

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

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

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

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

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

12 **Results:** Prescription records of 58 inpatients (average age 71.7 ± 12.8 [37-95] years) were analyzed.
13 The medication analysis showed that polypharmacy prevalence decreased from 74.1% at admission to
14 13.8% on the day of death. For regular medication, overall numbers of prescriptions decreased over the
15 patient stay while PRN medication decreased after the first consultation by the attending physician and
16 increased slightly towards death.

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

21

22 Introduction

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

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

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

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

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

51

52 **Methods**

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

61 *Table 1: Eligibility criteria for patient enrollment*

Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none">• ≥ 18 years old with inpatient stay ≥ 3 days	<ul style="list-style-type: none">• outpatients or inpatient stay < 3 days
<ul style="list-style-type: none">• admission to the hospice in 2020	<ul style="list-style-type: none">• discharge to the home care setting or hospital
<ul style="list-style-type: none">• time of death in the hospice in 2020	<ul style="list-style-type: none">• explicitly documented restriction from use of patient-specific data

62

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

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

81

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

85 Results

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

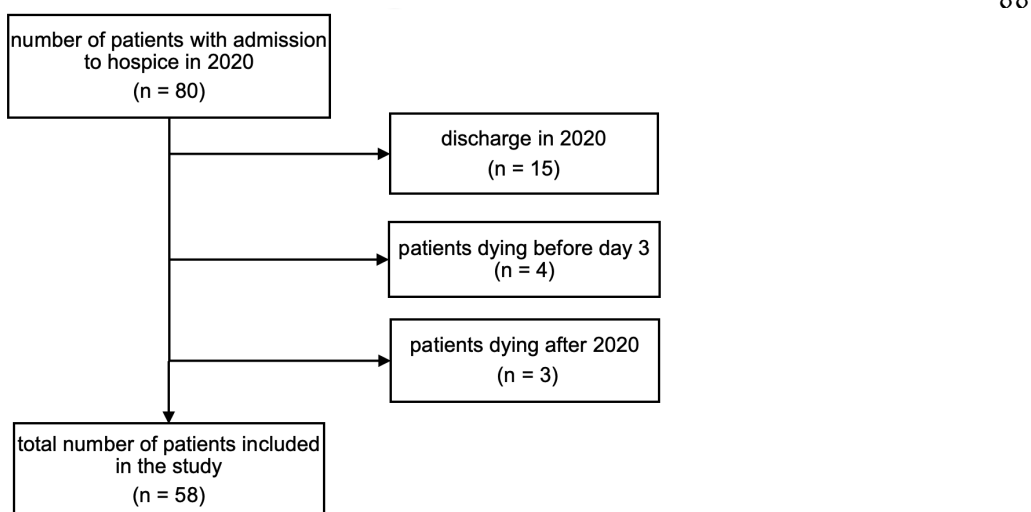


Figure 1: Flow chart of patient recruitment according to inclusion and exclusion criteria

97

98 Patient baseline data

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

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

105 *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	

106
 107 **Drug regimens**
 108 The total number of prescribed drugs decreased from t₁ to t₃ for regular medications; PRN medications
 109 initially decreased, then increased again near the time of death (see *Table 3*). The mean of prescribed
 110 drugs prescribed per patient varied significantly (ANOVA; F(2, 171) = [29.17], p<0.001) between the

111 measurement points for regular medication with significant decrease between t_1 and t_2 (Post hoc Tukey;
 112 $p < 0.001$), and between t_1 and t_3 (Post hoc Tukey; $p < 0.001$). No significant difference was observed
 113 between t_2 and t_3 (Post hoc Tukey; $p = 0.08$). For PRN medication, the average number of prescribed
 114 drugs also differed significantly (ANOVA; $F(2, 171) = [5.57]$, $p = 0.005$). The decrease in the mean number
 115 of PRN drugs per patient was significant between t_1 and t_2 (Post hoc Tukey test: $p = 0.004$) but fell slightly
 116 short of significance between t_1 and t_3 (Post hoc Tukey test: $p = 0.052$). The mean number of prescribed
 117 PRN medications per patient increased slightly between t_2 and t_3 (Post hoc Tukey test: $p = 0.658$),
 118 although not significantly.

119 The number of patients with no regular medications prescribed increased slightly after the first change
 120 of medication by the hospice physician (t_2) and decreased again on the day of death (t_3). Regarding
 121 patients receiving no PRN medications, the number first decreased rapidly from six (t_1) to one (t_2),
 122 increasing to two on the day of death (t_3). The number of patients with a polypharmacy drug regimen
 123 (≥ 5 drugs in regular drug regimen) was highest at admission (t_1 : $n = 43$) and was reduced by more than
 124 half between t_1 and t_2 ($n = 20$), and between t_2 and t_3 ($n = 8$) (see *Table 3*).

