HHS Public Access
Author manuscript
J Stroke Cerebrovasc Dis. Author manuscript; available in PMC 2024 September 01.

Published in final edited form as:
J Stroke Cerebrovasc Dis. 2023 September ; 32(9): 107249. doi:10.1016/j.jstrokecerebrovasdis.2023.107249.

Associations between early in-hospital medications and the development of delirium in patients with stroke

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Abstract

Objectives: Patients hospitalized with stroke develop delirium at higher rates than general hospitalized patients. While several medications are associated with existing delirium, it is unknown whether early medication exposures are associated with subsequent delirium in patients with stroke. Additionally, it is unknown whether delirium identification is associated with changes in the prescription of these medications.

Materials and Methods: We conducted a retrospective cohort study of patients admitted to a comprehensive stroke center, who were assessed for delirium by trained nursing staff during clinical care. We analyzed exposures to multiple medication classes in the first 48 hours of admission, and compared them between patients who developed delirium >48 hours after admission and those who never developed delirium. Statistical analysis was performed using univariate testing. Multivariable logistic regression was used further to evaluate the significance of univariately significant medications, while controlling for clinical confounders.

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Disclosures
MBW is a co-founder of Beacon Biosignals, which played no role in this work. This work was completed while RR was employed by Massachusetts General Hospital, RR is now an employee of UCB Pharma, which played no role in this work. Other authors report no disclosures relevant to the manuscript.

Declaration of interests
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Results: 1,671 unique patients were included in the cohort, of whom 464 (27.8%) developed delirium >48 hours after admission. Delirium was associated with prior exposure to antipsychotics, sedatives, opiates, and antimicrobials. Antipsychotics, sedatives, and antimicrobials remained significantly associated with delirium even after accounting for several clinical covariates. Usage of these medications decreased in the 48 hours following delirium identification, except for atypical antipsychotics, whose use increased. Other medication classes such as steroids, benzodiazepines, and sleep aids were not initially associated with subsequent delirium, but prescription patterns still changed after delirium identification.

Conclusions: Early exposure to multiple medication classes is associated with the subsequent development of delirium in patients with stroke. Additionally, prescription patterns changed following delirium identification, suggesting that some of the associated medication classes may represent modifiable targets for future delirium prevention strategies, although future study is needed.

Keywords

stroke; delirium; medications; polypharmacy

INTRODUCTION

Delirium is a disorder of attention and awareness that is common among patients with stroke and is associated with a longer length of stay, increased risk of readmission, and death.[1–3] Patients with stroke are particularly vulnerable to delirium compared to the general hospitalized population (13-48% occurrence in patients with stroke, compared to 10-25% occurrence among the general hospital population).[1] Given that delirium is often incident, arising after hospitalization,[4] it is important to identify factors that may affect or anticipate its development.[5] Delirium can be prevented through nonpharmacologic interventions in general medical[6] and general neurology[7] inpatients, however, it is less clear whether such interventions can prevent or treat delirium in patients with stroke.[8–10] The prevention and management of delirium remain an important challenge in the care of hospitalized patients with stroke.

Delirium has many potential contributing factors, both non-modifiable factors, such as age and cognitive impairment,[11–16] and potentially modifiable factors, including medications.[17–19] In addition to polypharmacy, certain classes of medications are thought to be potentially deliriogenic including sedatives,[20] antimicrobials,[21,22] opiates,[23] antiepileptics,[24] medications for the treatment of Parkinson's disease,[25–27] steroids[28,29], benzodiazepines[30], anticholinergics[31,32], antiemetics[33], mood stabilizers[34] and muscle relaxants.[35] Avoidance of potentially deliriogenic mediations, where clinically appropriate, may represent an opportunity for delirium prevention.

While associations between in-hospital medications and delirium have been examined in older patients,[36,37] ICU patients,[38,39] and post-operative patients,[30] it is not currently known how medications administered early in a hospitalization impact the subsequent development of delirium in patients with stroke. Additionally, there is no literature describing to what extent the administration of such medications may be clinically modifiable once delirium has occurred. We therefore conducted a retrospective cohort study to determine which medications administered in the first 48 hours of hospitalization predicted the subsequent development of delirium in patients with stroke. Additionally, we sought to characterize how prescribing patterns changed after delirium was identified.

METHODS

Data availability

Anonymized data not published within this article will be made available by request from qualified investigators.

Patient population

We performed a retrospective cohort study of all patients admitted to our comprehensive stroke center with acute neurovascular disease based on ICD10 coding, including ischemic stroke or intracranial hemorrhage, between January 2017 and April 2019. Intracranial hemorrhages included all compartments: intraparenchymal hemorrhage, subarachnoid hemorrhage, subdural hematoma, and epidural hematoma. Given that we were interested in the effect of medications administered within the first 48 hours of hospitalization on the subsequent development of delirium, only those with a hospital stay of greater than 48 hours and a recorded delirium screen were included. We excluded patients who screened positive for delirium in the first 48 hours and those who did not have any delirium screen recorded. Only one admission was included per patient. The sample size was determined by the number of admissions during this time as a sample of convenience. Race, ethnicity, marital status, English speaking and insurance payor were all obtained from an internal quality improvement database.

Clinical data

Delirium assessments were extracted from the electronic medical record, in addition to patient demographics, baseline characteristics, medication administration, and clinical outcomes. When available, the NIH stroke scale (NIHSS) was also extracted. Hemorrhage severity scores were not included due to the differences in measurement across the different hemorrhage types. We used routinely-collected data from admission nursing intake screens to estimate baseline characteristics including rates of visual and hearing impairment (based on whether (1) a patient was known to have glasses/hearing aids, (2) impairment was previously documented in the medical record, or (3) it was reported by the patient or a family member), denture use, dependence in activities of daily living, and memory impairment. Potentially hazardous alcohol use was determined by either an Audit C score on admission suggestive of alcohol overuse[40] or use of a Clinical Institute Withdrawal Assessment (CIWA) scale.[41] We also collected internal administrative data identify neurovascular intervention. Relative costs were determined from a hospital administrative database in relative units, as per hospital administrative policy.

Delirium assessment

The primary outcome of this study was the development of delirium 48 hours or more after admission. Delirium was assessed by trained neurology nurses once per shift (twice daily) as part of routine clinical care, using the CAM-ICU in the Intensive Care Unit[42,43] and a Confusion Assessment Method (CAM) framework on the wards.[44] CAM-based algorithms for delirium identification have been validated in various patient populations, including the general hospital population[44,45] and patients with acute stroke.[2,43,46] In patients who were intubated, delirium was assessed using the CAM-ICU, a scale using non-verbal responses to assess for delirium.[42,43]

Nursing staff were trained to perform assessments as part of a departmental quality initiative through a combination of in-person didactics, in-service sessions, online training, and targeted feedback including ongoing discussions from nurse supervisors. Nurses were specifically trained regarding CAM administration in the neurosciences population, including in the setting of aphasia and dementia. Nurses performed complete neurologic exams on every patient, every shift including assessing for aphasia and non-verbal signs of attention. This information was paired with longitudinal observation of the patient over the course of the entire shift, including evaluation of fluctuations, in order to make a determination of delirium status. Interpreter services were utilized for all patients who were non-fluent in English. Importantly, staff discussed complex or uncertain cases during daily interdisciplinary group rounds, where formalized interdisciplinary checklists prompted the identification of each patient's delirium status. Patients were stratified by their delirium status into those who never had a positive delirium assessment and those who first screened positive >48 hours after admission. We excluded patients who developed delirium within the first 48 hours of hospitalization, in order to examine the importance of potentially delirious medications prior to delirium onset.

