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The Association of Selective Serotonin Reuptake Inhibitors With Delirium in Critically Ill Adults: A Secondary Analysis of the Bringing to Light the Risk Factors and Incidence of Neuropsychologic Dysfunction in ICU Survivors ICU Study

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OBJECTIVES: To assess the association between selective serotonin reuptake inhibitors (SSRI) and delirium in the subsequent 24 hours after drug administration in critically ill adults.

DESIGN: Retrospective cohort study utilizing the Bringing to Light the Risk Factors and Incidence of Neuropsychologic Dysfunction in ICU Survivors dataset.

SETTING: Two large U.S. ICUs.

PATIENTS: Critically ill adults admitted to a medical or surgery ICU between March 2007 and May 2010 with respiratory failure or shock.

INTERVENTIONS: Our primary outcome was the occurrence rate of delirium or coma during each day in the ICU. Our exposure variable was SSRI administration on the prior day in the ICU. As a secondary question, we assessed the association of SSRI administration and delirium the same day of SSRI administration in the ICU.

MEASUREMENTS AND MAIN RESULTS: We analyzed 821 patients. The median age was 61.2 years old (interquartile range, 50.9–70.7), and 401 (48.8%) were female. A total of 233 patients (28.4%) received prescribed SSRIs at least once during their ICU admission. Delirium was present in 606 (74%) of the patients at some point during hospitalization in the ICU. Coma was present in 532 (64.8%) of the patients at some point during hospitalization in the ICU. After adjusting for multiple potential confounding factors, we found that SSRI administration in the ICU was associated with lower odds of delirium/coma (odds ratio [OR], 0.75; 95% CI, 0.57–1.00) the next day. An SSRI administered on the same day reduced the odds of delirium/coma as well (OR, 0.66; 95% CI, 0.50–0.87).

CONCLUSIONS: SSRI administration is associated with decreased risk of delirium/coma in 24 hours and on the same day of administration in critically ill patients in a medical or surgical ICU.

KEY WORDS: delirium; intensive care unit outcomes; neurophysiology; neurotransmitters; selective serotonin reuptake inhibitors

Delirium, a form of acute brain failure, defined by inattention and a fluctuating course, is highly prevalent in the critically ill adult population. Forty percent of all ICU patients will experience delirium during their admission. If a patient requires mechanical ventilation, the incidence increases to 70% (1–3). In addition to its high prevalence, delirium is detrimental to patients' short- and long-term outcomes. Patients who become delirious while in the ICU have an increased risk of hospital death, 1-year mortality, increased costs, and increased risk of post-ICU cognitive dysfunction (2, 4–6).

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Despite its prevalence and association with poor outcomes, delirium remains difficult to treat. One of the primary difficulties with defining a medical treatment for delirium is that our understanding of the physiologic cascades of delirium is in its infancy and that the physiology likely varies depending on the etiology of delirium. Therefore, the neuropathophysiology of delirium is complex and inherently difficult to study. There are numerous hypotheses for the neuropathophysiology, one of which focuses on neurotransmitter imbalance(s) as a cause of delirium (7–9). The neurotransmitter hypothesis takes into account potential variable changes in multiple neurotransmitters, including acetylcholine, dopamine, norepinephrine, glutamine, γ-Aminobutyric acid, and serotonin. Delirium is thought to usually be an acetylcholine deficient state (9). Therefore, previous researchers investigated the usage of acetylcholinesterase inhibitors in delirium (10). The neurotransmitter hypothesis, along with years of clinical usage of antidopaminergic medications such as antipsychotics in the ICU setting, led to a series of studies evaluating the role of antipsychotics in the management of ICU delirium. Both lines of research did not determine an effective treatment for delirium (10, 11).

Besides manipulation of the acetylcholine and dopamine activity in the brain, the role of neurotransmitter manipulation in the management of delirium remains poorly defined. However, given the ready availability of medications that affect serotonin in the brain, namely selective serotonin reuptake inhibitors (SSRIs), the role of serotonin in delirium management warrants further study.

