PALLIATIVE CARE IN NEUROLOGY

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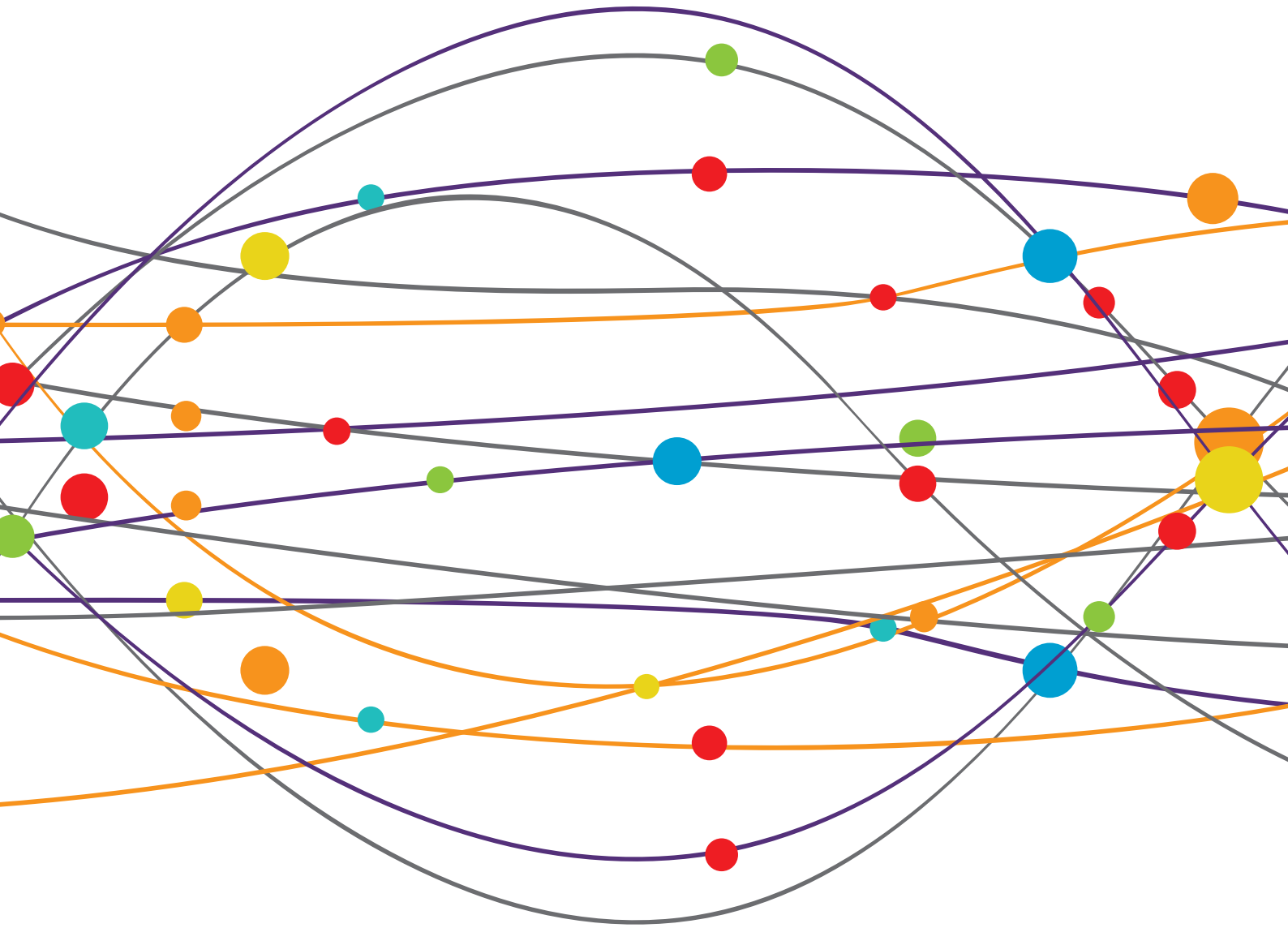

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PALLIATIVE CARE IN NEUROLOGY

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Over the last 50 years palliative care has usually been associated with cancer patients but more recently there has been increased discussion of the role of palliative care for neurological patients.

In the past years, neurology has moved from being a purely diagnostic area to a very therapeutically active one. A further step needs to be taken to modify the therapeutic activity from "cure" to "care" depending on the patient's disease trajectory. Palliative care has been associated with care at the end of life, whereas it may be appropriate earlier in the disease progression, and will extend after death in the support of bereaved families. The care of patients with neurological disease, and their families, will encompass the psychological, spiritual and existential issues and neurologists, and the teams in which they work, should develop skills to consider all aspects of care, in order to maximize the quality of life of all involved, and enable patients to die peacefully.

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EDITORIAL
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Editorial: Palliative Care in Neurology

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Editorial on the Research Topic

Palliative Care in Neurology

The role of palliative care for people with progressive neurological disease has been increasingly discussed over the last 20 years (1–3). Initially, the focus was on amyotrophic lateral sclerosis (ALS) which "represents a paradigm for palliative care in neurological diseases" (4). Indeed, progression in ALS is rapid, leading to severe disability, rendering the patients fully dependent on the support of carers, and death occurs ∼3 years after disease onset in half of the patients. More recently a palliative care approach also found its way to diseases such as high-grade glioma of which the course is also relentlessly progressive like in ALS, Parkinson's disease (PD), and multiple sclerosis (MS). The two latter are also associated with progressive disability and a shortened life expectancy but have a more prolonged and thus unpredictable course.

The European Academy of Neurology (EAN), in collaboration with the European Association for Palliative Care (EAPC) have produced a Consensus paper on neurological palliative care, which outlines the need for a wider assessment of patients—physical, psychological, social and spiritual, and including consideration of end of life care and discussion of hastened death (3). Moreover, the support of carers, both family and professional has been emphasized (3).

This Research Topic has aimed to look at new developments in the palliative care of patients with neurological disease and the editors were heartened by the response and the papers submitted. They consider many different aspects of care and several different disease groups.

The need to assess carefully the various symptoms of all patients is emphasized in the paper by Anneser et al.. They found that neurological symptoms were common, both in patients with neurological diseases and other patients receiving palliative care. These symptoms may affect the quality of life of patients. However, the survey of neurologists in the Netherlands (Walter et al.) showed that discussions about treatment restrictions and the consideration of palliative care in PD and MS were often delayed until the later stages of the disease progression—cognitive decline was often the trigger. This has again shown that education of neurologists is important in enabling discussion about deterioration and end of life to take place earlier in the disease progression, as was suggested by the EAN/EAPC paper (3).

One way of enabling professionals to become more aware of the prognosis of the patient may be the use of the "Surprise Question"—"Would you be surprised if your patient would die in the next 12 months?" This was found to be useful, particularly when combined with an assessment of the symptom burden (Ebke et al.). There is also a need to ensure that the necessary expertise in the management of palliative care issues for neurological patients is more widely available. The innovative use of telemedicine in Bavaria, Germany was shown to help and support palliative care teams in the management of patients with neurological disease, when they do not have the specific expertise required (Weck et al.).

The role of palliative care for patients with ALS has been established for many years (5). The physical aspects may be complex and in particular the use of non-invasive ventilation (NIV)

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for patients with respiratory muscle weakness was shown to be associated with improved QoL and survival (6), albeit many questions remained about timing and the minimum forced vital capacity (FVC). Khamankar et al. present a new approach to commencement of NIV with a protocol suggesting initiation for patients with a FVC of 80% or less, a higher level than is usually suggested, together with encouragement for regular usage and cough assistance. This approach would seem to improve survival−−30.8 months in their cohort, compared to a standard regime. This is a challenge to look carefully at how NIV is discussed and used.

The psychosocial issues for people with ALS are profound, facing a progressive deterioration in physical function over a short period of 2–3 years. Grabler et al. have shown that although depression, anxiety, and death anxiety are not particularly common in ALS patients, they found that they widely correlate with each other and should be addressed altogether. Caregivers' strain was related to both depression and anxiety. This again shows the importance of the care and support, and often intervention, for caregivers, to help them care for patients with ALS. A group in Leipzig in Germany are developing a short-term intervention "Managing Cancer and Living Meaningfully (CALM)" which has been adapted for patients with ALS (Oberstadt et al.). This now needs to be validated to ascertain if this approach would be helpful in allowing patients to receive the support they need, both in terms of symptoms, relationships, and psychosocial well-being. The use of high technology alternative and augmentative communication systems is often very important as communication becomes difficult and Linse et al. discuss the issues of ensuring that equipment is used effectively to help patients strengthen self-determination, improve quality of life and reduce caregiver burden.

There is increasing interest in the role of palliative care for people with Parkinson's disease. The paper from Hanover, Germany shows that the quality of life of people with PD is poor, with motor deficits, impairment of daily living, depression and cognitive loss (Klietz et al.). However, although 72% had an unmet palliative care need, only 2.6% had received palliative care input. A new approach is described by Eggers et al. where in Cologne, Germany a network has been developed, with a model of care provided by a movement disorder neurologist and a PD nurse collaborating with neurologists across the area. This service did not seem to see late-stage disease patients and there appeared to be poor access and loss of follow-up toward the end of life. Many PD patients may be admitted for nursing home care as the disease progresses. Lex et al. looked at residents who are in a late stage of Parkinson Disease in residential care in Salzburg, Austria, and found that despite their severe disease, limiting their activities and mobility, they did not have a significant symptom burden and were content with their quality of life. They appreciated the closeness of family and nursing home care and family members were often reassured that the resident was being cared for and their anxiety and burden had lessened.

van der Steen et al. have shown that people with PD and those with dementia face uncertainty and increasing disability and cognitive loss and that palliative care can be helpful. There is a need to develop a palliative care approach to cope with the variable and protracted deterioration, ensuring symptoms are managed effectively, carers are supported and advance care plans are considered earlier.

Although in the past palliative care for neurological patients has tended to focus on ALS, and to a lesser extent PD and MS, there is increasing awareness of the role for other disease groups. Stroke is a very common cause of disability and death across the World and there is a need to look at this patient group and their palliative care needs (7). Steigleder et al. consider the challenges of providing care for stroke, when the outcome is uncertain and there may be rapid changes. They argue for a wider consideration of palliative care and consider the barriers of the implementation of this, and look at possible ways forward. Patients with high-grade glioma also face an uncertain future and the paper from Renovanz et al. shows that both patients with glioma and their carers have many psychological issues, particularly when receiving chemotherapy. They press for greater support of both patients and carers at these difficult times.

Many patients receiving palliative care may have neurological symptoms which need to be assessed and addressed. Grönheit et al. discuss the difficult area of managing epileptic seizures and status epilepticus and provide practical advice on medication and the mode of administration. Restless legs can be a very distressing symptom, for both person and bed partner. Gärtner et al. provide an interesting insight with a case study of a patient who responded to morphine. There is still much to learn and case studies may give us an insight, which can in turn lead to a deeper understanding and more effective management of symptoms.

The papers in this volume provide an opportunity to look at palliative care for neurological patients. This is expanding and in the USA the concept of neuro-palliative care is increasing—neurologists with extra palliative care training and experience, who are able to develop the multidisciplinary approach to people with neurological diseases (8). There are many challenges and all involved in the care of patient with neurological disease—neurologists, rehabilitation physicians, the wider multidisciplinary teams, palliative care specialists, primary care teams, patients and families—need to face these issues, and may require training to cope with the new areas (3). However, with the increase in a generalist palliative care approach—listening to patients, helping to set goals and assessing all areas of care (physical, psychological, social, and spiritual)—and collaborating with specialist palliative care services for more complex areas we can all learn to help patients with neurological diseases, to maintain their quality of life and enable a better quality of death (9, 10).

