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Prescription Trends in Hospice Care: A Longitudinal Retrospective and Descriptive Medication Analysis

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Background: In hospice and palliative care, drug therapy is essential for symptom control. However, drug regimens are complex and prone to drug-related problems. Drug regimens must be simplified to improve quality of life and reduce risks associated with drug-related problems, particularly at end-of-life. To support clinical guidance towards a safe and effective drug therapy in hospice care, it is important to understand prescription trends.

Objectives: To explore prescription trends and describe changes to drug regimens in inpatient hospice care.

Design: We performed a retrospective longitudinal and descriptive analysis of prescriptions for regular and as-needed (PRN) medication at three timepoints in deceased patients of one Swiss hospice.

Setting/subjects: Prescription records of all patients (≥ 18 years) with an inpatient stay of three days and longer (admission and time of death in 2020) were considered eligible for inclusion.

Results: Prescription records of 58 inpatients (average age 71.7 ± 12.8 [37-95] years) were analyzed. The medication analysis showed that polypharmacy prevalence decreased from 74.1% at admission to 13.8% on the day of death. For regular medication, overall numbers of prescriptions decreased over the patient stay while PRN medication decreased after the first consultation by the attending physician and increased slightly towards death.

Conclusions: Prescription records at admission revealed high initial rates of polypharmacy that were reduced steadily until time of death. These findings emphasize the importance of deprescribing at end-of-life and suggest pursuing further research on the contribution of clinical guidance towards optimizing drug therapy and deprescribing in inpatient hospice care.

Introduction

In palliative care, symptom control is essential, particularly at end-of-life. Drug therapy is focused on decreasing patients' symptom burden and improving their quality of life.[1, 2] However, end-of-life medication must balance complex factors, which characterize the pathophysiological changes that are associated with the last phase of life. Drug-related problems (DRPs) may arise from the patients' general vulnerability, their comorbidities, and their high prevalence of polypharmacy (≥5 drugs administered regularly daily).[3-6] On average, palliative care patients receive 7.1-7.8 drugs daily.[7, 8] This level of polypharmacy increases the risks not only of drug-drug interactions and drug-disease interactions, but also of medication errors.[9, 10]

A study conducted in Germany in 2021 in patients of a palliative care unit demonstrated DRPs' impact on symptom progression: With increasing symptom control requirements and medication regimens becoming more complex, DRPs increased as well.[11] At end-of-life it is necessary to simplify drug regimens in order to optimize quality of life and reduce risks associated with DRPs.[12, 13] It is also necessary to balance desirable increases in prescribed drugs used for symptom control and avoid polypharmacy, especially in prescriptions with a focus on life extension and primary prevention.[14-16] Deprescribing involves weighing each drug's known or potential harm against its expected benefits.[17] This process is particularly relevant in hospice care where therapeutic goals change drastically with the decision to pursue non-curative treatment in favor of symptom management and quality of life.[18] These goals must constantly be assessed and adapted as necessary. Patients' individual goals as well as patients' and their families' requirements and needs must be considered. Thus, the discontinuation of medication can vary greatly over time.[19]

The problem of complex drug regimens in palliative care has been investigated and described in several studies.[2, 7, 20, 21] However, studies investigating whether drug regimens in hospice care are associated with similar levels of complexity remain low in number. Most of the available studies only assess medication cross-sectionally at one timepoint only, usually on the day of death. In order to gauge

what contributions could support clinical guidance towards a safe and effective drug therapy in hospice care, it is important to investigate prescription trends in this setting.

This study aims to analyze prescription trends and describe changes to drug regimens from hospice admission to death.

Methods

The retrospective longitudinal and descriptive analysis of prescriptions was performed in the *Hospice of Central Switzerland* in the Canton of Lucerne, a 12-bed institution that provides specialized palliative care (in Switzerland, provision of specialized palliative care in a hospice is considered hospice care).[22] One attending physician is responsible for the medication; prescriptions are written and collected on structured paper-based standard forms ("prescription sheets"). Data of patients and prescription sheets were anonymized using numeric coding. In compliance with Swiss data protection rights, the key for these codes was accessible only to the hospice administration team. Eligibility criteria for patient enrollment are displayed in *Table 1*.