Approximately 10% of the U.S. population is on an antidepressant, with SSRIs being the most commonly prescribed drug class (12). SSRIs primarily exert their antidepressant effects by neuronal remodeling that occurs weeks after drug initiation (13). Hence, the antidepressant effect is not observed typically until weeks after drug initiation. SSRIs, however, do cause acute changes in serotonin levels shortly after drug initiation (14). Given that the role of serotonin manipulation in delirium is unknown, it is possible this intervention could be used to manage delirium. Further, clinical equipoise exists on whether to continue or discontinue SSRIs if patients are prescribed them prior to an ICU admission during which they become delirious.

To further elucidate the relationship between SSRIs and delirium, we sought to examine the association of SSRIs and delirium incidence in a cohort of critically ill adults. Our primary research question is whether SSRIs are associated with delirium in the subsequent 24 hours after drug administration.

MATERIALS AND METHODS

We conducted a secondary analysis of the Bringing to Light the Risk Factors and Incidence of Neuropsychologic Dysfunction in ICU Survivors (BRAIN-ICU) data set (6). The BRAIN-ICU study examined the impact of ICU delirium on post-ICU cognitive function of survivors. It enrolled 821 critically ill patients between March 2007 and May 2010 and collected data on psychoactive medication administration (including SSRIs) and daily delirium assessments. These delirium assessments were initiated in the ICU upon enrollment and continued throughout the hospitalization until time of discharge or until day 30 of hospitalization.

The BRAIN-ICU study included adults admitted to a medical or surgical ICU with respiratory failure or shock. Exclusion criteria from the original study were: 1) substantial recent ICU exposure, inability to reliably assess for delirium (blindness, deafness, etc.), non-English speaking, active substance abuse, psychotic disorder, homelessness or residence greater than 200 miles from enrolling center, patients unlikely to survive greater than 24 hours, unable to obtain informed consent, and patients at high risk for preexisting cognitive deficits. Patients were screened for cognitive impairment using the Short Informant Questionnaire on Cognitive Decline in the Elderly (15). Those with a score of 3.3 or more were assessed by the Clinical Dementia Rating (CDR) scale (16). Patients with a CDR greater than 2.0 were excluded.

For the initial study, consent was obtained from all patients or their surrogates. The initial study was approved by the Vanderbilt Institutional Review Board (IRB). The University of North Carolina at Chapel Hill (UNC) IRB reviewed the current study plan, and it did not warrant full IRB review as it entailed analysis of an existing deidentified dataset (UNC IRB 17-1771, approved July 25, 2017). Study procedures followed were in accordance with the ethical standards of the Vanderbilt and UNC IRBs and with the Helsinki Declaration of 1975.

Demographic information was obtained via chart review. Medication administration prior to ICU

admission was determined by review of admission documents and medication lists. Daily medication administration during ICU admission was obtained via chart review.

Delirium was assessed daily for up to 30 days of hospitalization via the Confusion Assessment Method for the ICU (CAM-ICU) performed by trained research professionals. The CAM-ICU was assessed bid, once during a prespecified 2-hour window between 0,900 and 1,100 and then again between 1,500 and 1,700, to account for the inherent fluctuations in delirium. The CAM is a simple algorithm for the bedside assessment of delirium and is the most widely used delirium assessment tool in research and clinical settings. The CAM consists of four clinical features: 1) acute change or fluctuating course, 2) inattention, 3) disorganized thinking, and 4) altered level of consciousness. Patients must have feature 1 AND feature 2 present, as well as feature 3 OR feature 4 present to meet criteria for delirium. The CAM-ICU operationalizes assessment of these criteria for critically ill adults and is routinely used as part of daily assessments in U.S. ICUs. It has excellent test characteristics as it is 93% sensitive and 98% specific for the diagnosis of delirium in critically ill adults (17).