Medication data

The main exposures in this study were selected medication classes. Based on the literature and *a priori* clinical knowledge, we selected the following potentially deliriogenic medication classes for study: sedatives,[20] antimicrobials,[21,22] opiates,[23] antiepileptics,[24] medications for the treatment of Parkinson's disease,[25–27] steroids[28,29], benzodiazepines,[30] anticholinergics,[31,32] antiemetics,[33] mood stabilizers[34] and muscle relaxants.[35] We also looked at sleep aids, as these are often used to manage the disrupted sleep-wake cycles of delirious patients,[47,48] stimulants, which may cause hyperactive delirium and are sometimes used off-label for the treatment of hypoactive delirium,[49–51] and cholinesterase inhibitors and memantine,[52,53] which have been trialed in the prevention and treatment of delirium although data has been mixed. Finally, we also examined antipsychotic medications, which are frequently used off-label in the management of delirium but may also be potentially deliriogenic.[54,55]

Anticholinergic medications were defined according to the American Geriatric Society's 2019 Beers criteria.[19] We restricted each medication to appear in only a single therapeutic class based on clinical knowledge of common usage (e.g. quetiapine as an atypical antipsychotic, rather than also an anticholinergic). Medications in each class are listed in Supplementary Table S1. Lastly, when medications were administered via routes with minimal systemic absorption they were removed (i.e. topical, inhaled, eye or ear drops, etc).

Statistical analysis

Descriptive analyses were used to summarize the characteristics of patients who did and did not develop delirium in terms of (1) demographic characteristics; (2) clinical characteristics related to their hospitalization; (3) clinical outcomes. Medians and interquartile ranges were presented for continuous variables, and percentages were calculated for categorical variables.

We compared medication class exposures during the first 48 hours of admission between patients who did and did not develop delirium. Due to variability in the medications used, including doses and routes of administration, as well as a lack of consensus on dose conversion for several classes, we evaluated medication exposures rather than doses. Chi-square or Fisher's exact tests were used for categorical variables and the Wilcoxon rank sum test was used for continuous variables.

Based on the univariate analysis for medications and *a priori* knowledge, we built a multivariable logistic regression model to test whether medication classes that were statistically significant in the univariate analyses remained associated with the development of delirium in a multivariable context. We jointly included all medications statistically significant in the univariate analyses in a multivariable logistic regression to predict the development of delirium. We additionally controlled for selected potential clinical confounders in this model, including age, sex, intracranial hemorrhage, and ICU status. The specific covariates selected for the model were chosen based on standard demographic data (age and sex) and anticipated large clinical characteristic effect sizes (hemorrhage and ICU status). Additional baseline characteristics were not included due to a priori power concerns given the size of our dataset and the large number of medication classes we were studying, and the non-validated routine clinical way in which baseline data was collected. Restraints were not included due to concerns for strong confounding by indication and lack of documentation around reason for restraint application. Urinary catheters are clinically provider-dependent and therefore were not included in the model. Additionally, these factors and ventilation status were highly correlated with ICU status. Risk ratios and 95% confidence interval were presented in the multivariable regression analysis to describe the independent contribution of each factor.

Finally, among those patients who developed delirium, we compared the change in proportions of patients receiving potentially deliriogenic medications in the 48 hours before and after delirium identification, using McNemar's test. A p-value < 0.05 was considered statistically significant in all analyses. Descriptive statistics were performed using MATLAB (R2018b, MathWorks), and inferential statistics were performed using SAS software, version 9.4 (SAS Institute).

Approval

This study was approved by the Institutional Review Board at Massachusetts General Hospital (Boston).

RESULTS

Patient demographics and baseline characteristics

12,228 admissions to the clinical neuroscience wards occurred during the study period, of whom 1,671 unique patients with acute neurovascular diagnoses were included for analysis (Figure 1). Of these, 1,034 patients presented with primarily ischemic stroke and 637 patients presented with primarily intracranial hemorrhage. Delirium developed 48 hours or more after admission in 27.8% of patients (464/1671; Table 1). Patients who developed delirium 48 hours or more into their hospitalization, as compared to those who did not develop delirium, tended to be older, have Medicare or Medicaid insurance, have pre-existing hearing and memory impairment, and required assistance with more activities of daily living (ADLs) (Supplementary Table S2). Sex, ethnicity, race, and English fluency were similar between patients with and without delirium. Patients who did not have documented assessments for delirium during their hospitalization tended to be younger, were less likely to receive acute interventions, had shorter lengths of stay, and had higher rates of discharge home (Supplementary Table S3).

Acute clinical characteristics

Patients who developed delirium were more likely to have intracranial hemorrhage and less likely to have ischemic stroke than patients who did not develop delirium (Table 1). Median NIH stroke scale scores among ischemic stroke patients were higher for patients who developed delirium. Patients who developed delirium were also more likely to have received tissue plasminogen activator and neurovascular intervention, and more likely to have been in the ICU during the first 48 hours of admission and to have been on a ventilator. Patients who developed delirium were also more likely to receive physical restraints and urinary catheters within the first 48 hours of hospitalization.

Clinical outcomes

Clinical outcomes were worse in patients who developed delirium during their hospitalization (Table 1), including longer length of stay, higher rates of 30-day readmission, higher in-hospital mortality, and increased discharge to facilities rather than home. The relative total cost of hospitalization was more than two times higher among patients who developed delirium.

Medications classes significantly associated with delirium—Patients who developed delirium received more unique medications in the first 48 hours after admission (median 23.5, IQR 18-29) compared to those who never developed delirium (median 17, IQR 12-23, $p < 0.0001$).

Antipsychotics

Patients who developed delirium were more likely to have received early antipsychotics (Table 2). Haloperidol was the most commonly prescribed typical antipsychotic and quetiapine the most commonly prescribed atypical antipsychotic. Both typical and atypical antipsychotics were significantly associated with delirium, even in the multivariable model (Table 3). Following delirium identification, there was a significant reduction in the use of typical antipsychotics, but a significant increase in the use of atypical antipsychotics (Table 4).

Sedatives

Patients who developed delirium were more likely to have received early sedatives. Propofol and dexmedetomidine were the most commonly prescribed sedatives. In the multivariable model, sedatives remained significantly associated with delirium, even accounting for ICU status. Additionally, the association between sedatives and delirium remained present even when performing a stratified analysis for patients receiving mechanical ventilation (Supplementary Table S4). Following delirium identification there was a significant reduction in the use of sedatives.

Cholinesterase Inhibitors and Memantine

Patients who developed delirium were more likely to have received early cholinesterase inhibitors or memantine. However, only 1.8% of patients received such medications in this time frame (31/1710). Donepezil and memantine were the most commonly prescribed medications in this group. However, the association was not significant in the multivariable model and there was no significant change in administration after delirium identification.

