Original Article

Sedatives and Sedation at the End of Life in the Hospital

A Multicenter Retrospective Cohort Study

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Summary

Background: Data on sedation at the end of life (eol) in different medical disciplines are scarce and mostly based on subjective reports. We aimed to assess the use of sedatives with continuous effect in the last week of life and associated factors in different hospital departments, with the aid of objectifiable criteria.

Methods: We conducted a retrospective cohort study based on the medical records of patients who died in one of five clinical departments of German hospitals between January 2015 and December 2017 (hematology/oncology [two different departments], neurology, geriatrics, and gynecology). The use of sedatives that are recommended in guidelines for palliative sedation was analyzed, irrespective of indication and treatment intent, with the aid of published definitions of continuous effect and of at least moderately sedating doses. The analysis consisted of descriptive statistics and multivariate logistic regression analysis.

Results: 260/517 (50%) of the patients who died were given sedatives with continuous effect in the last week of life, 53/517 (10%) in at least moderately sedating doses. For 76/260 (29%) patients, no indication was noted. The term "sedation" was used in the medical records of 20/260 (8%) patients. The use of sedatives with continuous effect was significantly associated with the department in which the patient was treated (hematology/oncology II: OR 0.32, 95% CI [0.16: 0.63]; geriatrics: OR 0.23, 95% CI [0.10:0.50]; reference, hematology/oncology I).

Conclusion: It was not possible to draw a clear distinction between the use of sedatives for symptom control, without sedating effect or intent to sedate, and intentional sedation to relieve suffering. The observed differences between hospital departments and deviations from recommended practice, e.g. lack of documentation of the indication, warrant further exploration. Moreover, context-specific supportive measures for the use of sedatives and sedation at the end of life should be developed.

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Sedation in palliative care, also called palliative sedation, has been defined as "monitored use of medications intended to induce a state of decreased or absent awareness (unconsciousness) in order to relieve the burden of otherwise intractable suffering (...)" (1, 2). Indications for this therapy of last resort include intolerable suffering from refractory dyspnea or agitation (1, 3). However, definitions and concepts vary, even between guidelines (3–9). This heterogeneity is likely to be one of the reasons for the wide range of reported prevalence of palliative sedation—between 12% and 67% (6, 9–11). Accordingly, ongoing controversial discussions include the question of when the use of sedatives is palliative sedation, as well as clinical and ethical debates regarding indications and appropriate processes—especially of continuous deep sedation until death, the most far-reaching practice (3, 4, 12–15). The latter includes the problem of potential shortening of life. Empirical data show that the distinction between this practice and euthanasia—while clear-cut in guidelines (1, 16)—becomes blurred in practice. (17)

Empirical studies on the topic focus mainly on specialist palliative care settings, i.e., palliative care units and specialist palliative home care (10, 11). Besides, most studies rely on medical professionals' labeling of the practice as "palliative sedation" or "continuous deep sedation until death". These terms are not employed uniformly, making it difficult to interpret and compare reported findings (3, 4, 9, 18–21). This paper uses the descriptive term

"sedation at the end of life" and the definition of sedation from a recently published terminology for "intentional sedation" as a means to ease suffering: "result or process of inducing a state of reduced consciousness (= below normal alertness) by medical means" (16, 22).

There are no data for Germany on the use of sedatives and sedation at the end of life in hospital departments; moreover, objective data on the topic are generally lacking. The aim of this study was to assess the use of sedatives with continuous effect within the last week of life in different hospital departments based on objectifiable criteria, irrespective of indication and intention, and to identify associated factors.

Methods

For this retrospective cohort study, we analyzed the medical records, of all patients who died in five German hospital departments during the period January 2015 to December 2017: hematology/oncology (two separate departments), neurology, geriatrics, and gynecology.

We used the following definition of sedatives and published objectifiable criteria to differentiate distinct types of their use *(eTable1)* (23, 24):

- Sedatives: drugs recommended in guidelines for palliative sedation (benzodiazepines, levomepromazine, haloperidol ≥ 5 mg/day [as lower doses are unlikely to be sedating]) and propofol (1, 12, 25–27)
- Sedatives with continuous effect: either continuous parenteral infusion for ≥ 0.5 hours or repeated application expected to result in sustained clinical effect (not necessarily sedation) for ≥ 24 hours (e.g., one dose per 24 hours for levomepromazine and haloperidol, two doses for lorazepam) (irrespective of indication, intention, and sedating effect)
- Sedatives in probably at least moderately sedating doses: e.g., 24 mg for parenteral midazolam and 4 mg for oral lorazepam *(eTable 1)* (e1), irrespective of indication and intention
- Sedatives with continuous effect in probably at least moderately sedating doses: interpreted as probable sedation according to the definition above (22), regardless of indication and intention

By using these objectifiable criteria, we assessed and differentiated the use of sedatives independent of its labeling in the medical records. We conducted descriptive statistics, bivariate analysis and multivariable logistic regression analysis in R (version 3.6.1). For a detailed description, see the *eMethods*.

