIV infection conferred greater adjusted risks in our analyses. Unfortunately, there are few studies of death associated with drugs in the elderly with which to compare our results; one observational study found higher rates of death among those given a conventional drug (haloperidol) than among those given one of two atypical drugs (risperidone or olanzapine).[27] If confirmed, our results suggest that conventional antipsychotic medications may not be safer than atypical agents and should not simply replace atypical drugs that are stopped in response to recent FDA warnings, as may be happening.[7]

It is important to assess whether methodologic limitations, rather than true biologic relationships, might explain these findings. Confounding would occur if conventional drugs were more likely than atypical agents to be given to patients who were more frail or at greater risk of dying than others. Therefore, using traditional multivariate, propensity-score, and instrumental-variable techniques, we controlled for the demographic and clinical factors and use of health care services that were likely to be independent predictors of death.[14-17] We also restricted our analyses to only those patients who had used antipsychotic agents as well as to those who were new users, to control for the underlying reasons that patients use antipsychotic medications and for any selection bias from early emergence of symptoms, drug intolerance, or treatment failure among those already using antipsychotic medications.[13]

Because authorities[4,9-12,28] have recommended avoiding the use of conventional antipsychotic med-

Table 1. Characteristics of 22,890 New Users of Conventional and Atypical Antipsychotic Medications.

Characteristic	Users of Conventional Antipsychotic Medications (N=9142)	Users of Atypical Antipsychotic Medications (N=13,748)	P Value
	%	%	
Age (mean)	83.2	83.5	<0.001
Sex			
Female	77.6	83.0	<0.001
Male	22.4	17.0	
Race*			
White	92.8	94.7	<0.001
Nonwhite	7.2	5.3	
Diagnosis			
Cardiac arrhythmia	1.4	1.4	0.87
Cerebrovascular disease	29.1	30.9	0.003
Congestive heart failure	32.6	31.1	0.01
Diabetes	25.8	26.8	0.10
Myocardial infarction	3.5	3.5	0.85
Other ischemic heart disease	29.3	24.4	<0.001
Other cardiovascular disorders	12.7	12.3	0.39
Cancer	15.6	14.0	<0.001
HIV infection	<0.1	<0.1	0.36
Dementia	40.8	52.5	<0.001
Delirium	12.2	16.1	<0.001
Mood disorders	22.2	36.3	<0.001
Psychotic disorders	21.3	24.7	<0.001
Other psychiatric disorders	5.9	8.3	<0.001
Use of other drugs			
Antidepressants	28.0	43.5	<0.001
Other psychotropic medications	11.5	13.5	<0.001
Total no. of drugs used (mean)	6.8	7.9	<0.001
Hospitalization in previous 180 days	51.2	53.5	<0.001
Nursing home residence in previous 180 days	15.9	21.4	<0.001
Death within 180 days of index prescription for antipsychotic medication	17.9	14.6	<0.001

* Race was self-reported.

Table 2. Relative Risk of Death within 180 Days after Beginning Therapy with Conventional as Compared with Atypical Antipsychotic Medications.*

Model	Hazard Ratio (95% CI)
Unadjusted analysis	1.51 (1.43–1.59)
Adjusted analysis†	
Use of any conventional APM	1.37 (1.27–1.49)
Low dose of conventional APM (<median)	1.14 (1.04–1.26)
High dose of conventional APM (>median)	1.73 (1.57–1.90)
Adjusted analysis of death†	
<40 Days after beginning therapy	1.56 (1.37–1.78)
40–79 Days after beginning therapy	1.37 (1.19–1.59)
80–180 Days after beginning therapy	1.27 (1.14–1.41)
Adjusted analysis of patient subgroups†	
With dementia	1.29 (1.15–1.45)
Without dementia	1.45 (1.30–1.63)
In a nursing home	1.26 (1.08–1.47)
Not in a nursing home	1.42 (1.29–1.56)

* APM denotes antipsychotic medication, and CI confidence interval.
† Hazard ratios were adjusted for calendar year, age, sex, race, the presence or absence of cardiac arrhythmias, cerebrovascular disease, congestive heart failure, diabetes, myocardial infarction, other ischemic heart disease, other cardiovascular disorders, cancer, HIV infection, dementia, delirium, mood disorders, psychotic disorders, other psychiatric disorders, and the use or nonuse of other psychiatric medications, total number of medications used, hospitalizations, and nursing home stays.

