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**Complexity in palliative care –  
The example of sedation in palliative care**

Kumulative Habilitationsschrift

vorgelegt von  
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## **Part 1: Summary**

### **1 Introduction**

In this “kumulativer Habilitation”, the concept of “complexity” will be explored regarding its specific meaning for palliative care. Based on this, the complexity of the practice of sedation in palliative care will be assessed by means of a systematic review of practice guidelines and empirical research.

#### **1.1 Complexity – a basic characteristic of palliative care**

Palliative care has been defined by the World Health Organisation (WHO) as “an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual” (World Health Organization).

The concept of complexity is used in palliative care to describe and grade a patient’s situation and the extent of the resulting needs and demands for care ([Guideline programme oncology (German Cancer Society; German Cancer Aid; AWMF)] 2019). The S3 guideline “Palliativmedizin für Patienten mit einer nicht heilbaren Krebserkrankung (Palliative care for patients with incurable malignant disease)” recommends to use the complexity of patients’ needs as a basis to decide whether patients require specialist or general palliative care ([Guideline programme oncology (German Cancer Society; German Cancer Aid; AWMF)] 2019). Specialist palliative care describes services whose main activity is the provision of palliative care, for example palliative care units. General palliative care is provided by primary care professionals and specialists who care for patients with life-threatening diseases, e.g. on general hospital wards (Radbruch et al. 2009). In order to effectively use

resources, specialist palliative care teams, who work in multidisciplinary teams with specially trained professionals and a higher staff-patient-ratio, aim to care for patients with complex care needs. Patients with less complex needs are mainly cared for by general palliative care professionals, who can involve specialist palliative care professionals if need arises (Radbruch et al. 2010, Radbruch et al. 2009). However, the concept of complexity is not clearly defined and operationalised with respect to its particular application in palliative care.

Glouberman and Zimmerman distinguish between simple problems (e.g. following a recipe), complicated problems (e.g. sending a rocket to the moon) and complex problems (e.g. raising a child) (Glouberman et al. 2002, Glouberman et al. 2004). Simple and complicated problems can be part of complex problems, but complex problems cannot be reduced to them. According to Glouberman and Zimmerman, important characteristics of complex problems are their non-linearity, interdependency and their dynamics – in consequence, they are associated with ambiguity and uncertainty. They require an understanding of unique, individual circumstances and an ability to adapt to change. Formulae have limited application in their solution, and experience and expertise do not guarantee success (Glouberman et al. 2002, Glouberman et al. 2004).

Dealing with complex problems necessitates problem-solving methods tailored to specific situations. The theory of complex adaptive systems (CAS) provides a framework for locating problems and solutions. It has been used in various disciplines. In relation to health care, Plsek and Greenhalgh define a CAS as “a collection of individual agents with freedom to act in ways that are not always totally predictable, and whose actions are interconnected so that one agent’s actions change the context for other agents” (Plsek et al. 2001). A CAS is characterised by this interaction and interconnection of agents, non-linearity, unpredictability and the agents’ as well as the system’s ability to adapt their behaviour over time (Plsek et al. 2001).

## 1.2 Sedation in palliative care

Sedation in palliative care, also called “palliative sedation therapy” or “palliative sedation”, has been defined by the European Association of Palliative Care 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 in a manner that is ethically acceptable to the patient, family and health-care providers” (Cherny et al. 2009). “Intractability” or “refractoriness” of symptoms causing this “intractable suffering” have been defined as “lack of other methods for palliation within an acceptable time frame and without unacceptable adverse effects” (Cherny et al. 2009). The term “sedation in palliative care” includes a range of different types of sedation that can be characterised by the depth of sedation – i.e. light or deep – and by the time frame – i.e. intermittent or continuous (until death) (Cherny et al. 2009).

Sedation in palliative care is a debated, but accepted practice, with increased frequency documented for some countries in recent years (Beller et al. 2015, Bosshard et al. 2016, Jaspers et al. 2012, Klosa et al. 2014, Maltoni et al. 2012, Muller-Busch et al. 2003, Rietjens et al. 2018, Rietjens et al. 2019, Robijn et al. 2016, Schildmann et al. 2015, Schur et al. 2016, van der Heide et al. 2017). In the Netherlands, for example, the prevalence of continuous deep sedation until death – the most far-reaching practice – increased from 8.2% of all deaths in 2005 to 12.3% in 2010 to 18.3 % in 2015 (Rietjens et al. 2019). Empirical research indicates variation in practice between different care providers, which is reflected in the wide range of reported prevalence of sedation in palliative care (Beller et al. 2015, Bosshard et al. 2016, Hopprich et al. 2016, Jaspers et al. 2012, Klosa et al. 2014, Maltoni et al. 2012, Muller-Busch et al. 2003, Schildmann et al. 2015, Schur et al. 2016, van der Heide et al. 2017). For example, the prevalence ranges from 12 to 67% in different studies from various countries, according to two systematic reviews, and from 0 to 54% in different Austrian palliative care centres (Beller et al. 2015, Maltoni et al. 2012, Schur et al. 2016). These data raise concerns regarding “best practice” of sedation in palliative care, including potential abuse or “injudicious withholding” of this treatment

option (Cherny et al. 2009). Therefore, international medical associations and national bodies have taken up the task of developing guidelines and policies with the aim of informing about the appropriate practice of sedation in palliative care (Cherny et al. 2009, de Graeff et al. 2007, Dean et al. 2012, Kirk et al. 2010, Legemaate et al. 2007, Morita et al. 2005, Weixler et al. 2017).

The most frequently reported refractory symptoms requiring sedation in palliative care are agitation or delirium, pain and dyspnea (Arantzamendi et al. 2020, Beller et al. 2015, Heijltjes et al. 2020). In some studies, anxiety or so-called existential suffering are also mentioned as indications, with a trend for increased use of sedation in palliative care for such suffering from non-physical symptoms in recent years (Arantzamendi et al. 2020, Heijltjes et al. 2020). Midazolam is the drug most frequently used, according to systematic reviews (Arantzamendi et al. 2020, Beller et al. 2015, Heijltjes et al. 2020). Other reported medications include phenobarbital, promethazine, and propofol (Arantzamendi et al. 2020, Beller et al. 2015, Heijltjes et al. 2020). While guidelines explicitly recommend not to prescribe opioids for the purpose of sedation, several studies demonstrate that opioids are still used as the only medication to achieve sedation, especially in general palliative care settings (Cherny et al. 2009, Heijltjes et al. 2020, Mercadante et al. 2017, Robijn et al. 2016).

Clinical and ethical debates regarding indications and appropriate process of sedation in palliative care continue – especially regarding continuous deep sedation until death, the most far-reaching practice (Alt-Epping et al. 2015, Gurschick et al. 2015, Rietjens et al. 2018, Schildmann et al. 2014, Schildmann et al. 2015, Twycross 2019). The latter includes the problem of potential shortening of life, and empirical data demonstrate that the distinction between this practice and euthanasia – while clear-cut in guidelines (Cherny et al. 2009, Forschungsverbund SedPall [SedPall Study Group] in cooperation with German Association for Palliative Medicine 2021) – may become blurred in practice (Anquetin et al. 2013, Rietjens et al. 2019).

Complexity and the above stated characteristics of a complex problem are reflected in various ways in the context of sedation in palliative care: First, clinical care situations with “otherwise intractable suffering”, in which sedation is considered as the treatment option of last resort, are a complex problem, characterised by non-linearity, dynamics and highly unique individual circumstances. Second, decisions about sedation are complex, given the requirements for such decisions and the consequences for the patient and the family.

