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Inpatient opioid prescribing patterns and their effect on rehospitalisations: a nested case-control study using data from a Swiss public acute hospital

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Summary

AIMS OF THE STUDY: Opioid prescriptions have increased in Switzerland, even though current guidelines warn of their harms. If opioids for postoperative analgesia are not tapered before hospital discharge, patients are at risk of adverse events such as constipation, drowsiness, dependence, tolerance and withdrawal. The aim of this study was to investigate and quantify the potential association between opioids prescribed at discharge from hospital and rehospitalisation.

METHODS: We conducted a nested case-control study using routinely collected electronic health records from a Swiss public acute hospital. Cases were patients aged 65 years or older admitted between November 2014 and December 2018, with documented opioid administration on the day of discharge and rehospitalisation within 18 or 30 days after discharge. Each case was matched to five controls for age, sex, year of hospitalisation and Charlson Comorbidity Index. We calculated odds ratios for 18-day and 30-day rehospitalisation based on exposure to opioids using a conditional logistic regression adjusted for potential confounders. Secondary analyses included stratifications into morphine-equivalent doses of <50 mg, 50–89 mg and ≥90 mg, and co-prescriptions of gabapentinoids and benzodiazepines.

RESULTS: Of 22,471 included patients, 3144 rehospitalisations were identified, of which 1698 were 18-day rehospitalisations and 1446 were 30-day rehospitalisations. Documented opioid administration on the day of discharge was associated with 30-day rehospitalisation after adjustment for confounders (adjusted odds ratio 1.48; 95% CI 1.25–1.75, p <0.001), while no difference was observed in the likelihood of 18-day rehospitalisation. The combined prescription of opioids with benzodiazepines or gabapentinoids and morphine-equivalent doses >50 mg were rare.

CONCLUSIONS: Patients receiving opioids on the day of discharge were 48% more likely to be readmitted to hospital within 30 days. Clinicians should aim to discontinue opioids started in hospital before discharge if possible. Patients receiving an opioid prescription should be educated and monitored as part of opioid stewardship programmes.

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Introduction

Opioids are indicated for moderate or severe postoperative pain [1], but all patients undergoing surgery should be considered at risk of developing persistent postoperative opioid use [2]. Data from Canada show that about 7% of patients still have opioid prescriptions seven days after minor surgery, with a 44% increased risk of becoming long-term opioid users [3]. Interviews with patients with prescription opioid use disorder revealed that opioid treatment is often initiated in secondary care with little information about the potential risks of opioid use, and that the treatment is then continued in primary care without additional consultation [4]. Therefore, if opioids have been started for postoperative pain as part of multimodal analgesia, they should be weaned before hospital discharge if possible [2] and must have a definite end date [5].

In Switzerland, opioid sales increased by 91% between the years 2000 and 2019, with a particularly marked increase for oxycodone [6]. Their use contradicts current treatment guidelines [7, 8], as opioids seem to be primarily used for pain of non-malignant origin [9]. The increase in sales in Switzerland has been shown to be accompanied by an increase in the number of poisoning cases reported to the Swiss Tox Centre [6]. Harm from opioids includes physical and psychological dependence, tolerance, withdrawal, drowsiness, confusion, constipation, dry mouth, nausea, vomiting and rehospitalisations [1, 8, 10]. Rehospitalisations are “a return to the hospital shortly after discharge from a recent hospital stay” and their rates are used to assess the quality of hospital care [11]. A variety of factors influence the risk of being rehospitalised, including demographic factors, comorbidities, complexity of hospitalisations, previous hospitalisations and further social and medical factors [11–13]. These factors can be used in prediction models to identify patients at risk of rehospitalisa-

tion early for preventive measures. One of these models, the Potentially Avoidable Readmission-Risk Score (PAR-Risk Score), uses readily available electronic health information to calculate a risk score. Although an external validation noted a poor performance within the given dataset overall, 5 of the 12 predictors were still identified to be associated with rehospitalisation at 30 days. The use of opioids was one of these predictors [14].

The present study aimed to further investigate and quantify the potential association between opioids prescribed at hospital discharge and the risk of rehospitalisation, also depending on their dose. This study had the additional aim of exploring the effect of combining opioids with benzodiazepines and gabapentinoids on rehospitalisations, as their co-prescription carries an additional risk of sedation, increased risk of falls, respiratory depression and overdose, and is considered inappropriate for older patients [8, 15].

