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Protocol

[Translated article] Prospective observational follow-up study of psychoactive drug treatment initiated in the intensive care unit

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ABSTRACT

Objective: The treatment and prevention of delirium in the intensive care unit (ICU) have gained significant importance in patient care in recent years. Some studies have linked delirium with increased risks of mortality, prolonged hospital stay, and more days of mechanical ventilation. This study aims to analyse the use of psychotropic drugs initiated in the ICU and their continuation upon hospital discharge, as well as to evaluate their contribution to polypharmacy and associated adverse clinical effects.
Method: A multicentre prospective observational case study was designed, focusing on patients over 18 years old admitted to the ICU and treated with psychotropic drugs. Data on demographics, variables related to admission and psychotropic drug treatment, as well as clinical outcomes and adverse effects, will be collected. Among other variables, the frequency of psychotropic treatments initiated in the ICU and continued upon discharge from the ICU and the hospital will be measured. Data collection will be performed through review of electronic medical records and prescription programmes, and IBM SPSS 20.0 statistical package will be used for analysis.
Discussion: Delirium is common in ICU patients and is associated with long-term negative consequences. Although antipsychotics are used to treat delirium, their prolonged use can have adverse effects, and their continuation after ICU discharge contributes to polypharmacy. This study aims to provide information on the use of psychotropic drugs initiated in the ICU and their continuation upon discharge, with the goal of identifying opportunities for intervention and reducing unnecessary use of these medications.

Estudio prospectivo observacional de seguimiento del tratamiento con psicofármacos iniciados en la Unidad de Cuidados Intensivos

Palabras clave:
Delirium
Cuidados intensivos
Polifarmacia
Psicofármacos
Seguridad del medicamento
Transición hospitalaria

RESUMEN

Objetivo: El tratamiento y la prevención del delirium en la unidad de cuidados intensivos (UCI) han cobrado gran relevancia en la atención al paciente en años recientes. Algunos estudios han vinculado el delirium con mayores riesgos de mortalidad, estancia hospitalaria prolongada y más días de ventilación mecánica. Este estudio busca analizar el uso de psicofármacos iniciados en la UCI y su continuación al alta hospitalaria, así como evaluar su contribución a la polifarmacia y los efectos clínicos adversos asociados.
Metodología: Se ha diseñado un estudio multicéntrico prospectivo observacional de casos, en pacientes mayores de 18 años ingresados en UCI y tratados con psicofármacos. Se recogerán datos demográficos, variables relacionadas con el ingreso y el tratamiento con psicofármacos, así como resultados clínicos y efectos adversos. Se medirá (entre otras variables) la frecuencia de tratamientos con psicofármacos que se inician en la UCI y continúan al alta de la Unidad y del Hospital. La recogida de datos se realizará mediante revisión de historias clínicas electrónicas y programas de prescripción, y se utilizará el paquete estadístico IBM SPSS 20.0 para el análisis.

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Discusión: El delirium es común en pacientes ingresados en la UCI y está asociado con consecuencias negativas a largo plazo. Aunque los antipsicóticos se utilizan para tratar el delirium, su uso prolongado puede tener efectos adversos, y su continuidad después del alta de la UCI contribuye a la polifarmacia. Este estudio busca proporcionar información sobre el uso de psicofármacos iniciados en la UCI y su continuación al alta, con el objetivo de identificar oportunidades para intervenir y reducir el uso innecesario de estos medicamentos.