Our primary outcome of interest was presence delirium or coma during each day in the ICU. Coma was defined as a Richmond Agitation Sedation Scale score of –4 or –5. Our exposure was SSRI administration on the prior day in the ICU. As a secondary question, we assessed the association of SSRI administration and delirium on the same day of SSRI administration.

We measured the following covariates as potential confounding variables: age, SSRI prescription prior to hospitalization, number of days in the hospital, sex, Sequential Organ Failure Assessment (SOFA) score, opiate dose in the preceding 24 hours, benzodiazepine dose in the prior 24 hours, and Charlson comorbidity score. Covariates were selected a priori and based on expected relationships to the exposure and outcome (**Fig. 1**). Age was selected as delirium/coma risk increases with age. SSRI exposure has a relationship with age since adults in their middle age are more likely to be on SSRIs than younger ones. SSRI usage prior to hospitalization has a relationship to the exposure since patients who receive SSRIs as an inpatient are much more likely to have taken SSRIs as an outpatient prior to admission. SSRI usage prior to admission likely also reflects a depression diagnosis, and depression is associated with delirium/coma. Day of hospitalization was included as this variable likely relates to the exposure but in an unclear direction. Some patients that improve to the point that they no longer need the ICU may be then started on their home SSRIs. Providers occasionally hold these medications initially on ICU admission due to not having complete medication reconciliation or lack of enteral access. Patients remaining in the hospital longer are more likely to have delirium/coma versus those that get discharged, so this variable has a relationship to the outcome. We included SOFA score at time of admission because severity of illness is related to risk of delirium/coma, and severity of illness may have a relationship to likelihood of receiving SSRIs as outpatients. Finally, we included comorbidities as reflected by the Charlson comorbidity score because the of comorbid disease is related to the risk of delirium/coma, and patients with multiple comorbidities are more likely to receive SSRIs as outpatients. We included two other variables in the model to increase precision. Opiate dose and benzodiazepine dose in the preceding 24 hours were included as both are strongly linked to delirium/coma.

This analysis used generalized estimation equations that consider the correlation between observations from the same individual while treating observations from different individuals as independent observations. An exchangeable working correlation was used to represent the within-subject correlation. Potential confounding variables included in the model were considered a priori based on clinical rationale or published literature. Covariates selected as potential confounders included the number of days in the hospital since enrollment (continuous), the total dose of benzodiazepine equivalents in 24 hour (continuous), log of the total dose of opiate equivalents in 24 hour (continuous), age (continuous), Charlson Comorbidity Score (continuous), and received SSRIs prior to hospitalization (categorical). Each day of delirium/coma risk and SSRI exposure was analyzed independently for each patient while accounting for correlations within each subject.

RESULTS

We analyzed 821 patients. Of these, 233 (28.4%) received SSRIs at least once in the ICU. The median age was 61.2

