Title: New and Persistent Sedative Prescriptions Among Older Adults After Critical Illness: A Population-Based Cohort Study

Running head: Sedative use among older adults after critical illness

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Author contributions:

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- Accuracy of the data analyses (LB, AH, RP)
- Study conception and design (all)
- Statistical plan (LB, RP, HW, CB, SB, DS)
- Data interpretation (all)
- Draft manuscript (LB)
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Take-Home Points:

Study Question: How common is receipt of new and persistent sedative prescriptions for sedative-naïve older adult ICU survivors, and what factors are associated with receipt?

Results: One in 15 sedative-naïve, older adult ICU survivors filled a new sedative ≤7 days of discharge; more than half had persistent prescriptions in 6 months. The receipt of prescriptions at discharge varied widely across hospitals suggesting potentially modifiable practice through medication review and reconciliation.

Interpretation: A clinically important incidence of new and persistent sedative use exists after ICU admission, and various patient and institutional factors are associated with receipt.

ABSTRACT

Background: ICU survivors often have complex care needs and can experience insufficient medication reconciliation and polypharmacy. It is unknown which ICU survivors are at risk of new sedative use post-hospitalization.

Research Question: For sedative-naïve older adult ICU survivors, how common is receipt of new and persistent sedative prescriptions, and what factors are associated with receipt?

Study Design and Methods: Population-based cohort study of ICU survivors ≥66 years who had not filled sedative prescriptions ≤6 months pre-hospitalization (sedative-naïve) in Ontario, Canada (2003 - 2019). Using multilevel logistic regression, we described demographic, clinical, and hospital characteristics and their association with new sedative prescription ≤7 days of discharge. We quantified variation between hospitals using the adjusted median odds ratio (aMOR). Factors associated with persistent prescriptions (≤6 months) were examined with multivariable proportional hazards model.

Results: 250,428 patients were included (mean age 76, 61% male). 15,277 (6.1%) filled a new sedative prescription with variation across hospitals (2% (95% CI 1-3) to 44% (3-57)); 8,458 (3.4%) filled persistent sedative prescriptions. Adjusted factors associated with a new sedative included: discharge to long-term care facility (aOR 4.00, 3.72-4.31); receipt of inpatient geriatric (aOR 1.95, 1.80-2.10) or psychiatry (aOR 2.76, 2.62-2.91) consultation, invasive ventilation (aOR 1.59, 1.53-1.66), and ICU length of stay ≥7 days (aOR 1.50, 1.42-1.58). The residual heterogeneity between hospitals (aMOR 1.43, 1.35-1.49) had a stronger association with new sedative prescriptions than Charlson comorbidity score or sepsis. Factors associated with

persistent sedative use were similar with the addition of females (sHR 1.07, 1.02-1.13) and pre-existing polypharmacy (sHR 0.88, 0.80-0.93).

Interpretation: One in 15 sedative-naïve older adult ICU survivors filled a new sedative ≤7 days of discharge, of whom more than half filled persistent prescriptions. New prescriptions at discharge varied widely across hospitals and represent the potential value of modifying prescription practices, including medication review and reconciliation.

Keywords: critical care, prescription, sedatives, antipsychotic, non-benzodiazepine, post-hospitalization

Abbreviations:

ACG = John Hopkins Adjusted Clinical Groups system frailty marker
aOR = Adjusted odds ratio
CCI = Charlson Comorbidity Index
CI = 95% confidence intervals
ICU = intensive care unit
IQR = interquartile range
LOS = length of stay
SD = standard deviation
SMD = standard mean difference
sHR = subdistribution hazard ratios

Critically ill adults frequently suffer disturbing symptoms of agitation, delirium, anxiety, and insomnia.[1] The presence of these symptoms in the intensive care unit (ICU) leads to the widespread use of sedating drugs, including benzodiazepines and antipsychotics.[1,2] Those who survive critical illness can have complex care needs due to cognitive, psychological, or physical impairments.[3] As ICU survivors transition through the healthcare system, they can experience inadequate medication review, the continuation of medications no longer necessary, and harmful polypharmacy. Older adult ICU survivors are at higher risk of benzodiazepine and antipsychotic use post-hospitalization compared to older adults hospitalized without an ICU admission or those in the community.[4,5] In community-dwelling older adults, sedatives are considered potentially inappropriate due to the associated increased risk of serious adverse events, including falls, cognitive impairment, and mortality.[6-8]

It is currently unknown which ICU survivors are at risk of new sedative use after critical illness. Such data are needed to inform hospital resources to support patients at risk of new sedative use and enhance post-discharge pharmacotherapy. We used population-based data among sedative-naïve older adults who survived a hospitalization with ICU admission to determine the frequency of and risk factors associated with (1) a sedative prescription within 7 days of discharge and (2) persistent sedative prescriptions.