## **2. Scientific publications on complexity and sedation in palliative care**

### **2.1 Research questions of the publications relevant to this “Habilitation”**

Based on the above reported data and considerations, questions are raised regarding the concept of complexity in palliative care in general and regarding sedation in palliative care as an example for complexity in palliative care. The scientific projects on which this cumulative “Habilitation” is based, focus on the following questions:

- 1) Which criteria contribute to complexity of palliative care situations, and what can help to conceptualize and define the “complexity” of a palliative care situation?
- 2) How is complexity reflected in guidelines’ recommendations on sedation in palliative care, using a systematic review and critical appraisal of recommendations for sedation in palliative care as an example?
- 3) How is complexity reflected in clinical practice of sedation in palliative care – both in the specialist palliative care setting and in nursing homes?



## **2.2 Complexity in palliative care – qualitative data**

### **2.2.1 Understanding complexity – the palliative care situation as a complex adaptive system (Hodiamont et al. 2019)**

The concept of complexity is, as mentioned in chapter 1.1, recommended to be used in palliative care to describe the nature of patients' situations and to grade the extent of resulting needs and demands for care ([Guideline programme oncology (German Cancer Society; German Cancer Aid; AWMF)] 2019). Complexity of palliative care needs has been demonstrated to reflect both resource use and costs by studies in Australia (Eagar et al. 2004, Eagar et al. 2004). Besides, Spanish researchers have developed first approaches to grade palliative care needs according to their complexity (Comino et al. 2018, Tuca et al. 2018). However, the concept is still not clearly defined and operationalised with respect to its particular application in palliative care, especially not for the German context. This study aimed 1) to describe criteria contributing to complexity of palliative care situations from the view of experts in palliative care and 2) to develop a conceptual framework to improve the understanding of the concept of complexity and related elements of a palliative care situation by locating the complex problem "palliative care situation" in a CAS.

Semi-structured qualitative interviews were conducted with professionals with expertise in clinical practice, financial matters or health policy regarding palliative care. Purposive sampling was used to ascertain the sample's variation regarding profession, care setting, rural or urban area, university affiliation and geographical region. Two distinct interview guides were developed for the two groups of experts, following the four-step procedure described by Helfferich: collecting, reviewing, sorting and subsuming of topics (Helfferich 2005). The interviews were audio-recorded and transcribed verbatim. Data were analysed by qualitative content analysis using the Framework approach (Gale et al. 2013, Ritchie et al. 2013). The thematic framework was developed inductively. The applicability of the system approach to the research question became apparent during the interviews and the first steps of Framework analysis. In a process of inductive theorizing, the categories of the framework were related to the patient, the social system, the team, and

structural aspects. Consequently, CAS theory was deductively applied to the framework in a process of reviewing, subsuming and connecting categories, considering CAS theory. The study was performed in accordance with COREQ criteria (Tong et al. 2007).

Overall, 42 interviews were conducted, 27 with clinical experts and 15 with experts with a financial or health policy background. Based on the experts' accounts, we identified three subsystems of the CAS of a palliative care situation: the "system patient", the "social system", and the "system team".

Agents in the "system patient" were allocated to further subsystems on patient level: physical, psycho-spiritual, and socio-cultural. The agents within the physical subsystem of the patient system could be further categorised into three groups: physical symptoms and clinical signs, primary diseases and disabilities, and therapeutic measures. The interviewees' accounts indicated strong relations between agents in the physical and the psycho-spiritual subsystem. For example, anxiety or depression were affected by physical symptoms such as breathlessness or pain, and vice versa.

The "social system" and the "system team" were composed of social agents, who affect the CAS of the palliative care situation as carriers of characteristics, roles and relationships. Our interview data indicated that the meaning of a patient's social system for the CAS of a palliative care situation is at least three-fold: First, the "social system" and its individual agents influence the "system patient", e.g. the psycho-spiritual subsystem. Second, as part of the unit of care, the agents of the "social system" receive care themselves – as palliative care addresses the needs of informal carers, family members and friends close to the patient as well. Third, they are involved in the patient's care, and therefore a supporting resource for the professional team. The interviewees described a well-functioning "social system" as a factor which reduces complexity and helps the professional team in their care. However, the existence of a "social system" can also add to complexity. For example, difficult relations between individual carers or between carer and patient and resulting challenging communication increase the need for care resources and can be a burden

for the individual agents – the patient, the different agents in the “social system” and the team.

The “system team” has direct influence on the “system patient” by initiating therapeutic interventions. Besides, it reacts to the situation of the patient and the relatives on the emotional and social level and therefore co-produces complexity of the care situation. Cooperation within the team is complex itself, as it consists of interactions between many different professionals, which are also shaped by the individuals involved and their respective relations towards each other. The behaviour of the “system team” and its individual team members, according to our interviewees, has a direct influence on the quality of care it provides. The described factors which affect the team’s performance and, consequently, the behaviour of the palliative care situation as a CAS, could be subsumed under the following three categories: 1. Structural characteristics of the team, such as the number of team members, their professions and qualifications; 2. Characteristics of the individual team members as social agents – which are influenced by their emotional, cognitive and physical reactions to the situations they are faced with, by their abilities, experiences and their qualifications; 3. Relations producing complexity. This may apply to relationships between different team members and patients and carers, but also to relationships between the team and other professionals outside the overall CAS. For example, our interviewees described that attitudes and experiences of external professionals can result in differing information being communicated to patients and families, leading to insecurities and burden.

Environmental factors from outside the palliative care situation, such as factors of space and time and structures of the health care system, also interact with the system and influence its behaviour. Agents within subsystems and subsystems themselves interact on all hierarchical system levels with each other as well as with the environment and shape the overall behaviour of a palliative care situation (see figure 1).