Antimicrobials

Patients who developed delirium were more likely to have received early antimicrobials. The most commonly prescribed antimicrobials were cefazolin, vancomycin, and ciprofloxacin. In the multivariable model, antimicrobials remained significantly associated with delirium. Additionally, antimicrobials were significantly associated with delirium in patients with ischemic stroke for whom we could additionally control for stroke severity as measured by the NIH Stroke Scale (NIHSS) (Supplementary Table S5). Following delirium identification, there was a significant reduction in the use of antimicrobials.

Opiates

Patients who developed delirium were more likely to have received early opiates. Opiates were the most commonly prescribed medication class among all patients (475/1710, 27.8%), and oxycodone and hydromorphone were the most commonly prescribed opiates. In the multivariable model, opiates were no longer significantly associated with delirium. Following delirium identification, there was a significant reduction in opiate administration.

Antiepileptics

Patients who developed delirium were more likely to have received early antiepileptics. Levetiracetam was the most commonly prescribed antiepileptic medication. However, the association was not significant in the multivariable model. Following delirium identification, there was a significant reduction in antiepileptic administration.

Medications not significantly associated with delirium

Anticholinergics: Oxybutynin was the most commonly prescribed anticholinergic medication. Anticholinergics were not significantly associated with the development of delirium. Following delirium identification there was no significant change in anticholinergic administration.

Steroids: Dexamethasone was the most commonly prescribed steroid. Steroids were not significantly associated with the development of delirium. Following delirium identification, however, there was a significant reduction in steroid administration.

Benzodiazepines: Lorazepam was the most commonly prescribed benzodiazepine. Benzodiazepines were not significantly associated with the development of delirium. Following delirium identification, however, there was a significant reduction in benzodiazepine administration.

Stimulants: Only 1.6% of patients (28/1710) received stimulants, the most commonly prescribed of which was amantadine. Stimulants were not significantly associated with the development of delirium. Following delirium identification, however, there was a significant increase in stimulant administration.

Sleep Aids: Sleep aids were not significantly associated with the development of delirium in the univariate analysis. Melatonin and trazodone were the most common sleep aids prescribed. Following delirium identification, however, there was a significant increase in sleep aid administration.

DISCUSSION

Delirium is a complex, multifactorial syndrome that is common and associated with poor prognosis among patients with stroke, driving strong interest in identifying potentially modifiable risk factors to help prevent or treat it. In patients admitted to a comprehensive stroke center, several classes of medications administered in the first 48 hours were associated with the subsequent development of delirium, including antipsychotics, sedatives, opiates, and antimicrobials. Establishing a temporal context with medication administration preceding delirium is an understudied but important step to understanding the clinical significance of medications associated with delirium, as identified previously in other patient populations.

As in other studies, the association between a medication class and delirium is likely to be complex. For example, antipsychotics could be potentially deliriogenic by impairing cognition and movement.[56–58] However, the association may also reflect confounding by indication, as anti-psychotics are often used off-label for the treatment of agitation, which can be a premonitory symptom of delirium. Prospective, randomized controlled trials have provided equivocal evidence on the utility of anti-psychotics for delirium, but meta-analyses suggest their routine use should be avoided.[59,60] While the use of antipsychotics specifically for agitation is hard to track retrospectively, for the use of sedatives we were able to track ventilation status. Intriguingly, sedatives remained associated with delirium for patients receiving invasive ventilation, supporting the importance of interrupting sedation as early and as often as clinically appropriate.[20]

Opiates are also potentially deliriogenic,[23] though in our data an association with delirium was no longer maintained after controlling for ICU status. While some opiates, like meperidine, are thought to be highly deliriogenic, others, like hydromorphone, are perhaps less so.[23] Prescribing practices within our institution did not yield sufficient power to detect differences within classes. The results, however, suggest that providers may consider prescribing opiates as a class cautiously in stroke patients at high risk for delirium. The decision is admittedly complex in that pain may also be deliriogenic,[61] and further research is needed to balance these concerns, particularly when receiving care that may cause discomfort, for example in the ICU.

Early antimicrobials were associated with the subsequent development of delirium. Antimicrobials are prescribed to treat infections, which are highly likely to be deliriogenic and cause infection-associated encephalopathy. However, it is increasingly recognized that antimicrobials can have significant neuropsychiatric side effects, including delirium or encephalopathy.[21,22,62] While antimicrobial administration may at times be critical, there is also the potential for misuse or overuse. Even for routine clinical concerns, such as aspiration[63] or asymptomatic bacteriuria,[64,65] there is heterogeneity among prior studies regarding the risks and benefits of routine use of antibiotics among patients with altered mental status. Limited data do not always clarify the most appropriate framework or consensus to guide the use of antibiotics when clinical data is equivocal.[66,67] Most surprisingly, we observed that following delirium identification antimicrobials were deprescribed, with fewer patients receiving them at all, raising the possibility that they were not strictly always necessary. Because we could not determine the specific reason for deprescribing, these data suggest that a prospective study of antibiotic practices and delirium in the setting of stroke with standardized definitions of infection may be warranted, potentially enabling future randomized controlled trials comparing high vs. low thresholds for antibiotic treatment in this patient population.

Among pertinent negative results in our study was the lack of a clear association between anticholinergic medications and subsequent delirium. Anticholinergic medications are a class for which there seems to be plausible pathophysiologic rationale for delirium precipitation.[68] However, the association in prior literature has been inconsistent.[31,32,69] Notably, many medications with anticholinergic properties also fall into other classes, for example olanzapine is an anti-psychotic that is sometimes thought to have anticholinergic properties.[19] We retained such medications in their most recognized therapeutic class to reflect prescribing indications but may also have reduced the power to find an association.

At our comprehensive stroke center, there was significant deprescribing of potentially deliriogenic medications after delirium identification, with a smaller proportion of patients receiving benzodiazepines, steroids, opiates, anticholinergics, and sedatives after delirium identification. There was also an increase in sleep aid administration after delirium identification, likely reflecting attempts to regulate sleep-wake cycles. These findings suggest not only an awareness of delirium status on the part of the clinical staff but also efforts to reduce potentially deliriogenic medication exposure after delirium has been identified. Whether deprescribing effectively treats delirium or whether it would be more effective with earlier implementation remains unclear and requires future study. We also observed what is likely off-label use of antipsychotics for delirium management, with a decrease in typical antipsychotics but an increase in atypical antipsychotics after delirium identification. Given that some delirium symptoms such as agitation may present safety concerns or barriers to transfer to rehabilitation facilities, delirium symptom control will likely remain an ongoing clinical concern in this patient population.