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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ORIGINAL RESEARCH
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Neurological Symptoms in Palliative Care Patients

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Background: Neurological expertise in palliative care may be required not only for patients with primary neurological disorders but also for patients with non-neurological diseases suffering from burdensome neurological symptoms. The aim of this study was to determine the prevalence of neurological diagnoses and symptoms in palliative care patients, as well as the related burden and impact on everyday life.

Methods: We analyzed retrospectively the medical records of 255 consecutive patients from a tertiary medical center, at the time point of referral to an inpatient palliative care consultation service. In addition, 100 patients prospectively answered a questionnaire which included the assessment of neurological symptoms, as well as numeric rating scales for quality of life, symptom-specific burden, and restrictions in everyday life.

Results: Forty-one patients (16%) suffered from a primary neurological disease. Most decisions regarding the termination of life-sustaining measures concerned this group (20/22, 91%). Neurological symptoms (excluding pain) were documented in 122 patients (48%) with an underlying non-neurological disease. In the questionnaire study, 98/100 patients reported at least one neurological or neuropsychiatric symptom, most frequently sleeping problems ($N = 63$), difficulty concentrating ($N = 55$), and sensory symptoms ($N = 50$). Vertigo/dizziness ($N = 19$) had the greatest impact on everyday life (7.57/10 ± 2.17) and the highest symptom-specific burden (7.14 ± 2.51). Difficulty concentrating (restrictions in everyday life/burden) and pain intensity were the only symptoms significantly correlated with quality of life ($r = -0.36$, $p = 0.009$/$r = -0.32$; $p = 0.04$; $r = -0.327$, $p = 0.003$).

Conclusion: Neurological diseases and symptoms are frequent among palliative care patients and are often associated with a high symptom burden, which may severely affect the patients' lives. It is thus of paramount importance to implement neurological expertise in palliative care.

Keywords: palliative care, neurological symptoms, prevalence, symptom burden, quality of life

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INTRODUCTION

Palliative care aims to provide physical, psychosocial, and spiritual care for terminally ill patients and their families. Although differences between countries exist, palliative care has been linked traditionally to oncological diseases and internal medicine/oncology specialists still constitute the largest part of the palliative care workforce in many countries (e.g., Germany, USA, Japan, and

Canada) (1–4), while neurologists constitute less than 3% of physicians that are certified in palliative care (1, 2, 4). On the other hand, neurological and neurosurgical diseases have been found to be the second most common conditions in patients seen by a palliative care inpatient consultation service (5) and the most common diagnostic group in patients with non-malignant diseases (6).

Several reviews advocate a better integration of palliative care in the overall care of patients with neurological diseases (7–9). Both neurological and palliative care expertise are required, e.g., for patients with intracranial processes in order to assess prognosis, to substantiate decisions on the withholding or withdrawal of life-sustaining measures and to help the family understand the nature of an imminent persistent vegetative state or brain death. Although care concepts for people with motor neuron diseases may be an encouraging example of the successful integration of palliative care and neurology, many patients with neurodegenerative, neuro-oncological as well as neurovascular diseases still have a wide range of unmet palliative care needs (9, 10).

In addition, neurological expertise is required for non-neurological palliative care patients suffering from neurological symptoms. Scarce data are available on the prevalence of neurological symptoms in a general palliative care population and most of the data have been assessed retrospectively. In a meta-analysis looking at symptom prevalence in a total of 25,000 patients with incurable cancer (11), "neurological symptoms" (without further specification) were documented in 15% of all patients and in 34% within their last 2 weeks of life. Even less is known about the relevance of neurological symptoms for the patients' lives (e.g., their subjective burden, the impact on patients' quality of life (QoL), or possible restrictions in the patients' everyday lives). We therefore combined a review of patient charts with a prospective questionnaire study in order to gain an overview of the frequency of neurological symptoms as well as their clinical relevance in a general palliative care population.

MATERIALS AND METHODS

Retrospective Chart Analysis

The charts of 255 consecutive patients who had been referred to the palliative care inpatient consultation service, were analyzed. Data were collected over a period of 9 months. Demographic data, diagnosis, reasons for current admission to the hospital, previous treatments as well as neurological and neuropsychiatric symptoms and preconditions—as listed in the patient charts prior to the referral to the palliative care team—were assessed.

Prospective Questionnaire Study

A total of 100 consecutive inpatients, referred to the palliative care inpatient consultation service, who were willing to participate and able to give their written informed consent were included in the questionnaire study. The questionnaire was administered in the form of a structured interview. The specific symptom burden is the degree to which the patients' everyday lives were compromised by a symptom and the patients' overall QoL were assessed using 0–10 point numeric rating scales (NRSs). NRS is a validated measure for QoL and is considered to assess the patient's general QoL rather than only its health-related aspects (12).

In order to differentiate lightheadedness or pre-syncopal syndromes from vertigo/dizziness, we asked the patients for the sensation of spinning/swaying and/or unsteady gait.

Actual pain intensity was assessed using a visual analog scale (VAS). To be able to compare the symptom "pain" with other neurological/neuropsychiatric symptoms, we assessed also the symptom-specific burden and restrictions in everyday life due to pain. Neuropathic pain was diagnosed by clinical assessment of the pain characteristics and the association with typical symptoms in the same area (e.g., tingling, numbness).

The "Confusion Assessment Method" (CAM) questionnaire was used when delirium was suspected. The CAM is a validated instrument for the diagnosis of delirium in a variety of medical settings (13, 14).

The Patient Health Questionnaire (PHQ-4) was used to screen patients for anxiety and depression.

In addition, patients were asked to name the symptoms, which were currently most distressing to them (max. 5). All patients who agreed received a structured neurological examination. Diagnostic workup of burdensome neurological symptoms was offered if indicated (e.g., neuro-otologic tests in patients with vertigo/dizziness). In addition, all patients were offered psychological support if desired. Descriptive statistics was performed using SPSS 24 (IBM, Chicago, IL, USA). Correlation analysis (Spearman's rho) was performed. The study was carried out in accordance with the recommendations of the Ethics Committee of the Technical University Munich. The protocol was approved by the Ethics Committee of the Technical University Munich (No: 5682/13). All subjects gave written informed consent in accordance with the Declaration of Helsinki.

RESULTS

Analysis of Patient Charts

Reasons for Admission to the Hospital as Documented in the Patient Chart

Patients from nine different departments had been referred to the palliative care inpatient consultation service. For patient characteristics, see **Table 1**. In 84 out of 255 patients (33%), the main reasons or one of the main reasons for admission to the hospital were neurological symptoms (other than pain). 28 patients (11%) had been admitted directly to the departments of neurology or neurosurgery. The presence of neurological symptoms and preconditions—as documented in the admission examination or discovered in other examinations during the hospital stay—was assessed. Patients were assigned to one of four groups. (10 patients remained unclassified due to incomplete data or unclear assignment):

TABLE 1 | Analysis of patients' medical records: patients' characteristics and neurological symptoms.

Patient characteristics	**255 patients**	
Gender	118 (45%) female	
Mean age	67 ± 13 years	
Mean duration of disease	35 ± 54 months	
Cancer diagnosis	217 (85%)	
Primary brain tumor or cerebral metastases	49 (19%)	
Previous surgery	138 (55%)	
Previous chemotherapy	157 (63%)	
Previous radiotherapy	100 (40%)	
Neurological symptoms as documented in the patient chart		
Central paresis	41 (16%)	Group 1: 25/41 (61%) Group 2: 12/99 (12%) Group 3: 4/23 (17%)
Seizures	27 (11%)	Group 1: 22/41 (54%) Group 2: 14/99 (14%) Group 3: 1/23 (4%)
Dementia	14 (6%)	Group 1: 10/41 (24%) Group 2: 0/99 (0%) Group 3: 4/23 (17%)
Confusion	47 (19%)	Group 1: 15/41 (37%) Group 2: 27/99 (27%) Group 3: 4/23 (17%)
Other CNS symptoms	66 (26%)	Group 1: 33/41 (80%) Group 2: 27/99 (27%) Group 3: 6/23 (26%)
Peripheral paresis	27 (11%)	Group 1: 3/41 (7%) Group 2: 20/99 (20%) Group 3: 4/23 (17%)
Sensory symptoms	23 (9%)	Group 1: 0/41 (0%) Group 2: 20/99 (20%) Group 3: 3/23 (13%)

Group 1: primary neurological condition, group 2: neurological symptoms presumably caused by a non-neurological underlying disease, and group 3: neurological symptoms presumably independent from the underlying disease.

(1) A neurological condition is the primary underlying disease (e.g., stroke, neurodegenerative disorder, primary brain tumor): 41 patients (16%)
(2) Neurological symptoms (excluding pain) present and presumably caused by the (non-neurological) underlying disease and/or due to treatment of that disease: 99 patients (39%)
(3) Neurological symptoms (excluding pain) present and presumably independent from the basic disease: 23 patients (9%)
(4) No neurological preconditions or symptoms documented: 82 patients (32%)

In most cases, no detailed neurological medical history had been assessed and no in-depth neurological examination had been performed before admission to the palliative care team. The most frequent neurological symptoms mentioned in the patient files are shown in **Table 1**. Neuropsychiatric symptoms such as sleeping problems, difficulty concentrating and impaired memory had not been assessed on a regular basis. "Taste abnormalities" were documented in none of the patient records.

Termination of Life-Sustaining Measures

After palliative care consultation, life-sustaining measures had been terminated in 22 patients, and 20 (91%) of them had been classified in group I (neurological condition as primary disease).

Patient Questionnaire Study

Patient Characteristics

For the questionnaire study, 100 of 255 consecutive patients who were willing to participate and able to give their informed consent were included (50% female; 98 patients with cancer, 13 of them with brain metastases). 73 of 255 were not able to give their informed consent, 39 patients declined to participate, 32 patients could not be approached before the involvement of the palliative care consultation service, 11 lacked sufficient knowledge of the German language. None of the 41 neurologic patients could be recruited (20 were unconscious, 15 patients—mostly severe stroke or advanced glioblastoma—were conscious, but unable to consent, 5 refused to participate, and 1 lacked sufficient knowledge of the German language). 98 patients reported at least one neurological or neuropsychiatric symptom excluding pain, 38 patients stated that a neurologist or psychiatrist had treated them before admission to the hospital. Clinical neurological examination was performed after the patient interviews and objectified the symptoms reported (e.g., extent and degree of paresis or paresthesia). The values for "restrictions in everyday life" and "burden due to a specific symptom" were correlated, except for taste abnormalities.

Prevalence of Neurological Symptoms

The prevalence of neurological/neuropsychiatric symptoms, the symptom-specific burden, and restrictions in everyday life in patients participating in the questionnaire study is shown in **Table 2**. Sleeping problems (63/100), difficulties concentrating (55/100), and sensory symptoms (50/100) occurred most frequently. In addition, several neurological/neuropsychiatric symptoms were ranked among the most burdensome overall symptoms (**Table 3**).

Neurological Symptoms and QoL

The mean QoL (±SD) (NRS 0–10) of all patients was 3.7 (±2.3). The only neurological non-pain symptom significantly correlated to QoL was difficulty concentrating (restrictions in everyday life: $r = -0.36$, $p = 0.009$; symptom-specific burden: $r = -0.32$; $p = 0.04$). In addition, the sum scores (restrictions in everyday life and symptom-specific burden) comprising the three most frequent neurological/neuropsychological symptoms (sleeping problems, difficulty concentrating and sensory symptoms) were significantly correlated with QoL ($r = -0.348$, $p = 0.0004$; $r = -0.322$, $p = 0.001$).

