ORIGINAL RESEARCH | Annals of Internal Medicine

Atypical Antipsychotic Drugs and the Risk for Acute Kidney Injury and Other Adverse Outcomes in Older Adults

A Population-Based Cohort Study

Y. Joseph Hwang, MSc; Stephanie N. Dixon, PhD; Jeffrey P. Reiss, MD, MSc; Ron Wald, MD, MPH; Chirag R. Parikh, MD, PhD; Sonja Gandhi, BSc; Salimah Z. Shariff, PhD; Neesh Pannu, MD, SM; Danielle M. Nash, MSc; Faisal Rehman, MD; and Amit X. Garg, MD, PhD

Background: Several adverse outcomes attributed to atypical antipsychotic drugs, specifically quetiapine, risperidone, and olanzapine, are known to cause acute kidney injury (AKI). Such outcomes include hypotension, acute urinary retention, and the neuroleptic malignant syndrome or rhabdomyolysis.

Objective: To investigate the risk for AKI and other adverse outcomes associated with use of atypical antipsychotic drugs versus nonuse.

Design: Population-based cohort study.

Setting: Ontario, Canada, from 2003 to 2012.

Patients: Adults aged 65 years or older who received a new outpatient prescription for an oral atypical antipsychotic drug (n = 97 777) matched 1:1 with those who did not receive such a prescription.

Measurements: The primary outcome was hospitalization with AKI (assessed by using a hospital diagnosis code and, in a subpopulation, serum creatinine levels) within 90 days of prescription for atypical antipsychotic drugs.

Results: Atypical antipsychotic drug use versus nonuse was associated with a higher risk for hospitalization with AKI (relative risk [RR], 1.73 [95% CI, 1.55 to 1.92]). This association was consistent when AKI was assessed in a subpopulation for which information on serum creatinine levels was available (5.46% vs. 3.34%; RR, 1.70 [CI, 1.22 to 2.38]; absolute risk increase, 2.12% [CI, 0.80% to 3.43%]). Drug use was also associated with hypotension (RR, 1.91 [CI, 1.60 to 2.28]), acute urinary retention (RR, 1.98 [CI, 1.63 to 2.40]), and all-cause mortality (RR, 2.39 [CI, 2.28 to 2.50]).

Limitation: Only older adults were included in the study.

Conclusion: Atypical antipsychotic drug use is associated with an increased risk for AKI and other adverse outcomes that may explain the observed association with AKI. The findings support current safety concerns about the use of these drugs in older adults.

Primary Funding Source: Academic Medical Organization of Southwestern Ontario.

Ann Intern Med. 2014;161:242-248. doi:10.7326/M13-2796 www.annals.org
For author affiliations, see end of text.

Each year, millions of older adults worldwide are prescribed atypical antipsychotic drugs (quetiapine, risperidone, and olanzapine). These drugs are frequently used to manage behavioral symptoms of dementia, which is not an approved indication, and such use has raised safety concerns (1, 2). These drugs antagonize α-adrenergic, muscarinic, serotonin, and dopamine receptors (3). Acute kidney injury (AKI) (defined as a sudden loss of kidney function) from atypical antipsychotic drugs is described in several case reports (4–8). Adverse outcomes potentially attributable to these drugs, such as hypotension, acute urinary retention, and the neuroleptic malignant syndrome or rhabdomyolysis, are known to cause AKI (4–11). Moreover, pneumonia, acute myocardial infarction, and ventricular arrhythmia have been associated with these drugs in previous population-based studies and AKI may also cooccur with these events (12–14). However, no clinical or epidemiologic studies have quantified the risk for AKI from atypical antipsychotic drugs and information on outcomes of hypotension, acute urinary retention, and the neuroleptic malignant syndrome or rhabdomyolysis is limited. Such information would contribute to growing knowledge of potential adverse events from this drug class. The U.S. Food and Drug Administration warns of an increased risk for death in older patients treated with these drugs based on analyses of randomized, placebo-controlled trials (averaging 10 weeks in duration) (1). For these reasons, we did this population-based study of older adults to investigate the 90-day risk for hospitalization with AKI and other adverse outcomes from new use of an oral atypical antipsychotic drug initiated in the nonhospital setting.

See also:

Web-Only
Supplement

METHODS

Design and Setting

We conducted this study at the Institute for Clinical Evaluative Sciences according to a prespecified protocol that was approved by the research ethics board at Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada. Patient informed consent was not required.

We did a population-based, retrospective cohort study of older adults using linked health care databases in Ontario, Canada. Ontario residents have universal access to hospital care and physician services, and those aged 65 years or older have universal prescription drug coverage. The reporting of this study followed guidelines for obser-

vational studies (**Table 1** of the **Supplement**, available at www.annals.org) (15).

Data Sources

We ascertained patient characteristics, drug use, covariate information, and outcome data using records from 5 databases. We obtained vital statistics from the Registered Persons Database of Ontario, which contains demographic information on all Ontario residents who have ever been issued a health card. We used the Ontario Drug Benefit database to identify prescription drug use. This database contains highly accurate records—the error rate is less than 1%—of all outpatient prescriptions dispensed to patients aged 65 years or older (16). We identified diagnostic and procedural information on all hospitalizations from the Canadian Institute for Health Information Discharge Abstract Database. We obtained covariate information from the Ontario Health Insurance Plan database, which includes health claims for inpatient and outpatient physician services. We identified diagnostic information on all admissions to adult mental health beds from the Ontario Mental Health Reporting System. We have used these databases to research adverse drug reactions and health outcomes (including AKI) (17–22).