There are several limitations to our study. This study was performed at a single large, academic comprehensive stroke center. Although our center reflects the varying practices of many vascular neurologists, the results may not generalize to other settings. Approximately 1/3 of patients did not have documented assessments for delirium. Patients without documented delirium assessments tended to be lower acuity and have shorter lengths of stay, a population whose rates of delirium would be expected to be lower. This potential bias suggests the results may not immediately generalize to lower risk patients and demonstrates the need for ongoing efforts to improve clinical delirium assessment. Although our clinical neuroscience nurses were trained to administer delirium assessments and consider non-verbal signs of attention, it is possible delirium screens remained challenging in the setting of specific neurologic deficits, such as aphasia. Additionally, we specifically excluded patients who screened positive for delirium within the first 48 hours in order to clarify the temporal relationship between medications and the development of delirium, as confounding by indication is likelier when delirium presence and medication use are concurrent. More than three quarters of patients had their first positive delirium assessment recorded after 72 hours, creating at least a 24-hour buffer for most patients between early medication administration and subsequent development of delirium. Nonetheless, despite our attempts to evaluate medication administrations prior to delirium recognition, the onset of delirium could not be definitively determined, and therefore confounding by indication may still be present for some of the medications used. Future studies may require more frequent and sensitive prospective delirium assessments to determine the precise onset of delirium. While it is unknown whether the pathophysiology of hospital acquired or incident delirium differs from delirium already prevalent on admission, incident delirium as studied here is associated with longer length of stay.[70,71]

Given the retrospective nature of the study, some baseline characteristics were obtained using routine clinical intake data, rather than rigorously validated research grade criteria, and may have both overestimated (vision and hearing impairment) and underestimated (cognitive impairment) potential covariates. We also did not have access to home medications. However, most of the medications identified are not common outpatient medications. Additionally, although we included hemorrhage and ICU status in our multivariate model, it was not possible to fully adjust for stroke severity given the retrospective study design and the characteristics of different stroke pathologies (ischemic vs. hemorrhagic), which have unique severity assessments that can not be immediately harmonized. Fuller consideration of stroke severity and comorbidities will be an important goal for future work. Lastly, medications were grouped by classes for sufficient statistical power. Larger studies may help identify specific medications within such classes associated with higher or lower risks of delirium.

Conclusion

While several medications classes have been associated with concurrent delirium in various patient populations, it is unknown whether early administration of these medications are associated with subsequent delirium in patients with stroke. In a comprehensive stroke center, opiate, sedative, antimicrobial, and antipsychotic exposure were all significantly associated with the subsequent development of delirium when controlling for confounding. Additionally, there was significant deprescribing of several potentially deliriogenic medication classes in the setting of delirium identification. These findings suggest possible modifiable targets for future delirium prevention strategies in patients with stroke, although additional studies are needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

The authors acknowledge the efforts of the Massachusetts General Hospital Neuroscience Delirium Task Force and neurology nurses.

M. Brandon Westover reports financial support was provided by Glenn Foundation for Medical Research. M. Brandon Westover reports was provided by American Federation for Aging Research. M. Brandon Westover reports financial support was provided by American Academy of Sleep Medicine. M. Brandon Westover reports financial support was provided by National Institutes of Health. M. Brandon Westover reports financial support was provided by National Science Foundation. Eyal Y. Kimchi reports financial support was provided by National Institutes of Health. Sophia L. Ryan reports administrative support and statistical analysis were provided by Harvard University Harvard Catalyst. M. Brandon Westover reports a relationship with Beacon Biosignals, Inc. that includes: equity or stocks. co-author Rachel Renwick previously employed at UCB, after completion of their work on this study

Sources of Funding

MBW was supported by the Glenn Foundation for Medical Research and American Federation for Aging Research (Breakthroughs in Gerontology Grant); American Academy of Sleep Medicine (AASM Foundation Strategic Research Award); NIH (R01NS102190, R01NS102574, R01NS107291, RF1AG064312, R01AG062989, R01AG073410); and NSF (SCH-2014431). EYK was supported by a K08-MH116135. This work was conducted with support from Harvard Catalyst (NIH UL 1TR002541) and financial contributions from Harvard University and its affiliated academic healthcare centers.

References

1. Shi Q, Presutti R, Selchen D, Saposnik G. Delirium in Acute Stroke: A Systematic Review and Meta-Analysis. Stroke. 2012;43(3):645–649. doi:10.1161/STROKEAHA.111.643726 [PubMed: 22267831]
2. Oldenbeuving AW, de Kort PLM, Jansen BPW, Algra A, Kappelle LJ, Roks G. Delirium in the acute phase after stroke: Incidence, risk factors, and outcome. Neurology. 2011;76(11):993–999. doi:10.1212/WNL.0b013e318210411f [PubMed: 21307355]
3. McManus J, Pathansali R, Hassan H, et al. The course of delirium in acute stroke. Age Ageing. 2009;38(4):385–389. doi:10.1093/ageing/afp038 [PubMed: 19383773]
4. Siddiqi N, House AO, Holmes JD. Occurrence and outcome of delirium in medical in-patients: a systematic literature review. Age Ageing. 2006;35(4):350–364. doi:10.1093/ageing/afl005 [PubMed: 16648149]
5. Rhee JY, Colman MA, Mendu M, et al. Associations Between Stroke Localization and Delirium: A Systematic Review and Meta-Analysis. J Stroke Cerebrovasc Dis Off J Natl Stroke Assoc. 2022;31(3):106270. doi:10.1016/j.jstrokecerebrovasdis.2021.106270

