# **Title: Opioid, sedative, preadmission medication and iatrogenic withdrawal risk in UK adult critically ill patients: a point prevalence study**

# **Abstract**

Background: Iatrogenic withdrawal syndrome, after exposure medication known to cause withdrawal is recognised, yet under described in adult intensive care.

Aim: Investigate, opioid, sedation and preadmission medication practice in critically ill adults with focus on aspects associated with iatrogenic withdrawal syndrome

Methods: One-day point prevalence study in UK ICUs. We collected ICU admission medication and/or substances with withdrawal potential, sedation policy, opioid and sedative use, dose, and duration.

Results: 37 from 39 participating ICUs contributed data from 386 patients. The prevalence rate for parenteral opioid and sedative medication was 56.1%, (212 patients). 23 ICUs (59%) had no sedation/analgesia policy, and no ICUs screened for iatrogenic withdrawal. Patient admission medications with withdrawal-potential included antidepressants or antipsychotics (43, 20.3%) and nicotine (41, 19.3%). Of 212 patients, 202 (95.3%) received opioids, 163 (76.9%) sedatives and 153 (72.2%) both. 202 (95.3%) patients received opioids: 167 (82.7%) by continuous infusions and 90 (44.6%) patients for longer than 96-hours. 163 (76.9%) patients received sedatives: 157 (77.7%) by continuous infusions and 74 (45.4%) patients for longer than 96-hours.

Conclusion: Opioid and sedative prevalence rates were high, and a high proportion of ICUs had no sedative/analgesic policies. Nearly half of patients received continuous opioids and sedatives for longer than 96-hours placing them at high risk of iatrogenic withdrawal. No participating unit reported using a validated tool for iatrogenic withdrawal assessment.

**Keywords**

Analgesics, opioids critical care, cross-sectional study, sedatives.

**Impact Statements**

* In this study, a high proportion of the participating intensive care units did not have a policy for managing and weaning sedation and analgesia.
* The high prevalence of patients receiving opioid and/or sedative continuous infusion for greater than 96 hours places them at high risk of iatrogenic withdrawal.
* There is an urgent need for a validated screening tool for adult intensive care patients to assist healthcare professionals to assess for iatrogenic withdrawal syndrome.

**Word Count**

2924 words (main manuscript excluding abstract)

# Introduction

Patients admitted to the intensive care unit (ICU) frequently receive opioids and sedatives for treating pain and anxiety and to facilitate effective mechanical ventilation[1](#_ENREF_1). The longer that patients receive mechanical ventilation with opioids and sedatives, the higher the risk of delirium some of which may represent iatrogenic withdrawal syndrome (IWS) [2](#_ENREF_2). IWS manifests with a combination of signs and symptoms due to dysregulation of the autonomic nervous system. These symptoms occur upon abrupt discontinuation or rapid tapering of drugs known to produce physiological dependence and the syndrome shares features of both sedative-hypnotic and opioid withdrawal [3](#_ENREF_3).Signs of IWS overlap with delirium secondary to critical illness; and it is therefore challenging to diagnose IWS in critical illness without a validated assessment tool [4](#_ENREF_4),[5](#_ENREF_5).

In children, IWS is well described and associated with untoward outcomes such as an increased duration of mechanical ventilation, ICU, and hospital length of stay [5](#_ENREF_5),[6](#_ENREF_6) . IWS is largely unrecognised in adult intensive care and this under-recognition in adults may be due to challenges understanding the problem, its overlap with other conditions, lack of screening tools and management strategies, and it’s unclear impact on clinical outcome [1](#_ENREF_1). Risk factors could include prolonged and cumulative doses of opioids and benzodiazepines, prolonged duration of sedative use, high body mass index, young age, and a history of drug or alcohol dependence [2](#_ENREF_2),[7](#_ENREF_7).

International guidelines recommend assessment-driven, protocol-based strategies to manage pain and sedation and prevent complications, including IWS (conditional recommendation, moderate quality evidence[1](#_ENREF_1) . Within the UK, two previous sedation surveys of 214 and 157 adult ICUs respectively reported that 57 and 59% had a written sedation protocol; 94% and 78% had sedation hold policies [8](#_ENREF_8),[9](#_ENREF_9). The use of IWS protocols were not reported. Furthermore, the publication of the 2018 Society of Critical Care Medicine guidelines for pain, agitation/sedation, delirium, immobility, and sleep disruption (PADIS) in adult patients in the ICU do not address IWS [1](#_ENREF_1). Clearly there are gaps in understanding of assessment, prevention, and treatment of IWS.

The aim of this study was to investigate current opioid, sedation and preadmission medication practice in critically ill adults with a focus on aspects that could relate to IWS. The study objectives were to describe how adult ICU patients were weaned from continuously administered opioids and sedatives; compare those ICUs with and without a sedation policy; compare equivalence in patient opioid burden, describe opioids and sedatives used in participating ICUs; and identify what assessments or validated tools were used to identify IWS.

## **Ethical considerations**

The ALERT-ICU protocol was reviewed by the Wilkes University Institutional Review Board (IRB) [Ref: #116] and was provided an ethical exempt determination notification. In the UK, the study was classified as a service evaluation, reviewed by local Research and Development Offices in participating hospitals and Data Use Agreement and Institutional Authorisation Agreements were approved.