The databases were complete for all variables used in this study, except for prescriber information (which was missing for 10.8% of patients in the cohort). Codes from the International Classification of Diseases, Ninth Revision (before 2002), and Tenth Revision (after 2002), were used to assess baseline comorbid conditions in the 5 years before cohort entry (**Table 2** of the **Supplement**). Codes used to ascertain outcomes are detailed in **Table 3** of the **Supplement**, which lists only codes from the Tenth Revision because all events would have occurred after implementation of that coding system. A subpopulation in southwestern Ontario had information on outpatient serum creatinine levels available before cohort entry; this group was in the catchment area of 12 hospitals in which linked laboratory values were also available (23).

Patients

We established a cohort of older adults with evidence of a new outpatient prescription for an oral atypical antipsychotic drug (quetiapine, risperidone, or olanzapine) between June 2003 and December 2011. The date of this prescription served as the index date (cohort entry date) for the drug recipients. We matched a group of drug nonrecipients similar in health status to the recipients. We randomly assigned an index date to the entire Ontario population according to the index date of the drug recipients. For example, if more recipients had an index date between 2003 and 2005, a greater proportion of the population would have been randomly assigned an index date between 2003 and 2005. From these adults, after applying our exclusions to both groups, we matched a drug nonrecipient to each recipient on the following 11 characteristics: age (within 2 years); sex; residential status (community-dwelling or long-term care); evidence of comorbid conditions (dementia, schizophrenia or other psychotic disorder, bipolar disorder, major depression or anxiety disorder, Parkinson disease, and chronic kidney disease); constituency in the subpopulation with available information on serum creatinine levels; and the logit of the propensity score for the predicted probability of newly receiving an atypical antipsychotic drug (within a caliper of ±0.2 SDs). We derived this propensity score from a logistic regression model and selected 91 variables for inclusion in the score on the basis of their potential association with the study outcomes or atypical antipsychotic drug initiation (variables listed in **Table 4** of the **Supplement**) (24). One of the variables was the Johns Hopkins Adjusted Clinical Group Aggregated Diagnosis Groups (a validated measure of the complexity of comorbid conditions based on groups of diagnoses) (25, 26).

Before matching, we excluded the following patients from both groups: those with prescriptions for any antipsychotic drug in the 180 days before their index date to ensure that the drug was newly prescribed (or had the potential to be newly prescribed in the case of the nonrecipients); those who were discharged from a hospital in the 2 days before their index date to ensure that drug use was newly initiated in the nonhospitalized setting (as in Ontario, patients continuing atypical antipsychotic drug treatment initiated in a hospital would have their oral outpatient prescription dispensed the day of or the day after hospital discharge); and those with evidence of end-stage renal disease before their index date (because the development of AKI is no longer relevant). Among the drug recipients, those who received a prescription for more than 1 type of antipsychotic drug (for example, a prescription for

Context

Acute kidney injury (AKI) is reportedly associated with atypical antipsychotic drugs, although the risk has not been quantified.

Contribution

This population-based cohort study found that persons who had received a prescription for any of 3 atypical antipsychotic drugs in the previous 90 days had an elevated risk for hospitalization with AKI. These drugs were also associated with increased risk for hypotension, acute urinary retention, and death.

Caution

Only older adults and 3 antipsychotic agents were studied.

Implication

An association with specific adverse events may explain the increased risk for AKI observed with certain atypical antipsychotic drugs.

—The Editors

quetiapine and olanzapine) on their index date were excluded to compare mutually exclusive groups in subgroup analyses. Among the nonrecipients, those who did not have at least 1 outpatient medication dispensed in the 90 days before their index date were excluded to ensure that such persons were able to receive a prescription. Each drug recipient and nonrecipient could be selected only once for cohort entry.

Outcomes

We followed patients for 90 days after the index date to assess the prespecified outcomes. We chose 90 days to focus on acute adverse events, avoid potential crossovers between the 2 groups that might occur with longer follow-up, and mimic the duration of follow-up described in clinical trials of atypical antipsychotic drugs in older patients (1, 2, 27). The primary outcome was hospitalization with AKI. The secondary adverse outcomes were known causes of AKI (hospitalization with hypotension, acute urinary retention, the neuroleptic malignant syndrome or rhabdomyolysis, pneumonia, acute myocardial infarction, and ventricular arrhythmia) and all-cause mortality. The diagnosis codes used to identify the outcomes and information on their accuracy are presented in **Table 3** of the **Supplement** (28–30). For hospitalization records, up to 25 diagnosis codes can be assigned per hospitalization (for example, codes for AKI or rhabdomyolysis). Therefore, patients with codes for multiple study outcomes were accounted for in the assessment of each outcome.

