Journal of Critical Care 43 (2018) 102–107

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.jccjournal.org

Impact of restarting home neuropsychiatric medications on sedation outcomes in medical intensive care unit patients☆,☆☆

Mary K. La, PharmD [a], Melissa L. Thompson Bastin, PharmD, BCPS [b,c], Jenee T. Gisewhite, PharmD [d], Carrie A. Johnson, MD [e], Alexander H. Flannery, PharmD, BCCCP, BCPS [b,c,*]

[a] University of North Carolina Eshelman School of Pharmacy, Division of Practice Advancement and Clinical Education, Chapel Hill, NC, United States
[b] University of Kentucky HealthCare, Department of Pharmacy Services, 800 Rose Street, Room H110, Lexington, KY 40536, United States
[c] University of Kentucky College of Pharmacy, Department of Pharmacy Practice and Science, Lexington, KY, United States
[d] Beaumont Hospital – Royal Oak, Department of Pharmacy Services, Royal Oak, MI, United States
[e] Duke University, Raleigh, NC, United States

ARTICLE INFO

Keywords:
Sedation
Medication reconciliation
Antidepressants
Gabapentinoids
Benzodiazepines
Antipsychotics

ABSTRACT

Purpose: This single-center, retrospective cohort study investigated the effects of timing of initiating home neuropsychiatric medications (NPMs) on sedation-related outcomes.
Materials and methods: Subjects included adult medical intensive care unit (MICU) patients who had an NPM on their admission medication list; intubated before or on arrival to the intensive care unit (ICU); and were on benzodiazepine-based sedation. The intervention assessed was the timing of the initiation of home NPMs: early (≤5 days) vs. late (>5 days) into the ICU stay.
Results: There were 56 and 53 patients in the early and late restart groups, respectively. Early cohort patients maintained a median daily RASS of −1.5, while late cohort patients had a median daily RASS of −2.0 ($p = 0.02$). The effect was driven by the subgroup of patients on home anti-depressant therapy who were restarted early on these agents. The early restart group had a higher percentage of days with RASS scores within goal ($p = 0.01$) and less delirium ($p = 0.02$). Early restarting of home NPMs was associated with a non-significant decrease in ventilator days compared with late restarting ($p = 0.11$).
Conclusions: Restarting home NPMs was associated with lighter sedation levels and less delirium.

1. Introduction

Prolonged and deep sedation is associated with negative outcomes, including fewer ventilator-free days, prolonged hospital stay [1], cognitive deficits [2], and decreased in-hospital and two-year survival [3]. For these reasons, guidelines from the Society of Critical Care Medicine (SCCM) recommend to target light levels of sedation [4]. An unstudied strategy to facilitate light sedation includes a thorough medication history and reconciliation, particularly of the patient's neuropsychiatric medications[1] prior to admission. Nearly 17% of intensive care unit (ICU) patients have a selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI) on their admission medication lists [5]. Home NPMs may also include benzodiazepines (BZDs), antipsychotics, and gabapentinoids. These medications are associated with clinically significant withdrawal syndromes, which may become apparent within the first few days of abrupt discontinuation and could mimic or exacerbate agitation (Table 1) [6-9]. There is a lack of systematic, controlled studies evaluating NPM withdrawal and its management [10]. Reviews on the subject recommend reintroduction of the NPM or, if the withdrawal syndrome is severe, symptomatic management [11-13]. Increased agitation secondary to NPM withdrawal in the ICU may be treated with increasing doses of sedatives, while the underlying condition may be left untreated. Restarting home NPMs could avert withdrawal and more easily allow maintenance of light levels of sedation. While pharmacologic rationale exists to restart home NPMs in ICU patients, the concept is only alluded to once in the Pain, Agitation, Delirium (PAD) care bundle as a strategy for preventing delirium; however, this recommendation remains ungraded due to a lack of evidence and is not formally mentioned in the guideline text [4].