STUDY DESIGN and METHODS

We performed a population-based cohort study using health administrative data held at ICES (www.ices.on.ca). ICES is an independent, non-profit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyze health care and demographic data, without consent, for health system evaluation and improvement. The province of Ontario comprises more than 40% of Canada's population (~15 million residents) and is ethnically diverse.[9] The study was approved by the research ethics committees of Sunnybrook Health Sciences Centre (#2688) and Mount Sinai Hospital (19-02327-C). This study follows the Strengthening the Reporting of Observational Studies in Epidemiology guidelines and the Reporting of Studies Conducted using Observational Routinely Collected Health Data statement (eTable 1).[10]

Data sources

We used administrative, healthcare, and outpatient prescription data between April 1, 2003, and September 30, 2019. Ontario has universal health care for residents of all ages and outpatient prescription insurance coverage for those over 65 years. Datasets were linked at the individual patient level, using unique encoded identifiers, and were analyzed at ICES. These datasets have excellent validity, reliability, and minimal missing data (see eTable 2 for summary of databases).[11-18]

Cohort creation

We included all older adults, defined as ≥66 years, who were discharged alive from a hospitalization with ICU admission who had not filled a sedative prescription for any dose or duration in the six months preceding hospitalization ("sedative-naïve"). Age ≥66 years allowed a look-back period in the provincial drug insurance plan to identify sedative exposure pre-hospitalization. The index date was the date of hospital discharge. As pharmacotherapy for agitation, delirium, anxiety, and sleep is often administered for combinations of symptoms, we broadly defined a sedative as a filled prescription for either a benzodiazepine, a non-benzodiazepine sedative-hypnotic, or an antipsychotic (eTable 3).[1] We identified hospitalization with ICU admission with a validated algorithm (eTable 4).[19,20] The follow-up period for each patient was 180 days after discharge. At the time of cohort creation, follow-up data were available until March 31, 2020.

We excluded patients if: their health card number was missing/invalid; non-resident of Ontario or unknown residence; missing sex; missing age or age >105 or <66 years; the total hospital length of stay (LOS) was less than one day (limited hospital exposure). We excluded those with a discharge date from an acute care hospital ≤180 days before the index hospitalization admission date to prevent confounding from the last hospital admission. We excluded those discharged to inpatient institutions where prescription billing is not through the provincial prescription insurance program, specifically inpatient palliative, rehabilitative, or a mental health facility. We excluded patients who died or were re-hospitalized within 7 days of hospital discharge as the primary outcome could not be assessed.

Transfers between acute care hospitals for services within the index hospitalization were considered part of the same hospitalization episode and linked. If patients met inclusion criteria more than once during the study timeframe, we randomly selected one hospitalization for inclusion with a set seed to create a reproducible sample.

Outcomes and Measurements

The primary outcome was the proportion of patients who filled a sedative prescription (for any dose or duration) ≤7 days of hospital discharge. We used a 7-day window after discharge, as previously defined in similar studies, to relate prescriptions filled to the hospitalization. [4,5, 21,22] Secondary outcomes included the proportion of patients who filled: (1) a prescription for each specific sedative class ≤7 days of discharge; and (2) persistent sedative prescriptions ≤ 6 months of discharge. As previously described persistent sedative prescription was defined as the proportion of new sedative users who filled ≥1 additional prescription between day 8 and 180. [4,23]

We measured the following baseline patient characteristics at the index date: age (grouped as ≤69, 70-74, 75-79, 80-84, ≥85 years), sex, neighborhood-level median income quintiles (proxy for socioeconomic status), patient location before hospitalization (e.g., long-term care, rural vs. urban), patient type (surgical vs. medical), and Deyo-adapted Charlson Comorbidity Index (CCI)[24] based on a 3-year lookback window (CCI 0, 1-2, ≥3). The Johns Hopkins Adjusted Clinical

Groups (ACG®) system frailty marker version 10 was applied to identify frailty as a binary measure based on data available two years before the index hospitalization.[25] In the 6-month pre-hospitalization window, we measured prescriptions filled for opioids, antidepressants, and the number of unique drug names (polypharmacy was defined as ≥ 9 unique drug names).[26] We determined the following hospital characteristics: type (academic vs. community), location (urban vs. rural), and specific hospital identification code to account for clustering within hospitals. If more than one acute care hospital contributed to the hospitalization episode, we used the discharge hospital characteristics. We determined the following in-hospital events, exposures, and outcomes (see eTable 4 for definitions): acute kidney injury, dialysis, mechanical ventilation, receipt of geriatric, palliative, or psychiatry consultation, sepsis/septic shock, ICU and hospital LOS, and discharge disposition. For each prescription, we determined the dose, quantity, days of supply, and dispensing date.

