



King's Research Portal

DOI:

[10.1016/j.chest.2022.12.033](https://doi.org/10.1016/j.chest.2022.12.033)

Document Version

Peer reviewed version

[Link to publication record in King's Research Portal](#)

Citation for published version (APA):

Burry, L. D., Bell, C. M., Hill, A., Pinto, R., Scales, D. C., Bronskill, S. E., Williamson, D., Rose, L., Fu, L., Fowler, R., Martin, C. M., Dolovich, L., & Wunsch, H. (2023). New and Persistent Sedative Prescriptions Among Older Adults Following a Critical Illness: A Population-Based Cohort Study. *Chest*, 163(6), 1425-1436. <https://doi.org/10.1016/j.chest.2022.12.033>

Citing this paper

Please note that where the full-text provided on King's Research Portal is the Author Accepted Manuscript or Post-Print version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version for pagination, volume/issue, and date of publication details. And where the final published version is provided on the Research Portal, if citing you are again advised to check the publisher's website for any subsequent corrections.

General rights

Copyright and moral rights for the publications made accessible in the Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognize and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the Research Portal

Take down policy

If you believe that this document breaches copyright please contact librarypure@kcl.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.

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

3 **Running head:** Sedative use among older adults after critical illness

4 Lisa D. Burry, PharmD, FCCP Department of Pharmacy and Medicine, Sinai Health System; Leslie Dan
5 Faculty of Pharmacy and Interdepartmental Division of Critical Care, University of Toronto, Toronto, ON,
6 Canada

7
8 Chaim M. Bell, MD, Ph.D., Department of Medicine, Sinai Health System; Departments of Medicine and
9 Health Policy, Management, and Evaluation, University of Toronto, Toronto, ON, Canada

10
11 Andrea Hill, Ph.D., Department of Critical Care Medicine, Sunnybrook Health Sciences Centre;
12 Sunnybrook Research Institute, Toronto, ON, Canada

13
14 Ruxandra Pinto, Ph.D., Department of Critical Care Medicine, Sunnybrook Health Sciences Centre,
15 Toronto, ON, Canada

16
17 Damon C. Scales MD Ph.D., Department of Critical Care Medicine, Sunnybrook Health Sciences Centre;
18 Interdepartmental Division of Critical Care, University of Toronto; ICES, Toronto, ON, Canada

19
20 Susan E. Bronskill Ph.D., ICES; Institute of Health Policy, Management and Evaluation, Dalla Lana School
21 of Public Health, University of Toronto; Sunnybrook Research Institute, Toronto, ON, Canada

22
23 David Williamson, Ph.D., Faculté de Pharmacie, Université de Montréal; Pharmacy department, Hôpital
24 du Sacré-Cœur de Montréal; and Research center, CIUSSS du Nord-de-l'Île-de-Montréal, PQ, Canada

25
26 Louise Rose, Ph.D., Florence Nightingale Faculty of Nursing, Midwifery and Palliative Care, King's College
27 London, London, UK

28
29 Longdi Fu, MSc, ICES, Toronto, ON, Canada

30
31 Robert Fowler MD MSc, Department of Critical Care Medicine, Sunnybrook Health Sciences Centre;
32 Interdepartmental Division of Critical Care, University of Toronto; ICES, Toronto, ON, Canada

33
34 Claudio M. Martin, MD, Division of Critical Care, Department of Medicine, Schulich School of Medicine
35 and Dentistry, Western University, and Lawson Health Research Institute, London, ON, Canada. ORCID
36 0000-0003-3971-3166

37
38 Lisa Dolovich, PharmD MSc Leslie Dan Faculty of Pharmacy University of Toronto, Toronto, ON, Canada.
39 ORCID 0000-0002-0061-6783

40
41 Hannah Wunsch, MD, MSc Department of Critical Care Medicine, Sunnybrook Health Sciences Centre;
42 Department of Anesthesiology and Pain Medicine and Interdepartmental Division of Critical Care,
43 University of Toronto; ICES, Toronto, ON, Canada