Results

A total of 530 patients died in the five centers between January 2015 and December 2017. The medical records of 13 patients were missing for unknown reasons, leaving the data of 517 patients available for analysis. The median age was 77 years, and 51% of the patients were female. Fifty-two percent died from cancer, 30% from neurological/neurovascular disease *(Table 1)*. Half of all decedents were supported by the palliative care consultation team during the last week of life *(Table 1)*.

Use of sedatives with continuous effect

Two hundred sixty of 517 patients (50%) received a sedative with continuous effect at least once during the last week of life. The percentage of patients receiving this treatment increased towards the day of death *(eFigure)*. The median duration of this treatment was 2 days (interquartile range [IQR] 1–3, range 1–7), and 229/260 patients (88%) received it until death. The most frequently documented indications for the use of sedatives with continuous effect were agitation (55%), anxiety (41%), and pain (19%) (multiple indications possible). Insomnia was the indication in four patients. For 29% of patients, no indication was noted *(Table 2)*. Involvement of the patient or their legal representatives or family members in decision making was documented for 4/260 (2%) and 9/260 (4%) patients, respectively.

Midazolam was used most frequently (226/260; 87%), followed by lorazepam (50/260; 19%) *(eTable 2)*. The median total daily dose of midazolam with continuous effect within the last week of life was 10 mg (IQR 5–15, range 0.1–144). It increased towards death from 6.9 mg 6 days before death to 10 mg on the day of death *(Figure)*. Of the 260 patients receiving sedatives with continuous effect, 253 (97%) were also prescribed opioids in the last week of life. Their median total daily oral morphine equivalent was 41.88 mg/day (IQR 20–80, range 0.35–800). In the group of patients not receiving sedatives with continuous effect, 186/257 (72%) were prescribed opioids in the last week of life. Their median total daily oral morphine equivalent was 40.0 mg/day (IQR 17–76, range 0.33–738). Fifty-three of 517 patients (10%) received sedatives with continuous effect in maximum total daily doses judged as at least moderately sedating *(eTable 2)*. For this subgroup, involvement of the patient/their legal representative or family members in the decision-making process was documented for 3/53 (6%) and 3/53 (6%), respectively. Level of consciousness and monitoring were not systematically documented. Thirty-seven of the 53 patients (70%) receiving sedatives with continuous effect in at least moderately sedating doses received support from the palliative care consultation team.

The term "sedation" or an equivalent was used in the medical records of 23/517 decedents (4%). Of these, 20 patients had received sedatives with continuous effect, two had been on opioids, and one on sedatives that did not fulfill the criteria for continuous effect. Within the subgroup of 53 patients receiving sedatives with continuous effect in at least moderately sedating doses, the term sedation or an equivalent was recorded for nine patients (17%).

TABLE 1

Comparison of sociodemographic and clinical characteristics of patients with and without use of sedatives with continuous effect within the last seven days of life

	Total group	Use of sedatives with continuous effect		
	All (n = 517)	Yes (n = 260)	No (n = 257)	p-value
Age				**< 0.001**
Median (IQR; range)	77 (65–85, 22–105)	75 (63–83, 29–100)	79 (70–85, 22–105)	
Mean (σ)	74.3 (13.9)	72.7 (13.6)	76.0 (14.0)	
Gender, n (%)				**0.020**
Male	252 (49)	113 (44)	139 (54)	
Female	265 (51)	147 (57)	118 (46)	
Department, n (%)*[1]				**< 0.001**
Hematology/oncology I	190 (37)	105 (55)*[1]	85 (45)*[1]	
Hematology/oncology II	58 (11)	22 (38)*[1]	36 (62)*[1]	
Neurology	168 (33)	110 (66)*[1]	58 (35)*[1]	
Geriatrics	83 (16)	11 (13)*[1]	72 (87)*[1]	
Gynecology	18 (3)	12 (67)*[1]	6 (33)*[1]	
Length of stay (days)				**< 0.001**
Median (IQR; range) Mean (σ)	8 (4–16, 1–209) 13.6 (17.0)	9 (5–19, 1–110) 14.9 (16.0)	7 (3–14, 1–209) 12.2 (17.9)	
Cause of death, n (%)				
Malignant disease	270 (52)	142 (55)	128 (50)	0.336
Neurological + neurovascular disease*[2]	156 (30)	95 (37)	61 (24)	**0.002**
Cardiovascular disease	31 (6)	8 (3)	23 (9)	**0.008**
Respiratory disease	14 (3)	2 (1)	12 (5)	**0.014**
Other	45 (9)	13 (5)	32 (13)	*[3]
Missing	n = 1	n = 0	n = 1	
Support by palliative care consultation team, n (%)				**< 0.001**
Yes	248 (48)	181 (70)	67 (26)	
No	269 (52)	79 (30)	190 (74)	
Artificial hydration*[4] n (%)				0.765
Yes [parenteral/enteral]	436 [421/15] (84)	221 [214/7] (85)	215 [207/8] (84)	
No	81 (16)	39 (15)	42 (16)	
Artificial nutrition*[4], n (%)				**0.0130**
Yes [parenteral/enteral]	113 [59/54] (22)	69 [38/31] (27)	44 [21/23] (17)	
No	404 (78)	191 (74)	213 (83)	
"Palliative situation" or "palliative treatment" documented*[5], n (%)				**< 0.001**
Yes	266 (51)	165 (64)	101 (39)	
No	251 (49)	95 (37)	156 (61)	