Materials and methods

Study design and data source

We conducted a nested case-control study using routinely collected electronic health records from a Swiss public acute hospital. The hospital is one of two public hospitals in the canton, each serving one geographical area. A previously generated dataset of inpatients (surgical and non-surgical) over the age of 65 and hospitalised for at least 48 hours between November 2014 and December 2018 was used as the base cohort for identifying cases and controls [16]. The dataset, originally sourced from the hospital's clinical information system for each patient, provided detailed information on demographic characteristics, comorbidities including the Charlson Comorbidity Index, and medication use during hospital stay, and was used by medical coders for claiming insurance payments [16]. Patients who were in intensive care for more than 24 hours had to be excluded from dataset generation because a different clinical information system is used for them.

We report this study according to the RECORD-PE (REporting of studies Conducted using Observational Routinely collected Data for PharmacoEpidemiological research) checklist [17]. A study protocol was not previously published.

Patient selection and outcomes

From the base cohort, eligible patients for the nested cohort were those who were discharged from the hospital (cohort entry date). We excluded patients with mental and behavioural disorders caused by opioids and by multiple substances (ICD-10 F11 and F12), and patients with malignant neoplasms (ICD-10 C and D). Patients with skin cancer (ICD-10 C43 and C44) were not excluded, because of the lesser association with pain and opioids [18].

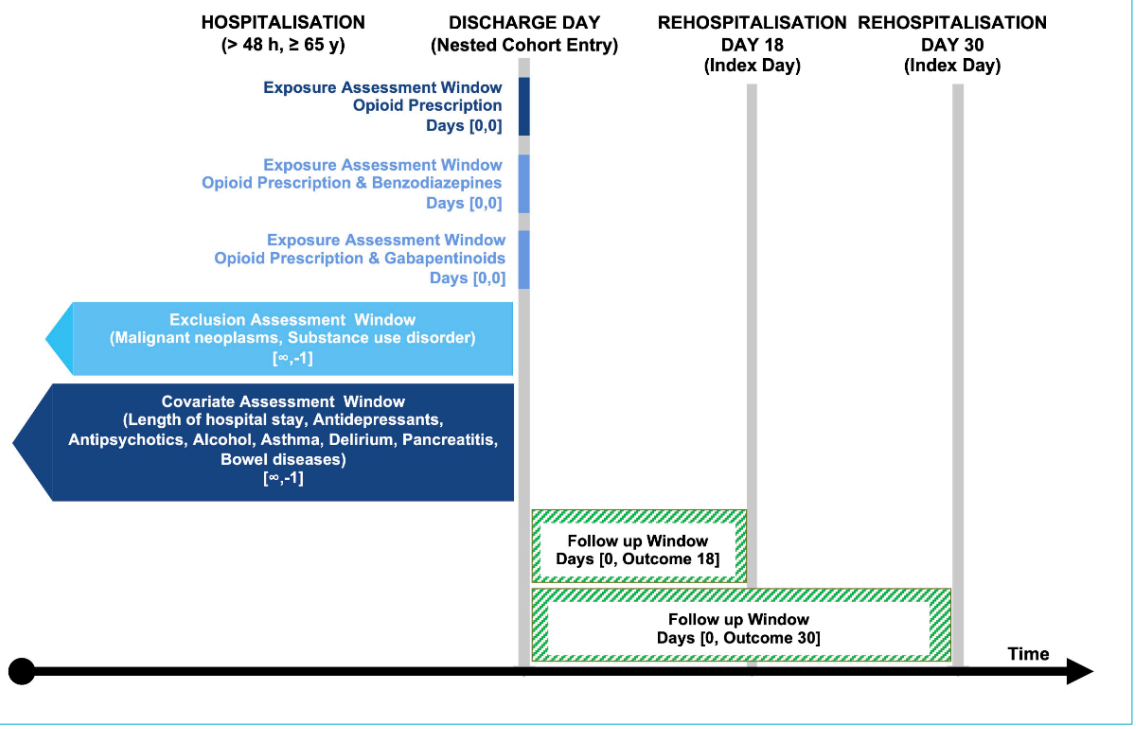
Within this nested cohort, we identified patients who were rehospitalised 18 and 30 days after discharge (cases). Potential controls were randomly selected from the nested cohort who were not rehospitalised within the 18 or 30 days following discharge, respectively.

A visualisation of the study design is shown in figure 1. [19]

Exposure

The primary exposure of interest was defined as a documented opioid administration on the cohort entry date (i.e. the last day of hospitalisation), assuming that patients were discharged with an opioid prescription as well. Opioids

Figure 1: Visualisation of the study design depicting nested cohort entry, index day (18-day or 30-day rehospitalisation), and the assessment windows for the exposures, inclusion and exclusion criteria, and covariates. Visualisation template by Schneeweiss et al. [19].



considered were buprenorphine, codeine, dihydrocodeine, fentanyl, hydromorphone, morphine, methadone, oxycodone, tapentadol, tilidine and tramadol. Methadone is used by the pain service of this hospital as an additional strong opioid for opioid-refractory pain and is therefore not an indicator of substitution treatment. All parenteral, intramuscular and subcutaneous formulations were excluded as these can only be administered with the assistance of medical personnel and a switch to oral use would not usually occur on the day of discharge.

