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Antipsychotic Utilization in the Intensive Care Unit and in Transitions of Care

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Abstract

Purpose—The objective of this study was to quantify the rate at which newly-initiated antipsychotic therapy is continued on discharge from the Intensive Care Unit and describe risk factors for continuation post ICU discharge.

Materials and Methods—Retrospective cohort study of all patients receiving an antipsychotic in the Intensive Care Units of a large academic medical center from January 1, 2005, to October 31, 2011. Chart review was conducted to ascertain whether a patient was newly-started on antipsychotic therapy and whether therapy was continued post ICU discharge.

Results—A total of 39,248 ICU admissions over the 7 year period were evaluated. Of these, 4468 (11%) were exposed to antipsychotic therapy, of which 3119 (8%) were newly-initiated. In the newly-initiated cohort, 642 (21%) were continued on therapy on discharge from the hospital. Type of drug (use of quetiapine versus no use of quetiapine, odds ratio 3.2, 95% CI 2.5–4.0, $p < 0.0001$ and use of olanzapine OR 2.4, 95% CI 2.0–3.1 $p < 0.0001$) were significant risk factors for continuing antipsychotics on discharge, despite adjustment for clinical factors.

Conclusions—Antipsychotic use is common in the intensive care unit setting, and a significant number of newly-initiated patients have therapy continued upon discharge from the hospital.

Keywords

Antipsychotic agents; delirium; medication reconciliation

Introduction

Antipsychotic medications are frequently initiated in the intensive care unit to treat a variety of conditions including, but not limited to, acute psychosis, substance withdrawal, agitation not responding to other therapies, or delirium. Antipsychotics are a potentially attractive alternative to other sedatives as they can, in many circumstances, control acute agitation without suppressing respiratory drive. The most recent guidelines from the Society of Critical Care Medicine (SCCM)¹ indicate that there is no published evidence that haloperidol reduces the duration of delirium in ICU patients, and only weak evidence exists for atypical antipsychotics. Despite the lack of reliable evidence supporting their use in the ICU, antipsychotic agents are used routinely in over a tenth of all ICU patients². While a small proportion of this use is in patients who were admitted on these agents, the majority of ICU antipsychotic utilization is for new-onset agitation or delirium².

A potential consequence of antipsychotic use in the ICU is the continued use on transition to less acute settings, including on discharge from the hospital. Other classes of medications, including inhaled bronchodilators and proton pump inhibitors, are frequently started during hospitalizations and continued following discharge, many times inappropriately^{3,4}. When combined with the multitude of other factors that contribute to medication management in transitions of care, high-risk medications such as antipsychotics may also be continued inappropriately. The rate at which newly initiated antipsychotics are continued following discharge has only been described in a small patient cohort to date⁵, and data is lacking regarding the risk factors for continuation outside the hospital setting.

We sought to describe ICU antipsychotic utilization at a large, urban, academic medical center over a 7 year period and to determine if there were patient-specific characteristics that increased the likelihood of exposure to newly-initiated antipsychotic therapy, and the prevalence/risk factors for continuation of antipsychotic therapy at hospital discharge.

Materials and Methods

Setting and Design

We performed a retrospective cohort study of all admissions receiving an antipsychotic in the Intensive Care Units from January 1, 2005, to October 31, 2011 at the Beth Israel Deaconess Medical Center, a large, urban, tertiary care center in Boston, Massachusetts. The hospital's institutional review board approved the study with a waiver of informed consent.

Data Sources

Data were obtained from electronic medical records and medical databases created through usual care. We extracted patient age, race and gender, comorbidities (as defined by Elixhauser⁶), patient-level case-mix, admission source (admission from the emergency room or other), ICU type (medical, surgical or other type of ICU), day of the week of discharge, length of hospital and ICU stay, total charges, disposition, and in-hospital mortality.

Patients and Definitions

All patients who were at least 18 years of age were identified as receiving an antipsychotic medication through the use of automated dispensing cabinet records. Once identified, we reviewed the charts of all patients who received an antipsychotic to evaluate whether the antipsychotic therapy was present pre-admission or if it was newly initiated while in the ICU. Antipsychotics included in the analysis included haloperidol, aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone. Those patients deemed to be a new initiation were then evaluated to determine whether the antipsychotic was continued on discharge from the hospital.