This study investigated the effects of timing of initiation of home NPMs on sedation outcomes in MICU patients. We hypothesized that

☆ Conflicts of Interest: No authors have any conflicts of interest to disclose.
☆☆ Funding: The project described was supported by the National Center for Advancing Translational Sciences, National Institutes of Health, through grant number UL1TR001998. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.
* Corresponding author at: University of Kentucky HealthCare, Department of Pharmacy Services, 800 Rose Street, Room H110, Lexington, KY 40536, United States.
E-mail addresses: mary_la@unc.edu (M.K. La), mlthompson@uky.edu (M.L. Thompson Bastin), jenee.gisewhite@beaumont.org (J.T. Gisewhite), carrie.a.johnson@duke.edu (C.A. Johnson), alex.flannery@uky.edu (A.H. Flannery).
[1] NPM – neuropsychiatric medication.

http://dx.doi.org/10.1016/j.jcrc.2017.07.046
0883-9441/

Table 1
Withdrawal syndromes of common neuropsychiatric medications.

Drug or drug class	Onset of withdrawal	Duration of withdrawal	Withdrawal signs and symptoms
Benzodiazepines [6,8]	Short-acting: 2–4 days Long-acting: 4–7 days	2 weeks (anxiety may persist)	**Agitation**, **anxiety**, irritability, **restlessness**, **sleep disturbances**, **hallucinations**, seizures, hypertension, tachycardia, tachypnea
Anti-psychotics [7]	1–4 days	1–2 weeks	**Agitation**, **anxiety**, **psychosis**, nausea, vomiting, **insomnia**, myalgia, tremor
SSRIs/SNRIs [9]	3 days	3 weeks	Flu-like symptoms, nausea, vomiting, diarrhea, **insomnia**, **nightmares**, **anxiety**, **agitation**, paresthesias, dizziness

Bolded signs and symptoms can be associated with exacerbation of agitation.

early restarting (≤5 days) of the majority (≥50%) of a patient's home NPM regimen would improve sedation scores and clinical outcomes compared with those patients not started on their home NPMs or restarted >5 days into the ICU stay.

2. Materials and methods

2.1. Patients

The present work is a single-center, retrospective cohort study evaluating two groups of medical intensive care (MICU) patients. The early restart cohort was defined as having the majority (≥50%) of their home NPMs restarted within the first 5 days of their ICU stay. The late restart cohort was either not restarted at all on their home NPMs, or restarted after 5 days of their ICU stay (Fig. 1). For example, if a patient was on 2 home NPMs and the first was restarted on day 3 and the second on day 6, that patient would be categorized in the early restart group since at least 50% of their home NPMs were restarted within the first 5 days of ICU admission. Restarting was defined as receiving >1 dose of the home NPM. The 5-day mark was selected because most clinically significant withdrawal syndromes could manifest within this time frame as shown in Table 1 [6-9].

Adult patients admitted to the University of Kentucky (UK) Albert B Chandler Hospital's MICU between January 2011 – January 2015 were included in the study if their documented home admission medication lists included at least one of the following: an anti-depressant (SSRI, SNRI, bupropion), gabapentinoid, benzodiazepine (BZD), or antipsychotic; if they were intubated prior to or on admission to the MICU, and were receiving BZD-based sedation while in the MICU. All included patients were admitted directly from the ED to the ICU, or were direct-to-ICU inter-institutional transfers. The list of home neuropsychiatric medications was selected based on the clinical opinions of the authors by the likelihood for withdrawal, frequency of encountering these medications on home medication lists, and the review by Papadopoulos and Cook [8]. BZD-based sedation was chosen as it was the preferred continuous infusion sedative during the study period at our institution and allows standardizing of sedative doses received.