Table 1: Eligibility criteria for patient enrollment

Inclusion criteria	Exclusion criteria
• ≥18 years old with inpatient stay ≥ 3 days	• outpatients or inpatient stay < 3 days
• admission to the hospice in 2020	• discharge to the home care setting or hospital
• time of death in the hospice in 2020	• explicitly documented restriction from use of patient-specific data

In the study hospice, patients' baseline data (gender, age at admission, diagnoses, duration of stay) are collected for all patients upon admission. Within three days, the attending physician reviews their medications and makes the first changes to their drug regimens. All patients with an inpatient stay of three or more days that were admitted to the hospice in 2020 and died in the hospice in the same year were considered eligible for inclusion. To determine the most relevant diagnosis that led to hospice admission, we extracted the five diagnoses of each patient based on ICD-10 classifications we considered the most relevant. We extracted medication-related information from the prescription sheets at three timepoints: first day of admission (t_1); day 3 post-admission (after first consultation and changes to medication by attending physician) (t_2); and day of death (t_3). Data on regular medication and as-needed medication (PRN) were collected separately at the same three timepoints. Medication data (i.e., active substance, brand name, dosage, formulation, dosage interval, route of application, off-

label use) was extracted for the medication analysis and collected in an Excel® table. Anatomical Therapeutic Chemical (ATC) codes were used to categorize the drugs according to the fourteen main anatomical or pharmacological groups (first level).[23] The route of application was classified according to the WHO abbreviations.[23] Descriptive analysis was performed for the baseline data to allow calculation of the relevant means and standard deviations. To compare the number of medications across the three timepoints, we performed a one-way ANOVA test followed by a post hoc Tukey HSD test. Statistical analyses were performed in R studio (*R version 3.6.3*).

Ethical approval for this study was obtained from the Ethics Committee of Northwestern and Central Switzerland (EKNZ, ID 2021-00411). Authors followed the STROBE Statement for cross-sectional studies.[24]

Results

Fifty-eight patients met the study's inclusion criteria. Their medical records were assessed for data extraction (see *Figure 1*).

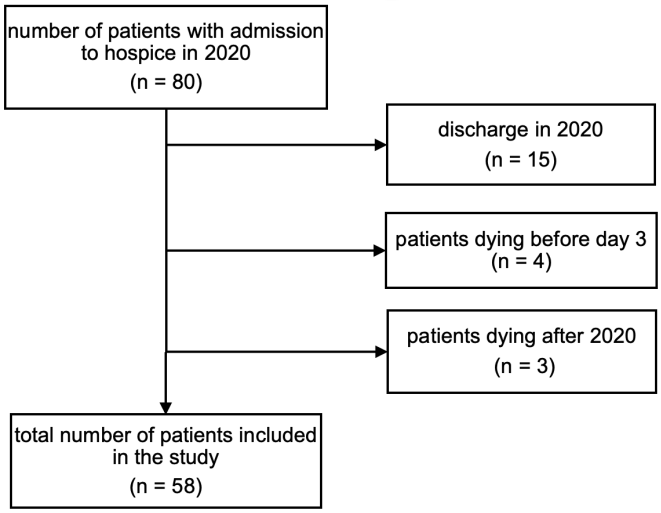

Figure 1: Flow chart of patient recruitment according to inclusion and exclusion criteria

Patient baseline data

Extracted baseline patient data are shown in *Table 2 (*for detailed patients' baseline data see *supplementary material SA1)*. The median duration of stay (range) was 13.5 (3-146) days. However, the

range was very heterogeneous: the majority of patients stayed between 21 and 50 days (n=16). Thirteen patients stayed three to five days, and another 13 stayed six to ten days. Eight patients stayed 11 to 20 days; and five 51 to 100 days. Three patients stayed much longer, 101, 112, and 146 days, respectively. The most common hospice-relevant diagnoses (ICD-10) were neoplasms in 51/58 patients (88.0%).