The relative frequencies are column percentages, with one exception: for the variable department, row percentages are reported. The relative frequencies correspond to valid percentages, i.e., they are based on the number of patients for whom data for the respective variable were available.
Figures in bold denote statistically significant differences between patients with and without use of sedatives with continuous effect. Statistical tests for differences between these groups: chi-square test for categorical variables, Mann–Whitney U-test for continuous data. Owing to the exploratory nature of the study, we did not adjust for multiple testing despite the relatively high number of statistical tests. Therefore, the p-values have to be interpreted cautiously.
*[1] For department, row percentages are reported.
*[2] Including intracranial hemorrhage, stroke, and dementia
*[3] Test for difference judged as not clinically important
*[4] Within the last 7 days of life
*[5] includes palliative therapy/treatment/measures/situation, palliative status, symptom control, symptom-oriented/symptom-based therapy/treatment/measures, limitation of therapy, change of treatment goal (from curative to palliative)
IQR, interquartile range

TABLE 2

Documented indications for the use of sedatives with continuous effect *1

Indication (multiple indications possible; documented in any part of the medical records, including the daily nursing records)	n = 260 (%)
Agitation/restlessness	143 (55)
Anxiety	106 (41)
Pain	49 (19)
Dyspnea	28 (11)
Sleep disorders	4 (2)
Delirium/hallucinations	4 (2)
Other	22 (8)*2
No indication documented	76 (29)

*1 Due to the study´s methodology, no further differentiation was possible regarding the treatment team's intention when using the sedatives or the sedatives' actual sedating effect in the individual situations.

*2 Nausea/vomiting n = 6, epileptic seizures n = 3, patient's wish n = 2, malaise/no adequate symptom control n = 3, aggressiveness n = 1, groaning n = 2, cough n = 1, palliative situation n = 1, sedation n = 1, emergency situation n = 1, not adequately responsive n = 1.

Factors associated with use of sedatives with continuous effect

Bivariate analyses detected differences between the groups receiving and not receiving sedatives with continuous effect in respect of age, gender, department, length of stay, causes of death, support by a palliative care consultation team, artificial nutrition, and documentation of "palliative situation/treatment" or equivalent terms in the medical records *(Table 1)*.

Multivariable logistic regression analysis demonstrated the following significant associations with use of sedatives with continuous effect: With an increase in age by 1 year, the odds for this treatment decreased slightly (odds ratio [OR] 0.98, 95% confidence interval [0.96; 1.00]). The odds were higher when a palliative care consultation team was involved (OR 5.59, [3.65; 8.69)] and when "palliative situation/treatment" or equivalent terms were documented in the medical records (OR 2.25, [1.39; 3.70)]. Compared with hematology/oncology I, the odds were lower in hematology/oncology II (OR 0.32, [0.16; 0.63)] and in geriatrics (OR 0.23, [0.04; 0.19)]. The odds in neurology and gynecology did not differ significantly from hematology/oncology I *(Table 3)*.

Discussion

To our knowledge, this is the first study investigating use of sedatives and sedation at the end of life based on objectifiable criteria, rather than on professionals' self-reports, in different hospital departments.

International comparison

The comparison with data from other countries is difficult due to differences in methodology, including use of different terms and definitions for (palliative) sedation. Taking these limitations of comparability into account, the proportion of 10% of patients receiving sedatives with continuous effect in at least moderately sedating doses can cautiously be contrasted with figures of 17% and 33% for patients in Flemish and Swiss hospitals, respectively, receiving continuous deep sedation until death (labeling by treating physicians, population-based surveys), and with 3% of Canadian and 16% of South Korean inpatients receiving sedation (chart reviews) (19, 28–30). Non-methodological reasons for the different prevalences may include varying practice regarding transfers of patients with complex symptoms to palliative care units and different sociocultural backgrounds, including a more liberal stance regarding end-of-life decisions in Belgium and Switzerland (20).