6. Inouye SK, Bogardus ST, Charpentier PA, et al. A Multicomponent Intervention to Prevent Delirium in Hospitalized Older Patients. N Engl J Med. 1999;340(9):669–676. doi:10.1056/NEJM199903043400901 [PubMed: 10053175]
7. Brown EG, Josephson SA, Anderson N, Reid M, Lee M, Douglas VC. Evaluation of a multicomponent pathway to address inpatient delirium on a neurosciences ward. BMC Health Serv Res. 2018;18(1):106. doi:10.1186/s12913-018-2906-3 [PubMed: 29433572]
8. Nydahl P, Baumgarte F, Berg D, et al. Delirium on stroke units: a prospective, multicentric quality-improvement project. J Neurol. Published online February 14, 2022. doi:10.1007/s00415-022-11000-6
9. Rice KL, Bennett MJ, Berger L, et al. A Pilot Randomized Controlled Trial of the Feasibility of a Multicomponent Delirium Prevention Intervention Versus Usual Care in Acute Stroke. J Cardiovasc Nurs. 2017;32(1):E1–E10. doi:10.1097/JCN.0000000000000356
10. Song J, Lee M, Jung D. The Effects of Delirium Prevention Guidelines on Elderly Stroke Patients. Clin Nurs Res. 2018;27(8):967–983. doi:10.1177/1054773817721400 [PubMed: 28737064]
11. Morandi A, McCurley J, Vasilevskis EE, et al. Tools to Detect Delirium Superimposed on Dementia: A Systematic Review. J Am Geriatr Soc. 2012;60(11):2005–2013. doi:10.1111/j.1532-5415.2012.04199.x [PubMed: 23039270]
12. Morandi A, Davis D, Bellelli G, et al. The Diagnosis of Delirium Superimposed on Dementia: An Emerging Challenge. J Am Med Dir Assoc. 2017;18(1):12–18. doi:10.1016/j.jamda.2016.07.014 [PubMed: 27650668]
13. Jones RN, Fong TG, Metzger E, et al. Aging, Brain Disease, and Reserve: Implications for Delirium. Am J Geriatr Psychiatry. 2010;18(2):117–127. doi:10.1097/JGP.0b013e3181b972e8 [PubMed: 20104068]
14. Alvarez-Perez FJ, Paiva F. Prevalence and Risk Factors for Delirium in Acute Stroke Patients. A Retrospective 5-Years Clinical Series. J Stroke Cerebrovasc Dis. 2017;26(3):567–573. [PubMed: 28012839]
15. Caeiro L, Ferro JM, Albuquerque R, Figueira ML. Delirium in the first days of acute stroke. J Neurol. 2004;251(2):171–178. doi:10.1007/s00415-004-0294-6 [PubMed: 14991351]
16. Ding G, Hua S, Chen J, Yang S, Xie R. Does cognitive decline/dementia increase Delirium risk after stroke? Psychogeriatr Off J Jpn Psychogeriatr Soc. 2021 ;21(4):605–611. doi:10.1111/psyg.12720
17. Gaudreau JD, Gagnon P, Roy MA, Harel F, Tremblay A. Association Between Psychoactive Medications and Delirium in Hospitalized Patients: A Critical Review. Psychosomatics. 2005;46(4):302–316. doi:10.1176/appi.psy.46.4.302 [PubMed: 16000673]
18. Sieber F, Neufeld KJ, Gottschalk A, et al. Depth of sedation as an interventional target to reduce postoperative delirium: mortality and functional outcomes of the Strategy to Reduce the Incidence of Postoperative Delirium in Elderly Patients randomised clinical trial. BJA Br J Anaesth. 2019;122(4):480–489. doi:10.1016/j.bja.2018.12.021 [PubMed: 30857604]
19. By the 2019 American Geriatrics Society Beers Criteria®) Update Expert Panel. American Geriatrics Society 2019 Updated AGS Beers Criteria®) for Potentially Inappropriate Medication Use in Older Adults: 2019 AGS BEERS CRITERIA® UPDATE EXPERT PANEL. J Am Geriatr Soc. 2019;67(4):674–694. doi:10.1111/jgs.15767 [PubMed: 30693946]
20. Reade MC, Finfer S. Sedation and Delirium in the Intensive Care Unit. N Engl J Med. 2014;370(5):444–454. doi:10.1056/NEJMra1208705 [PubMed: 24476433]
21. Bhattacharyya S Antibiotic-associated encephalopathy. Published online 2016:11.
22. Bangert MK, Hasbun R. Neurological and Psychiatric Adverse Effects of Antimicrobials. CNS Drugs. 2019;33(8):727–753. doi:10.1007/s40263-019-00649-9 [PubMed: 31321707]
23. Swart LM, van der Zanden V, Spies PE, de Rooij SE, van Munster BC. The Comparative Risk of Delirium with Different Opioids: A Systematic Review. Drugs Aging. 2017;34(6):437–443. doi:10.1007/s40266-017-0455-9 [PubMed: 28405945]
24. Bohlken J, Kostev K. Prevalence and risk factors for delirium diagnosis in patients followed in general practices in Germany. Int Psychogeriatr. 2018;30(4):511–518. doi:10.1017/S1041610217002587 [PubMed: 29235430]

25. Serrano-Dueñas M, Bleda MJ. Delirium in Parkinson's disease patients. A five-year follow-up study. Parkinsonism Relat Disord. 2005;11(6):387–392. doi:10.1016/j.parkreldis.2005.05.002 [PubMed: 16111911]
26. Young BK, Camicioli R, Ganzini L. Neuropsychiatric Adverse Effects of Antiparkinsonian Drugs. Drugs Aging. 1997;10(5):367–383. doi:10.2165/00002512-199710050-00005 [PubMed: 9143857]
27. Ebersbach G, Ip CW, Klebe S, et al. Management of delirium in Parkinson's disease. J Neural Transm. 2019;126(7):905–912. doi:10.1007/s00702-019-01980-7 [PubMed: 30725186]
28. Koh YI, Choi IS, Shin IS, Hong SN, Kim YK, Sim MK. Steroid - induced delirium in a patient with asthma / report of one case. Korean J Intern Med. 2002;17(2):150–152. doi:10.3904/kjim.2002.17.2.150 [PubMed: 12164094]
29. The Boston Collaborative Drug Surveillance Program. Acute adverse reactions to prednisone in relation to dosage. Clin Pharmacol Ther. 1972;13(5part1):694–698. doi:10.1002/cpt1972135part1694 [PubMed: 5053810]
30. Marcantonio ER, Juarez G, Goldman L, et al. The Relationship of Postoperative Delirium With Psychoactive Medications. :5.
31. Gustafson Y, Olsson T, Eriksson S, Asplund K, Bucht G. Acute Confusional States (Delirium) in Stroke Patients. Cerebrovasc Dis. 1991;1:257–264.
32. Campbell N, Perkins A, Hui S, Khan B, Boustani M. Association Between Prescribing of Anticholinergic Medications and Incident Delirium: A Cohort Study. J Am Geriatr Soc. 2011;59:S277–S281. doi:10.1111/j.1532-5415.2011.03676.x [PubMed: 22091573]
33. Athavale A, Athavale T, Roberts DM. Antiemetic drugs: what to prescribe and when. Aust Prescr. 2020;43(2):49–56. doi:10.18773/austprescr.2020.011 [PubMed: 32346211]
34. Alagiakrishnan K. An approach to drug induced delirium in the elderly. Postgrad Med J. 2004;80(945):388–393. doi:10.1136/pgmj.2003.017236 [PubMed: 15254302]
35. Whitlock EL, Vannucci A, Avidan MS. POSTOPERATIVE DELIRIUM. Published online 2013:12.
36. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. Lancet. 2014;383:911–922. [PubMed: 23992774]
37. Han L, McCusker J, Cole M, Abrahamowicz M, Primeau F, Élie M. Use of Medications With Anticholinergic Effect Predicts Clinical Severity of Delirium Symptoms in Older Medical Inpatients. Arch Intern Med. 2001;161(8):1099. doi:10.1001/archinte.161.8.1099 [PubMed: 11322844]
38. Cui Y, Li G, Cao R, Luan L, Kla KM. The effect of perioperative anesthetics for prevention of postoperative delirium on general anesthesia_ A network meta-analysis. J Clin Anesth. 2020;59:89–98. doi:10.1016/j.jclinane.2019.06.028 [PubMed: 31284222]
39. Dale CR, Kannas DA, Fan VS, et al. Improved Analgesia, Sedation, and Delirium Protocol Associated with Decreased Duration of Delirium and Mechanical Ventilation. Ann Am Thorac Soc. 2014;11(3):367–374. doi:10.1513/AnnalsATS.201306-210OC [PubMed: 24597599]
40. Bush K, Kivlahan DR, McDonell MB, Fihn SD, Bradley KA. The AUDIT alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking. Ambulatory Care Quality Improvement Project (ACQUIP). Alcohol Use Disorders Identification Test. Arch Intern Med. 1998;158(16):1789–1795. doi:10.1001/archinte.158.16.1789 [PubMed: 9738608]
41. Sullivan JT, Sykora K, Schneiderman J, Naranjo CA, Sellers EM. Assessment of alcohol withdrawal: the revised clinical institute withdrawal assessment for alcohol scale (CIWA-Ar). Br J Addict. 1989;84(11):1353–1357. doi:10.1111/j.1360-0443.1989.tb00737.x [PubMed: 2597811]
42. Ely EW, Margolin R, Francis J, et al. Evaluation of delirium in critically ill patients: validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). Crit Care Med. 2001;29(7):1370–1379. [PubMed: 11445689]
43. Mitasova A, Kostalova M, Bednarik J, et al. Poststroke delirium incidence and outcomes: Validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU)*. Crit Care Med. 2012;40(2):484–490. doi:10.1097/CCM.0b013e318232da12 [PubMed: 22001583]
44. Inouye SK. Clarifying Confusion: The Confusion Assessment Method: A New Method for Detection of Delirium. Ann Intern Med. 1990;113(12):941. doi:10.7326/0003-4819-113-12-941 [PubMed: 2240918]

