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.** ***CHEST 2014; 145(4):1–8***

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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and comorbidities used for subset analysis were likewise defined by the ICD-9 diagnoses. All ICD-9 diagnoses noted for the hospital admission were considered equally. The mean, maximum, minimum, and SDs of three vital signs (heart rate, BP, and temperature) were obtained over the first 24 h of admission. The first values of routine laboratory results were also extracted, including hemoglobin, partial thromboplastin time, platelet count, and troponin-T level. Vital signs data were usually reported once per hour, whereas routine laboratory data frequency varied per patient.

Patient variables and outcomes in the groups with and without SSRI/SNRI use were compared using the Wilcoxon rank-sum test for continuous variables and a χ^2 test for categorical variables. Elixhauser scores were combined into a single weighted score using the method described by van Walraven et al[18] and used as a covariate. Multivariate logistic regression was performed to test the relationship between SSRI/SNRI use and the study outcome, adjusted for confounding variables.

Covariates included in the models were age, sex, SAPS, Elixhauser score, ventilator use, and vasopressor use. Using a graph to represent causal effects between variables is one way to understand if bias could be reduced or increased by conditioning on specific covariates. In Figure 1, we describe the causal model connecting pre-ICU admission SSRI use with other confounders and modifier effects.[19] In causal directed acyclic graphs, arrows between variables indicate causation, whereas unconnected variables have no direct causal association. We followed the steps described by Pearl[19] to ensure that the statistical model including only the chosen covariates will minimize the bias of the estimate of X (SSRI) on Y (mortality). All data processing and modeling was performed using MATLAB R2011a (The MathWorks, Inc).

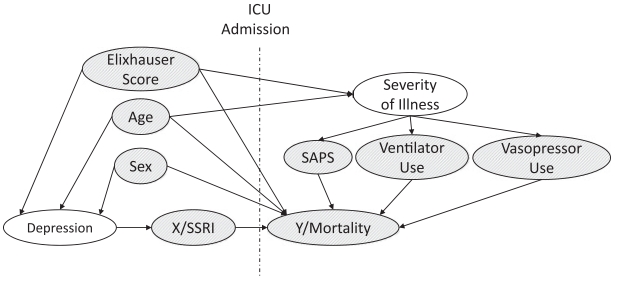

Figure 1. Directed acyclic graph describing the relationship between covariates and the outcome. Note that preadmission and postadmission factors are separated by the labeled vertical line. This graph depicts our model of the observed causal relations connecting pre-ICU admission SSRI use with other confounders and modifier effects. These connections are represented by the arrow lines, with the arrow positioned specifically at the impacted factor. For example, age may have an impact on the preadmission occurrence of depression as well as on the severity of illness and mortality after admission. The figure represents a visual display of our data-driven examination of possible causal factors on mortality (Y) in addition to the causal factor of SSRI use (X). Observed variables are shaded, whereas unobserved variables are clear. Age, sex, and Elixhauser score were used as the confounding variables for SSRI use, because they share a "back door" path that needs to be adjusted for. Other ICU-specific modifier effects, such as SAPS, ventilator use, and vasopressor use, are not confounding but are strongly tied to the outcome Y (mortality) in the ICU setting and are, therefore, adjusted for in the model. Note that the precise vertical or horizontal positions of the variables do not imply more or less quantitative impact (eg, severity of illness is not a more impactful factor than the three grouped below it). The positioning of the factors is designed to facilitate understanding by eliminating or minimizing the complexity of the relationship arrows (eg, avoiding overlaps so far as possible). SAPS = Simplified Acute Physiology Score; SSRI = selective serotonin reuptake inhibitor.

Results

Validation of Inclusion Criteria

Of the eligible adult patients with an admitting SAPS (17,189), 2,480 were excluded for having no admitting medication section or for use of other types of antidepressants, leaving 14,709 patients for the study (12,238 unexposed, 2,471 SSRI/SNRI) (Fig 2). Patients with preadmission SSRI/SNRI use differed from the control group in that they were more often women, had lower Elixhauser scores, were slightly more likely to have COPD and diabetes mellitus, and were less likely to require mechanical ventilation or the use of vasopressors (Table 1).[20] There were no significant clinical differences in the initial (first 24 h) laboratory results and vital signs between the groups (Table 2).

