Journal of Integrative Nursing and Palliative Care (JINPC)

Original Article

Volume 5 | Issue 2 | Page 272-280

Retrospective Analysis of Continuous Subcutaneous Infusions Containing Morphine or Oxycodone in Specialized Palliative Care

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Abstract

Subcutaneous infusions that deliver several medications together are a standard practice in palliative care, especially when dealing with intense pain. That said, giving drugs by injection or infusion has repeatedly been linked to mistakes. Past research has shown that creating standardized recipes for these injectable mixtures can markedly improve medication safety. To explore how far parenteral drug mixtures used in palliative and hospice care could be standardized, by pinpointing the compositions that appear most often when morphine or oxycodone is included. A retrospective analysis of medical charts for all recorded parenteral mixtures containing morphine or oxycodone. Records of drug administrations for 120 patients who had died while receiving care were collected from two hospital wards and the home-based palliative service in Helsinki, Finland. Descriptive statistics were applied to examine the data. Across the 120 patients, a total of 329 mixtures containing morphine or oxycodone were given as continuous subcutaneous infusions during the 10 months running from 28 April 2022 to 28 February 2023. In all, 29 different drug combinations were recorded. The two most frequent were haloperidol plus midazolam mixed with morphine, and the same two drugs mixed with oxycodone (accounting for 26.4% and 21.9% of administrations, respectively). From the 329 infusions, 175 distinct formulations were identified. In several of these mixtures, raising the opioid dose tended to coincide with increases in the amounts of the accompanying drugs. Even though people in palliative and hospice care usually need personalized prescriptions, it may still be realistic to introduce standard mixtures for those based on morphine, and especially for combinations that include midazolam and haloperidol together with either morphine or oxycodone.

Keywords: Palliative care, Hospice care, Pain management, Parenteral infusions, Subcutaneous infusions, Patient safety

Introduction

Due to the worldwide increase in elderly individuals and the growing burden of cancer, together with other persistent health conditions, the requirement for palliative and hospice services keeps expanding [1, 2]. During palliative treatment, taking drugs orally can become impossible—for example, when neurological disorders cause trouble swallowing or when dysphagia appears in a patient's last days [3, 4]. As a result, healthcare teams often turn to parenteral delivery methods [5–7]. Even so, these injection- or infusion-based approaches create distinct safety difficulties, including concerns over how well the drugs remain stable [8], how precisely concentrations are measured [9], and risks from microbes [10].

In palliative settings, continuous subcutaneous infusions that combine various medications are frequently used, even though the compatibility and long-term stability of many of these blends have not been adequately verified [11]. These preparations generally incorporate agents that relieve symptoms such as pain, nausea, confusion or restlessness, and breathing difficulties. Opioids, powerful enough to handle intense pain regularly, form a core part of the blend, with additional substances like midazolam and haloperidol added in [5–7]. Within Finland, morphine (in hydrochloride form) and oxycodone (in hydrochloride form) stand out as the opioids chosen most

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Received: 28 May 2024; **Accepted:** 19 October 2024; **Published:** 20 December 2024

How to Cite This Article: Hernandez M, Vega C. Retrospective Analysis of Continuous Subcutaneous Infusions Containing Morphine or Oxycodone in Specialized Palliative Care. J Integr Nurs Palliat Care. 2025;5(2):272-80. https://doi.org/10.51847/SvCDzQt2hJ

often [12], and authorities list both as high-alert medications [13]. Therefore, apart from any compatibility problems that might disrupt the infusion, these particular drugs also present a serious hazard of unwanted effects — for instance, deep sedation or suppressed breathing — should an accidental overdose occur [14, 15].