Table 2: Patient baseline data

Baseline Patient Characteristics	
patients total N (%)	58 (100%)
gender	**n (%)**
female	26 (45%)
male	32 (55%)
age (years)	**n (%)**
mean ± SD (range)	71.7 ±12.80 (37-95)
≥30 to ≤39	2 (3.4%)
≥40 to ≤49	2 (3.4%)
≥50 to ≤59	3 (5.2%)
≥60 to ≤69	17 (29.3%)
≥70 to ≤79	16 (27.6%)
≥80 to ≤89	14 (24.1%)
≥90	4 (6.9%)
duration of stay	**(in days)**
median (range)	13.5 (3-146)
most common hospice-relevant diagnosis (ICD-10)	**n (%)**
Neoplasms	51 (88.0%)
Amyotrophic lateral sclerosis	1 (1.7%)
Asthenia	1 (1.7%)
Chronic kidney disease	1 (1.7%)
Chronic obstructive lung disease	1 (1.7%)
Creutzfeldt-Jakob disease	1 (1.7%)
Pelvic fracture	1 (1.7%)
Severe cachexia	1 (1.7%)
patients with polypharmacy* drug regimen	**n (%)**
t_1	43 (74.1%)
t_2	20 (34.5%)
t_3	8 (13.8%)
t_1: admission, t_2: first change to medication on day three, t_3: day of death, SD: standard deviation, *regular medication ≥5 drugs per day	

Drug regimens

The total number of prescribed drugs decreased from t_1 to t_3 for regular medications; PRN medications initially decreased, then increased again near the time of death (see *Table 3*). The mean of prescribed drugs prescribed per patient varied significantly (ANOVA; $F(2, 171) = [29.17]$, $p<0.001$) between the

measurement points for regular medication with significant decrease between t_1 and t_2 (Post hoc Tukey; $p<0.001$), and between t_1 and t_3 (Post hoc Tukey; $p<0.001$). No significant difference was observed between t_2 and t_3 (Post hoc Tukey; $p=0.08$). For PRN medication, the average number of prescribed drugs also differed significantly (ANOVA; $F(2, 171) =[5.57]$, $p=0.005$). The decrease in the mean number of PRN drugs per patient was significant between t_1 and t_2 (Post hoc Tukey test: $p=0.004$) but fell slightly short of significance between t_1 and t_3 (Post hoc Tukey test: $p = 0.052$). The mean number of prescribed PRN medications per patient increased slightly between t_2 and t_3 (Post hoc Tukey test: $p = 0.658$), although not significantly.

The number of patients with no regular medications prescribed increased slightly after the first change of medication by the hospice physician (t_2) and decreased again on the day of death (t_3). Regarding patients receiving no PRN medications, the number first decreased rapidly from six (t_1) to one (t_2), increasing to two on the day of death (t_3). The number of patients with a polypharmacy drug regimen (≥5 drugs in regular drug regimen) was highest at admission (t_1: n=43) and was reduced by more than half between t_1 and t_2 (n=20), and between t_2 and t_3 (n=8) (see *Table 3*).

The number of drugs prescribed off-label (defined by European Medicines Agency as 'Use of a medicine for an unapproved indication or in an unapproved age group, dosage, or route of administration'[25]) is larger in PRN medications compared to regular medications. For both regular and PRN medications, the percentage of drugs administered for off-label uses increased towards death. Of a total of 436 drugs prescribed at time of death, 105 (24.1%) were used off-label; at admission only 30/794 drugs prescribed (3.8%) were used off-label (see *Table 3*).

