of withdrawal dyskinesia. This theory proposes that when postsynaptic dopamine receptors are occupied by serotonin-dopamine antagonists with strong affinity to D_2 receptors (eg, risperidone), this blockade can lead to physiologic denervation. In response, these receptor sites up-regulate and are more sensitive to dopaminergic tone. Only 1 patient (case 1) had ever received a first-generation antipsychotic that could have sensitized her brain to develop a dyskinesia. Once the supersensitivity is established, minute quantities of dopamine present in the ambient environment could trigger dyskinesias or psychomotor-activating effects upon discontinuation of the D_2 receptor blocking effects of the drug, risperidone or aripiprazole in these cases.[15]

Interestingly, aripiprazole has an even higher affinity for the D_2 receptor than risperidone,[16] yet functions as a dopamine partial agonist-antagonist. This mechanism of action is purported to be the reason for the reduced production of EPSs. While the potency of aripiprazole to up-regulate dopamine D_2 receptors in the striatum is much smaller than that of haloperidol,[17] nevertheless, this small up-regulation may be sufficient to produce withdrawal dyskinesia.

The clinical significance of the cases reported here is for psychiatrists to be alerted to the development of withdrawal dyskinesia as a possible complication of prescribing atypical antipsychotic medication. Both of these drugs have had reports of the development of tardive dyskinesia, although they are rare. It was unexpected that withdrawal dyskinesia could occur; therefore, patients were not significantly informed of this potential side effect. It would be important to include information about the possibility of withdrawal dyskinesias in our discussion with patients about medication side effects for both clinical as well as medicolegal reasons.

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Ventricular Arrhythmias and Cerebrovascular Events in the Elderly Using Conventional and Atypical Antipsychotic Medications

To the Editors:

The US Food and Drug Administration (FDA) issued an advisory in 2005 that atypical antipsychotic medications (APMs) significantly increased the risk of death versus placebo among the elderly with dementia.[1] The Advisory did not cover conventional APMs because of insufficient data on the mortality associated with them.[1] However, in the absence of warnings for conventional APMs, clinicians may simply switch elderly patients to these older agents particularly because their use had until recently been widespread.[2] In a recent observational study, we found that elderly patients initiating conventional agents had a 37% greater, dose-dependent risk of short-term mortality than those starting atypicals.[3] A recent meta-analysis of randomized trials among elderly with dementia found the conventional agent, haloperidol, increased short-term mortality versus placebo by 107%, a risk greater than that for atypical agents.[4] Another observational study found higher mortality for haloperidol versus 2 atypical drugs.[5]

An important next step in understanding whether conventional APMs truly pose greater hazards than atypical agents is to investigate potential mechanisms through which they may act. In the FDA's analysis, heart-related events (heart failure and sudden death) and infections (mostly pneumonia) accounted for many deaths.[1] Furthermore, anticholinergic properties affecting blood pressure and heart rate and Q-T prolongation causing conduction delays, as well as sedation and extrapyramidal symptoms causing potential swallowing problems, are all more common with conventional than atypical agents.[6] For these reasons, cardiac (eg, myocardial infarction and ventricular arrhythmias), cerebrovascular (eg, stroke and transient ischemic events), and

infection (eg, aspiration pneumonia) outcomes may all be potential mediators of an increased risk of death from conventional versus atypical agents. The aims of the current study were to examine whether the elderly newly started on conventional versus atypical APMs in our earlier study[3] had greater risks of cardiac, cerebrovascular, and infection outcomes. (Please see our previous publication for additional details concerning this study's methods.[3])

Information from the Pennsylvania Pharmaceutical Assistance Contract for the Elderly Program, the largest state prescription benefits program for the elderly, was available from January 1, 1994, to December 31, 2003. Medicare data included both parts A and B on all Pennsylvania Pharmaceutical Assistance Contract for the Elderly enrollees during January 1, 1994, to December 31, 2003. All traceable person-specific identifiers were transformed into anonymous, coded study numbers to protect subjects' privacy. This study was approved by the Brigham and Women's Hospital institutional review board.