Rapidly and adaptively supplying tailored medications to individuals suffering severe symptoms remains vital. For this reason, staff frequently prepare the mixtures in the clinical area rather than relying on pharmacy services, although the Finnish Medicines Agency has established clear rules on the matter [16]. Preparing these injectable combinations on the ward nevertheless requires numerous detailed and complex procedures [9]. When preparation methods lack consistency, they can undermine sterile handling practices and increase the risk of infection [10]. In addition, the methods for ordering and managing continuous subcutaneous infusions vary across sites because solid, evidence-based instructions are lacking. In wards that seldom use this delivery method, concerns about making mistakes can lead to delayed starts or even skipping parenteral treatment altogether.

Organizations are increasingly focusing on proactive risk-reduction strategies to prevent patient harm from medication errors [17]. Robust, evidence-driven protections at the system level aim to reduce such errors [18]. Studies confirm that creating standardized recipes for parenteral mixtures and shifting preparation to a centralized location can greatly reduce errors, especially those related to dose calculations or concentration errors [9, 19, 20]. Before any decision to adopt standard recipes, however, it is essential to review the actual mixture compositions used in real-world palliative and hospice environments.

The goal of the present study was therefore to determine whether standardization of parenteral drug mixtures in palliative and hospice care is realistic, achieved by pinpointing which compositions involving morphine or oxycodone are administered most often.

Materials and Methods

Study design and setting

Finnish guidelines recommend structuring palliative care around a three-tier system that adds specialized levels A, B, and C to the basic level [21]. Basic-level and level-A services operate within every health and social care organization that supports people at the end of life, ranging from local clinics and residential care homes to general hospitals. Level-B services focus specifically on palliative care and include, among other things, dedicated wards in community hospitals and home-based hospice programs. The most advanced and demanding level-C care is provided in university hospital palliative units. The current research was carried out in two specialized in-patient palliative and hospice wards, each with 25 beds, as well as the home-hospital program, which cares for 350-400 hospice patients per year. All three locations deliver specialized level B palliative care within the City of Helsinki, Finland. At the moment, these services mix all the required drug combinations for their patients directly on the ward premises.

The retrospective information drawn from medical files for this project covered 120 patients who had died following treatment in the units described. Attention was limited strictly to parenteral mixtures that contained morphine or oxycodone, so these two active ingredients plus the choice of parenteral route formed the defined inclusion standards for pulling out data. One further condition concerned the timing of death: it had to occur on or before 28 February 2023, and the study continued until the required total of 120 cases had been assembled. Details, including patient age, sex, main diagnosis, presenting symptoms, or treatment duration, did not influence inclusion or exclusion.

Reporting in this article complies with the Reporting of Studies Conducted using Observational Routinely-collected Health Data (RECORD) statement to promote openness and clarity [22].

Data extraction

The data were obtained from the EPIC-based electronic health record system, Apotti. Due to restrictions imposed by the Act on the Secondary Use of Health and Social Data, which prevents researchers from directly accessing patient record systems, the extraction process was handled by an external analytics expert from Apotti Oy. The complete dataset included specific items extracted from medical administration records.

Data collection followed a reverse-chronological sequence, ordered by date of death, beginning on 28 February 2023 and progressing to earlier dates. The decision to include 120 deceased patients was informed by a projection that the patient population would turn over 1–2 times, an approach anticipated to help lower the likelihood of bias. Information regarding the makeup and utilization of parenteral drug mixtures that included morphine or oxycodone was gathered. Relevant patient demographic details and the associated medication orders for these administrations were also incorporated.

Data analysis

Input from a biostatistician was sought during the analysis phase. Descriptive statistical methods were applied to the data using Microsoft Excel and IBM SPSS Statistics. Patient characteristics were evaluated according to age and ICD-10 diagnosis categories [23]. The frequency of individual drug products (components) in the

