mhc
MENTAL HEALTH CLINICIAN

ORIGINAL RESEARCH Open Access

Impact of early home psychotropic medication reinitiation on surrogate measures of intensive care unit delirium

Matthew Li, PharmD, BCPS[1]; Mei H. Chang, BA, PharmD, BCPS, AQ-ID, BCCCP[2]; Yeismel Miranda-Valdes, PharmD, BCPS[3]; Kirsten Vest, PharmD, BCPS[4]; Troy D. Kish, PharmD, BCPS[5]

How to cite: Li M, Chang MH, Miranda-Valdes Y, Vest K, Kish TD. Impact of early home psychotropic medication reinitiation on surrogate measures of intensive care unit delirium. Ment Health Clin [Internet]. 2019;9(4):263-8. DOI: 10.9740/mhc.2019.07.263.

Abstract

Introduction: Intensive care unit (ICU) delirium is a major contributing factor to increased mortality, length of stay, and cost of care. Psychotropic medications may often require extensive tapering to prevent withdrawal symptoms; during ICU admission, home psychotropics are frequently held which may precipitate acute drug withdrawal and subsequent delirium.

Methods: This is a single-center, observational, retrospective chart review. The primary endpoint was the total number of new-start antipsychotics used to treat ICU delirium. Secondary endpoints included use of restraints, ICU length of stay, and hospital length of stay.

Results: A total of 2334 charts were reviewed for inclusion; 55 patients were categorized into each group. There was no statistically significant difference in the requirement for new-start antipsychotics ($P = 1.0$), restraint use ($P = .057$), or ICU length of stay ($P = .71$). There was a statistically significant decrease in hospital length of stay ($P = .048$).

Discussion: Early reinitiation was associated with a decrease in hospital length of stay but was not associated with a decrease in the number of new-start antipsychotics, use of restraints, or ICU length of stay.

Keywords: delirium, intensive care units, critical care, psychotropic drugs, antidepressant, antipsychotic

[1] (Corresponding author) Pharmacy Resident, James J. Peters Veterans Affairs Medical Center, Bronx, New York, ORCID: https://orcid.org/0000-0003-1320-7134; [2] Clinical Pharmacy Specialist, James J. Peters Veterans Affairs Medical Center, Bronx, New York, ORCID: https://orcid.org/0000-0002-8785-5460; [3] Clinical Pharmacy Specialist, James J. Peters Veterans Affairs Medical Center, Bronx, New York, ORCID: https://orcid.org/0000-0003-1639-5468; [4] Clinical Pharmacy Specialist, James J. Peters Veterans Affairs Medical Center, Bronx, New York, ORCID: https://orcid.org/0000-0003-0861-7278; [5] Clinical Pharmacy Specialist, James J. Peters Veterans Affairs Medical Center, Bronx, New York; Associate, LIU Pharmacy (Arnold and Marie Schwartz College of Pharmacy and Health Sciences), Brooklyn, New York, ORCID: https://orcid.org/0000-0002-7393-8097

Disclosures: The authors have no conflicts of interest to disclose. In terms of funding, M.L. reports grants from The New York State Council of Health-System Pharmacists during the conduct of the study.

Introduction

Delirium is a syndrome characterized by the acute onset of cerebral dysfunction with a change or fluctuation in baseline mental status, inattention, or an altered level of consciousness.[1] The pathophysiology of intensive care unit (ICU) delirium is largely uncharacterized and may vary depending on the cause.[2] Some causes of ICU delirium include environmental factors, organ dysfunction, and drug withdrawal. Intensive care unit delirium is a major contributing factor to increased mortality, length of stay, and cost of care in the critically ill patient population.[1,3] The incidence of delirium for ICU patients ranges from 20% to 80% and results in an estimated $4 to $16 billion cost annually in the United States.[1]

Psychotropic medications such as selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), and antipsychotics often require tapering to prevent withdrawal symptoms such as hyperarousal, sensory disturbances, and insomnia, all of which may emerge within the first few days after abrupt discontinuation of therapy.[4] Home psychotropic medications are frequently held during ICU admission for a variety of reasons such as altered mental status or hemodynamic instability.

La et al[4] conducted a single-center, retrospective cohort chart review of 109 ICU patients to investigate the effects of early ($\leq$5 days) versus late ($>$5 days) home neuropsychiatric medication reinitiation on sedation-related outcomes. Delirium was also assessed by measuring positive Confusion Assessment Method for the ICU (CAM-ICU) scores and new-start inpatient antipsychotics as secondary endpoints.[4] The authors found that restarting home neuropsychiatric medications within the first 5 days of admission resulted in a decrease in positive CAM-ICU scores (17% vs 43%, $P=.02$) but had no effect on the number of new-start antipsychotics.