We previously examined the validity of the database code for hospitalization with AKI used in the current study. In this previous validation study (30), the database code for AKI identified a median increase in serum creatinine level of 98 μmol/L (1.11 mg/dL) (interquartile range [IQR], 43 to 200 μmol/L [0.49 to 2.26 mg/dL]) at the time of hospital presentation from the most recent value before hospitalization. The absence of such a code represented no statistically significant change in serum creatinine level (6 μmol/L [0.07 mg/dL]; IQR, −4 to 20 μmol/L [−0.05 to 0.23 mg/dL]) (30). Although specificity was greater than 95%, the sensitivity of the hospital diagnosis was limited for milder forms of the condition. Particularly, the incidence of AKI as defined by the diagnosis code can be underestimated up to 5-fold when compared with definitions using serum creatinine measurements. For this reason, we examined a subpopulation with linked hospital laboratory values and defined hospitalization with AKI by evidence of an absolute increase in serum creatinine level of 27 μmol/L (0.31 mg/dL) or more from baseline or a relative increase of 50% or more (31).

Statistical Analysis

We compared baseline characteristics between atypical antipsychotic drug recipients and nonrecipients using standardized differences (32). This metric describes differences between group means relative to pooled SD and, when greater than 10%, indicates a meaningful difference. We expressed the risk for an outcome in relative and absolute terms. We estimated odds ratios and 95% CIs using conditional logistic regression, which accounted for matching. The conditional logistic regression model was adjusted for local health integration network, which refers to 14 geographically defined health authorities in Ontario that are responsible for regional administration of different health care services (including regional physicians' offices, hospitals, community mental health and addiction centers, community health centers, and long-term care facilities) (33). Odds ratios can be interpreted as relative risks (RRs), and such an interpretation was appropriate given the odds ratios observed. Absolute risk increase for the outcomes diagnosed in the hospital is underestimated because the codes used to identify the conditions are insensitive.

Using tests for interaction, we analyzed the primary outcome of AKI in the following 4 prespecified subgroups: antipsychotic drug type (quetiapine, risperidone, or olanzapine); antipsychotic drug dose (high or low [high dose was defined by a higher-than-median starting daily dose for the study cohort [>25 mg/d for quetiapine, >0.5 mg/d for risperidone, and >2.5 mg/d for olanzapine]); evidence of chronic kidney disease; and residential status (community-dwelling or long-term care). In Ontario, the validated algorithm for chronic kidney disease identifies older adults with a median estimated glomerular filtration rate of 38 mL/min/1.73 m^2 (IQR, 27 to 52 mL/min/1.73 m^2), whereas its absence identifies those with a median estimated glomerular filtration rate of 69 mL/min/1.73 m^2 (IQR, 56 to 82 mL/min/1.73 m^2) (34).

To assess the temporality and robustness of our primary findings, we reapplied the exclusion criteria to our existing cohort on the day that preceded the index date by 180 days. After reapplying exclusions, we followed the retained matched pairs for the 90-day outcomes and estimated odds ratios and 95% CIs using conditional logistic regression. Because there was no plausible reason why the 2 groups would differ in outcomes before the initiation of an atypical antipsychotic drug, we reasoned that null associations would enhance assertions that the 2 groups were similar in baseline risk for the study outcomes. We did all analyses with SAS, version 9.3 (SAS Institute). In all outcome analyses, we interpreted 2-tailed *P* values less than 0.05 as statistically significant.

Role of the Funding Source

The study design and conduct, opinions, results, and conclusions in this article are those of the authors and are independent of the funding sources.

RESULTS

Cohort selection is presented in the **Appendix Figure** (available at www.annals.org), and baseline characteristics are presented in **Table 5** of the **Supplement**. There were 122 610 atypical antipsychotic drug recipients and 1 204 613 nonrecipients before matching. The recipients

Table 1. **90-Day Risk for Hospitalization With AKI and Other Adverse Outcomes and All-Cause Mortality in Atypical Antipsychotic Drug Recipients and Nonrecipients After the Index Date**

Variable	Events, *n* (%)*		Relative Risk (95% CI)†	Absolute Risk Increase (95% CI), %
	Drug Recipients (*n* = 97 777)	Nonrecipients (*n* = 97 777)		
AKI	1002 (1.02)	602 (0.62)	1.73 (1.55–1.92)	0.41 (0.33–0.49)
Other adverse outcomes				
Hypotension	384 (0.39)	215 (0.22)	1.91 (1.60–2.28)	0.17 (0.12–0.22)
Acute urinary retention	329 (0.34)	170 (0.17)	1.98 (1.63–2.40)	0.16 (0.12–0.20)
The neuroleptic malignant syndrome or rhabdomyolysis	99 (0.10)	69 (0.07)	1.36 (0.96–1.92)	0.03 (0.00–0.06)
Pneumonia	1692 (1.73)	1137 (1.16)	1.50 (1.39–1.62)	0.57 (0.46–0.67)
Acute myocardial infarction	652 (0.67)	492 (0.50)	1.36 (1.20–1.53)	0.16 (0.10–0.23)
Ventricular arrhythmia	214 (0.22)	151 (0.15)	1.47 (1.18–1.82)	0.06 (0.03–0.10)
All-cause mortality	6666 (6.82)	2985 (3.05)	2.39 (2.28–2.50)	3.76 (3.58–3.95)