administered mixtures, along with their various pairings, was examined to provide a general picture of the sample. Infusion lengths for the prepared mixtures were assessed by merging details from free-text instructions in the medication orders with data from structured fields listing the exact quantities of all components in each mixture.
The predominant formulations of parenteral morphine and oxycodone mixtures were determined by counting how many mixtures shared the same drug components in identical quantities. To explore opportunities for standardizing selected parenteral opioid mixtures, Spearman's correlation coefficient was used to measure associations between the amounts of different drug components within the mixtures (e.g., whether higher opioid doses tended to coincide with higher doses of accompanying drugs). These correlations were computed specifically for the 10 most common drug pairings. Statistically significant results ($P < 0.05$) were grouped by relationship strength [24, 25]. Furthermore, the drug combinations exhibiting the greatest diversity in formulations were pinpointed to gauge the extent of variation and the scope for potential standardization.
Because the data extraction yielded inadequate details for certain bolus mixtures, these bolus administrations were omitted from the analysis to minimize bias.

Results and Discussion

The average age of the patients (n = 120) was 79 years (range 54–103), with 90% (n = 108) aged 65 years or older. The total count of ICD-10-classified diagnoses recorded per patient ranged from 0 to 28. 58% (n = 70) of the patients carried the ICD-10 code Z51.5 (palliative care), the most common diagnosis in the group. Neoplasms, disorders affecting the circulatory, genitourinary, nervous, or digestive systems, and infections occurred in 21%–63% (n = 25–76) of patients.
During the timeframe from 28 April 2022 to 28 February 2023, the study group was given parenteral drug mixtures incorporating morphine or oxycodone. The bulk of these administrations occurred in January and February 2023, coinciding with the point at which the target sample size of 120 deceased patients was reached; only 4 patients had met the inclusion criteria before January 2023. Overall, the dataset encompassed 329 administered drug mixtures in which morphine or oxycodone served as the opioid ingredient. Individual patients could have been given multiple mixtures over the course of their care. Every mixture was delivered via continuous subcutaneous infusion. The large majority of the mixtures (94.5%) were prepared for a continuous infusion lasting 4 days. Less common durations were 1 day (2.1%) and 5 days (0.3%). In contrast, in 3% of cases, the duration remained unclear owing to mismatches between the free-text instructions and the structured component quantity fields in the medication orders.
Morphine was used more frequently than oxycodone, and it was employed at elevated concentrations spanning a wider spectrum. In 6 patients, the opioid was changed from oxycodone to morphine or the reverse at some stage of treatment. Apart from morphine and oxycodone, a total of 10 other distinct drugs appeared as ingredients in the mixtures within the study group. Midazolam and haloperidol ranked as the most commonly added agents.
Across the entire cohort, 29 distinct drug combinations were delivered **(Figure 1)**. Beyond these multi-drug options, a single mixture consisted solely of oxycodone diluted in sodium chloride 0.9%. The pairings of morphine with haloperidol and midazolam, and of oxycodone with haloperidol and midazolam, were each employed markedly more often than any of the remaining combinations.

Figure 1. Drug combinations administered (N = 329) and their prevalence by combination (%) in the study cohort. Abbreviations "mo" and "oxy" refer to morphine and oxycodone, respectively.

Three-drug mixtures made up the largest share at 58.1%, followed by those with four drugs at 19.5% and two-drug options at 16.1%. The only diluent encountered in the entire cohort was 0.9% sodium chloride, which was present in 225 mixtures, accounting for 68.4%. Overall mixture volumes varied widely, ranging between 2.2 ml and 80 ml. More than half the mixtures — 55.9% — had a total volume of precisely 20 ml. Volumes above this threshold accounted for 135 mixtures (41%), while those below 20 ml were limited to 10 mixtures (3%). Diluent use was closely tied to the 20 ml volume: 178 out of 184 mixtures at exactly 20 ml (96.7%) included a diluent. In contrast, only 47 of the mixtures exceeding 20 ml (35.1%) contained any diluent, and none of the sub-20 ml mixtures used any diluent.

Across all 329 drug mixtures, 175 unique compositions emerged. These varied not just by which drugs were chosen but also by the exact doses and volumes applied, even when the same drugs were combined **(Figure 2)**.