Evidence regarding the efficacy of specific pharmacologic agents to prevent ICU delirium remains inconsistent. Prophylaxis with antipsychotics such as haloperidol has only demonstrated benefit in 1 retrospective chart review consisting of elderly patients undergoing hip surgery.[5] In addition, there is a lack of evidence to support the routine use of antipsychotics for the treatment of ICU delirium.[6] However, the short-term use of haloperidol or an atypical antipsychotic may be reasonable to manage patients who experience significant distress secondary to the symptoms of delirium, especially if the agitation may be harmful to themselves or to others.[7] The inadequacy of new pharmacologic agent initiation to prevent or treat ICU delirium further emphasizes the importance of alternative interventions such as reinitiating home psychotropics.

The goals of this retrospective chart review are to examine the impact of early ($\leq$24 hours) versus late ($>$24 hours) reinitiation of home psychotropic medication in the ICU on new-start inpatient antipsychotics, ICU length of stay, hospital length of stay, and use of restraints.

Methods

Setting and Design

This was a single-center, observational, retrospective chart review conducted at a 150-bed tertiary care Veterans Affairs medical center in Bronx, New York. The institutional review board deemed this study exempt from review and provided a waiver for approval.

Definitions

Home psychotropics were defined as SSRIs, SNRIs, antipsychotics, or bupropion. Early reinitiation was defined as restart of home psychotropics within 24 hours of emergency department triage or critical care assessment for admissions. Patients that did not have their home psychotropics restarted within 24 hours of assessment were included in the late reinitiation group. Patients that were prescribed multiple home psychotropic drugs were included in the early reinitiation group if at least 1 psychotropic was started within 24 hours. Documentation of delirium was not evaluated for new-start antipsychotics unless the patient was restarted on the same antipsychotic prescribed prior to admission. For these patients, a positive documentation of delirium in a physician note in the electronic medical record during the ICU treatment course was required to categorize the patient as having a new-start antipsychotic.

Patient Population

Patients admitted to the ICU between July 1, 2013, and February 1, 2018 with at least 1 active home psychotropic prescription for at least 30 days prior to admission were included in the evaluation. Patients were excluded for transfer from an outside hospital or from inpatient unit other than the emergency department, ICU length of stay less than 24 hours, positive urine toxicology screen, Richmond Agitation-Sedation Scale $\leq$–3 (unable to maintain eye contact or respond to verbal stimulation) on admission, concomitant therapy with stimulants or long-acting injectable antipsychotics, and monotherapy with benzodiazepines, medications for the treatment of insomnia (mirtazapine or trazodone) or psychotropics that do not require tapering (fluoxetine).

Statistical Analyses

A sample size of 96 was calculated (version 3.1.2; Dupont, Nashville, TN) with a prespecified alpha of 0.05 and 80% power in order to detect a difference of 26% (in number of new-start antipsychotics).[4] Primary and secondary outcomes were evaluated using the χ^2 test of independence or Fisher exact test for nominal variables and the Student *t* test for continuous variables.

Endpoints

The primary outcome was the total number of new-start antipsychotics to treat ICU delirium. Secondary outcomes included use of restraints, ICU length of stay, and hospital length of stay.

TABLE 1: Patient demographics and baseline risk factors for delirium

Characteristic	Early Reinitiation (N = 55)	Late Reinitiation (N = 55)	*P* Value
Age (y), Median (IQR)	66 (60, 72)	64 (57, 69)	.14
	No. (%)		
Male	49 (89)	50 (91)	.75
Race			
African American	23 (42)	25 (45)	.70
White	16 (29)	15 (27)	.83
Hispanic	15 (27)	12 (22)	.51
Other	1 (2)	3 (6)	.31
Intensive care unit setting			
Medical	19 (35)	21 (38)	.69
Surgical	16 (29)	24 (44)	.11
Cardiac	20 (36)	10 (18)	.03
Baseline risk factors			
Elective procedure	13 (24)	16 (29)	.52
History of dementia	5 (9)	2 (2)	.24
History of hypertension	46 (84)	44 (80)	.62
History of alcoholism	0 (0)	4 (7)	.12
Psychiatry consult	6 (11)	10 (18)	.28
Anticholinergics	11 (20)	8 (15)	.45
Anxiolytics	1 (2)	0 (0)	>.99
Benzodiazepine dose > home dose	12 (22)	13 (24)	.82
Dopamine agonists	1 (2)	0 (0)	>.99
High-dose corticosteroids[a]	2 (4)	3 (5)	.65
Mood stabilizers	8 (15)	8 (15)	1.0
Opioids	25 (45)	33 (60)	.13
Sleep medications	18 (33)	22 (40)	.43

[a]Defined as ≥40 mg prednisone or equivalent.