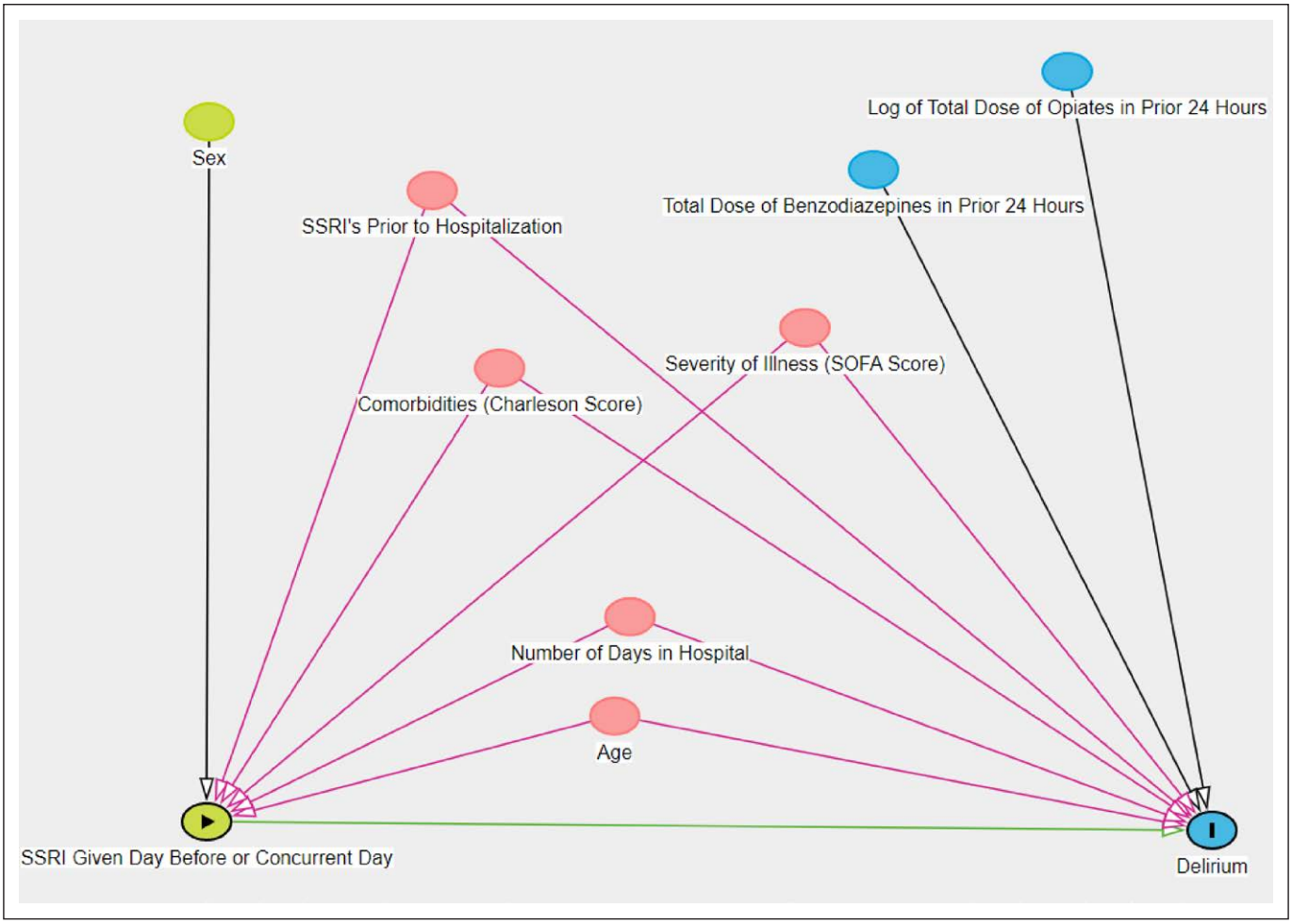

Figure 1. Directed acyclic graph of modeling approach. SOFA = Sequential Organ Failure Assessment, SSRI = selective serotonin reuptake inhibitor.

years old (interquartile range [IQR], 50.9–70.7), and 401 (48.8%) were female. The majority of the patients were White (740 [90.1%]). A total of 211 patients (25.7%) were prescribed SSRIs prior to ICU admission. The median ICU length of stay (LOS) was 5.0 days (IQR, 2.8–11.1 d), and the median hospital LOS was 10.0 days (IQR, 5.9–17.1 d). The number of patients who died during hospitalization was 144 (17.5%) (**Table 1**). Delirium was present in 606 (74%) of patients at some point during their hospitalization. Coma was present in 532 (64.8%) of patients at some point during hospitalization in the ICU.

Most of the patients that received SSRIs during their ICU stay (146 [67.0%]) were prescribed them as outpatients prior to ICU admission. However, many patients that were given SSRIs in the ICU were not prescribed them as outpatients prior to ICU admission (65 [33.0%]) (**Table 2**).

In unadjusted analyses, we found that SSRI administration was associated with a decreased likelihood of delirium/coma the subsequent day at a statistically significant level (OR, 0.60; 95% CI, 0.48–0.76). SSRI administration was also associated with lower odds of delirium/coma on the same day (OR, 0.75; 95% CI, 0.58–0.97) (**Table 3**).