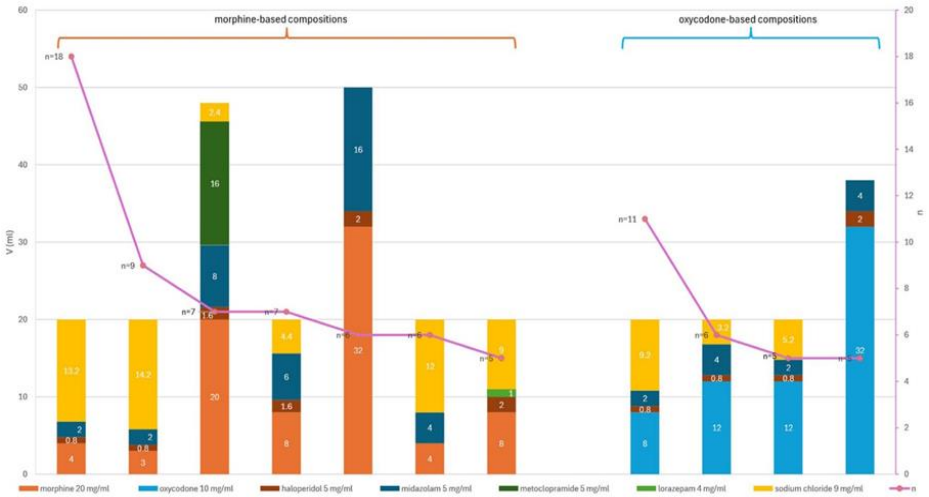

Figure 2. Prevalence of administered drug compositions occurring more than four times in the data (85/329). A bar chart shows the volumes of the components in each composition (left Y-axis). A line chart shows the prevalence of the compositions (right Y-axis).

The two dominant combinations — morphine with haloperidol and midazolam, and oxycodone with haloperidol and midazolam **(Figure 1)** — together explained the bulk (8 out of 11) of the compositions featured in **Figure 2**. Yet these same pairings also showed the greatest diversity in their formulation **(Table 1)**.

Table 1. Number of different compositions among the 10 drug combinations with the greatest variation in compositions.

Drug combination	No. of different compositions
Morphine + haloperidol + midazolam	37
Oxycodone + haloperidol + midazolam	33
Oxycodone + midazolam	14
Morphine + haloperidol + midazolam + glycopyrronium	12
Oxycodone + haloperidol + midazolam + metoclopramide	9
Morphine + haloperidol + midazolam + metoclopramide	8
Oxycodone + haloperidol + midazolam + glycopyrronium	7
Morphine + haloperidol + glycopyrronium + ondansetron + octreotide	6
Morphine + midazolam	6
Morphine + haloperidol + lorazepam	6

In half of the ten most-used drug combinations, statistically significant correlations were observed between the quantities of each component **(Table 2)**. One clear case involved the 87 mixtures with differing amounts of morphine, midazolam, and haloperidol: significant correlations were observed among morphine and midazolam levels, morphine and haloperidol levels, and midazolam and haloperidol levels. For 4 of the 10 combinations, correlations reached significance for only selected components, and in one combination, no meaningful correlations were detected whatsoever.

Table 2. The ten most frequently administered drug combinations are categorized by the statistical significance of the correlation between their component quantities.