Introduction

There is a high prevalence of patients with psychiatric disorders in intensive care units (ICUs), who may have a range of organic and psychopathological disorders.[1] In addition, many ICU patients develop new psychiatric disorders or experience a worsening of existing ones. Therefore, appropriate psychopharmacological management is essential to reduce the psychopathological consequences associated with ICU stays in these patients.[2]

In recent years, the treatment and prevention of delirium in ICUs has become a central issue in patient care. Previous studies have associated delirium and poor mental health with an increased risk of mortality, longer hospital stays, extended ICU stays, and additional days on mechanical ventilation.[3–5] Furthermore, delays in treatment may be associated with increased mortality.[6] Thus, the recognition and treatment of delirium has resulted in an increased use of antipsychotics and tools for its detection in ICUs.[7] Although antipsychotics may reduce delirium in ICUs, they may not reduce mortality.[8] These medications may also be used for longer than necessary, even outside the hospital, increasing the risk of polypharmacy and adverse events.[9] It is common for antipsychotic treatment, once initiated, to continue beyond the context for which it was prescribed.[10,11]

Patients with delirium or agitation may also be started on benzodiazepines, opioids, or sedative anticonvulsants. These factors make delirium a major contributor to polypharmacy at hospital discharge, particularly in critically ill older adults.

The progressive aging of the population, the optimisation of chronic disease management leading to longer survival, and the use of more aggressive therapies in elderly patients contribute to an increase in the number of elderly patients admitted to ICUs and, consequently, medication-related problems.

The prolonged use of antipsychotics after hospital admission may be associated with serious safety issues in older adults with dementia,[12,13] which can increase short-term mortality,[13] adverse drug effects, and the risk of readmission.[14]

There is little research on how often treatment is continued after ICU discharge after patients develop delirium during their stay, but available data suggest rates ranging from 23% to 50%.[15,16]

Flurie *et al.*[15] assessed the continuation of antipsychotic therapy during transitions in care, finding that approximately 25% of patients who started antipsychotics in ICUs continued them after transfer to the medical ward, and of these, 39% continued them at hospital discharge. The CAM-ICU score is a test designed to detect confusional states and is based on a series of questions and instructions that is routinely administered in the ICU setting. This test was negative in about 65% of patients who continued therapy after ICU discharge.

Benzodiazepines are used in ICUs to treat agitation, alcohol deprivation symptoms, and to induce deep sedation. There is increasing evidence that the prolonged use of high doses of benzodiazepines, mainly midazolam and lorazepam, is associated with worsening delirium, morbidity, mechanical ventilation time, and ICU stay. Although their use is declining, they remain the most commonly used sedatives, with midazolam being the most widely used.[17]

The incidence of depression in critically ill patients, is not known with certainty, but estimates in these patients range from 10% to 30% depending on the disease and age.[18,19] The percentage can reach 40% in critically ill geriatric patients when adjustment disorders, depressive symptoms secondary to the use of certain drugs, and the underlying disease itself are considered.[18] This condition is commonly underdiagnosed by intensivists and has a negative impact on medium- and long-term prognosis. Pre-ICU depression is an important factor contributing to post-ICU depression.[20] Weinert and Winterman studied the incidence of major depression (MD) and the use of pharmacological treatments in patients with acute respiratory failure. Within 2 months of ICU discharge, the incidence of MD was 28% and the prevalence of antidepressant medication use was 49%.[21]

Nearly 1 in 5 patients with chronic critical illness will experience an episode of MD up to 6 months after prolonged mechanical ventilation in ICUs.[22] The implementation of programmes for rational drug use in critical care units may reduce the rates of therapy continuation at discharge, thereby reducing possible associated adverse effects. In this sense, D'angelo *et al.* were able to reduce the rates of antipsychotic therapy continuation at ICU discharge (27.9% vs 17.7%) after implementing a multidisciplinary training programme that included recommendations for the effective use of antipsychotics in delirium and an algorithm for their early discontinuation.[23]

Psychotropic drugs initiated during ICU stay are commonly continued after ICU discharge. The aim of this study is to analyse and measure the frequency with which psychotropic drugs initiated in the ICU are continued after discharge and to assess their contribution to patient polypharmacy. It also aims to lay the groundwork for the design of a potential future intervention to reduce polypharmacy related to these medications.

Methods

This protocol was developed in accordance with the international guidelines for the development and publication of research protocols (SPIRIT Guidelines).[24]

Design

A multicentre, observational, prospective descriptive case series study.