AKI = acute kidney injury.
* Events (and the proportion of patients with an event) were assessed by using hospital diagnosis codes. For some outcomes, such as the neuroleptic malignant syndrome or rhabdomyolysis, this underestimates the true event rate because these codes have high specificity but low sensitivity.
† The conditional logistic regression model was adjusted for local health integration network, which refers to 14 geographically defined health authorities in Ontario responsible for regional administration of different health care services (including regional physicians' offices, hospitals, community mental health and addiction centers, community health centers, and long-term care facilities).

were older than the nonrecipients and were more likely to reside in a long-term care facility. The recipients were more likely to be diagnosed with dementia, psychiatric diseases, Parkinson disease, and cardiovascular diseases. A total of 97 777 drug recipients were successfully matched to 97 777 nonrecipients. The 2 groups were well-balanced and showed no meaningful differences in the 91 measured baseline characteristics (**Table 5** of the **Supplement**) (demographics, comorbid conditions, concurrent medication use, and health care contacts and use). The mean age was 80.7 years, 23.8% of patients resided in a long-term care facility, and 53.8% had a diagnosis of dementia. The most frequently prescribed atypical antipsychotic drug was risperidone (*n* = 44 707; 45.7%), followed by quetiapine (*n* = 34 498; 35.3%) and olanzapine (*n* = 18 572; 19.0%). The median starting daily dose for quetiapine was 25 mg/d (IQR, 25 to 50 mg/d); for risperidone, 0.5 mg/d (IQR, 0.3 to 0.6 mg/d); and for olanzapine, 2.5 mg/d (IQR, 2.5 to 5.0 mg/d). When prescriber information was available (*n* = 87 228; 89.2%), the most frequent prescribers were family physicians (*n* = 71 714; 82.2%) followed by psychiatrists (*n* = 5925; 6.8%) and geriatricians (*n* = 4104; 4.7%). Baseline distribution of the region of Ontario (local health integration network) was well-balanced in matched recipients and nonrecipients (**Table 5** of the **Supplement**). Baseline characteristics were similar in a subpopulation of patients with available serum creatinine levels (1796 matched pairs of drug recipients and nonrecipients) (**Table 6** of the **Supplement**).

The primary outcome was 90-day hospitalization with AKI assessed by using a hospital diagnosis code (**Table 1**). Atypical antipsychotic drug use versus nonuse was associated with a higher risk for hospitalization with AKI when assessed by using a hospital diagnosis code (1002 of 97 777 recipients [1.02%] vs. 602 of 97 777 nonrecipients [0.62%]; RR, 1.73 [95% CI, 1.55 to 1.92]; absolute risk increase, 0.41% [CI, 0.33% to 0.49%]). In the subpopulation with available information on serum creatinine levels, atypical antipsychotic drug use versus nonuse was associated with a higher risk for hospitalization with AKI (98 of 1796 recipients [5.46%] vs. 60 of 1796 nonrecipients [3.34%]; RR, 1.70 [CI, 1.22 to 2.38]; absolute risk increase, 2.12% [CI, 0.80% to 3.43%]).

The secondary outcomes assessed using hospital diagnosis codes are presented in **Table 1**. Atypical antipsychotic drug use versus nonuse was associated with a higher 90-day risk for hospitalization with hypotension (RR, 1.91 [CI, 1.60 to 2.28]), acute urinary retention (RR, 1.98 [CI, 1.63 to 2.40]), pneumonia (RR, 1.50 [CI, 1.39 to 1.62]), acute myocardial infarction (RR, 1.36 [CI, 1.20 to 1.53]), and ventricular arrhythmia (RR, 1.47 [CI, 1.18 to 1.82]). The relative risk for the neuroleptic malignant syndrome or rhabdomyolysis was not significant (RR, 1.36 [CI, 0.96 to 1.92]). Atypical antipsychotic drug use versus nonuse was also associated with a higher 90-day risk for all-cause mortality (RR, 2.39 [CI, 2.28 to 2.50]).

Subgroup analyses are presented in **Table 2**. Antipsychotic drug type and dose did not influence the association between atypical antipsychotic drug use and hospitalization with AKI (interaction $P = 0.10$ and 0.59, respectively). Similarly, the presence of chronic kidney disease did not influence the observed association (interaction $P = 0.16$). The absolute increase in the incidence of AKI associated with atypical antipsychotic drug use versus nonuse was greater in patients with chronic kidney disease (absolute risk increase, 1.28% [CI, 0.72% to 1.84%]) than in those without chronic kidney disease (absolute risk increase, 0.34% [CI, 0.26% to 0.41%]). The association between drug use and AKI was higher in community dwellers (RR, 1.90 [CI, 1.67 to 2.16]) than in long-term care residents (RR, 1.46 [CI, 1.14 to 1.71]) (interaction $P < 0.01$).