Drug combination (n)	Drug components in pairs	Statistical significance (P)	Correlation coefficient
Significant correlation (P < 0.05) between all drug components			
Morphine and midazolam (13)	Morphine and midazolam	0.009	0.687
Morphine, midazolam, and haloperidol (87)	Morphine and midazolam	< 0.001	0.629
	Morphine and haloperidol	< 0.001	0.462
	Midazolam and haloperidol	< 0.001	0.708
Morphine, midazolam, haloperidol, and metoclopramide (18)	Morphine and midazolam	< 0.001	0.965
	Morphine and haloperidol	< 0.001	0.725
	Morphine and metoclopramide	< 0.001	0.779
	Midazolam and haloperidol	0.01	0.588
	Midazolam and metoclopramide	0.006	0.618
	Haloperidol and metoclopramide	< 0.001	0.805
Oxycodone and midazolam (29)	Oxycodone and midazolam	0.017	0.441
Oxycodone, midazolam, and haloperidol (72)	Oxycodone and midazolam	0.013	0.291
	Oxycodone and haloperidol	0.024	0.267
	Midazolam and haloperidol	< 0.001	0.603
Significant correlation between some drug components			
Morphine, haloperidol, and lorazepam (12)	Morphine and haloperidol	< 0.001	0.844
	Morphine and lorazepam	0.252	−0.359
	Haloperidol and lorazepam	0.909	−0.037
Morphine, midazolam, haloperidol, and glycopyrronium (13)	Morphine and midazolam	0.002	0.764
	Morphine and haloperidol	0.262	0.336
	Morphine and glycopyrronium	0.903	−0.038
	Midazolam and haloperidol	0.013	0.666
	Midazolam and glycopyrronium	0.933	0.026
	Haloperidol and glycopyrronium	0.627	−0.149
	Oxycodone and midazolam	0.076	0.556

Oxycodone, midazolam, haloperidol, and glycopyrronium (11)	Oxycodone and haloperidol	0.022	0.676
	Oxycodone and glycopyrronium	0.399	0.283
	Midazolam and haloperidol	< 0.001	0.933
	Midazolam and glycopyrronium	0.415	−0.274
	Haloperidol and glycopyrronium	0.932	−0.029
Oxycodone, midazolam, haloperidol, and metoclopramide (12)	Oxycodone and midazolam	0.009	0.712
	Oxycodone and haloperidol	0.334	0.306
	Oxycodone and metoclopramide	0.779	−0.091
	Midazolam and haloperidol	0.347	0.298
	Midazolam and metoclopramide	0.346	−0.299
	Haloperidol and metoclopramide	0.565	−0.185
No statistically significant correlation between drug components			
Morphine, haloperidol*, glycopyrronium, ondansetron, and octreotide (12)	Morphine and glycopyrronium	0.676	−0.135
	Morphine and ondansetron	0.341	0.302
	Morphine and octreotide	0.676	−0.135
	Glycopyrronium and ondansetron	0.145	−0.447
	Glycopyrronium and octreotide	0.533	−0.200
	Ondansetron and octreotide	0.145	0.447

Statistically significant correlations (P < 0.05) are highlighted in bold. The drug combinations appear (1) sorted by increasing number of components, (2) with all morphine-based mixtures listed before oxycodone-based ones, and (3) ordered by descending prevalence of each component in the dataset. Component pairs within them follow (1) opioid-containing pairs first and (2) descending order of component prevalence in the data.
*Correlation could not be calculated due to a constant variable.

Pairwise analysis of drug components revealed statistically significant correlations in 8 of the 20 possible pairs, with at least some of the most common combinations showing significant correlations **(Table 3)**. These correlations ranged in strength from weak to very strong.

Table 3. Drug component pairs from the 10 most commonly administered combinations.

Drug components in pairs (*n*)	Strength of the correlation			
	Moderately strong (cc 0.5–0.79)	Very strong (cc ⩾ 0.8)	Weak (cc < 0.3)	Fair (cc 0.3–0.49)
Morphine and midazolam (4)	3	1		
Morphine and haloperidol (3)	1	1	0	10
Morphine and metoclopramide (1)	1			
Oxycodone and midazolam (3)	1		1	1
Oxycodone and haloperidol (2)	1		1	
Midazolam and haloperidol (5)	4	1		
Midazolam and metoclopramide (1)	1			
Haloperidol and metoclopramide (1)		1		

cc: correlation coefficient value.
The count of drug combinations with pairwise quantity correlations is grouped by correlation strength. Only results reaching statistical significance (P < 0.05) are shown. Drug pairs are sequenced by (1) those including morphine first, (2) those including oxycodone second, and (3) in descending order of component prevalence.