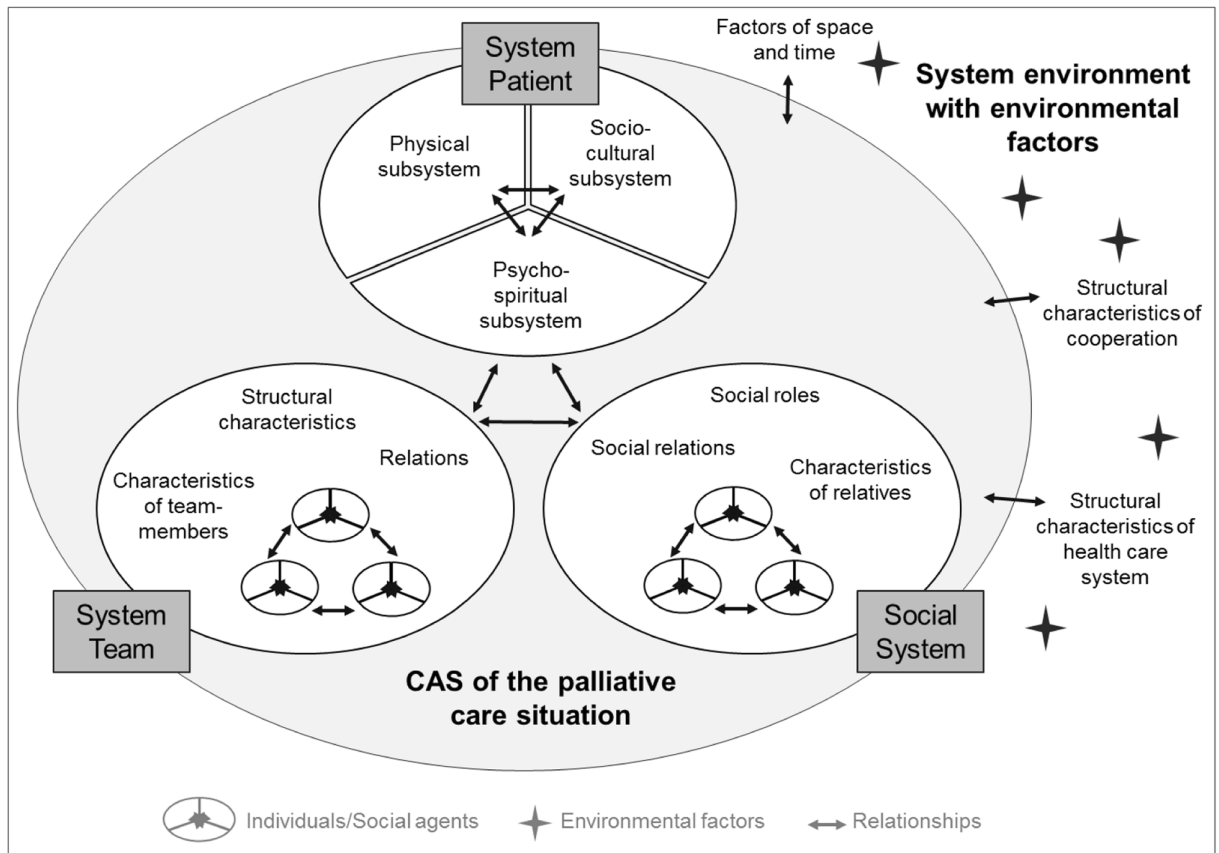


Figure 1: The palliative care situation as a complex adaptive system (Hodiamont et al. 2019)

This analysis provides a conceptual framework which supports a comprehensive understanding of complexity in palliative care. On the practical care level, the systemic view can help to understand individual palliative care situations and to shape their dynamics. On higher hierarchical level, it can support the development of care structures and concepts as well as the management of change processes when implementing new structures or concepts. Besides, the framework provides a foundation for the development of a model to differentiate palliative care situations by complexity of patients and their care needs.

### **2.3 Sedation in palliative care – complexity reflected in published guidelines´ recommendations**

In the following, sedation in palliative care – and decision making about it – is used as an example for complexity in palliative care, bearing numerous challenges. First, published guidelines´ recommendations regarding sedation in palliative care are assessed by means of a systematic review.

As mentioned, above, empirical research indicates that there are considerable variations in clinical practice of sedation, for example reflected in the wide range of reported frequency (Beller et al. 2015, Klosa et al. 2014, Maltoni et al. 2012, Schur et al. 2016). In light of the clinical as well as ethical challenges associated with sedation in palliative care, international medical associations, national bodies and local institutions have developed guidelines and policies (Cherny et al. 2009, de Graeff et al. 2007, Dean et al. 2012, Kirk et al. 2010, Schuman et al. 2005).

#### **2.3.1 Sedation in palliative care: a systematic literature review and critical appraisal of available guidance on indication and decision making (Schildmann et al. 2014)**

The content of published guidelines on sedation in palliative care has been subject to critique on medical as well as ethical grounds (de Graeff et al. 2007, Dean et al. 2012, Janssens et al. 2012, Juth et al. 2010). The medical critique is mainly based upon concerns around the scarcity of clinical evidence for sedation in palliative care, a deficiency acknowledged in a number of guidelines (Cherny et al. 2009, de Graeff et al. 2007, Dean et al. 2012). In the focus of the ethical critique are implicit value judgements and lack of transparency regarding the normative foundations for ethical positions taken as part of the guidance (Janssens et al. 2012, Juth et al. 2010). The aim of this study was to systematically review and critically appraise published guidelines on indication and decision making for sedation in palliative care, focussing on clinically and ethically relevant aspects.

We performed a systematic literature search in CINAHL, Cochrane Library, EMBASE, PsycINFO and PubMed, covering the period from January 1, 1980 to February 28, 2013. The search terms used were (“palliative sedation” OR “sedation”) AND (“guideline” OR “policy” OR “framework”), with minor modifications according to the controlled vocabulary of the databases searched. Additionally, we screened the reference lists of eligible papers found by this literature search for further published guidelines. Selection criteria were that papers included a palliative sedation therapy guideline and were written in English or German. We used the definition of the subject heading “Practice Guideline” in MEDLINE to define “guideline”. Two investigators independently reviewed all resulting citations according to title and abstract. Disagreements regarding eligibility were resolved by consensus after reading the full text. Two investigators independently extracted information on the guidelines’ recommendations on indication and decision making according to pre-defined categories. For reporting, we followed the PRISMA checklist (Moher et al. 2009).

Nine guidelines were eligible (Braun et al. 2003, Cherny et al. 2009, de Graeff et al. 2007, Dean et al. 2012, Kirk et al. 2010, Legemaate et al. 2007, Morita et al. 2005, Pace et al. 2004, Schuman et al. 2005). Two of these have been developed on an international level (Cherny et al. 2009, de Graeff et al. 2007). In addition, four national guidelines (Dean et al. 2012, Kirk et al. 2010, Legemaate et al. 2007, Morita et al. 2005) and three guidelines from regional or local institutions (Braun et al. 2003, Pace et al. 2004, Schuman et al. 2005) fulfilled the selection criteria. The nine included guidelines differed in their definitions of sedation in palliative care (see Table 1 in the original publication which can be found in part 2 of this “kumulative Habilitation”). In addition, key terms such as “refractory symptom” or “intolerable suffering” were used differently. These criteria were also weighed differently in their relevance for indication and decision making. Sedation in palliative care for psychological distress was regarded as exceptional by eight guidelines, but only two guidelines provided reasons for this exceptionalism in comparison with sedation for suffering due to physical symptoms. In the majority of guidelines, the role of different stakeholders involved in decision making was not specified. With regards to the limitation of life-sustaining measures, e.g., intravenous hydration, in the context of sedation in palliative care, the

analysed guidelines differed in their recommendations (for details, see Table 1 of the original publication which can be found in part 2 of this “kumulative Habilitation”).

From the findings of this systematic review it can be concluded that guidelines on sedation in palliative care differed considerably in their definitions as well as in aspects of indication and decision making about sedation in palliative care which are relevant from a clinical as well as ethical perspective. The comparison and critical appraisal of the different recommendations contributes to the ongoing debate about good clinical practice of sedation in palliative care and can serve as a starting point for the improvement of future policies.

### **2.3.2 Medication and monitoring in sedation in palliative care: a systematic review and quality assessment of published guidelines (Schildmann et al. 2015)**

In addition to the lack of consensus regarding indication and decision making on sedation in palliative care, the literature also indicates differences in the practice of medication and monitoring (Beller et al. 2015, Maltoni et al. 2012). Besides, the different guidelines on sedation in palliative care, which have been developed by different associations and institutions (see above), have not been systematically assessed regarding their quality so far. Therefore, the aim of this study was to assess published guidelines on sedation in palliative care regarding their quality and their recommendations on medication and monitoring.