We conducted two separate analyses. In the first analysis, our primary outcome of interest was the initiation of an antipsychotic during the patient's stay in the ICU. We examined patient-level risk factors (demographics, comorbidities defined using Elixhauser's method⁶, and severity of illness using the DRG cost weight of each admission as the individually-adjusted casemix) as well as hospital-level risk factors (admission to medical or surgical ICU, admission from emergency room versus other) for initiation of antipsychotic therapy. We identified delirious patients with ICD9 codes, as previously used in Swan et al: 290.11, 290.3, 290.41, 291.0–291.9, 292.81, 293.0, 293.1, 293.9, 300.11, 308.09, 780.02, 780.09². The coding of delirium was handled as a binary variable. We also examined secondary analyses of the association of newly-started antipsychotics in the ICU and hospital and ICU lengths of stay, total hospital charges, in-hospital death, and likelihood of discharge home. In our second analysis, we restricted our population to those admissions during which antipsychotics were newly started in the ICU and to those patients who survived to discharge. In this analysis, our primary outcome was continuation of these medications on discharge from the hospital. We examined patient- and hospital-level risk factors (as identified in the first analysis) for continuing these medications on discharge. Further, we examined whether patients greater than 65 years old might be at greater risk for initiation of therapy, given that older patients might face more delirium. We specifically explored whether the day of the week of discharge (weekend versus weekday) and the type of antipsychotic (specifically haloperidol, olanzapine or quetiapine) to which the patient was exposed would be associated with continuation on discharge. We also explored the secondary analysis of the association of continuation of antipsychotics on discharge and total hospital charges, disposition to locations other than home, and likelihood of readmission at 30 days.

Statistical Methods

The unit of analysis was hospital admission. We performed unadjusted comparisons using Student's *t* test, the X^2 test, or the Fisher exact test, as appropriate. We assessed bivariable associations between patient- and hospital-level factors and initiating antipsychotics in the ICU. We then performed bivariable analyses of the same risk factors and continuing antipsychotics on discharge, conditional on survival to discharge and conditional on the antipsychotics starting in the ICU. We performed a multivariable logistic regression model of discharge on antipsychotics among new initiators, adjusting for all variables with p-value greater than 0.2 using a forward selection process. All analyses were conducted using version 9.3 of SAS software (SAS Institute Inc, Cary, North Carolina).

Results

Patient exposure to antipsychotic therapy is described in Figure 1. Overall, 11% of ICU admissions were exposed to antipsychotic therapy, with 8% being new exposures. Of the patients newly exposed, 21% were discharged from the hospital with a prescription for continued antipsychotic therapy.

Patient characteristics associated with starting antipsychotics in the ICU are presented in Table 1, as compared with ICU patients not newly initiated on antipsychotics (i.e. non-users and those with preadmission use). Patients newly started on antipsychotics were significantly more likely to be male (44% versus 40%, $p<0.001$), younger (mean age 64 years versus 66 years, $p<0.001$), and non-white (26% versus 23%, $p=0.0004$) than patients not newly initiated on antipsychotics. Newly starting on antipsychotics was associated with diagnosis of delirium during the admission, higher severity of illness, admission from the emergency room, and with the presence of several comorbidities (Table 1). These newly initiated patients also had significantly longer hospital and ICU lengths of stay, greater total charges, and a lower likelihood of returning home at discharge, although they did have a significantly lower risk of re-admission at 30 days.

Among all patients newly initiated on antipsychotics during their ICU stay, we then compared patients who continued on any antipsychotic on discharge to those who had these medications discontinued, presented in Table 2. Patients who continued on antipsychotics were not significantly different from those who had these medications discontinued with respect to age, gender or race. Patients who had their antipsychotic continued on discharge were more likely to have a diagnosis of delirium, had greater severity of illness, a greater likelihood of having some component of their ICU stay include the surgical intensive care unit, and had higher rates of several comorbidities, including neurologic disease, chronic lung disease, weight loss, and psychiatric disease.

Patients who were discharged on their newly-started antipsychotics also had longer lengths of hospital stays and ICU stays, greater total charges, and only a 12% chance of returning home on discharge as compared with a 29% chance of discharge to home if the medications were not continued ($p<0.0001$). These patients also had a significantly greater risk of readmission at 30 days (27% versus 23%, $p=0.03$).

In multivariable analyses, a number of risk factors remained significant for continuing antipsychotics on discharge among new initiators. In particular, discharge to a facility (OR 2.4, 95% CI 1.9–3.1), admission through the emergency room (OR 1.4, 95% CI 1.2–1.7) and individually-adjusted casemix (OR 1.04, 95% CI 1.02–1.06) were all risk factors for any of these medications being continued on discharge.