Statistical analyses

We summarized baseline characteristics using proportions, means and standard deviation (SD) or medians, and interquartile range (IQR as appropriate. We compared characteristics of those who filled a new sedative prescription ≤7 days of discharge to those who did not, reporting standardized mean differences (SMD) with an absolute value of <0.1 indicating balance.[27]

To facilitate comparisons and calculation of mean daily dose, we converted prescribed quantities of benzodiazepines to lorazepam equivalents and antipsychotics to haloperidol

equivalents; non-benzodiazepine sedatives were treated as individual entities.[28] If a patient filled multiple prescriptions for a sedative drug class within the initial 7-day window, we selected the first fill date only to calculate initial days supplied and mean daily dose. If a patient filled multiple prescriptions for the same drug class on the same day (e.g., lorazepam 1 mg and clonazepam 0.5 mg) we calculated the total dose by summing all, taking into consideration conversion equivalence factors. We calculated the mean daily dose from the total prescribed dose divided by total days supplied.

We examined the associations between patient and institution characteristics and primary outcome using multivariable, multilevel logistic regression[29], adjusting for clustering of patients within hospitals with a random intercept term for hospital. We restricted the analysis to hospitals that contributed ≥50 patients to the study cohort to more precisely estimate the cluster random intercepts and variance.[30] The following factors were selected a priori based on published evidence and clinical importance: age, sex, neighbourhood income quintile, rural residency, frailty, CCI, pre-hospital exposure to opioids or antidepressants, polypharmacy, surgical status, receipt of consultation geriatric, psychiatry or palliative services, sepsis, dialysis, invasive mechanical ventilation, ICU length of stay, discharge destination, and hospital characteristics. We included year of discharge as a continuous variable to account for possible linear time trends. We quantified variation between hospitals using the adjusted median odds ratio (aMOR).[31] For model assumptions, we examined random effects distribution for normality. We repeated the analysis for each sedative drug class (secondary outcomes) using the same modeling approach.

We examined the association between baseline measures and time to meeting the definition of a persistent sedative prescription with a multivariable proportional hazards model accounting for the competing risks of rehospitalization and death, with censoring at 180 days.[32] We reported estimates of the associations as adjusted sub-distribution hazard ratios (sHR) with 95% confidence intervals (CI). We repeated this model with the cohort restricted to only those patients who filled a new sedative ≤7 days of discharge to allow examination of initially filled sedative class effect. We examined Schoenfeld residuals to assess model assumptions.[33]

We performed all analyses in SAS Enterprise Guide version 7.15 (SAS Institute, Inc., Cary, NC, USA) at ICES. All tests were two-sided; we considered a p-value <0.05 statistically significant.

RESULTS

Cohort characteristics

250,428 sedative-naïve older adults met inclusion criteria (Figure 1). Mean age was 75.8 years (SD 6.9); 61.0% were male; most (85.5%) were community-dwelling on admission, and 8.3% were frail (Table 1). During hospitalization, 63.6% had surgery, 26.3% received invasive mechanical ventilation, and 14.8% had sepsis (Table 2).

Primary and secondary outcomes

Of the study cohort, 15,277 (6.1%) filled at a sedative prescription ≤7 days from hospital discharge. The median time from discharge to prescription fill was 0 days (IQR 0-3). Benzodiazepines were the predominate sedative class filled: 8824 (3.5%) filled a benzodiazepine, 2749 (1.1%) non-benzodiazepine, 2745 (1.1%) antipsychotic, and 959 (0.4%) filled multiple sedative classes. There was variation in the proportion of patients filling a new sedative across discharge hospitals (153 hospitals), ranging from 2.1% (95% CI 1.2-2.8) to 44.0% (95% CI 3.0-57.8) (Figure 2). The initial days supply dispensed varied between a median of 19 days to 30 days, depending on the sedative class (eTable 5).