All procedures described in this protocol are standard clinical practice for the intervention under study. Participants will not receive any additional procedures over and above what they would already be receiving if they were not taking part in the study.

Objectives

The primary objective of this study is to analyse the use of psychotropic drugs initiated in the ICU and their continuation after ICU and hospital discharge, as well as during the following 30 and 90 days post-discharge. The secondary objectives are as follows:

- To describe the profile of psychotropic drug use in critically ill patients admitted to the ICU.
- To determine discontinuation patterns of psychotropic drugs initiated in the ICU, including duration of treatment, place of discontinuation, and frequency of adverse reactions.

- To assess the contribution of psychotropic drug use to polypharmacy in critically ill patients.

Environment

Spanish pharmacy services where pharmacists perform pharmacotherapeutic review and validation for adult critically ill patients admitted to the ICU.

Study period

A time frame of 8 weeks was established for the recruitment period and a follow-up period of 3 months.

Inclusion and exclusion criteria

Inclusion criteria: Patients older than 18 years of age admitted to the ICU and treated with any de novo psychotropic drug (antidepressants, antipsychotics, and/or anxiolytics). Exclusion criteria: Patients younger than 18 years of age or patients who have received psychotropic drugs during the 3 months prior to admission to the ICU.

Variables

During this observational study, the following variables will be collected anonymously from electronic medical records and the ICU, hospital, and primary care prescription programmes. Data will be recorded in a specially designed data collection notebook on the Research Electronic Data Capture (REDCap) platform:

Main variables

- Number of patients initiating psychotropic drug treatment in the ICU.
- Number of patients initiating de novo psychotropic drug treatment in the ICU.
- Proportion of de novo psychotropic drug treatments initiated in the ICU out of the total number psychotropic drug treatments during ICU admission.
- Proportion of de novo psychotropic drug treatments continuing at ICU discharge out of the total number of de novo treatments during ICU admission.
- Proportion of psychotropic drug treatments initiated in the ICU that continue at hospital discharge.
- Proportion of psychotropic drug treatments initiated in the ICU that continue at 30- and 90-days post-discharge.

For patients starting de novo treatment, the following variables will also be collected:

Demographic variables

- Age (years).
- Sex (male/female).
- Diagnosis on ICU admission.
- Category on ICU admission (medical or surgical disease).

Admission-related variables

- ICU days (*n*).
- Hospital days (*n*).
- 30-day mortality after ICU discharge (Yes/No).

Variables related to psychotropic drugs

- Active ingredient used (most common psychotropic drugs: olanzapine, quetiapine, risperidone, ziprasidone, haloperidol, citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, desvenlafaxine, duloxetine, venlafaxine, alprazolam, clonazepam, diazepam, lorazepam, aripiprazole, and others).
- Days from ICU admission to the start of treatment with psychotropic drugs.
- Indications for treatment.
- Continuation of treatment (at hospital discharge, more than 30 days, more than 90 days).
- Duration of treatment (days).
- Place where psychotropic drug was withdrawn (hospital, outpatient, primary care).
- Starting dose (mg), daily dose (mg), and maximum dose achieved (mg).
- Total number of concomitant drugs at baseline, ICU discharge, and hospital discharge.
- Appropriateness of the psychotropic drug regimen according to its data sheet, taking into account the following criteria: Renal function (yes/no), hepatic function (yes/no), age (yes/no), and weight (yes/no).
- Presence of adverse effects (yes/no) and type of adverse effects.

Variables related to polypharmacy

- Number of patients initiating psychotropic drug treatment in the ICU and meeting the polypharmacy criterion (more than 10 drugs according to the ATC classification).

Recruitment

No specific patient recruitment procedure or materials have been established. All participants will be selected from patients undergoing psychotropic drug treatment and who are eligible for inclusion based on the defined selection criteria.

Data sources

Clinical pharmacists will review the clinical history and prescriptions of critically ill patients admitted to the ICU.