44

45

46 **CORRESPONDENCE TO:**
47 Dr. Lisa Burry
48 Department of Pharmacy, Room 18-377e, Mount Sinai Hospital
49 600 University Avenue, Toronto, ON, M5G 1X5, Canada
50 email: lisa.burry@sinaihealth.ca
51 ORCID orcid.org/0000-0002-6545-3890

52	Manuscript summary:
53	Word count:
54	Abstract: 300
55	Text: 3159
56	Take home message: 95
57	References: 52
58	Tables: 2
59	Figures: 4
60	Supplement
61	

62 **ACKNOWLEDGEMENTS**

63

64 As a prescribed entity under Ontario’s privacy legislation, ICES is authorized to collect and use health
65 care data for the purposes of health system analysis, evaluation, and decision support. Secure access to
66 these data is governed by policies and procedures that are approved by the Information and Privacy
67 Commissioner of Ontario. Parts of this material are based on data and/or information compiled and
68 provided by CIHI. However, the analyses, conclusions, opinions, and statements expressed in the
69 material are those of the author(s), and not necessarily those of CIHI. We thank IQVIA Solutions Canada
70 Inc. for use of their Drug Information File.

71

72 **Author contributions:**

- 73 • Access to full data and responsibility for data integrity (LB, LF)
- 74 • Accuracy of the data analyses (LB, AH, RP)
- 75 • Study conception and design (all)
- 76 • Statistical plan (LB, RP, HW, CB, SB, DS)
- 77 • Data interpretation (all)
- 78 • Draft manuscript (LB)
- 79 • All authors read and approved the final version.
- 80 • Guarantor (LB)

81

82 **FUNDING**

83 This study was supported by ICES, which is funded by an annual grant from the Ontario Ministry of
84 Health (MOH) and the Ministry of Long-Term Care (MLTC). Funding was also provided by the Canadian
85 Institutes of Health Research (Grant no. # 159696). The analyses, conclusions, opinions, and statements
86 expressed herein are solely those of the authors and do not reflect those of the funding or data sources;
87 no endorsement is intended or should be inferred.

88 **DISCLOSURES**

89 HW is supported by a Canada Research Chair [Tier 2] in Critical Care Organization and Outcomes. HS, DS,
90 RF, and LB hold grants from the Canadian Institute for Health Research. The remaining authors have
91 disclosed that they do not have any conflicts of interest to declare.

92 **Take-Home Points:**

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

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

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

101 **ABSTRACT**

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

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

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

114 **Results:** 250,428 patients were included (mean age 76, 61% male). 15,277 (6.1%) filled a new
115 sedative prescription with variation across hospitals (2% (95% CI 1-3) to 44% (3-57)); 8,458
116 (3.4%) filled persistent sedative prescriptions. Adjusted factors associated with a new sedative
117 included: discharge to long-term care facility (aOR 4.00, 3.72-4.31); receipt of inpatient geriatric
118 (aOR 1.95, 1.80-2.10) or psychiatry (aOR 2.76, 2.62-2.91) consultation, invasive ventilation (aOR
119 1.59, 1.53-1.66), and ICU length of stay ≥ 7 days (aOR 1.50, 1.42-1.58). The residual
120 heterogeneity between hospitals (aMOR 1.43, 1.35-1.49) had a stronger association with new
121 sedative prescriptions than Charlson comorbidity score or sepsis. Factors associated with

