AJKD

In the Literature

Acute Kidney Injury and Mortality in the Elderly: Add Atypical Antipsychotics to the List

Commentary on Hwang YJ, Dixon SN, Reiss JP, et al. Atypical antipsychotic drugs and the risk for acute kidney injury and other adverse outcomes in older adults: a population-based cohort study. Ann Intern Med. 2014;161(4):242-248.

Polypharmacy is common in the elderly and leads to a number of complications that likely escalate morbidity and mortality. One important complication, acute kidney injury (AKI), is increasing in this population, and drugs are a leading cause of this adverse event.[1] This is not a surprise when one considers the AKI risk profile in the elderly. The aging kidney is predisposed to nephrotoxic insults due to reduced kidney function reserve, increased oxidative stress, and perturbed renoprotective mechanisms. Other factors that increase susceptibility include concurrent exposure to agents that affect the ability of the kidney to autoregulate, such as nonsteroidal anti-inflammatory drugs and inhibitors of the renin-angiotensin-aldosterone system, and altered pharmacokinetics, which disrupt drug distribution, metabolism, and excretion. Finally, age-related systemic changes and various comorbid conditions such as hypertensive arteriosclerosis, benign prostatic hyperplasia, and orthostatic hypotension enhance risk for AKI.

While a long list of nephrotoxins in the elderly populate textbooks and review articles, the atypical antipsychotic agents are not noted. Reduced extrapyramidal effects make these drugs appealing; however, their antagonism of α-adrenergic, muscarinic, and serotonin receptors yields other complications. These include hypotension, acute urinary retention, and rhabdomyolysis, adverse events that these patients already may be predisposed to develop and all of which can lead to AKI. However, most concerning is the risk for death from either AKI or other complications, such as aspiration pneumonia, arrhythmia, or other events, in this vulnerable population. While increased mortality in the elderly has been described with the atypical antipsychotics, there is little information on risk for AKI.

WHAT DOES THIS IMPORTANT STUDY SHOW?

Hwang et al[2] examined adults 65 years and older in Ontario, Canada, using 5 linked health care databases to find an association between prescription of commonly used outpatient atypical antipsychotic agents (quetiapine, risperidone, and olanzapine) and AKI. The 8-year retrospective population-based cohort study, with data from June 2003 through December 2011, included 97,777 patients prescribed atypical antipsychotics who were matched 1:1 with controls. The primary study outcome was 90-day hospitalization for AKI based on diagnosis codes. AKI also was identified using creatinine-based AKI definition in 1,796 patients (1.8%). Secondary outcomes included hospitalization for hypotension, acute urinary retention, rhabdomyolysis, pneumonia, acute myocardial infarction, and ventricular arrhythmias and all-cause mortality.

In the overall population, patients prescribed atypical antipsychotic drugs were characterized by older age, long-term care facility residence, concomitant dementia, and care by family physicians, who prescribed the bulk of these drugs (82.2%). No significant baseline differences remained after matching. A 73% increase in diagnosis code–based AKI was noted in this group, although the absolute risk was low in both groups (1.02% vs 0.62%). Of note, the subpopulation for which serum creatinine level was available demonstrated higher AKI risk in both groups (5.46% vs 3.34%) compared with diagnosis codes, whereas the relative risk was similar to the overall cohort. The risk of AKI was higher in community dwellers than in long-term care residents. For secondary outcomes, the antipsychotic drugs were associated with increased hypotension, acute urinary retention, pneumonia, acute myocardial infarction, and ventricular arrhythmia, but not with rhabdomyolysis (Fig 1). Importantly, all-cause mortality was increased in drug recipients (6.8% vs 3.1%).

What do these numbers mean to prescribing clinicians and patients who receive these drugs? The absolute risk increase and number needed to harm for the clinical outcomes described are a more meaningful way to understand the significance of the study results. Figure 1 notes the absolute increases and number needed to harm for the various outcomes. For every pill prescribed, 1 in 27 patients will die and, depending on the definition used, either 1 in 47 or 1 in 244 will develop AKI.