While benzodiazepine infusions were the predominant sedative used upon admission, choice of sedative throughout the ICU stay and whether or not any home medications were restarted was up to the medical team caring for the patient. Sedation level was monitored using the Richmond Agitation-Sedation Scale (RASS). Patients were excluded for the following: deep sedation indicated for any reason (e.g. acute respiratory distress syndrome, receipt of a continuous infusion neuromuscular blocker, alcohol withdrawal treatment, status epilepticus), admission for suspected drug overdose, the NPM was explicitly stated to be indicated for a non-neuropsychiatric reason (e.g. lorazepam for nausea/vomiting), chronic ventilation prior to admission, or sustained severe anoxic brain injury. Patients also were excluded if they were declared comfort care within the first 7 days of their ICU stay, or were extubated, transferred out of the ICU, discharged, or expired <72 h within the ICU admission.

2.2. Outcomes and data collection

Data sources included the UK Center for Clinical and Translational Science Enterprise Data Trust and the UK HealthCare electronic health record. This study was approved by the Institutional Review Board of the University of Kentucky. Data points collected included patients' demographics, admission medication history, RASS, Confusion Assessment Method for the ICU (CAM-ICU), sedatives, new-start inpatient antipsychotics, ICU length of stay (LOS), and ventilator days. Data on sedation and delirium outcomes were collected during the first 7 days of the patient's ICU admission. Baseline disease severity was measured by the Sequential Organ Failure Assessment (SOFA) score on day 1 of ICU admission, and the Charlson comorbidity index [14,15]. The Charlson comorbidity index reflects baseline clinical illness status and can predict 1-year mortality. Both the SOFA score and Charlson indices give complementary views on the clinical status of the patient. Data collected on sedation agent regimens included BZD infusion rates and duration, PRN BZD use, and whether non-BZD sedatives were used.

The primary outcomes were median daily RASS score and percentage of days that the median daily RASS was maintained at −2 to +1. For all of the RASS scores recorded for a specific day for a given patient,

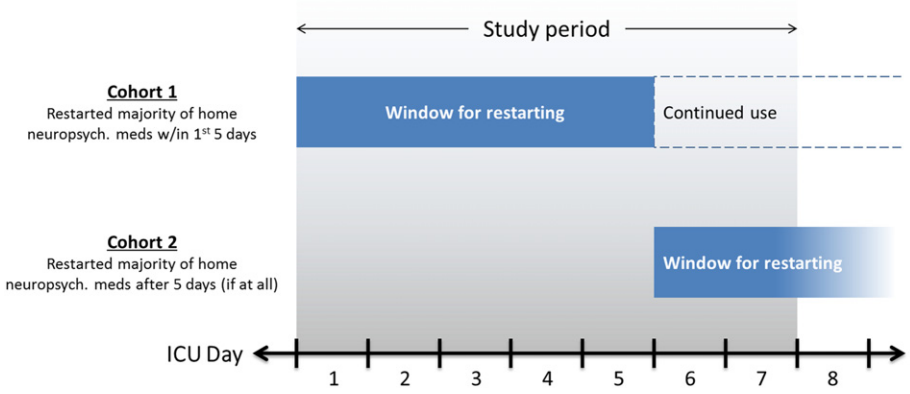

Fig. 1. Study overview.