Results

A total of 2334 charts were reviewed between July 1, 2013, and February 1, 2018. The majority of patients (N = 1482) were excluded due to an inactive psychotropic prescription or duration of therapy for less than 30 days. A total of 110 patients were included after applying inclusion and exclusion criteria; 55 patients were enrolled into the early reinitiation group and 55 patients were included into the late reinitiation group. Of the 55 patients in the late reinitiation group, 18 patients did not have their home psychotropic medication restarted during their hospital course.

The majority of patients in this retrospective chart review were African American males over the age of 60 (Table 1). The early reinitiation group was comprised of more cardiac ICU patients when compared to the late reinitiation group. There were no statistically significant differences between the 2 groups when comparing baseline risk factors (eg history of dementia, hypertension, alcoholism, etc) and inpatient medications (eg anticholinergics, anxiolytics, benzodiazepines, etc) that may have confounded the results of this retrospective chart review (Table 1).

The most commonly prescribed home psychotropic medication prior to admission were SSRIs, with no notable difference in home psychotropic medications prior to admission between the 2 groups (Table 2).

Primary and secondary endpoints are reported as early reinitiation versus late reinitiation (Table 3). There was no statistically significant difference in the primary endpoint of new-start antipsychotics (5 [9.1%] vs 5 [9.1%], respectively, $P = 1.0$) or secondary endpoints of restraint use (7 [12.7%] vs 15 [27.3%], respectively, $P = .057$) or ICU length of stay (4 days vs 4.3 days, respectively, $P = .71$). There was a statistically significant difference in hospital length of stay (6.5 days vs 8.6 days, respectively, $P = .048$).

TABLE 2: Home psychotropic medications

Psychotropic	No. (%) Early Reinitiation (N = 55)	Late Reinitiation (N = 55)	*P* Value
Citalopram	13 (24)	7 (13)	.14
Sertraline	11 (20)	8 (15)	.45
Paroxetine	9 (16)	6 (11)	.40
Bupropion	8 (15)	11 (20)	.45
Quetiapine	6 (11)	10 (18)	.28
Venlafaxine	6 (11)	4 (7)	.51
Risperidone	3 (6)	5 (9)	.46
Aripiprazole	2 (4)	4 (7)	.40
Escitalopram	2 (4)	0 (0)	.50
Duloxetine	1 (2)	1 (2)	1.0
Clozapine	1 (2)	0 (0)	>.99
Lurasidone	1 (2)	2 (4)	.56
Mirtazapine	1 (2)	3 (6)	.31
Olanzapine	0 (0)	2 (4)	.50
Haloperidol	0 (0)	1 (2)	>.99
Loxapine	0 (0)	1 (2)	>.99
Trazodone	0 (0)	2 (4)	.50
Fluoxetine	0 (0)	1 (2)	>.99

Discussion

Time to reinitiation of psychotropic medications in the ICU was not significantly associated with new-start antipsychotics for ICU delirium ($P = 1.0$). Contrary to the retrospective chart review conducted by La et al,[4] this evaluation excluded patients receiving benzodiazepine monotherapy. Benzodiazepine use in the ICU can precipitate withdrawal if abruptly discontinued and is a common risk factor for ICU delirium.[1] For patients who were prescribed benzodiazepines prior to admission, inpatient benzodiazepine use was only quantified if the administered dose was greater than the outpatient dose. Another major difference between this evaluation and the retrospective chart review performed by La et al[4] was the definition of early and late reinitiation. Early reinitiation in this evaluation was defined as ≤24 hours since abrupt discontinuation of psychotropics with shorter half-lives (eg the half-life of venlafaxine is approximately 5 hours) could theoretically precipitate withdrawal symptoms and subsequent delirium within that time period.[8] A shorter window for reinitiation would also theoretically allow for greater specificity for delirium related to home psychotropic withdrawal as ICU delirium is multifactorial.

