CHEST

Original Research

CRITICAL CARE

Leveraging a Critical Care Database

Selective Serotonin Reuptake Inhibitor Use Prior to ICU Admission Is Associated With Increased Hospital Mortality

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Background: **Observational studies have found an increased risk of adverse effects such as hemorrhage, stroke, and increased mortality in patients taking selective serotonin reuptake inhibitors (SSRIs). The impact of prior use of these medications on outcomes in critically ill patients has not been previously examined. We performed a retrospective study to determine if preadmission use of SSRIs or serotonin norepinephrine reuptake inhibitors (SNRIs) is associated with mortality differences in patients admitted to the ICU.**

Methods: **The retrospective study used a modifiable data mining technique applied to the publicly available Multiparameter Intelligent Monitoring in Intensive Care (MIMIC) 2.6 database. A total of 14,709 patient records, consisting of 2,471 in the SSRI/SNRI group and 12,238 control subjects, were analyzed. The study outcome was in-hospital mortality.**

Results: **After adjustment for age, Simplified Acute Physiology Score, vasopressor use, ventilator use, and combined Elixhauser score, SSRI/SNRI use was associated with significantly increased in-hospital mortality (OR, 1.19; 95% CI, 1.02-1.40; *P* = .026). Among patient subgroups, risk was highest in patients with acute coronary syndrome (OR, 1.95; 95% CI, 1.21-3.13; *P* = .006) and patients admitted to the cardiac surgery recovery unit (OR, 1.51; 95% CI, 1.11-2.04; *P* = .008). Mortality appeared to vary by specific SSRI, with higher mortalities associated with higher levels of serotonin inhibition.**

Conclusions: **We found significant increases in hospital stay mortality among those patients in the ICU taking SSRI/SNRIs prior to admission as compared with control subjects. Mortality was higher in patients receiving SSRI/SNRI agents that produce greater degrees of serotonin reuptake inhibition. The study serves to demonstrate the potential for the future application of advanced data examination techniques upon detailed (and growing) clinical databases being made available by the digitization of medicine.**

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Abbreviations: ICD-9 = *International Classification of Diseases, Ninth Revision;* MIMIC = Multiparameter Intelligent Monitoring in Intensive Care; RCT = randomized controlled trial; SAPS = Simplified Acute Physiology Score; SNRI = serotonin norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor

There are questions in clinical medicine that cannot be answered through a traditional prospective randomized controlled trial (RCT). These types of issues tend to be complex, multifactorial, and context dependent in ways that exceed the constraints of traditional RCTs (eg, important factors may be lost upon exclusion of patients on the basis of age, disease, or medication use). One such issue is the effect of the long-term prior use of particular medications on outcomes during the course of ensuing conditions, such as the onset of critical illness. This type of clinical question is currently best addressed by the targeted analysis of large databases.

In a previous article, we described a system that uses clinical database networks to accumulate safety and efficacy evidence when drugs are used in wider, more diverse patient populations than those, typically, examined during premarket approval clinical studies.[1] This is in accordance with the vision of a nationwide, data-driven learning system that monitors for ongoing safety signals after a new drug comes to market.[2] In this article, using a public, deidentified clinical database,

we report an analysis of patients admitted to the ICU who are receiving antidepressants—specifically, selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs).

The use of antidepressants, including SSRIs and SNRIs, has increased significantly in recent years. One in 10 Americans now takes an antidepressant; among women in their 40s and 50s, the figure is one in four.[3,4] However, Mojtabai[5] found that nearly two-thirds of a sample of 5,639 patients who had received a diagnosis of depression within the previous 12 months did not meet the *Diagnostic and Statistical Manual of Mental Disorders* criteria. Elderly patients were most likely to receive a misdiagnosis; six out of seven patients aged 65 years and older did not fit the criteria. The majority of the sample patients received prescription antidepressants, most for at least 2 years, and some took them for a decade or more. This unnecessary administration is of particular concern, as there is a growing body of literature reporting adverse effects with the long-term use of SSRIs and SNRIs.[6,7] Furthermore, a substantial percentage of truly depressed people remain undiagnosed and untreated with appropriate medications.[8]