Pain

52 patients reported having only one pain localization, 27 patients reported having two, and 5 reported having three pain localizations. The most frequent type of pain was predominantly nociceptive (45 patients), followed by mixed pain (29 patients), and predominantly neuropathic pain (10 patients). Actual pain intensity—as measured by a VAS—correlated significantly with

TABLE 2 | Prevalence of symptoms, restrictions in everyday life and burden due to specific symptoms (NRS 0–10).

Neurological symptoms	$n = 100$	Restrictions in everyday life Mean (±SD)	Burden due to a specific symptom Mean (±SD)
Pain	84	6.52 (±3.04)	6.48 (±3.08)
Sensory symptoms (numbness, tightness, tingling, burning)	50	4.67 (±3.27)	4.21 (±3.34)
Taste abnormalities	32	3.62 (±2.79)	5.62 (±2.83)
Hearing impairment	28	3.69 (±3.28)	3.85 (±3.16)
Muscular symptoms other than paresis (cramps, fasciculation)	28	NA	NA
Vertigo/dizziness	19	7.57 (±2.17)	7.14 (±2.51)
Paresis	16	6.08 (±3.36)	6.06 (±3.2)
Coordination difficulties	12	6.58 (±3.26)	5.75 (±3.08)
Double images	10	6.00 (±3.2)	5.90 (±3.38)
Seizures	6	4.75 (±4.43)	5.00 (±4.08)
Speech disorders	4	4.00 (±3.65)	6.50 (±3.11)
Neuropsychiatric symptoms			
Sleeping problems	63	5.70 (±2.93)	5.64 (±3.34)
Difficulty concentrating	55	3.85 (±3.18)	4.44 (±3.12)
Impaired memory	44	3.36 (±3.21)	4.29 (±3.11)
Symptoms with possible neurological causes			
Bladder or bowel disorder	30	2.56 (±3.00)	3.90 (±3.56)
Dysarthria and/or dysphagia	22	6.27 (±3.10)	6.45 (±2.96)

TABLE 3 | Most distressing symptoms at the time of the interview named by 100 palliative care patients.

Frequency of mention	Symptoms
43×	General weakness, **pain**
20×	Dyspnea
13×	Nausea, fatigue, loss of appetite
9×	**Being worried/rumination**
5×	**Paresis**
4×	Loss of autonomy, social isolation, bleeding, **concentration problems, dysphagia**
3×	**Sensory symptoms, vertigo/dizziness**, diarrhea
2×	Problems with stoma care, **dysarthria, unsteady gait, anxiety, vision disturbances** fever
1×	Restlessness, cough, **sleep disturbances**, ascites, edema

Neurological and neuropsychiatric symptoms as assessed in the questionnaire study are printed in bold.

QoL ($r = -0.327$, $p = 0.003$). Restrictions in everyday life and subjective burden due to pain did not correlate significantly with patients' QoL ($r = -0.135$, $p = 0.21$; $r = -0.07$, $p = 0.517$).

Depression and Anxiety (PHQ-4)

Normal scores (0–2) were found in 28 patients, mild distress (3–5) in 28 patients, moderate (6–8) in 23, and severe distress (9–12) in 21 patients. PHQ-4 showed a moderate correlation with QoL ($r = 0.271$, $p = 0.007$). The PHQ-4 depression subscore was significantly correlated with the neuropsychological symptom "difficulty concentrating" ($r = 0.361$ $p = 0.003$) and moderately, but significantly correlated with QoL ($r = -0.271$, $p = 0.007$).

Delirium

"Confusion" was documented in 47 patient charts (18.4%), 12 were able to give their informed consent to study enrollment and underwent a screening test for delirium (CAM). The test-specific criteria for the diagnosis of "delirium" were fulfilled in 11 patients. No significant correlation with regard to age or gender was found in our study group.

DISCUSSION

Several studies investigated the presence of burdensome symptoms in patients with advanced cancer and palliative care patients [for a review, see Ref. (11, 15)]. Isolated neurological symptoms such as agitation/delirium or vertigo/dizziness have been assessed in this context. However, a systematic and detailed analysis of neurological symptoms in palliative care patients has not been carried out before. We found that almost half of the palliative care patients without a primary neurological disease had neurological symptoms documented in their charts, and 98% of patients in the prospective study reported at least one burdensome neurological/neuropsychological symptom. This is considerably higher than previously described (11). These findings have an immediate clinical relevance in that significant suffering arises from symptoms, which are underdiagnosed and therefore insufficiently treated. Our data suggest that this may be the case for a variety of neurological symptoms, which come with a high subjective burden and/or restrictions in everyday life, e.g., vertigo/dizziness, coordination difficulties, or double vision (**Table 2**).

Sensory Symptoms

The prevalence of sensory symptoms (numbness, tightness, tingling, and burning) reported in patients with advanced cancer and in palliative care patients varies widely from 6 to 36% (16–19). These variations may be caused by the different characteristics of the populations investigated, but also by the differing assessment methods used. Not surprisingly, it has been found that the prevalence of many symptoms is considerably lower when assessed using medical records as compared with studies using questionnaires or structured interviews (11). Correspondingly, the prevalence of sensory symptoms in our questionnaire study (50%) was markedly higher than the results from the chart reviews (9%).

Dysgeusia

Similar results were obtained for the prevalence of "taste abnormalities" (dysgeusia) in palliative care patients: in our study, the occurrence of dysgeusia in the patients' charts was 0%, while 32% of patients in the questionnaire study reported taste abnormalities. Similarly, a previous interview study found that 86% of palliative care patients had taste abnormalities (20), while dysgeusia was documented in only 1–2% of patients' charts (17, 18).

Dizziness/Vertigo

Interestingly, our questionnaire study revealed "dizziness/vertigo" as the most burdensome symptom with the greatest impact on everyday life. "Vertigo"—defined as an erroneous sense of motion

and unsteadiness—is a relatively common condition, which also occurs in the general population: a survey in Germany reported a 12-month prevalence of 22.9% (21), while the point prevalence in palliative care patients with cancer was 10% (18). "Dizziness" is a term mostly used in a wider sense, which includes symptoms that range from a vague feeling of unsteadiness to severe vertigo. Pooled prevalence of dizziness in patients with incurable cancer was 17% in a previous study (11) and is similar to the occurrence found in our study (19%). Our questionnaire allowed only an initial screening for dizziness/vertigo without providing an accurate diagnosis. A detailed analysis of dizziness/vertigo in palliative care patients is urgently warranted, since effective treatment is available for many forms of this symptom (22).

Pain

Pain had a prevalence of 84% in our palliative care population with a high symptom-specific burden and relevance for everyday life. Actual pain intensity correlated significantly with QoL, while symptom-related burden and restrictions in everyday life due to pain did not. An association between pain and QoL has been described previously, using the "brief pain inventory" (23, 24), but also an NRS (25). In contrast to the VAS assessing actual pain intensity, our items asking for a "symptom-specific burden" or "restrictions in everyday life" implicate significant elements of personal judgment and/or coping and may therefore provide different results when correlated with QoL. 39% of our—predominantly oncologic—patients suffered from neuropathic pain. This matches the prevalence of neuropathic pain in cancer patients assessed in palliative care (43%) and hospice settings (35%) (26). A recent review revealed that neuropathic pain in cancer patients is often insufficiently treated because of "incorrect use of co-analgesics" (27).

Delirium

In 47 (19%) patient charts from our cohort, "confusion" was documented. This percentage matches previous observations in a palliative care population (28). Since patients had to give informed consent to participate in the prospective study, only 12 patients underwent CAM testing in the context of our study, which was positive in 11 patients. Prevalence, diagnosis, treatment, and prognosis of confusion/delirium in palliative care patients have been widely studied (29). Recently, a randomized controlled trial showed that palliative care patients treated with standard neuroleptic medication had more delirium-specific symptoms, more side effects and a shorter survival rate than placebo-treated patients (30). This underscores the necessity of a careful diagnostic evaluation and individualized management of delirium in palliative care. Expertise in neuropharmacology and in the early detection of extra-pyramidal side effects of neuroleptic medication may be helpful to tailor treatment for these patients.

Anxiety and Depression

Anxiety and depression are common symptoms in palliative care patients (31) with an estimated prevalence ranging between 7 and 49% (32). Correspondingly, 21% of our patients scored 9–12/12 in the PHQ, indicating severe psychological distress.

Sleeping Problems

Similar to previous studies (33–35), sleeping problems were a frequent complaint among palliative care patients with a relatively high symptom-specific burden and impact on everyday activities. Sleep problems are multifactorial in many patients, although the moderate correlation with subjective burden due to pain suggests that inappropriate pain therapy may contribute to sleep disturbances in our patient population.

Cognitive Symptoms

A frequent occurrence of mild-to-moderate self-reported cognitive symptoms, such as difficulty concentrating or memory disturbances, has been described previously in palliative care and cancer patients (16, 17). In addition, in a previous study, cancer outpatients named "difficulty concentrating" as one of the 13 top-ranked symptoms (36). Correspondingly, difficulty concentrating was the only symptom (except pain) significantly correlated with QoL in our study. A previous report showed that complaints of difficulty concentrating did not correlate with objective measurements of cognitive function in palliative care patients (37). In our study group "difficulty concentrating" correlated significantly with the PHQ-4 depression subscore. It has been shown previously that the prevalence of depression in palliative care patients and patients with advanced cancer is greater than in the general population (38). Since difficulty concentrating is a complaint which is frequently associated with depression (39), this symptom may be part of a coexisting depressive syndrome. However, cognitive impairment and difficulty concentrating may also be accompanying symptoms of CNS processes or side effects of radiation therapy [for review, see Ref. (40)]. Expertise in organic forms of cognitive impairment may be helpful for the diagnostic classification of these symptoms in order to initiate appropriate treatment.

Neurological/Neuropsychological Symptoms and QoL

The significant correlations between the sum scores of the three most frequently reported neurological/neuropsychiatric symptoms (sleeping problems, difficulty concentrating, and sensory symptoms) and QoL, as well as the frequency at which neurological problems are reported to be one of the most distressing overall symptoms (**Table 3**), underscore the extent to which these symptoms may compromise the patients' well-being. Many neurological symptoms that turned out to be burdensome in the questionnaire study had not been assessed prior to the referral to the palliative care team. This underlines previous findings that physicians frequently tend to focus on their specialized scope of practice rather than giving sufficient attention to burdensome (e.g., neurological) symptoms in severely ill patients (41).

Patients With Primary Neurological Diagnoses

The percentage of patients with a primary neurological diagnosis (16%) in our retrospective cohort is higher than the proportions found in previous studies (9.2 and 8.8%) (5, 6); one of which however excluded patients with primary brain

tumors (5). In our study, the overwhelming majority (91%) of decisions regarding termination of life-sustaining measures (e.g., terminal extubation, termination of artificial hydration, and nutrition) were taken in patients with primary neurological diseases. This is in line with the findings of Liu et al. (6), who showed that "eliciting goals of care" was the most frequent reason for palliative care consultations among neurological patients. In-depth knowledge of the course and prognosis of neurological diseases is indispensable when discussing treatment options with the patients' families. Generally, there is an increasing awareness that many patients suffering from neurological diseases have palliative care needs (7, 8) and efforts have been made to improve the education of neurologists in this context (42).

Neurological Expertise in Palliative Care

Given the high prevalence and the considerable burden of neurological symptoms in palliative care patients, as well as the relatively high percentage of patients with primary neurological disorders, it becomes evident that neurological expertise is crucial in palliative care. It can be fostered by increased neurological training in postgraduate palliative care education, as well as by recruiting neurologists in specialized palliative care centers. However, relatively few neurologists choose to abandon their primary specialty to concentrate on palliative medicine full-time. Clinical rotations of neurologists in palliative care teams may not only help to integrate neurological knowledge into palliative care, but also open up career options for young neurologists (2).