The adjusted odds of continuation of newly-initiated antipsychotics varied by the type of antipsychotics to which patients were exposed. As compared to patients not exposed to each type of drug, patients exposed to quetiapine were 3-fold more likely to continue this medication on discharge (OR 3.1, 95% CI 2.5–3.9 $p<0.0001$), patients exposed to olanzapine were 2.5-fold more likely (OR 2.4, 95% CI 2.0–3.1 $p<0.0001$), while patients

exposed to haloperidol were (OR 1.2, 95% CI 0.99–1.5, $p=0.06$) at a modest but nonsignificantly increased risk of continuation (Figure 2).

While it was not significant, discharges that took place on the weekend trended towards an increased risk of continuation (OR 1.2, 95% CI 0.9–1.7, $p=0.18$).

Discussion

This study demonstrates that antipsychotic use in the intensive care unit is a common occurrence, and that patients who receive newly-initiated antipsychotic therapy are generally more ill, have greater ICU and hospital length of stay and higher costs of care. Our data also raise the concern that other factors may be contributing to whether antipsychotics are continued on discharge, such as the type of antipsychotic utilized.

We found that a significant number of newly initiated patients (21%) continue therapy at hospital discharge. The reason for antipsychotic therapy continuation on discharge in this cohort is unclear. Contributing factors may include persistent delirium/agitation, use as a sleep aid, newly diagnosed psychiatric illness, and improper/incomplete medication reconciliation. Cognitive impairment persists after critical illness, with up to 26% of patients having global cognition scores 2 standard deviations below population means⁷. Further, survivors of critical illness are at an increased but transient risk of new psychiatric diagnosis, with the risk of new psychoactive medication prescriptions of 12.7% for ICU survivors versus 5% for the hospital cohort.⁸ An additional reason for antipsychotic continuation may reside in the indication chosen. Antipsychotic agents are sedating, and these sedative properties are often utilized to treat insomnia/enhance sleep. Providers may consider continued hospitalization as a reason to maintain these agents to optimize sleep, despite the lack of evidence to support this indication.⁹

Of greater concern may be the contribution of improper medication reconciliation contributing to the high rates of continuation of newly initiated antipsychotics. Other classes of medications such as acid suppressive agents (proton pump inhibitors, histamine receptor antagonists) and albuterol are continued after discharge from the Intensive Care Unit^{3,4} and up to half of potentially inappropriate medications in the elderly on discharge from the hospital were initiated in the ICU.¹⁰ Pronovost and colleagues identified that the transition of care from the Intensive Care Unit to lower levels of care place patients at increased risk for errors in medication therapy.¹¹ They were able to design a tool, administered by nurses, that greatly reduced the number of medications errors at the transition from ICU to floor-based care. At our institution, medication reconciliation is conducted on ICU admission and in transitions of care by medical and surgical house staff. Throughout the time period studied, electronic physician order entry was present, but without a dedicated tool or process to reconcile medications. An electronic tool was implemented in July of 2012, and we are in the process of examining the impact of the tool on the rates of antipsychotic continuation. Further research is necessary to replicate whether antipsychotics started in the ICU are continued at the same rate, and with similar risk factors in other institutions.

The high rate of continuation of antipsychotic therapy is concerning, as antipsychotic use is associated with significant risk. In addition to the well-described cardiac effects (prolonged QT interval), neuroleptic malignant syndrome and extrapyramidal symptoms may also occur. Longer-term use can predispose patients to metabolic disturbances and increase the risk of death in elderly patients with dementia¹². If the rate of continuation observed in our study is extrapolated to the entire US population, (assuming 5 million ICU admissions per year), over 80,000 patients per year would have their newly-initiated antipsychotic continued on discharge from the hospital. Additionally, we observed increased 30 day readmission rates in patients who had antipsychotic therapy continued versus those who had therapy stopped prior to discharge.

When examining the specific factors that may contribute to a patient being discharged on an antipsychotic, we found that the specific antipsychotic utilized correlated with risk of continuation, with both olanzapine (odds ratio 2.5) and quetiapine (odds ratio 3.2) having a greater likelihood of being continued than haloperidol (odds ratio 1.3). This could suggest either that ease of use of the atypical antipsychotics compared to haloperidol, which is more often given in intravenous formulation, promotes discharge on these agents, or that physicians perceive less long term risk from atypical agents and are therefore more likely to continue them on discharge. Although atypical antipsychotic agents tend to cause less tardive dyskinesia, they are known to be associated with similar rates of other adverse events compared to typical agents, and have been linked to an increase risk of sudden cardiac death and pneumonia in the elderly.^{12,13}

Evaluation of why antipsychotics are continued outside the ICU setting deserves mention. While specific indication for therapy was not evaluated in this study, it is important to note that all newly-initiated antipsychotic utilization in the ICU setting is off-label. While there is limited data suggesting that quetiapine may be beneficial in reducing time in delirium and agitation while in the intensive care unit¹⁴, continuing therapy outside the ICU setting and on discharge from the hospital has not been described in the literature, while the risks of such continuation are well-described.^{12,13}

Our study has several important strengths. Ours is the first large-scale examination of antipsychotic use initiated in the ICU and continued on transitions of care over a multi-year period. Second, our findings are consistent with other patterns of care, both in antipsychotic use nationally² and in continuation of other medications.