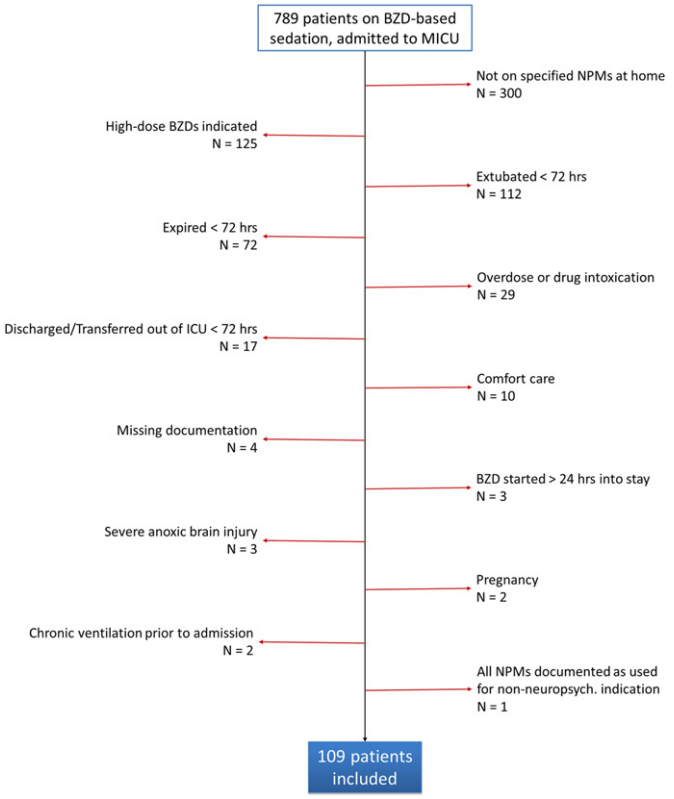

Fig. 2. Patient population screening results.

these scores were averaged, resulting in (at most) 7 daily average RASS scores. The median of these daily average RASS scores was then computed, providing an overall RASS score for the study period. To be considered within goal RASS for a specific day, the daily average RASS for that day would have to be between −2 and +1. The secondary outcomes included cumulative total daily dose (TDD) of BZD-based sedation during the first 7 days of the ICU stay, incidence of delirium using the CAM-ICU, rates of new-start antipsychotics, time on mechanical ventilation, and ICU LOS. A post-hoc analysis was undertaken to assess correlations between patient characteristics and cumulative amount of BZD sedation required.

2.3. Statistical analysis

The Shapiro-Wilk test was used to determine whether the continuous variable measurements were normally distributed. Student's *t*-test was used to evaluate for differences in continuous variables between cohorts. The Mann-Whitney *U* test analyzed continuous variables that were not normally distributed. The chi-squared or Fisher's exact test was used for nominal variables, and the Mann-Whitney *U* test for ordinal variables. Correlation testing was done with the Spearman rank-order correlation. SPSS (Version 23, Armonk, NY) and R (Version 3.3.1, Vienna, Austria) were used for statistical analyses.

3. Results

As shown in Fig. 2, 789 patients were admitted to the MICU on BZD-based sedation during the study period. Of those patients, 109 (13.8%) met inclusion criteria: 56 patients in the early-restart cohort, and 53 patients in the late-restart cohort. The most common reason for exclusion was the patient not taking any of the specified NPMs prior to admission (300/789 or 38.0% of screened patients). Patient demographics are shown in Table 2. There were only minor differences in prognostic baseline characteristics between the two cohorts. Patients in the early restart cohort were more likely to have enteral access on day1 of ICU admission; however, by day 5 nearly all patients in the study had enteral access. Patients in the early restart group were more often prescribed SSRIs/SNRIs prior to admission than those in the late restart cohort (73% vs. 49% respectively; p = 0.02). The distribution of home NPM agents is listed in Table A, Supplemental Appendix. Formulary therapeutic interchange does occur at our institution; this occurred for 10 patients evaluated in the study (Table B, Supplemental Appendix). The BZD-based sedation received by all patients was midazolam.

Restarting home NPMs early was associated with a median daily RASS of −1.5 (−2.0, −1.0), compared with late restarts with median daily RASS of −2.0 (−3.0, −1.3) (p = 0.02), as shown in Table 3. This outcome was driven primarily by the patient subgroup restarted earlier on their home anti-depressant. The percentage of days spent where daily average RASS was within goal range (−2 to +1) was higher in the early cohort (67% vs. 57%, p = 0.01). There was no significant difference in cumulative BZD doses (early: 313.6 mg (185.1 mg, 540.2 mg) vs. late: 200.9 mg (111.0 mg, 484.0 mg), p = 0.11). The median duration of continuous BZD infusion was similar between cohorts (82 h [53–117] vs. 77 h (45–120), p = 0.99). There was no difference in the proportion of patients in each cohort who received non-BZD continuous infusion sedation (i.e. propofol or dexmedetomidine), nor in the

Table 2
Patient demographics.