Table 2. **The Association Between Atypical Antipsychotic Drug Use and Hospitalization With AKI***

Variable	Events/At Risk, *n/N* (%)†		Relative Risk (95% CI)‡	Interaction *P* Value	Absolute Risk Increase (95% CI), %
	Drug Recipients	Nonrecipients			
Antipsychotic drug type					
Quetiapine	372/34 498 (1.08)	194/34 498 (0.56)	2.00 (1.66–2.41)	0.10	0.52 (0.38–0.65)
Risperidone	457/44 707 (1.02)	305/44 707 (0.68)	1.59 (1.36–1.86)	0.10	0.34 (0.22–0.46)
Olanzapine	173/18 572 (0.93)	103/18 572 (0.55)	1.76 (1.35–2.30)	0.10	0.38 (0.20–0.55)
Antipsychotic drug dose§					
High	372/34 644 (1.07)	214/34 644 (0.62)	1.80 (1.51–2.15)	0.59	0.46 (0.32–0.59)
Low	630/63 133 (1.00)	388/63 133 (0.61)	1.73 (1.51–1.97)	0.59	0.38 (0.29–0.48)
Chronic kidney disease‖					
Yes	305/7656 (3.98)	207/7656 (2.70)	1.61 (1.33–1.96)	0.16	1.28 (0.72–1.84)
No	697/90 121 (0.77)	395/90 121 (0.44)	1.82 (1.60–2.07)	0.16	0.34 (0.26–0.41)
Residential status					
Community-dwelling	733/74 468 (0.98)	400/74 468 (0.54)	1.90 (1.67–2.16)	<0.01	0.45 (0.36–0.53)
Long-term care	269/23 309 (1.15)	202/23 309 (0.87)	1.46 (1.14–1.71)	<0.01	0.29 (0.11–0.47)

AKI = acute kidney injury.

* Assessed in subgroups defined by antipsychotic drug type, antipsychotic drug dose, evidence of chronic kidney disease, and residential status. Sets of drug recipients and nonrecipients were matched on the presence of chronic kidney disease and residential status. For antipsychotic drug type and dose, matched sets were categorized according to this characteristic in drug recipients.

† AKI (and the proportion of patients with the event) was assessed by using a hospital diagnosis code. The true event rate of AKI is underestimated for some outcomes because the code for AKI has high specificity but low sensitivity.

‡ The conditional logistic regression model was adjusted for local health integration network, which refers to 14 geographically defined health authorities in Ontario responsible for regional administration of different health care services (including regional physicians' offices, hospitals, community mental health and addiction centers, community health centers, and long-term care facilities).

§ High dose was defined as >25 mg/d for quetiapine, >0.5 mg/d for risperidone, and >2.5 mg/d for olanzapine. Low dose was defined as ≤25 mg/d for quetiapine, ≤0.5 mg/d for risperidone, and ≤2.5 mg/d for olanzapine.

‖ Chronic kidney disease was identified by using an algorithm of hospital diagnosis codes validated for older adults in the study region (34). The algorithm identified patients with a median estimated glomerular filtration rate of 38 mL/min/1.73 m^2 (interquartile range, 27–52 mL/min/1.73 m^2), whereas its absence identified patients with a median estimated glomerular filtration rate of 69 mL/min/1.73 m^2 (interquartile range, 56–82 mL/min/1.73 m^2).

When we repeated the analysis by following retained eligible matched pairs from the day that preceded the index date (cohort entry date) by 180 days, there was no observed association with 90-day risk for study outcomes, except for pneumonia (RR, 0.87 [CI, 0.79 to 0.97]) (**Table 7 of the Supplement**).

DISCUSSION

In this population-based cohort study of older adults, we observed that new use of an atypical antipsychotic drug was common in routine care and associated with a higher 90-day risk for hospitalization with AKI. Drug use was also associated with an increased risk for other adverse outcomes, including hypotension, acute urinary retention, pneumonia, and acute cardiac events. These outcomes are known potential causes of AKI.

We also observed a higher 90-day risk for all-cause mortality after new use of an atypical antipsychotic drug (6.8% in recipients vs. 3.1% in nonrecipients). This finding is similar to the results from randomized trials. In 2005, the U.S. Food and Drug Administration issued a black-box warning based on the analyses of 17 randomized, placebo-controlled trials (averaging 10 weeks in duration) that showed an approximate 1.6- to 1.7-times greater risk for death in older patients with dementia treated with atypical antipsychotic drugs versus placebo (incidence of death, 4.5% vs. 2.6%) (1). A meta-analysis of randomized, placebo-controlled trials (10 to 12 weeks in duration) also provided supporting evidence for the warning (27).

The current available evidence calls for a careful reevaluation of prescribing atypical antipsychotic drugs in older adults, especially for the unapproved indication of managing behavioral symptoms of dementia (35). The drugs should be used only after other approaches have been exhausted; when prescribed, patients must be warned about potential adverse effects. Proactive clinical monitoring shortly after initiation seems reasonable (for example, serum creatinine and blood pressure measurement, and if readily available, a bladder scan to detect urinary retention). When patients present with AKI, atypical antipsychotic drugs should be considered a potential cause and be promptly discontinued if feasible.

In our study, although the incidence of AKI was slightly increased in patients prescribed a high versus a low initial dose of the atypical antipsychotic drug, the observed difference in risk by dose was not statistically significant. Although an association between drug use and AKI was seen in both community dwellers and long-term care residents, it was more pronounced in community dwellers. Older adults residing in the community may have less follow-up surveillance than those living in a long-term care facility. Further, long-term care residents may be relatively more predisposed to AKI than community dwellers, such

that additional risk posed by the atypical antipsychotic drug use is not as pronounced.

Our study has several strengths. To our knowledge, this is the first population-based study of AKI resulting from antipsychotic drugs. Population-based studies complement information generated from clinical trials by providing the opportunity to study uncommon but important adverse drug reactions with adequate statistical power, inclusive of vulnerable groups who are not enrolled in clinical trials, and allowing effects to be studied in routine practice, where treatments and monitoring are less regimented than in trials (13, 14, 36, 37). We found that use of these drugs in routine care was common, which provided good precision for estimates of associated effects that are generalizable.