Table 3: Summary of prescriptions and active substances at each point in time

Regimen	Time	Mean number of prescribed drugs per patient (range)	Number of patients with polypharmacy regimen (n=)	Number of patients without prescription (n=)	Total number of prescriptions (N=)	Number of different prescribed drugs [a] (n=)	Number of different prescribed substances[b] (n=)	Number of off-label prescriptions[c]
Regular	**t_1**	7.0 (0-19)	43 (74.1%)	4	406	247	131	6/405 (1.5%)
	t_2	3.8 (0-13)	20 (34.5%)	8	220	138	72	7/215 (3.3%)
	t_3	2.5 (0-11)	8 (13.8%)	6	143	97	44	18/143 (12.6%)
PRN[+]	**t_1**	6.7 (0-19)	n/a	6	390	155	82	24/389 (6.2%)
	t_2	4.4 (0-20)	n/a	1	257	72	41	63/257 (24.5%)
	t_3	5.1 (0-20)	n/a	2	293	74	46	87/293 (29.7%)

[a]number of all drugs prescribed at specific point in time (t_x), where one drug could contain multiple substances
[b]number of all substances prescribed at specific point in time (t_x), where one substance could be prescribed and administered in different formulations (e.g., morphine drops for oral intake and morphine solution for subcutaneous administration)
[c]prescriptions with unknown off-label status were excluded
[†]PRN: pro re nata medication (as-needed medication)

Over the whole study period, the five active ingredients most frequently prescribed for regular use were morphine (n=60), fentanyl (n=48), sodium picosulfate (n=34), pantoprazole (n=26), and dexamethasone (n=23) (n=number of prescriptions). For PRN medications, morphine (n=152), lorazepam (n=96), haloperidol (n=95), midazolam (n=85), and metoclopramide (n=31) were most frequently prescribed.

ATC codes and routes of administration

The drugs were categorized according to their ATC codes (see figure 2) and routes of administration (see figure 3).