Descriptor	Cohort 1: restarted home NPMs ≤ 5 days N = 56	Cohort 2: restarted home NPMs > 5 days (if at all) N = 53	Overall: cohort 1 + cohort 2 N = 109
Male	28 (50%)	26 (49%)	54 (50%)
Age (years)	58.3 ± 13.1	59.4 ± 13.0	58.8 ± 13.0
SOFA scores	7 (6, 9)	8 (5, 10)	8 (6, 10)
Charlson comorbidity index	5 (3, 9)	5 (3, 8)	5 (3, 8)
Documented oral or per tube medication administration within first 24 h of ICU admission[a]	44 (79%)	32 (60%)	76 (70%)
Documented oral or per tube medication administration within first 5 days of ICU admission	56 (100%)	51 (96%)	107 (98%)
Home NPMs			
Home SSRI/SNRI[b]	41 (73%)	26 (49%)	67 (61%)
Home gabapentinoid	26 (46%)	21 (40%)	47 (43%)
Home BZD	24 (43%)	23 (43%)	47 (43%)
Home antipsychotic	10 (18%)	6 (11%)	16 (15%)

BZD = benzodiazepine, NPM = neuropsychiatric medication, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor.
[a] p = 0.039.
[b] p = 0.02.

Table 3
Primary and secondary study outcomes.

Parameter		Cohort 1: early home NPM restart N = 56	Cohort 2: late home NPM restart N = 53	p-Value
Primary outcomes				
Median daily RASS	Overall	−1.5 (−2.0, −1.0)	−2.0 (−3.0, −1.3)	0.02
	SSRI/SNRI	−1.5 (−2.0, −1.0)	−2.2 (−3.1, −1.5)	0.01
	Gabapentinoids	−1.5 (−2.0, −1.0)	−1.8 (−2.7, −1.3)	0.16
	BZDs	−1.8 (−2.1, −1.3)	−1.5 (−2.4, −1.1)	0.85
	Antipsychotics	−1.8 (−2.6, −1.4)	−1.8 (−2.3, −1.1)	0.48
Percent of days assessed where daily average RASS within goal (−2 to +1)		67%	57%	0.01
Secondary outcomes				
Cumulative BZD TDD (mg)		313.6 (185.1, 540.2)	200.9 (111.0, 484.0)	0.11
Patients receiving non-BZD continuous intravenous infusion sedation w/in 1st week		27 (48%)	26 (49%)	1.00
Days of non-BZD continuous intravenous infusion sedation		0 (0, 2)	0 (0, 2)	0.95
New-start antipsychotic		17 (30%)	12 (23%)	0.49
Any CAM-ICU positive during study period[a]		6/35 (17%)	16/37 (43%)	0.02
Ventilator time (days)		7.0 (6.0, 9.3)	8.0 (6.0, 11.0)	0.11
ICU length of stay (days)		10.0 (7.8, 14.0)	11.0 (9.0, 16.0)	0.37

BZD = benzodiazepine, NPM = neuropsychiatric medication, TDD = total daily dose.
[a] Complete data available for 72 patients.

median number of days on non-BZD continuous infusion sedation. Early restarting of home NPMs was associated with a non-significant decrease in ventilator days (early: 7.0 days [6.0, 9.3], late: 8.0 days [6.0, 11.0], p = 0.11). During the first week of ICU admission, 72 (66%) patients had at least one charted CAM-ICU score (35 in early vs. 37 in late; p = 0.55). The early restart cohort had fewer CAM-ICU positive assessments at any point during the study period compared with the late restart cohort (17% vs. 43%, p = 0.02). The delirium prevalence over the seven day study period is displayed in Fig. 3. The CAM-ICU is done twice daily in our unit. There were no significant differences observed between cohorts in days requiring a continuous infusion benzodiazepine, new-start antipsychotics, or ICU LOS.

The amount of BZD-based sedation varied widely across the entire cohort and in some cases, the doses received were quite substantial (median 248 mg [128–523 mg], range 6–1531 mg). In a post-hoc analysis, we investigated potential correlations between patient characteristics and cumulative BZD doses to better understand drivers of the requirement for higher doses of sedatives, particularly in light of the fact that we excluded patients requiring deep sedation secondary to their clinical condition.