Limitations

The single center design may limit the generalizability of the study. However, referral of patients from nine different departments of our university hospital resulted in a highly heterogeneous study population with a wide range of diagnoses. Our study was conducted in a tertiary medical center that has departments of neurology and neurosurgery. Therefore, the number of patients with primary neurological disorders may be higher than in less specialized hospitals. In the prospective cohort, 98% of patients suffered from cancer. The significance of the results from the questionnaire study may therefore apply primarily to oncological palliative care patients. Unfortunately, this also reflects the disproportionate prevalence of tumor patients in most specialized palliative care centers worldwide.

Similar to other centers (43, 44) patients with non-malignant diseases including primary neurological disorders were referred to our palliative care consult service only at a very late stage. These patients were unable to consent and could not recruited for the prospective study. Similarly, patients of all disease stages and neurological symptoms that affected their ability to consent (e.g., delirium) were excluded from the study. Hence, the prevalence of neurologic symptoms in a general palliative care population may be even higher and the symptoms more burdensome than found in our prospective study group.

Finally, the NRSs for the assessment of symptom-specific burden and for restrictions in everyday life used in our study had not been validated previously. However, NRSs allow for a direct comparison between specific neurological symptoms and help reducing the study burden for the severely ill patients to a minimum.

CONCLUSION

A majority of palliative care patients in our study suffered from neurological symptoms in varying degrees, frequently causing considerable symptom burden and restrictions in everyday life. Some of these symptoms are not well documented in patient charts and may remain undiagnosed and untreated. In addition, the question of withdrawal of life-sustaining treatment is most frequently posed in patients with primary neurological diseases. In consequence, palliative care teams are confronted on a daily basis with complex neurological questions and burdensome neurologic symptoms. This underscores the importance of the neurological expertise in palliative care teams.

AUTHOR CONTRIBUTIONS

JA was involved in the conception and design of the study, the statistical analysis and interpretation of data, and drafted the manuscript. VA was involved in the design of the study, in the acquisition of data, and approved the final manuscript. GB was involved in the conception of the study, and critically reviewed, revised, and approved the manuscript.

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The Role of Palliative Care in Chronic Progressive Neurological Diseases—A Survey Amongst Neurologists in the Netherlands

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Background: Chronic progressive neurological diseases like high grade glioma (HGG), Parkinson's disease (PD), and multiple sclerosis (MS) are incurable, and associated with increasing disability including cognitive impairment, and reduced life expectancy. Patients with these diseases have complex care needs. Therefore, timely advance care planning (ACP) is required. Our aim was to investigate timing and content of discussions on treatment restrictions, i.e., to initiate, withhold, or withdraw treatment in patients with HGG, PD, and MS, from the neurologists' perspective.

Methods: We performed a national online survey amongst consultants in neurology and residents in The Netherlands. The questionnaire focused on their daily practice concerning timing and content of discussions on treatment restrictions with patients suffering from HGG, PD or MS. We also inquired about education and training in discussing these issues.

Results: A total of 125 respondents [89 neurologists (71%), 62% male, with a median age of 44 years, and 36 residents (29%), 31% male with a median age of 29 years] responded. Initial discussions on treatment restrictions were said to take place during the first year after diagnosis in 28% of patients with HGG, and commonly no earlier than in the terminal phase in patients with PD and MS. In all conditions, significant cognitive decline was the most important trigger to advance discussions, followed by physical decline, and initiation of the terminal phase. Most discussed issues included ventilation, resuscitation, and admission to the intensive care unit. More than half of the consultants in neurology and residents felt that they needed (more) education and training in having discussions on treatment restrictions.

Conclusion: In patients with HGG discussions on treatment restrictions are initiated earlier than in patients with PD or MS. However, in all three diseases these discussions usually take place when significant physical and cognitive decline has become apparent and commonly mark the initiation of end-of-life care. More than half of the responding consultants in neurology and residents feel the need for improvement of their skills in performing these discussions.

Keywords: palliative care, advance care planning, nervous system diseases, decision making, Parkinson's disease, multiple sclerosis, glioma

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INTRODUCTION

Chronic progressive neurological diseases like amyotrophic lateral sclerosis (ALS), high grade glioma (HGG), Parkinson's disease (PD), and multiple sclerosis (MS) are incurable and often associated with a shortened life expectancy. Patients with these diseases have a host of unmet physical, cognitive, psychosocial, and spiritual needs and experience problems in coordination and continuity of care (1, 2). There is growing evidence that early integration of palliative care improves the quality of life of these patients and their significant others. However, realization of this integration appears to be challenging in every day practice (3–8). The presence of communication barriers, e.g., speech impairment frequently observed in ALS and PD, and cognitive or behavioral disturbances as are found in HGG, PD, and MS complicate matters even more.

Misconceptions about palliative care are common, amongst health care professionals and patients. First, palliative care is often considered to be synonymous with hospice care or end-of-life care (9). Second, illness trajectories of progressive neurological diseases vary from rapidly progressive (ALS, HGG) to prolonged and fluctuating (PD, MS). Patients with these diseases have significantly different symptom profiles, psychosocial issues, and spiritual needs (1, 10, 11). Consequently, their caregivers' burden is equally variable. Third, knowledge about palliative care needs in chronic progressive neurological diseases is just emerging (3, 12, 13). Fourth, health care professionals in general are found to not be familiar with communication skills needed to deliver bad news and to discuss advance care planning (ACP) (14–19).

ACP is a communication process in which patients' wishes, preferences, and goals with regard to future (palliative) care, including end-of-life care, are discussed in a timely, and iterative manner (20, 21). ACP includes considerations about disease- and symptom-specific treatment, resuscitation and other life-prolonging modalities, treatment restrictions, end-of-life wishes and appointment of surrogate decision-makers. There is an increasing body of evidence, mostly from research in patients with cancer and other non-neurological chronic progressive diseases, that ACP improves both the quality of end-of-life care, as well as patient and family satisfaction, and may reduce stress, anxiety, and depression in surviving relatives (22, 23). In ALS, the paradigmatic disease for palliative care in neurodegenerative disorders, it is common knowledge that discussions about future care should be done in an ongoing, iterative way (2, 24, 25). There is sparse evidence that in patients who are severely ill after stroke or with dementia, ACP is restricted to discussions about the care in the last phase of life (26). The same applies to ACP in patients with HGG (12, 27). Whether and how ACP takes place in long-term follow-up of patients with PD and MS has not been investigated so far.

The objective of our study was 2-folded. First, we aimed to investigate timing and content of discussions on treatment restrictions, i.e., to initiate, withhold, or withdraw treatment in the course of HGG, PD, and MS, from the neurologist's perspective. The focus was on these three conditions because in the Netherlands neurologists generally are involved in the follow-up of patients with HGG, PD, and MS, whereas specialists of other disciplines take care of patients with ALS, dementia, and post-stroke sequelae. Second, we compared our results with international data about ACP in patients with ALS.

MATERIALS AND METHODS

Study Design and Population

We conducted a national cross-sectional survey amongst consultants in neurology and residents in The Netherlands. For reasons of privacy, we approached the potential participants via the secretariat of the neurology departments with the request to provide the physicians with the link to the online questionnaire. In order to maximize the response rate, two reminders were sent within the following 3 months. Data collection started in February 2016 and ended in August 2016. The questionnaire focused on three progressive neurological diseases, i.e., HGG, PD, and MS.

Ethics Approval

Dutch law specifies that ethics approval is only needed when 'participants are subject to procedures or are required to follow rules of behavior' (http://www.ccmo.nl/en/your-research-does-it-fall-under-the-wmo). As this was not the case, written informed consent was not required from the participants, as confirmed in a letter from the AMC local research ethics committee (REC) from 11th October 2018. Participants knew that the received data would be treated confidentially and used anonymized only, and that they could withdraw from the study at any moment, without explanation.

Survey Questionnaire

The questionnaire was designed by the authors, partly based on the literature and partly based on the results of in-depths interviews with neurologists by one of the authors (AAS) (28). The online tool Survey Monkey (www.surveymonkey.com) was used. The questionnaire consisted of 57 questions, subdivided into three different sections. In the first section, questions were raised about the experiences of neurologists and residents with timing and content of discussions on potential treatment restrictions held with patients suffering from HGG, PD, and MS. Actually, we used the terms "considerations," "initiating," "withholding," and/or "withdrawing," and "common/accepted treatment option." In the second section, neurologists were asked to elaborate on a recent case of HGG, PD, or MS in which such discussions took place. In the third section, there were questions on education and training in communicating treatment restrictions with patients and families. The questions were either pre-structured or open-ended. Two pilots were done amongst 10 neurologists and the questionnaire was adjusted according to their feedback.

Analysis

Data analysis was conducted by SPSS (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp). Frequencies and proportions were calculated by descriptive statistics for categorical variables. Mean and standard

deviation and median and range were calculated for continuous variables. Open-ended questions were analyzed and coded by three authors (HAWW, AAS, MdV).

RESULTS

There were 991 consultants and 341 residents who were contacted via their medical secretariats. One hundred twenty-five of them responded to the online survey, 89 (71%) consultants and 36 (29%) residents, from 63 hospitals (out of 79), yielding an overall response rate of 15% participants, but a response rate of 80% neurology practices. A total of 72 (58%) respondents (58 neurologists and 14 residents) filled in the survey completely. Therefore, the data was analyzed with a varying number of missing values.

Profile of Respondents

Table 1 shows the demographics of the respondents. Amongst consultants in neurology, 48 (54%) worked as general neurologist, 35 (39%) also had a subspecialty area, and 41 (46%) worked in a subspecialty area only. Twenty (22%) neurologists had specific expertise in movement disorders, 18 (20%) in neuro-oncology and 19 (19%) in MS. Within the group of residents, 25 (75%) worked in general neurology, and 15 (44%) also worked in a subspecialty area. Nine residents (26%) worked in a subspecialty niche only. Eight (22%) residents had specific expertise in neuromuscular diseases, 4 (12%) in movement disorders, 3 (9%) in neuro-oncology, 1 (3%) in MS, and 6 (18%) in vascular neurology.

The demographics of the respondents of our survey were consistent with those of the general population of neurologists in the Netherlands ("Nivel survey") (29). The median age of neurologists in our survey was 44 years (range 39–56.5), compared to 49 years in the Nivel survey. Sixty-two percent was male compared to 72% in the Nivel survey. **Figure 1** shows that the distribution of our respondents across the 13 Dutch provinces was similar to that of specialists in general[1].

TABLE 1 | Demographics of consultants in neurology and residents.

		Consultant *n* (%)		Resident *n* (%)
n (% male/ % female)		89 (62/38)		36 (31/69)
Age in years (median, range) (*n*= 61)		44 (33–64)		29 (25–40)
Number of working years	0–5	21 (24)	0–2	15 (42)
	5–10	23 (26)	2–4	9 (25)
	10–15	17 (19)	4–6*	12 (33)
	>15	28 (31)		

In The Netherlands, the duration of neurological training is 6 years.

[1]Available online at: https://capaciteitsorgaan.nl/app/uploads/2017/04/2017_04_24-DEF-Regionale-spreiding-medisch-specialisten.pdf

Discussions on Treatment Restrictions: Frequency and Participants

Most consultants in neurology ($n = 74$, 85%) and residents ($n = 32$, 91%) reported to have had discussions on treatment restrictions more than once per 6 months. Thirteen percent ($n = 14$) of the consultants had had one or more discussions per week. Thirty-four (40%) of the neurologists reported that they had had a discussion on treatment restrictions with more than 5 patients over the past 12 months. Of the residents 37% ($n = 13$) had had one or two of these conversations over the past 12 months. Ninety-two percent ($n = 75$) of the consultants in neurology and 65% ($n = 22$) of the residents reported that most of the time these discussions had taken place with the patient and a caregiver, in 8% ($n = 7$) and 35% ($n = 12$), respectively, only with a caregiver, and not once with the patient only. Fifty-five percent ($n = 44$) of the consultants and 53% ($n = 17$) of the residents reported to have had two-tiered discussions on treatment restrictions.