Study Outcome Analysis

Our outcome analysis tested the relationship between preadmission SSRI/SNRI use and in-hospital mortality. After adjusting for differences in age, sex, SAPS, Elixhauser score, ventilator use, and vasopressor administration, multivariate logistic regression found a significant increase in the odds of death for those with preadmission SSRI/SNRI use (OR, 1.19; 95% CI, 1.02-1.40; $P = 0.026$).

Subgroup Examination of Study Outcome

Patients were divided into several subcategories to determine if the relationship between preadmission SSRI/SNRI use and in-hospital mortality varied across patient subsets. Separate logistic regression models were built for each subgroup using the same confounding variables (age, sex, SAPS, Elixhauser score, ventilator usage, and vasopressor usage), shown in Table 3. Using Holm's stepdown procedure to determine significance, we found that SSRI/SNRI use was associated with higher mortality in patients with cardiovascular disease (OR, 1.24; $P = .025$), those admitted to the cardiac surgery recovery unit (OR, 1.45; $P = .016$), and those with acute coronary syndrome (OR, 1.95; $P = .006$).

Medication-Specific Primary Outcome Analysis

We examined the role that the degree of serotonin reuptake inhibition might play, given the variation in this factor among the SSRIs (Table 4).[21] As SSRI and SNRI medications operate via different mechanisms, we included only SSRI agents in this segment

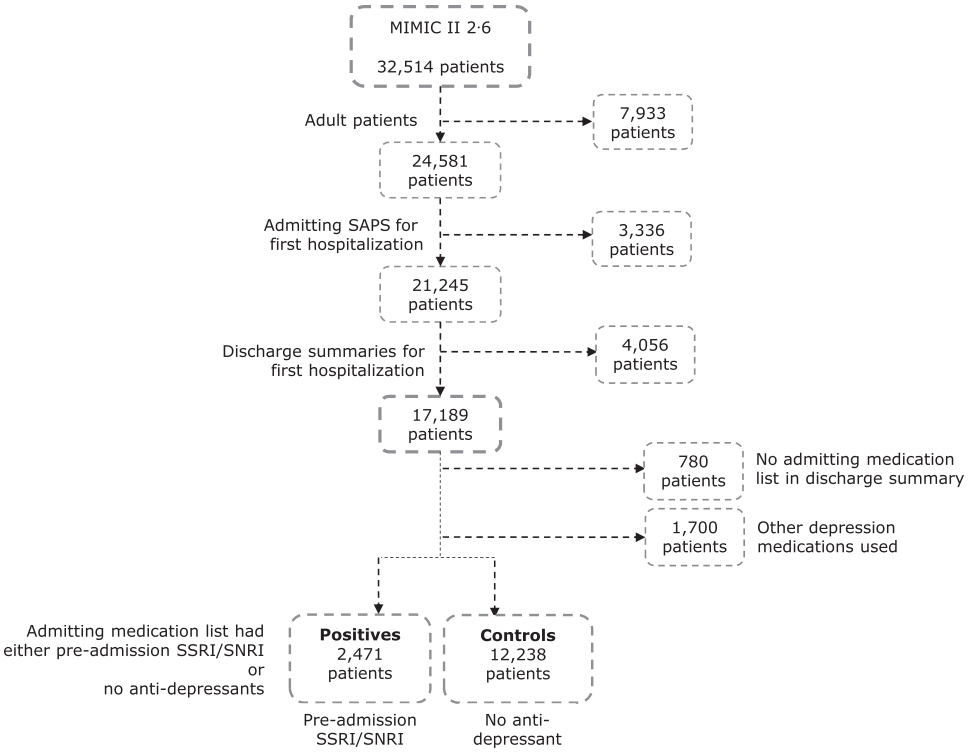

FIGURE 2. Cohort selection process. MIMIC = Multiparameter Intelligent Monitoring in Intensive Care; SNRI = serotonin norepinephrine reuptake inhibitor. See Figure 1 legend for expansion of other abbreviations.

of the analysis. Here, we compared the five main SSRI types found: citalopram (622 patients), escitalopram (203 patients), fluoxetine (388 patients), paroxetine (406 patients), and sertraline (555 patients). We excluded fluvoxamine, as the number of patients taking this medication was small (15 patients).