In a secondary exposure analysis, we calculated the daily dose of opioids on the last day of hospitalisation for each patient. The cumulative daily morphine-equivalent doses (MEDs) were determined by strength of dosing unit, number of units per day and the morphine conversion factor of the opioid. We used the carefully curated and published conversion factors by Wertli and colleagues [20]. Morphine-equivalent doses were then stratified into doses of <50 mg, 50–89 mg and ≥90 mg [21].

In an additional secondary exposure analysis, we examined patients who received a co-prescription of opioids and benzodiazepines or a co-prescription of opioids and gabapentinoids. Benzodiazepine and gabapentinoid prescriptions were restricted to oral and rectal formulations.

As part of the review process, a further secondary exposure analysis was proposed based on the categorisation of weak and strong opioids. Opioids considered as weak were codeine, dihydrocodeine and tramadol, including combination formulations with paracetamol.

Covariates

We assessed covariates potentially associated with the exposure and rehospitalisation from data collected prior to cohort entry on the day of discharge, which included age, sex, year of discharge, Charlson Comorbidity Index, length of stay, department (medicine, surgery), alcohol use disorder, delirium during hospital stay, asthma, pancreatitis, chronic inflammatory bowel diseases and documented administration of antidepressants and antipsychotics.

Statistical analysis

One case was matched to five controls on age, sex, year of discharge and Charlson Comorbidity Index (strata: 0, 1–2, 3–4, ≥5) [19]. Matching was performed separately for 18- and 30-day rehospitalisations. We required an exact match for sex and year, and allowed a caliper of 5/standard deviation for age, and a mean standard difference of 0.2 for the Charlson Comorbidity Index ranges [22]. The matched cases and controls for 18- and 30-day rehospitalisations were also used for the secondary outcomes.

Descriptive statistics and standardised differences were used to summarise and compare the patient characteristics of matched cases and controls, where a standardised difference >0.1 indicates a clinically important difference [23]. Using the exposure information, we calculated the frequency of opioid administration by opioid on the last day of hospitalisation. Two continuous variables were transformed into categorical variables: the Charlson Comorbidity Index (0; 1–2; 3–4; ≥5) and morphine-equivalent doses (<50 mg; 50–89 mg; ≥90 mg). To normalise the distribution, we performed a logarithmic transformation on the variable length of stay. Missing entries were interpreted as the absence of the variable (i.e. not missing at random), as the dataset was also used by medical coders to claim insurance payments.

To compare the odds of rehospitalisation under the influence of each exposure, we estimated the odds ratios (OR) and 95% confidence intervals (CI) using conditional logistic regression. Additionally, our models were adjusted for potentially confounding variables based on standardised differences after matching. Model 1 included adjustments for covariates that showed a standardised difference of >0.1, while model 2 included adjustments for covariates that showed a standardised difference of ≥0.1 (after rounding to one decimal point).

A sample size calculation was performed to adequately interpret the results. An a priori sample size calculation (one-sided Fisher's exact test) was performed with an alpha of 0.05, a power of 0.8 and an allocation ratio of 1:5 using previously determined proportions of opioid use in rehospitalised (36.2%) and non-rehospitalised (26.0%) patients within the same dataset [14, 24]. The sample size calculation indicated a minimum sample size of 169 opioid-exposed rehospitalisations and 845 matched controls for statistically correct conclusions.

All analyses were performed using R statistical software (v 4.2.3) [25]. Matching was performed with the *optmatch* package (v 0.10.6) [26]. Standardised differences were calculated using the *stddiff* package (v 3.1) [27]. Odds ratios were calculated using the *epitools* package (v 0.5.10.1) [28].

Ethics approval

The Ethics Committee of Northwest and Central Switzerland approved the protocol for the study from which the data were originally extracted (EKNZ project ID: 2018-01000). The committee also approved the amendment for the rehospitalisation study. The data were extracted anonymously and informed consent was not required.

Results

Out of 28,276 inpatient cases, aged 65 years or older, who were discharged alive between 2014 and 2018, we excluded 5781 cancer patients and 26 patients with mental and behavioural disorders caused by opioids and by multiple substance use (with overlapping diagnoses). From the remaining 22,471 patient cases, a total of 3144 rehospitalisations were identified, of which 1698 were rehospitalised within 18 days after discharge and 1446 within 30 days after discharge. After matching, 8490 controls were assigned to 1698 18-day rehospitalisations and 7230 controls to 1446 30-day rehospitalisations. A detailed overview of the number of patients can be found in figure 2.