Main findings

This investigation revealed a wide diversity of drug formulations delivered via continuous subcutaneous infusions, highlighting that patients in palliative and hospice settings frequently need tailored medication regimens. Nevertheless, pinpointing the most common combinations and examining links between component quantities offered valuable insights into which admixtures might be suitable candidates for standardization. The pairings of (a) morphine, haloperidol, and midazolam, and (b) oxycodone, haloperidol, and midazolam emerged as the predominant drug combinations. When statistically significant, the associations between drug component quantities proved especially robust in morphine-based mixtures. These results indicate that standardization could be achievable, particularly for selected morphine-based preparations that include midazolam and haloperidol. However, any potential standardization must weigh clinical appropriateness alongside the observed quantitative correlations.

What this study adds

The present results mark an initial move toward standardizing drug mixtures given as continuous subcutaneous infusions to palliative and hospice care patients. As far as we are aware, no earlier research has focused specifically on standardizing subcutaneous drug admixtures. In contrast, the advantages of standardizing intravenous mixtures have received extensive attention in the literature [20, 26, 27]. Standardizing continuous subcutaneous infusions could similarly enhance medication safety.

Midazolam and haloperidol ranked as the most commonly added agents alongside morphine and oxycodone in this cohort. Earlier publications have likewise documented the regular co-administration of midazolam and haloperidol with opioids in parenteral mixtures used in palliative care [5–7, 28]. Previous work has also drawn attention to other opioids and different salt forms, such as hydromorphone and morphine sulfate [5–7, 29]. Levomepromazine and hyoscine butylbromide have been reported frequently in mixtures elsewhere, a pattern that contrasts with the current findings [5–7]. When applying such results locally, variations in the availability of approved drug products across regions must be taken into account.

In the present study, morphine and oxycodone were employed with comparable frequency, implying that both opioids would need inclusion in any standardized mixtures to cover different clinical scenarios. The opioid was changed from one to another in six patients over the course of treatment. Although opioid rotation represents a routine practice in palliative care, supporting evidence for this strategy is still relatively scarce [30, 31]. Selection of a particular opioid may depend on factors such as renal or hepatic impairment, patient tolerability, or logistical issues like the required infusion volume. Additional influences can include the prescriber's personal experience, medication cost, and local availability. More studies are required to clarify why morphine-based combinations exhibited stronger quantity correlations than those based on oxycodone.

The correlation analysis indicated that certain morphine-based mixtures showed strong, statistically significant relationships among component quantities. Assessing these relationships is clinically important when exploring standardization options, especially because medication orders often allow increases in infusion rates that simultaneously raise doses of all ingredients. Spearman's correlation coefficient remains a statistical tool for estimating standardization potential and does not reflect whether the resulting doses would be clinically suitable. Given that opioids typically have a broader safe and effective dosing window than many other agents, component quantities may cease to correlate once opioid doses reach higher levels. In every case, the dose of each drug should be titrated individually based on symptom intensity and patient tolerance.

Although standardization of the mixtures observed in this study appears feasible, several areas warrant further investigation, including clinical needs, drug compatibility and stability, and the overall advantages of a standardized approach. First, the Delphi method might be useful for identifying clinically appropriate mixtures, as it has been successfully applied in prior research [7, 26]. Second, while compatibility and stability data exist for many commonly used combinations, the precise formulations chosen for standardization would still require targeted testing, as differences in concentration can influence outcomes [29, 32]. Finally, implementing standardized compounding and centralized preparation could bring particular value to basic-level palliative care settings by reducing the time clinicians spend on preparation tasks and enabling less specialized staff to initiate parenteral therapy more readily when indicated. At the same time, it remains essential to maintain rapid and adaptable drug delivery.