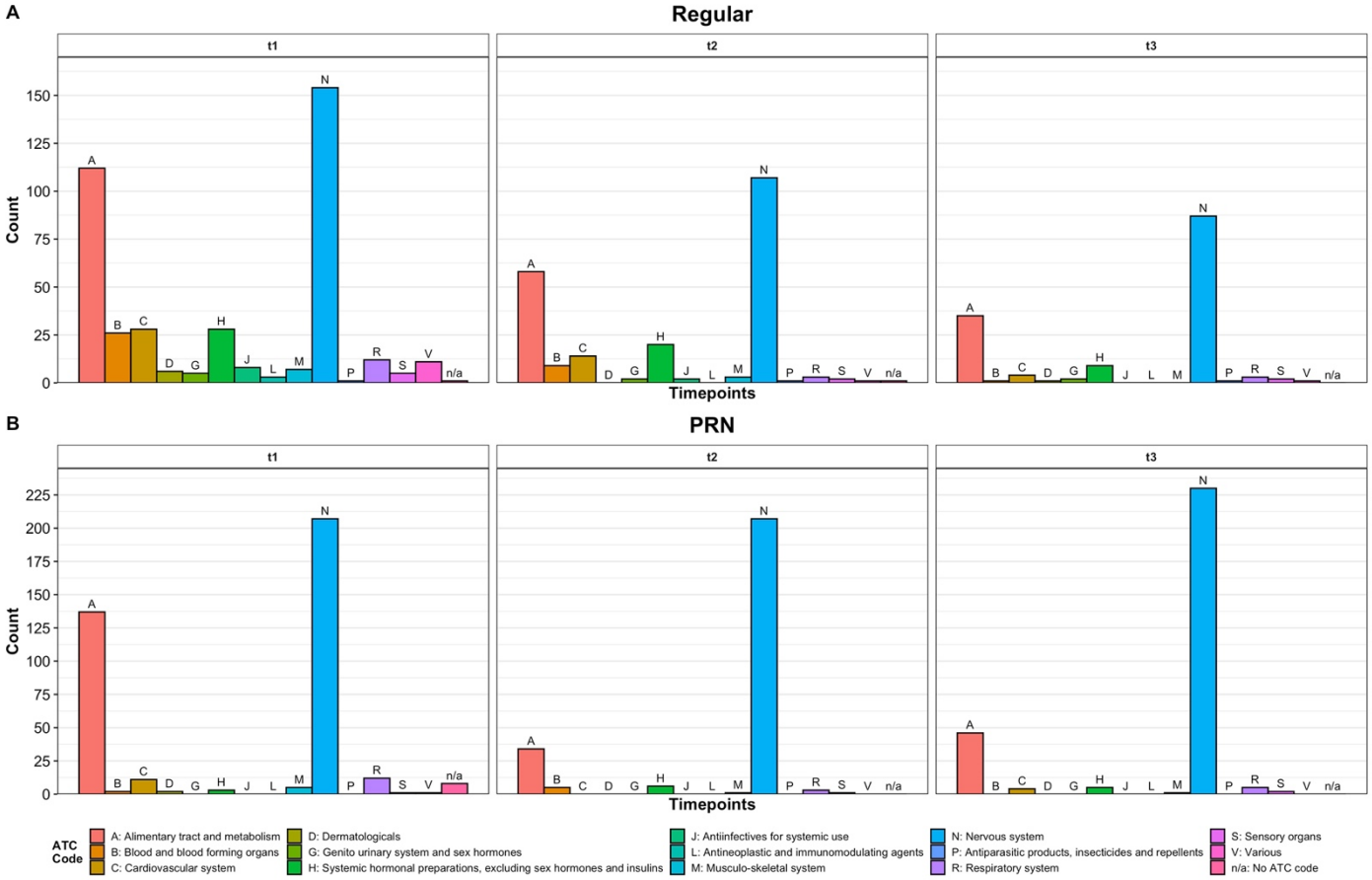

Figure 2: ATC codes

Figure 2 shows the counts of each ATC code for the regular (A) and PRN medication (C). **ATC Codes: A**: Alimentary tract and metabolism, **B**: Blood and blood forming organs, **C**: Cardiovascular system, **D**: Dermatologicals, **G**: Genito urinary system and sex hormones, **H**: Systemic hormonal preparations, excluding sex hormones and insulins, **J**: Antiinfectives for systemic use, **L**: Antineoplastic and immunomodulating agents, **M**: Musculo-skeletal system, **N**: Nervous system, **P**: Antiparasitic products, insecticides and repellents, **R**: Respiratory system, **S**: Sensory organs, **V**: Various

At admission, the majority of drugs prescribed for regular use belonged to the ATC code category *Nervous system* (t_1: 154/406, 37.9%), followed by *Alimentary tract and metabolism* (t_1: 112/406, 27.6%), *Cardiovascular system* (t_1: 28/406, 6.9%), and *Systemic hormonal preparations* (t_1: 28/406, 6.9%). Nearing death, the proportion of prescriptions within the category *Nervous system* increased (t_2: 107/220, 48.6%, t_3: 87/143, 60.1%), while prescriptions for the categories *Alimentary tract and metabolism* (t_2: 58/220, 26.4%, t_3: 35/143, 22.9%) and *Cardiovascular system* (t_2: 14/220, 6.4%, t_3: 4/143, 2.8%) decreased slightly. At admission, the majority of PRN medications prescribed were in the

category *Nervous system* (t_1: 207/390, 53.1%). That proportion increased drastically after three days (t_2: 207/257, 80.5%) and thereafter only decreased slightly on the day of death (t_3: 230/293, 78.5%). As for regular medication regimens, the second most common PRN category was *Alimentary tract and metabolism* (t_1: 137/390, 35.1%). In this case, though, the proportion of prescriptions decreased on t_2 (34/257, 13.2%), then increased slightly on the day of death (t_3: 46/293, 15.7%).