Compared to patients who did not fill a new sedative, those who did had more comorbidity burden (38.6% with ≥3 CCI vs 31.7%, SMD 0.14), frailty (12.9% vs 8.0%, SMD 0.16), sepsis (25.9% vs. 14.1%, SMD 0.30), acute kidney injury (13.2% vs. 8.2%, SMD 0.16), invasive mechanical ventilation (35.6% vs. 25.6%, SMD 0.22), and days in ICU and hospital (Table 1 & 2). Of those receiving a new sedative prescription, 8,458 (55%) met the definition of persistent sedative prescription. The median time to fill the first persistent prescription was 26 days after discharge (IQR 14, 41). Patients with persistent prescriptions filled a median of 2 prescriptions (IQR 1,3) in the 8 to 180-day window.

Factors associated with a new sedative prescription

Factors associated with filling a new sedative prescription are presented in Figure 3 (eTable 6, eFigure 1 for model assumptions). Discharge to a long-term care facility (compared to discharge to the community, adjusted OR (aOR) 4.00, 95% CI 3.72-4.31, receipt of inpatient geriatric (aOR 1.95, 95% CI 1.80-2.10) or psychiatry (aOR 2.76, 95% CI 2.62-2.91) services, invasive mechanical ventilation (aOR 1.59, 95% CI 1.53-1.66), and ICU LOS stay ≥7 days (aOR 1.50, 95% CI 1.42-1.58) were associated with new prescription. Discharge from a community hospital (vs. academic) (aOR 1.40, 95% CI 1.16-1.70) or a hospital in a rural location (vs. urban) (aOR 1.67, 95% CI 1.36-2.05) were also associated with new sedative prescriptions. The residual heterogeneity between hospitals was aMOR 1.43, 95% CI 1.35-1.49 (the reciprocal of this aMOR is 1/1.430 =0.70). All other patient-level characteristics had an aOR between 0.70 and 1.43. For example, patients with pre-existing polypharmacy (aOR 0.91, 95% CI 0.88-0.95) and those with advanced age were less likely to fill a new sedative prescription, especially those 80-84 years (aOR 0.87, 95% CI 0.83-0.93) or ≥ 85 years of age (aOR 0.88, 0.83-0.94). Frailty and sex were independently associated with the type of sedative class prescribed (eTable 7).

Factors associated with persistent sedative prescriptions

Factors associated with persistent sedative prescriptions are presented in Figure 4 (eTable 8, eFigure 2 for model assumptions). Discharge to a long-term care facility (vs. community) was associated with persistent prescriptions (sHR 4.45, 95% CI 4.08-4.87). Female sex was associated with persistent prescriptions (sHR 1.07, 95% CI 1.02-1.13); patients with pre-existing polypharmacy were less likely to fill persistent prescriptions (sHR 0.88, 95% CI 0.84-0.93). Those who filled an antipsychotic (sHR 1.45, 95% CI 1.35-1.56), a non-benzodiazepine (sHR 1.44, 955

CI 1.34-1.53), or more than one sedative class (sHR 2.16, 95% CI 1.97-2.37) (eTable 8) were more likely to fill persistent sedative prescriptions compared to those who filled a benzodiazepine alone as their first sedative.

DISCUSSION

In this population-based cohort study of sedative-naïve older adult ICU survivors, 6.1% filled a new sedative prescription within 7 days of hospital discharge, and more than half of these continued to fill sedative prescriptions in the subsequent 6 months. Factors associated with new and persistent sedative prescriptions included discharge destination, markers of critical illness severity, pre-existing comorbidities, and the drug class prescribed. However, we also identified substantial variation between sites, even after adjusting for other factors, suggesting that hospital-level interventions may represent a target for quality improvement.

These findings support the need for careful medication review prior to discharge given that 1 in 15 sedative-naive older adult ICU survivors filled a sedative prescription on discharge and sedatives are considered potentially inappropriate in community-dwelling older adults. Our data suggest prescribing practices need further reform given that prescriptions were for substantial dose and duration, similar to historical reports.[4,5,8] To determine associations with new or persistent sedative prescription on hospital discharge, we evaluated an extensive list of factors known to be associated with ICU sedative use.[1,2] As hypothesized, patients with a high burden of comorbidities and critical illness severity, for example, those with extended ICU stay,

