Journal of Critical Care 59 (2020) 112–117

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.journals.elsevier.com/journal-of-critical-care

Psychotropic medication use in former ICU patients with mental health problems: A prospective observational follow-up study

Debbie G.A. Janssen [a,*], Joep Jonker [b], Diederik van Dijk [c], Eibert R. Heerdink [b,d,e], Toine C.G. Egberts [b,d], Arjen J.C. Slooter [c]

[a] Expert Centre of Military Pharmacy, Primary Healthcare Institute, Ministry of Defense, PO Box 90004, 3509 AA Utrecht, the Netherlands
[b] Division Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences (UIPS), Faculty of Science, Utrecht University, PO Box 80082, 3508 TB Utrecht, the Netherlands
[c] Department of Intensive Care Medicine and UMC Utrecht Brain Center, University Medical Center Utrecht, Utrecht University, PO Box 85500, 3508 GA Utrecht, the Netherlands
[d] Department of Clinical Pharmacy, University Medical Center Utrecht, Utrecht University, PO Box 85500, 3508 GA Utrecht, the Netherlands
[e] Research Group Process Innovations in Pharmaceutical Care, HU University of Applied Sciences Utrecht, PO Box 12011, 3501 AA Utrecht, the Netherlands

ARTICLE INFO

Available online xxxx

Keywords:
ICU-survivors
Posttraumatic stress disorder
Psychotropic medication
Depression
Anxiety

ABSTRACT

Purpose: To describe the extent to which patients with mental health problems after admission to an Intensive Care Unit (ICU) initiate and use psychotropic medication.
Methods: All adult patients who stayed in the ICU of the University Medical Center Utrecht for 48 h or more between 2013 and 2017, alive after 1 year and not admitted to the ICU with brain injury, were eligible. Questionnaires were used to identify mental health problems, depression, anxiety and posttraumatic stress disorder (PTSD) and psychotropic medication use.
Results: Of the 1328 former ICU patients, 24.3% ($n = 323$) had developed any of the mental health problems. Of this group, 29.7% ($n = 96$) used psychotropic medication one year after discharge versus the 10.6% ($n = 107$) of patients without these problems (OR 3.17, 95% CI 2.29–4.38). They were further 4.33 (95% CI 2.62–7.16) times more likely to initiate psychotropic medication (18.7% vs 4.8%) after ICU admission. Similar patterns were observed for individual groups of psychotropics: antidepressants, antipsychotics and benzodiazepines.
Discussion: Former ICU patients with mental health problems were almost four times more likely to use psychotropic medication than former ICU patients without these problems. Future research should investigate whether mental health problems are properly diagnosed and treated in former ICU patients.

1. Introduction

An increasing number of patients with critical illness survive an admission to the intensive care unit (ICU) because of advancements in critical care. However, approximately 50–70% of these survivors develop some time after ICU discharge symptoms of mental, physical and/or cognitive impairments known as post-intensive care syndrome (PICS) [1-3]. A stay at an ICU is a stressful event that may result in symptoms of PICS including mental health problems due to the acute illness, the multiple life-supporting interventions and procedures and the use of medications. The long-term effects after admission to the ICU are still largely unknown.

The mental problems of PICS are characterized by anxiety, depression and/or posttraumatic stress disorder (PTSD). The risk of developing one of these problems after an ICU stay varies across studies: 12–43% for anxiety, 10–45% for depression and 5–64% for PTSD [1,2,4-6]. Furthermore, patients often develop more than one of these mental health problems [4]. Mental health problems after ICU admission are associated with a lower quality of life and an increased risk of mortality in the next 24 months [1,5,7].

For those suffering from mental health problems after ICU stay, the road from recognizing symptoms to finding the best treatment is not a clear trajectory, as the treatment of ICU survivors comprises a rather new discipline [8,9]. Although we know that the frequency of occurrence of mental health problems in ICU survivors and the impact thereof can be extensive, little is known on 'whether' and 'how' these patients are being treated.

* Corresponding author at: Ministry of Defense/DGO/EGB/DFD, PO Box 90004, 3509 AA, Utrecht, the Netherlands.
E-mail address: DGA.Knotnerus.Janssen@mindef.nl (D.G.A. Janssen).

https://doi.org/10.1016/j.jcrc.2020.06.002
0883-9441/

The objective of the present study was to describe to what extent mental health problems after ICU admission are associated with the initiation and use of psychotropic medication.