# **Methods**

This UK study was part of an international point prevalence study. The study was registered on ClinicalTrials.gov (AduLt iatrogEnic withdRawal sTudy in the ICU [ALERT-ICU], Bolesta 2021, NCT04422808). The study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement.

## **Study design and participants**

A prospective, observational, one-day point prevalence study of opioid, sedation, and drug withdrawal practices in National Health Service, NHS UK ICUs. ICUs selected a one-day study period between June 1st and September 30th, 2021. Patients aged 18-years and older admitted to adult ICUs were eligible for inclusion. Patients were included if they received either parenteral opioids and/or sedatives in the 24-hours prior to the data collection day. There were no exclusion criteria.

All electronic study data were kept in password-protected computer files. Data were coded by assigning a unique identification number to participating institutions and individual ICUs and patients were assigned a unique study identification number. Analysis was performed using the coded data. Only aggregate data without personal identifiers have been included in results.

## **Data collection**

Recruitment of data collectors was achieved by contacting national representatives from professional networks including the UK Clinical Pharmacy Association (UKCPA), the Intensive Care Society (ICS), and the UK Critical Care Research Group (UKCCRG). Networks advertised the study on a national level and recruited members as investigators. The local investigators liaised with their Research and Development Offices to secure approval, collected data and acted as guarantor for the integrity and quality of data. To maximise consistency in reporting, registered local investigators received training on data collection through virtual meetings (led in UK by RE), and online tutorials, recorded training sessions and the Operations Manual available on the ALERT-ICU website (https://www.iatrogenicwithdrawalstudy.com/).

Anonymous patient data were collected using the Research Electronic Data Capture (Redcap) secure web-based data collection tool. The system allowed real-time input of data by local investigators.

Data were collected at the point of enrolment pertaining to ICU type, its daily interprofessional ward rounds (defined as doctor, and other disciplines including, but not limited to nurse, pharmacist and physiotherapist) or use of opioids, sedation, admission drugs with withdrawal potential and withdrawal assessment tools and protocols. Patient characteristics and clinical data were obtained from the patient’s clinical record. Daily and cumulative amounts of opioids and sedatives were recorded along with durations of therapy and medication weaning. Patient hours on mechanical ventilation and length of ICU stay were also documented up to point of data collection.

### **Medicines reconciliation data**

A history of recreational substance use and long-term medication with a documented predisposal to withdrawal syndrome was also collected [10](#_ENREF_10). The history included information about prescription of gabapentinoids, antidepressants, opioids, and history of nicotine (including tobacco), alcohol and other drug use.

## **Data analysis**

Data were analysed by RE, DH and BB using appropriate descriptive statistics (number, proportion; mean, standard deviation; or median, interquartile range) and are presented in tabular format. Opioid and sedative doses were expressed as total in milligrams on day of data collection. Relationships were explored between units that did/did not have sedative and opioid analgesia policies in types of analgesia and sedatives used, dosages, and reduction in dosage percentages using Chi square and Mann-Whitney U using Social Science Statistics. (https://www.socscistatistics.com/tests/chisquare2/default2.aspx).

Opioid and Sedation Equivalence.

For comparison purposes, opioid doses were expressed in terms of fentanyl equivalence [11](#_ENREF_11). For sedation therapy, equivalent dosing was not calculated because the selected sedatives had different pharmacological properties e.g., benzodiazepines and alpha-2-agonists; therefore, sedative duration was used to compare sedatives.

# **Opioid Equivalence**

**In both conversion of alfentanil and remifentanil to fentanyl scenarios, expert advice was first sought from the Pharmaceutical Press (publishers of Palliative Care Formulary)**[**11**](#_ENREF_11)**. Their advice was to convert both alfentanil and remifentanil into morphine and then to fentanyl. The Palliative Care Formulary was the reference source for conversion of alfentanil to morphine and a publication by Amiraal at al was used for remifentanil to morphine**[**12**](#_ENREF_12)**. The PCF was reference source for conversion of morphine to fentanyl.**[**11**](#_ENREF_11)

# **Results**

## **ICU and patient characteristics**

39 ICUs from 17 UK NHS Trusts participated, and 212 of 378 screened patients (56.1%) from 37 ICUs met inclusion criteria and were included in the study (Table 1). The major ICU type was mixed medical/surgical (59%). Multidisciplinary bedside rounds were conducted in most (33, 84.6%), and were conducted a minimum of four times per week in 17 ICUs (43.6 %). A minority of ICUs reported policies that addressed daily sedation interruption (17 ICUs, 43.6%), general sedation/analgesia (14 ICUs, 36%), sedation/analgesia weaning (8, 20.5%), and IWS 4 (10.3%). All ICUs reported having tools to assess the level of sedation only three units did not use a pain assessment tool. None of the 39 ICUs reported a validated tool to assess for IWS.

A greater proportion of patients were admitted with respiratory system disease (79, 37.3%) and were white (162, 76.4%) (Table 2). At the point of recruitment, patients had been in the ICU for a median of 6 (IQR 2 to 14) days; 165 (78.3%) were receiving invasive mechanical ventilation; and 54 (25.5%) were COVID-19 positive.