Patients were required to have an active psychotropic for at least 30 days prior to admission in order to prevent an underestimation of delirium secondary to drug withdrawal. The 30-day threshold was chosen to increase the likelihood that the home psychotropic drugs would be at steady state and produce clinically significant withdrawal symptoms if abruptly discontinued. In addition to the 30-day threshold, prescriptions were also required to be active in the electronic medical record that served as a surrogate marker for adherence. Since discontinuation of illicit substances may also manifest clinically significant withdrawal symptoms, patients with a positive urine toxicology screen (Siemens ADVIA®1800 screens [Tarrytown, NY] for cocaine, amphetamines, barbiturates, opiates, methadone, benzodiazepines, and cannabinoids) upon admission were excluded.

In an attempt to account for the numerous confounding factors that may affect our results, baseline and iatrogenic risk factors were compared between the 2 groups. Baseline risk factors that are positively and significantly associated with the development of ICU delirium include preexisting dementia, history of hypertension, history of alcoholism, and severity of illness at admission.[9] There were no differences between the 2 groups in history of dementia, hypertension, or alcoholism. In addition, there were no notable differences in the use of drugs associated with the development of ICU delirium such as benzodiazepines, opioids, and corticosteroids.[10,11] Factors that

TABLE 3: Primary and secondary endpoints

Outcome	Early Reinitiation (N = 55)	Late Reinitiation (N = 55)	*P* Value
	No. (%)		
New-start antipsychotics[a]	5 (9.1)	5 (9.1)	1.0
Restraint use	7 (12.7)	15 (27.3)	.057
	Days		
Intensive care unit length of stay	4	4.3	.71
Hospital length of stay	6.5	8.6	.048

[a]New-start antipsychotics: initiation of new or reinitiation of home antipsychotics for the treatment of delirium.

may have reduced the risk of delirium such as use of sleep-promoting agents or an active psychiatry consult were also documented and compared between the 2 groups (Table 1) with no statistically significant differences noted.

The primary endpoint of this evaluation was the incidence of new-start antipsychotic drugs commonly used to treat delirium including, but not limited to, quetiapine, olanzapine, risperidone, and haloperidol.[2] Because a routine delirium monitoring protocol was not used in the treatment setting at the time of data collection, a documentation of delirium in a physician note in the electronic medical record was required in order to meet the study definition of a new-start antipsychotic. The concomitant requirement of documentation in the electronic medical record allowed for patients prescribed one of the aforementioned antipsychotics prior to admission to still be classified as positive for delirium if the same antipsychotic was reinitiated during their ICU stay.

The use of restraints appears to be less frequent in the early reinitiation group, although this difference was not statistically significant ($P = .057$). Decreasing the use of restraints not only benefits the patient, but the ICU staff workload as well. In addition, there was a statistically significant decrease in overall hospital length of stay, which may indicate that patients who had their psychotropics initiated within 24 hours of admission may have been more stable and suitable for discharge.

This evaluation has several limitations. There is limited external validity given the small sample size and single-center design. We were unable to account for the timing of delirium diagnosis relative to antipsychotic initiation because of the retrospective design of this study. CAM-ICU scores are not performed at our institution and therefore were not available as a measure of baseline or newly developed ICU delirium. For that reason, the use of new-start antipsychotics and the use of restraints served as indirect measures of ICU delirium. Although documentation of delirium in the electronic medical record was required for home antipsychotic reinitiation to meet the study definition of a new-start antipsychotic, we cannot exclude the possibility that the agent was resumed for continued treatment of the underlying psychiatric condition. The precise etiology of ICU delirium was not established for patients in this study as we did not attempt to differentiate between symptoms of drug withdrawal versus clinical rebound symptoms. Non-pharmacologic factors that may have impacted delirium in the ICU such as family visits, music, and circadian light were not accounted for.[12,13] The requirement for prescriptions to have an active status in the electronic medical record is an indirect measure of adherence to therapy, and use of a measure such as the medication possession ratio over a longer period of time may have allowed for a more accurate representation of adherence. Although baseline characteristics were similar between the 2 groups, a baseline severity of illness score was not calculated.

Conclusion

Restarting home psychotropic medications within 24 hours of ICU admission did not result in a decrease in the number of new-start antipsychotics. Early reinitiation was associated with a decrease in hospital length of stay but was not associated with a statistically significant decrease in the use of restraints or ICU length of stay. Larger studies are needed to evaluate similar endpoints and to draw further conclusions regarding the impact of early home psychotropic reinitiation on surrogate measures of ICU delirium.