Data collection

A data collection notebook will be prepared to record the variables using the REDCap platform. Each research member will access the system with a personal password and record their pharmaceutical interventions. All data entered will be anonymised. A protocol with instructions for data collection will be distributed to researchers and collaborators. As a data collection quality control measure, any situation or issue that arises during the data collection process and that could compromise the quality, integrity, or validity of the collected data will be reviewed by the main investigator, and discrepancies will be evaluated in consensus with the project's lead investigators.

Patient safety

If a suspected reaction related to any medication is detected, the Regional Pharmacovigilance Centre will be notified using the yellow card (www.notificaRAM.es), or the marketing authorisation holder of the suspected drug will be contacted.

Sample size

Patients meeting criteria during an initial study period of 8 weeks will be enrolled in this study. It is estimated that 250 patients will be enrolled during the study period. Due to the limited literature available to justify the sample size, this estimate is provisional.

Statistical methods

A descriptive analysis will be conducted. Quantitative variables will be expressed as measures of central tendency (mean) and dispersion

(standard deviation). Qualitative/categorical variables will be expressed as relative/absolute frequencies.

A comparative analysis of the different clinical variables will be conducted using the Mann–Whitney *U*-test for continuous variables and chi-square for categorical variables.

A *P*-value of <.05 will be used as a cut-off for statistical significance. Data analysis will be performed using the IBM SPSS 20.0 v2.1 statistical package.

All statistical tests to be used to analyse the data collected, based on the study objectives, are detailed in the statistical analysis plan. This statistical analysis plan will be mandatory for the person responsible for the statistical analysis. All deviations from the original statistical plan will be described and justified in the final results report.

Discussion

Delirium affects a large proportion of patients admitted to ICUs and may contribute to the development of anxiety disorders, post-traumatic stress disorder, and long-term major depressive disorder in patients who experience it.[1–3]

In addition to delirium, there are other reasons why a patient may be started on psychotropic drug treatment, such as psychosis. It is common for patients' psychological state to worsen both during and after their ICU stay.[2]

Antipsychotics have traditionally been used in the treatment of delirium in ICUs to control agitation and associated psychotic symptoms. However, their use should be carefully considered and a short and targeted approach is recommended.

Although previous studies have investigated the impact of the psychotropic prescriptions initiated in the ICU on different care transitions,[13,21] to date, research is very scarce and there are no data on what is happening in Spain.

All these aspects highlight the need to know how these drugs are being used in the ICU setting, so that, if necessary, an educational intervention can be implemented a posteriori to reduce their use and the impact of their prescription.

Contribution to the scientific literature and originality

On behalf of the Intensive Care and Critical Care Pharmacists Working Group (FARMIC) of the Spanish Society of Hospital Pharmacy (SEFH), we would like to publish the protocol for the PSICU-ALTA study, an observational study on the continuation of psychotropic drugs at ICU discharge, funded by the Spanish Foundation for Hospital Pharmacy (FEFH) in the 2023–2024 Working Group Grants Call. This is a national, multicentre study designed to analyse and measure the use of psychotropic drugs initiated during ICU admission, to raise awareness of patient polypharmacy, and to lay the groundwork for the design of a potential future intervention to reduce it.

Presentation at congresses

This work has not been previously presented at any congress or scientific meeting, has not been previously published, and is not currently under review by any other journal. It has not received any prizes or citations.

Ethical responsibilities

The study has been evaluated and approved as an observational drug study (prospective) by the Ethics Committee for Medicines Research (CEIM) of the Vall d'Hebron University Hospital on 29 September 2023 (promoter code PSICU-ALTA). All collaborating researchers will sign an undertaking guaranteeing compliance with the Standards of Good Clinical Practice and the Declaration of Helsinki. Given the observational nature of the noninterventional study, a waiver of informed consent was approved. The confidentiality and anonymity of the information obtained regarding the patients, professionals, and ICUs involved will be guaranteed at all times, ensuring compliance with Organic Law 3/2018, of 5 December, on Personal Data Protection and guarantee of digital rights. The results of the study will not impose or entail any obligations on professionals or patients, but there is still a commitment to publish both positive and negative results.