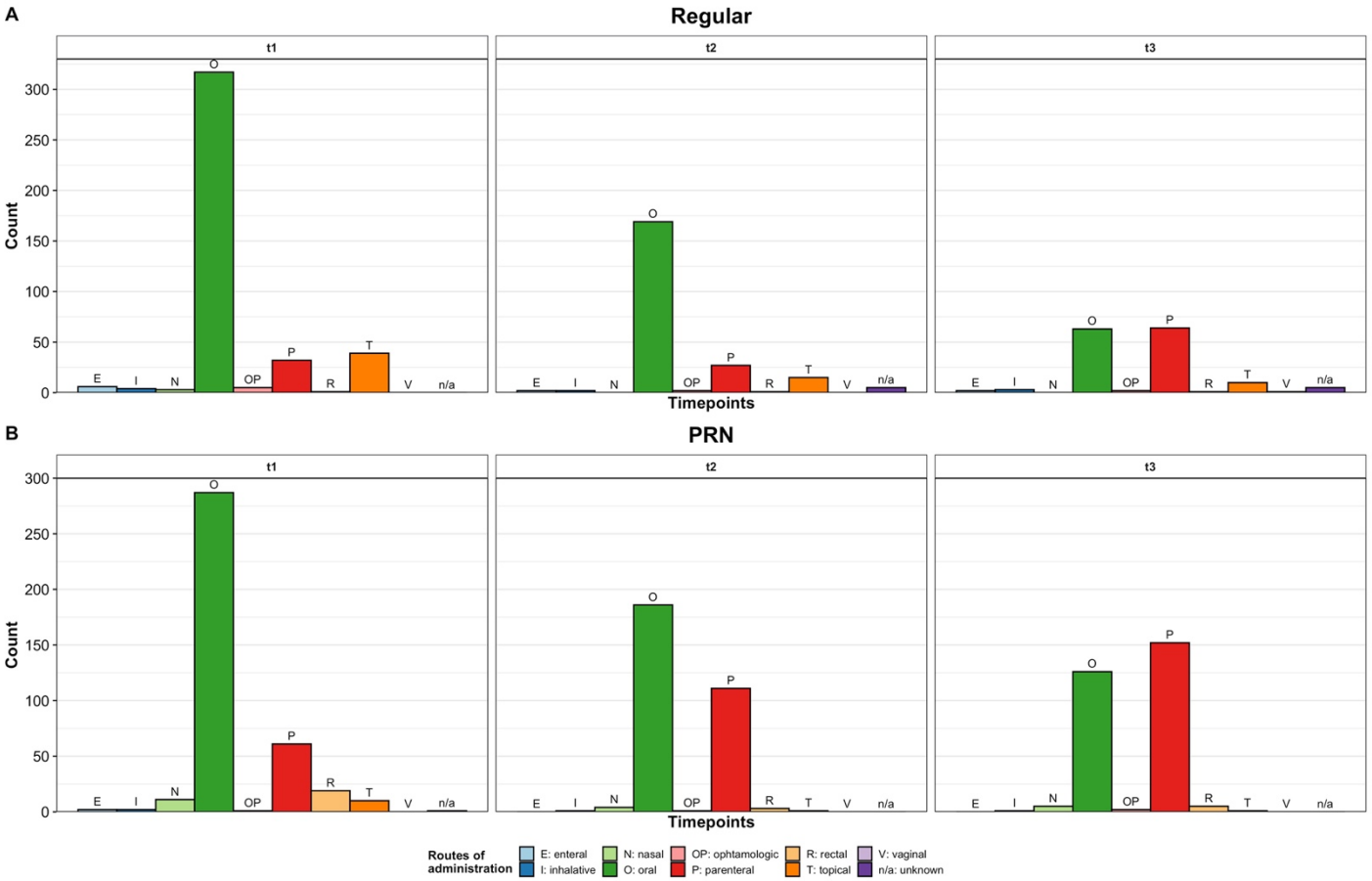

Figure 3: Routes of administration at each timepoint

Figure 3 shows the distribution of the identified routes of administration for the regular (A) and PRN (B) medication.