Baseline characteristics of cases and matched controls for both the 18-day and 30-day outcomes are shown in table 1. Patients' characteristics were well balanced on all matching criteria.

18-day rehospitalisation

The matched sample for the 18-day rehospitalisation group consisted of patients with an average age of approximately

78 years, with 51.8% being males. Most patients exhibited a Charlson Comorbidity Index of 1–2, with a minority having an index of 5 or higher. The median length of stay was significantly longer for cases compared to matched controls (14 days [interquartile range 9–21] vs 7 days [4–11]). Analysis of documented opioid administration on the last day of hospitalisation revealed that 15.1% of patients being readmitted received an opioid, while only 11.5% of their matched controls did. The majority of opioid administrations involved morphine-equivalent doses below 50 mg. Co-prescription rates of benzodiazepines and gabapentinoids with opioids were low.

30-day rehospitalisation

In the matched sample for the 30-day rehospitalisation group, patients had an average age of approximately 79 years, with 47.8% being males. Similar to the 18-day rehospitalisation group, most patients had a Charlson Comorbidity Index of 1–2. The median length of stay was again longer for cases compared to matched controls (8 days [5–13] vs 7 days [4–11]), although less pronounced than in the 18-day rehospitalisation group. Analysis of opioid administration on the day of discharge showed a less balanced distribution between cases and controls compared to the 18-day rehospitalisation group, with 17.7% of rehospitalised patients having a documented opioid administration on the last day of hospitalisation, compared to 12.0% of matched controls.

Overall analysis

Aggregated over both rehospitalisation groups, oxycodone/naloxone was the opioid most commonly administered on the last day of hospitalisation (37.2%), followed by morphine (14.8%), oxycodone (14.7%) and tramadol (9.0%) (appendix table S1).

Unadjusted and adjusted ORs and 95% CIs for both the 18-day and 30-day rehospitalisation groups stratified by exposure are presented in table 2.

Adjusted ORs and 95% CIs are visualised in figure 3. Prior to adjustment, documented opioid administration on the last day of hospitalisation was associated with 18-day rehospitalisation (OR 1.39; 95% CI 1.19–1.61, p = 0.001) and 30-day rehospitalisation (OR 1.60; 95% CI 1.38–1.88, p = 0.001). After adjusting for the covariates length of

Table 1:
Baseline characteristics of matched cases and controls, stratified by 18-day and 30-day rehospitalisations. Variables had no missing data.

	Rehospitalisation within 18 days			Rehospitalisation within 30 days		
	Cases (n = 1698)	**Controls (n = 8490)**	**Std. Diff.**	**Cases (n = 1446)**	**Controls (n = 7230)**	**Std. Diff.**
Age in years, mean ± SD	78.06 ± 7.36	78.06 ± 7.32	<0.01	79.14 ± 7.49	79.14 ± 7.45	<0.01
Male, n (%)	880 (51.8%)	4400 (51.8%)	<0.01	691 (47.8%)	3455 (47.8%)	<0.01
Year of discharge, n (%)			<0.01			<0.01
2015	382 (22.5%)	1907 (22.5%)		339 (23.4%)	1680 (23.2%)	
2016	409 (24.1%)	2045 (24.1%)		360 (24.9%)	1818 (25.1%)	
2017	442 (26.0%)	2229 (26.3%)		388 (26.8%)	1944 (26.9%)	
2018	465 (27.4%)	2309 (27.2%)		359 (24.8%)	1788 (24.7%)	
Charlson Comorbidity Index, n (%)			<0.01			<0.01
0	403 (23.7%)	2015 (23.7%)		307 (21.2%)	1535 (21.2%)	
1–2	838 (49.4%)	4191 (49.4%)		768 (53.1%)	3840 (53.1%)	
3–4	389 (22.9%)	2013 (23.7%)		320 (22.1%)	1620 (22.4%)	
≥5	68 (4.0%)	271 (3.2%)		51 (3.5%)	235 (3.3%)	
Length of stay in days, median (IQR)	14 (12)	7 (7)	0.85	8 (8)	7 (7)	0.20
Department, n (%)			0.05			0.03
Medicine	1031 (60.7%)	5343 (62.9%)		915 (63.3%)	4661 (64.5%)	
Surgery	667 (39.3%)	3147 (37.1%)		531 (36.7%)	2569 (35.5%)	
Prescriptions, n (%)						
Opioid	257 (15.1%)	973 (11.5%)	0.11	256 (17.7%)	865 (12.0%)	0.16
Weak*	37 (2.2%)	135 (1.6%)	0.04	34 (2.4%)	107 (1.5%)	0.06
Opioid dose, n (%)						
MED <50 mg	215 (12.7%)	846 (10.0%)	0.09	223 (15.4%)	753 (10.4%)	0.15
MED 50–89 mg	12 (0.7%)	63 (0.7%)	<0.01	12 (0.8%)	57 (0.8%)	0.01
MED ≥90 mg	30 (1.8%)	64 (0.8%)	0.09	21 (1.5%)	55 (0.8%)	0.07
Benzodiazepines**, n (%)	13 (0.8%)	48 (0.6%)	0.03	13 (0.9%)	44 (0.6%)	0.03
Gabapentinoids**, n (%)	44 (2.6%)	137 (1.6%)	0.07	38 (2.6%)	126 (1.7%)	0.06
Confounders, n (%)						
Antidepressants	532 (31.3%)	2641 (31.1%)	0.01	527 (36.4%)	2399 (33.2%)	0.07
Antipsychotics	462 (27.2%)	2181 (25.7%)	0.03	448 (31.0%)	1962 (27.1%)	0.09
Alcohol use disorder	46 (2.7%)	268 (3.2%)	0.03	46 (3.2%)	201 (2.8%)	0.02
Delirium	200 (11.8%)	761 (9.0%)	0.09	150 (10.4%)	718 (9.9%)	0.02
Asthma	36 (2.1%)	208 (2.4%)	0.02	42 (2.9%)	187 (2.6%)	0.02
Pancreatitis	21 (1.2%)	55 (0.6%)	0.06	12 (0.8%)	52 (0.7%)	0.01
Chronic inflammatory bowel diseases	12 (0.7%)	59 (0.7%)	<0.01	16 (1.1%)	49 (0.7%)	0.05