125 The number of drugs prescribed off-label (defined by European Medicines Agency as ‘Use of a medicine
 126 for an unapproved indication or in an unapproved age group, dosage, or route of administration’ [25])
 127 is larger in PRN medications compared to regular medications. For both regular and PRN medications,
 128 the percentage of drugs administered for off-label uses increased towards death. Of a total of 436 drugs
 129 prescribed at time of death, 105 (24.1%) were used off-label; at admission only 30/794 drugs prescribed
 130 (3.8%) were used off-label (see *Table 3*).

131

132 *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%)

^anumber of all drugs prescribed at specific point in time (t_x), where one drug could contain multiple substances

^bnumber 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)

^cprescriptions with unknown off-label status were excluded

^dPRN: pro re nata medication (as-needed medication)

133

134 Over the whole study period, the five active ingredients most frequently prescribed for regular use were

135 morphine (n=60), fentanyl (n=48), sodium picosulfate (n=34), pantoprazole (n=26), and dexamethasone

136 (n=23) (n=number of prescriptions). For PRN medications, morphine (n=152), lorazepam (n=96),

137 haloperidol (n=95), midazolam (n=85), and metoclopramide (n=31) were most frequently prescribed.

138

139 *ATC codes and routes of administration*

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

141 (see figure 3).