This effect on delirium/coma the subsequent day is mitigated slightly on adjusted analyses. After adjusting for multiple confounding factors, we found that SSRI administration was associated with lower odds of delirium/coma (OR, 0.73; 95% CI, 0.55–0.96) the next day. An SSRI administered on the same day reduced the odds of delirium/coma (OR, 0.64; 95% CI, 0.49–0.82) (Table 3). This association was consistent across the 30-day study period (**Fig. 2**).

DISCUSSION

In our secondary analysis of a large cohort of medical and surgical critically ill patients, we found that administration of an SSRI was associated with decreased risk of delirium and/or coma in the subsequent 24

TABLE 1.
Demographics and Outcomes

Characteristics	Total Sample, *n* = 821
Age, yr, median (IQR)	61.2 (50.9-70.7)
Sex, *n* (%)	
Female	401, (48.8)
Male	420, (51.2)
Race, *n* (%)	
White	740 (90.1)
Black	77 (9.4)
Other	4 (0.5)
Prescribed Selective Serotonin Reuptake Inhibitor prior to admission, *n* (%)	
Yes	211 (25.7)
No	610 (74.3)
Charlson score, median (IQR)	2 (1–4)
Sequential Organ Failure Assessment, median (IQR)	9 (7–12)
Total benzodiazepine equivalents in 24 hr	8 (0–53)
Total opiate equivalents in 24 hr	1,950 (120–9,740)
Outcomes	
ICU length of stay, d, median (IQR)	5.0 (2.8–11.1)
Hospital length of stay, d, median (IQR)	10.0 (5.9–17.1)
Duration of mechanical ventilation, d, median (IQR)	3.1 (1.04–8.9)
Expired during hospitalization, *n* (%)	144 (17.5)

IQR = interquartile range.

TABLE 2.
Proportions of Patients Prescribed Selective Serotonin Reuptake Inhibitors as Outpatient Receiving Selective Serotonin Reuptake Inhibitors in ICU

Prescribed SSRI as Outpatient	Received SSRI at Least 1 d in ICU	Did Not Receive SSRI at Least 1 d in ICU
Yes	146 (67.0%)	87 (14.3%)
No	65 (33.0%)	523 (85.7%)
Total	221	610

SSRI = selective serotonin reuptake inhibitor.

TABLE 3.
Analysis of the Effects of Selective Serotonin Reuptake Inhibitor Use on Delirium/Comatose Outcomes

Analyses	OR (CI)	*p*
Unadjusted		
Received SSRI then next day status	0.60 (0.48–0.76)	< 0.0001
Received SSRI then same day status	0.75 (0.58–0.97)	0.0279
Adjusted[a]		
Received SSRI then next day status	0.73 (0.55–0.96)	0.0242
Received SSRI then same day status	0.64 (0.49–0.82)	0.0006

OR = odds ratio, SSRI = selective serotonin reuptake inhibitor.
[a]Adjusted using number of days in study, total dose of benzodiazepines in 24 hr, log of the total dose of opiates in 24 hr, age enrolled, enrollment Sequential Organ Failure Assessment score, Charlson score, and received SSRIs prior to hospitalization.

hours. SSRI administration was also associated with decreased risk of delirium/coma on the same day of administration. This effect was mitigated slightly but still statistically significant when adjusted for multiple potential confounders.

It is also notable that the percentage of patients prescribed SSRIs in our sample was higher than the general population with 211 patients (25.7%) prescribed SSRIs prior to ICU admission compared with the prevalence rate of antidepressant use by 10% in the general U.S. population (12). This finding supports prior work that indicated that patients experiencing a critical illness have a higher degree of mental health comorbidity compared with the general population (18).

To our knowledge, this is first study examining the association of SSRIs and ICU delirium. Our findings are important for multiple reasons. First, the serotoninergic pathway has been implicated in the pathogenesis of delirium, but it is not well defined. The association of a medication that alters serotonin levels with delirium builds on the importance of this pathway in delirium pathogenesis.