Several limitations need to be considered. As with all observational studies, our study is subject to confounding by unmeasured health characteristics that may have differed between patients who did and did not receive an antipsychotic drug. The very impetus for an atypical antipsychotic drug prescription (such as severe behavioral challenges that may compromise oral intake) may have predisposed recipients to AKI and other adverse outcomes. However, such confounding probably does not explain the entire observed association. First, we did not detect a difference in 90-day risk for the study outcomes between the 2 groups when the cohort was examined 180 days before an atypical antipsychotic drug was initiated. This suggests the recipients and nonrecipients had a similar baseline risk for the study outcomes. Second, the association is supported by many case reports and the known biological effects of these drugs (4–14). Last, we used the "new user design" and followed study patients for a short duration (90 days) to show a temporal association with the risk for acute adverse outcomes soon after initiation of an atypical antipsychotic drug (38).

The elevated risk for AKI after initiation of an atypical antipsychotic drug may have been underestimated because the diagnosis code for AKI is insensitive (30). To address this concern, we supplemented our findings in a subpopulation with available serum creatinine levels and observed consistent results. It should be noted that patients who had AKI without hospitalization were not considered in this study. In addition, we generalize our findings only to older adults because we could not reliably study younger patients with our data sources. Finally, we can apply our findings only to quetiapine, risperidone, and olanzapine—the most commonly used atypical antipsychotic drugs in our region. Nonetheless, similar caution should extend to aripiprazole, ziprasidone, paliperidone, and other atypical antipsychotic drugs because the U.S. Food and Drug Administration warning for mortality risk in older patients with dementia extends to the entire class of atypical antipsychotic drugs (1, 2).

In conclusion, atypical antipsychotic drugs are associated with an increased risk for AKI and other adverse outcomes that may explain the observed association with AKI. The findings support current safety concerns about the use of these drugs in older adults.

From Case Western Reserve University School of Medicine, Cleveland, Ohio; Western University, London, Ontario, Canada; Institute for Clinical Evaluative Sciences, Keenan Research Centre in the Li Ka Shing Knowledge Institute of St Michael's Hospital, and University of Toronto, Toronto, Ontario, Canada; Yale University School of Medicine, New Haven, Connecticut; and University of Alberta, Edmonton, Alberta, Canada.

Grant Support: This study was supported by the Institute for Clinical Evaluative Sciences (ICES) Western site and conducted by members of the provincial ICES Kidney, Dialysis and Transplantation Program. ICES is funded by an annual grant from the Ontario Ministry of Health and Long-Term Care, and ICES Western is funded by an operating grant from the Academic Medical Organization of Southwestern Ontario, the Schulich School of Medicine & Dentistry at Western University, and the Lawson Health Research Institute.

Disclosures: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M13-2796.

Reproducible Research Statement: *Study protocol and statistical code*: Portions are available to approved individuals through written agreements with Dr. Garg (e-mail, amit.garg@lhsc.on.ca). *Data set*: Not available.

Requests for Single Reprints: Amit X. Garg, MD, PhD, London Kidney Clinical Research Unit, Room ELL-101, Westminster, London Health Sciences Centre, 800 Commissioners Road East, London, Ontario N6A 4G5, Canada; e-mail, amit.garg@lhsc.on.ca.

Current author addresses and author contributions are available at www.annals.org.

References

1. **U.S. Food and Drug Administration.** Public health advisory: deaths with antipsychotics in elderly patients with behavioral disturbances. Silver Spring, MD: U.S. Food and Drug Administration; 2005. Accessed at www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/PublicHealthAdvisories/ucm053171.htm on 25 April 2013.

2. **Health Canada.** Increased mortality associated with the use of atypical antipsychotic drugs in elderly patients with dementia. Ottawa, Ontario, Canada: Health Canada; 2005. Accessed at www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2005/14307a-eng.php on 25 April 2013.

3. **Finkel S.** Pharmacology of antipsychotics in the elderly: a focus on atypicals. J Am Geriatr Soc. 2004;52:S258-65. [PMID: 15541166]

4. **Cohen R, Wilkins KM, Ostroff R, Tampi RR.** Olanzapine and acute urinary retention in two geriatric patients. Am J Geriatr Pharmacother. 2007;5:241-6. [PMID: 17996664]

5. **Raitasuo V, Vataja R, Elomaa E.** Risperidone-induced neuroleptic malignant syndrome in young patient [Letter]. Lancet. 1994;344:1705. [PMID: 7527886]

6. **Ahuja N, Palanichamy N, Mackin P, Lloyd A.** Olanzapine-induced hyperglycaemic coma and neuroleptic malignant syndrome: case report and review of literature. J Psychopharmacol. 2010;24:125-30. [PMID: 18801826] doi: 10.1177/0269881108096901

7. **Duggal HS, Singh I.** Neuroleptic malignant syndrome presenting with acute renal failure [Letter]. Prog Neuropsychopharmacol Biol Psychiatry. 2008;32:1074-5. [PMID: 18281139] doi:10.1016/j.pnpbp.2008.01.010