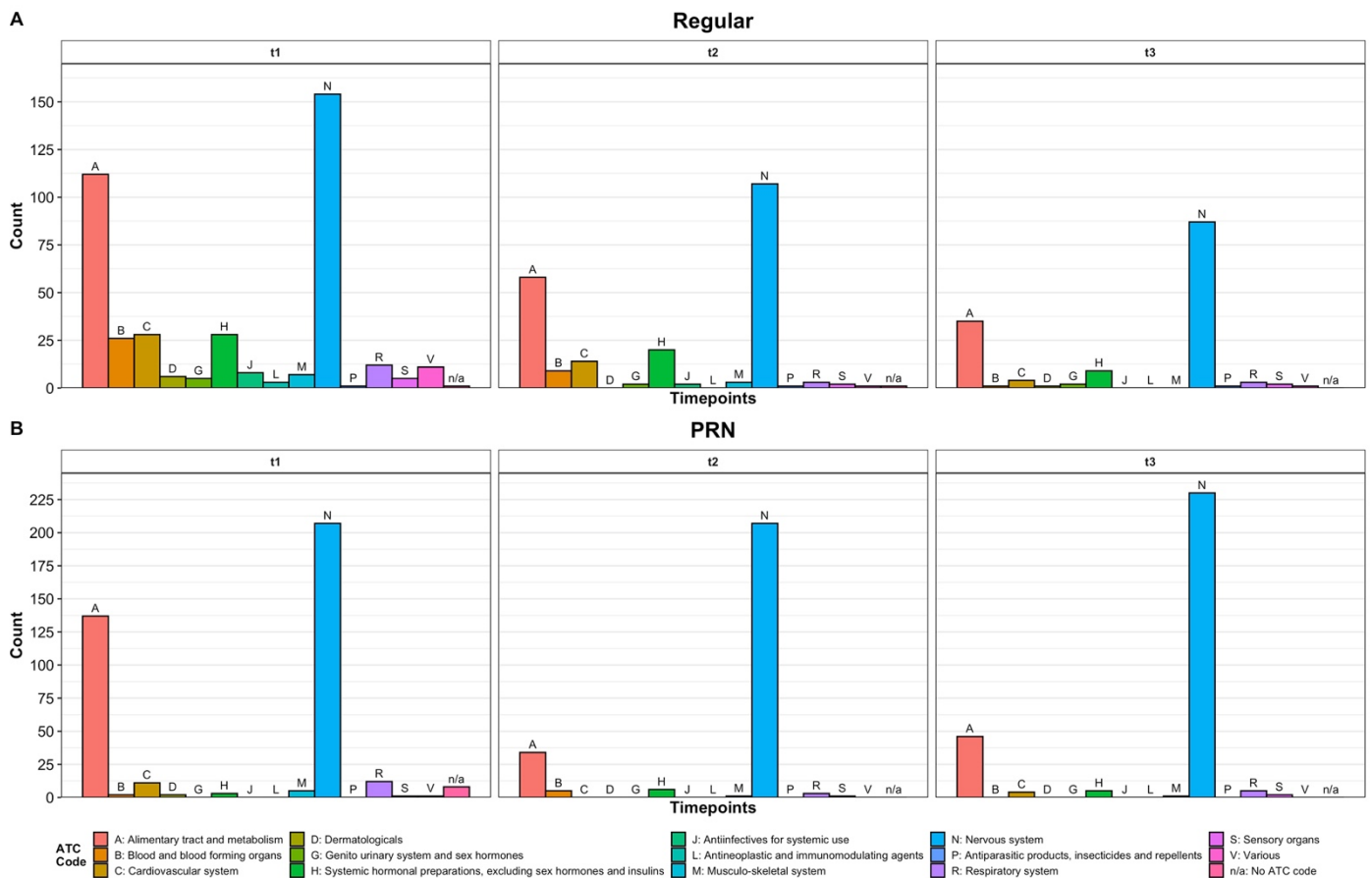


Figure 2: ATC codes

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

142

143 At admission, the majority of drugs prescribed for regular use belonged to the ATC code category

144 *Nervous system* (t₁: 154/406, 37.9%), followed by *Alimentary tract and metabolism* (t₁: 112/406, 27.6%),

145 *Cardiovascular system* (t₁: 28/406, 6.9%), and *Systemic hormonal preparations* (t₁: 28/406, 6.9%).

146 Nearing death, the proportion of prescriptions within the category *Nervous system* increased (t₂:

147 107/220, 48.6%, t₃: 87/143, 60.1%), while prescriptions for the categories *Alimentary tract and*

148 *metabolism* (t₂: 58/220, 26.4%, t₃: 35/143, 22.9%) and *Cardiovascular system* (t₂: 14/220, 6.4%, t₃:

149 4/143, 2.8%) decreased slightly. At admission, the majority of PRN medications prescribed were in the

150 category *Nervous system* (t_1 : 207/390, 53.1%). That proportion increased drastically after three days (t_2 :
 151 207/257, 80.5%) and thereafter only decreased slightly on the day of death (t_3 : 230/293, 78.5%). As for
 152 regular medication regimens, the second most common PRN category was *Alimentary tract and*
 153 *metabolism* (t_1 : 137/390, 35.1%). In this case, though, the proportion of prescriptions decreased on t_2
 154 (34/257, 13.2%), then increased slightly on the day of death (t_3 : 46/293, 15.7%).