The study has a number of strengths worth noting. A large population cohort with multiple comorbid conditions was examined, giving a real-world flavor to the adverse drug effects. It is the first study of its kind evaluating AKI as an untoward complication of atypical antipsychotics. This study leveraged the

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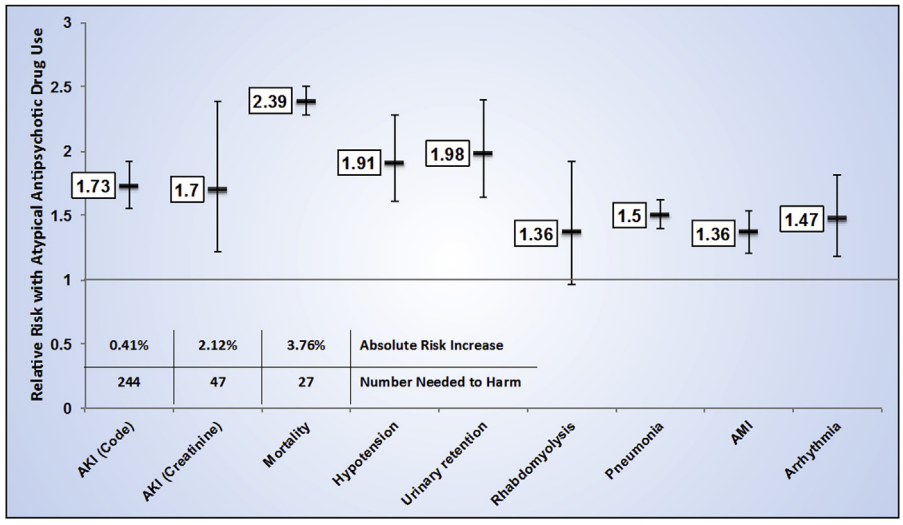

Figure 1. Relative risk for various outcomes in elderly patients prescribed atypical antipsychotics. Values indicate relative risk. Error bars indicate 95% confidence intervals. In addition, absolute risk increase and number needed to harm are shown for acute kidney injury (AKI; code and serum creatinine) and mortality. Abbreviation: AMI, acute myocardial infarction. Based on data from Hwang et al.[2]

universal health care available to Ontario residents. The 5 databases provided highly reliable information about demographics, drug prescriptions, and discharge diagnosis codes. Rigorous matching was performed for a number of variables, and the success of matching is reflected in almost identical baseline characteristics and baseline risk of outcomes in the 2 arms.

As with any observational study, the major limitation is lack of randomization, which leads to possible unmeasured residual confounding. The same factors that led to antipsychotic prescription conceivably could have led to higher AKI and mortality risk. The authors address this issue by matching both groups for key characteristics. In addition, the authors examined baseline risk in these cohorts 180 days prior to drug prescription and found no increase in AKI, hypotension, or urinary retention risk in the period from 180 days to 90 days prior to drug prescription. Use of diagnosis codes for outcome measurement is another limitation as noted by their suboptimal positive predictive values for many outcomes. The AKI codes had poor sensitivity (emergency department, 37.4%; hospital admission, 61.6%) but were highly specific (>95%).[3] However, the finding that creatinine-based AKI outcomes were similar adds credence to the code-generated results. The measurement of mortality was highly accurate with sensitivity of 97.8% and positive predictive value of 100%. Finally, AKI likely was underestimated because only hospital-acquired disease was included in the study.

HOW DOES THIS STUDY COMPARE TO PRIOR STUDIES?

Off-label use of the atypical antipsychotics is highly prevalent in the elderly.[4,5] Several studies demonstrate increased mortality in drug-exposed elderly. A meta-analysis of placebo-controlled trials by Schneider et al[6] showed a 54% mortality increase associated with these agents. Similarly, Gill et al[7] also found an increase in mortality in a long-term care cohort prescribed these drugs (3.9% vs 2.7%). In 2005, the US Food and Drug Administration issued a black box warning for antipsychotic drug therapy in the elderly, highlighting the increased cerebrovascular accidents and mortality risk.[8-10] Thus, this large study confirms previously raised concerns over atypical antipsychotics in the elderly and adds more granularity about the complications, in particular AKI.

Why are the elderly predisposed to such complications? In addition to existing comorbid conditions, pharmacologic differences may be one such factor. These drugs undergo hepatic metabolism and are excreted by the kidneys. Either decreased liver or kidney function can impair clearance and increase plasma levels. Pharmacokinetic studies in the elderly reveal that the elimination half-life of atypical antipsychotics is prolonged, which may predispose to increased adverse drug effects.[11-13] Postmarketing drug surveillance has brought to light several important adverse drug effects, including numerous reports of urinary retention in older men associated with atypical antipsychotic therapy.[14-16] Neuroleptic malignant syndrome and rhabdomyolysis also are reported with these drugs.[17-22] Along these lines, 8% of 106 cases of rhabdomyolysis were associated with quetiapine use.[22] Two retrospective studies document hypotension as a complication. Atypical antipsychotics were 80% more likely to cause hypotension compared with first-generation antipsychotics, whereas a 29% incidence of hypotension was noted in 122 risperidone-treated hospitalized elderly patients.[23,24] Another trial