Discussions on Treatment Restrictions: Timing

Eighty-seven percent ($n = 59$) of the consultants in neurology and 92% ($n = 23$) of the residents were of the opinion that a doctor should initiate the discussions. Twenty-four to 33% of our respondents replied that they initiated the discussion "when the patient brings up the subject" and 16–26% "when the patient's family brings up the subject." In PD and MS, discussions on treatment restrictions took rarely place at diagnosis, and not once within the first year of diagnosis (**Figure 2**). Seventy-one percent ($n = 56$) of the neurologists and 70% ($n = 77$) of the residents, respectively, discussed treatment considerations in the terminal stages of PD and MS. In HGG, 28% ($n = 18$) of the respondents discussed treatment restrictions within the first year of diagnosis, 68% ($n = 60$) "when physical decline started" and 61% ($n = 54$) in the terminal phase. "The start of cognitive decline" triggered a discussion in 8, 5, and 4% in HGG, PD, and MS, respectively, whereas "when clear cognitive decline had started" led to discussions in 56, 47, and 44% in HGG, PD and MS, respectively (**Figure 2**).

Reflections on Discussions on Treatment Restrictions in Recent Cases

Respondents were asked to recall the most recent patient with HGG, PD, or MS with whom they had discussed a treatment restriction. Demographics and diagnosis of respondents' cases are summarized in **Table 2**. The median time since the discussion had taken place was 1 month (range 1 week−60 months). Sixty percent ($n = 38$) of the patients had cognitive decline and 23% ($n = 15$) were incompetent, of whom 13 (87%) had HGG and 2 (13%) PD. Eighty percent ($n = 53$) of the respondents reported that both patients and caregivers had been present during the discussions. In two instances (3%) the patient was alone, and in 4 (6%) only the caregiver was present. The mean duration of conversations was 29 (SD 13.3) min for neurologists, and 31 min (SD 14.1) for residents.

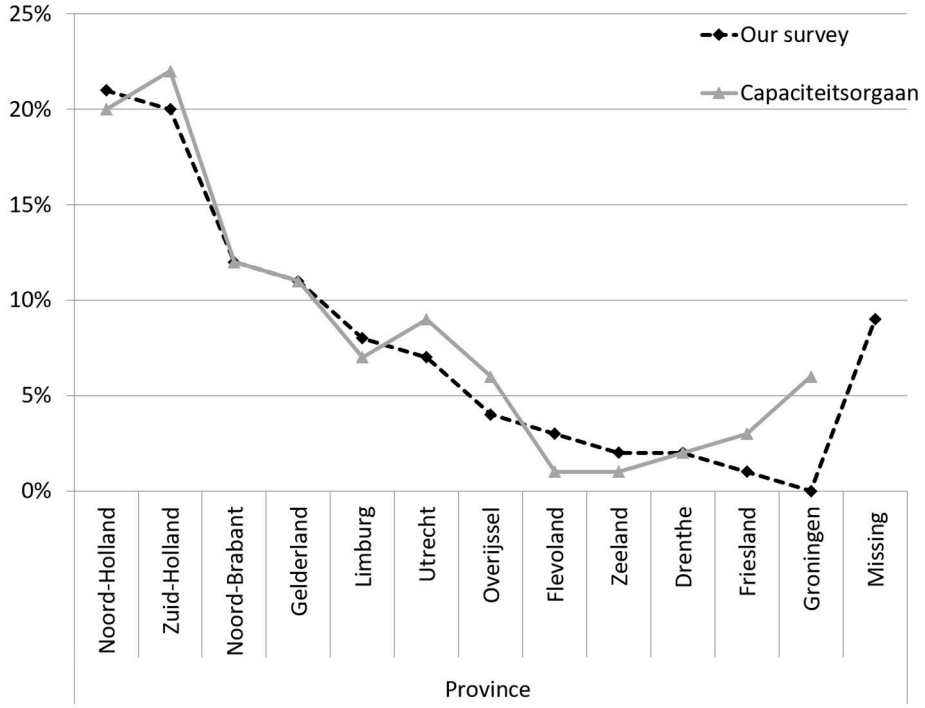

FIGURE 1 | Neurologists and other medical specialists per province, in percentages. Adapted from https://capaciteitsorgaan.nl/app/uploads/2017/04/2017_04_24-DEF-Regionale-spreiding-medisch-specialisten.pdf.

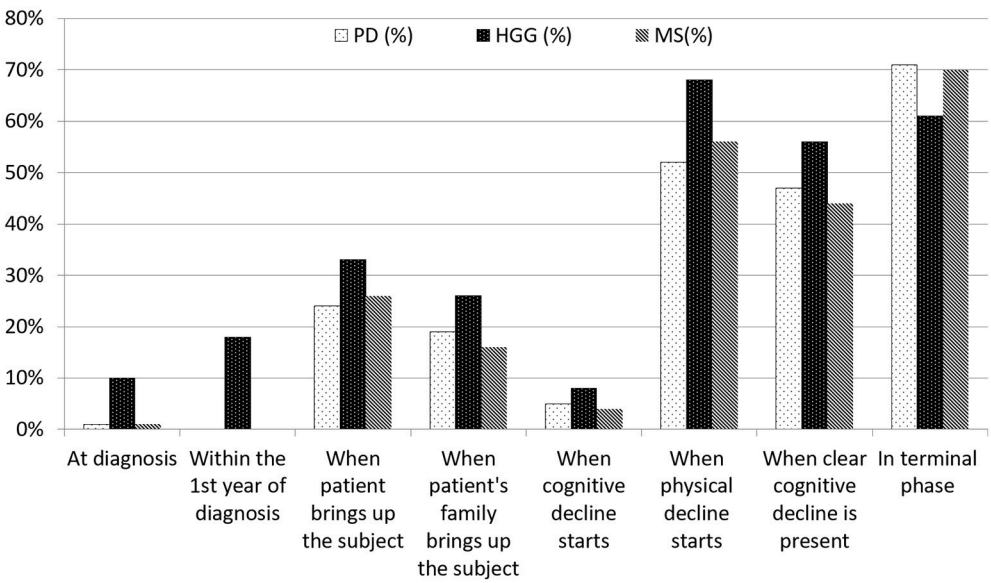

FIGURE 2 | Timing of discussions on treatment restrictions by consultants in neurology and residents. There was no definition provided regarding 'when cognitive decline starts'. 'When clear cognitive decline is present' was defined as 'incapacitating tha patient to (fully) understand and take part in decision-making'.

There was no consensus on the treatment policy between physician and patient or caregiver/family in 23% ($n = 15$) of the cases for the following reasons: "The patient was not ready to discuss the subject," "Patients' caregivers were not ready to discuss the subject," "The patient did not understand why a treatment should be stopped" or "The patient's relatives did not understand why a treatment should be stopped". In 12 cases (80%) a follow-up appointment was planned, and in 7 cases (47%) the respondent said to have complied with the patient's or relatives' wishes.

TABLE 2 | Demographics and diagnosis of respondents' cases.

		Respondents' cases *n* (%)
Diagnosis	PD	16 (24)
	HGG	43 (65)
	MS	7 (11)
Time since diagnosis, in months (median, range)		12 (1 day−20 years)
Age, in years (mean, SD)		65 (15)
Gender (male)		43 (68)

PD, Parkinson's disease; HGG, high grade glioma; MS, multiple sclerosis.

TABLE 3 | Considered treatment options per disease (percentages).

	PD $n = 16$ (*n* (%) initiate | *n* (%) withhold/withdraw)	HGG $n = 43$ (*n* (%) initiate | *n* (%) withhold/withdraw)	MS $n = 7$ (*n* (%) initiate | *n* (%) withhold/withdraw)
Resuscitation	0 | 12 (75)	0 | 33 (77)	0 | 3 (43)
Ventilation	0 | 12 (75)	0 | 34 (79)	1 (14) |2 (29)
Feeding tube	0 | 10 (63)	5 (12) | 18 (42)	1 (14) | 1 (14)
Surgery	0 | 9 (56)	5 (12) | 27 (63)	1 (14) | 1 (14)
Antibiotics	3 (19) |6 (38)	6 (14) | 19 (44)	2 (29) | 1 (14)
Corticosteroids	1 (6) | 7 (44)*	13 (30) | 10 (23)	1 (14) | 1 (14)
Admission to hospital	3 (19) | 5 (31)	5 (12) | 13 (30)	2 (29) | 2 (29)
Admission to ICU	0 | 12 (75)	1 (2) | 30 (70)	1 (14) | 2 (29)
Disease specific medication	5 (31) | 4 (25)	10 (23) | 18 (42)	0 | 5 (71)
Non-disease specific medication	5 (31) | 4 (25)	7 (16) | 12 (28)	4 (57) | 0

**In a small number of responses "corticosteroids" were mentioned as discussed treatment option in PD patients. Perhaps this should be considered an error, since this drug is very unusual in PD.*

Discussing Treatment Initiation or Withdrawal

Reasons to discuss treatment restrictions varied. "Acceleration of the disease process" was the main reason in 37% ($n = 22$) of the respondents and "Unexpectedly severe functional decline" was mentioned in 10% ($n = 6$). Other reasons included "Exhaustion of the possibilities to favorably influence the disease process" in 28% ($n = 11$) and the "The patient brought up the issue" in 8% ($n = 5$) of the cases. When asked which treatment modalities were considered, respondents could choose "initiate" or "withhold/withdraw". For patients with PD, resuscitation ($n = 12$, 75%), ventilation ($n = 12$, 75%), admission to intensive care unit ($n = 12$, 75%), and feeding tube ($n = 10$, 63%) were the most discussed issues. In HGG, respondents discussed ventilation ($n = 34$, 79%), resuscitation ($n = 33$, 77%), surgery ($n = 32$, 74%), and admission to the intensive care unit ($n = 31$, 72%). In MS, disease-specific medication was discussed in five instances (71%), non-disease specific medication in four (57%) (i.e., medication for urine incontinence or anti-depressants) and admission to hospital in four (57%).

Table 3 shows the discussions of treatment modalities (initiate or withhold/withdraw) in the specific disease groups in percentages.

When asked which terminal care options were discussed, pain alleviation was mentioned in 70% ($n = 28$) of the cases, alleviation of dyspnea in 55% ($n = 22$), and psychosocial support in 53% ($n = 21$) of the cases. Palliative sedation was discussed in 60% ($n = 24$) of the cases.

When asked if, in retrospect, the respondents would have discussed treatment restrictions earlier in the disease process, 27% ($n = 17$) agreed with this statement. Asked for reasons to postpone discussions the following statements were provided: "The patient could not handle it" (25%, $n = 4$), "I did not want to deprive hope" (19%, $n = 3$), "Lack of suffering of the patient" (19%, $n = 3$) and in one case the neurologist said it would have taken too much time.

Preferred location for terminal care was discussed by 88% ($n = 36$) of the respondents. The option "treatment at home" was mentioned in 42% ($n = 15$) of the cases, and the options "hospice" in 36% ($n = 13$).