2. Material and Methods

2.1. Setting and Study Population

A prospective observational follow-up study was performed in patients who had been admitted to the 32-bed, mixed medical-surgical-cardio ICU of the University Medical Centre Utrecht (UMCU), a large academic hospital in the Netherlands. Included were patients older than 18 years of age who had stayed in the ICU for more than 48 h between January 2013 and December 2017 with at least 1 year of follow-up available. Patients were excluded if they were admitted to the ICU due to brain injury [10], if they had died within the first year after ICU discharge, or if they failed to return the 1-year follow-up questionnaire. The ethics committee of the UMCU approved the study and provided a waiver for informed consent (protocol number 10/006). The patients, who returned the questionnaires gave written consent to use their anonymized data for research purposes.

2.2. Data Collection

Baseline characteristics and clinical data were prospectively collected during ICU admission using the ICU's Patient Data Management System (PDMS) *Metavision*; this information included data on age, gender, planned or unplanned ICU admission, Acute Physiology and Chronic Health Evaluation fourth edition (APACHE IV) [11] score (severity of disease) and Simplified Acute Physiology Score second edition(SAPSII) [12] score (severity of disease), sedation, days in the ICU and mechanical ventilation. Sedation was defined with a score ≤ −3 on the Richmond Agitation and Sedation Scale (RASS) combined with continuous midazolam or propofol administration. Receiving mechanical ventilation was registered dichotomously and positive if a patient had received mechanical ventilation at any moment during ICU admission.

All patients still alive one year after ICU discharge according to the Dutch municipal population register received a questionnaire by mail. If the questionnaire was not returned within several weeks, patients were reminded by mail and/or telephone to send in the questionnaire.

The questionnaire contained a set of standardized and validated questions on quality of life (Euroqol-5D (EQ-5D) [13,14], physical impairment (Barthel) [15,16], and cognitive symptoms (Cognitive Failure Questionnaire (CFQ)) [17]. The questionnaire included standardized and validated questions on depression and anxiety (Hospital Anxiety and Depression Scale [HADS]) [18,19] and current medication use. Symptoms of PTSD were measured using the Impact of Event Scale (IES) until November 2017. Thereafter, the Impact of Event Scale-Revised (IES-R) was used. Revisions in the IES-R versus the IES include seven items on hyperarousal in addition to the 15 items on intrusion and avoidance in the IES [20-22]. All these sets of questions in the questionnaire assessed the situation during the preceding 7 to 14 days. In addition, the patient was asked whether he or she could recall having pain during ICU admission.

2.3. Psychotropic Medication Use

Data on psychotropic medication use before ICU admission was obtained from the PDMS *Metavision*. The data in the PDMS was collected by the hospital pharmacy as part of the medication reconciliation process and included data on the type of drug and prescribed daily dose of all the medication dispensed during the 6 months before admission and still in use at the time of admission. The data on psychotropic medication use 1 year after ICU discharge were obtained from the questionnaires, including information on the type of drug and prescribed daily dose. Psychotropic medication was identified using the anatomical therapeutic chemical classification system. A distinction was made between the different psychotropic medication groups: antipsychotics (N05A; excluding lithium: N05AN), antidepressants (N06A) and benzodiazepines (N05B or N05C; excluding melatonin receptor agonists: N05CH). The use of psychotropic medication 1 year after discharge was defined as using one of the drugs from the groups above on the questionnaire.

2.4. Mental Health Problems

Data on depression, anxiety and PTSD symptoms were obtained from the HADS and IES/IES-R questionnaires. Depression was defined as a score of ≥8 for the HADS depression items; anxiety was defined as a score of ≥8 for the HADS anxiety items and PTSD as a score of ≥33 for the IES-R questionnaire or a score of ≥35 for the IES questionnaire. All the scores for depression, anxiety and PTSD were dichotomized using these threshold scores.

2.5. Data Analysis

Student *t*-tests and Mann–Whitney *U* tests were used to determine the differences in baseline characteristics between patients with and without mental health problems. Logistic regression analysis was used to quantify the strength of the association between mental health problems and using psychotropic medication 1 year after ICU discharge, expressed as odds ratios (ORs) with a corresponding 95% confidence interval (95% CI). These analyses were adjusted for the following potential confounding variables: age, gender, admission type (elective or acute), pain during ICU stay, days in ICU, Apache IV, SAPSII, sedation and mechanical ventilation. In addition, a subgroup analysis was done for the group of ICU survivors that did not use any psychotropic medication at the time of admission to the ICU. Patients that used any psychotropic medication at the time of admission were excluded from this subgroup analysis. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 25.