Methods of the literature search and assessment of eligibility for this systematic review are described in chapter 2.3.1. Two investigators extracted information on drug selection and monitoring. Disagreements were resolved by discussion among all three authors. The same two investigators independently assessed the quality of the guidelines using the Appraisal of Guidelines for Research and Evaluation II instrument (AGREE Next Steps Consortium, Brouwers et al. 2010). Each item was assessed on a seven-point scale from 1 = strongly disagree to 7 = strongly agree. It was decided in advance that if an AGREE II item was not applicable to the particular guideline, it would be rated as 1, as suggested in the AGREE II instructions (AGREE Next Steps

Consortium). Domain scores for each of the six AGREE II domains were calculated using the scores from both assessors as recommended by AGREE II (AGREE Next Steps Consortium).

The same nine publications on guidelines were included as in the systematic review on indication and decision making (Braun et al. 2003, Cherny et al. 2009, de Graeff et al. 2007, Dean et al. 2012, Kirk et al. 2010, Legemaate et al. 2007, Morita et al. 2005, Pace et al. 2004, Schildmann et al. 2014, Schuman et al. 2005). Eight of the nine eligible guidelines received high quality scores for the domain “scope and purpose” (median 69%, range 28 – 83%), whereas in the other domains the guidelines’ quality differed considerably. The domain “applicability” received the lowest scores (median 15%, range 0 – 25%). Table 1 summarizes the overall and guideline-specific results of the quality assessment. The majority of guidelines suggested midazolam as drug of first choice. Recommendations on dosage and alternatives varied (see Table 2 of the original publication which can be found in part 2 of this “kumulative Habilitation”). The guidelines’ recommendations regarding monitoring of palliative sedation therapy showed wide variation in the number and details of outcome parameters and methods of assessment (see Table 3 of the original publication which can be found in part 2 of this “kumulative Habilitation”).



**Table 1: Assessment of included guidelines using the AGREE II instrument (Schildmann et al. 2015)**

Guideline	AGREE II-Domain					
	1) Scope and purpose	2) Stakeholder involvement	3) Rigour of development	4) Clarity of presentation	5) Applicability	6) Editorial independence
“Health region guideline” Braun et al. (2003)	58%	28%	23%	28%	15%	0%
“Massachusetts protocol” Hospice & Palliative Care Federation (2004)	28%	28%	1%	36%	8%	0%
“Hospital guideline” Schuman et al. (2005)	69%	28%	13%	42%	19%	33%
“Japanese guideline” Morita et al. (2005)	83%	92%	43%	67%	25%	38%
“Dutch guideline” Legemaate et al. (2007)	58%	28%	15%	39%	0%	0%
“International guideline” De Graeff et al. (2007)	72%	22%	49%	67%	0%	13%
“EAPC Framework” Cherny and Radbruch (2009)	67%	36%	42%	64%	19%	25%
“NHPCO statement” Kirk et al. (2010)	75%	44%	16%	39%	25%	63%
“Canadian Framework” Dean et al. (2012)	69%	28%	45%	56%	15%	63%
<b>Median</b>	<b>69%</b>	<b>28%</b>	<b>23%</b>	<b>42%</b>	<b>15%</b>	<b>25%</b>
<b>Range</b>	<b>28%-83%</b>	<b>22%-92%</b>	<b>1%-49%</b>	<b>28%-67%</b>	<b>0%-25%</b>	<b>0%-63%</b>

AGREE II = Appraisal of Guidelines for Research and Evaluation II

In conclusion, the published guidelines on sedation in palliative care identified in this systematic review were of varying, but overall limited quality, measured against established criteria for guideline development (AGREE Next Steps Consortium). Moreover, they varied considerably regarding their recommendations on drug dosing and methods of monitoring. This comparative analysis, including the findings regarding strengths and weaknesses of the individual guidelines, may serve as a starting point for the development of improved guidance on sedation in palliative care.

The fact that the published guidelines vary regarding their content reflects the complexity of sedation in palliative care – and at the same time contributes to the complexity of using this treatment option in practice. In the following, empirical studies on the use of sedatives and sedation in palliative care in two different settings are summarized.

## **2.4 Sedation in palliative care – complexity reflected in clinical practice**

### **2.4.1 “Palliative sedation?” – Use and labelling of continuously administered sedatives on a palliative care unit (Schildmann et al. 2018)**

Sedatives are frequently used in palliative care towards the end of life. However, there is scarce information when their use is labelled “palliative sedation”. As mentioned in chapter 1.2, empirical research studies report a wide range of frequencies of sedation in palliative care (Beller et al. 2015, Bosshard et al. 2016, Hopprich et al. 2016, Jaspers et al. 2012, Klosa et al. 2014, Maltoni et al. 2012, Muller-Busch et al. 2003, Schildmann et al. 2015, Schur et al. 2016, van der Heide et al. 2017). Even despite the existence of guidelines on sedation in palliative care, the variation in practice – as e.g. reflected in the wide range of reported frequencies – continues (Klosa et al. 2014, Schur et al. 2016). This variation is likely to be partly associated with differences in the care settings, patient populations and study methodology, but also with different definitions and concepts of “sedation in palliative care” or “palliative sedation” (Klosa et al. 2014, Maltoni et al. 2012, Morita 2004, Papavasiliou et al. 2013, Raus et al. 2016, Seymour et al. 2015). Most empirical data rely on self-reported “palliative

sedation” or “continuous (deep) sedation (until death)” by the health care team, and most focus solely on the latter (Beller et al. 2015, Bosshard et al. 2016, Hopprich et al. 2016, Jaspers et al. 2012, Klosa et al. 2014, Maltoni et al. 2012, Miccinesi et al. 2006, Rietjens et al. 2009, Rietjens et al. 2008, Robijn et al. 2016, Seymour et al. 2015, van der Heide et al. 2017). However, the term “palliative sedation” or “sedation in palliative care” includes a range of different types of sedation, and there is a lack of consensus regarding the definition of “palliative sedation” (Alt-Epping et al. 2015, Cherny et al. 2009, Morita et al. 2017, Morita et al. 2016, Papavasiliou et al. 2013, Raus et al. 2016). This is also reflected in the heterogeneity of the international guidelines’ definitions of “palliative sedation” (Abarshi et al. 2017, Gurschick et al. 2015, Schildmann et al. 2014). The aim of this study was to assess the use and labelling of “continuous administration of sedatives within the last 7 days of life”, based on objective criteria, on a palliative care unit. Objectives were to describe and compare clinical and sociodemographic characteristics of (1) patients with or without “continuous administration of sedatives within the last 7 days of life” and (2) patients with or without the label “(palliative) sedation” for this therapy.

We conducted a retrospective cohort study, using information from medical records. Patients who died on a palliative care unit from August 2014 to July 2015 were included. As “sedatives”, we recorded the drugs recommended for “palliative sedation” by guidelines: benzodiazepines, levomepromazine, haloperidol  $\geq 5$  mg/day (as lower doses are unlikely to be sedating; in recent guidelines only recommended for “palliative sedation” for delirium in combination with midazolam) and propofol (Cherny et al. 2009, de Graeff et al. 2007, Morita et al. 2005, Remi et al. 2018, Schildmann et al. 2015, Twycross et al. 2018). The definition of “continuous administration” of sedatives was based on the available literature and on consensus by pharmacists and physicians experienced in specialist palliative care: either continuous parenteral infusion for at least 0,5 hours or regular intermittent administration resulting in a continuous blood level of the sedative for at least 24 hours (for levomepromazine and haloperidol one dose, for lorazepam two doses per 24 hours) (Remi et al. 2018, Schur et al. 2016, Twycross et al. 2018). We used these objective criteria to describe and classify different types of use of sedatives,

regardless of the labelling of the therapy in the medical records. Explorative statistical analysis was performed, using SPSS 23. Medians and minimums of drug doses were determined for all patients who received the drug on the respective day(s), that is, excluding dose values of 0 mg. Group differences regarding nominal or ordinal data were tested using the chi-square test, regarding metric data using the Mann-Whitney-U test. Alpha level was set at 0.05.