Interpretation of the Meaning of Palliative Care

Respondents were asked "What does palliative care mean in your opinion?" Amongst the 77 neurologists and residents who responded to this question, 48% ($n = 37$) used the word "comfort," 29% ($n = 22$) considered palliative care as "relief of suffering" and in 17% ($n = 13$) it was coded as "quality of life." "Terminal phase," "end-of-life" or "no extension of life" was mentioned in 21% ($n = 16$). Thirteen percent ($n = 10$) of respondents used the description "no cure possible" and 12% ($n = 9$) "symptomatic treatment." The term "supportive care" was used by 9% ($n = 7$).

Education in Palliative Care

Sixty-four percent ($n = 44$) of the consultants in neurology and 75% ($n = 18$) of the residents reported that they were neither educated nor trained in discussions on treatment restrictions in chronic progressive neurological disease. Fifty-seven percent ($n = 39$) reported that they felt a need for education. Amongst the 25 consultants and 6 residents who were educated or trained, 14 consultants and 4 residents received this education as undergraduates, 18 consultants, and 3 residents during training, and 12 consultants on-the-job. Twenty-two consultants and 5 residents had had education via interactive lessons, for example a role-play, 13 consultants, and 2 residents had had education by supervision. Twenty one of the educated or trained consultants and 5 residents felt that their education/training had been sufficient for their work in clinical practice.

DISCUSSION

Our survey indicates that in The Netherlands the timing of discussions on treatment restrictions in patients with three chronic progressive neurological diseases (HGG, PD, and MS) varies considerably. The consultants in neurology and residents who responded to our online survey, reported that these discussions regularly took place in the first year of diagnosis in HGG, and mostly in the terminal phase of PD and MS. In all conditions, significant cognitive decline was the most important

trigger for the respondents to advance discussions, followed by physical decline, and the terminal phase.

As the response rate was rather low and selection bias might have taken place the findings of our survey have to be interpreted with caution (see also "strengths and limitations"). Importantly, the results are in line with previously reported findings that discussions on treatment restrictions in chronic progressive neurological diseases most often take place after a sudden decline of patients' condition (12, 26, 30).

In ALS, which is considered a paradigmatic disease for palliative care, rapid motor deterioration often includes bulbar impairment leading to speech impairment (31). According to (best practice) guidelines the imminent communication barrier allows no delay in initiating discussions on patients' expectations, wishes and preferences regarding treatment options/restrictions and end-of-life issues (2). There is also a rapid decline in patients with HGG, and in addition the presence of significant cognitive impairment, delirium, communication difficulties, and loss of consciousness impairs their decision-making capacities (12). Up to 79% of patients with HGG have cognitive impairment before treatment, and more than 50% lack full decision-making capacity 4 months after diagnosis (32, 33). This percentage increases, especially in the last months of life (27). However, initiating ACP from diagnosis onwards is still a matter of debate in this patient group (34). In PD and MS, cognitive impairment is also common. In PD, 60% of patients have dementia after a disease duration of 12 years, preceded by a period of mild cognitive impairment, which can even be present at diagnosis (35, 36). Frequencies of cognitive impairment in patients with MS range from 40 to 75% and can become manifest at all stages and in all subtypes of the disease (37, 38) Importantly, cognitive impairment in MS at time of diagnosis is considered a marker of most aggressive pathology (39). In the first consensus review on the development of palliative care in neurology it is therefore recommended to initiate discussions on future care options and wishes early in the course of chronic progressive neurological diseases, especially when cognitive, and communication impairment are likely to occur (40).

Literature on optimal timing of ACP in chronic progressive neurological diseases is scarce. In ALS, ongoing communication of future (palliative) care from diagnosis onwards is strongly recommended, preferably by a multidisciplinary team (40, 41). However, in practice, even in the follow-up of patients with ALS ACP appears to be regularly delayed or triggered by the occurrence of life-threatening complications (30, 42). It is of note that there is a perceived lack of awareness of advance directives amongst health care professionals, in particular hospital staff, which obviously limits the effectiveness of such documents (43, 44). Advance directives are equally underutilized by patients since a study found that only 30% patients with ALS complete them (7). To support both physicians and ALS patients to be better prepared, the recently published NICE guideline recommends to offer patients with ALS the opportunity to discuss their treatment preferences and concerns about care at the end of life at trigger points such as "at diagnosis," "if there is a significant change in respiratory function," or "if interventions such as gastrostomy or non-invasive ventilation are needed" (2). Regarding the timing of the discussions, the guideline also advises to take into account the person's current communication ability, cognitive status, and mental capacity. These recommendations are partly based on interviews with patients or (bereaved) caregivers' views. They want sufficient information to be able to take well-considered decisions, as it gives them a feeling of having choice and control over their treatment (14, 45, 46). Timely discussions on end-of life care, options and preferences, have also been shown to lower anxiety, and distress in ALS patients and their caregivers (44).

In the first guideline of the European Association for Neuro-Oncology for palliative care in adults with glioma ACP is defined as a process which is 'concerned with [. . .] preferences related to non-treatment decisions or preferred place of death. The guideline stresses that ACP is most effective when it is started in a timely fashion, allowing patients, caregivers, and physicians to proactively address the challenges together during the course of the disease'(12) . Indeed, there is growing awareness of the importance to openly communicate about patients' expectations, wishes, and preferences during the entire disease trajectory (34). However, in daily practice ACP in patients with HGG is still closely linked to the terminal phase, concerning both timing and content (47). Up to 40% of patients with HGG seem not to be involved in any end-of-life discussion, and the timing of end-of-life discussions may vary widely (1–140 days) (48). A retrospective study amongst physicians on end-of-life decision-making in patients with HGG showed that important topics were life-prolonging treatment (38%), admission to hospital (49%), palliative sedation (29%), and euthanasia (38%). Treatment was withheld in 29% of patients and concerned medication (antibiotics, dexamethasone), radiotherapy, placement of ventricular drain, and artificial administration of food or fluids (27). In our survey the most discussed topics were "resuscitation," "invasive ventilation," and "admission to ICU." One reason for these differences might be that we tried to avoid focusing on the last phase of life in our survey.

In contrast to both ALS and HGG, PD and MS are slowly progressive diseases with an often fluctuating course, unexpected declines, and gradual accumulation of impairments causing significant unmet needs (10, 49, 50). Recently, a study on preferences of patients with PD for communication about ACP showed that most (but not all) of them want prognosis and treatment information early, and that many expect their healthcare providers to bring up these issues (51). A qualitative study involving patients with PD underlined this: about half of the interviewees wanted their neurologist to raise the subject of ACP as an adjunct to usual care (49). And a survey amongst surrogates of patients in advanced stages of PD indicated that living wills might be completed by up to 94% of the patients, but shared with a physician by only 38% of them (52).

In a survey study on MS patients' palliative care needs the majority of respondents found it important to address the progression of disease and ACP. More than one-third wished to talk about end-of-life issues (53). One study addressing long-term care planning showed that on average only 11% healthcare providers discussed this issue, ranging from 10 to 26% for mildly affected and severely affected patients, respectively (54).

Currently, there are efforts being made to incorporate palliative care principles in PD and MS patients' long-term follow-up (1, 7, 8, 40). In line with that, the use of triggers to identify significant deterioration has been suggested, and end-of-life care needs are being mapped (15, 55). Pertinent topics to discuss in advanced PD and MS should include tube feeding, the use of antibiotics in case of infection, non-invasive ventilation in case of respiratory failure, and resuscitation (56).

In our survey, the most discussed treatment options with PD patients or their caregivers were "resuscitation," "invasive ventilation," "admission to ICU," and "use of a feeding tube." In MS the issues of "disease-specific medication" and "non-disease specific medication" and "admission to hospital" were most frequently discussed. Due to the small sample size (PD = 16, MS = 7) it is not possible to draw any conclusions about this discrepancy.

The results of our survey suggest that in most cases the consultants in neurology decided on the timing of discussions on treatment restrictions, and indeed the respondents were of the opinion that a doctor should initiate these conversations. However, they also appeared to be sensitive to the wishes of the patient or the patient's family if they brought up the subject. Uncertainty about optimal timing often causes postponement of discussions on treatment restrictions (57). In our survey reasons to postpone discussions included "I did not want to deprive hope" and "The patient could not handle it." A "wait and see policy" concerning discussions about the appropriate amount of future care seems to be a quite common strategy of many healthcare professionals (58–63).

At the end of our survey, we asked via an open-ended question what "palliative care" meant to the participating consultants in neurology and residents. There was a great variety of responses of which the terms "comfort," "quality of life," "end-of-life care," and "terminal care" were mentioned most frequently. This is consistent with previous research amongst health care professionals, including neurologists (1). One common misconception is that discussions on future (palliative) care may signal the 'beginning of the end', despite the finding that usual neurological care during follow-up of patients with chronic progressive diseases can go hand in hand with palliative care, including ACP (9, 64). The term "palliative care" is not only confusing for neurologists, but also for patients who might not be interested in "palliative care," but willing to attend a team-based clinic providing intensive symptom management and psychosocial support (15). Therefore, some clinicians suggest to talk about "supportive care" (65). In our survey 7% of the consultants in neurology associated palliative care with supportive care.

In our study, most neurologists reported that they were experienced in having discussions on treatment restrictions, i.e., not initiating or withdrawing treatment. However, when asked about their education 66% of the respondents reported that they had not been educated or trained in having these conversations, and about half of them indicated that they felt a need for education on this topic. Those who were trained felt that it was sufficient for daily practice. Various authors have described a general lack of education in palliative care skills amongst physicians, residents, and students (15, 66–70). A recent study investigating the effectiveness of training in palliative and end-of-life communication skills in medical students showed that nearly 80% indicated retention of communication skills after 1 year with regard to "giving bad news," followed by "talking about death and dying," and "end-of-life preferences/do not resuscitate" in 40–45% of the students (71). Overall, there is quite some evidence that communication training improves discussions on diagnosis, treatment options, and preferences including end-of-life care as experienced by both healthcare professionals and patients with progressive diseases and their caregivers (16, 72–76). Interestingly, a lack of an empathic response was noted as a gap in the neurologists' skills by patients and caregivers (14).

Strengths and Limitations

To the best of our knowledge our survey is the first addressing the daily practice of consultants in neurology and residents in the Netherlands concerning discussions on treatment restrictions in patients with PD and MS. We found one study in which physicians and bereaved relatives were questioned about decision-making and end-of-life practices in patients with HGG (27).

The overall response rate to our survey was 15%, which is rather low. However, we assume that this still represents a fair proportion of the neurological practices since in most hospitals subspecialized neurologists care for patients with HGG, PD, or MS, respectively. Additionally, the relatively low response rate may be explained by the distribution of the questionnaire via the secretariat of the neurology department for privacy reasons. There are other limitations. First, there may have been "self-selection bias." The majority of respondents had a specialization area so we cannot exclude that consultants in neurology and residents with a special affinity with the topic filled in the questionnaire. Second, due to privacy reasons we do not have information about the non-respondents. Third, we might have influenced the respondents' views. As we aimed to study discussions on treatment restrictions during the whole disease process, we cautiously avoided to use the terms "palliative care" and "end-of-life care" in the questionnaire. Still, it may well be that the phrasing of our questionnaire has triggered certain associations given the responses suggesting that discussing treatment restrictions was closely linked to (starting) end-of-life care. Finally, our data concerning the content of discussions are more representative of HGG than PD and MS due to unequal response rates.

In conclusion, our study suggests that discussions on initiating, withholding, or withdrawing treatment in patients with HGG, PD, and MS are mainly determined by significant cognitive and physical deterioration or the imminent terminal phase. Thus, they usually take place at advanced stages of the disease. The reasons are multilayer and changing daily practice will be a complex challenge. However, education in palliative care skills and knowledge of the overall interest of patients to be involved may be an important step to improve daily clinical practice.

Concrete future research projects arising from our findings should specifically investigate patients' wishes and preferences

regarding timing and content of discussions about future care options.