Acknowledgments

The authors thank William Ho, PharmD, Clinical Pharmacy Specialist, Automated Data Processing Applications Coordinator.

References

1. Barr J, Fraser GL, Puntillo K, Ely EW, Gélinas C, Dasta JF, 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. DOI: 10.1097/CCM.0b013e3182783b72. PubMed PMID: 23269131.
2. Reade MC, Finfer S. Sedation and delirium in the intensive care unit. N Engl J Med. 2014;370(5):444-54. DOI: 10.1056/NEJMra1208705. PubMed PMID: 24476433.
3. Pisani MA, Kong SYJ, Kasl SV, Murphy TE, Araujo KLB, Van Ness PH. Days of delirium are associated with 1-year mortality in an older intensive care unit population. Am J Respir Crit Care Med. 2009;180(11):1092-7. DOI: 10.1164/rccm.200904-0537OC. PubMed PMID: 19745202; PubMed Central PMCID: PMC2784414.
4. La MK, Thompson Bastin ML, Gisewhite JT, Johnson CA, Flannery AH. Impact of restarting home neuropsychiatric medications on sedation outcomes in medical intensive care unit patients. J Crit Care. 2018;43:102-7. DOI: 10.1016/j.jcrc.2017.07.046. PubMed PMID: 28865338.
5. Kalisvaart KJ, de Jonghe JFM, Bogaards MJ, Vreeswijk R, Egberts TCG, Burger BJ, et al. Haloperidol prophylaxis for elderly hip-surgery patients at risk for delirium: a randomized placebo-controlled study. J Am Geriatr Soc. 2005;53(10):1658-66. DOI: 10.1111/j.1532-5415.2005.53503.x. PubMed PMID: 16181163.
6. Siddiqi N, Holt R, Britton AM, Holmes J. Interventions for preventing delirium in hospitalised patients. Cochrane Database Syst Rev. 2007;2:CD005563. DOI: 10.1002/14651858.CD005563.pub2. PubMed PMID: 17443600.
7. Devlin JW, Smithburger P, Kane JM, Fraser GL, Skrobik Y. Intended and unintended consequences of constraining clinician prescribing. Crit Care Med. 2016;44(10):1805-7. DOI: 10.1097/CCM.0000000000002103. PubMed PMID: 27635480.
8. Aurobindo Pharma Limited. Venlafaxine hydrochloride capsule [Internet]. Bethesda (MD): National Library of Medicine (US); c2012 [updated 2018 Dec 4; cited 2019 Jan 1]. Available from:

https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=85d3ce8b-8966-45d9-bdaf-f6f0475096e1
9. Pisani MA, Murphy TE, Araujo KLB, Slattum P, Van Ness PH, Inouye SK. Benzodiazepine and opioid use and the duration of intensive care unit delirium in an older population. Crit Care Med. 2009;37(1):177-83. DOI: 10.1097/CCM.0b013e318192fcf9. PubMed PMID: 19050611; PubMed Central PMCID: PMC2700732.
10. Schreiber MP, Colantuoni E, Bienvenu OJ, Neufeld KJ, Chen K-F, Shanholtz C, et al. Corticosteroids and transition to delirium in patients with acute lung injury. Crit Care Med. 2014;42(6):1480-6. DOI: 10.1097/CCM.0000000000000247. PubMed PMID: 24589640; PubMed Central PMCID: PMC4028387.
11. Pandharipande P, Shintani A, Peterson J, Pun BT, Wilkinson GR, Dittus RS, et al. Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. Anesthesiology. 2006;104(1):21-6. DOI: 10.1097/00000542-200601000-00005. PubMed PMID: 16394685.
12. Trogrlić Z, van der Jagt M, Bakker J, Balas MC, Ely EW, van der Voort PHJ, et al. A systematic review of implementation strategies for assessment, prevention, and management of ICU delirium and their effect on clinical outcomes. Crit Care. 2015;19:157. DOI: 10.1186/s13054-015-0886-9. PubMed PMID: 25888230; PubMed Central PMCID: PMC4428250.
13. Estrup S, Kjer CKW, Poulsen LM, Gøgenur I, Mathiesen O. Delirium and effect of circadian light in the intensive care unit: a retrospective cohort study. Acta Anaesthesiol Scand. 2017;62(3):367-75. DOI: 10.1111/aas.13037. PubMed PMID: 29148046.