Prior research has examined the association of the serotonin metabolic pathways with delirium. One study examined the association of serotonin precursors and metabolites with delirium. This study by Pandharipande et al (19) demonstrated an increased risk of delirium in patients with both elevated and decreased serum tryptophan levels (a serotonin

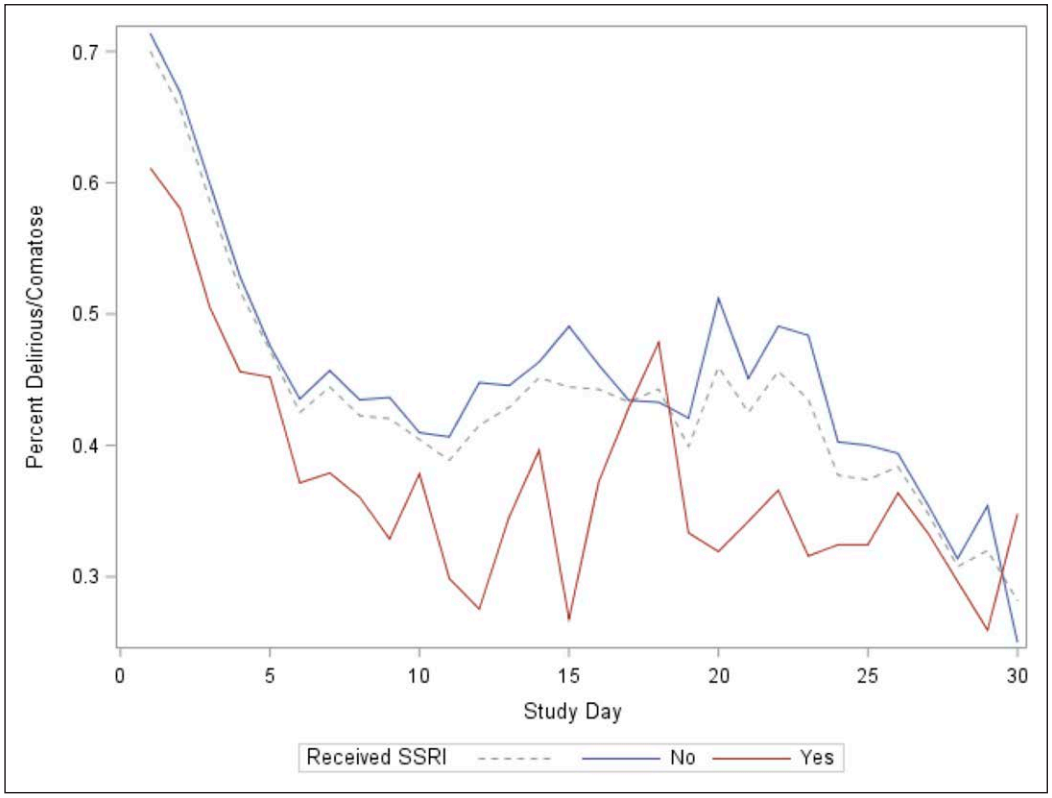

Figure 2. Percentage of delirious/comatose patients for each day in study by selective serotonin reuptake inhibitor (SSRI) status.

precursor). They hypothesized that low tryptophan levels can decrease past a threshold that can decrease serotonin efflux and that this may lead to delirium (**Fig. 3**). Our study advances this work by measuring the association of delirium with a commonly prescribed drug class that manipulates serotonin levels in the CNS. One explanation for our findings is that SSRI administration may increase serotonin levels and keep patients above this deleterious threshold.