AUTHOR CONTRIBUTIONS

HAWW contributed in analyzing the data, interpretation of the data, writing, and revising of the manuscript, and accepts responsibility for the corresponding author. AAS contributed to the study design, data collection, interpretation of the data, and writing and revising of the manuscript. DLW contributed to the study design, interpretation of the data, and writing and revising of the manuscript. MdV contributed to the study design, interpretation of the data, and writing and revising of the manuscript. All authors are in agreement with the contents of the manuscript and provide approval for publication of the content.

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Impaired Quality of Life and Need for Palliative Care in a German Cohort of Advanced Parkinson's Disease Patients

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Background: Parkinson's disease (PD) is the second most frequent neurodegenerative disease of the elderly. Patients suffer from various motor and non-motor symptoms leading to reduced health-related quality of life (HRQOL) and an increased mortality. Their loss of autonomy due to dementia, psychosis, depression, motor impairments, falls, and swallowing deficits defines a phase when palliative care interventions might help to sustain or even improve quality of life.

Objective: The aim of this study was to investigate the current status of palliative care implementation and quality of life in a local cohort of advanced PD patients in order to frame and improve future care.

Methods: 76 geriatric patients with advanced idiopathic PD meeting the inclusion criteria for palliative care interventions were clinically evaluated by neurological examination using Movement Disorders Society Unified Parkinson's Disease Rating Scale, Barthel Index, Montreal Cognitive Assessment Test, and a structured interview concerning palliative care implementation.

Results: HRQOL is severely reduced in our cohort of geriatric advanced PD patients. We found motor deficits, impairment of activities of daily living, depression, and cognitive decline as most relevant factors determining decreased HRQOL. Only 2.6% of our patients reported present implementation of palliative care. By contrast, 72% of the patients indicated an unmet need for palliative care.

Conclusion: Quality of life is dramatically affected in advanced PD patients. However, we found palliative care to be implemented extremely rare in their treatment concept. Therefore, geriatric patients suffering from advanced PD should be enrolled for palliative care to provide adequate and holistic treatment which may improve or sustain their quality of life.

Keywords: advanced Parkinson's disease, palliative care, end-of-life care, quality of life, non-motor symptoms

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INTRODUCTION

Parkinson's disease (PD) is the second most frequent neurodegenerative disease of the elderly (1). Despite good treatment options in early disease with fair sustainment of quality of life, in advanced stages of PD therapy can be challenging and quality of life is dramatically reduced (2–4). Additional to motor symptoms such as rigidity, tremor, bradykinesia, and postural instability, patients are affected

by non-motor symptoms such as depression, obstipation, urinary incontinence, psychiatric disease, and cognitive deficits (5). This symptom burden markedly affects quality of life measured as health-related quality of life (HRQOL) of PD patients and induces caregiver burden as well (6–11). HRQOL and influencing factors are well characterized in early PD, especially dementia is related to poor quality of life and shortened survival (12). Comparatively little is known about determining factors of HRQOL in patients with advanced PD suitable for palliative care interventions (13). Advanced PD patients live with a high symptom burden and an increased risk of mortality, thus, meeting criteria for palliative care. Caregivers of these patients have a high caregiver burden showing a high incidence of depressive symptoms in a small cohort in Germany (caregivers of 20 advanced PD patients) (10).

For advanced PD patients, early implementation of palliative care (e.g., hospice and nursing service, advanced care planning, like feeding in the case of swallowing deficits, airway management, and symptom focused therapy) and end-of-life planning may be the key to adequate treatment and sustainment of quality of life (14). Still, palliative care is offered rarely to these patients (15). Geriatric PD patients are seldomly admitted to a hospice and often die in a hospital because adequate palliative care settings are not provided at home (16). In geriatric patients with advanced PD, drug therapy is often limited by side effects and contraindications due comorbidity. Thus, sufficient symptomatic therapy provided by palliative care concepts can be crucial.

In contrast to the emerging acknowledgment and integration of palliative care in other medical fields, the implementation of palliative care remains uncommon in the treatment of advanced PD in Germany (17). Currently, there are no data available on palliative care implementation in advanced PD treatment and its effects on HRQOL in Germany. Miyasaki et al. report good relief of symptoms in a Canadian study using the Edmonton Symptom Assessment System for PD for palliative care interventions in advanced PD patients (14). Another study reports clinical palliative care interventions for patients with atypical parkinsonisms (18).

To specify the needs of geriatric PD patients in advanced stages of disease, we performed a clinical study investigating HRQOL, its influencing factors, and the extent of palliative care implementation in a local cohort. The aim of this study was to investigate the current status of palliative care implementation in the German health system and to evaluate HRQOL and its influencing factors in this particular group of patients, in order to frame and improve future interventions.

PATIENTS AND METHODS

We obtained approval from the local Ethics Committee of Hannover Medical School (No. 3123-2016), and patients or their caregivers gave written informed consent. 76 patients with idiopathic PD were recruited from (1) our movement disorder outpatient clinic, (2) our neurological wards, (3) local PD patient support groups, and (4) outpatient neurologists in the region of Hannover, Germany. PD patients who had been admitted *via* the emergency department to our neurological wards were not included in our study until successful treatment had led to a stable condition again. Inclusion criteria for geriatric advanced PD were defined as Hoehn and Yahr stage (H&Y) 3 or more (scored during the on period), 65 years of age or older, disease duration of at least 5 years, and loss of autonomy due to PD (19) because these patients are most likely suitable for palliative care interventions. Patients with atypical parkinsonism and those suffering from much more troublesome comorbidities were excluded from this study.

Participants were examined using MDS-UPDRS (assessment of PD symptoms in the clinical on), MoCA test [cognitive screening test, range from 0 to 30 points, 30–26 points were considered as normal cognitive function, 25–21 points as mild cognitive impairment, and below 21 points as suspicious for dementia (20, 21)], Barthel Index (general performance, activities of daily living), and PDQ-39 (HRQOL specifically constructed and validated for PD). To avoid anosognosia affecting HRQOL measurement, we included demented PD patients only after involvement of the corresponding caregivers who were able to exclude anosognosia as relevant confounder. Furthermore, a structured interview was performed to define the need for and evaluate the frequency of palliative care in these patients. In detail, we evaluated patients' current accommodation and care, such as living at their own home either with or without help by professional caregivers or residing in a nursing home or in a hospice. Participants were asked if they had an advance directive including specific restrictions of therapy and whether they had determined a health-care proxy or someone granted general power of attorney. Patients were interviewed on current implementation of palliative care, such as an outpatient palliative care or hospice service. They also stated if palliative care matters had been addressed by their physicians in the past and whether they had discussed palliative care matters within their family. Finally, they were asked if and with whom—their doctors, family, and friends or others—they wished to discuss palliative care matters and where they would wish to die. Deep brain stimulation, duodopa treatment, and subcutaneous apomorphine therapy as well as oral PD medication was noted for each patient and the equivalence dosage of levodopa was calculated according to Tomlinson et al. (22). A full medical history of all participants was taken, if available, comorbidities and medication were noted from the most updated physician's letter.

Statistical analysis was performed using Graphpad Prism 5.00 (San Diego, CA, USA). Data were analyzed by calculating mean, SD, and range. Comparison between two groups was performed by unpaired Student's *t*-test. Comparison between more than two groups was performed by one-way ANOVA and Newman–Keuls post-test. Correlations were calculated by linear regression analysis ($r^2 = 1 - SS_{reg}/SS_{tot}$, where SS_{reg} is the variance (sum of squares) of the data of the linear regression model and SS_{tot} is the total variance of the Y values) and using the sample Pearson correlation coefficient. A p-value lower than 0.05 was considered as significant.

RESULTS

Quality of Life in Patients with Advanced Parkinson's Disease

In our study, we included 76 patients with advanced PD, 53.9% were female. Our patients presented with a mean H&Y of 4.0 (SD

0.7; range 3–5), and the mean age was 76 years (SD 6.1; range 65–89 years). Mean disease duration was 17.3 years (SD 7.3; range 5–38 years). Participants suffered from severe restrictions in the activities of daily living measured by the Barthel Index (mean 61.8 points; SD 25.4; range 10–100) and by the MDS-UPDRS part II (mean 31.4; SD 8.1; range 16–48).

68 out of 76 PD patients (89.5%) presented with cognitive deficits estimated by a MoCA test score below 26 points and a mean score of 18.4 points (SD 7.8; range 0–30). 50.0% of patients scored below 21 points in the MoCA test which is considered to be highly suggestive for dementia (20, 21). Before study participation, some of our patients (22.4%) had already been diagnosed with dementia according to the S3 guideline for dementia of the German Society of Neurology based on (23). To our surprise, antidementive drugs had been prescribed to only two patients (2.6%). Psychiatric symptoms, measured by the MDS-UPDRS part I item 1.1 "hallucinations and psychosis" (score equal to 2 or more), were reported by 34 patients (44.7%). Almost the same proportion of patients (38.2%) was prescribed neuroleptic drugs (e.g., clozapine or quetiapine).

Depressive mood was present in 52.6% of our patients (40/76) measured by the MDS-UPDRS part I item 1.3 "depressed mood" (score equal to 2 or more). However, a diagnosis of depression in the patients' previous medical documents had been established in only 10.5%, whereas antidepressive medication was prescribed to 15.8% of patients. More extensive and time consuming additional assessments of specific depression and anxiety symptoms could not be performed in this study due to the limited general condition of the patients.

Our patients presented with severe motor impairment determined by the MDS-UPDRS III (60.8 points; SD 16; range 24–96) in the clinical examination. In the MDS-UPDRS part IV, 64.5% of patients reported dyskinesias and 48.7% complained about functional impairments due to dyskinesias. Off-phases were present in 75% of the patients with functional impairment of daily activities. Dystonia in the off-phase was reported by 26.3% of the patients.

The PDQ-39 scale HRQOL was drastically reduced (mean 50.8%; SD 12.4%; range 16.7–75%). Patient characteristics are summarized in **Table 1**.

We found highly significant correlations between HRQOL and the activities of daily living measured by the Barthel Index ($p < 0.0001$; $r = -0.6946$; $r^2 = 0.4825$; **Figure 1A**), the MDS-UPDRS part II ($p < 0.0001$; $r = 0.6586$; $r^2 = 0.4338$; **Figure 1B**), and motor impairment evaluated by MDS-UPDRS part III ($p < 0.0001$; $r = 0.4562$; $r^2 = 0.2081$; **Figure 1C**). MDS-UPDRS part I did not correlate in total score with HRQOL ($p = 0.12$; $r = 0.2049$; $r^2 = 0.0420$); however, the items "depressed mood" ($p < 0.0001$; $r = 0.4862$; $r^2 = 0.2364$; **Figure 1E**), "hallucinations and psychosis" ($p = 0.0018$; $r = 0.4841$; $r^2 = 0.2344$; **Figure 1F**), and "anxious mood" ($p = 0.0431$; $r = 0.2689$; $r^2 = 0.0723$; **Figure 1G**) correlated significantly with the PDQ-39. HRQOL correlated significantly with cognitive deficits measured by MoCA test ($p = 0.0002$; $r = -0.4136$; $r^2 = 0.1711$; **Figure 1D**) and the item "cognitive impairment" of MDS-UPDRS part I ($p < 0.0001$; $r = -0.5833$; $r^2 = 0.3402$).