Factors associated with use of sedatives with continuous effect

This study indicates differences in the prevalence of use of sedatives with continuous effect among specialties. The clearest differences are between geriatrics and hematology/oncology. The potential reasons include the relatively large proportion of cardiovascular and respiratory causes of death in geriatrics, which are known to be associated with continuous deep sedation less often than cancer (20).

Possible additional factors include the use of other drugs, such as antipsychotics not analyzed here; a higher prevalence of renal failure resulting in reduced consciousness; and uncertainties regarding use of sedatives in this frail population.

Furthermore, our study demonstrates differences in the odds of use of sedatives with continuous effect between the two hematology/oncology departments. The contributing factors may include structural or personal aspects such as the team members' palliative care training or their notions of a "good death" (19, 31).

The higher odds for sedatives with continuous effect when a palliative care consultation team was involved may be explained by the fact that palliative care consultation teams should by definition be involved in the care of patients with complex needs, who are more likely to require sedatives. Moreover, other results from the underlying mixed-methods study indicate that the treating professionals are uncertain about the indication and dosing of sedatives and sometimes rely on palliative care team support to start this treatment (32, 33). As for intentional sedation to relieve suffering, the relevant guidelines recommend the involvement of specialized palliative care teams, e.g., the palliative care consultation team (1, 16).

Deviations from best practice

Some deviations from guideline recommendations were identified in this study. First, involvement of the patients or their legal representatives in the decision-making process was mostly not documented, even for patients receiving at least moderately sedating doses.

Sometimes, this may mainly reflect a lack of proper documentation in the medical record; however, this deviates from the guidelines on sedation (e.g., those of the European Association for Palliative Care (EAPC)), which encourage such involvement, together with informed consent and adequate documentation (1, 3, 16).

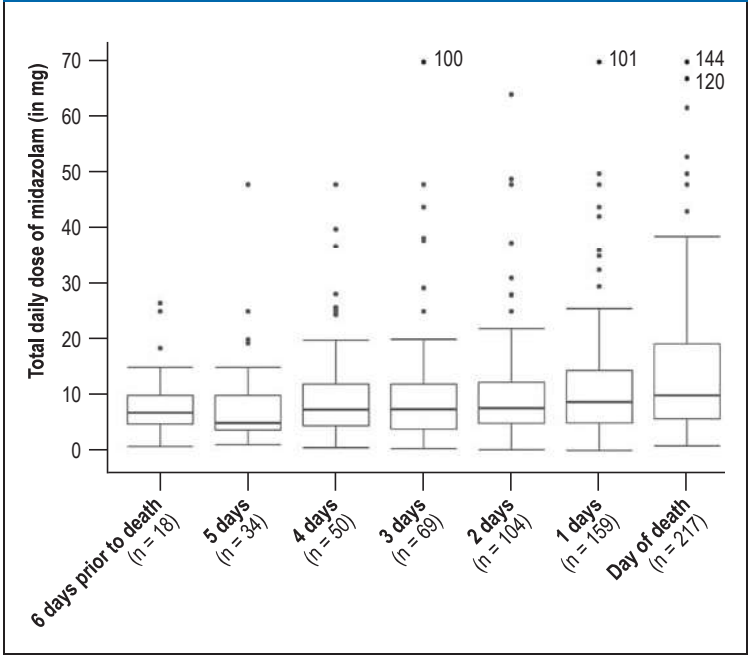
Second, documentation of the indication for sedatives was lacking in about a third of patients. This may also simply reflect failure to document these data or may imply lack of proper consideration of the indications altogether. Both deviate from best practice, and legally it would be difficult to prove proper consideration of the indications without corresponding documentation. The documented indications are also not always in accordance with guideline recommendations. Most importantly, pain without documentation of refractoriness does not justify the use of sedatives (1, 3). Third, in individual cases (n = 2), treatment with opioids alone was termed "(analgo-)sedation" in the records, although the guidelines emphasize that opioids should not be used for sedation (1, 12, 16). Finally, treatment that probably resulted in at least moderate sedation was labeled as "sedation" in only a minority of patients (17%). This may be explained by qualitative findings from the underlying mixed-methods study. According to the interviewed professionals, they almost never used sedation intentionally to relieve suffering, but rather perceived it as an accepted or even desirable side effect of sedatives. This seemed to be related to a negative connotation of the term "sedation," which was often equated with inducing unconsciousness, and sometimes associated with hastening death (34).