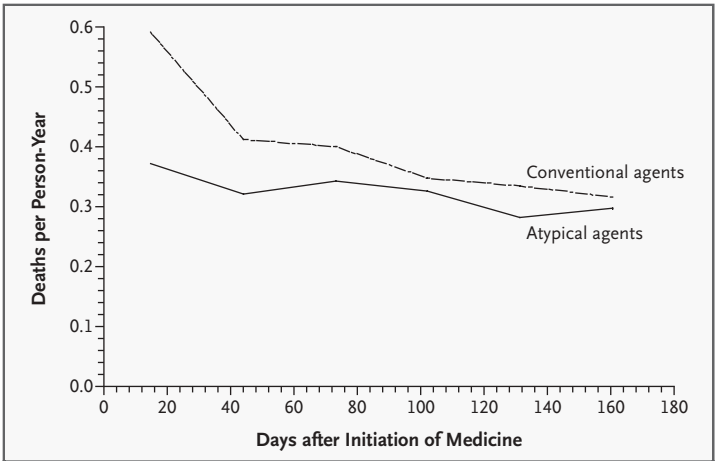

Figure 1. Rates of Death after the Initiation of Conventional and Atypical Antipsychotic Medications.
The rate of death before 10 days was not calculated, owing to insufficient data.

ications for frail elderly persons, any residual confounding may have led to an underestimation of mortality resulting from the use of conventional agents. Any misclassification of exposure status that occurred nondifferentially with respect to the class of antipsychotic agent (e.g., a lack of consumption of filled prescriptions or a switch from a conventional to an atypical antipsychotic agent, or vice versa) would bias results toward the null; differential misclassification (e.g., decreased adherence among patients taking conventional agents, as has been found[29]) may have led to an underestimation of the rates of death associated with conventional agents. Misclassification of information from Medicare with regard to mortality is less likely, given the Social Security Administration's extensive verification process for data from the Death Master File,[21] and such misclassification would presumably bias our findings toward the null.

Finally, we controlled for calendar time, to adjust for any improvements in health care over the study period that could lead to improved survival in later years, when the use of atypical drugs would be more common. However, in spite of these safeguards and the convergence of results from confirmatory and sensitivity analyses, it is important to keep in mind that our study is based on nonexperimental data. There may be other factors with regard to patients who were newly prescribed conventional antipsychotic medications that we were unable to control for, requiring a circumspect interpretation of these findings.

Potential mechanisms through which conventional antipsychotic medications might increase the risk of death in the short term are unclear, and the causes of death were unavailable. In the FDA analysis on which the April 2005 advisory was based, heart-related events (e.g., heart failure and sudden death) and infections (mostly pneumonia) accounted for most deaths.[6] Anticholinergic properties (affecting blood pressure and heart rate), prolongation of the QT interval (causing conduction delays), and extrapyramidal symptoms (causing swallowing problems) are at least as common with conventional drugs as with atypical agents, and probably more so, and should be investigated as potential underlying causes of death.[4,9-12] Whatever the underlying cause or causes are, they most markedly elevate the risk of death with the use of conventional as compared with atypical antipsychotic medications immediately after the initiation of therapy, after which their influence subsides somewhat.

The hazard ratios associated with conventional as compared with atypical agents were not confined to high-risk elderly persons with dementia or those residing in nursing homes. However, because the clinical trials that the FDA initially reviewed exclu-

sively involved patients with dementia, more data are needed on the absolute risk of death associated with atypical antipsychotic agents in elderly persons who do not have dementia. Our results suggest only that conventional antipsychotic medications do not appear to be safer than atypical agents in populations of elderly persons without dementia.

If confirmed, our results suggest that conventional antipsychotic medications should be included in the FDA's Public Health Advisory, which currently warns only of the increased risk of death with the use of atypical antipsychotic drugs in elderly persons who have dementia. Beyond arousing new concern about conventional agents, our data provide no guidance with regard to which pharmacologic or nonpharmacologic interventions should be used to manage the many conditions and symptoms for which antipsychotic medications are used.[4] Traditionally, the benefits and risks of treatments in the elderly have simply been extrapolated from studies involving younger populations.[9-12] As the recent FDA advisory and the results of this study show, such a practice can be misleading, given the unique needs and susceptibilities of older persons. Well-designed studies specifically involving the elderly are sorely needed to define optimal care.

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