3. Results

During the study period, 2166 former ICU patients received a questionnaire. Of these, 838 (38.7%) were excluded because they did not return the questionnaire ($n = 515$, response rate 76.2%), were admitted to the ICU with brain injury ($n = 290$), died in the time between checking the Dutch municipal population register and sending the questionnaires ($n = 18$) or were younger than 18 years old ($n = 15$) during admission. Thus, a total of 1328 former ICU patients were included in this study (Fig. 1). Overall the mean age was 59.2 years, the majority being men (67.5%). Of all admissions to the ICU 34.4% of these were planned admissions and patients had an average stay at the ICU of 9.2 days. During that admission 36.3% of the patients experienced pain. The mean SAPS II score was 38.8 and the mean Apache IV score was 61.1. There were no differences in these scores for patients who developed mental health problems 1 year after discharge and those who did not. Almost all patients (98.3%) received mechanical ventilation during the ICU stay. Patients who described mental health problems 1 year after discharge were more likely to use antidepressants, antipsychotics and benzodiazepines at the time of admission than those who did not.

Approximately a quarter (24.3%, $n = 323$) of the included individuals suffered from one or more of mental health problems 1 year after ICU discharge: 14.7% ($n = 196$) of the individuals suffered from depression, 15.2% ($n = 202$) from anxiety and 8.5% ($n = 113$) from PTSD a year after ICU discharge. In total, 11.2% ($n = 149$) suffered from two or three mental health disorder.

Former ICU patients with depression, anxiety and/or PTSD symptoms were younger, had more pain during their ICU stay and used more antidepressants, benzodiazepines and antipsychotics before ICU admission in comparison to former patients without these mental

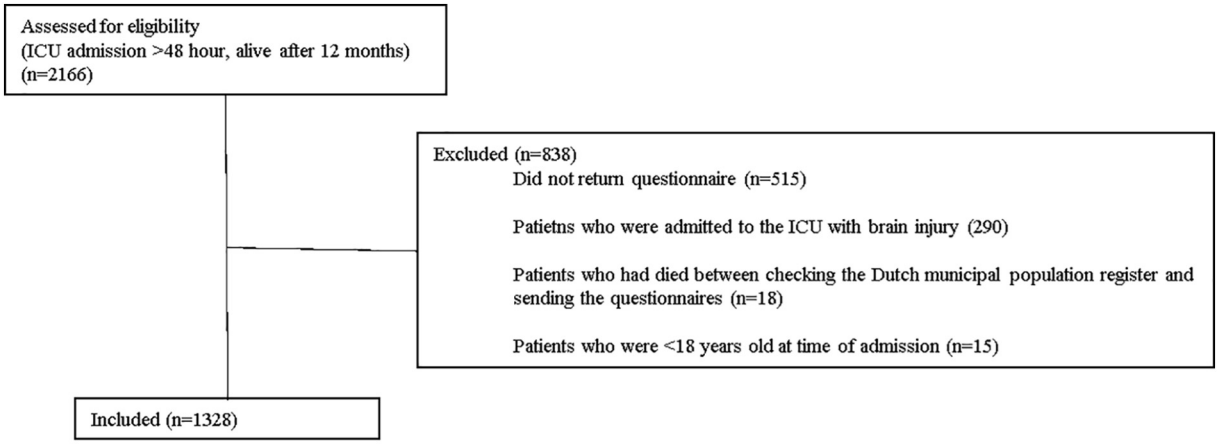

Fig. 1. Inclusion of ICU survivors

Table 1
Patient characteristics.