Strengths and limitations

The study's main strengths are first the use of published objectifiable criteria to assess treatment practice independent of its labeling in the medical records (23, 24) and second the assessment of the whole range of use of sedatives, not only continuous deep sedation until death. A third strength is evaluation of treatment practice across different hospital departments.

The study's retrospective design is a major limitation, as some data, e.g., symptoms, level of consciousness and medical professionals' intentions, were not recorded systematically and could not be assessed. Therefore, a clear distinction cannot be drawn between use of sedatives for symptom control without sedating effect/intention and intentional sedation to relieve suffering. The lack of corresponding statements in advance directive forms precluded assessment of whether the treatment accorded with the patients' wishes. However, a prospective design could have influenced the treating professionals' decisions and the documentation of their practice (24, 35, 36). Medications, e.g. opioids, that are still sometimes used for sedation but are not recommended in guidelines were not analyzed (19, 20). The restriction of data collection to a small number of centers in one region limits the generalizability. Nevertheless, the hypotheses generated may serve as a starting point for more representative future research.

FIGURE



Total daily dose of midazolam with continuous effect in the last week of life
Bottom of box: first quartile; top of box: third quartile; band inside box: median; 'whiskers' with maximum 1.5 × interquartile range; the dots represent outliers beyond 1.5 × interquartile range. Outliers > 70 mg are depicted at the top of the figure with their exact values in numbers

Implications and conclusions

This study demonstrates that the majority of dying inpatients received low doses of sedatives with continuous effect or none at all in their last week of life. Furthermore, the data indicate differences in the handling of sedatives among the different departments together with deviations of documented practice from guideline recommendations. In order to boost good clinical practice at the end of life in hospital, the following steps are advisable:

- Clarification of the essential question of what sedation is, to ensure that sedation is used intentionally as a means to relieve suffering, rather than in a masked way as a (desirable) side effect of symptom control (22, 34). Recognizing and labeling the use of sedatives in sedating doses as sedation is the prerequisite for compliance with guideline recommendations, e.g., regarding informed consent. When symptom control by sedatives results in reduced consciousness, reevaluation and, if the treatment is continued, labeling of the treatment as intentional sedation should ensue (16, 22).
- Emphasis on indications, informed consent, and corresponding documentation as ethical and legal requirements when using sedatives in (potentially) sedating dosage.

TABLE 3

Factors associated with use of sedatives with continuous effect, estimated from a multivariable logistic regression model

	OR	95% CI	p-value
Age	0.98	[0.96; 1.00]	0.028
Gender (ref.: female)	0.72	[0.47; 1.10]	0.130
Support by palliative care team (ref.: no)	5.59	[3.65; 8.69]	< 0.001
"Palliative situation" or "palliative treatment"* documented (ref.: no)	2.25	[1.39; 3.70]	0.001
Department (ref.: hematology/oncology I)			
– Hematology/oncology II	0.32	[0.16; 0.63]	0.001
– Neurology	1.44	[0.79; 2.61]	0.232
– Geriatrics	0.23	[0.10; 0.50]	< 0.001
– Gynecology	0.51	[0.16; 1.76]	0.266

* Includes palliative therapy/treatment/measures/situation, palliative status, palliation, symptom control, symptom-oriented/symptom-based therapy/treatment/measures, limitation of therapy, change of treatment goal (from curative to palliative).
Owing to the strong association between cause of death and institution, cause of death could not be incorporated into the model as independent variable.
CI, Confidence interval; ref., reference

- Education and training of professionals regarding the concept of (intentional) sedation and the relevant recommendations.
- Involvement of specialized palliative care teams (e.g., the hospital palliative care consultation team) in the event of uncertainties; case discussions and ward rounds (32).

Future mixed-methods research should both explore the reasons for differences in use of sedatives between departments and possible implications for further promotion of best practice and evaluate the development, implementation, and effectiveness of the proposed measures to support end-of-life care in the hospital setting.

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Conflict of interest statement
The authors declare that no conflict of interest exists.