Of the 192 deceased patients, 149 (78%) patients received continuous sedatives within the last week of life. Midazolam was used most frequently (145 patients; 97%), followed by haloperidol (18 patients; 12%) and levomepromazine (4 patients; 3%), mostly in combination with midazolam. The term “(palliative) sedation” was used in the records for 22 of 149 (15%) patients with continuous sedatives. This corresponds to 11% of the 192 patients who died in the study period. “Palliative sedation” was documented for two patients. All patients with documentation of “(palliative) sedation” in the records received continuous midazolam. Their median total daily dose of midazolam increased from 6 days before death (median, 10.0 mg; range, 7.5–80.0 mg) until the penultimate day (median, 20.5 mg; range, 1.0–210.0 mg), with a slight decrease on the day of death (median, 19.5 mg; range, 7.5–240.0 mg; Figure 2 (a)). The two patients whose therapy was labelled “palliative sedation” had maximum total daily doses of midazolam within the last 7 days of life of 58.0 and 135.0 mg. The maximum total daily dose of midazolam within the last 7 days of life was at least 60.0 mg for three additional patients whose therapy was labelled “sedation”. Maximum total daily midazolam doses of 60.0 mg or higher (maximum 80.0 mg) were also given to 5 of 123 patients with continuous midazolam without the label “sedation” (Figure 2(b)). Depth of sedation was not consistently documented. The patients for whom the term “(palliative) sedation” was noted in the records had significantly higher total daily midazolam doses 2 days before death (median (range) 15.0 (6.0 - 185.0) mg vs 11.5 (1.0 - 70.0) mg,  $p = 0.04$ ) and on the day of death (median (range) 19.5 (7.5–240.0) mg vs 12.5 (2.0–65.0) mg,  $p = 0.01$ ). The dose range was large in both groups.

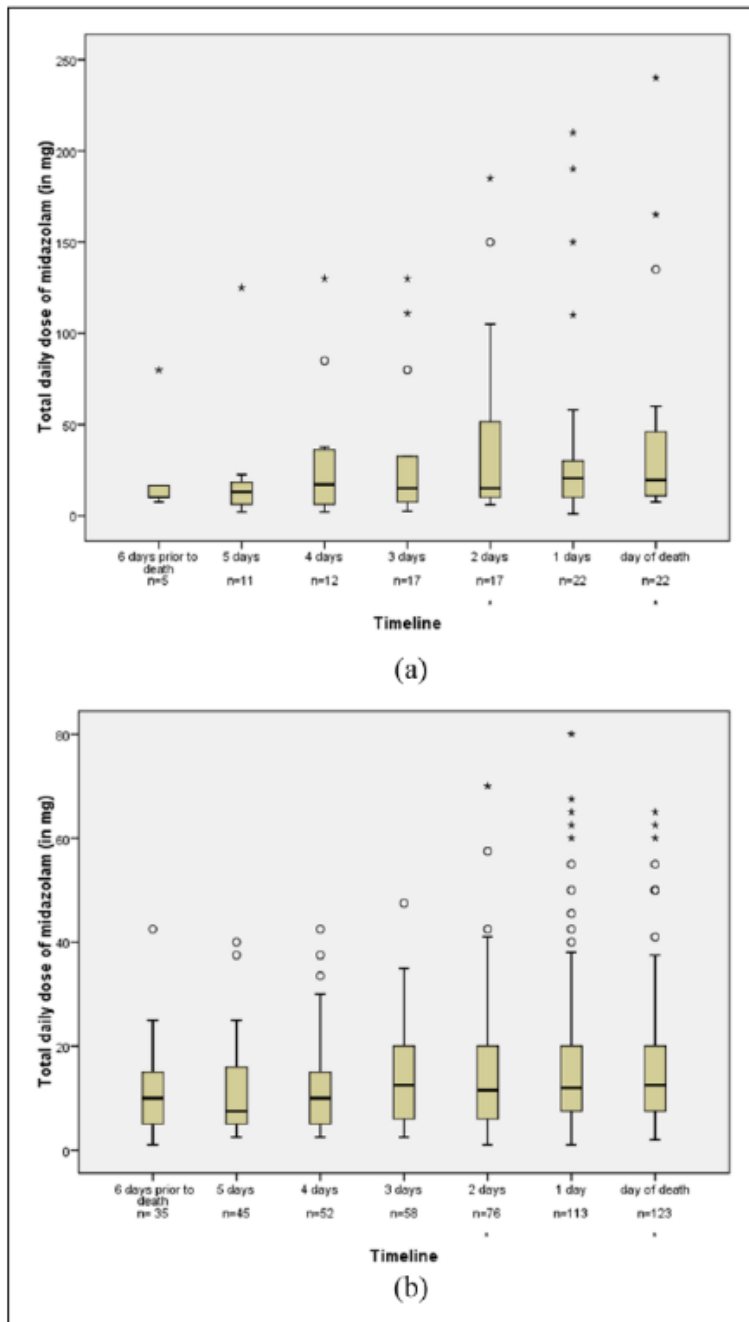


Figure 2: Total daily dose of midazolam over the last 7 days of life for the patients with continuous administration of midazolam (Schildmann et al. 2018):

(a) with documentation of the term "sedation" (n = 22) and

(b) without documentation of the term "sedation" (n = 123) (Mind: different scale on the y-axis compared to Figure 2(a)).

\*Under boxplots: significant differences between the groups of patients with and without documentation of the term "sedation": Total daily midazolam dose 2 days before death: median (range) 15.0 (6.0–185.0) mg versus 11.5 (1.0–70.0) mg,  $p = 0.04$ . Total daily midazolam dose on the day of death: median (range) 19.5 (7.5–240.0) mg versus 12.5 (2.0–65.0) mg,  $p = 0.01$ .

Boxplots:

Bottom of the box: first quartile; top of the box: third quartile; band inside the box: median; "whiskers" with maximum  $1.5 \times$  interquartile range. °Mild outliers: lying between  $1.5$  and  $3 \times$  interquartile range. \*Extreme outliers: lying beyond  $3 \times$  interquartile range.

This study describes the continuous use of sedatives in the last 7 days of life on a palliative care unit, based on objective criteria, and characterizes this practice, to the best of our knowledge for the first time, with reference to the label '(palliative) sedation'. The continuous administration of sedatives was labelled "sedation" or "palliative sedation" for only a minority of patients with continuous application of sedatives. While patients with documentation of the term "(palliative) sedation" received significantly higher doses of midazolam two days before and on the day of death than the patients without this label, there were large ranges of dose in both groups, and overall, no consistent pattern was detected regarding the use of the label "(palliative) sedation". Such lack of consistency is relevant for future research and clinical practice. Regarding research, current heterogeneous data on self-reported "palliative sedation" practice may be due to differing labelling of comparable practices. In clinical practice, not labelling the continuous use of sedatives in sedating doses at the end of life as "sedation" may result in failure of compliance with existing guidelines on "palliative sedation". Multicentre qualitative, quantitative and mixed-methods research as well as conceptual analysis are needed for a better understanding and characterization of sedation practices and their labelling in palliative care. Based on such analyses, consensus for defining different types of sedation and their differentiation from "symptom control with secondary sedation" should be sought. Such consensus is needed 1) for policy makers to further refine the existing guidelines on "palliative sedation", 2) for practitioners to know when to apply guidelines for "palliative sedation" and 3) for researchers to generate comparable results – crucial factors to further promote best practice of sedation in palliative care.