8. **Khan I, Vasudevan V, Arjomand F, Ali R, Shahzad S.** Quetiapine induced fatal neuroleptic malignant syndrome (NMS) and hyperosmolar hyperglycemic nonketotic coma (HHNC). Chest. 2011;140:113A. doi:10.1378/chest.1114380
9. **Sajatovic M, Calabrese JR, Mullen J.** Quetiapine for the treatment of bipolar mania in older adults. Bipolar Disord. 2008;10:662-71. [PMID: 18837860] doi: 10.1111/j.1399-5618.2008.00614.x
10. **Ritchie CW, Chiu E, Harrigan S, MacFarlane S, Mastwyk M, Halliday G, et al.** A comparison of the efficacy and safety of olanzapine and risperidone in the treatment of elderly patients with schizophrenia: an open study of six months duration. Int J Geriatr Psychiatry. 2006;21:171-9. [PMID: 16416458]
11. **Sokolski KN, Brown BJ, Melden M.** Urinary retention following repeated high-dose quetiapine [Letter]. Ann Pharmacother. 2004;38:899-900. [PMID: 15039480]
12. **Knol W, van Marum RJ, Jansen PA, Souverein PC, Schobben AF, Egberts AC.** Antipsychotic drug use and risk of pneumonia in elderly people. J Am Geriatr Soc. 2008;56:661-6. [PMID: 18266664] doi:10.1111/j.1532-5415.2007 .01625.x
13. **Pariente A, Fourrier-Réglat A, Ducruet T, Farrington P, Béland SG, Dartigues JF, et al.** Antipsychotic use and myocardial infarction in older patients with treated dementia. Arch Intern Med. 2012;172:648-53. [PMID: 22450214] doi: 10.1001/archinternmed.2012.28
14. **Ray WA, Chung CP, Murray KT, Hall K, Stein CM.** Atypical antipsychotic drugs and the risk of sudden cardiac death. N Engl J Med. 2009;360:225-35. [PMID: 19144938] doi:10.1056/NEJMoa0806994
15. **von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative.** The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Ann Intern Med. 2007;147:573-7. [PMID: 17938396]
16. **Levy AR, O'Brien BJ, Sellors C, Grootendorst P, Willison D.** Coding accuracy of administrative drug claims in the Ontario Drug Benefit database. Can J Clin Pharmacol. 2003;10:67-71. [PMID: 12879144]
17. **Patel AM, Shariff S, Bailey DG, Juurlink DN, Gandhi S, Mamdani M, et al.** Statin toxicity from macrolide antibiotic coprescription: a population-based cohort study. Ann Intern Med. 2013;158:869-76. [PMID: 23778904] doi: 10.7326/0003-4819-158-12-201306180-00004
18. **Lam NN, Weir MA, Yao Z, Blake PG, Beyea MM, Gomes T, et al.** Risk of acute kidney injury from oral acyclovir: a population-based study. Am J Kidney Dis. 2013;61:723-9. [PMID: 23312723] doi:10.1053/j.ajkd.2012.12.008
19. **Zhao YY, Weir MA, Manno M, Cordy P, Gomes T, Hackam DG, et al.** New fibrate use and acute renal outcomes in elderly adults: a population-based study. Ann Intern Med. 2012;156:560-9. [PMID: 22508733] doi:10.7326/ 0003-4819-156-8-201204170-00003
20. **Shih AW, Weir MA, Clemens KK, Yao Z, Gomes T, Mamdani MM, et al.** Oral bisphosphonate use in the elderly is not associated with acute kidney injury. Kidney Int. 2012;82:903-8. [PMID: 22695327] doi:10.1038/ki.2012.227
21. **Gandhi S, Fleet JL, Bailey DG, McArthur E, Wald R, Rehman F, et al.** Calcium-channel blocker-clarithromycin drug interactions and acute kidney injury. JAMA. 2013;310:2544-53. [PMID: 24346990] doi:10.1001/jama.2013 .282426
22. **Weir MA, Beyea MM, Gomes T, Juurlink DN, Mamdani M, Blake PG, et al.** Orlistat and acute kidney injury: an analysis of 953 patients [Letter]. Arch Intern Med. 2011;171:703-4. [PMID: 21482850] doi:10.1001 /archinternmed.2011.103
23. **Gandhi S, Shariff SZ, Beyea MM, Weir MA, Hands T, Kearns G, et al.** Identifying geographical regions serviced by hospitals to assess laboratory-based outcomes. BMJ Open. 2013;3. [PMID: 23293246] doi:10.1136/bmjopen-2012 -001921
24. **Austin PC.** An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivariate Behav Res. 2011;46: 399-424. [PMID: 21818162]
25. Johns Hopkins ACG System. Baltimore: Johns Hopkins Univ; 2013. Accessed at http://acg.jhsph.org/index.php/the-acg-system-advantage/acgs on 15 January 2014.
26. **Reid RJ, MacWilliam L, Verhulst L, Roos N, Atkinson M.** Performance of the ACG case-mix system in two Canadian provinces. Med Care. 2001;39:86-99. [PMID: 11176546]
27. **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;294:1934-43. [PMID: 16234500]
28. **Juurlink D, Preyra C, Croxford R, Chong A, Austin P, Tu J, et al.** Canadian Institute for Health Information Discharge Abstract Database: a validation study. Toronto, Ontario, Canada: Institute for Clinical Evaluative Sciences; 2006. Accessed at www.ices.on.ca/flip-publication/canadian-istitute-for-health -information-discharge/index.html#41/z on 23 June 2014.
29. **Jha P, Deboer D, Sykora K, Naylor CD.** Characteristics and mortality outcomes of thrombolysis trial participants and nonparticipants: a population-based comparison. J Am Coll Cardiol. 1996;27:1335-42. [PMID: 8626941]
30. **Hwang YJ, Shariff SZ, Gandhi S, Wald R, Clark E, Fleet JL, et al.** Validity of the International Classification of Diseases, Tenth Revision code for acute kidney injury in elderly patients at presentation to the emergency department and at hospital admission. BMJ Open. 2012;2. [PMID: 23204077] doi:10.1136/ bmjopen-2012-001821
31. **Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group.** KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney Int Suppl. 2012;2:1-138. Accessed at www.kdigo.org/clinical _practice_guidelines/pdf/KDIGO%20AKI%20Guideline.pdf on 23 June 2014.
32. **Austin PC.** Using the standardized difference to compare the prevalence of a binary variable between two groups in observational research. Commun Stat Siml Comput. 2009;38:1228-34.
33. Ontario's Local Health Integration Networks. Accessed at www.lhins.on.ca /aboutlhin.aspx on 20 April 2014.
34. **Fleet JL, Dixon SN, Shariff SZ, Quinn RR, Nash DM, Harel Z, et al.** Detecting chronic kidney disease in population-based administrative databases using an algorithm of hospital encounter and physician claim codes. BMC Nephrol. 2013;14:81. [PMID: 23560464] doi:10.1186/1471-2369-14-81
35. **Rabins PV, Lyketsos CG.** Antipsychotic drugs in dementia: what should be made of the risks? [Editorial]. JAMA. 2005;294:1963-5. [PMID: 16234504]
36. **Hilmer SN, Gnjidic D, Abernethy DR.** Pharmacoepidemiology in the post-marketing assessment of the safety and efficacy of drugs in older adults. J Gerontol A Biol Sci Med Sci. 2012;67:181-8. [PMID: 21653991] doi:10.1093/gerona/ glr066
37. **Stürmer T, Jonsson Funk M, Poole C, Brookhart MA.** Nonexperimental comparative effectiveness research using linked healthcare databases. Epidemiology. 2011;22:298-301. [PMID: 21464649] doi:10.1097/EDE.0b013 e318212640c
38. **Ray WA.** Evaluating medication effects outside of clinical trials: new-user designs. Am J Epidemiol. 2003;158:915-20. [PMID: 14585769]