At t_1 and t_2, most prescribed drugs (both regular and PRN) were administered orally (i.e., buccal, oral, sublingual). On the day of death (t_3), the number of orally (n=58) and parenterally (i.e., intramuscularly, intrathecally, intravenously, subcutaneously; n=64) administered drugs was almost identical within the regular drug regimen, indicating an overall increase in the use of the parenteral route. For PRN drugs, the number administered parenterally increased steadily (t_1: n=61, t_2: n=111, t_3: n=152), while the number of orally administered drugs decreased (t_1: n=287, t_2: n=186, t_3: n=126). Topically administered regular medications decreased at both t_2 and t_3 (t_1: 39, n=, t_2: n=15, t_3: n=10). For PRN medications, the

number administrated topically first decreased sharply, then remained stable between t_2 and t_3 (t_1: n=10, t_2: n=1, t_3: n=1). Few regular medications were administered nasally (t_1: n=3, t_2: n=0, t_3: n=0). Among PRN prescriptions, nasal application first decreased (t_1: n=11, t_2: n=4), then increased again nearing death (t_3: n=5). Likewise, for both regular and PRN medications, the vaginal administration route was used only marginally (regular medication: t_1: n=0, t_2: n=0, t_3: n=1, PRN: t_1: n=0, t_2: n=0, t_3: n=0).

Discussion

Our medication analysis revealed the complexity of drug regimens in hospice patients during the course from admission to time of death, making the drug regimens especially prone to DRPs.[4] Among these DRPs, occurring adverse drug reactions can easily be mistaken for symptoms that are common in hospice and palliative care (e.g., mouth dryness, vertigo, fatigue). At admission, the included patients were receiving an average of seven prescribed drugs for regular use. These findings are consistent with a 2019 US retrospective cohort study that found a mean of 7.1 prescribed medications on discharge to hospice care [8] and a 2014 European cross-sectional study that reported an average of 7.8 medications in palliative care patients [7].

At end of life, significant medication burden is placed on patients.[16] However, polypharmacy prevalence was reduced consistently over the three measurement points (from 74.1% of patients at admission to 13.8% on day of death). This dramatic decrease in number of prescribed drugs between admission and time of death exemplifies the shift from disease-focused acute care to hospice care, with strong prioritization of comfort and symptom management. Further, findings indicate the relevance of deprescribing in hospice care, while maintaining optimal symptom control.

Structured approaches to balance out factors of undertreatment and overtreatment are growing, especially after studies in certain medical disciplines investigating adverse effects of polypharmacy on survival failed to show this effect.[26, 27] However, in hospice care representing end-of-life care, polypharmacy is still considered a valid indicator to assess quality of drug regimens. It is essential to find a good balance between prescribed medications with a benefit on quality of life for appropriate

187 symptom management and to reduce the medication burden in patients.[16] This is highly desirable in
188 hospice care, where patients are highly vulnerable to issues that could reduce their quality of life even
189 for a short time.[4, 28]

190 A 2015 multicenter, parallel-group, unblinded, pragmatic clinical trial on discontinuation of statin
191 therapy in patients with life-limiting illness suggested that discontinuing statins is safe, associated with
192 improved quality of life, and a decrease in total number of prescribed medications. The 60-days
193 mortality in patients with discontinued statin therapy was not significantly different compared to
194 patients with continued therapy (23.8% vs. 20.3%, 90% CI -3.5% to 10.5%, p=0.36).[29] Time to benefit
195 of statin in patients between 50 and 75 years is suspected to be approximately 1.5 to 3.0 years.[30]
196 Assuming a life expectancy of 6 months in hospice care, the effect of statin therapy is questionable. At
197 admission, only one patient received a statin which was discontinued after t_2. This shows that
198 deprescribing of statin therapy is already applied in clinical settings preceding hospice admission.
199 However, at admission, pantoprazole was prescribed in 26 patients. On the day of death, it was only
200 prescribed in two patients. Timely medication review after admission to hospice seems an important
201 step to critically assess clinical benefits and appropriateness of prescribed medications, carefully
202 considering clinical situations as well as patients' and families conceptions and wishes, and to reduce
203 polypharmacy in the last phase of life, as shown in other settings.[31, 32]