We failed to find significant correlations for Charlson comorbidity index or SOFA scores with cumulative BZD dosing. Minor statistically significant correlations existed for age (r = −0.34), severity of illness (r = −0.25), and day 1 total daily dose of BZD (r = 0.25). However, the number of home NPMs was most significantly correlated with the cumulative BZD dose received during the study period (r = 0.40, p < 0.0001).

4. Discussion

The use of NPMs prior to ICU admission is common, and restarting these medications may often be de-prioritized during the other complexities of a patient's ICU admission. Early initiation of home NPMs was associated with higher RASS scores (yet still within goal), a greater percentage of days where daily average RASS was within an acceptable goal, less delirium, and potentially fewer ventilator days. We did not observe a difference in the rates of propofol or dexmedetomidine initiations between cohorts, suggesting that differences in sedation-related outcomes are less likely due to differences in non-BZD sedative use.

There are few studies that evaluate the safety of restarting home NPMs in the ICU [10]. Ghassemi and colleagues published a retrospective clinical database study including over 14,000 patients associating pre-admission SSRI/SNRI use with increased in-hospital mortality, especially in cardiac surgery or myocardial infarction patients [5]. Mulloy and colleagues presented a poster abstract describing their retrospective cohort analysis of over 4000 medical ICU patients admitted with severe sepsis, which found an association between patients taking SSRIs/SNRIs at home and higher rates of clinical delirium [16]. However, neither of these studies report whether these agents were restarted while the patients were in the ICU. Though these retrospective studies cannot establish a causal association between pre-admission SSRI/SNRI use and harm, it appears that taking these medications prior to admission may not be insignificant. Scarce data are available regarding any altered pharmacokinetics of these agents in critically ill patients. Conversely,

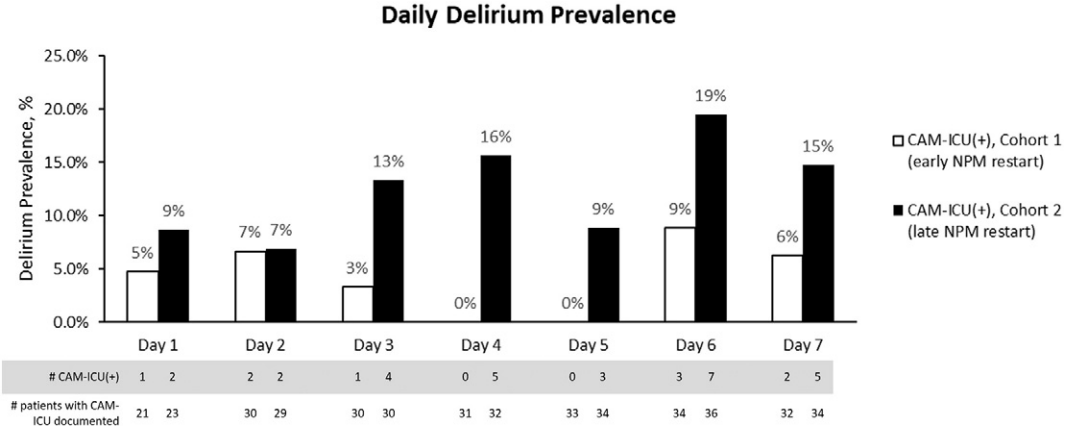

Fig. 3. Daily prevalence of delirium.

our study demonstrated comparable safety outcomes with potential benefit of maintaining lighter levels of sedation and reduced delirium.

Our study results are the first to test the association between restarting home NPMs and sedation-related outcomes in the critically ill. We found that restarting the majority (≥50%) of these NPMs within 5 days of the ICU stay was associated with optimal RASS scores and more days spent with a daily average RASS score within goal. While we were not able to discern whether restarting the NPMs was effective by preventing withdrawal or simply treated the underlying condition, this early medication reconciliation appears to be associated with improved sedation and delirium-related outcomes. In particular, the effect appeared to be driven in large part by the antidepressants (SSRI/SNRIs), which were also the most frequently prescribed home NPMs in the cohort.