Characteristics	All patients (n = 1328)	Patients with mental health problems (n = 323)	Patients without mental health problems (n = 1005)	P value
Characteristics IC admission				
Age, mean (SD)[a]	59.19 (15.45)	57.30 (16.38)	59.79 (1.10)	0.016
Male, n (%)[b]	897(67.5%)	210 (65%)	687 (68.4%)	0.264
Planned admission, n (%)[a]	456 (34.4%)	104 (32.3%)	352 (35.0%)	0.370
Days in ICU, mean (SD)[a]	9.21 (12.45)	9.29 (11.99)	9.19 (12.60)	0.902
Pain, n(%)[b]	414 (36.3%)	132 (42.2%)	282 (34.1%)	0.011
SAPS II score, mean (SD)[a]	38.77 (13.51)	38.23 (13.00)	38.95 (13.67)	0.406
Apache IV score, mean (SD)[a]	61.12 (24.22)	59.32 (23.37)	61.70 (24.47)	0.162
Sedation, n(%)[b]	892 (67.4%)	231 (72.0%)	661 (66.0%)	0.046
Received mechanical ventilation, n (%)[b]	1297 (98.3%)	316 (98.4%)	981 (98.3%)	0.859
Antidepressant use before ICU admission, n (%)[b]	132 (10.1%)	50 (15.5%)	82 (8.3%)	<0.001
Antipsychotic use before ICU admission, n(%)[b]	41 (3.1%)	16 (5.0%)	25 (2.5%)	0.029
Benzodiazepine use before ICU admission, n(%)[b]	239 (18.3%)	83 (25.8%)	156 (15.8%)	<0.001
Characteristics one year after ICU discharge				
Barthel Score, mean (SD)[a]	18.65 (3.46)	17.52 (4.66)	19.08 (2.77)	<0.001
CFQ Score, mean (SD)[a]	21.98 (15.89)	32.95 (18.02)	18.14 (13.07)	<0.001
EQ-5D, mean (SD)[a]	0.77 (0.25)	0.59 (0.29)	0.84 (0.20)	<0.001
Filled in the questionnaire themself, n (%)[b]	959 (82.6%)	227 (70.5%)	732 (87.2%)	<0.001
Back to work, n (%)[b]	1015 (87.7%)	242 (76.3%)	773 (92.0%)	<0.001

SD: standard deviation, SAPS II: Simplified Acute Physiology Score second edition, APACHE IV: Acute Physiology and Chronic Health Evaluation fourth edition, CFQ: Cognitive Failure Questionnaire, EQ-5D: Euroqol-5D.
[a] Student t-test.
[b] Mann-Whitney U test.

health problems (Table 1). Furthermore, individuals with any of the mental health problems also mentioned accompanying problems as they had more physical impairment (a lower average score on the Barthel questionnaire) and an inferior quality of life (a lower score for EQ5D), less cognitive function (a higher average score for the CFQ questionnaire) and required more help with completing the questionnaire, while a lower percentage went back to work.

Individuals with mental health problems were 3.17 (CI 95% 2.29–4.38) times more likely to use psychotropic medication (29.7% versus 10.7%) 1 year after ICU discharge than individuals without mental health problems. A larger effect was observed when only the initiators of psychotropic medication were included in the analysis. Individuals with mental health problems were 4.33 (CI 95% 2.62–7.16) times more likely to initiate psychotropic medication (18.7% versus 4.8%) 1 year after ICU discharge than individuals without mental health problems. Benzodiazepines were used by 19.5% ($n = 63$) of the individuals with mental health problems, while 15.5% ($n = 50$) used an antidepressant, and 3.1% ($n = 10$) used an antipsychotic. For each of the psychotropic medication groups, the individuals with mental health problems were over three times more likely to use the medication compared to the individuals without mental health problems (Table 2).

Fig. 2 shows the use of psychotropic medication in former ICU patients differentiated for the mental health problems depression, anxiety and PTSD. The figure demonstrates that not all mental health problems led to similar percentages of treatment with psychotropic medication. Patients received treatment with psychotropic medication most often when they had combined symptoms of depression, anxiety and PTSD symptoms (17 out of 39; 43.6%) 1 year after ICU discharge, while the group of patients with depression and PTSD received treatment with psychotropic medication 2.5 times less frequently (2 out of 11, 18.2%).

Fig. 2b shows the same parameters as Fig. 2 but showing the patients who initiated any psychotropic medication. When it came to new users, patients with depression and PTSD initiated psychotropic medication treatment most often (2 out of 11; 18.2%), while in the group of patients with anxiety and PTSD, only 7.7% (2 out of 26) initiated new psychotropic medication after discharge.

Table 2
The association between mental health problems and psychotropic medication use one year after ICU discharge.

