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Title: Medication related problems in ICU survivors: learning from a multi-centre programme

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Introduction

Few data measure the problems critically ill patients have with medications after hospital discharge, which medications are involved, and how severe the consequences are (1-3). We sought to assess the prevalence and severity of medication related problems in intensive care unit (ICU) survivors and explore pain management strategies. We did so among patients attending a 5-site post-ICU programme in Scotland between September 2016 and June 2018.

Methods

Ethical approval was granted by The North West (Liverpool Central) Research Ethics Committee, REC Reference Number: 17/NM/0199. All patients provided written consent.

Intensive Care Syndrome: Promoting Independence and Return to Employment (InS:PIRE) is a 5-week rehabilitation programme for ICU survivors. Previous research has described this programme (4-6). Participants were invited between four- and twelve-weeks after hospital discharge. Patients were eligible if they received level three care or more than seven days of level two care. UK Level three patients require multiple organ support or invasive respiratory support alone. Level two patients are patients requiring single organ support or post-operative care (7). Patients who were otherwise deemed high risk were invited (for example, one patient who received non-invasive ventilation for a prolonged duration was invited), as were patients who self-referred.

A pharmacist provided a standardised review for all patients, this included: medicines reconciliation; assessment of medication appropriateness; identification of problems; assessing adherence; and providing education. Prescribed medications were documented at four time points: pre-ICU admission; ICU discharge; at hospital discharge and at InS:PIRE (at the start of the programme). Data were gathered from primary care, in-hospital notes, and the patient and caregiver. Standardisation across sites was ensured by one to one training, regular multi-site meetings and the availability of a website

with instructional materials. There was no standardised pharmacy pre-hospital discharge intervention/medicine reconciliation provided across the sites involved.

The *type* of Medication related problem was categorised using a modified version of the Hepler and Strand framework (8). Categories of problems, alongside an example of each are provided in **S1.** The *significance* of these problems was classified using Blix's scale (9). A problem which had a significance rating of one was deemed low risk, two- moderate, three- major and a problem which was attributed a score of four was deemed potentially catastrophic. For a detailed breakdown of the Blix scoring system, see S1. Scores of $\geq$2 were deemed clinically significant. Associated clinical factors and the pharmacy recommendation were collated and the significance of the problem independently scored by two clinicians. Drugs involved were categorised according to their British National Formulary (BNF) classification (10).

McNemar's test was used to compare the difference between patients who were prescribed analgesia before admission and during InS:PIRE visit. Pearson's chi-squared test was used to compare post-ICU opioid prescribing. Logistic regression determined if demographic factors were associated with clinically significant medication related problems. An unadjusted model was generated; variables with p-values less than 0.1 or clinically significant (age, severity of illness and length of exposure), were used to create the adjusted model. IBM SPSS Statistics 24[1] was utilised (11).

Results

253 patients attended InS:PIRE across 5 sites. 183 patients had a documented pharmacy review and provided consented**.** Baseline demographics are shown in **Table 1.**

The median number of medications prescribed before ICU admission was 5 (IQR 3-9), at ICU discharge 6·5 (IQR 4-9); hospital discharge 7 (IQR 5-10); and at InS:PIRE 6 (IQR 4-9). Patients were prescribed a total of 1216 medications at InS:PIRE; 171 were associated with a medication related problem and 27 necessary medications had been omitted, a total of 198 problems.

62·8% (n=115) patients required at least one pharmacy intervention, such as clarifying duration of treatment (n=44), followed by education (n=33), and correcting drug omissions (n=27). 27 pharmacy interventions were classified as minor, 141 as moderate, and 30 as severe. Thus, 86·4% (n=171) were clinically significant**.** A breakdown, alongside examples of the severe interventions are shown in **Table 2.**

Neurological drugs were most commonly problematic (n=65), including analgesic (n=45, e.g. Tramadol, Dihydrocodeine) and psychiatric medications (n=20, e.g., Sertraline)—a majority of these were in new medications prescribed at or after ICU 55·4% (n=36). Cardiovascular (n=40), gastrointestinal (n=34), and nutritional medications (n=25) were other common problematic classes.

33·3% of patients (n=61) were prescribed regular analgesia before ICU; this increased to 60·7% (n=111) at InS:PIRE, an absolute increase of 27·4% (95% CI: 20·2% - 34·4%, p<0·001). Similarly, 22·4% (n=41) of patients were prescribed a regular opioid pre-ICU compared to 38·7% (n=71) at InS:PIRE, an absolute increase of 16·3% (95% CI: 9·8% -22·8%, p<0·001). There was not a significant difference between the use of opiates between surgical and medical admissions (p=0.445).

Logistic regression was used to explore if clinical demographics predicted a clinically significant medication related problem. The adjusted model included age, ICU LOS, hospital LOS, APACHE II, number of days of RRT, number of days of ventilation, the number ICU discharge medications and the WHO analgesia classification at InS:PIRE (**Table 3**) The unadjusted analysis can be found in **S2**.

Discussion

This multi-centre study has demonstrated that over 60% of ICU patients have issues with medicines in the post hospital discharge period, with a large proportion of these issues related to psychiatric and pain medications. Longer durations of ICU treatment and complex ICU discharge prescriptions were identified as risk factor for a medication related problem.