The main medications with iatrogenic withdrawal potential taken by patients prior to admission were antidepressants or antipsychotics (20.3%) and opioids (14.2%), with 41 (19.3%) taking nicotine and 12 (5.7%) with a history of taking recreational drugs (Table 2). Alcohol misuse was noted in 25 (11.8%) patients.

In the 24-hours prior to data collection, 202 patients (95.3%) received parenteral opioids; 163 (76.9%) received parenteral sedatives; and 153 (72.2%) received both.

## **Opioids**

Of 202 patients who received parenteral opioids the most used were fentanyl (35.1%) and alfentanil (33.2%) (**Table 3**). There were 167 (83%) patients who received opioids by continuous infusion and 44.6% received opioids for more than 96 hours. 150 patients received opioids for 24 hours or more, and 36.3% had the dose reduced within the previous 24 hours. Sixteen patients (29.6%) had their dose reduced by more than 50%. 171 (84%) patients were receiving the shorter acting opioids, remifentanil, alfentanil and fentanyl.

Within 14 ICUs that had a sedation/analgesia policy in place there were more patients on fentanyl and less patients on alfentanil and morphine (*X2* 36.87 [df 3], *N* = 186, p = <.001). No patients in ICUs with a policy received oxycodone in comparison to 20 patients in non-policy ICUs. For patients with an opioid duration of 24 hours or more; there was no relationship between policy/no policy ICUs and opioid duration (*X2* 1.99 [df 3], *N* = 202, p =.57) or the proportionate reduction in opioids over the previous 24-hours (*X2* 4.37 [df 3], *N* = 54, p =.36).

Higher doses of fentanyl as continuous infusion were administered to patients in ICUs with no sedation/analgesia policy in comparison to those with a policy (Mann-Whitney test (two-tailed) N=71, p=0.047. In contrast, doses of alfentanil doses were higher in ICUs with a sedation/analgesia policy and these ICUs recorded higher total overall opioid exposure (Mann-Whitney test (two-tailed) alfentanil, N=67 p=0.0029.

Opioid Equivalence

The conversion of alfentanil to morphine was estimated as 1mg alfentanil approximates to 15mg of morphine; then morphine to fentanyl is 75mg morphine is approximately 1mg fentanyl. In converting alfentanil to fentanyl, 1mg alfentanil is approximately equivalent to 0.3mg fentanyl. [11](#_ENREF_11) After conversion , the median 24-hour equivalent doses were 2.9(1.4-4.8)mg and 14.5 (9.8-27.8) for fentanyl and alfentanil respectively. (Table 3)

For remifentanil to fentanyl, a conversion of 30mg of remifentanil is estimated as 1mg morphine, and again converted from fentanyl to morphine at the same factor of 75mg morphine is 1mg fentanyl.[12](#_ENREF_12) The estimated equivalent doses were 2.9 (2.4-4.8mg) and 6.4 ((1.9-8.7) for fentanyl and remifentanil respectively.(Table 3)

Morphine was equivalent, and oxycodone was approximately 0.5 less [11](#_ENREF_11). (Table 3)

## **Sedatives**

163 patients received sedatives and the most common was propofol (83.4%), followed by midazolam (20.2%) (**Table 4**). The main method of administration was continuous infusion, and 45.4% of patients received sedatives for more than 96 hours. 120 patients received sedatives for 24 hours or more, and 36.7% patients had a reduction in dosage and 31.8% had their dose reduced by more than 50%.

There was no significant relationship between policy/no policy ICUs and types of sedative used(X2 1.42 [df 4], N = 197, p = .84), duration of sedative use (X2 1.3 [df 3], N = 163, p =.73), or the proportionate reduction over the previous 24-hour period (X2 1.7 [df 3], N = 41, p =.62). For those patients receiving sedatives for greater than 72 hours, there was a later increase in alpha-2-agonists and midazolam use. (Table 5, Supplementary File 2).

**Medicines reconciliation data**

From a total of 212 patients, there were 178 pre-ICU admission historical prescriptions for medications associated with a withdrawal syndrome, or a medical history of alcohol , nicotine, or substance dependence [10](#_ENREF_10).The overall prescription rate was 0.47 per included patient. The highest rate was for antidepressants/antipsychotics at 20.3%, followed by nicotine dependence (including tobacco) in 19.3% of patients, followed by long term opioids (14.2%), and 11.8% had a report of alcohol dependence.

# **Discussion**

This prospective, observational, one-day point prevalence study reported: (1) high exposure of ICU patients to continuous infusions of opioids and sedatives, with over 50% of participants receiving continuous sedation or opioids for more than 72 hours; (2) a higher incidence of opioid than sedative administration; (3) heterogenous practice relating to sedation and opioid use, including medication choice and weaning strategies; (4) an absence of validated tools to allow identification and treatment of IWS; (5) limited use of policies or protocols to guide sedation and opioid practice; and (6) high prevalence of preadmission substances and medication known to cause a withdrawal syndrome.