We first tested for the statistical existence of a trend in the baseline mortality rate. This rate tends to increase as the dissociation constant decreases, so that those medications with a higher degree of serotonin reuptake inhibition (eg, sertraline and paroxetine) are associated with higher mortality rates. Using the reuptake inhibition coefficient as the ordinal population value and the in-hospital mortality as the outcome, the cumulative Mann-Kendall trend test rejected the null hypothesis that there was no trend ($P < .001$).

To determine if some SSRIs are more strongly associated with mortality than others, we performed a likelihood ratio test between a logistic regression model that dummy codes each SSRI used and a null model with a single indicator variable for SSRI use. Both models adjusted for age, sex, SAPS, and combined Elixhauser Score. The SSRI-specific model had a better log-likelihood than the single indicator variable model, with $P = .02$. This demonstrates that an in-hospital mortality model that includes SSRI type is significantly better than the one that does not.

Results of the SSRI-specific model are shown in Table 5. We found that paroxetine and sertraline use (which possess the two strongest degrees of serotonin reuptake) were more strongly correlated with in-hospital mortality (OR, 1.52; $P = .015$; OR, 1.47 $P = .007$; respectively) than the other SSRI drugs.

Falsification Hypothesis Analysis

We defined two falsification hypotheses: Hospital mortality is not associated with the use of either stool softeners or calcium supplements. We evaluated the relationship between hospital mortality and use of stool softeners (senna, Dulcolax, docusate, milk of magnesia, Colace, MiraLAX, and bisacodyl) in both the entire cohort (1,449 positive, 13,260 control subjects) and in those ≥ 75 years old (450 positive, 4,047 control subjects). We also examined the relationship between hospital mortality and use of calcium supplements in both the entire cohort (647 positive, 14,062 control subjects) and in female patients ≥ 50 years old without end-stage renal disease (ICD-9. 585.6) (225 positive, 4,4323 control subjects). Using logistic regression adjusted for age, sex, SAPS, vasopressor use, ventilator use, and combined Elixhauser score, we found that medication use in all scenarios was not associated with in-hospital mortality ($P > .1$ in all cases).

Table 1—*Population Information on Groups Included in Study*

Variable	Included in Study: Control (12,238)	Included in Study: SSRI/SNRI Admission (2,471)	Rank Sum *P* Value
Demographics			
Sex, % male	61	44	< .05
Age, y	66, IQR 26	64, IQR 25	.4
SAPS	13, IQR 7	13, IQR 8	< .05
ICU type, %			
CCU	23	21	.05
CSRU	38	33	< .05
MICU	33	40	< .05
SICU	6	5	.2
Selected acute diagnoses, %			
Acute coronary syndrome (serum troponin > 0.5 ng/mL)	8	7	.2
Sepsis (Martin criteria[a])	3	4	.7
Comorbidities by ICD-9, %			
COPD	7	11	< .05
Diabetes	17	21	< .05
Cardiovascular disease	70	68	.06
Treatments, %			
Ventilator use	55	49	< .05
Vasopressor use	39	31	< .05
Blood products transfused, mL			
Total RBC volume	750, IQR 1,125	750, IQR 1,125	.2
Total FFP volume	608, IQR 866	614, IQR 895	.6
Total platelet volume	325, IQR 487	27,5 IQR 380	.07