All users[c]	All patients (n = 1328)	Patients with mental health problems (n = 323)	Patients without mental health problems (n = 1005)	OR (95% CI)[a] Crude	OR (95% CI) Adjusted[b]
Antidepressants	113 (8.5%)	50 (15.5%)	63 (6.3%)	2.74 (1.85–4.07)	2.41 (1.60–3.62)
Antipsychotics	17 (1.3%)	10 (3.1%)	7 (0.7%)	4.56 (1.72–12.07)	3.46 (1.22–9.79)
Benzodiazepines	118 (8.9%)	63 (19.5%)	55 (5.5%)	4.19 (2.84–6.16)	3.76 (2.51–5.61)
Any psychotropic medication	203 (15.3%)	96 (29.7%)	107 (10.6%)	3.54 (2.60–4.85)	3.17 (2.29–4.38)
Initiators only[d]	All initiators (*n* = 979)	Patients with mental health problems (*n* = 209)	Patients without mental health problems (*n* = 770)	OR (95% CI)[a] Crude	OR (95% CI) Adjusted[b]
Antidepressants	38 (3.9%)	19 (9.1%)	19 (2.5%)	3.95 (2.05–7.61)	3.62 (1.81–7.23)
Antipsychotics	3 (0.3%)	2 (1.0%)	1 (0.1%)	7.43 (0.67–82.34)	6.18 (0.48–78.88)
Benzodiazepines	45 (4.6%)	26 (12.4%)	19 (2.5%)	5.62 (3.04–10.37)	5.16 (2.74–9.72)
Any psychotropic medication	76 (7.8%)	39 (18.7%)	37 (4.8%)	4.55 (2.81–7.43)	4.33 (2.62–7.16)

[a] OR = Odds Ratio and CI = Confidence interval
[b] Adjusted for age, gender, planned admission, pain during ICU, days in ICU, Apache IV, SAPS II, sedation and mechanical ventilation.
[c] All use of psychotropic medication 1 year after ICU discharge.
[d] Subgroup analysis of psychotropic medication use 1 year after ICU discharge, for patients with no psychotropic medication use at the time of admission.

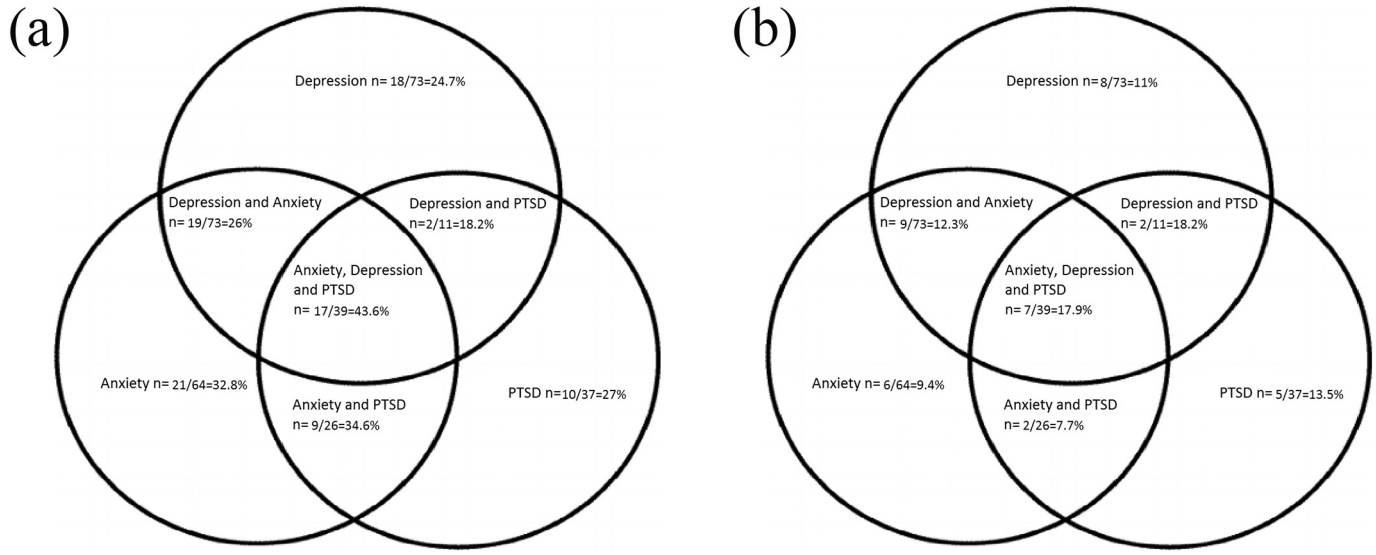

Fig. 2. a Use of psychotropic medication one year after ICU discharge. Categorized on each of the mental health problems one year after ICU discharge. b Initiation of psychotropic medication after ICU discharge. Categorized on each of the mental health problems one year after ICU discharge.