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► **Supplementary material**

eReferences, eMethods, eTables, eFigures, eBox:
www.aerzteblatt-international.de/m2022.0194

Supplementary material to:

Sedatives and Sedation at the End of Life in the Hospital

A Multicenter Retrospective Cohort Study

by Eva Schildmann, Sophie Meesters, Bettina Grüne, Ann Sophie Licher, Anna Bolzani, Constanze Remi, Georg Nübling, C. Benedikt Westphalen, Michael Drey, Nadia Harbeck, Marcus Hentrich, and Claudia Bausewein

Dtsch Arztebl Int 2022; 119: 373–9. DOI: 10.3238/arztebl.m2022.0194

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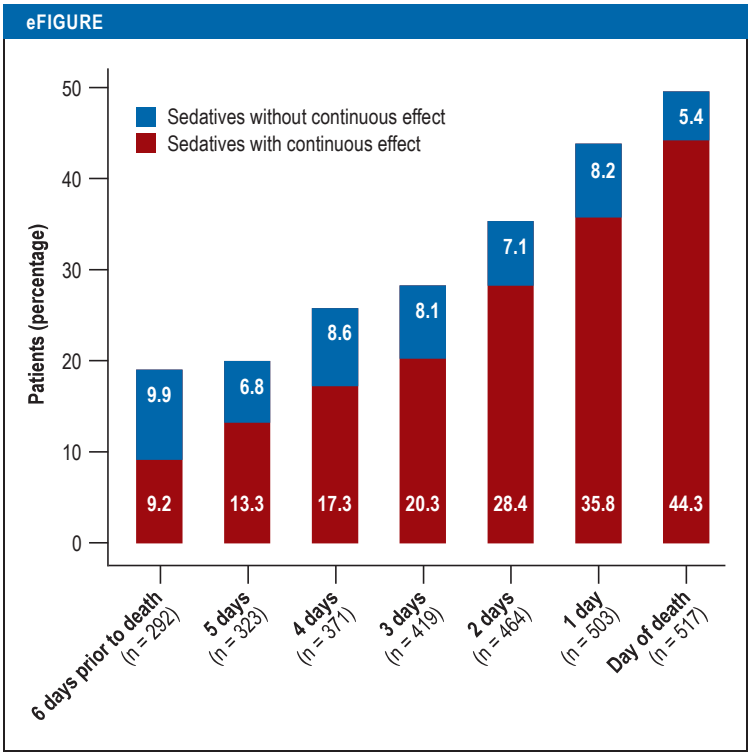
eFIGURE



Percentage of patients receiving sedatives, in relation to the total number of patients who were cared for in the five analyzed departments on the respective days. These numbers are given in parentheses beneath the respective days.

Sedatives with continuous effect: Use of sedatives either as continuous parenteral infusion for ≥ 0.5 hours or as repeated application expected—on the basis of the pharmacokinetic characteristics of the substance—to result in a sustained clinical effect (not necessarily sedation) of the drug for ≥ 24 hours (e.g., one dose per 24 hours for levomepromazine and haloperidol, two doses for lorazepam) *(eTable 1)*

Sedatives without continuous effect: Use of sedatives that do not fulfill the criteria for "with continuous effect"

eTABLE 1

Definition of sedative with continuous effect and dose judged as probably at least moderately sedating for the analyzed drugs, adapted from (e1)

Drug	Plasma half-life*1	Defined as sedative with continuous effect, when administered via continuous infusion ≥ 0.5 hours (h) or × times per day*2	Total daily dose judged as at least moderately sedating in these dying patients (oral dose equivalents, except for midazolam)*3
Clonazepam	30–40 h	1×	Not judged, as no information available regarding sedating effect for certain doses
Diazepam	1 h, active metabolites up to 100 h	1×	5 mg
Flunitrazepam	16–35 h	2×	2 mg
Lorazepam	12–19 h	2×	4 mg
Midazolam	Highly dependent on renal function, for patients > 60 years 1.5–10 h	7×	24 mg
Oxazepam	6–12 h	2×	30 mg
Lormetazepam	8–15 h	3×	3 mg
Haloperidol > 5 mg/day	13–36 h	1×	Not judged due to large variability in individual sedating effect
Levomepromazine	15–30 h	1×	30 mg
Propofol	2–4 min	-	Continuous administration judged as always used for at least moderate sedation

*1 According to the drugs' prescribing information and a widely used textbook for drug therapy in palliative care (e10, e14).

*2 Agreed between specialist palliative care clinicians and pharmacists, based on the available data regarding the half-life and duration of action of the drugs in weak and/or elderly patients, as stated in the drugs' prescribing information as well as a widely used textbook for drug therapy in palliative care (e10, e14).