This study gives contextual information for IWS in the adult ICU population; and gives evidence for IWS risk in adults. The majority of IWS research literature has been derived from work conducted in the paediatric critical care population where IWS is recognised, assessed with validated tools

(benzodiazepine and opioid withdrawal scale (SOPHIA); clinical opioid withdrawal scale (COWS)) and managed with longer acting opioid agents including methadone [6](#_ENREF_6),[7](#_ENREF_7) . In the paediatric critical care literature, children exposed to opioids or sedatives for greater than 72 hours are deemed at IWS risk [3](#_ENREF_3). In the context of this point prevalence, almost half of included patients could be at risk of developing IWS[3](#_ENREF_3). Finally, the study was conducted in 39 UK ICUs and therefore gives a broad perspective of IWS risk and include preadmission medication, and prevalence of opioid and sedative exposure.

There were limitations to the point prevalence data;. 78 ICUs originally offered to participate with only 39 (50%) ICUs finally contributing their data. One in four of ICU patient admissions were admitted with Covid-19 related pathophysiology and thus the data may not reflect ICU admissions during a non-pandemic time. Relevant clinical outcome data after the day of point prevalence, including duration of mechanical ventilation of ICU length of stay, were not collected. Alcohol and nicotine dependence is widely acknowledged to be underreported [13](#_ENREF_13). Furthermore, the data were derived using observational point prevalence methodology and were dependent on patient demographic and opioid/sedation data on the day of data collections, thus there may be a risk of selection bias.

The proportion of opioid administration was high in patients in comparison to sedatives. Whether or not this is a consequence of recent guidelines [SCCM 2018] that recommend that pain is treated before considering sedation is difficult to establish [1](#_ENREF_1). An assessment driven, protocol-based approach to pain and sedation management is recommended in PADIS [1](#_ENREF_1). Such an approach was not evident in the findings that reported less than half of ICUs had interprofessional rounds, just over a third had general policies for sedation and analgesia, and very few ICUs with guidelines for weaning medications, and monitoring for signs of IWS. The lack of monitoring is contrary to the general view that during the reduction of sedative-analgesic medications, patients should be closely monitored for acute withdrawal phenomenon [14](#_ENREF_14). Indeed, no ICUs used any validated withdrawal screening tool and there is currently no validated IWS screening tool for adult ICU.

In this dataset, five different opioids were administered mainly by continuous infusion (alfentanil, fentanyl, morphine, remifentanil, and oxycodone). For ease of comparison, all were converted into fentanyl equivalence [11](#_ENREF_11). The findings suggest that the shorter acting the opioid is, the greater the fentanyl equivalence. Remifentanil’s median fentanyl equivalent was 6.4 times greater, alfentanil 3.3 times more than fentanyl, morphine approximately equivalent and oxycodone appearing to be about half [15](#_ENREF_15) .These findings align with opioid potency and µ receptor affinity where the higher the affinity, the greater the dose, the higher overall opioid exposure to patient and potential higher risk of IWS [16](#_ENREF_16),[17](#_ENREF_17).

Accepting the bias of observation data collected using single day point prevalence methodology, we suggest these findings give evidence of high risk of IWS in adult ICU patients, and this risk could be higher in patients exposed to -short acting opioids with greater affinity for the µ receptor [15](#_ENREF_15),[17](#_ENREF_17). This concurs with a retrospective cohort study of 126 patients treated with remifentanil (n = 58), fentanyl (n = 47), or morphine (n = 21), where IWS was seen in 31.0%, 36.2%, and 9.5% of patients, respectively (*P* = 0.078) [18](#_ENREF_18).

Close to half (44.6%) of patients receiving opioids had a continuous infusion for 96 hours or more, with a dose reduction in the previous 24 hours in only 3 (5.6%) patients. Thus, if most patients were on short acting agents (n= 171 (84%) for 96 hours or greater; this might have a greater impact on IWS risk. In 2021, Maffei et al assessed risk factors for IWS in an adult Covid-19 ICU population. Using a multivariable model they showed that each additional day of IV opioid therapy was associated with an 8% increase in odds of IWS (95% CI, 1.02-1.14)[5]. However, their findings should be treated with caution, as they did not use a validated assessment tool. Instead, they defined and measured IWS as the receipt of scheduled oral opioid, benzodiazepine, and/or clonidine regimens after cessation of IV analgesics and sedatives while in the ICU.[5](#_ENREF_5" \o "Maffei, 2022 #164)They concluded prolonged and high dose exposures to IV opioids and benzodiazepines should be limited when feasible [5](#_ENREF_5). Further, Arroyo et al reported that in 50 ICU patients receiving benzodiazepines and/or opioids, of which 84% of patients were taking a mixture of midazolam (84%) and lorazepam (70%), probable withdrawal syndrome occurred in 55% of patients [2](#_ENREF_2)

With respect to sedatives, propofol was the most used agent in (n =136 (85%) of patients which corresponds with international sedative guidance (e.g., PADIS 2018) [1](#_ENREF_1). What was perhaps surprising was that one in five patients were receiving midazolam despite international guidelines that advise against benzodiazepines, especially midazolam and lorazepam, because of risk of delirium and over sedation [19](#_ENREF_19),[20](#_ENREF_20) . The higher use of benzodiazepines may have reflected the high prevalence (25.2%) of ICU Covid-19 admissions during data collection. Greater use of benzodiazepines and more challenging sedation were reported in Covid-19 ICU admissions by Pun et al in 2020 and Hanks et al in 2022 [21](#_ENREF_21),[22](#_ENREF_22). Maffei et al reported a higher incidence of IWS after benzodiazepine administration, the risk being 3 times higher after receiving lorazepam (95% CI 1.12 to 8.15 [5](#_ENREF_5).