#### **2.4.2 Sedatives and sedation at the end of life in nursing homes: a retrospective multi-centre cohort study (Schildmann et al. 2021)**

Most research on sedatives and sedation at the end of life focuses on specialist palliative care. However, many people die in nursing homes, and this number is predicted to increase, based on the recent demographic developments (Dasch et al. 2015, Robijn et al. 2016, Simon et al. 2012). Until now, data on sedatives and sedation at the end of life in nursing homes are scarce, and the existing studies focus on “continuous deep sedation”, i.e. the most far-reaching type of sedation (Rietjens et al. 2019, Robijn et al. 2016, Rys et al. 2014, Rys et al. 2014, Van Deijck et al. 2010, Ziegler et al. 2018, Ziegler et al. 2019). It has been shown that this specific type of sedation was used in 6% to 9% of Belgian nursing home residents and in 14% of dying persons treated by Dutch older adult care physicians (Anquinet et al. 2013, Rietjens et al. 2019, Robijn et al. 2016). Because of different ethico-legal backgrounds regarding end-of-life practices as well as different healthcare systems, these data cannot be extrapolated to other countries (Anquinet et al. 2012, Rietjens et al. 2014, Seymour et al. 2015). Given the lack of research on the whole range of sedation practices, i.e. practices other than continuous deep sedation, in nursing homes internationally and a lack of any data for German nursing homes, this study has the following aims: (1) to assess the use of sedatives generally and of “sedatives with continuous effect” (based on objective operational criteria) within the last week of life in German nursing homes and (2) to assess factors associated with this treatment.

As part of a mixed-methods study, we conducted a multicentre retrospective cohort study of residents who died in four German nursing homes between January 2015 and December 2017, using the nursing homes` medical records. Nursing homes differing regarding number of residents, affiliation (municipal, Protestant, and Catholic), and location (urban and suburban) were selected by respective contact persons for municipal, Protestant, and Catholic nursing homes and asked for participation. Sedatives analysed were those recommended by guidelines for “palliative sedation”: benzodiazepines, levomepromazine, haloperidol  $\geq$  5 mg/day (as lower doses are unlikely to be sedating) and propofol (Cherny et al. 2009, de

Graeff et al. 2007, Morita et al. 2005, Schildmann et al. 2015, Twycross et al. 2018). For readability purposes, they are called “sedatives” in this article. The definition of “sedatives with continuous effect” of a previous single centre study was used: either continuous parenteral infusion for  $\geq 0.5$  hours or repeated application expected to result in sedation for  $\geq 24$  hours (see Table 2) (Schildmann et al. 2019). This definition was based on the literature, including the drugs’ prescribing information and the own previous study on the palliative care unit, and consensus by SPC pharmacists and clinicians (Schildmann et al. 2018, Twycross et al. 2018). In addition, doses judged as probably at least moderately sedating in this older adult population were consented by specialist palliative care pharmacists and clinicians, based on the drugs’ prescribing information and other available literature (see Table 2) (Cherny et al. 2009, de Graeff et al. 2007, Stephenson 2008, Sykes et al. 2003, Twycross et al. 2018). By using these objective operational criteria, we assessed and classified the use of sedatives independent of its labelling in the medical records.

We conducted descriptive statistics, bivariate analysis, and multivariate logistic regression analysis using R, version 3.6.1. Alpha level was set at 0.05.



**Table 2: Definition of “Sedative with continuous effect” and “dose judged as at least moderately sedating” for the analysed drugs (Schildmann et al. 2021)**

Drug	Defined as “sedative with continuous effect“, when administered X times per day <sup>*</sup>	Dose judged as at least moderately sedating in these dying patients (oral dose equivalents, except for midazolam) <sup>†</sup>
Clonazepam	1x	Not judged, as no information available regarding sedating effect for certain doses.
Diazepam	1x	5 mg
Flunitrazepam	2x	2 mg
Lorazepam	2x	4 mg
Midazolam	7x	24 mg
Oxazepam	2x	30 mg
Lormetazepam	3x	3 mg
Haloperidol > 5 mg/day	1x	Not judged due to large variability in individual sedating effect
Levomepromazine	1x	30 mg
Propofol	-	Continuous administration judged as always used for at least moderate sedation

\*Consented between specialist palliative care (SPC) clinicians and pharmacists, based on the available data regarding the half-life and duration of action of the drugs in weak and/or older adult patients, as stated in the drugs’ prescribing information as well as a widely used textbook for drug therapy in palliative care, available online (Twycross et al. 2018).

†Consented between SPC clinicians and pharmacists, based on the drugs’ prescribing information and other available literature (Cherny et al. 2009, de Graeff et al. 2007, Stephenson 2008, Sykes et al. 2003, Twycross et al. 2018). For the drugs that are licensed for anxiety and agitation, we chose the highest licensed dose for older adult and weak patients. For the drugs licensed for sleep disorders, we made a clinical-pharmaceutical judgement 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 licensed doses for sedation in anaesthesia or acute agitation, respectively, as well as the lowest doses recommended or recorded for “sedation in palliative care” (Cherny et al. 2009, de Graeff et al. 2007). We aimed for conservative judgements, in order to rather underestimate than overestimate the number of residents with moderately sedating doses. For comparison, in 2 previous studies, cut-off doses of midazolam 10 mg and levomepromazine 25 mg per 24 hours were used for defining a sedating dose (Stephenson 2008, Sykes et al. 2003).

110/512 (21%) deceased residents received a sedative at least once during the last week of life, mostly lorazepam (n=98). Most frequent indications for sedatives were agitation (58/110; 53%) and anxiety (35/110; 32%), no indication was noted for 36/110 (33%) residents. Involvement of the resident or family members in the decision for sedatives was documented in 3/110 (3%) and 5/110 (5%), respectively. The proportion of residents receiving sedatives at least once during

their last week of life differed significantly between the nursing homes, ranging from 14% to 36% ( $p < 0.001$ ). Multivariate logistic regression analysis showed significant associations between use of sedatives and age (OR = 0.94,  $p < 0.001$ ) as well as institution ( $p < 0.001$ ) (Table 3).