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

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

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

130 **Abbreviations:**

131 ACG = John Hopkins Adjusted Clinical Groups system frailty marker

132 aOR = Adjusted odds ratio

133 CCI = Charlson Comorbidity Index

134 CI = 95% confidence intervals

135 ICU = intensive care unit

136 IQR = interquartile range

137 LOS = length of stay

138 SD = standard deviation

139 SMD = standard mean difference

140 sHR = subdistribution hazard ratios

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

152

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

159

160 **STUDY DESIGN and METHODS**

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

171

172 ***Data sources***

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

179

180 ***Cohort creation***

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

192

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

202

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

207

208 ***Outcomes and Measurements***

209 The primary outcome was the proportion of patients who filled a sedative prescription (for any
210 dose or duration) ≤ 7 days of hospital discharge. We used a 7-day window after discharge, as
211 previously defined in similar studies, to relate prescriptions filled to the hospitalization.^{4,5, 21,22}

212 Secondary outcomes included the proportion of patients who filled: (1) a prescription for each
213 specific sedative class ≤ 7 days of discharge; and (2) persistent sedative prescriptions ≤ 6 months
214 of discharge. As previously described persistent sedative prescription was defined as the
215 proportion of new sedative users who filled ≥ 1 additional prescription between day 8 and 180.
216^{4,23}

217

218 We measured the following baseline patient characteristics at the index date: age (grouped as
219 ≤ 69 , 70-74, 75-79, 80-84, ≥ 85 years), sex, neighborhood-level median income quintiles (proxy
220 for socioeconomic status), patient location before hospitalization (e.g., long-term care, rural vs.
221 urban), patient type (surgical vs. medical), and Deyo-adapted Charlson Comorbidity Index
222 (CCI)²⁴ based on a 3-year lookback window (CCI 0, 1-2, ≥ 3). The Johns Hopkins Adjusted Clinical

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

235

236 ***Statistical analyses***

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

241

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

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

251

252 We examined the associations between patient and institution characteristics and primary
253 outcome using multivariable, multilevel logistic regression²⁹, adjusting for clustering of patients
254 within hospitals with a random intercept term for hospital. We restricted the analysis to
255 hospitals that contributed ≥ 50 patients to the study cohort to more precisely estimate the
256 cluster random intercepts and variance.³⁰ The following factors were selected a priori based on
257 published evidence and clinical importance: age, sex, neighbourhood income quintile, rural
258 residency, frailty, CCI, pre-hospital exposure to opioids or antidepressants, polypharmacy,
259 surgical status, receipt of consultation geriatric, psychiatry or palliative services, sepsis, dialysis,
260 invasive mechanical ventilation, ICU length of stay, discharge destination, and hospital
261 characteristics. We included year of discharge as a continuous variable to account for possible
262 linear time trends. We quantified variation between hospitals using the adjusted median odds
263 ratio (aMOR).³¹ For model assumptions, we examined random effects distribution for
264 normality. We repeated the analysis for each sedative drug class (secondary outcomes) using
265 the same modeling approach.

266

267 We examined the association between baseline measures and time to meeting the definition of
268 a persistent sedative prescription with a multivariable proportional hazards model accounting
269 for the competing risks of rehospitalization and death, with censoring at 180 days.³² We
270 reported estimates of the associations as adjusted sub-distribution hazard ratios (sHR) with
271 95% confidence intervals (CI). We repeated this model with the cohort restricted to only those
272 patients who filled a new sedative ≤ 7 days of discharge to allow examination of initially filled
273 sedative class effect. We examined Schoenfeld residuals to assess model assumptions.³³

274

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

277

278 **RESULTS**

279 ***Cohort characteristics***

280 250,428 sedative-naïve older adults met inclusion criteria (Figure 1). Mean age was 75.8 years
281 (SD 6.9); 61.0% were male; most (85.5%) were community-dwelling on admission, and 8.3%
282 were frail (Table 1). During hospitalization, 63.6% had surgery, 26.3% received invasive
283 mechanical ventilation, and 14.8% had sepsis (Table 2).