*3 Agreed between specialist palliative care clinicians and pharmacists, based on the drugs' prescribing information and other available literature (e4, e6, e8, e10, e15). For the drugs which are licensed for anxiety and agitation, we chose the highest licensed dose for elderly/weak patients. For the drugs licensed for sleep disorders, we made a clinical-pharmaceutical judgment as to which total daily dose would probably result in at least moderate sedation, based on the doses licensed for sleep disorders. For midazolam and levomepromazine, the judgment was based on the doses licensed for sedation in anesthesia or acute agitation, respectively, as well as the lowest doses recommended or reported for sedation in palliative care (e6, e8). We aimed for conservative judgements in order to underestimate rather than overestimate the number of patients with moderately sedating doses. For comparison, in two previous studies cut-off doses of midazolam 10 mg and levomepromazine 25 mg per 24 hours were used to define a sedating dose (e4, e15).

eTABLE 2

Details of use of sedatives with continuous effect within the last week of life

Drug	Number of patients receiving this sedative with continuous effect	Total daily dose Median (IQR) [range] Oral dose equivalents (except for midazolam)	Number of patients receiving this sedative – with continuous effect and – at the maximum dose judged as at least moderately sedating*1
	Total n = 260*2	Total n = 260*2	Total n = 53*2
Clonazepam	1	[1.0–3.0 mg]	0
Diazepam	6	11.5 mg (5.0–13.3) [5.0–19.5]	6
Flunitrazepam	0	–	0
Lorazepam	50	2.0 mg (2.0–3.0) [1–10.0]	5
Midazolam	226	10.0 mg (5.0–15.0) [0.1–144.0]	44
Oxazepam	0	–	0
Lormetazepam	0	–	0
Haloperidol > 5 mg/day	17	7.4 mg (6.7–8.0) [5.0–19.1]	Not applicable
Levomepromazine	19	10.0 mg (6.0–26.6) [1.0–216.0]	4
Propofol	1	[20.0 mg]	1

[a] Combinations of different sedatives were not considered.
[b] Some patients (n = 49) received more than one sedative with continuous effect, in combination or consecutively. Therefore, the sum of the numbers in the rows below may exceed the total n given here
IQR, Interquartile range

eMETHODS

Design, setting, and participants

The study was part of a mixed-methods study on the use of sedatives and sedation at the end of life in German hospital departments and nursing homes (SedEol). We conducted a multicenter retrospective cohort study of all patients who died in five different hospital departments between 1 January 2015 and 31 December 2017: two hematology/oncology departments (at a university hospital and a teaching hospital, both in Bavaria) and one department each of neurology, geriatrics, and gynecology (all at a university hospital in Bavaria). Medical specialties were selected that regularly care for dying patients, aiming for at least two departments caring mainly for cancer patients and one caring mainly for patients with non-malignant conditions. Fourteen departments were invited to participate; five consented. Two departments declined participation because they had concerns regarding data protection or did not possess the necessary resources to give the study team access to their data in accordance with data protection regulations. (The new General Data Protection Regulation had just come into effect.) The remaining seven invited departments did not reply. The study was approved by the research ethics committee of Ludwig-Maximilians-University Munich (reference number 17–792; 12/2017).

Data collection

The methods of data collection have previously been reported for our cohort study in nursing homes (e1). Four specifically trained researchers retrieved data from electronic as well as paper medical records, using a piloted data extraction tool. The data extraction tool had been developed based on the literature, including the authors' own data from a palliative care unit, and had been used successfully in the previous nursing home study (e1–e4). To ensure rigor of data extraction, detailed instructions were developed and the researchers who extracted the data were thoroughly trained. In accordance with guidelines for data collection from medical records, two researchers jointly extracted data for a randomly selected 20% of all records (e5). This was important to guarantee a common standard of data extraction and minimize errors in data extraction, especially in face of the sometimes unclear and hardly legible documentation in various digital and paper formats.

As the sedatives for analysis in this study, we defined the drugs recommended in guidelines for palliative sedation: benzodiazepines, levomepromazine, haloperidol ≥ 5 mg/day (as lower doses are unlikely to be sedating), and propofol (e1, e2, e6–e11). For readability purposes they are called "sedatives" in this article although pharmacologically they belong to different drug categories. As in previous studies, we chose this criterion for selecting the analyzed drugs (e1, e2), firstly because it is a clearly comprehensible and objectifiable selection criterion and secondly because it can provide at least one point of comparison (tertium comparationis) regarding the mainly assessed drugs when cautiously comparing this study to studies on "palliative sedation." Most such studies assess the practice which is labeled palliative sedation or continuous (deep) sedation by the responsible professionals themselves, referring to terms used in the respective guidelines (e6, 19, 20, 28).

We collected details on the use of sedatives including doses per day, indication, routes of administration and labeling of the treatment in the medical records. Additionally extracted demographic and clinical data included age, gender, length of stay, cause of death, support by a hospital palliative care consultation team, artificial nutrition and hydration, prescription of opioids, and use of the words "palliative," "sedation," and "palliative sedation" in the medical records.