Potential risk factors for IWS were present in 47% of patients pre-admission, these were alcohol or nicotine dependence or presence of chronic medication that have withdrawal symptoms on cessation including gabapentinoids and antidepressants [5](#_ENREF_5). We speculate that most patients would have had these medications withheld on ICU admission (especially if the oral or enteral route is not available) and this could contribute to IWS [23](#_ENREF_23).

Future research should include: (1)Development and validation of tools for WS detection in adult ICU patients (2) Establish whether use of short acting opioids including remifentanil and alfentantil increases likelihood of IWS and (3) Ascertain if greater use of alpha-2-agonists over propofol and benzodiazepines, known to manage opioid, alcohol and nicotine, reduce likelihood IWS [24](#_ENREF_24),[25](#_ENREF_25).

**Conclusion**

This prospective, observational, one-day point prevalence study conducted in 39 National Health Service UK ICUs’ showed a high incidence of opioid and sedation administration, with almost half of ICU admissions receiving opioids for over 96 hours; and high prevalence of preadmission medication and substances with withdrawal potential. Thereby likely increasing the risk of IWS in adult ICU.

**Acknowledgements**

The authors would like to thank the United Kingdom Clinical Pharmacy Association (UKCPA) Critical Care Pharmacy Group for their support in delivering this project and all contributors for providing their data (Supplementary file 1. Name of investigators )

**Funding**

Rebekah Eadie received funding from Health and Social Care (HSC) Research and Development Bridging Scheme-Predoctoral Support HSC Public Health Agency, Northern Ireland (Ref EAT/5665/21). Dr Cathrine A McKenzie receives funding from the National Institute for Health and Care Research (NIHR) Applied Research Collaborative (ARC) Wessex. The views expressed in this publication are those of the author(s) and not necessarily those of the National Institute for Health and Care Research or the Department of Health and Social Care.**Conflict of interest**

Dr McKenzie reports an honorarium for her work as editor in chief for Critical Illness (www.medicinescomplete.com) published by the Pharmaceutical Press. All remaining authors report no additional conflicts of interest

**References**

1. Devlin J, Skrobik Y, Gélinas Cl, et al. Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU. *Critical care medicine.* 2018;46(9):1532-1548.

2. Arroyo-Novoa CM, Figueroa-Ramos MI, Puntillo KA. Opioid and Benzodiazepine Iatrogenic Withdrawal Syndrome in Patients in the Intensive Care Unit. *AACN advanced critical care.* 2019;30(4):353-364.

3. Tobias J, Broquet A, Jacqueline Cd, et al. Tolerance, withdrawal, and physical dependency after long-term sedation and analgesia of children in the pediatric intensive care unit. *Critical care medicine.* 2000;28(6):2122-2132.

4. Girard TD, Pandharipande PP, Ely EW. Delirium in the intensive care unit. *Critical Care.* 2008;12(Suppl 3):S3.

5. Maffei MV, Laehn S, Bianchini M, Kim A. Risk Factors Associated With Opioid/Benzodiazepine Iatrogenic Withdrawal Syndrome in COVID-19 Acute Respiratory Distress Syndrome. *J Pharm Pract.* 2022;2022(Generic):8971900221116178.

6. Sneyers, Duceppe, Frenette, et al. Strategies for the Prevention and Treatment of Iatrogenic Withdrawal from Opioids and Benzodiazepines in Critically Ill Neonates, Children and Adults: A Systematic Review of Clinical Studies. *Drugs (New York, NY).* 2020;80(12):1211-1233.

7. Best K, Wypij D, Asaro L, Curley M. Randomized Evaluation of Sedation Titration For Respiratory Failure Study Investigators: Patient, process, and system predictors of iatrogenic withdrawal syndrome in critically ill children. *Crit Care Med.* 2017;45(1):e7-e15.

8. Yassin S, Terblanche M, Yassin J, McKenzie CA. A web-based survey of United Kingdom sedation practice in the intensive care unit. *Journal of critical care.* 2014;30(2):436.e431-436.e436.

9. Richards-Belle A, Canter RR, Power GS, et al. National survey and point prevalence study of sedation practice in UK critical care. In*.* Vol 20: Springer Science and Business Media LLC; 2016.

10. Excellence NIoC. Medicines associated with dependence or withdrawal symptoms safe prescribing and withdrawal management for adults. In: NICE, ed. United Kingdown2022.

11. Andrew Wilcock PHSC. Palliative Care Formulary (PCF8).

12. Admiraal M, Hermanns H, Hermanides J, et al. Study protocol for the TRUSt trial: a pragmatic randomised controlled trial comparing the standard of care with a transitional pain service for patients at risk of chronic postsurgical pain undergoing surgery. *BMJ Open.* 2021;11(8):e049676.

13. Boniface S, Kneale J, Shelton N. Drinking pattern is more strongly associated with under-reporting of alcohol consumption than socio-demographic factors: evidence from a mixed-methods study. *BMC Public Health.* 2014;14(1):1297.

14. Lamey PS, Landis DM, Nugent KM. Iatrogenic opioid withdrawal syndromes in adults in intensive care units: a narrative review. *Journal of Thoracic Disease.* 2022;14(6):2297-2308.