284

285 ***Primary and secondary outcomes***

286 Of the study cohort, 15,277 (6.1%) filled at a sedative prescription ≤ 7 days from hospital
287 discharge. The median time from discharge to prescription fill was 0 days (IQR 0-3).
288 Benzodiazepines were the predominate sedative class filled: 8824 (3.5%) filled a
289 benzodiazepine, 2749 (1.1%) non-benzodiazepine, 2745 (1.1%) antipsychotic, and 959 (0.4%)
290 filled multiple sedative classes. There was variation in the proportion of patients filling a new
291 sedative across discharge hospitals (153 hospitals), ranging from 2.1% (95% CI 1.2-2.8) to 44.0%
292 (95% CI 3.0-57.8) (Figure 2). The initial days supply dispensed varied between a median of 19
293 days to 30 days, depending on the sedative class (eTable 5).

294

295 Compared to patients who did not fill a new sedative, those who did had more comorbidity
296 burden (38.6% with ≥ 3 CCI vs 31.7%, SMD 0.14), frailty (12.9% vs 8.0%, SMD 0.16), sepsis
297 (25.9% vs. 14.1%, SMD 0.30), acute kidney injury (13.2% vs. 8.2%, SMD 0.16), invasive
298 mechanical ventilation (35.6% vs. 25.6%, SMD 0.22), and days in ICU and hospital (Table 1 & 2).
299 Of those receiving a new sedative prescription, 8,458 (55%) met the definition of persistent
300 sedative prescription. The median time to fill the first persistent prescription was 26 days after
301 discharge (IQR 14, 41). Patients with persistent prescriptions filled a median of 2 prescriptions
302 (IQR 1,3) in the 8 to 180-day window.

303

304 ***Factors associated with a new sedative prescription***

305 Factors associated with filling a new sedative prescription are presented in Figure 3 (eTable 6,
306 eFigure 1 for model assumptions). Discharge to a long-term care facility (compared to discharge
307 to the community, adjusted OR (aOR) 4.00, 95% CI 3.72-4.31, receipt of inpatient geriatric (aOR
308 1.95, 95% CI 1.80-2.10) or psychiatry (aOR 2.76, 95% CI 2.62-2.91) services, invasive mechanical
309 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)
310 were associated with new prescription. Discharge from a community hospital (vs. academic)
311 (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-
312 2.05) were also associated with new sedative prescriptions. The residual heterogeneity
313 between hospitals was aMOR 1.43, 95% CI 1.35-1.49 (the reciprocal of this aMOR is $1/1.430$
314 $=0.70$). All other patient-level characteristics had an aOR between 0.70 and 1.43. For example,
315 patients with pre-existing polypharmacy (aOR 0.91, 95% CI 0.88-0.95) and those with advanced
316 age were less likely to fill a new sedative prescription, especially those 80-84 years (aOR 0.87,
317 95% CI 0.83-0.93) or ≥ 85 years of age (aOR 0.88, 0.83-0.94). Frailty and sex were independently
318 associated with the type of sedative class prescribed (eTable 7).

319

320 ***Factors associated with persistent sedative prescriptions***

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

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

330

331 **DISCUSSION**

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

339

340 These findings support the need for careful medication review prior to discharge given that 1 in
341 15 sedative-naïve older adult ICU survivors filled a sedative prescription on discharge and
342 sedatives are considered potentially inappropriate in community-dwelling older adults. Our
343 data suggest prescribing practices need further reform given that prescriptions were for
344 substantial dose and duration, similar to historical reports.^{4,5,8} To determine associations with
345 new or persistent sedative prescription on hospital discharge, we evaluated an extensive list of
346 factors known to be associated with ICU sedative use.^{1,2} As hypothesized, patients with a high
347 burden of comorbidities and critical illness severity, for example, those with extended ICU stay,