45. Carin-Levy G, Mead GE, Nicol K, Rush R, van Wijck F. Delirium in acute stroke: screening tools, incidence rates and predictors: a systematic review. J Neurol. 2012;259(8):1590–1599. doi:10.1007/s00415-011-6383-4 [PubMed: 22234842]
46. McManus J, Pathansali R, Stewart R, Macdonald A, Jackson S. Delirium post-stroke. Age Ageing. 2007;36(6):613–618. doi:10.1093/ageing/afm140 [PubMed: 17965033]
47. Al-Aama T, Brymer C, Gutmanis I, Woolmore-Goodwin SM, Esbaugh J, Dasgupta M. Melatonin decreases delirium in elderly patients: A randomized, placebo-controlled trial. Int J Geriatr Psychiatry. 2011;26(7):687–694. doi:10.1002/gps.2582 [PubMed: 20845391]
48. Campbell AM, Axon DR, Martin JR, Slack MK, Mollon L, Lee JK. Melatonin for the prevention of postoperative delirium in older adults: a systematic review and meta-analysis. BMC Geriatr. 2019;19(1):272. doi:10.1186/s12877-019-1297-6 [PubMed: 31619178]
49. Keen JC, Brown D. Psychostimulants and delirium in patients receiving palliative care. Palliat Support Care. 2004;2(2):199–202. doi:10.1017/S147895150404026X [PubMed: 16594250]
50. Lodewijckx E, Debain A, Lieten S, Bravenboer B, Mets T. Pharmacologic Treatment for Hypoactive Delirium in Adult Patients: A Brief Report of the Literature. J Am Med Dir Assoc. 2021;22(6):1313–1316.e2. doi:10.1016/j.jamda.2020.12.037 [PubMed: 33549562]
51. Eskildsen MA. Use of Modafinil in Two Patients with Hypoactive Delirium. :2.
52. Tampi RR, Tampi DJ, Ghori AK. Acetylcholinesterase Inhibitors for Delirium in Older Adults. Am J Alzheimers Dis Dementiasr. 2016;31(4):305–310. doi:10.1177/1533317515619034
53. Tabet N, Howard R. Pharmacological treatment for the prevention of delirium: review of current evidence. Int J Geriatr Psychiatry. 2009;24(10):1037–1044. doi:10.1002/gps.2220 [PubMed: 19226527]
54. Inouye SK, Marcantonio ER, Metzger ED. Doing Damage in Delirium: The Hazards of Antipsychotic Treatment in Elderly Persons. Lancet Psychiatry. 2014;1(4):312–315. doi:10.1016/S2215-0366(14)70263-9 [PubMed: 25285270]
55. Boettger S, Breitbart W. Atypical antipsychotics in the management of delirium: A review of the empirical literature. Palliat Support Care. 2005;3(3):227–237. doi:10.1017/S1478951505050352 [PubMed: 16594462]
56. Ballard C, Howard R. Neuroleptic drugs in dementia: benefits and harm. Nat Rev Neurosci. 2006;7(6):492–500. doi:10.1038/nrn1926 [PubMed: 16715057]
57. Huo Z, Lin J, Bat BKK, Chan TK, Yip BHK, Tsoi KKF. Cost-effectiveness of pharmacological therapies for people with Alzheimer's disease and other dementias: a systematic review and meta-analysis. Cost Eff Resour Alloc CE. 2022;20(1):19. doi:10.1186/s12962-022-00354-3
58. Rosenheck RA, Leslie DL, Sindelar JL, et al. Cost-benefit analysis of second-generation antipsychotics and placebo in a randomized trial of the treatment of psychosis and aggression in Alzheimer disease. Arch Gen Psychiatry. 2007;64(11):1259–1268. doi:10.1001/archpsyc.64.11.1259 [PubMed: 17984395]
59. Oh ES, Needham DM, Nikooie R, et al. Antipsychotics for Preventing Delirium in Hospitalized Adults: A Systematic Review. Ann Intern Med. 2019;171(7):474–484. doi:10.7326/M19-1859 [PubMed: 31476766]
60. Nikooie R, Neufeld KJ, Oh ES, et al. Antipsychotics for Treating Delirium in Hospitalized Adults: A Systematic Review. Ann Intern Med. 2019;171(7):485–495. doi:10.7326/M19-1860 [PubMed: 31476770]
61. Almeida TML de, Azevedo LCP de, Nosé PMG, Freitas FGR de, Machado FR. Risk factors for agitation in critically ill patients. Rev Bras Ter Intensiva. 2016;28(4). doi:10.5935/0103-507X.20160074
62. Mattappalil A, Mergenhagen KA. Neurotoxicity with Antimicrobials in the Elderly: A Review. Clin Ther. 2014;36(11):1489–1511.e4. doi:10.1016/j.clinthera.2014.09.020 [PubMed: 25450476]
63. Mandell LA, Niederman MS. Aspiration Pneumonia. N Engl J Med. 2019;380(7):651–663. doi:10.1056/NEJMra1714562 [PubMed: 30763196]
64. Joo P, Grant L, Ramsay T, et al. Effect of inpatient antibiotic treatment among older adults with delirium found with a positive urinalysis: a health record review. BMC Geriatr. 2022;22(1):916. doi:10.1186/s12877-022-03549-8 [PubMed: 36447157]