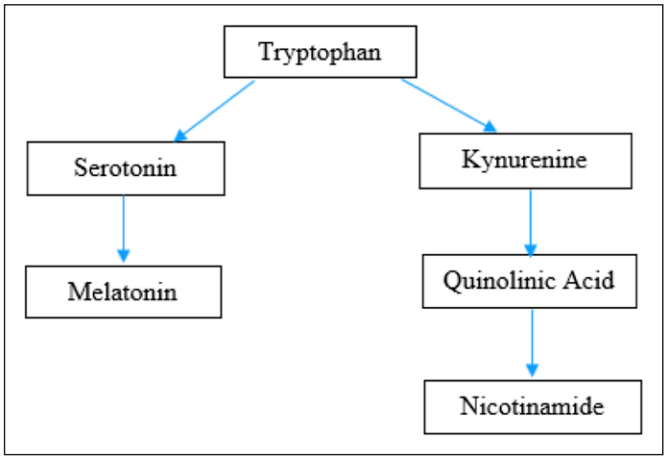

Figure 3. Tryptophan metabolic pathways.

A recent large randomized controlled trial examined the usage of fluvoxamine, an SSRI, for the reduction of need for hospitalization or emergency care in outpatients with COVID-19 (20). They found that fluvoxamine was associated with a reduced need for hospitalization or emergency care in this population. The authors hypothesize that SSRIs may have an anti-inflammatory effect that leads to the improvements observed in their study. An anti-inflammatory effect could also explain our findings that SSRI administration is associated with reduced delirium as delirium is a pro-inflammatory state (9). An alternate explanation for the fluvoxamine findings is that it modulates sigma-1-receptor binding, and it just happens that some SSRIs have sigma-1-receptor agonism with fluvoxamine having the strongest affinity (21). Therefore, it is possible that effects associated with SSRIs are independent of serotonin modulation. Examining the relationship of specific SSRIs with stronger sigma- receptor agonism compared with those with weaker agonism with delirium would offer a method to explore this potential mechanism further, but it is outside the scope of this current project.

A final possible explanation for our findings is that SSRIs may be exerting an antianxiety effect that reduces the rate of delirium. Many of the patients in the ICU have hypoxic respiratory failure or other issues that cause dyspnea. Hypoxia and dyspnea can lead to anxiety (22). SSRIs are standard treatment of anxiety disorders (23). Therefore, SSRI usage in hypoxic patients, even in the potential short term, may assist with some of the associated anxiety, which may contribute to delirium.

Currently, there is clinical equipoise on whether to continue critically ill patients on SSRIs if they were prescribed them prior to admission. Our findings suggest that continuing them may be beneficial to patients, potentially either due to maintaining adequate central nervous serotonin concentrations or due to a global anti-inflammatory effect. It is notable that a third of patients that received SSRIs in the ICU were not prescribed them prior to ICU admission. This suggests that SSRIs may not only be beneficial to those patients that were on them prior to ICU admission. Finally and potentially most importantly, our finding that SSRIs may decrease the risk of delirium could be impactful for delirium prevention and management in the ICU. Currently, there is no proven medication for the prevention or treatment of delirium. Our findings, if replicated in a prospective study, could form the basis of a new line of clinical research into using SSRIs for delirium prevention and treatment.

Our study has a few limitations. First, the retrospective cohort design raises the potential for unmeasured confounders that are affecting our observations. Given that certain drugs of abuse may affect serotonin levels, toxicology results may potentially be helpful in accounting for potential confounding. However, we do not have these data available. Our data included information on prescription of SSRIs prior to ICU admission. However, we did not have information on adherence to these prescriptions. As with all clinical diagnostic instruments, the CAM-ICU could have misclassified some patients as to their true delirium category, though it has excellent reliability, sensitivity, and specificity. Further, the data we used were collected at a center with a long history of delirium research (Vanderbilt), which mitigates this risk. Finally, the study was conducted at a single academic tertiary medical center, and results may not be generalizable to other settings. However, the study enrolled patients from medical and surgical ICUs, which increases the sample's heterogeneity and generalizability.

In conclusion, SSRI administration is associated with decreased risk of delirium or coma in 24 hours and on the same day of administration in critically ill patients. For patients who are taking SSRIs prior to ICU admission, it may be advisable to continue the medications through the ICU admission. The role of SSRIs for delirium prevention or treatment should be explored in future prospective research.

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