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

368

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

389

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

410

411 **INTERPRETATION**

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

424 REFERENCES

- 425 1. Devlin JW, Skrobik Y, Gelinas C, et al. Clinical Practice Guidelines for the Prevention and
426 Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult
427 Patients in the ICU. *Crit Care Med*. 2018;46(9):e825-e873.
- 428 2. Burry LD, Williamson DR, Perreault MM, et al. Analgesic, sedative, antipsychotic, and
429 neuromuscular blocker use in Canadian intensive care units: a prospective, multicentre,
430 observational study. *Can J Anaesth*. 2014;61(7):619-630.
- 431 3. Brown SM, Bose S, Banner-Goodspeed V, et al. Approaches to Addressing Post-Intensive Care
432 Syndrome among Intensive Care Unit Survivors. A Narrative Review. *Annals of the American
433 Thoracic Society*. 2019;16(8):947-956.
- 434 4. Bell CM, Fischer HD, Gill SS, et al. Initiation of benzodiazepines in the elderly after
435 hospitalization. *J Gen Intern Med*. 2007;22(7):1024-1029.
- 436 5. Scales DC, Fischer HD, Li P, et al. Unintentional Continuation of Medications Intended for Acute
437 Illness After Hospital Discharge: A Population-Based Cohort Study. *J Gen Intern Med*.
438 2016;31(2):196-202.
- 439 6. Finkle WD, Der JS, Greenland S, et al. Risk of fractures requiring hospitalization after an initial
440 prescription for zolpidem, alprazolam, lorazepam, or diazepam in older adults. *J Am Geriatr Soc*.
441 2011;59(10):1883-1890.
- 442 7. Maust DT, Kim HM, Seyfried LS, et al. Antipsychotics, other psychotropics, and the risk of death
443 in patients with dementia: number needed to harm. *JAMA Psychiatry*. 2015;72(5):438-445.
- 444 8. American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate
445 Medication Use in Older Adults. *J Am Geriatr Soc*. 2015;63(11):2227-2246.
- 446 9. Canada S. Population estimates, quarterly. 2022;
447 <https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1710000901>. Accessed June 30, 2022,
448 2022.
- 449 10. Benchimol EI, Smeeth L, Guttmann A, et al. The REporting of studies Conducted using
450 Observational Routinely-collected health Data (RECORD) statement. *PLoS Med*.
451 2015;12(10):e1001885.
- 452 11. Gibson D RH, Chapman A. The National Ambulatory Care Reporting System: factors that affect
453 the quality of its emergency data. *International Journal of Information Quality*. 2008;2(2):97-
454 114.
- 455 12. Hux J, Naylor C, Fielding D. The Ontario Drug Benefit Program copayment: its impact on access
456 for Ontario seniors and charges to the program. *Institute for Evaluative Sciences*. 1997.
- 457 13. Jha P, Deboer D, Sykora K, Naylor CD. Characteristics and mortality outcomes of thrombolysis
458 trial participants and nonparticipants: a population-based comparison. *J Am Coll Cardiol*.
459 1996;27(6):1335-1342.
- 460 14. Juurlink D PC, Croxford R, Chong A, Austin P, Tu J, Laupacis A. *Canadian Institute for Health
461 Information Discharge Abstract Database: A Validation Study*. . Toronto, Institute for Clinical
462 Evaluative Sciences.;2006.
- 463 15. Levy AR, O'Brien BJ, Sellors C, Grootendorst P, Willison D. Coding accuracy of administrative
464 drug claims in the Ontario Drug Benefit database. *Can J Clin Pharmacol*. 2003;10(2):67-71.
- 465 16. Naylor CD AG, Goel V. *Patterns of health care in Ontario*.: Toronto: Institute for Clinical
466 Evaluative Sciences;1994.
- 467 17. Raina P, Torrance-Rynard V, Wong M, Woodward C. Agreement between Self-reported and
468 Routinely Collected Health-care Utilization Data among Seniors. *Health Services Research*.
469 2002;37(3):751-774.
- 470 18. Williams JI YW. A summary of studies on the quality of health care