4. Discussion

Overall, we found an association between depression, anxiety and/or PTSD symptoms and the use of psychotropic medication 1 year after ICU discharge. We demonstrated that former ICU patients with mental health problems were over three to four times more likely to initiate and use psychotropic medication 1 year after ICU discharge than former patients without these mental health problems. Furthermore, less than one third of the patients who had symptoms of depression, anxiety and/or PTSD used any form of psychotropic medication.

This study further showed that approximately a quarter of the patients with symptoms of depression used a psychotropic medication 1 year after ICU discharge, and almost one third of the patients with symptoms of anxiety were treated with medication. We know from other populations that, following diagnosis, up to 80% receives pharmacological treatment for their depression [23] and a little more than 60% receives pharmacological treatment for anxiety [24]. This result suggests that these problems may not be known to health care professionals, or that pharmacological therapy is not started. To receive treatment, a patient must recognize the mental health problems, then decide to visit a physician who need to recognize and diagnose these mental health problems. Afterwards, the physician needs to decide whether psychotropic medication should be prescribed to treat these mental health problems. For pharmacological treatment of depression, anxiety and/or PTSD, several types of psychotropic medication can be used. But, as shown by this study, treatment with psychotropic medication has not reached the majority of these patients.

To our knowledge, only one study has assessed information on mental health problems and psychotropic medication use before and after ICU stay. This study demonstrated that critically ill patients who

received mechanical ventilation had an increased risk of a new psychiatric diagnosis and new use of psychotropic medication in the first 3 months after ICU admission, compared to other hospitalized patients and the general population [25]. This increased risk disappeared after 9 and 12 months. This study consisted of two parts, one part before ICU admission and one follow-up after ICU admission. All surgical patients were excluded for both parts of the study and all patients with a psychiatric diagnosis or psychotropic medication use before their ICU admission were excluded for the follow-up in this study.

One other study followed patients leaving the ICU for a long-term, acute-care facility. In this study group, 47% of the patients used an antidepressant (two-thirds initiated their antidepressant after ICU discharge) in the first few weeks after ICU discharge [26]. In our study group, only one in six patients used antidepressants 1 year after discharge, and only 6.5% of the patients with mental health problems initiated an antidepressant. This significant difference can be explained by the intensity of treatment and possibly by the alertness to mental health problems in the long-term, acute-care facility. This difference might also be because the other study explored the use of antidepressants within 3 weeks after ICU discharge, while we explored the use of psychotropic medication 1 year after ICU discharge. This difference could indicate that either many patients discontinue their antidepressant use before the end of the first year after ICU discharge or that different indications are being used for prescription 3 weeks or 1 year after ICU discharge.

The literature has shown that prior psychopathology impacts the development of delirium in ICU patients [27]. Our study did not obtain data about psychopathology prior to critical illness, and we speculate that prior psychopathology could also be a risk factor for the development of mental health problems after ICU admission.

Recently, a study has been published on almost the same population [28]. In this study, higher percentages of depression (33% vs 15%), anxiety (34% vs 15%) and PTSD (19% vs 11%) were found due to differences in inclusion and exclusion criteria. Furthermore, the treatment policy considering sedation has changed dramatically over time. The effects of these changes should be explored further in future research.

The results in our study show that former ICU patients with mental health problems did not only suffer from mental health problems, but also reported a lower quality of life, more physical impairment and a lower cognition. As a result, these patients needed help with filling out the questionnaire more often. Also, a lower percentage went back to work. However, we cannot distinguish between cause and effect of PICS and the multiple factors of PICS.

In this study only psychotropic medication, related to mental health problems were investigated. Other medication frequently used in patients post-ICU may also be interesting, including the (over) use of opioids. The method that was used in this study would also be appropriate to evaluate the use of opioids 1 year after ICU discharge.

Our study has some limitations. First, the indication for the prescribed psychotropic medication was not available. Furthermore, data on possible psychiatric evaluations was unknown to the researchers. Therefore, we may have overestimated or underestimated the use of psychotropic medication related to the mental health problems of the post ICU syndrome, as not all mental health problems may be related to the former critical illness and treatment during ICU admission. Second, in this study, questionnaires were used to determine whether patients suffered from mental health problems. Although these questionnaires are validated and used as a diagnostic tool by psychiatrists, in this study, they were completed by the patients in their home setting. Therefore, we do not know under what circumstances the questions were answered; we could have overestimated the number of actual mental health problems. Last, this single-center study did not include data from other hospitals. It is well possible that the results differ between treatment facilities.