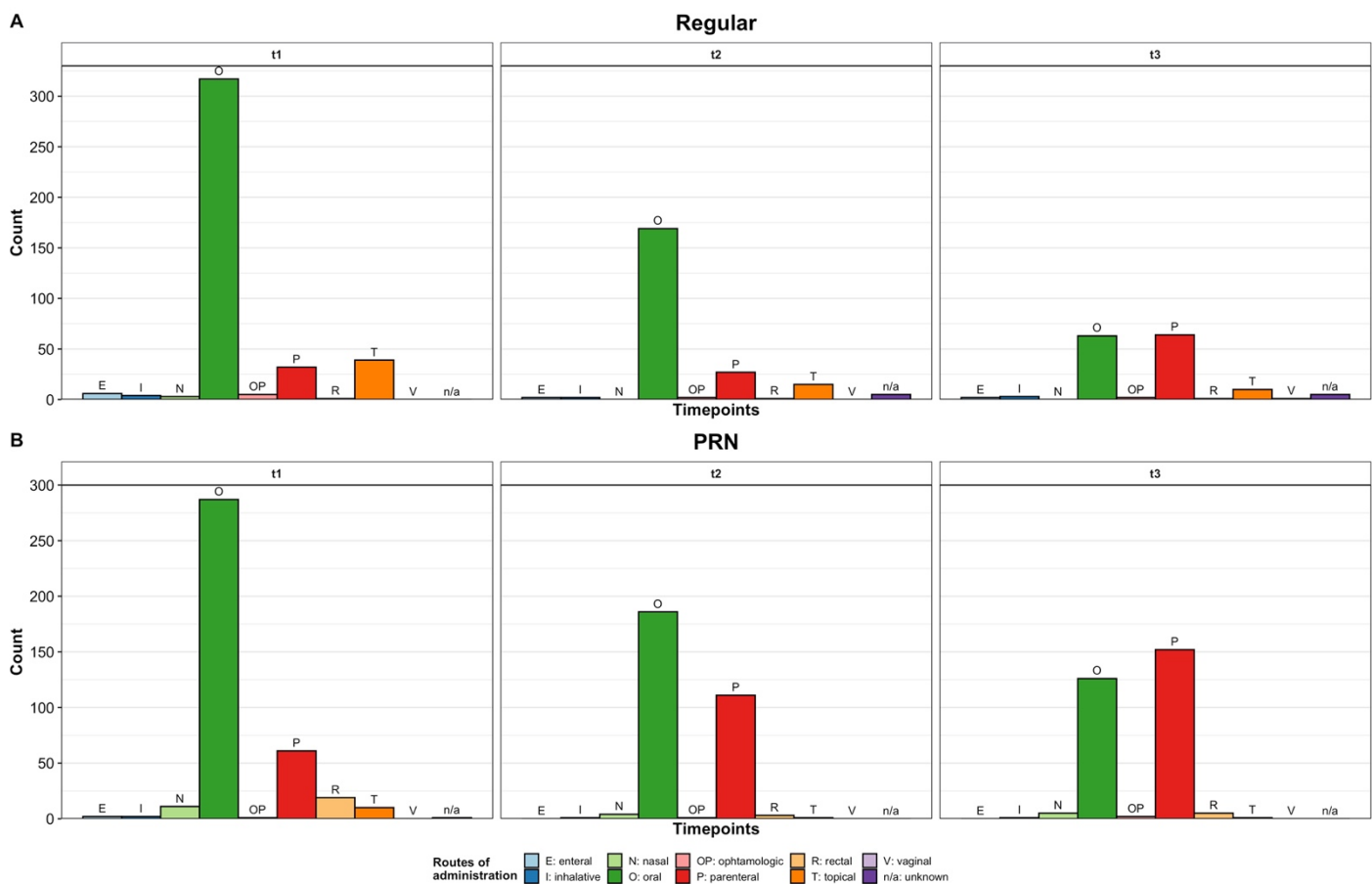


Figure 3: Routes of administration at each timepoint

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

155 At t_1 and t_2 , most prescribed drugs (both regular and PRN) were administered orally (i.e., buccal, oral,
 156 sublingual). On the day of death (t_3), the number of orally ($n=58$) and parenterally (i.e., intramuscularly,
 157 intrathecally, intravenously, subcutaneously; $n=64$) administered drugs was almost identical within the
 158 regular drug regimen, indicating an overall increase in the use of the parenteral route. For PRN drugs,
 159 the number administered parenterally increased steadily (t_1 : $n=61$, t_2 : $n=111$, t_3 : $n=152$), while the
 160 number of orally administered drugs decreased (t_1 : $n=287$, t_2 : $n=186$, t_3 : $n=126$). Topically administered
 161 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

162 number administered topically first decreased sharply, then remained stable between t_2 and t_3 (t_1 :
163 $n=10$, t_2 : $n=1$, t_3 : $n=1$). Few regular medications were administered nasally (t_1 : $n=3$, t_2 : $n=0$, t_3 : $n=0$).
164 Among PRN prescriptions, nasal application first decreased (t_1 : $n=11$, t_2 : $n=4$), then increased again
165 nearing death (t_3 : $n=5$). Likewise, for both regular and PRN medications, the vaginal administration route
166 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 : $n=0$).

167 Discussion

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

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

182 Structured approaches to balance out factors of undertreatment and overtreatment are growing,
183 especially after studies in certain medical disciplines investigating adverse effects of polypharmacy on
184 survival failed to show this effect.[26, 27] However, in hospice care representing end-of-life care,
185 polypharmacy is still considered a valid indicator to assess quality of drug regimens. It is essential to find
186 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,

213 18, 21] Complex and frequently changing drug therapy regimens, as identified in the medication
214 analysis, require thorough and regular assessment (e.g., medication review) and interprofessional
215 exchange.[28, 35, 36]

216 A high rate of off-label prescriptions was identified. This finding reflects the increasing need for
217 alternative routes of drug administration to manage symptoms at end-of-life. The most common shift
218 pertaining to the routes of administration concerned orally administered drugs shifting towards
219 parenteral use (mainly for PRN medication but also for regular medication). This finding is in accordance
220 with the preference of alternative routes of administration in hospice care.[21, 37, 38] Subcutaneous
221 drug administration offers a minimal invasive alternative when oral intake of drugs is severely limited
222 [39, 40]. This complies with the comfort-oriented approach of hospice care. Among the most frequently
223 prescribed drugs for regular and PRN use, the findings are comparable to the findings of a 2015 study
224 by Masman et al. revealing morphine, midazolam, and haloperidol as the most frequently prescribed
225 drugs during end-of-life care in a palliative care center.[2]

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

229 **Strengths and limitations**

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

238 8, 20, 21] Both the complexity of patients' drug regimens observed at admission and the progression of
239 their medication therapies support the general assumption in palliative care that regular medications
240 decrease steadily towards death, while the need for PRN medications increases.

241 **Conclusion**

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

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

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260 **Authors' Contributions**

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

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268 Author Disclosure Statement

269 One of the authors is employed at the institution where the medication analysis was performed.
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368 **Supplementary Material**

369 SA1: Detailed table of patients' baseline data

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