The potential sedation-related benefits of restarting home NPMs earlier in the ICU stay may be more prominent in patients who remain ventilated for longer than 5 days, whereas patients with shorter ventilation periods may not see similar effects. This aligns with the expected timeline of withdrawal for several of these NPM classes. Although based on their withdrawal windows there does not appear to be an urgent indication to restart these medications on the first day of ICU admission, our results suggest that ensuring these agents are restarted in a timely fashion (within 5 days based on our results) can improve sedation-related outcomes. In their recent systematic review [10], Kelly and colleagues advocate for further investigation with more rigorous drug administration data standards to guide the reinstatement of SSRIs/SNRIs in the ICU setting. The present work provides supporting data in this regard. Interestingly, we found a correlation between the number of home NPMs and cumulative BZD received, suggesting that higher sedation requirements may be anticipated for patients receiving multiple home NPMs, and offering a selection of patients for whom this medication reconciliation may benefit even earlier on in the ICU stay. In addition to the sedation scores and delirium rates, there was a corresponding non-significant trend towards decreased ventilator days favoring the early restart cohort, though this study may have been underpowered to detect this difference. Given the correlations in the literature between deeper sedation, delirium, and increased durations of mechanical ventilation, it would be plausible that the benefits of restarting home NPMs may be associated with reductions in mechanical ventilation [4].

An additional benefit of early restarting of home NPMs may be in transitions of care. The medication reconciliation process is especially disturbed in ICU care transitions, with significantly higher rates of discontinuation of chronic medications in hospitalized patients with ICU exposure [17]. Restarting home NPMs early in the ICU stay can help with maintaining continuity of chronic disease pharmacotherapies across levels of care.

Though not statistically significant, the higher BZD cumulative dosing in the early restart cohort is an unusual finding from this study. This may be due to the fact that in our practice, restarting these NPMs is at times a strategy for attempting to reduce sedation dosing in patients with high requirements. Paradoxically, the early restart cohort was found to overall achieve and maintain lighter levels of sedation compared with the late restart group. Despite receiving numerically higher BZD doses (though not statistically significant), the rates of delirium were lower in the early restart cohort of patients.

This study has important limitations that must be reviewed in light of the findings. There is potential for selection bias, in that home medications may be restarted in more clinically stable patients. This phenomenon may be similar to the observed higher rates of restarting statins in less critically ill patients [18]. The SOFA score was collected to facilitate clinical comparison of cohorts. The lack of difference in SOFA scores between cohorts suggests comparable severities of clinical status. This is confirmed in a similar duration of ICU stay between the cohorts as well. However, given the retrospective nature of this study, it is not possible to conduct subject randomization, nor fully capture the clinical reasoning behind each pharmacotherapy decision. In addition, the degree of adherence to home NPM regimens and durations of therapy prior to admission could not be captured in the current study, with high adherence and long durations of therapy predisposing patients to withdrawal symptoms upon abrupt discontinuation of their home NPM regimens. Only patients receiving continuously infused BZD-based sedation were included given the historical prescribing habits at our institution and since at present, there is a lack of a universally agreed-upon and validated equipotent interconversion between the various sedative agents. Opioid use was not tracked because, during the time period under consideration, our ICU did not necessarily adopt an analgesia-first approach to sedation. Moreover, agitation induced by withdrawal from home NPMs could not be treated with opioids or analgesics alone. It is standard ICU practice at our institution to establish enteral access and initiate enteral nutrition within the first 24 h of admission. Even with enteral access for administration, some NPMs with delayed/extended release formulations cannot be crushed and administered per tube. This is acknowledged as a limitation, though it is customary in our institution's ICUs to attempt conversion of these formulations to immediate release (which can be crushed) or another per tube-amenable formulation. The present work was not able to evaluate incidence of any serotonergic toxicities. While the available CAM-ICU scores suggest an association with delirium in the late-start cohort, compliance with CAM-ICU documentation was poor. The external validity of this study is limited by its single-center design and lack of representation of other ICU patients. Future prospective studies investigating this phenomenon in a variety of critically ill patients are warranted to generate more data on the exact agents, and subsequent timing important to restart in order to optimize sedation-related outcomes.