Our study has several limitations. First, this was a retrospective, single center study at a large, urban, academic medical center and may not be generalizable to other settings. However, the overall percentage of patients exposed to antipsychotic therapy (11%) is identical to that of previously published data that evaluated 71 US academic medical centers². Second, although every effort was made to adjust for confounding variables, unmeasured confounders may explain some of our results. We were not able to assess for the indications of the antipsychotics prescribed (delirium, sleep, agitation), thus confounding by indication may have played a contributing role in the continuation of therapy. Third, we used administrative data, which occasionally lacks the detail of clinical data. As a result, we were unable to assess the four known risk factors for ICU delirium, which include preexisting

dementia, history of alcoholism or hypertension, or high severity of illness on admission. Relying on ICD 9 codes also most likely underrepresented delirium in our cohort, as only hyperactive delirium would likely be coded, with hypoactive delirium, (which makes up the majority of ICU delirium) being under-reported. We attempted to mitigate the effects of this on our exposure and outcomes of interest by performing individualized chart reviews to accurately extract data surrounding medication continuation on transitions of care.

Conclusion

We found that newly-initiated antipsychotic therapy is a common occurrence in the intensive care unit, and that approximately one fifth of newly initiated patients are discharged from the hospital with these medications newly added to their medication lists in our single center study. Perhaps even more concerning, we have identified that a patient's likelihood of continuing on these medications may not be entirely driven by the clinical needs of the patient but rather by nonclinical factors such as the type of antipsychotic used. Additional research is needed to better define the role of antipsychotic therapy post critical illness and better delineate which patient populations would be suitable for continued treatment.

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Table 1

Bivariable (or Unadjusted) comparisons of risk factors associated with administering antipsychotics at least once during the ICU admission to patients not routinely taking this class of medication prior to admission. All comparisons performed using chi-square or t-tests unless indicated below.

		Patients Newly Initiated on Antipsychotics N = 3119	Other patients N = 36129	p-value
Demographics	Female	1244 (40%)	15887 (44%)	<0.0001
	White	2415 (77%)	26628 (74%)	0.0004
	Age (mean)	66	64	<0.0001
Features of admission	Mean casemix	4.9	2.9	<0.0001
	Admission from ED	2046 (66%)	21249 (59%)	<0.0001
	Admission to MICU ~	1491 (48%)	13292 (37%)	<0.0001
	Admission to SICU ~	1142 (37%)	10789 (30%)	<0.0001
	Delirious	775 (25%)	1462 (4%)	<0.0001
Comorbidities	CHF	840 (27%)	6416 (18%)	<0.0001
	Valvular disease	283 (9%)	2684 (7%)	0.0009
	Pulmonary circulation disease	169 (5%)	1470 (4%)	0.0003
	Perivascular disease	339 (11%)	4015 (11%)	0.68
	Paralysis	131 (4%)	1070 (3%)	0.0001
	Neurologic disease	336 (11%)	2821 (8%)	<0.0001
	Chronic lung disease	728 (23%)	6822 (19%)	<0.0001
	Diabetes	663 (21%)	7656 (21%)	0.93
	Diabetes with complications	214 (7%)	2766 (8%)	0.11
	Hypothyroidism	344 (11%)	3751 (10%)	0.26
	Renal failure	619 (20%)	5981 (17%)	<0.0001
	Liver disease	232 (7%)	2388 (7%)	0.08
	Ulcer disease	4 (<0.5%)	42 (<0.5%)	0.78 *
	AIDS	14 (<0.5%)	182 (0.5%)	0.79 *
	Lymphoma	43 (1%)	497 (1%)	0.99
	Metastatic disease	108 (3%)	1572 (4%)	0.02
	Solid malignancy	75 (2%)	1000 (3%)	0.23
	Arthritis	74 (2%)	1069 (3%)	0.06
	Coagulopathy	469 (15%)	3384 (9%)	<0.0001
	Obesity	169 (5%)	1843 (5%)	0.44
	Weight loss	214 (7%)	1076 (3%)	<0.0001
	Electrolyte imbalance	1317 (42%)	9622 (27%)	<0.0001
	Blood loss anemia	76 (2%)	719 (2%)	0.09