All individuals were 65 years old or older and filled a first recorded (index) prescription for an oral APM from January 1, 1994, to December 31, 2003. All study subjects were required to have utilized 1 or more medical services and 1 or more prescriptions, both within the 6 months before the index date as well as in more than 6 months before the index date.

Atypical APM agents included aripiprazole, clozapine, olanzapine, quetiapine, risperidone, and ziprasidone. Other APMs were considered conventional APMs.

Outcomes Potentially Mediating the Increased Hazards of Conventional Versus Atypical APMs

The following outcomes were assessed in the 180 days after the index day:

1. *Acute myocardial infarction*: hospitalization with *International Classification of Diseases, Ninth Revision* diagnoses (in the principal or secondary position) or *diagnosis related group* codes for acute myocardial infarction.
2. *Ventricular arrhythmia*: ventricular arrhythmia diagnosis plus use of group I-IV antiarrhythmia medication.
3. *Cerebrovascular events*: diagnoses of cerebrovascular events (eg, both cerebral hemorrhagic and ischemic events).
4. *Congestive heart failure*: hospitalization with a diagnostic code for congestive heart failure.
5. *Pneumonia*: diagnostic codes for pneumonia plus prescription for an antibiotic medication.
6. *Other serious bacterial infections*: hospitalization for bacteremia/septicemia, cellulitis, encephalitis/meningitis, endocarditis/myocarditis, pyelonephritis, septic arthritis, osteomyelitis, or opportunistic infection.

Other Covariates

We defined the following in the 6 months before each subject's index date:

1. *Sociodemographic data*: age, sex, and race.
2. *Comorbidities*: We employed *International Classification of Diseases, Ninth Revision* diagnostic codes, *current procedural terminology* procedure codes, *diagnosis related group* hospitalization codes, and medication use to define the presence of clinical conditions prior to initiation of APM. Acute myocardial infarction, cardiac arrhythmia, cerebrovascular events, congestive heart failure, pneumonia, and other serious bacterial infections were defined as above. Diabetes was defined by the presence of diagnoses plus use of antidiabetic medications. Additional conditions included ischemic heart disease (eg, angina, percutaneous transluminal coronary angioplasty, coronary artery bypass graft, or nitroglycerin use), other cardiovascular conditions (eg, valvular disease, aneurysms, peripheral vascular disease), cancers, HIV, dementia, delirium, mood disorders, psychotic disorders, and other psychiatric disorders.
3. *Health care utilization*: Health care utilization assessed included hospitalizations, nursing home stays, other psychiatric medication use, and total medications used (excluding APMs and drugs used to define covariates).

Distributions of sociodemographic, clinical, and utilization characteristics among conventional and atypical APM users were calculated. Multivariable (controlling for calendar year and all covariates listed above) Cox proportional hazards models were constructed of developing outcomes within 30, 60, and 120 days of APM initiation (based on our earlier finding of roughly proportional hazards of death between conventional and atypical APM users within these time intervals).[3] In confirmatory analyses, we used propensity scores derived from predicted probabilities in logistic regression models that strongly predicted the type of APM used (c statistic = 0.845). We stratified Cox models of individual outcomes across deciles of the propensity score. We also used instrumental variable (IV) analysis, using the prescribing physician's preference for conventional versus atypical APMs (as indicated by their most recent new APM prescription) as the instrument.[7] Using 2-stage linear regression for the IV estimation and additional adjustment for measured patient characteristics, we calculated the risk difference of developing 180-day outcomes between conventional versus atypical APM users.

For characteristics of patients who began use of conventional (n = 9142) and atypical APMs (n = 13,748), please see our previous publication.[3] Adjusted hazard ratios comparing the risk of developing conditions for new users of conventional versus atypical APMs are shown in Table 1. By 30 days, adjusted hazards were significantly higher for conventional than atypical APM use only in models of developing ventricular arrhythmias. By 60 days, conventional versus atypical APM use was only associated with a significantly increased hazard of developing cerebrovascular events. Similarly, only the hazards of developing cerebrovascular events were significantly greater for conventional than atypical APM use at 120 days.