15. Barton G, McKenzie C, Philips B. *Critical Illness.* First ed. London: Pharmaceutical Press; 2021.

16. Smith HS. Opioid Metabolism. *Mayo Clinic Proceedings.* 2009;84(7):613-624.

17. Ellis CR, Kruhlak NL, Kim MT, Hawkins EG, Stavitskaya L. Predicting opioid receptor binding affinity of pharmacologically unclassified designer substances using molecular docking. *PLOS ONE.* 2018;13(5):e0197734.

18. Hyun D-g, Huh JW, Hong S-B, Koh Y, Lim C-M. Iatrogenic Opioid Withdrawal Syndrome in Critically Ill Patients: a Retrospective Cohort Study. *J Korean Med Sci.* 2020;35(15).

19. McKenzie Ca, McKinnon W, Naughton DP, et al. Differentiating midazolam over-sedation from neurological damage in the intensive care unit. *Critical care (London, England).* 2005;9(1).

20. Pandharipande P, Shintani A, Peterson J, et al. Lorazepam Is an Independent Risk Factor for Transitioning to Delirium in Intensive Care Unit Patients. *Anesthesiology.* 2006;104(1):21-26.

21. Pun BT, Heras La Calle G, Orun OM, et al. Prevalence and risk factors for delirium in critically ill patients with COVID-19 (COVID-D): a multicentre cohort study. *The lancet respiratory medicine.* 2021;9(3):239-250.

22. Loudet CI, García EE, Jorro BF, et al. ESICM LIVES 2022: part 1. *Intensive care medicine experimental.* 2022;10(Suppl 2):39.

23. Barrett NA, Jones A, Whiteley C, Yassin S, McKenzie CA. Management of long-term hypothyroidism: a potential marker of quality of medicines reconciliation in the intensive care unit. *International Journal of Pharmacy Practice.* 2012;20(5):303-306.

24. Rayner SG, Weinert CR, Peng H, Jepsen S, Broccard AF. Dexmedetomidine as adjunct treatment for severe alcohol withdrawal in the ICU. *Annals of Intensive Care.* 2012;2(1):12.

25. Bentz CJ. Review: clonidine is more effective than placebo for long term smoking cessation, but has side effects. *Evidence-Based Medicine.* 2005;10(1):19-19.

**Funding**

Rebekah Eadie received funding from Health and Social Care (HSC) Research and Development Bridging Scheme-Predoctoral Support HSC Public Health Agency, Northern Ireland (Ref EAT/5665/21). Dr Cathrine A McKenzie receives funding from the National Institute for Health and Care Research (NIHR) Applied Research Collaborative (ARC) Wessex. The views expressed in this publication are those of the author(s) and not necessarily those of the National Institute for Health and Care Research or the Department of Health and Social Care.

**Author Contributions**

Scott Bolesta devised, conceived, and led the international study AduLt iatrogEnic withdRawal in The Intensive Care Unit (ALERT-ICU) ( https://www.iatrogenicwithdrawalstudy.com/). Rebekah Eadie led the investigators UK arm of ALERT-ICU . Rebekah Eadie Daniel Hadfield, Bronagh Blackwood, Cathrine McKenzie and Nicola Kalk designed the methodology and conducted the analyses. The first draft of the manuscript was written by Cathrine McKenzie, all authors commented and revised previous versions of the manuscript. All authors read and approved the final manuscript.

**Data Availability**

The datasets generated during and/or analysed during the current study are available from authors Rebekah Eadie and Scott Bolesta on reasonable request.

**Table 1. ICU speciality, interprofessional ward rounds, policy and assessment tools**

a Numbers do not total to 39 as some units had more than one policy/protocol or assessment tool

Data are number (%). Patients were recruited from 37 out of the 39 ICUs

IWS = Iatrogenic Withdrawal Syndrome

|  |  |
| --- | --- |
|  | **No (%)** |
| *ICUs* | 39 |
| *ICU patient type* |  |
| Mixed medical/surgical | 23 (59.0) |
| Neurological | 5 (12.8) |
| Cardiothoracic surgery | 5 (12.8) |
| Medical | 3 (7.7) |
| General surgical | 1 (2.6) |
| Other | 2 (5.1) |
| *Interprofessional bedside rounds* |  |
| >/= 4 days/week | 17 (43.6) |
| Daily | 14 (35.9) |
| <4 days/week | 2 (5.1) |
| None | 6 (15.4) |
| *Sedation and analgesia policies/protocols a* |  |
| Daily sedation interruption | 17 (43.6) |
| General sedation/analgesia policy, with/without daily interruption | 14 (35.9) |
| Sedation/analgesia weaning | 8 (20.5) |
| IWS policy to monitor signs/symptoms | 4 (10.3) |
| *Assessment tools a* |  |
| Sedation | 39 (100) |
| Pain | 36 (92.3) |
| Withdrawal | 0 |