204 The shift to comfort care and deprescribing raises the issue of assessing the appropriateness of drug
205 therapy in hospice care. Medication appropriateness should be carefully considered. However,
206 particularly in hospice care, assessments to identify potentially inappropriate medications are
207 challenging due to the high rates of comorbidities, rapid changes in manifestation of symptoms, and
208 uncertainty regarding life expectancy. Large, controlled intervention studies are avoided due to
209 patients' high frailty. Hence, only few guidelines are available to assess the appropriateness of
210 medications in end-of-life care settings (e.g., STOPP Frail criteria, OncPal).[33, 34] We observed a high
211 prevalence of medications for managing and treating comorbidities that are not directly associated with
212 the main diagnosis responsible for hospice care. Other studies have previously discussed this issue.[16,

18, 21] Complex and frequently changing drug therapy regimens, as identified in the medication analysis, require thorough and regular assessment (e.g., medication review) and interprofessional exchange.[28, 35, 36]

A high rate of off-label prescriptions was identified. This finding reflects the increasing need for alternative routes of drug administration to manage symptoms at end-of-life. The most common shift pertaining to the routes of administration concerned orally administered drugs shifting towards parenteral use (mainly for PRN medication but also for regular medication). This finding is in accordance with the preference of alternative routes of administration in hospice care.[21, 37, 38] Subcutaneous drug administration offers a minimal invasive alternative when oral intake of drugs is severely limited [39, 40]. This complies with the comfort-oriented approach of hospice care. Among the most frequently prescribed drugs for regular and PRN use, the findings are comparable to the findings of a 2015 study by Masman et al. revealing morphine, midazolam, and haloperidol as the most frequently prescribed drugs during end-of-life care in a palliative care center.[2]

Even in small settings of hospice care where the variety of prescriptions is limited, support and guidance towards a safe and effective drug therapy is important, especially in end-of-life care patients with complex regimens and with strong considerations for maximizing quality of life.

Strengths and limitations

This is the first study that performed a longitudinal retrospective and descriptive medication analysis to reveal the complexity of medication regimens in hospice care. In this study, retrospective data collection and analysis of anonymized patient prescription records reduced the risk of selection bias. However, as the study was performed in a single institution, the medication analyses are only representative for one single institution and not necessarily nationwide. Only one physician is responsible for changes in drug regimens. Variability among prescribing physicians and deprescribing preferences are not well represented in this medication analysis. Nevertheless, characteristics of the medication regimens and aspects of medication safety identified here are consistent with those revealed in other studies. [2, 7,

8, 20, 21] Both the complexity of patients' drug regimens observed at admission and the progression of their medication therapies support the general assumption in palliative care that regular medications decrease steadily towards death, while the need for PRN medications increases.

Conclusion

This retrospective longitudinal and descriptive medication analysis provides an overview of hospice patients' medication prescriptions and their changes over time. The findings help to understand prescription trends and highlight important aspects of medication safety in inpatient hospice care, such as high initial rates of polypharmacy at hospice admission which can compromise medication safety and quality of life, especially in highly frail patients. The findings emphasize the importance of deprescribing at end-of-life and the need for timely medication review after admission. Beneficial effects of deprescribing on polypharmacy and on the quality of life, considering time to benefit, should be assessed in patients with a limited life expectancy. Guidelines to improve assessment of appropriateness for most commonly prescribed medications and documents that inform clinical decision-making towards deprescribing, especially those treating comorbidities or prescribed for prevention, are explicitly needed.

Overall, findings suggest pursuing further research on the contribution of clinical guidance towards optimizing drug therapy and deprescribing in inpatient hospice care, rendering drug regimens safe and effective.

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Authors' Contributions

CMM was responsible for the study concept and the ethics commission proposal. DH collected the prescription records, DH and UW analyzed the prescription records. UW performed statistical analyses and created the graphs. The manuscript was finalized by UW and CMM. The project was supervised by CMM, AK, AP, and CRM; and SJPM contributed her specialist knowledge of hospice care. All authors read and approved the final manuscript.

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Author Disclosure Statement

One of the authors is employed at the institution where the medication analysis was performed. However, there are no conflicts of interest to disclose. All authors declare no competing interests nor personal financial interests.

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Supplementary Material

SA1: Detailed table of patients' baseline data