- 471 administrative databases in Canada. In: Association OCM, ed. In: *Goel V, Williams JI, Anderson GM,*
472 *Blackerstein-Hersch P, Fooks C, Naylor CD.* Vol 2nd1996:339–345.
- 473 19. Garland A, Yogendran M, Olafson K, Scales DC, McGowan KL, Fransoo R. The accuracy of
474 administrative data for identifying the presence and timing of admission to intensive care units
475 in a Canadian province. *Med Care.* 2012;50(3):e1-6.
- 476 20. Scales DC, Guan J, Martin CM, Redelmeier DA. Administrative data accurately identified
477 intensive care unit admissions in Ontario. *J Clin Epidemiol.* 2006;59(8):802-807.
- 478 21. Wunsch H, Hill AD, Fu L, et al. New Opioid Use after Invasive Mechanical Ventilation and
479 Hospital Discharge. *Am J Respir Crit Care Med.* 2020;202(4):568-575.
- 480 22. Jackevicius CA, Mamdani M, Tu JV. Adherence with statin therapy in elderly patients with and
481 without acute coronary syndromes. *JAMA.* 2002;288(4):462-467.
- 482 23. Coe AB, Vincent BM, Iwashyna TJ. Statin discontinuation and new antipsychotic use after an
483 acute hospital stay vary by hospital. *PLoS One.* 2020;15(5):e0232707.
- 484 24. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM
485 administrative databases. *J Clin Epidemiol.* 1992;45(6):613-619.
- 486 25. Abrams C LR, Weiner J. *Development and evaluation of the Johns Hopkins University risk*
487 *adjustment models for Medicare+choice plan payment.* Baltimore, MD: John Hopkins University
488 Press; 2003.
- 489 26. O'Dwyer M, Peklar J, McCallion P, McCarron M, Henman MC. Factors associated with
490 polypharmacy and excessive polypharmacy in older people with intellectual disability differ from
491 the general population: a cross-sectional observational nationwide study. *BMJ Open.*
492 2016;6(4):e010505.
- 493 27. Austin PC. Using the Standardized Difference to Compare the Prevalence of a Binary Variable
494 Between Two Groups in Observational Research. *Communications in Statistics - Simulation and*
495 *Computation.* 2009;38(6):1228-1234.
- 496 28. *Clinical Handbook of Psychotropic Drugs.* 24th ed: Hogrefe Publishing.; 2021.
- 497 29. Austin PC, Merlo J. Intermediate and advanced topics in multilevel logistic regression analysis.
498 *Stat Med.* 2017;36(20):3257-3277.
- 499 30. Austin PC, Leckie G. The effect of number of clusters and cluster size on statistical power and
500 Type I error rates when testing random effects variance components in multilevel linear and
501 logistic regression models. *Journal of Statistical Computation and Simulation.* 2018;88(16):3151-
502 3163.
- 503 31. Merlo J, Chaix B, Ohlsson H, et al. A brief conceptual tutorial of multilevel analysis in social
504 epidemiology: using measures of clustering in multilevel logistic regression to investigate
505 contextual phenomena. *J Epidemiol Community Health.* 2006;60(4):290-297.
- 506 32. Austin PC, Fine JP. Practical recommendations for reporting Fine-Gray model analyses for
507 competing risk data. *Stat Med.* 2017;36(27):4391-4400.
- 508 33. Van Houwelingen H. Modelling Survival Data in Medical Research. D. Collett, Chapman & Hall,
509 London, 1994. No of pages: XVII + 347. Price: E19.99. ISBN 0-41 2-44890-4. *Statistics in Medicine.*
510 1995;14(9):1147-1148.
- 511 34. Burry L, Cook D, Herridge M, et al. Recall of ICU Stay in Patients Managed With a Sedation
512 Protocol or a Sedation Protocol With Daily Interruption. *Crit Care Med.* 2015;43(10):2180-2190.
- 513 35. Pandharipande PP, Girard TD, Jackson JC, et al. Long-Term Cognitive Impairment after Critical
514 Illness. *New England Journal of Medicine.* 2013;369(14):1306-1316.
- 515 36. Sivanathan L, Wunsch H, Vigod S, Hill A, Pinto R, Scales DC. Mental illness after admission to an
516 intensive care unit. *Intensive Care Medicine.* 2019;45(11):1550-1558.