Confirmatory analyses using propensity score adjustments yielded nearly identical results to the traditional multivariable Cox analyses. Results from the IV analysis agreed with the direction and statistical significance of the traditional multivariable Cox analyses for all outcomes examined.

DISCUSSION

In this study of more than 20,000 elderly patients initiating APM treatments,

TABLE 1. Adjusted Relative Hazards of Developing Conditions Among Elderly New Users of Conventional Versus Atypical Antipsychotic Medications

Condition	Adjusted HR* (95% CI) in 30 d	Adjusted HR* (95% CI) in 60 d	Adjusted HR* (95% CI) in 120 d
Acute myocardial infarction	0.89 (0.59–1.33)	1.02 (0.75–1.40)	1.16 (0.91–1.48)
Cerebrovascular event	1.08 (0.99–1.18)	1.10 (1.02–1.19)	1.09 (1.02–1.16)
Congestive heart failure	1.04 (0.95–1.11)	1.00 (0.93–1.07)	1.01 (0.95–1.07)
Pneumonia	1.11 (0.76–1.63)	1.03 (0.76–1.38)	0.84 (0.66–1.05)
Other serious infection	1.20 (0.98–1.48)	1.03 (0.87–1.21)	1.00 (0.88–1.14)
Ventricular arrhythmia	1.20 (1.03–1.39)	1.10 (0.98–1.24)	1.06 (0.96–1.17)

*Controlled for calendar year, age, sex, race, prior arrhythmias, cerebrovascular disease, congestive heart failure, diabetes, myocardial infarction, hypertension, other evidence of ischemic heart disease, other cardiovascular conditions, cancers, HIV, pneumonia, other serious infection, dementia, delirium, mood disorders, psychotic disorders, other psychiatric disorders, use of other psychiatric medications, total number of medications, hospitalizations, and nursing home stays.

HR indicates hazard ratio; CI, confidence interval.

conventional agents were associated with modestly increased hazards of developing ventricular arrhythmias and cerebrovascular events compared with atypical agents. The increased hazards for these 2 conditions may explain at least in part the greater risk of mortality that we observed from conventional versus atypical APMs among elderly patients in our earlier analysis.[3]

On the one hand, our finding of a possibly greater risk of ventricular arrhythmias from conventional APM use is not new and provides some reassurance concerning our analyses' ability to identify known effects. Conventional APMs have been associated with the development of arrhythmias, cardiac arrest, and sudden death.[8–12] Prolongation of cardiac repolarization and QTc intervals is thought to be responsible and generally more common with conventional than atypical agents, an exception being ziprasidone.[13] Most[13,14] but not all[9] earlier epidemiological data have found higher risks of ventricular arrhythmia and cardiac arrest with conventional versus atypical use.

On the other hand, our finding of a potentially greater hazard of cerebrovascular accidents from conventional versus atypical APMs has not been established. Because of the paucity of trials involving conventional agents, the FDA has warned only of increased risks for strokes and transient ischemic events from the atypical agents risperidone, olanzapine, and aripiprazole. One potential mechanism through which conventional agents might increase risks of cerebrovascular events is suggested by their known anticholinergic effects on heart rate and blood pressure. Hypoperfusion has been shown to lead to microinfarcts in dementia patients, and investigators have proposed that conventional APMs, in particular, may accentuate this process.[15] Two epidemiologic studies comparing conventional versus atypical agents have not found statistically significant differences.[16,17] One possible explanation for the discrepancy with our results is raised by our finding that the greater hazards from conventionals did not emerge immediately and may require separately examining intermediate or longer periods of follow-up.