IQR: interquartile range; MED: morphine-equivalent dose; SD: standard deviation; Std. Diff.: standardised difference (>0.1 indicates a clinically important difference).

* Codeine, dihydrocodeine, tramadol.

** Number of patients with co-prescribed opioids.

stay, department, gabapentinoids, delirium and pancreatitis for 18-day rehospitalisation, and length of stay, gabapentinoids, antidepressants, antipsychotics and chronic inflammatory bowel diseases for 30-day rehospitalisation in our conditional logistic regression, only 30-day rehospitalisation maintained its statistically significant association with opioid administration (adjusted odds ratio [aOR] 1.48; 95% CI 1.25–1.75, p <0.001).

Figure 2: Flowchart of included inpatient cases and 18-day and 30-day rehospitalisations with matched controls and opioid exposure status on the last day of hospitalisation.

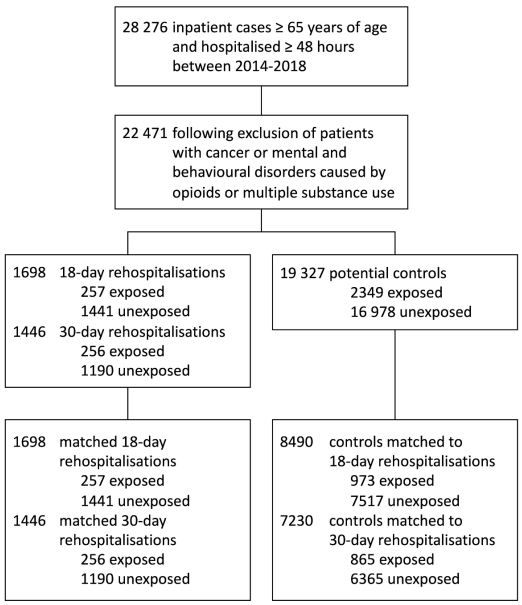


Figure 3: Adjusted odds ratios and 95% confidence intervals (95% CI) for 18-day and 30-day rehospitalisation stratified by exposure. Exposures included any documented opioid administration on the last day of hospitalisation, opioid dose as morphine-equivalent dose (MED), co-prescribed benzodiazepines and co-prescribed gabapentinoids. Adjustment was made for covariates that showed a standardised difference ≥0.1 (rounded): length of stay, department, gabapentinoids, delirium and pancreatitis for 18-day rehospitalisation; length of stay, gabapentinoids, antidepressants, antipsychotics and chronic inflammatory bowel diseases for 30-day rehospitalisation (Model 2).