5. Conclusions

Restarting home NPMs within 5 days of an ICU stay is associated with maintenance of higher (yet still within goal) RASS scores, and less delirium as compared with restarting home NPMs later in the ICU stay. Accurate and complete medication reconciliation, particularly of home NPMs, may help to achieve light sedation and optimize sedation-related outcomes in ICU patients.

Acknowledgements

We would like to thank Mr. Andrew McLaughlin, who assisted with extraction of clinical data from the UK Center for Clinical and Translational Science Enterprise Data Trust.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jcrc.2017.07.046.

References

[1] Robinson BRH, Mueller EW, Henson K, Branson RD, Barsoum S, Tsuei BJ. An analgesia-delirium-sedation protocol for critically ill trauma patients reduces ventilator days and hospital length of stay. J Trauma 2008;65(3):517–26.
[2] Treggiari MM, Romand J-A, Yanez ND, et al. Randomized trial of light versus deep sedation on mental health after critical illness. Crit Care Med 2009;37(9):2527–34.
[3] Balzer F, Weiß B, Kumpf O, et al. Early deep sedation is associated with decreased in-hospital and two-year follow-up survival. Crit Care 2015;19:197.
[4] Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med 2013;41(1):263–306.
[5] Ghassemi M, Marshall J, Singh N, Stone DJ, Celi LA. Leveraging a critical care database: selective serotonin reuptake inhibitor use prior to ICU admission is associated with increased hospital mortality. Chest 2014;145(4):745–52.
[6] Devlin JW, Mallow-Corbett S, Riker RR. Adverse drug events associated with the use of analgesics, sedatives, and antipsychotics in the intensive care unit. Crit Care Med 2010;38(6 Suppl):S231–243.
[7] Moncrieff J. Antipsychotic maintenance treatment: time to rethink? PLoS Med 2015;12(8):e1001861.

[8] Papadopoulos S, Cook AM. You can withdraw from that? The effects of abrupt discontinuation of medications. Orthopedics 2006;29(5):413–7.
[9] Warner CH, Bobo W, Warner C, Reid S, Rachal J. Antidepressant discontinuation syndrome. Am Fam Physician 2006;74(3):449–56.
[10] Kelly JM, Rubenfeld GD, Masson N, Min A, Adhikari NKJ. Using selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors in critical care: a systematic review of the evidence for benefit or harm. Crit Care Med 2017;45:e607–16.
[11] Haddad PM. Antidepressant discontinuation syndromes: clinical relevance, prevention and management. Drug Saf 2001;24(3):183–97.
[12] Haddad PM, Anderson IM. Recognizing and managing antidepressant discontinuation syndromes. Adv Psychiatr Treat 2007;13(6):447–57.
[13] Wilson E, Lader M. A review of the management of antidepressant discontinuation symptoms. Ther Adv Psychopharmacol 2015;5(6):357–68.
[14] Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. Intensive Care Med 1996;22(7):707–10.
[15] Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40(5):373–83.
[16] Mulloy B, Simpson S. Severe sepsis and ICU delirium: risk associated with serotonergic reuptake inhibitors. Chest 2014;146(4_MeetingAbstracts):239A.
[17] Bell CM, Brener SS, Gunraj N, et al. Association of ICU or hospital admission with unintentional discontinuation of medications for chronic diseases. JAMA 2011;306(8):840–7.
[18] Yende S, Milbrandt EB, Kellum JA, et al. Understanding the potential role of statins in pneumonia and sepsis. Crit Care Med 2011;39(8):1871–8.