**Table 2. Patient characteristics**

|  |  |
| --- | --- |
| *Patients (from 37 ICUs)* | 212 |
| Female | 79 (37.7) |
| Age, median (IQR) a | 58.0 (44.0 – 68.0) |
| BMI, kg/m2, median (IQR) b | 27.3 (23.5 – 31.9) |
| Days in ICU prior to data collection, median (IQR) | 6.0 (2.0 – 14.0) |
| *Ethnicity* |  |
| Caucasian | 162 (76.4) |
| Asian | 14 (6.6) |
| Black/African | 13 (6.1) |
| Other | 3 (1.4) |
| Unknown | 20 (9.4) |
| *COVID-19 status* |  |
| PCR positive | 54 (25.5) |
| *Reason for ICU admission* |  |
| Respiratory system disease | 79 (37.3) |
| Circulatory system disease | 37 (17.5) |
| Nervous system disease | 28 (13.2) |
| Digestive system disease | 27 (12.7) |
| Other | 41 (19.3) |
| *Preadmission medications* |  |
| Antidepressants/antipsychotics | 43 (20.3) |
| Opioids | 30 (14.2) |
| Paracetamol | 22 (10.4) |
| Gabapentin or Pregabalin | 18 (8.5) |
| Non/benzodiazepine sleeping medication | 10 (4.7) |
| NSAIDs | 7 (3.3) |
| *Preadmission nicotine, alcohol and recreational drug use* |  |
| Nicotine | 41 (19.3) |
| Alcohol misuse | 25 (11.8) |
| Recreational/illicit drugs | 12 (5.7) |
| *Mechanical ventilation treatment in the ICU* |  |
| Invasive mechanical ventilation | 165 (77.8) |
| Non-invasive ventilation | 8 (3.8) |
| *Parenteral opioid and sedative use over previous 24 hours (inclusion criteria)* | |
| Opioid | 202 (95.3) |
| Sedative | 163 (76.9) |
| Received BOTH opioid and sedative | 153 (72.2) |
| Received ONLY opioid | 49 (23.1) |
| Received ONLY sedative | 10 (4.7) |
| Patients were recruited from 37 out of the 39 ICUs  Data are number (%) of patients unless otherwise stated.  IWS = Iatrogenic Withdrawal Syndrome; IQR = Interquartile Range; BMI = Body Mass Index; PCR = Polymerase Chain Reaction a n = 191; missing data for 21 patients  b n = 178; missing/unknown = 34 | |

**Table 3. Opioid use over 24 hours**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **All** | **ICU with sedation policy** | **ICU without sedation policy** |
| *Patients receiving opioids, N (%) a* | *202* | *78* | *124* |
| Fentanyl | 71 (35.2) | 49 (62.8) | 22 (17.7) |
| Alfentanil | 67 (33.2) | 15 (19.2) | 52 (41.9) |
| Remifentanil | 33 (16.3) | 13 (16.7) | 20 (16.1) |
| Oxycodone b | 20 (9.9) | 0 | 20 (16.1) |
| Morphine | 15 (7.4) | 2 (2.6) | 13 (10.5) |
| Tramadol b | 2 (1.0) | 0 | 2 (1.6) |
| Methadone b | 1 (0.5) | 0 | 1 (0.8) |
| *Methods of administration, N (%) of patients receiving opioids via each route a, c* | | | |
| Continuous IV infusions | 167 (82.7) | 68 (87.2) | 99 (79.8) |
| PCA | 21 (10.4) | 8 (10.3) | 13 (10.5) |
| Non-scheduled intermittent | 11 (5.4) | 0 (0) | 11 (8.9) |
| Scheduled intermittent | 7 (3.5) | 1 (1.3) | 6 (4.8) |
| Regional anaesthesia | 2 (1.0) | 1 (1.3) | 1 (0.8) |
| *24-hour dose via continuous IV infusion, mg, Median (IQR)* | | | |
| Fentanyl | 2.9 (1.4 – 4.8) | 3.5 (1.7 – 5.5)) | 1.9 (0.8 – 3.9) |
| Alfentanil | 48.0 (32.5 – 92.0) | 96.0 (38 – 120) | 43.0 (25.3 – 65.9) |
| Remifentanil | 16.1 (4.8 – 21.7) | 14.6 (5.3 – 24.8) | 16.1 (4.4 – 18.5) |
| Oxycodone | 50.5 (40.0 – 61.0) | 0 (0) | 50.5 (40.0 – 61.0) |
| Morphine | 208.0 (66.0 – 240.0) | 344.0 (208.0 – 480.0) | 144.0 (5.0 – 240.0) |
| *Fentanyl equivalent (mg) 24-hour dose via continuous IV infusion, Median (IQR) d* | | | |
| Fentanyl | 2.9 (1.4 – 4.8) | 3.5 (1.7 – 5.5)) | 1.9 (0.8 – 3.9) |
| Alfentanil | 14.5 (9.8-27.8) | 29.0(11.5-36.4) | 13.0-(7.6-20.0) |
| Remifentanil | 6.4 ((1.9-8.7) | 5.84-(5.3-9.92) | 6.4(1.8-7.4) |
| Oxycodone | 1.4 (1.1-1.6) | 0 | 1.4 (1.1-1.6) |
| Morphine | 2.8 (0.9-3.2) | 4.6 (2.8-6.4) | 1.9 (0.1-3.2) |
| *Duration of opioid treatment to the point of data collection-* | | | |
| < 24 hours | 52 (25.7) | 23 (29.5) | 29 (23.4) |
| 24 to 72 hours | 47 (23.3) | 15 (19.2) | 32 (25.8) |
| 72 to 96 hours | 13 (6.4) | 4 (5.1) | 9 (7.3) |
| >96 hours | 90 (44.6) | 36 (46.2) | 54 (43.5) |
| *Opioid reduction in previous 24 hours e*  *N (%)* | | | |
| Yes | 54 (36.0) | 23 (41.8) | 31 (32.6) |
| *Reduction % in previous 24 hours e*  *N (%)* | | | |
| < 10% | 3 (5.6) | 1 (4.3) | 2 (6.5) |
| 10-20 % | 12 (22.2) | 7 (30.4) | 5 (16.1) |
| 21-30% | 12 (22.2) | 5 (21.7) | 7 (22.6) |
| 31-50% | 11 (20.4) | 2 (8.7) | 9 (29.0) |
| > 50% | 16 (29.6) | 8 (34.8) | 8 (25.8) |
| *Enteral opioids started in previous 24 hours e*  *N (%)* | | | |
| Yes | 11 (5.4) | 7 (63.6) | 4 (36.4) |
| Data are number (%) of patients, unless otherwise stated  a Numbers different to column total as some patients received more than one type of opioid  b These opioids were free form entries  c PCA = Patient Controlled Analgesia (; Non-scheduled intermittent refers to one-off or as needed intravenous, subcutaneous or intramuscular doses; Scheduled intermittent refers to single, non-continuous intravenous, subcutaneous or intramuscular doses administered according to a schedule.  d Fentanyl equivalent conversion:  e Only patients receiving opioids for 24 hours or more | | | |