Our study also has several strengths. First, we investigated a relatively large population of 1328 former patients. Other studies in the ICU have often included relatively small populations. Additionally, we achieved a response rate of 76% for the questionnaires, which is relatively high. Although we do not know why almost a quarter of the former ICU patients did not complete the questionnaire, we still had a viable group to analyze. This is further the first study to explore the use of psychotropic medication in patients with mental health problems 1 year after ICU discharge.

The findings in this study suggest that there is an opportunity to improve diagnosis and treatment mental health problems in former ICU patients. This trajectory could then focus on all the aspects of PICS. Therefore, we suggest further research on the topic and the possibility of a post-ICU trajectory where the development of mental health problems can be monitored and possibly treated. While suggesting this topic for future research, we recognize that UMC Utrecht offers outpatient ICU aftercare. The response to the invitations to these outpatient sessions is however considered low (approximately 10%).

5. Conclusion

In conclusion, our study demonstrated that former ICU patients with depression, anxiety and/or PTSD were approximately three to four times more likely to use and initiate psychotropic medication. On the other hand, not even one third of the patients with any of these mental health problems used psychotropic medication. Future research should investigate whether mental health problems are properly recognized, diagnosed and treated in former ICU patients.

Funding

None.

Declaration of Competing Interest

None.

Acknowledgements

None.

References

[1] Hatch R, Young D, Barber V, Griffiths J, Harrison DA, Watkinson P. Anxiety, depression and post traumatic stress disorder after critical illness: a UK-wide prospective cohort study. Crit Care 2018;22(1):310. https://doi.org/10.1186/s13054-018-2223-6.

[2] Sivanathan L, Wunsch H, Vigod S, Hill A, Pinto R, Scales DC. Mental illness after admission to an intensive care unit. Intensive Care Med 2019;45(11):1550–8. https://doi.org/10.1007/s00134-019-05752-5.

[3] Wang S, Allen D, Kheir N, Campbell N, Khan B, Science I, et al. Aging and post-intensive care syndrome (PICS): a critical need for geriatric psychiatry. Am J Geriatr Psychiatry 2019;26(2):212–21. https://doi.org/10.1016/j.jagp.2017.05.016.

[4] Wolters AE, Peelen LM, Welling MC, Kok L, de Lange DW, Cremer OL, et al. Long-term mental health problems after delirium in the ICU. Crit Care Med J 2016;44(10). https://doi.org/10.1097/CCM.0000000000001861.

[5] Myhren H, Ekeberg Ø, Tøien K, Karlsson S, Stokland O. Posttraumatic stress, anxiety and depression symptoms in patients during the first year post intensive care unit discharge. Crit Care 2010;14(1):1–10. https://doi.org/10.1186/cc8870.

[6] Warlan H, Howland L, Connelly C. Detection of posttraumatic stress symptoms in patients after discahrge from intensive care. Am J Crit 2016;25(6). https://doi.org/10.4037/ajcc2016573.

[7] Davydow DS, Gifford JM, Desai SV, et al. Posttraumatic stress disorder in general intensive care unit survivors : a systematic review. Gen Hosp Psychiatry 2008;30:421–34. https://doi.org/10.1016/j.genhosppsych.2008.05.006.

[8] Labuzetta JN, Rosand J, Vranceanu AM. Review : post - intensive care syndrome : unique challenges in the neurointensive care unit. Neurocrit Care 2019. https://doi.org/10.1007/s12028-019-00826-0.

[9] Wang BS, Allen D, Perkins A, Khan S, Lasiter S, Boustani M, et al. Validation of a new clinical tool for post-intensive care syndrome. Am J Crit Nurses 2019;28(1):10–8. https://doi.org/10.4037/ajcc2019639.

[10] van Eijk M, van den Boogaard M, van Marum RJ, Benner P, Eikelenboom P, Honing ML, et al. Routine use of the confusion assessment method for the intensive care unit: a multi centre study. Am J Respir Crit Care Med 2011 Aug 1;184(3):340–4. https://doi.org/10.1164/rccm.201101-0065OC.

[11] Zimmerman JE, Kramer AA, Mcnair DS, Malila FM. Acute Physiology and Chronic Health Evaluation (APACHE) IV: hospital mortality assessment for today's critically ill patients. Crit Care Med 2006;34(5):1297–310. https://doi.org/10.1097/01.CCM.0000215112.84523.F0.