		Patients Newly Initiated on Antipsychotics N = 3119	Other patients N = 36129	p-value
	Anemia	657 (21%)	6647 (18%)	0.0002
	Alcohol abuse	381 (12%)	2265 (6%)	<0.0001
	Drug abuse	160 (5%)	1073 (3%)	<0.0001
	Psychiatric disease	190 (6%)	1428 (4%)	<0.0001
	Depression	278 (9%)	3247 (9%)	0.89
	Chronic hypertension	1739 (56%)	20594 (57%)	0.18
Outcomes	Total charges (mean)	135,025	63,175	<0.0001
	Readmission 30 days	753 (24%)	9593 (27%)	0.003
	Discharge to home	787 (25%)	20463 (57%)	<0.0001
	LOS (mean)	17 days	8 days	<0.0001
	ICU LOS (mean)	10 days	3 days	<0.0001

* Comparison performed using Fisher's exact test due to small cell sizes.

~ Reference group = patients not admitted to MICU or SICU during their hospitalization

Table 2

Bivariable (or Unadjusted) comparisons of risk factors associated with continuation of antipsychotics on discharge from the hospital, restricted to patients who were not admitted already taking this class of medication. All comparisons performed using chi-square or t-tests unless indicated below.

		Antipsychotics not continued on discharge n = 2477	Antipsychotics continued on discharge n = 642	p
Demographics	Female	984 (40%)	260 (41%)	0.72
	White	1905 (77%)	510 (79%)	0.88
	Age (mean)	67	66	0.25
Features of admission	Mean casemix	4.6	6.1	<0.0001
	Admission from ED	1590 (64%)	456 (71%)	0.06
	Weekend discharge	339 (14%)	74 (12%)	0.15
	Admission to MICU	1185 (48%)	306 (48%)	0.94
	Admission to SICU	881 (36%)	261 (41%)	0.02
	Delirious	580 (23%)	195 (30%)	0.003
Comorbidities	CHF	661 (27%)	179 (28%)	0.54
	Valvular disease	228 (9%)	55 (9%)	0.61
	Pulmonary circulation disease	135 (5%)	34 (5%)	0.88
	Perivascular disease	280 (11%)	59 (9%)	0.13
	Paralysis	102 (4%)	29 (5%)	0.65
	Neurologic disease	287 (12%)	49 (8%)	0.004
	Chronic lung disease	557 (22%)	171 (27%)	0.03
	Diabetes	538 (22%)	125 (19%)	0.21
	Diabetes with complications	167 (7%)	47 (7%)	0.61
	Hypothyroidism	280 (11%)	64 (10%)	0.34
	Renal failure	502 (20%)	117 (18%)	0.25
	Liver disease	196 (8%)	36 (6%)	0.05
	Ulcer disease	3 (0.12%)	1 (0.16%)	1.0*
	AIDS	12 (0.5%)	2 (0.3%)	0.75*
	Lymphoma	49 (2%)	3 (0.5%)	0.02*
	Metastatic disease	93 (4%)	15 (2%)	0.08
	Solid malignancy	55 (2%)	20 (3%)	0.19
	Arthritis	55 (2%)	19 (3%)	0.27
	Coagulopathy	389 (16%)	80 (12%)	0.04
	Obesity	128 (5%)	41 (6%)	0.22
	Weight loss	158 (6%)	56 (8%)	0.04
	Electrolyte imbalance	1048 (42%)	269 (42%)	0.85
	Blood loss anemia	64 (3%)	12 (2%)	0.3

		Antipsychotics not continued on discharge n = 2477	Antipsychotics continued on discharge n = 642	p
	Anemia	511 (21%)	146 (23%)	0.24
	Alcohol abuse	294 (12%)	87 (14%)	0.25
	Drug abuse	122 (5%)	38 (6%)	0.31
	Psychiatric disease	134 (5%)	56 (8%)	0.002
	Depression	218 (9%)	60 (9%)	0.67
	Chronic hypertension	1392 (56%)	347 (54%)	0.33
Outcomes	Total charges (mean)	130,309	153,223	0.0006
	Readmission 30 days	577 (23%)	176 (27%)	0.03
	Likelihood of d/c home	29%	12%	<0.0001
	LOS (mean)	16 days	19 days	<0.0001
	ICU LOS (mean)	9 days	13 days	<0.0001