Binary variables reported as prevalence percentages, continuous variables reported as data median with IQR, lengths of stay reported as data mean SD. CCU = coronary care unit; CSRU = cardiac surgery recovery unit; FFP = fresh frozen plasma; ICD-9 = *International Classification of Diseases, Ninth Revision;* IQR = interquartile range; MICU = medical ICU; SAPS = Simplified Acute Physiology Score; SICU = surgical ICU; SNRI = serotonin norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.
[a]As described in Martin et al.[20]

Discussion

In our study, we found that after adjustment for confounding variables, patients being treated with an SSRI or SNRI prior to admission to the ICU had significantly higher hospital mortalities than patients not receiving one of these medications. This article explores whether there is an association between SSRI use and ICU outcomes; our results do not reflect risk of harm from SSRI use among those who do not develop critical illness.

Table 2—*Comparison of Initial Laboratory Values and First 24-h Vital Signs in Groups Included in Study*

Variable	Control (12,238)	SSRI/SNRI Admission (2,471)
Selected initial laboratory values		
Initial creatinine	1, IQR 0	1, IQR 1
Initial hematocrit	35, IQR 9	35, IQR 8
Initial platelet count	222, IQR 123	239, IQR 129
Selected vital signs		
Total min with abnormal HR[a]	125, IQR 1,020	155, IQR 1,020
Total min with abnormal BP[b]	60, IQR 315	75, IQR 360

Variables were reported as data median with IQR; lengths of stay were reported as data mean SD. HR = heart rate. See Table 1 legend for expansion of other abbreviations.
[a]Heart rate > 100 beats/min.
[b]Mean arterial pressure < 60 mm Hg.

One difficult question to answer in any study investigating possible adverse effects of antidepressants is whether the observed effect is related to the drug or to the disease. To complicate matters, the population receiving antidepressants may include a substantial number of patients who are not depressed by standard criteria. Depression has been shown to be associated with worse outcomes in multiple medical conditions, and we were unable to control for or measure the degree of depression in this study. In an effort to answer this question, we analyzed patients based on which specific SSRI they were taking prior to admission.[21-23] SSRIs have varying degrees of serotonin reuptake inhibition (see Table 4), as has been reported previously,[14] but the literature suggests that the choice of SSRI is based primarily on provider preference rather than the degree of depression or other patient factors.[9] We, therefore, posited that if the effect on mortality is related to the medication, then mortality would be expected to vary by the potency of the specific SSRI rather than by the severity of depression. Our analysis revealed that mortality in patients taking citalopram and escitalopram was not significantly

Table 3—*OR of SSRI/SNRI vs Control for Multivariate Logistic Regression for Hospital Mortality*

Patient Subgroup	Population Total (Control/Positive)	OR	95% CI	*P* Value
Entire cohort[a]	14,709 (12,238/2,471)	1.19	(1.02-1.40)	.026
Comorbidities by ICD-9				
Cardiovascular disease[a]	10,195 (8,521/1,674)	1.24	(1.03-1.49)	.025
Diabetes mellitus	2,571 (2,063/508)	1.08	(0.75-1.58)	.7
Selected ICU types				
CSRU[a]	5,463 (4,647/816)	1.45	(1.07-1.95)	.016
MICU	5,000 (4,006/994)	1.05	(0.83-1.34)	.7
Selected acute diagnoses				
Acute coronary syndrome[a] (serum troponin > 0.5 ng/mL)	1,171 (990/181)	1.95	(1.21-3.13)	.006
Acute renal failure by ICD-9	2,071 (1,670/401)	1.22	(0.90-1.66)	.2
Acute respiratory failure by ICD-9	1,847 (1,448/399)	1.05	(0.79-1.38)	.7
Sepsis (Martin criteria)	509 (420/89)	1.31	(0.67-2.54)	.4

Each row was obtained from the regression model for the specific patient subset. See Table 1 legend for expansion of abbreviations.
[a]These results reject the null hypothesis using Holm's stepdown procedure on the families previously defined, with an initial *P* value of .05 for the entire cohort of < .05.

higher than in control subjects. Citalopram is known to be a lower-affinity SSRI,[21] and as escitalopram is the active enantiomer of citalopram, it is presumed to be similar in affinity. In contrast, patients taking paroxetine and sertraline, both higher-affinity SSRIs,[14] demonstrated significantly higher mortalities.