**Table 3: Factors associated with use of sedatives estimated from a multivariate logistic regression model (Schildmann et al. 2021)**

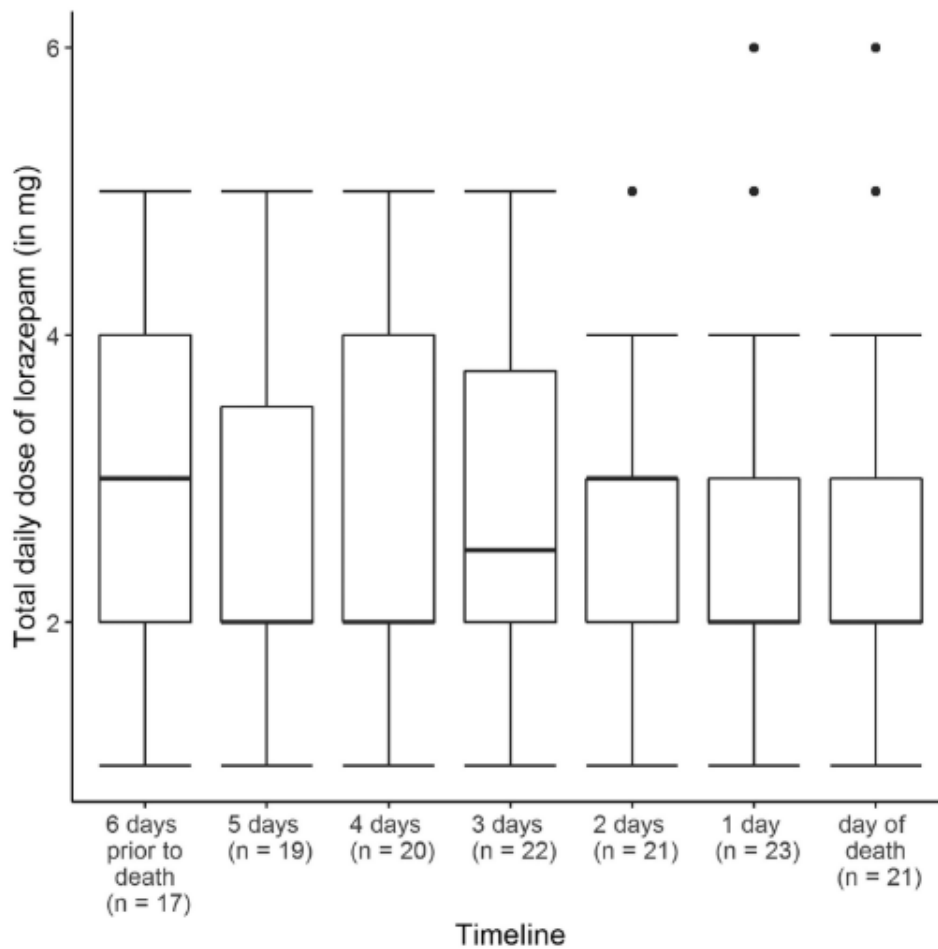
	OR	95% CI	p value
<b>Age</b>	0.94	0.92 – 0.97	<b>&lt;0.001</b>
<b>Gender (female)</b>	1.56	0.94 – 2.66	0.09
<b>Dementia (no)</b>	1.56	0.99 – 2.48	0.06
<b>Institution</b>			
Nursing home A <sup>(ref)</sup>			
Nursing home B	0.26	0.14 – 0.47	<b>&lt;0.001</b>
Nursing home C	0.28	0.15 – 0.54	<b>&lt;0.001</b>
Nursing home D	0.52	0.24 – 1.06	0.08

Ref, reference.

Although the frequency of “care by specialist palliative care team” differed significantly between use of sedatives and no use of sedatives in bivariate analysis, it was not entered into the model because of the small number of cases.

Figures in bold denote statistically significant associations.

46 of the 110 residents who were prescribed sedatives (42%, corresponding to 9% of the total sample) received these “with continuous effect” on at least one day within the last week of life, mostly lorazepam ( $n=41$ ). The median total daily dose of lorazepam “with continuous effect” within the last week of life was 2 mg (range 1 – 6 mg). It varied between 3 mg (range 1 – 5 mg) six days before death and 2 mg (range 1 – 6 mg) on the day of death (Figure 3). Nine residents (2% of all deceased residents) received sedatives “with continuous effect” in doses judged to be at least moderately sedating. None of these nine residents received support by a specialist palliative care team. The terms “sedation” or equivalents were never used in the medical records. Symptoms and level of consciousness were not systematically recorded.



**Fig. 3: Total daily dose of lorazepam “with continuous effect” within the last 7 days of life (Schildmann et al. 2021)**

Bottom of the box: first quartile; top of the box: third quartile; band inside the box: median; “whiskers” with maximum 1.5 x interquartile range; • outliers: lying beyond 1.5 x interquartile range.

This is the first multicentre study on different types of use of sedatives and sedation at the end of life in nursing homes, which uses objective criteria to assess the practice independent from its labelling by the care team. For Germany, to our knowledge, it is the first study at all providing data about the practice of sedation at the end of life in nursing homes. While median doses were low, probably with mostly anxiolytic or lightly sedating effects, 2% of residents received sedatives “with continuous effect” in doses judged as at least moderately sedating. Even for these

residents, the terms “sedation” or equivalents were never noted in the medical records. The complete lack of documentation of these terms, i.e. the practice of sedation at the end of life labelled as such, in the medical records of our sample stands in contrast to Belgian and Dutch surveys that demonstrated the use of “continuous deep sedation” (labelled as such by the professionals) in 6% to 14% of nursing home residents or persons treated by older adult care physicians (Anquinet et al. 2013, Chambaere et al. 2010, Rietjens et al. 2019, Robijn et al. 2016). In addition, our study demonstrates considerable differences regarding prevalence of use of sedatives between individual nursing homes. Reasons for these differences between countries and between nursing homes may include varying practice regarding transfers of residents with more complex symptoms to hospital, different perceptions regarding the need for sedatives and sedation at the end of life, and various levels of self-perceived competence or uncertainty regarding the use of these treatments by the responsible healthcare professionals (Seymour et al. 2015). The study also found deviations from best practice standards such as lack of documentation of the involvement of the residents and family members in the decision regarding sedatives, lack of documentation of the indication for sedatives, and the already mentioned fact that treatment that probably resulted in at least moderate sedation was not recorded as “sedation” in the records. If this is not only a problem of documentation, but of not perceiving the treatment as sedation, this may be an important reason for nonadherence to relevant guidance.

These results can – supplemented by findings from future research – inform adaptations of guidance to the nursing home setting and development of additional support measures for use of sedatives and sedation at the end of life in nursing homes.

### **3. Summary and conclusions**

The concept of complexity is often used in palliative care, but a clear definition of what complexity means in palliative care has been lacking so far. As an example for complexity, this “Habilitation” uses the practice of sedation in palliative care. Complexity is reflected in various ways in the context of sedation in palliative care: First, clinical care situations with “otherwise intractable suffering”, in which sedation is considered as the treatment option of last resort, are a complex problem. Second, decisions about sedation are complex, given the requirements for such decisions and the consequences for the patient and the family. The scientific work of this “kumulative Habilitation” explored the concept of complexity regarding its specific meaning for palliative care by a qualitative interview study. Based on this, the complexity of the practice of sedation in palliative care was assessed by means of a systematic review of practice guidelines and by retrospective cohort studies on a palliative care unit and in nursing homes.

The analysis of the qualitative interviews with palliative care experts provides a conceptual framework and comprehensive understanding of complexity in palliative care (Hodiamont et al. 2019). It can be used as a foundation for the development of a model to differentiate palliative care situations by complexity of patients’ needs. Such a classification of complexity can help to distinguish which patients need referral to specialist palliative care services, and which patients can be cared for by professionals within the general palliative care setting. Therefore, it can contribute to sensible and just allocation of scarce resources of specialist palliative care. Besides, it can – additionally to criteria used in clinical studies on early integration of palliative care – be used to identify the point in the patients’ disease trajectory, at which first contact to a specialist palliative care team is advisable, and the intensity of such specialist involvement. Other areas where such a classification of complexity can be of great benefit to clinical practice as well as policy are benchmarking – as measured outcomes can be adjusted for complexity of patient situations – quality management, and possibly the development of a new reimbursement system for palliative care, as demonstrated in Australia (Eagar et al. 2004, Eagar et al. 2004, Eagar et al. 2010, Gordon et al. 2009). A consortium project developing and testing a casemix-

classification for palliative care in Germany, based on the conceptual framework of complexity identified in the qualitative interview study and on the existing casemix-classification for palliative care in Australia, is currently ongoing, funded by the “Innovationsfond” (Eagar et al. 2004, Eagar et al. 2004, Gordon et al. 2009, Hodiament et al. 2019).