Current Author Addresses: Mr. Hwang; Drs. Dixon, Shariff, and Garg; Ms. Gandhi; and Ms. Nash: London Kidney Clinical Research Unit, Room ELL-101, Westminster, London Health Sciences Centre, 800 Commissioners Road East, London, Ontario N6A 4G5, Canada.
Dr. Reiss: London Health Sciences Centre, Room B8-142, 800 Commissioners Road East, London, Ontario N6A 5W9, Canada.
Dr. Wald: Division of Nephrology, St. Michael's Hospital, 61 Queen Street East, Room 9-140, Toronto, Ontario M5C 2T2, Canada.
Dr. Parikh: Yale University and Veterans Affairs Medical Center, 60 Temple Street, Suite 6C, New Haven, CT 06510.
Dr. Pannu: Division of Nephrology and Critical Care, University of Alberta, 11-107 CSB, 8440 112 Street, Edmonton, Alberta T6G 2G3, Canada.
Dr. Rehman: University Hospital, Room ALL-139, 339 Windermere Road, London, Ontario N6A 5A5, Canada.

Author Contributions: Conception and design: Y.J. Hwang, S.N. Dixon, J.P. Reiss, C.R. Parikh, S. Gandhi, S.Z. Shariff, A.X. Garg.
Analysis and interpretation of the data: Y.J. Hwang, S.N. Dixon, J.P. Reiss, C.R. Parikh, S. Gandhi, S.Z. Shariff, N. Pannu, F. Rehman, A.X. Garg.
Drafting of the article: Y.J. Hwang, J.P. Reiss, C.R. Parikh, F. Rehman, A.X. Garg.
Critical revision of the article for important intellectual content: Y.J. Hwang, S.N. Dixon, J.P. Reiss, R. Wald, C.R. Parikh, S. Gandhi, S.Z. Shariff, N. Pannu, D.M. Nash, F. Rehman, A.X. Garg.
Final approval of the article: Y.J. Hwang, S.N. Dixon, J.P. Reiss, R. Wald, C.R. Parikh, S. Gandhi, S.Z. Shariff, N. Pannu, D.M. Nash, F. Rehman, A.X. Garg.
Provision of study materials or patients: A.X. Garg.
Statistical expertise: Y.J. Hwang, S.N. Dixon, S.Z. Shariff, A.X. Garg.
Obtaining of funding: A.X. Garg.
Administrative, technical, or logistic support: Y.J. Hwang, J.P. Reiss, A.X. Garg.
Collection and assembly of data: S.N. Dixon, S.Z. Shariff, A.X. Garg.

Appendix Figure. **Study flow diagram.**