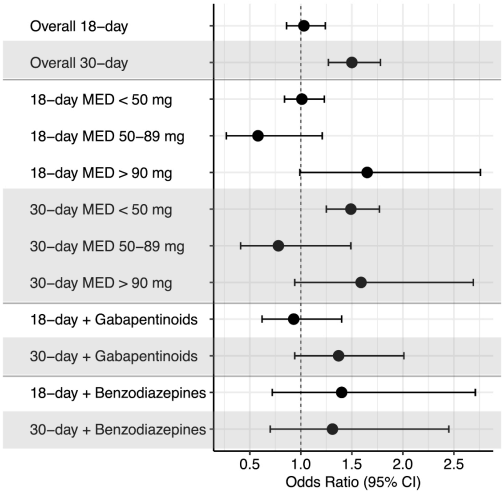


Table 2:
Unadjusted and adjusted odds ratios for 18-day and 30-day rehospitalisation stratified by exposure. Exposures included any documented opioid administration on the last day of hospitalisation, opioid doses with morphine-equivalent doses, co-prescribed benzodiazepines and co-prescribed gabapentinoids.

			Number of exposed cases	Number of exposed controls	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI), Model 1*	Adjusted Odds Ratio (95% CI), Model 2**
Primary analysis	18-day rehospitalisation		257	973	1.39 (1.19–1.61)	0.89 (0.75–1.06)	0.90 (0.74–1.08)
	30-day rehospitalisation		256	865	1.60 (1.38–1.88)	1.49 (1.27–1.74)	1.48 (1.25–1.75)
Secondary analysis: Morphine-equivalent dose (MED)	18-day rehospitalisation	MED <50 mg	215	846	1.32 (1.12–1.55)	0.89 (0.74–1.07)	0.90 (0.74–1.09)
		MED 50–89 mg	12	63	0.95 (0.51–1.77)	0.54 (0.26–1.12)	0.58 (0.28–1.22)
		MED ≥90 mg	30	64	2.37 (1.53–3.66)	1.26 (0.78–2.08)	1.28 (0.76–2.16)
	30-day rehospitalisation	MED <50 mg	223	753	1.59 (1.35–1.87)	1.49 (1.26–1.76)	1.46 (1.23–1.73)
		MED 50–89 mg	12	57	1.05 (0.56–1.97)	0.93 (0.49–1.74)	0.81 (0.43–1.54)
		MED ≥90 mg	21	55	1.92 (1.16–3.18)	1.66 (1.00–2.77)	1.53 (0.91–2.60)
Secondary analysis: Co-prescribed gabapentinoids***	18-day rehospitalisation		44	137	1.62 (1.15–2.23)	0.92 (0.62–1.37)	0.90 (0.60–1.33)
	30-day rehospitalisation		38	126	1.54 (1.06–2.24)	1.38 (0.95–2.01)	1.35 (0.92–1.97)
Secondary analysis: Co-prescribed benzodiazepines	18-day rehospitalisation		13	48	1.36 (0.73–2.52)	1.21 (0.61–2.39)	1.30 (0.65–2.56)
	30-day rehospitalisation		13	44	1.48 (0.80–2.76)	1.38 (0.74–2.57)	1.29 (0.69–2.42)
Secondary analysis: Weak opioids****	18-day rehospitalisation		37	135	1.38 (0.95–1.99)	1.37 (0.90–2.09)	1.46 (0.97–2.18)
	30-day rehospitalisation		34	107	1.61 (1.09–2.38)	1.62 (1.10–2.41)	1.60 (1.08–2.38)

CI : confidence interval.

* Model 1 included adjustment for covariates that showed a standardised difference >0.1 (rounded): length of stay for 18-day rehospitalisation; length of stay for 30-day rehospitalisation.

** Model 2 included adjustment for covariates that showed a standardised difference ≥0.1 (rounded): length of stay, department, gabapentinoids, delirium and pancreatitis for 18-day rehospitalisation; length of stay, gabapentinoids, antidepressants, antipsychotics and chronic inflammatory bowel diseases for 30-day rehospitalisation.

*** Models 1 and 2 were not adjusted for gabapentinoids in this stratification.

**** Codeine, dihydrocodeine, tramadol.

Secondary exposure analysis

In the secondary exposure analysis, only morphine-equivalent doses <50 mg were associated with 30-day rehospitalisation (aOR 1.46; 95% CI 1.23–1.73, p <0.001), while none of the stratified morphine-equivalent doses were statistically significantly associated with 18-day rehospitalisation after adjustment (figure 3).

In the additional secondary exposure analysis, which included co-prescription of opioids and benzodiazepines or co-prescription of opioids and gabapentinoids, none of the exposures resulted in a statistically significant association with 18-day or 30-day rehospitalisation (figure 3).

In the suggested further secondary exposure analysis, which included the categorisation of weak and strong opioids, weak opioids (codeine, dihydrocodeine, tramadol) were associated with 30-day rehospitalisation (aOR 1.60; 95% CI 1.08–2.38, p <0.01).