This study examines the effect of preadmission SSRI/SNRI use on mortality in critically ill patients. We are aware of the challenge in determining whether an association, if found in observational studies, is due to the underlying condition or the use of the medication. Clearly, the population receiving SSRIs and SSRNs is not a precise match with the population with true depression in view of the previously noted observations of both unnecessary and inadequate treatments with these agents. Therefore, our study is intended specifically to measure the impact of these particular agents on patient outcomes rather than the impact of depression, per se. With this in mind, we have observed that the literature suggests that antidepressants with different degrees of activity are often prescribed based on provider preference independent of the degree of depression (ie, the specific SSRI prescribed is more strongly influenced by provider preference than by the severity of the depression or other patient factors).[9] We, therefore, examined whether the pharmacologic degree of serotonin reuptake was associated with ICU outcomes.

Materials and Methods

We conducted a retrospective cohort study using the Multiparameter Intelligent Monitoring in Intensive Care (MIMIC) II database. MIMIC II is a large database, freely available in the public domain, which includes information from electronic medical records of patients admitted to the ICUs at Beth Israel Deaconess Medical Center since 2001.[10] The creation and use of the MIMIC database was approved by the institutional review boards of both Beth Israel Deaconess Medical Center and Massachusetts Institute of Technology (IRB protocol 2001-P-001699/3).

All adult patient records in the database were screened for purposes of inclusion, with only the first hospital admission considered for analysis for those with multiple admissions. Patients were excluded if there was uncertainty regarding their pre-ICU admission medications or if they did not have an admitting Simplified Acute Physiology Score (SAPS) recorded. The exposure studied was documented use of SSRI, SNRI, or both immediately prior to ICU admission. Assessing SSRI/SNRI was the a priori primary outcome before any data had been extracted or analysis done. Preadmission use was defined by the presence of an SSRI/SNRI in the team-reconciled admission medication list in a patient's discharge summary. Nonexposure was defined as the absence of any SSRI or SNRI on the admission medication list.

The study outcome was in-hospital mortality among the entire patient cohort. This outcome was also analyzed across patient subsets and by specific drug type. We used 0.05 as the family-wise error rate for subgroup analyses. Because there is a family of hypotheses to be tested, Holm's stepdown procedure was used to control the false-positive rate.[11] It is a more powerful method than the Bonferroni procedure but does not increase the chances of a false positive. As we used a closed test (hypotheses are rejected in sequential order starting from the global), these analyses are protected against type 1 error inflation. We used families of hypotheses instead of having each subgroup analysis stand on its own, given that this data analysis is exploratory, rather than confirmatory. A cumulative Mann-Kendall trend test was used to test for the existence of a trend in hospital mortality with respect to the level of serotonin reuptake inhibition.[12,13] The degree of serotonin reuptake inhibition used is based on those reported by Tatsumi et al.[14]

We also examined two prespecified falsification hypotheses. As noted by Prasad and Jena,[15] prespecified falsification hypotheses can provide intuitive safeguards when examining observational data. To determine if the association between SSRIs and mortality is an artifact of the dataset, another hypothesis that could not be true was tested. If such an association was found to be statistically significant, the association between SSRIs and mortality would likely be similarly spurious. Our falsification hypotheses were that two other chosen admission medications (stool softeners and calcium supplements) would not be associated with in-hospital mortality. We examined these medication types in both the general cohort and in smaller subsets of the population where use was more common.

Data regarding each patient's age, sex, SAPS,[16] laboratory values, vital signs, *International Classification of Diseases, Ninth Revision* (ICD-9) diagnoses, and disease-related group were extracted. Medical comorbidities were represented by the Elixhauser scores for 30 comorbidities as calculated from the ICD-9 codes.[17] Diagnoses

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