[12] Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. JAMA 1993 Dec;270(24):2957–63. https://doi.org/10.1001/jama.270.24.2957.

[13] Devlin NJ, Brooks R. EQ-5D and the EuroQol group : past, present and future. Appl Health Econ Health Policy 2017;15(2):127–37. https://doi.org/10.1007/s40258-017-0310-5.

[14] Stolk E, Ludwig K, Rand K, Houtvan B, Ramos-go JM. Overview, update, and lessons learned from the international EQ-5D-5L valuation work : version 2 of the EQ-5D-5L valuation protocol. Value Health 2019 Jan;22(1):23–30. https://doi.org/10.1016/j.jval.2018.05.010.

[15] Collin C, Wade DT, Davies S, Horne V. The Barthel ADL Index: a reliability study. Int Disabil Stud 1988;10(2):61–3. https://doi.org/10.3109/09638288809164103.

[16] Wade DT, Hewer RL. Functional abilities after stroke : measurement, natural history and prognosis, 0; 1987; 177–82. https://doi.org/10.1136/jnnp.50.2.177.

[17] Broadbent DE, Cooper PF, Fibgerald P, Parkes KR. The Cognitive Failures Questionnaire (CFQ) and its correlates; 1982; 1–16. https://doi.org/10.1111/j.2044-8260.1982.tb01421.x.

[18] Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983 Jun;67(6):361–70. https://doi.org/10.1111/j.1600-0447.1983.tb09716.x.

[19] Bjelland I, Dahl AA, Tangen T, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale An updated literature review, 52; 2002; 69–77. https://doi.org/10.1016/s0022-3999(01)00296-3.

[20] Horowitz M, Wilner N, Alvarez W. Impact of event scale: a measure of subjective stress. Psychosom Med 1979;41(3). https://doi.org/10.1097/00006842-197905000-00004.

[21] Creamer M, Bell R, Failla S. Psychometric properties of the impact of event scale — revised. Behav Res Ther 2003;41:1489–96. https://doi.org/10.1016/j.brat.2003.07.010.

[22] Parker AM, Sricharoenchai T, Raparla S, Schneck KW, Bienvenu OJ, Needham DM. Posttraumatic stress disorder in critical illness survivors: a metaanalysis. Crit Care Med J 2014:1121–9. https://doi.org/10.1097/CCM.0000000000000882.

[23] Martin-Merino E, Ruigomez A, Johansson S, Wallander MA, Garcia-Rodriguez LA. Study of a cohort of patients newly diagnosed with depression in general practice: prevalence, incidence, comorbidity, and treatment patterns. Prim Care Companion J Clin Psychiatry 2010;12(1). https://doi.org/10.4088/PCC.08m00764blu PCC.08m00764.

[24] Martin-Merino E, Ruigomez A, Wallander MA, Johansson S, Garcia-Rodriguez LA. Prevalence, incidence, morbidity and treatment patterns in a cohort of patients diagnosed with anxiety in UK primary care. Fam Pract 2010 Feb;27(1):9–16. https://doi.org/10.1093/fampra/cmp071.

[25] Wunsch H, Christiansen CF, Johansen MB, Olsen M. Psychiatric diagnoses and psychoactive medication use among nonsurgical critically ill patients receiving mechanical ventilation. JAMA 2019;311(11):1133–42. https://doi.org/10.1001/jama.2014.2137.

[26] Weinert CR. Epidemiology of psychiatric medication use in patients recovering from critical illness at a long-term acute- care facility. Chest 2001;119(2):547–53. https://doi.org/10.1378/chest.119.2.547.

[27] Sajjad A, Wolters AE, Veldhuijzen DS, Peelen LM, Welling MC, Zaal IJ, et al. Psychopathology prior to critical illness and the risk of delirium onset during intensive care unit stay. Intensive Care Med 2018;44(8):1355–6. https://doi.org/10.1007/s00134-018-5195-8.

[28] Dijkstra-kersten SMA, Kok L, Kerckhoffs MC, Cremer OL, D.W. Lange de, D. Dijk van, et al.. Neuropsychiatric outcome in subgroups of Intensive Care Unit survivors : implications for after-care. J Crit Care 2020;55(December 2016):171–6. https://doi.org/10.1016/j.jcrc.2019.11.006.