Discussion

In this case-control study of patients aged 65 years and older who were hospitalised for more than 48 hours, patients taking opioids on the day of discharge were 48% more likely to be rehospitalised within 30 days, while no difference was observed for the likelihood of 18-day rehospitalisation. When stratified by combined prescription of opioids with benzodiazepines or with gabapentinoids and morphine-equivalent dose >50 mg, no significant differences in rehospitalisation were identified; however, the number of events was low and did not reach the necessary sample size.

Our finding of a 48% increased risk of 30-day rehospitalisation is consistent with estimates from the external validation of the PAR-Risk Score, where the prevalence of opioids was 36.2% in rehospitalised patients and 26.0% in non-rehospitalised patients [14]. Woitok and colleagues, who examined patterns of prescription opioid use among patients presenting to Swiss emergency departments, also calculated an increased aOR of 3.57 (95% CI 2.87–4.44, p <0.001) for the association between opioid use and hospital readmission within 30 days [10]. The higher aOR compared to our results may be explained by the fact that Woitok and colleagues included less serious adverse effects of opioids leading to an emergency department visit without hospitalisation and, in addition, patients with neoplasms prone to hospitalisation. Potentially less serious adverse effects include gastrointestinal symptoms such as constipation, nausea and vomiting, as well as somnolence, dizziness, delirium, euphoria, sedation and cholinergic effects such as bradycardia or sweating [29]; approximately 80% of patients prescribed opioids will experience at least one adverse effect [30], even with short-term use [31]. In addition, dizziness and fatigue can lead to more serious outcomes such as falls, fractures and traffic accidents [31–34]. Herzig and colleagues were able to show that patients aged 65 years and older with an opioid claim one week after hospital discharge had a higher incidence of death, healthcare utilisation and any potential adverse effects, including falls and fractures, compared with a matched active control group who had only claimed nonsteroidal anti-inflammatory drugs [35].

The association between taking opioids on the day of discharge and 18-day rehospitalisation lost its statistical significance after adjusting for the potential confounder length of stay and in a second model when adjusted for length of stay, department, gabapentinoids, delirium and pancreatitis. Length of stay is an important variable in predictive models of 30-day rehospitalisation which may have influenced our results [36, 37]. Although adjusted for and matched on Charlson Comorbidity Score, the difference in length of stay could be an indication that the cases were more complex patients overall. Kurteva and colleagues showed that current opioid use was associated with opioid-related adverse events, with the risk increasing with cumulative exposure: compared with shorter exposures of 1 to 30 days, longer exposures (60 to 90 days and >90 days) were associated with a 2-fold increase in the risk of adverse events [31]. In their analysis of patients with repeated opioid claims from 2006 to 2014 in Switzerland, Burgstaller and colleagues observed a clear dose-response relationship between opioid intake and hospitalisation rates [38]. In particular, hospital admissions were significantly higher for daily doses above 100 mg, at 54%, compared with 10.7% for doses below 20 mg. In addition, the duration of opioid treatment showed a steady increase in the odds with prolonged use, particularly in chronic (>90 days) and very chronic (>360 days) cases. An analysis of Cochrane reviews that focused on adverse events associated with opioid use for “medium” (two weeks to two months) or “long-term” (two months or longer) treatment of chronic non-cancer pain showed a significantly higher risk of adverse events with opioids than with placebo [39]. In addition, there was a higher rate of withdrawal from the trials due to adverse events compared to an active comparator. Adverse events included constipation, dizziness, drowsiness, fatigue, hot flushes, increased sweating, nausea, pruritus and vomiting.

In our analysis, oxycodone was identified as the most prescribed opioid. The same prescription pattern was, again, observed by Woitok and colleagues in patients presenting to Swiss emergency departments [10]. Switzerland has seen a significant increase in oxycodone sales from 2000 to 2019, with a market share of 12.9%, second only to tramadol [6]. Standardised to the population, the number of any opioid sales increased by 91.3%, while the rate of calls for opioid-related poisonings to the Swiss National Poisons Information Centre also increased by 177%, consequently increasing the risk of rehospitalisation. A study from the Netherlands, where sales and poisonings increased as well, additionally showed an increase in the hospital admission rate due to poisoning by (prescription) opioids [6, 40].