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Use of artificial intelligence (AI) tools

The artificial intelligence tool ChatGPT was used to assist with the English translation of the abstract.

CRediT authorship contribution statement

Laura Doménech-Moral: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Javier Santader-Reboreda:** Writing – review & editing, Writing – original draft, Validation, Investigation, Funding acquisition, Conceptualization. **Meri Martin-Cerezuela:** Writing – review & editing, Writing – original draft, Validation, Supervision, Software, Funding acquisition. **Amaia Egüés Lugea:** Writing – review & editing, Writing – original draft, Validation, Software, Funding acquisition. **Marcos Buj Vicente:** Writing – review & editing, Writing – original draft, Conceptualization. **Sofía Contreras Medina:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization.

Declaration of competing interest

None declared.

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References

1. Bieber ED, Philbrick KL, Shapiro JB, Karnatovskaia LV. Psychiatry's role in the prevention of post-intensive care mental health impairment: stakeholder survey. BMC Psychiatry [Internet]. 2022;22(1) Available from: https://doi.org/10.1186/s12888-022-03855-w.
2. Phadke S, Marwale A, Kocher A. Psychiatric management of patients in intensive care units. Indian J Psychiatry [Internet]. 2022;64(8):292. Available from: https://doi.org/10.4103/indianjpsychiatry.indianjpsychiatry_28_22.
3. Ely EW. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. JAMA [Internet]. 2004;291(14):1753. Available from: https://doi.org/10.1001/jama.291.14.1753.
4. Lat I, McMillian W, Taylor S, Janzen JM, Papadopoulos S, Korth L, et al. The impact of delirium on clinical outcomes in mechanically ventilated surgical and trauma patients. Crit Care Med [Internet]. 2009;37(6):1898–905. Available from: https://doi.org/10.1097/CCM.0b013e31819ffe38.
5. 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 [Internet]. 2009;180(11):1092–7. Available from: https://doi.org/10.1164/rccm.200904-0537OC.
6. Heymann A, Radtke F, Schiemann A, Lütz A, MacGuill M, Wernecke KD, et al. Delayed treatment of delirium increases mortality rate in intensive care unit patients. J Int