65. Krinitski D, Kasina R, Klöppel S, Lenouvel E. Associations of delirium with urinary tract infections and asymptomatic bacteriuria in adults aged 65 and older: A systematic review and meta-analysis. J Am Geriatr Soc. 2021;69(11):3312–3323. doi:10.1111/jgs.17418 [PubMed: 34448496]
66. Dasgupta M, Brymer C, Elsayed S. Treatment of asymptomatic UTI in older delirious medical in-patients: A prospective cohort study. Arch Gerontol Geriatr. 2017;72:127–134. doi:10.1016/j.archger.2017.05.010 [PubMed: 28624753]
67. Latuga NM, Grant PC, Levy K, Luczkiewicz DL. Treatment of Positive Urine Cultures at End-of-Life and the Effect on Terminal Delirium Management. Am J Hosp Palliat Care. Published online December 10, 2021:10499091211057848. doi:10.1177/10499091211057848
68. Hshieh TT, Fong TG, Marcantonio ER, Inouye SK. Cholinergic deficiency hypothesis in delirium: a synthesis of current evidence. J Gerontol A Biol Sci Med Sci. 2008;63(7):764–772. [PubMed: 18693233]
69. Schor JD, Levkoff SE, Lipsitz LA, et al. Risk Factors for Delirium in Hospitalized Elderly. JAMA. 1992;267(6):5.
70. McCusker J, Cole MG, Dendukuri N, Belzile E. Does delirium increase hospital stay? J Am Geriatr Soc. 2003;51(11):1539–1546. doi:10.1046/j.1532-5415.2003.51509.x [PubMed: 14687382]
71. Guillory J, Fitz-Gerald C, Banik A, et al. Comparison of hospital course and outcome in hospital-acquired vs pre-existing delirium. Ann Clin Psychiatry Off J Am Acad Clin Psychiatr. 2021;33(1):35–44. doi:10.12788/acp.0021

140-character message:

Early exposure to specific medication classes is associated with delirium in patients with stroke & may be targets for future prevention.

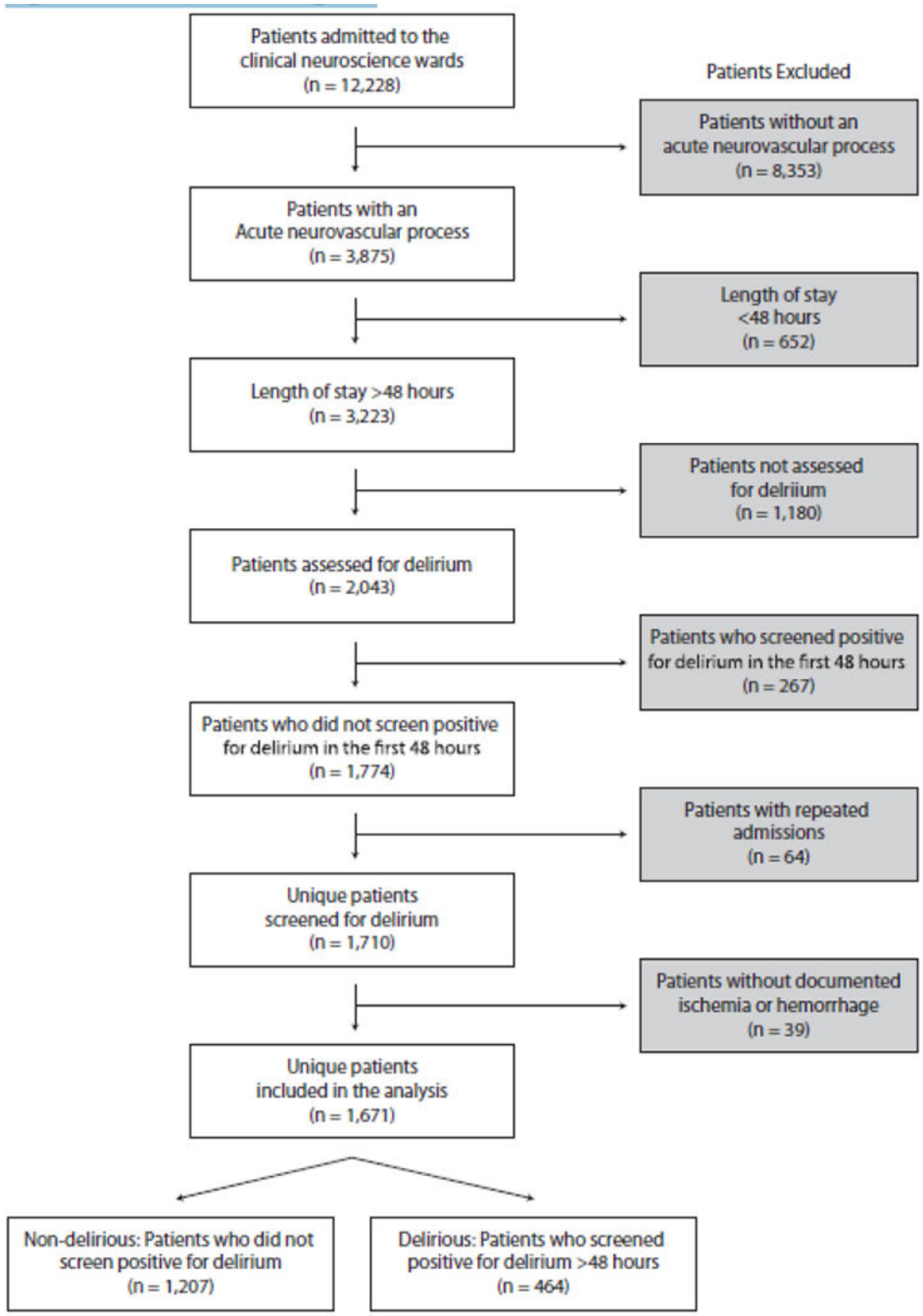

Figure 1.
Patient Flow Diagram

Table 1.

Demographic, clinical characteristics, and health outcomes for the study cohort according to patients who did not develop delirium or who developed delirium 48 hours or more after admission.

Patients assessed indicate the number of patients for whom data was potentially available for the characteristics depicted in the relevant row. Costs were determined from a hospital administrative database and can only be reported in relative units, as per hospital administrative policy.

	Patients who did not develop delirium		Patients who developed delirium		
	Patients assessed	# patients (%)	Patients assessed	# patients (%)	p-value*
Delirium development		1207 (72.2% of cohort)		464 (27.8% of cohort)	n/a
Time to delirium development, days, median (IQR)	1207	n/a	464	5.75 (3.36, 10.55)	n/a
Num of delirious days, median (IQR)	1207	n/a	464	3 (2, 7)	n/a
Demographics					
Age, median (IQR)	1207	67.19 (56.31, 77.38)	464	72.37 (61.02, 82.02)	<0.0001
Female sex, n (%)	1207	563 (46.64%)	464	199 (42.89%)	0.17
Married, n (%)	1147	622 (54.23%)	428	206 (48.13%)	0.03
English speaker, n (%)	1207	1049 (86.91%)	464	393 (84.70%)	0.24
Latinx ethnicity, n (%)	1102	73 (6.62%)	403	32 (7.94%)	0.37
Race, n (%)					
White	1206	909 (75.37%)	464	349 (75.22%)	0.97
Black		99 (8.21%)		37 (7.97%)	
Other		198 (16.42%)		78 (16.81%)	
Insurance Payer, n (%)					
Commercial	1207	355 (29.41%)	464	74 (15.95%)	<0.0001
Medicaid		152 (12.59%)		72 (15.52%)	
Medicare		669 (55.43%)		307 (66.16%)	
Other		31 (2.57%)		11 (2.37%)	
Clinical characteristics					
Intracranial hemorrhage, n (%)	1207	399 (33.06%)	464	238 (51.29%)	<0.0001
Ischemic stroke, n (%)	1207	808 (66.94%)	464	226 (48.71%)	<0.0001
ICU (within first 48hrs), n (%)	1207	523 (43.33%)	464	378 (81.47%)	<0.0001
Ventilator (within first 48hrs), n (%)	1207	168 (13.92%)	464	133 (28.66%)	<0.0001
Restraints (within first 48hrs), n (%)	1207	173 (14.33%)	464	238 (51.29%)	<0.0001
Urinary catheter (within first 48hrs), n (%)	1207	407 (33.72%)	464	317 (68.32%)	<0.0001
Data for Ischemic Stroke Patients	n=808		n=226		
NIHSS (ischemic stroke patients only), median (IQR)	693	3 (1, 8)	202	12 (4, 18)	<0.0001
tPA received (for ischemic stroke patients), n (%)	808	77 (9.53%)	226	49 (21.68%)	<0.0001