Analysis

We used the following previously published criteria to differentiate distinct types of use of sedatives, which have also in part been used by other authors in the meantime (e1, e11, e12):

- Sedatives with continuous effect: either continuous parenteral infusion for ≥ 0.5 hours or repeated administration that can be expected on the basis of the pharmacokinetic characteristics of the substance to result in a sustained clinical effect (not necessarily sedation) of the drug for ≥ 24 hours (e.g., one dose per 24 hours for levomepromazine and haloperidol, two doses for lorazepam; *eTable 1*) (irrespective of indication, intention and sedating effect).
- The total daily dose judged as probably at least moderately sedating in this dying population was 24 mg for parenterally administered midazolam and 4 mg for oral lorazepam, irrespective of indication and intention *(eTable 1)*.
- Sedatives with continuous effect in probably at least moderately sedating doses are interpreted as probable sedation according to the definition of Kremling et al. (e13), regardless of indication and intention.

These definitions were based on the drugs' prescribing information and other available literature as well as on consensus by specialist palliative care pharmacists and physicians (e4, e6, e8, e10, e14, e15). By using these objectifiable criteria, we assessed and differentiated the use of sedatives independent of their labeling in the medical records. Judgements on continuous effect and at least moderately sedating doses were made conservatively in order to underestimate rather than overestimate continuous and at least moderately sedating effects. Furthermore, the administration of more than one sedative was not taken into account, which may also lead to underestimation of rates of sedatives with continuous effect and/or moderately sedating effects.

Total daily dose was defined as the actually administered total dose within 24 hours, taking into account the time when treatment was started, any dose changes, and doses given as needed. An exception was the day of death, for which the total daily dose was defined as the dose prescribed for the full day, not only the dose administered until the time of death. The reason for this decision was as follows: Taking the actually administered total dose for the day of death would result in underestimation of the (prescribed) total daily dose of the day of death. This underestimation would be most pronounced in those cases, in which the patient died in the early morning hours. Example: If a patient was prescribed midazolam 3 mg/h via continuous infusion on the day before death and on the day of death, the total daily dose on the day before death (without

additional as-needed doses) would be 3 mg/h × 24 h = 72 mg. If this patient died at 3 a.m. on the next day, for example, the actually administered total daily dose on the day of death would be 3 mg/h × 3 h = 9 mg, i.e., markedly lower than on the day before, although the prescribed dose was not reduced.

According to the selection criterion mentioned above, opioids were not analyzed as sedatives for this article. Nevertheless, as they may have additional sedating effects, we analyzed median opioid doses in our sample. We used standard equivalence factors to convert opioid doses to oral morphine equivalents (in mg) as follows: fentanyl transdermal (in mg/h) × 100 × 24 h, buprenorphine transdermal (in mg/h) × 75 × 24 h, hydromorphone oral (in mg) × 5, levomethadone oral (in mg) × 16, oxycodone oral (in mg) × 1.5, piritramide s.c. (in mg) × 0.7/0.3, tapentadol oral (in mg) × 0.4, tilidine oral (in mg) × 0.1, tramadol oral (in mg) × 0.1 (e14, e16).

Descriptive analyses, bivariate analyses, and multivariable logistic regression analyses were carried out using R version 3.6.1. Prevalence of use of sedatives, indications, doses and the labeling of the treatment in the medical records were analyzed. The relative frequencies are reported in valid percentages. For determining medians, interquartile ranges (IQR), and ranges of drug doses, values of 0 were excluded.

We analyzed differences between the group of patients that received sedatives with continuous effect and the group of patients that did not receive sedatives with continuous effect with regard to sociodemographic and clinical characteristics.

The clinical characteristics included variables that have been described in the literature as influencing the practice of sedation or that we hypothesized might have such an influence in our sample, based on clinical experience within our team. We used the chi-square test for categorical and the Mann–Whitney U-test for continuous data.

A multivariable logistic regression analysis was performed to identify factors associated with the use of sedatives with continuous effect. Variables that were of clinical interest and/or displayed significant group differences in bivariate analyses were entered into the model. As the causes of death were strongly associated with department specialization (malignant cause of death with the departments of hematology/oncology and gynecology, neurological causes of death with the department of neurology), we could not include both variables in the model. The department had to be included in order to control for clustered data. We used hematology/oncology I as the reference category, first because cancer patients are the best researched disease group regarding sedation and second because it had the largest number of decedents (e17, e18).

We decided against calculating a multilevel model, because the number of institutions did not fulfill recommendations of minimum sample sizes on the second level (department), and sample sizes on the first level (patients) differed extremely (e19, e20). However, we calculated multilevel models for sensitivity analyses. These showed results similar to those of the logistic regression model with fixed effects.

The alpha level was set at 0.05. Due to the study´s exploratory nature, we did not adjust for multiple testing.