Most patients in our dataset had received opioid doses of less than 50 mg morphine-equivalent dose, which is also true of the analysis of patients in Swiss emergency departments by Woitok and colleagues, with a median morphine-equivalent dose of 30 mg [10]. Usually, an increase in risk with higher morphine-equivalent dose would be expected [31, 41]. Gomes and colleagues similarly found an unexpectedly attenuated effect on road trauma in their highest dose category, which also contradicted otherwise clear dose-response relationships. They discussed this attenuation with the likelihood of drug diversion and physiological opioid tolerance in this patient population [34]. How-

ever, the most likely explanation for our results is that stratification outside the >50 mg dose range resulted in sample sizes that were too small to be statistically significant and hence should be interpreted with utmost caution. The same applies to the additional secondary analysis, which should have looked at the co-prescription of gabapentinoids and benzodiazepines. Here, according to a study by Wertli and colleagues, we would have expected the prevalence of opioids and concomitant benzodiazepines in chronic non-cancer pain to be around one third [9].

Limitations

Our analysis has important limitations, which have implications for generalisability and possibly influence the true effect of opioids on rehospitalisation. In particular, no direct causal relationship can be inferred between opioid prescriptions at discharge and rehospitalisation, but rather an association. First, our sample of inpatients over 65 years of age may have been in poorer health than the general discharged population. Second, as there was no information on hospital stays of less than 48 hours, it is possible that a proportion of patients with opioid-related complaints (e.g. constipation, nausea) were not present in our sample. Therefore, the adverse effects of opioids may have been underestimated. Third, discharge with an opioid was presumed by a documented use of an opioid on the day of discharge, excluding patients on parenteral opioids. We were not able to monitor actual opioid use after discharge. It is therefore possible that the actual number of opioid users after discharge differs from our figures. Fourth, the cause of 30-day rehospitalisation and the indication for opioids were unknown. While administrative 18-day rehospitalisations only included unplanned rehospitalisations, it is possible that a 30-day rehospitalisation was not related to the initial hospitalisation or that the indication treated with opioids led to hospitalisation (e.g. exacerbated pain), leading to an overestimation of the association between opioids and rehospitalisation. At the same time, the patients could not be followed up, so any hospitalisations in other institutions could not be identified. Fifth, while we matched patients based on disease status using the Charlson Comorbidity Index and length of hospital stay, we cannot rule out the possibility that there are important unmeasured confounders. For example, socioeconomic status and family support may be important mitigators of the likelihood of rehospitalisation. Finally, we had a rather small number of patients in some of the exposure groups, which ultimately limited the interpretability of some results. By including a sample size calculation, we avoided drawing erroneous conclusions from these results.

Implications for practice

In light of our findings and those of others who have shown that opioid use at or after hospital discharge is associated with an increased likelihood of rehospitalisation, it is recommended that opioid stewardship programmes be enhanced/implemented to encourage tapering of opioid use during or immediately after hospitalisation [5, 42]. Opioid stewardship is described as “coordinated interventions designed to improve, monitor, and evaluate the use of opioids in order to support and protect human health” [43]. Besides interventions at different levels and monitoring, a key element is patient education, including information on risks and adverse effects, and clear instructions on appropriate weaning after discharge from hospital [2]. While our study cannot be used to make causal inferences about opioids causing adverse effects leading to rehospitalisation, our results show that patients receiving opioids are at risk of rehospitalisation and need to be cared for.

Conclusion

This study found a significant association between opioid prescription at discharge and 30-day rehospitalisations in patients aged 65 years or older. Oxycodone was the most prescribed opioid in this dataset from a tertiary teaching hospital. Clinicians should be aware of the potential adverse effects of prescribing opioids at discharge and should strive to discontinue opioids started in hospital before discharge, or give patients and carers clear instructions for weaning after hospitalisation. Patients should be educated and monitored, potentially as part of opioid stewardship programmes.

Availability of data and materials

The dataset analysed and the unformatted statistical code used are available from the corresponding author upon request.

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Potential competing interests

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. No potential conflict of interest related to the content of this manuscript was disclosed.

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Appendix

Table S1:
Frequency of opioids administered on the last day of hospitalisation to exposed cases and matched controls.

ATC	Substance(s)	Number (%)
N02AA55	Oxycodone/naloxone	1206 (37.2%)
N02AA01	Morphine	479 (14.8%)
N02AA05	Oxycodone	475 (14.7%)
N02AX02	Tramadol	293 (9.0%)
N02AE01	Buprenorphine	275 (8.5%)
N07BC02	Methadone	172 (5.3%)
N02AA03	Hydromorphone	120 (3.7%)
N02AX06	Tapentadol	81 (2.5%)
N02AJ13	Tramadol and paracetamol	74 (2.3%)
N02AB03	Fentanyl	46 (1.4%)
N02AA59	Codeine and combinations	19 (0.5%)
N02AA08	Dihydrocodeine	2 (0.1%)

ATC: Anatomical Therapeutic Chemical classification.