	Patients who did not develop delirium		Patients who developed delirium		
	Patients assessed	**# patients (%)**	**Patients assessed**	**# patients (%)**	**p-value***
Neurovascular intervention (within first 48hrs for ischemic stroke patients), n (%)	808	52 (6.44%)	226	35 (15.49%)	<0.0001
Clinical Outcomes					
LOS, median (IQR)	1207	4.96 (3.26, 8.04)	464	13.68 (7.97, 21.33)	<0.0001
30-day readmissions, n (%)	1207	214 (17.73%)	464	107 (23.06%)	0.01
Total cost, $/constant, mean	1204	2737	463	5692	<0.0001
Discharge disposition					
Discharge to home	1207	662 (54.85%)	464	49 (10.56%)	<0.0001
SNF/Rehab/LTC		468 (38.77%)		364 (78.45%)	
In-hospital death		41 (3.40%)		26 (5.60%)	
Hospice		22 (1.82%)		17 (3.66%)	
Other		14 (1.16%)		8 (1.72%)	

*Rank-sum test was used for continuous variables and Chi-square test or Fisher exact test were used for categorical variables.

Table 2.

Comparison of medication exposures within the first 48 hours between non-delirious and delirious patients.

	Non-delirious # patients=1207	Delirious # patients=464	Risk Ratio [95% CI]	p-value*
Antipsychotics (all)	80 (6.63%)	102 (21.98%)	3.97 [2.89, 5.44]	<0.0001
Typical Antipsychotics	41 (3.40%)	66 (14.22%)	4.72 [3.14, 7.08]	<0.0001
Atypical Antipsychotics	50 (4.14%)	62 (13.36%)	3.57 [2.42, 5.27]	<0.0001
Sedatives	130 (10.77%)	121 (26.06%)	2.92 [2.22, 3.85]	<0.0001
Cholinesterase inhibitors	17 (1.41%)	14 (3.02%)	2.18 [1.06, 4.45]	0.03
Antimicrobials	251 (21.80%)	162 (34.91%)	2.04 [1.61, 2.59]	<0.0001
Opiates	359 (29.74%)	219 (47.20%)	2.11 [1.69, 2.63]	<0.0001
Antiepileptic	424 (35.13%)	231 (49.78%)	1.83 [1.47, 2.27]	<0.0001
Parkinson's Medications	17 (1.41%)	8 (1.72%)	1.23 [0.53, 2.87]	0.63
Steroids	101 (8.37%)	50 (10.78%)	1.32 [0.93, 1.89]	0.13
Benzodiazepines	289 (23.94%)	117 (25.22%)	1.07 [0.84, 1.37]	0.59
Anticholinergics	67 (5.55%)	27 (5.82%)	1.05 [0.66, 1.67]	0.83
Antiemetic	305 (25.27%)	118 (25.43%)	1.01 [0.79, 1.29]	0.95
Sleep aids	142 (11.76%)	50 (10.78%)	0.91 [0.64, 1.27]	0.57
Stimulant	20 (1.66%)	7 (1.51%)	0.91 [0.38, 2.16]	0.83
Mood stabilizer	282 (23.36%)	94 (20.26%)	0.83 [0.64, 1.08]	0.17
Muscle relaxants	19 (1.57%)	4 (0.86%)	0.54 [0.18, 1.61]	0.26

*Chi-square test or Fisher exact test were used for categorical variables.

Table 3.

Multivariable model to test which medication classes were independently associated with the development of delirium even when considered jointly, while controlling for potential clinical confounders (age, sex, hemorrhage, and ICU status).

	Relative risk	95% CI	p-value*
Patient’s age	1.03	1.02, 1.04	<0.0001
Female	0.73	0.57, 0.93	0.01
Intracranial Hemorrhage	1.00	0.73, 1.38	0.99
ICU used within first 48 hours	4.79	3.56, 6.45	<0.0001
Typical antipsychotic used within first 48 hours	2.25	1.42, 3.57	0.0006
Atypical antipsychotic used within first 48 hours	2.41	1.51, 3.84	0.0002
Sedative used within first 48 hours	1.45	1.04, 2.02	0.03
Cholinesterase inhibitor used within first 48 hours	1.44	0.61, 3.40	0.40
Antimicrobial used within first 48 hours	1.45	1.09, 1.93	0.01
Opiate used within first 48 hours	1.31	0.98, 1.75	0.07
Antiepileptic used within first 48 hours	0.97	0.71, 1.34	0.87

Table 4.

Comparison of medications pre- and post-delirium identification for delirious patients only

	Pre-delirium (n=464)	**Post-delirium (n=464)**	**Absolute Change (%)**	**p-value**
Whether the medication was taken, n (%)				
Antipsychotics (all)	190 (40.95%)	209 (45.04%)	+4.09%	0.07
Typical Antipsychotics	99 (21.34%)	64 (13.79%)	−7.55%	0.0008
Atypical Antipsychotics	155 (33.41%)	201 (43.32%)	+9.91%	<0.0001
Sedatives	140 (30.17%)	30 (6.47%)	−23.70%	<0.0001
Cholinesterase inhibitors	17 (3.66%)	20 (4.31%)	+0.65%	0.18
Antimicrobials	237 (51.08%)	204 (43.97%)	−7.11%	0.01
Opiates	263 (56.68%)	200 (43.10%)	−13.58%	<0.0001
Antiepileptic	255 (54.96%)	210 (45.26%)	−9.70%	<0.0001
Parkinson's Medications	11 (2.37%)	14 (3.02%)	+0.65 %	0.18
Steroids	79 (17.03%)	57 (12.28%)	−4.75%	0.004
Benzodiazepines	173 (37.28%)	89 (19.18%)	−18.10%	<0.0001
Anticholinergics	55 (11.85%)	50 (10.78%)	−1.07%	0.47
Antiemetic	178 (38.36%)	112 (24.14%)	−14.22%	<0.0001
Sleep aids	194 (41.81%)	260 (56.03%)	+14.22%	<0.0001
Stimulant	55 (11.85%)	76 (16.38%)	+4.53%	0.0004
Mood stabilizer	154 (33.19%)	178 (38.36%)	+5.17%	0.001
Muscle relaxants	11 (2.37%)	16 (3.45%)	+1.08%	0.23

McNemar's test was used to compare agreement of medication used before and after delirium.