These results are contextualized by evidence that providing a pharmacy review at transitions of care can improve safety and reduce 30-day hospital readmission in heart failure patients and primary care (12-13). Similarly, a recent study has shown that a pharmacy review, as part of a 'bundled' approach to care may reduce long term mortality in the sepsis group (14). More research is required to understand the potential of this intervention and how to integrate it within the complexities of ICU care. We would recommend, based on our learning, that a medicines reconciliation exercise should be utilised at all transitions of care for this group of patients, especially at hospital discharge. A clear plan for escalation and de-escalation of medicines should also be made, which should be shared with patients and ongoing care providers across the recovery arc.

Our findings contrast with a recent Canadian study which demonstrated that opiate use did not increase after critical illness (16). This may be explained by differences in how data was collected between these studies (in person vs retrospective electronic health records) and the timepoints at which opioid use was measured. Other work has focussed on medication issues following critical illness and has shown a high rate of unintentional continuation of antipsychotics (17). However inappropriate drug continuation did not appear to be the primary problem in our cohort, with only 15% of neurological medication problems related to duration of treatment. This is one of the first studies to explore *all* issues related to medication in the post discharge period and thus may be why a greater range of issues were found.

The rise in opiate prescription is troublesome given concerns that the international opioid addiction epidemic, is in part fuelled by iatrogenic provision and easy access to opiates (17-18). This post-discharge excess may mirror the in-ICU challenge clinicians face: caught between a desire to relieve symptoms, and available tools that may worsen longer-term outcomes (19-20).

Strengths of this study include its multi-centre involvement and its systematic approach to analysis, however there are limitations. However, we did not control other services which patients attended; patients may have already had pharmacy reviews—that is, we have documented problems found *after*

usual care. As such, we may have under-measured problems among participating patients, but generalizing from these patients to other populations should be done with caution. Additionally, a small number of patient self-referred to the programme; this may have impacted the results reported.

In summary, this study demonstrated that over 60% of ICU patients have problems with medicines in the post hospital discharge period, with a large proportion of these problems related to psychiatric and pain medications.

Characteristic	Cohort (n=183)
Gender, male (%)	97 (56·3)
Age, years (median, IQR)*	58(50-65)
ICU LOS, days (median, IQR)	12 (7-19)
Hospital LOS, days (median, IQR)	28 (16-47)
APACHE II (median, IQR)	20 (15-25)
SIMD decile (median, IQR)**	3 (1-6)
Number of patients ventilated (%)	159 (86·9)
Median Duration, days (IQR)	8 (4-14)
Number of patients requiring RRT (%)	35 (19·1)
Median Duration, days (IQR)	7 (2-12)
Number of patients requiring multiple vasoactive drugs (%)	90 (49·2)
Median Duration, days (IQR)	3 (1-7)
Medical diagnosis (%)	112 (61·2)
Surgical diagnosis (%)	71 (38·8)

Table 1: Baseline demographics of InS:PIRE participants

**IQR: Interquartile Range*

***SIMD: The Scottish Index of Multiple Deprivation is a measure of socio-economic deprivation; decile one represents the most deprived and decile ten the most affluent (21).*

Severe Medication Interventions (n=30)	Clinical Example
Drug Omissions (n=11)	Prophylactic antibiotics not restarted in a splenectomy patient
Adverse Event (n=2)	Intolerable side effects from Pregabalin commenced during admission resulting in non-adherence and poor pain management
New Treatment Recommendation (n=1)	Omeprazole initiated for Aspirin related melaena
Dose Increase (n=3)	Titrate Gabapentin to pre-hospital admission dose to treat ongoing neuropathic pain
Dose Decrease (n=2)	Theophylline dose increased during admission, symptoms of toxicity at clinic, level checked, and dose decreased
Clarification of treatment duration (n=5)	Morphine commenced during admission, plan made with patient to reduce and stop
Education (n=5)	Non-adherence with Apixiban, patient was unaware of why it had been started.
Monitoring/Referral (n=2)	Patient on 5 analgesics with poorly controlled pain, referred to the chronic pain team

Table 2: A breakdown and examples of the severe interventions undertaken.

Variable	Adjusted Logistic Regression		
	OR	**95%CI**	***p***
Age	0·99	0·96-1·02	0·55
ICU LOS	0·95	0·89-1·02	0·14
Hospital LOS	**1·03**	**1·01-1·05**	**0·02**
APACHE II	1·04	0·99-1·10	0·16
Days of Renal Replacement Therapy	1·03	0·94-1·14	0·51
Days of Ventilation	1·04	0·97-1·11	0·29
Number of ICU Discharge Medications	**1·15**	**1·04-1·28**	**0·01**
WHO Classification at InS:PIRE	-	-	**-**
-No Analgesia	1	-	-
-Step 1*	2·02	0·84-4·86	0·12
-Step 2*	**5·20**	**2·07-13.20**	**0·001**
-Step 3*	1·95	0·61-6·26	0·26

Table 3: Results of Multivariable Logistic Regression

**Step 1 is non-opioid analgesia for mild pain (e.g. paracetamol), Step 2 is weak opioid analgesia for mild to moderate pain (e.g. codeine), and Step 3 is strong opioid analgesia for moderate to severe pain (e.g. morphine) (22).*

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