These results should be interpreted with the following potential limitations kept in mind. Conventional agents may have been more likely than atypical APMs to be given to patients at risk of developing arrhythmias and cerebrovascular accidents. For this reason, we controlled for sociodemographic, clinical, and health care utilization factors through traditional multivariable, propensity score, and IV techniques.[7] We restricted analyses to only APM users as well as to just-new users, to control for underlying reasons for APM use and any selection bias among prevalent users from early symptom emergence, drug intolerance, or treatment failure. In addition, we limited our examination to data from essentially before the first warnings regarding atypical agents and stroke to avoid overestimating cerebrovascular risks from conventional APMs. We also controlled for calendar time to adjust for any improvements in the prevention of cardiac or cerebrovascular events which could otherwise lead to reduced risks in later years when atypical use was more common. However, despite these safeguards, it is imperative to keep in mind that there still may be other aspects of patients newly prescribed conventional APMs that we were unable to control for, leaving open the possibility of residual confounding. For this reason, circumspect interpretation of these findings is critical.

Other potential limitations include that the hazards we observed were only modest in magnitude, and we may have detected spurious associations because of having made multiple comparisons. Our study may also have had inadequate statistical power to observe true associations; furthermore, grouping together conventional APM s or atypical agents may have inadvertently combined drugs with different effects on our outcomes of interest, again, weakening our ability to observe potential hazards associated with specific medications. Misclassification of exposures or outcomes is possible and would presumably bias our results toward the null.Finally, the generalizability of these findings to other elderly populations may be uncertain.

If confirmed, these results add to growing evidence that conventional APMs may not be safer than atypical APMs for the elderly and should not simply replace the latter drugs stopped in response to recent FDA warnings.[3–5,18] They suggest that conventional APMs may raise the risks of mortality through the development of ventricular arrhythmias and cerebrovascular accidents. However, beyond suggesting caution regarding conventional APM use in

older populations, our results leave many important questions unanswered. First, any greater risk for ventricular arrhythmias or cerebrovascular accidents from conventional agents may only partially mediate the greater mortality observed among conventional versus atypical APM users, and more research is needed to identify other possible intervening conditions. Furthermore, our study sheds no light on other pharmacologic or nonpharmacologic interventions that could preferentially be used to manage the many conditions and symptoms in older populations for which APMs are currently used.[6] Well-designed studies shedding light on optimal care are sorely needed.

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Repeated Creatine Kinase Elevation Under Treatment With Quetiapine, Clozapine, and Aripiprazole in an Adolescent

To the Editors:

A level of increased serum creatine kinase (CK) is a potential side effect associated with the use of atypical antipsychotics. Several cases of increased serum CK during or after quetiapine, clozapine, or olanzapine treatment have been reported.[1–4] However, to our knowledge, no adolescent cases have been reported. This article reports a case of 2 antipsychotic-drug–induced episodes with serum CK increase in a 17-year-old paranoid schizophrenic male adolescent.

In 2001, the 11-year-old boy had been presented at the clinic for the first time, where he was diagnosed with a schizotypal personality disorder (*Diagnostic and Statistical Manual of Mental Disorders Fourth Edition, Text Revision* 301.22). Initially, he was treated with risperidone until 2005, showing good social functioning during this period. However, in February 2006, 6 months before admission, his mental condition deteriorated with symptoms of delusion and depersonalization, thereby fulfilling the diagnostic criteria for paranoid schizophrenia (*Diagnostic and Statistical Manual of Mental Disorders Fourth Edition, Text Revision* 295.30).

For this reason, the psychiatrist in private practice altered antipsychotic medication to quetiapine treatment, with an initial dosage of 300 mg/d. Concurrent laboratory tests (renal, liver, thyroid, and blood parameters) have shown no pathological results. The dosage of 300 mg/d over 4 months did not improve symptoms; furthermore, he developed significant negative symptoms. Consequently, the quetiapine dose was stepwise increased to 1200 mg/d. Despite a 4-week treatment period on this dose, the patient's symptoms did not improve, making hospitalization for substitute treatment with clozapine inevitable.