Med Res [Internet]. 2010;38(5):1584–95. Available from: https://doi.org/10.1177/147323001003800503.
7. Devlin JW, Bhat S, Roberts RJ, Skrobik Y. Current perceptions and practices surrounding the recognition and treatment of delirium in the intensive care unit: a survey of 250 critical care pharmacists from eight states. Ann Pharmacother [Internet]. 2011;45(10):1217–29. Available from: https://doi.org/10.1345/aph.1Q332.
8. Al-Qadheeb NS, Balk EM, Fraser GL, Skrobik Y, Riker RR, Kress JP, et al. Randomized ICU trials do not demonstrate an association between interventions that reduce delirium duration and short-term mortality: a systematic review and meta-analysis: a systematic review and meta-analysis. Crit Care Med [Internet]. 2014;42(6):1442–54. Available from: https://doi.org/10.1097/CCM.0000000000000224.
9. Jasiak KD, Middleton EA, Camamo JM, Erstad BL, Snyder LS, Huckleberry YC. Evaluation of discontinuation of atypical antipsychotics prescribed for ICU delirium. J Pharm Pract [Internet]. 2013;26(3):253–6. Available from: https://doi.org/10.1177/0897190012465987.
10. Marshall J, Herzig SJ, Howell MD, Le SH, Mathew C, Kats JS, et al. Antipsychotic utilization in the intensive care unit and in transitions of care. J Crit Care [Internet]. 2016;33:119–24. Available from: https://doi.org/10.1016/j.jcrc.2015.12.017.
11. Rowe AS, Hamilton LA, Curtis RA, Davis CR, Smith LN, Peek GK, et al. Risk factors for discharge on a new antipsychotic medication after admission to an intensive care unit. J Crit Care [Internet]. 2015;30(6):1283–6. Available from: https://doi.org/10.1016/j.jcrc.2015.08.009.
12. Hwang YJ, Dixon SN, Reiss JP, Wald R, Parikh CR, Gandhi S, et al. Atypical antipsychotic drugs and the risk for acute kidney injury and other adverse outcomes in older adults: a population-based cohort study: a population-based cohort study. Ann Intern Med [Internet]. 2014;161(4):242–8. Available from: https://doi.org/10.7326/M13-2796.
13. Trifirò G, Gambassi G, Sen EF, Caputi AP, Bagnardi V, Brea J, et al. Association of community-acquired pneumonia with antipsychotic drug use in elderly patients: a nested case–control study: a nested case–control study. Ann Intern Med [Internet]. 2010;152(7):418–25 W139–40. Available from: https://doi.org/10.7326/0003-4819-152-7-201,004,060-00006.
14. By the 2019 American Geriatrics Society Beers Criteriace:sup]® Update Expert Panel. American Geriatrics Society 2019 updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults: 2019 Ags beers criteria® update expert panel. J Am Geriatr Soc [Internet]. 2019;67(4):674–94. Available from: https://doi.org/10.1111/jgs.15767.
15. Flurie RW, Gonzales JP, Tata AL, Millstein LS, Gulati M. Hospital delirium treatment: continuation of antipsychotic therapy from the intensive care unit to discharge. Am J Health Syst Pharm [Internet]. 2015;72(23 Suppl 3):S133–9. Available from: https://doi.org/10.2146/ajhp150474.
16. Farrokh S, Castle AC, Heavner M, Pisani MA. Continuation rate of atypical antipsychotics after discharge when initiated in the intensive care unit. J Pharm Pract [Internet]. 2017;30(3):342–6. Available from: https://doi.org/10.1177/0897190016645026.
17. Celis-Rodríguez E, Cortés D, Bolívar C. Evidence-based clinical practice guidelines for the management of sedoanalgesia and delirium in critically ill adult patients. Guías de práctica clínica basadas en la evidencia para el manejo de la sedoanalgesia y delirium en el paciente adulto críticamente enfermo. Med Intensiva (Engl Ed) [Internet]. 2020;44(3):171–84. Available from: https://doi.org/10.1016/j.medin.2019.07.013.
18. Sandiumenge A, Torrado H. Depresión y uso de antidepresivos en el paciente crítico [Depression and use of antidepressants in the critical patient]. Med Intensiva. 2008;32(1):92–9.
19. Goldman LS, Kimball CP. Depression in intensive care units. Int J Psychiatry Med [Internet]. 1987;17(3):201–12. Available from: https://doi.org/10.2190/yayv-u8xa-yef2-8fm6.
20. Wang S, Mosher C, Gao S, Kirk K, Lasiter S, Khan S, et al. Antidepressant use and depressive symptoms in intensive care unit survivors. J Hosp Med [Internet]. 2017;12(9):731–4. Available from: 10.12788/jhm.2814.
21. Weinert C, Meller W. Epidemiology of depression and antidepressant therapy after acute respiratory failure. Psychosomatics [Internet]. 2006;47(5):399–407. Available from: https://doi.org/10.1176/appi.psy.47.5.399.
22. Wintermann G-B, Rosendahl J, Weidner K, Strauß B, Petrowski K. Predictors of major depressive disorder following intensive care of chronically critically ill patients. Crit Care Res Pract [Internet]. 2018;2018, 1586736. Available from: https://doi.org/10.1155/2018/1586736.
23. D'Angelo RG, Rincavage M, Tata AL, Millstein LS, Gulati MS, Flurie RW, et al. Impact of an antipsychotic discontinuation bundle during transitions of care in critically ill patients. J Intensive Care Med [Internet]. 2019;34(1):40–7. Available from: https://doi.org/10.1177/0885066616686741.
24. Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med [Internet]. 2013;158(3):200–7. Available from: https://doi.org/10.7326/0003-4819-158-3-201,302,050-00583.