Long-term SSRI use has previously been linked to increased mortality, perhaps most notably in the Women's Health Initiative study. That data revealed that SSRI use was associated with a hazard ratio for death of 1.32 and a hazard ratio of 1.45 for stroke, compared with patients not taking an antidepressant.[6]

Another study found that continuation of SSRIs during the perioperative period is associated with a higher risk of adverse events, including hospital mortality and readmission at 30 days.[24] These authors state that determining whether patient factors or SSRIs themselves are responsible for elevated risks requires prospective study. Unfortunately, it would not be possible to prospectively examine the interaction between long-term SSRI use and critical illness.

We were unable to find any evidence in our database that would indicate that any of the known adverse effects of SSRIs were a potential cause for the increased mortality in these patients. Specifically, there was no significant difference in hematocrit level, initial BP, or heart rate between patients taking SSRIs and control subjects. Patients taking SSRIs did not require more blood transfusions.

Of the different patient subsets, we found the most significant correlation between SSRI/SNRI use and hospital mortality among cardiac surgery patients and patients who developed acute coronary syndrome with significant troponin elevation (troponin-T level > 0.5 ng/mL). A trend was also noted among patients with chronic cardiovascular disease based on ICD-9 diagnoses, suggesting that the association is secondary to the interaction between SSRI/SNRI and cardiovascular disease, or between SSRI/SNRI and a cardiovascular medication. In view of the very strong effect noted in acute coronary syndrome, one speculative possibility is that the increased mortality

Table 4—*Proportion of In-Hospital Death for Specific Drugs as Compared With Those in the Control Population*

Drug	Population on Medication	Hospital Mortality Rate in Positives, %	Dissociation Constant for Serotonin Transporter[a]
Citalopram	622	9	1.16
Escitalopram	203	5	Unknown[b]
Fluoxetine	388	10	0.81
Sertraline	555	14	0.29
Paroxetine	406	12	0.13

The hospital mortality rate in the control group is 10%.
[a]Lower dissociation constant denotes a higher degree of serotonin reuptake inhibition. From Tatsumi et al.[14]
[b]Escitalopram is the active s-enantiomer of citalopram and is, thus, presumed to have a similar dissociation constant.

Table 5—*ORs Associated With Specific Drugs and Relevant Risk Factors in the Control and SSRI Population*

Covariate	OR (95% CI)	*P* Value
Sex	0.87 (0.77-0.98)	.2
Age	1.01 (1.01-1.02)	< .001
SAPS	1.13 (1.12-1.15)	< .001
Ventilator use	1.67 (1.42-1.98)	< .001
Vasopressor use	1.52 (1.33-1.74)	< .001
Combined Elixhauser	1.23 (1.21-1.25)	< .001
Citalopram	1.06 (0.78-1.43)	.7
Escitalopram	0.54 (0.28-1.04)	.07
Fluoxetine	1.11 (0.76-1.62)	.6
Sertraline	1.47 (1.11-1.94)	.007
Paroxetine	1.52 (1.08-2.12)	.015

See Table 1 legend for expansion of abbreviations.

seen might be a withdrawal effect on the control of coronary vascular tone.

Our study has several limitations. First, our data are retrospective, which prevents us from evaluating causality. We were also unable to control for smoking, which is a potentially significant confounder for mortality, as the prevalence of smoking is significantly higher in patients with depression than in the general population. Neither the dose nor the duration of the SSRI administration was available, so we were unable to assess any potential effects of these factors.