sepsis, and mechanical ventilation, had higher odds of filling a new sedative and persistent prescriptions on discharge. Many ICU patients have heavy sedative exposure during critical illness, and it is plausible these newly initiated sedatives intended for short-term use are continued as oversight as patients transition out of ICU. However, it is also possible that sedative continuation is not an oversight; rather, some patients have continued indications or sequalae from their critical illness that require ongoing sedative intervention. Sleep disturbances and delirium can persist after critical illness. Furthermore, new-onset mental health conditions such as depression and anxiety are common in ICU survivors and are plausible explanations for sedative use after hospitalization.[3,34-37] We found discharge to long-term care had the strongest association with new and persistent sedative prescriptions. Survivors of critical illness are known to have prolonged cognitive dysfunction characterized by new or exacerbations of pre-existing deficits in global cognition or executive functioning, especially those with delirium, potentially explaining this finding and the association with psychiatric and geriatric service consultations.[35,38,39] Post-ICU recovery services may offer an appropriate time to address medication management including deprescribing and tapering medications when no longer indicated. However, these resources are limited and not routinely available, particularly in the Canadian context.[40-42] Of note, we found controlling for time trends in our models was important, especially for benzodiazepines. This time trend might have been influenced by ICU sedation guidelines or other safety bodies that advocate for the avoidance of benzodiazepines in recent years. [1,43,44,8]

We found the discharge hospital was more strongly associated with a new prescription than many markers of illness severity or comorbidity, with substantial variation across hospitals. In the US, Coe and colleagues demonstrated in older adults hospital-level variation for new antipsychotic prescriptions following discharge despite adjustment for mental health diagnoses.[23] Similar variation in new antipsychotic prescription after discharge was found in a US study of older adults following cardiac surgery, with those at higher prescribing hospitals more likely to receive an antipsychotic on discharge and for a longer duration.[45] These findings and ours raise concerns that institutional prescribing practices can influence discharge sedative use, implying there could be modifiable prescribing practices that could be targeted . Interventions could include re-evaluation of paper or electronic prescription standard order sets and stewardship programs to assess drug selection, duration, de-escalation, or tapering as patients transition out of ICU and on hospital discharge.[46] As part of sedative medication reconciliation, inclusion of information on the indication, planned duration of therapy, and tapering plan would be important for ICU patients, families, and the clinical team to communicate with primary care physicians and pharmacists who support post-ICU recovery.[47] This information would alleviate ambiguity of the therapeutic plan and support prescription reassessment in the community as patients recover.[48] While medication reconciliation has demonstrated positive results in general studies,[47,49] there is a need to closely examine the resources and quality that may vary between institutions to optimize it in relation to sedatives post-ICU.

One strength of our study is the use of large contemporary diverse population-based data to examine rates of new and persistent sedative use. We broadly defined a 'sedative' to allow for the interplay of drugs commonly used for sedation or delirium management and to include benzodiazepine alternatives, as endorsed by international practice guidelines.[1] We also used analytical methods that considered clustering within hospitals to account for site-specific prescribing practices. The most important limitation is that in-hospital prescription data were not available and therefore, we cannot directly link the post-discharge prescription to specific sedative exposure during the ICU admission. It is plausible some of these outpatient prescriptions were initiated after hospital discharge and do not represent a continuation of in-hospital therapy. However, we anticipate this scenario is less likely based on observational studies that have demonstrated very high sedative and antipsychotic exposure within the ICU that is continued on discharge in up to 40% of patients.[50-52] We were also unable to establish the clinical indication or appropriateness of the sedative prescription and thus it is not possible to determine if these prescriptions were clinically indicated as part of post-ICU recovery management or continued as an oversight. Unmeasured confounders could account for the high median odds ratio (e.g., site-specific ICU characteristics, medication review processes) that we cannot adjust for in our models. We also note limited international research to provide global context for our findings. The prescribing patterns we identified may differ for other settings where ICU sedation practices rely less on benzodiazepines or where there are regulatory rules that restrict outpatient prescribing of sedatives.

INTERPRETATION

Our study demonstrates a clinically important incidence of new sedative use after hospitalization for older adult sedative-naïve ICU survivors. Half of these patients proceeded to persistent prescriptions. The wide variability in sedative prescription by hospital and the impact of systemic variation on the odds of new sedative use suggests potentially modifiable prescribing practices. Such modifications could include sedation stewardship and targeted discharge medication review with collaborative care pathways involving community-based physicians and pharmacists who can reassess the continued sedative needs after critical illness. Detailed review of sedative pharmacotherapy after an ICU admission can enhance post-discharge pharmacotherapy regimens and communication for survivors, their families and multiple care teams to support recovery. Given the many critically ill patients discharged every year, even small changes in prescribing practices may yield large benefits across a healthcare system.

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