Strengths and limitations

This study drew on real-world data extracted from medical records of specialized palliative and hospice care inpatient wards and home hospital services, which rank among the largest palliative care providers in Finland. Unlike earlier investigations that mainly described commonly used drug combinations delivered via continuous subcutaneous infusions [5–7], the present work specifically examined the prospects for standardizing those combinations. For this reason, the analysis went beyond simply listing the components of the most frequent mixtures and also explored the actual quantities of those components, along with their correlations.

The current analysis concentrated primarily on the most prevalent drug component combinations. Several other critical factors for standardization still need to be assessed in future studies, including infusion lengths and pharmacotherapeutic suitability. Infusion duration directly influences the length of time the admixture must maintain microbiological, physical, and chemical stability. Moreover, the justification for combining components intended for extremely brief infusions warrants scrutiny. Ultimately, any mixtures proposed for standardization must undergo thorough review to confirm their pharmacotherapeutic value.

The retrospective design based on medical record review carries inherent constraints, including potential inaccuracies, missing information, and complex data [33, 34]. In this cohort, the ICD-10 code Z51.5 (palliative care) was documented in only 70 patients (58.3%), even though guidelines recommend documenting it from the start of palliative care to support proper management [21]. The lack of this code in the electronic medication record could stem from documentation omissions or the absence of a formal decision to initiate palliative treatment. Although this issue did not restrict the present study, since Z51.5 was not used as an inclusion criterion, future research should consider the possibility of outdated or incomplete diagnostic coding. Additionally, the dataset contained ten continuous subcutaneous infusion administrations with volumes under 20 ml. In routine

practice, a minimum volume of 20 ml is usually needed to properly fill the cassette reservoir employed in patient care units for continuous delivery. While the exact reasons for these smaller volumes could not be confirmed, the administrations were included in the analysis exactly as documented.

Although the sample size was deliberately chosen after weighing the risk of bias, the relatively modest number of patients limits the extent to which the results can be generalized. Furthermore, because bolus doses and any dose increases achieved by increasing the infusion rate were deliberately excluded from the analysis, the true daily medication use was probably greater, and the actual infusion durations were shorter than the figures reported here.

Data extraction proved to be a notable challenge for this research. Under the Finnish Act on the Secondary Use of Health and Social Data, investigators cannot directly access patient record systems. Hence, the dataset had to be prepared by an external analytics specialist. As a result, the research team was unable to confirm the extraction process. Even so, the data proved sufficiently reliable and consistent once the analysis began.

Conclusion

Although patients receiving palliative and hospice care frequently need personalized medication regimens, the present findings indicate that standardization could be realistic for mixtures that combine midazolam, haloperidol, or both, together with morphine or oxycodone. According to the statistical results, morphine-based mixtures appear to offer the greatest potential for standardization.

Acknowledgments: We are grateful to Professor Tiina Saarto, Chief Physician Taina Toivanen, and Chief Physician Jaana Saarenheimo for their time and for sharing their expertise in palliative care. We thank Kanerva Korhonen and Annika Häkkinen for their assistance in understanding the protocols in care units and within the electronic health record system, Apotti, and Sanni Kylkilahti for collecting background information from care units providing palliative care in Helsinki and in wellbeing services counties in the region. Finally, we would like to thank Marisa Eronen and Maiju Visti for their collegial support and contributions during the research project.

Conflict of interest: None

Financial support: The authors disclosed receipt of the following financial support for the research, authorship, and publication of this article: The data extraction performed by an external analytics specialist was funded by Helsinki Hospital. The open-access publication fee is funded by the University of Helsinki.

Ethics statement: This study was conducted in accordance with the World Medical Association Declaration of Helsinki and the Finnish Act on the Secondary Use of Health and Social Data, which comply with the EU's General Data Protection Regulation. The guidelines for the responsible conduct of research by the Finnish National Board on Research Integrity (TENK) were followed. Study approval was obtained from the Helsinki Social Services and Health Care Division.

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