Although our report examines the impact of specific drugs on outcomes, the potential for the approach described is not so limited. In fact, there are far-reaching implications for this mode of data examination that can include and analyze any of the elements captured in the available database. Although the current MIMIC database is limited to one academic hospital in the United States, plans are already in motion to extend the data to other hospitals, including institutions outside the United States. As the database expands quantitatively and qualitatively across diverse care environments, the power and significance of any individual analysis will only increase over time. Furthermore, such analyses can be easily repeated, modified, and strategically improved based on iterative interpretation of prior findings.

Although this study specifically reports the evaluation of outcomes in critically ill patients who have received SSRI/SSRN agents prior to admission, there is a more general and ultimately more important implication of this work: the use of an open clinical database for targeted analyses with documented methodologies and subsequent expert interpretation of the findings.[25] We advocate that these analyses can be (1) repeated by other investigators using the same, updated, or another ICU database; (2) selectively modified to include and/or exclude covariates as more clinicians weigh in on the theoretical causal pathway between the exposure, the confounders, and the outcome of interest; and (3) repeated using other (including nonparametric) algorithms that might be better suited to represent the complexities of the relationship between the covariates, either real or perceived, during clinical decision-making. This kind of powerful, generalizable approach, requiring transparency in both data and methods, is necessary to realize and optimize the potentially achievable benefit of the secondary use of health data in the oncoming era of evidence-generating medicine.

Conclusions

In conclusion, we found in-hospital mortality to be increased in patients admitted to an ICU who were receiving SSRI or SNRI agents prior to admission. This relationship persisted after adjustment for several confounders, and risk appeared to be higher with increasing potency of the SSRIs. This information raises important questions about the long-term safety of these commonly prescribed medications, which require further investigation.

Currently, no recommendations can be made on the basis of this study regarding the continued use of these agents in patients who are in or discharged from an ICU. The next step is to validate our findings in another ICU database and design additional analyses that will address the limitations of this study, including taking into consideration the dose and duration of SSRI/SNRI use prior to critical illness. We envision using the same data-based approach in investigating an unlimited variety of clinical questions, such as potential interactions in diverse populations between drugs (or medical devices), and illuminating complex clinical scenarios, such as systemic inflammatory response syndrome, surgery, general anesthesia, and acute coronary syndrome, which, typically, are not captured during premarket testing.

As we learn more about maximizing the clinical information and guidance that can be gained from such an approach, we will begin to enter an era of transparency in data and methods based on what will be virtually continuous addition to and use of the accrued data. This lends to numerous benefits. First, the digitization of the medical record will then begin to truly pay off for clinicians burdened with what they may perceive as onerous data entry duties of dubious value. Second, this will begin to reduce the nearly universal loss of the precious information that is gained in every clinical encounter, enabling population-based clinical guidelines to be customized to individual patients across clinical contexts. Third, we will begin to create a beneficial and transparently cooperative clinical environment in which the care of each patient extends well beyond the individual to benefit larger patient populations, and the care of populations, in turn, powerfully benefits individuals. In addition, the increasing availability of all necessary data will enable users to perform such studies in a more complete and timely manner and, thus, complement and supplement traditional RCTs for the study of new (as well as accepted) therapies in diverse populations and settings. Finally, we will be able to rapidly identify even subtle adverse effects from drugs, devices, and practices and understand treatment effect heterogeneity that may be inadvertently glossed over in traditional RCTs.

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Ms Ghassemi: contributed to the conception of the study, the study design, and the approach to data analysis; extracted the data

from MIMIC-II; performed the statistical analysis; and participated in the interpretation of the findings and in the writing of the manuscript.
Dr Marshall: contributed to the conception of the study, the study design, and the approach to data analysis and participated in the interpretation of the findings and in the writing of the manuscript.
Mr Singh: contributed to the conception of the study, the study design. and the approach to data analysis; performed the statistical analysis; and participated in the interpretation of the findings and in the writing of the manuscript.
Dr Stone: contributed to the conception of the study, the study design, and the approach to data analysis and participated in the interpretation of the findings and in the writing of the manuscript.
Dr Celi: contributed to the conception of the study, the study design, and the approach to data analysis and participated in the interpretation of the findings and in the writing of the manuscript**.**
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