In clinical practice, the conceptual framework of complexity can also help to understand individual care situations. This pertains to the delivery of palliative care in general. In particular, it relates to situations of unbearable suffering from treatment-refractory symptoms, in which the treatment of last resort is considered, i.e. sedation in palliative care. As demonstrated in the systematic review, the complexity of sedation in palliative care is reflected in the heterogeneity of guidelines’ recommendations. The published guidelines differ considerably on aspects of definition, indication and decision making about sedation in palliative care as well as in their recommendations regarding drugs and monitoring (Schildmann et al. 2014, Schildmann et al. 2015). Besides, they were shown to be of varying, but overall limited quality (Schildmann et al. 2015). This heterogeneity and overall limited quality of guidelines, in turn, contribute to the uncertainty and complexity of using this treatment option in practice.

As demonstrated by the retrospective cohort study on a palliative care unit, comparable use of sedatives (e.g. regarding dose and indication) was only partly labelled as “sedation” in the medical records. Overall, we found no consistent pattern in our data regarding the use of the label “(palliative) sedation” (Schildmann et al. 2018). In the cohort study in nursing homes, not even the use of sedatives with continuous effect in doses judged as at least moderately sedating in this elderly, dying population was labelled as “sedation”. Besides, considerable differences regarding prevalence of use of sedatives with continuous effect between different nursing homes as well as deviations from best practice standards were detected. These results illustrate that – despite the existence of guidelines – uncertainty prevails as to when the use of sedatives constitutes “sedation”. This may be one important reason for the demonstrated non-compliance with relevant best practice standards.

Both the results from the empirical research and from the systematic review of guidelines can serve as a starting point for further improvement of the complex practice of sedation in palliative care. The systematic analysis of published guidelines identified existing consensus and discrepancies as well as underlying justifications for recommendations. Based on these data as well as additional empirical and ethico-legal analyses, we have developed recommendations on the use of sedative drugs for Germany in a consortium project funded by the German Ministry of Education and Research/Bundesministerium für Bildung und Forschung (Forschungsverbund SedPall [SedPall Study Group] in cooperation with German Association for Palliative Medicine 2021). The core of these recommendations is a systematically constructed terminology and definition for “intentional sedation” to relieve suffering in palliative care (Kremling et al. 2022).

The empirical research studies presented in this “Habilitation” have, to our knowledge for the first time, assessed the use of sedatives and sedation in palliative care independent from the labelling of the practice by the responsible professionals, proposing objectifiable criteria to define and differentiate different types of use of sedatives and sedation (“with continuous effect”, “at least moderately sedating dose”). Given the still prevailing variability of terms, definitions and concepts of sedation in palliative care and the fact that, until now, most research studies have been based on professionals’ accounts of the practice labelled as “palliative sedation” or “continuous sedation until death” by these professionals, this methodological approach may help to increase the interpretability and comparability of research on the topic (Kremling et al. 2020, Ziegler et al. 2019).

The presented empirical research results as well as recent data e.g. from Belgium and from our own Mixed-Methods study on use of sedatives and sedation in hospital departments and nursing homes in Germany expand the knowledge base regarding practice, challenges and potential strategies to meet challenges of sedation in different care settings (Grune et al. 2021, Meesters et al. 2021, Meesters et al. 2021, Robijn et al. 2021, Robijn et al. 2021). Future Mixed-Methods research should also explore reasons for differences in use of sedatives and sedation between institutions,

and possible implications for further promotion of best practice. The results of the existing and future empirical research can be used to adapt guidance to different clinical contexts and their specific challenges. However, as sedation in palliative care is a complex problem, it has to be kept in mind that even clear, consistent terminology and definitions as well as setting-specific recommendations on sedation in palliative care alone are not sufficient to ensure best practice. They have to be complemented by additional measures of support, for example training sessions – tailored to the respective needs of professionals in all care settings where sedation in palliative care takes place. In an ongoing consortium project, funded by the German Ministry of Education and Research/ Bundesministerium für Bildung und Forschung, we are currently developing a multimodal intervention to support best practice use of sedative drugs in different specialist palliative care settings, and will test its feasibility. The long-term aim is to help professionals to actually put existing recommendations on use of sedative drugs and sedation into practice – to continue to improve quality of care in these complex care situations.



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## **Part 2: Publications relevant to this “Kumulative Habilitation”**

### **Publications summarized in Part 1:**

- Hodiament, F., S. Junger, R. Leidl, B. O. Maier, **E. Schildmann\*** and C. Bausewein\* (2019). "Understanding complexity - the palliative care situation as a complex adaptive system." BMC Health Serv Res **19**(1): 157.
- **Schildmann, E.** and J. Schildmann (2014). "Palliative sedation therapy: a systematic literature review and critical appraisal of available guidance on indication and decision making." J Palliat Med **17**(5): 601-611.
- **Schildmann, E. K.**, J. Schildmann and I. Kiesewetter (2015). "Medication and monitoring in palliative sedation therapy: a systematic review and quality assessment of published guidelines." J Pain Symptom Manage **49**(4): 734-746.
- **Schildmann, E.**, S. Pornbacher, H. Kalies and C. Bausewein (2018). "'Palliative sedation'? A retrospective cohort study on the use and labelling of continuously administered sedatives on a palliative care unit." Palliat Med **32**(7): 1189-1197.
- **Schildmann, E.**, S. Meesters, B. Grüne, A. Bolzani, B. Habboub, A. Hermann, C. Remi and C. Bausewein (2021). "Sedatives and Sedation at the End of Life in Nursing Homes: A Retrospective Multicenter Cohort Study." J Am Med Dir Assoc **22**(1): 109-116 e101.

\*geteilte Letztautorenschaft

### **Additional own publications related to the topic of this “Habilitation”:**

- **Schildmann, E.**, A. Bolzani, S. Meesters, B. Grüne, A. Marheineke, C. Remi and C. Bausewein (2019). "Sedatives and sedation at the end of life: a nursing home retrospective cohort study." BMJ Support Palliat Care. Published Ahead of Print.
- Grüne, B., S. Meesters, C. Bausewein and **E. Schildmann** (2021). "Challenges and Strategies Regarding Sedation at the End of Life in Hospitals and Nursing Homes." J Pain Symptom Manage. Published Ahead of Print.

- Meesters, S., B. Grüne, C. Bausewein and **E. Schildmann** (2021). "Palliative Syringe Driver"? A Mixed-Methods Study in Different Hospital Departments on Continuous Infusions of Sedatives and/or Opioids in End-of-Life Care." Journal of Patient Safety Published Ahead of Print.
- Meesters, S., B. Grüne, C. Bausewein and **E. Schildmann** (2021). "We don't want to sedate him" - A qualitative interview study on intentions when administering sedative drugs at the end of life in nursing homes and hospitals." BMC Palliat Care **20**(1): 141.