**Table 4. Sedative use over 24 hours**

|  |  |  |  |
| --- | --- | --- | --- |
| Variable | All | ICU with sedation policy | ICU without sedation policy |
| Patients receiving sedatives, N (%) a | 163 | 64 | 99 |
| Propofol | 136 (83.4) | 57 (89.1) | 79 (79.8) |
| Midazolam | 33 (20.2) | 12 (18.8) | 21 (21.2) |
| Clonidine | 17 (10.4) | 5 (7.8) | 12 (12.1) |
| Dexmedetomidine | 9 (5.5) | 3 (4.7) | 6 (6.1) |
| Ketamine | 2 (1.2) | 1 (1.6) | 1 (1) |
| Lorazepam | 3 (1.8) | 0 (0) | 3 (3) |
| Methods of administration, N (%) of patients receiving sedatives via each route a, b | | | |
| Continuous infusion | 157 (77.7) | 63 (98.4) | 94 (94.9) |
| Scheduled intermittent | 7 (3.5) | 2 (3.1) | 5 (5.1) |
| Non-scheduled intermittent | 5 (2.5) | 1 (1.6) | 4 (4.0) |
| Cumulative 24-hour dose via continuous IV infusion, (mg), median (IQR) | | | |
| Propofol | 2680.0 (1000.0 – 4520.0) | 2840.0 (960.0 – 4697.5) | 2600.0 (1050.0 – 4520.0) |
| Midazolam | 158.0 (99.4 – 240.0) | 191.5 (95.8 – 240.0) | 144.0 (99.4 – 238.0) |
| Clonidine | 1.1 (0.4 – 2.5) | 0.4 (0.3 – 2.2) | 1.3 (0.9 – 2.9) |
| Dexmedetomidine | 2.0 (0.9 – 2.3) | 2.0 (0.7 – 2.4) | 1.7 (0.9 – 2.5) |
| Ketamine | 230.0 (230.0 – 230.0) | 230.0 (230.0 – 230.0) | – |
| Duration of sedative treatment to the point of data collection | | | |
| < 24 hours | 43 (26.4) | 16 (25.0) | 27 (27.3) |
| 24 to 72 hours | 36 (22.1) | 12 (18.8) | 24 (24.2) |
| 72 to 96 hours | 10 (6.1) | 5 (7.8) | 5 (5.0) |
| >96 hours | 74 (45.4) | 31 (48.4) | 43 (43.4) |
| Sedative reduction in previous 24 hours c |  |  |  |
| Yes | 44 (36.7) | 19 (29.7) | 25 (25.3) |
| Reduction % in previous 24 hours c |  |  |  |
| < 10% | 3 (6.8) | 0 (0) | 3 (12.0) |
| 10-20 % | 10 (22.7) | 6 (31.6) | 4 (16.0) |
| 21-30% | 7 (15.9) | 2 (10.5) | 5 (20.0) |
| 31-50% | 10 (22.7) | 5 (26.3) | 5 (20.0) |
| > 50% | 14 (31.8) | 6 (31.6) | 8 (32.0) |
| Enteral sedative started in previous 24 hours c | | | |
| Yes | 11 (9.2)) | 4 (21.1) | 7(28.0) |
| Data are number (%) of patients, unless otherwise stated  a Numbers different to column total as some patients received more than one type of sedative  b PCA = Patient Controlled Analgesia (; Non-scheduled intermittent refers to one-off or as needed intravenous, subcutaneous or intramuscular doses; Scheduled intermittent refers to single, non-continuous intravenous, subcutaneous or intramuscular doses administered according to a schedule.  c Only patients receiving opioids for 24 hours or more | | | |