517 37. Wunsch H, Christiansen CF, Johansen MB, et al. Psychiatric diagnoses and psychoactive
518 medication use among nonsurgical critically ill patients receiving mechanical ventilation. *JAMA*.
519 2014;311(11):1133-1142.

520 38. Ehlenbach WJ, Hough CL, Crane PK, et al. Association between acute care and critical illness
521 hospitalization and cognitive function in older adults. *JAMA*. 2010;303(8):763-770.

522 39. Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term Cognitive Impairment and Functional
523 Disability Among Survivors of Severe Sepsis. *JAMA*. 2010;304(16):1787.

524 40. Stollings JL, Caylor MM. Postintensive care syndrome and the role of a follow-up clinic. *Am J*
525 *Health Syst Pharm*. 2015;72(15):1315-1323.

526 41. Needham DM, Davidson J, Cohen H, et al. Improving long-term outcomes after discharge from
527 intensive care unit: report from a stakeholders' conference. *Crit Care Med*. 2012;40(2):502-509.

528 42. Sevin CM, Bloom SL, Jackson JC, Wang L, Ely EW, Stollings JL. Comprehensive care of ICU
529 survivors: Development and implementation of an ICU recovery center. *J Crit Care*. 2018;46:141-
530 148.

531 43. Pottie K, Thompson W, Davies S, et al. Deprescribing benzodiazepine receptor agonists:
532 Evidence-based clinical practice guideline. *Can Fam Physician*. 2018;64(5):339-351.

533 44. Conn DK, Hogan DB, Amdam L, et al. Canadian Guidelines on Benzodiazepine Receptor Agonist
534 Use Disorder Among Older Adults. *Canadian Geriatrics Journal*. 2020;23(1):116-122.

535 45. Kim DH, Mahesri M, Bateman BT, et al. Longitudinal Trends and Variation in Antipsychotic Use in
536 Older Adults After Cardiac Surgery. *J Am Geriatr Soc*. 2018;66(8):1491-1498.

537 46. Marshall J, Finn CA, Theodore AC. Impact of a clinical pharmacist-enforced intensive care unit
538 sedation protocol on duration of mechanical ventilation and hospital stay. *Crit Care Med*.
539 2008;36(2):427-433.

540 47. Pronovost P, Weast B, Schwarz M, et al. Medication reconciliation: a practical tool to reduce the
541 risk of medication errors. *J Crit Care*. 2003;18(4):201-205.

542 48. Martin P, Tamblyn R, Benedetti A, Ahmed S, Tannenbaum C. Effect of a Pharmacist-Led
543 Educational Intervention on Inappropriate Medication Prescriptions in Older Adults. *JAMA*.
544 2018;320(18):1889.

545 49. Feldman LS, Costa LL, Feroli ER, Jr., et al. Nurse-pharmacist collaboration on medication
546 reconciliation prevents potential harm. *J Hosp Med*. 2012;7(5):396-401.

547 50. Jasiak KD, Middleton EA, Camamo JM, Erstad BL, Snyder LS, Huckleberry YC. Evaluation of
548 discontinuation of atypical antipsychotics prescribed for ICU delirium. *J Pharm Pract*.
549 2013;26(3):253-256.

550 51. Phan SV, Lugin Y, Morgan K. Rates of new antipsychotic prescriptions and continuation at
551 discharge from a medical unit in a community teaching hospital serving rural counties. *Ment*
552 *Health Clin*. 2019;9(2):88-92.

553 52. Tomichek JE, Stollings JL, Pandharipande PP, Chandrasekhar R, Ely EW, Girard TD. Antipsychotic
554 prescribing patterns during and after critical illness: a prospective cohort study. *Critical Care*.
555 2016;20(1).

556