We also correlated the Barthel Index and MoCA scale with the MDS-UPDRS scores to check for co-correlations. Scores from the Barthel Index correlated significantly with MDS-UPDRS part I ($p < 0.0001$; $r = 0.5177$; $r^2 = 0.2680$), part II ($p < 0.0001$; $r = 0.7601$; $r = 0.5778$) and part III ($p < 0.0001$; $r = 0.6920$; $r^2 = 0.4789$), interestingly, they did not correlate with motor complications in the MDS-UPDRS part IV ($p = 0.9910$; $r = 0.0013$; $r^2 < 0.0001$). Concerning the MoCA score of the patients we found significant correlations with the MDS UPDRS part I ($p < 0.0001$; $r = -0.4843$; $r^2 = 0.2345$), part II ($p < 0.0001$; $r = -0.5160$; $r^2 = 0.2663$) and

TABLE 1 | Patient characteristics ($n = 76$).

	Mean	SD	Min	Max
Age	75.5	6.1	65	89
Sex			Male 46.1%	Female 53.9%
Barthel Index	61.8	25.4	10	100
H&Y	4.0	0.7	3	5
Disease duration in years	17.3	7.3	5	38
MDS-UPDRS I	20.5	6.3	9	37
MDS-UPDRS I "cognitive impairment"	1.5	1.3	0	4
MDS-UPDRS I "depressed mood"	1.8	1.0	0	4
MDS-UPDRS I "hallucinations and psychosis"	1.3	1.4	0	4
MDS-UPDRS II	31.4	8.1	16	48
MDS-UPDRS III	60.8	16	24	96
MDS-UPDRS IV	8.5	5.1	0	17
MDS-UPDRS IV dyskinesia duration	1.1 (25–50% of the day)	1.1	0	4
MDS-UPDRS IV dyskinesia functional impairment	1.1	1.4	0	4
MDS-UPDRS IV off-phase duration	1.2 (25–50% of the day)	1.9	0	4
MDS-UPDRS IV functional impairment of off-phases	2.3	1.6	0	4
MDS-UPDRS IV off-dystonia	0.6	1.2	0	4
MoCA	18.4	7.8	0	30
PDQ-39 (%)	50.8	12.4	16.7	75
LED (mg)	1,103	541	275	2,552

H&Y, Hoehn and Yahr stage; MDS-UPDRS, Movement Disorders Society Unified Parkinson's Disease Rating Scale part I-IV; MoCA, Montreal Cognitive Assessment test; PDQ-39, Parkinson's Disease Quality of life form 39; LED, calculated L-DOPA equivalence dosage.

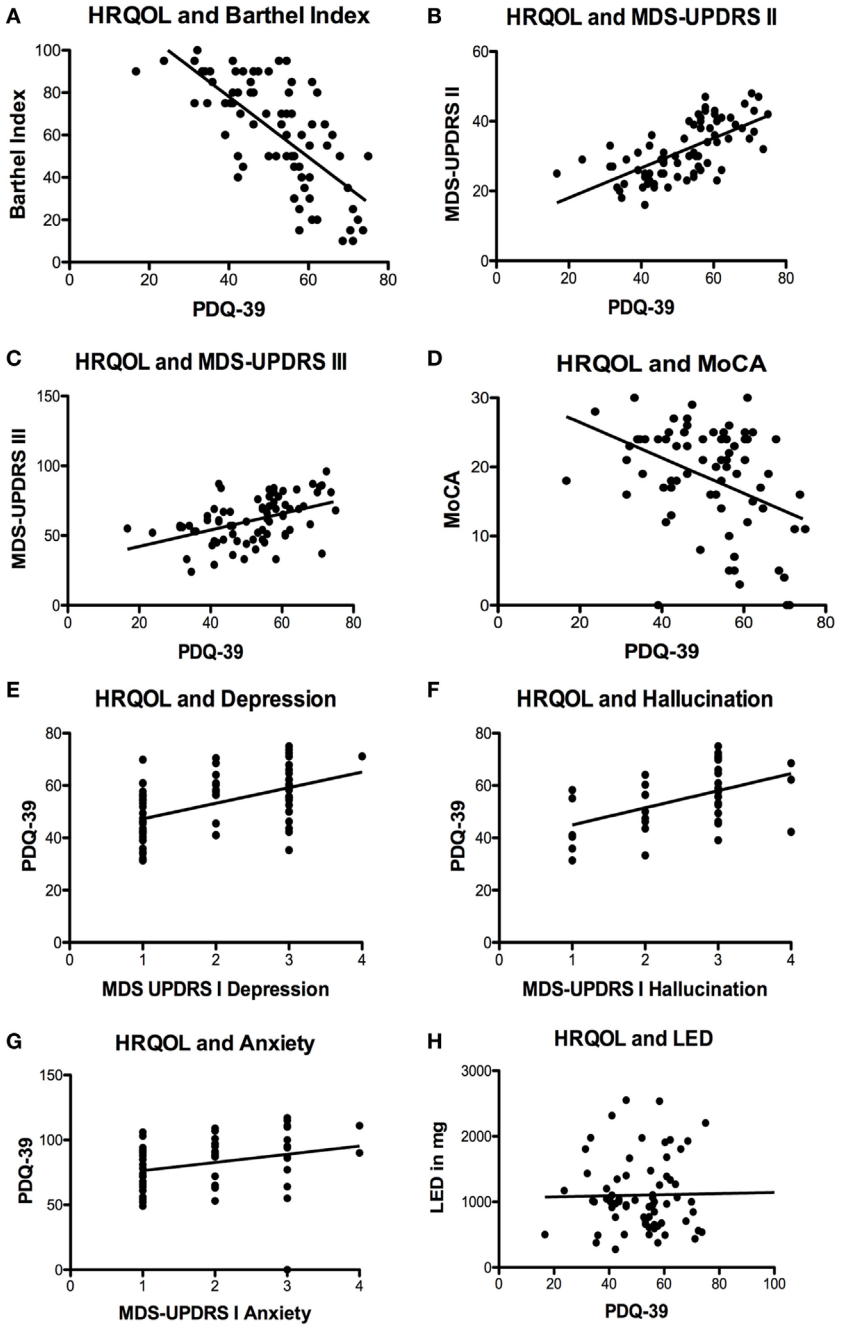

FIGURE 1 | Significant correlations of health-related quality of life (HRQOL) with different scales und symptoms. **(A)** Negative correlation of HRQOL and Barthel Index ($p < 0.0001$; $r = -0.6946$; $r^2 = 0.4825$). **(B)** Correlation of HRQOL with Movement Disorders Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part II ($p < 0.0001$; $r = 0.6586$; $r^2 = 0.4338$) and **(C)** MDS-UPDRS part III ($p < 0.0001$; $r = 0.4562$; $r^2 = 0.2081$). **(D)** Negative correlation of HRQOL and Montreal Cognitive Assessment test (MoCA) ($p = 0.0002$; $r = -0.4136$; $r^2 = 0.1711$). **(E)** Correlations of HRQOL with MDS-UPDRS part I item "depressed mood" ($p < 0.0001$; $r = 0.4862$; $r^2 = 0.2364$) and **(F)** MDS-UPDRS part I item hallucinations and psychosis ($p = 0.0018$; $r = 0.4841$; $r^2 = 0.2344$) and **(G)** MDS-UPDRS item "anxious mood" ($p = 0.0431$; $r = 0.2689$; $r^2 = 0.0723$). **(H)** Non-significant correlation of HRQOL and levodopa equivalence dosage (LED) ($p = 0.5035$; $r = 0.0825$; $r^2 = 0.0068$).

III ($p < 0.0001$; $r = -0.7163$; $r^2 = 0.5131$) but not with part IV ($p = 0.2849$; $r = -0.1241$; $r^2 = 0.0154$). Additionally, we found a significant correlation of MoCA scores and the MDS-UPDRS part I items "anxious mood" ($p = 0.0063$; $r = -0.3108$; $r^2 = 0.0966$) and "hallucinations and psychosis" ($p = 0.0011$; $r = -0.3667$; $r^2 = 0.1345$).

Regarding motor complications measured by the MDS-UPDRS part IV and their impact on HRQOL, we found no

correlation of dyskinesias and HRQOL (MDS-UPDRS IV item 1, $p = 0.9342$; $r = 0.0096$; $r^2 < 0.0001$ and 2, $p = 0.3794$; $r = 0.1029$; $r^2 = 0.0106$). The frequency of off-time correlated significantly with HRQOL ($p = 0.0339$; $r = 0.2454$; $r^2 = 0.0602$); however, the functional impairment of off-time (item 4, $p = 0.1267$; $r = 0.1779$; $r^2 = 0.0316$) and the complexity of off-phases (MDS-UPDRS IV item 5, $p = 0.1480$; $r = 0.1686$; $r^2 = 0.0284$) did not correlate with HRQOL. Off-dystonia correlated significantly with HRQOL ($p = 0.0490$; $r = 0.2280$; $r^2 = 0.0520$).

Treatment regimens markedly differed between individual patients. The number of prescribed PD drugs ranged from one to six groups of medication [levodopa + decarboxylase inhibitor; dopamine agonist; MAO_B inhibitor (14.5%); safinamide (8.7%); amantadine (17.6%); COMT inhibitor (40.1%)]. The vast majority received levodopa therapy (98.5%). More than one-third was treated with additional dopamine agonists (41.2%). Interestingly, the calculated equivalence dosage of levodopa did not correlate with HRQOL at all ($p = 0.5035$; $r = 0.0825$; $r^2 = 0.0068$; **Figure 1H**). We included 14 patients with DBS (18.4%), 9 patients with duodopa intrajejunal therapy (11.8%) and 3 patients with apomorphine subcutaneous pump (3.9%). No significant differences in HRQOL and motor impairment were found in patients with DBS or duodopa therapy compared to each other and to the cohort with oral medication only ($p > 0.05$, one-way ANOVA and Newman–Keuls post-test). Due to the low number of patients, we did not calculate any data for the apomorphine group.

In the medical documents of our PD patients, we screened for systemic diseases. Note, we excluded patients predominantly suffering from another severe disease than PD. We found 30.3% of patients to be diagnosed with arterial hypertension. Cardiovascular disease, excluding arterial hypertension, was present in 27.6% of the cohort. Diabetes type 1 or 2 was diagnosed in 7.9%; other endocrine diseases, such as hypothyreosis, were present in 13.2% of the patients.

Palliative Care in Advanced Parkinson's Disease

Approximately half of our patients managed to schedule regular appointments with an outpatient neurologist. Most neurological consultations of the other patients had to be done *via* the emergency department.

We found 70% of our patients to have an advance directive and a health-care proxy. However, hardly any patient was provided with additional palliative care at their home or had ever consulted their treating physicians on palliative care matters (**Table 2**). Overall, we found palliative care to be provided to only 2 out of 76 severely diseased PD patients (2.6%). 72% of the patients expressed an unmet need for information concerning palliative care, especially about advance care planning concerning end-of-life care (EoLC). In more than 40% of the patients, there had been no discussion about EoLC in the family. Almost half of the patients preferred to consult with their general physician or outpatient neurologist about palliative care matters (**Figure 2**). The majority of patients wishes to die at home. However, it remains challenging to simultaneously receive professional palliative and neurological care guaranteeing fair symptom control in order to honor this wish in dignity (**Figure 2**).

DISCUSSION

By applying the following inclusion criteria, we defined a palliative care intervention phase of advanced PD according to Saleem et al. (15): H&Y 3 or more, 65 years of age or older, disease duration of at least 5 years, and loss of autonomy due to PD. Patients' parameters such as treatment plans and equivalence dosage of levodopa were in line with earlier reports of long-term surviving PD cohorts from Australia (24) and the US (13). However, patients recruited in our study were older (75.5 years) compared to the Sidney cohort (71 years) (24) and the US cohort (69.5 years) (13). Our patients presented with a higher mean H&Y and a mean disease duration of 17 years, which was 2 years longer than in the study of Hely et al. from 2005 (24). We specifically aimed to measure a geriatric population and, thus, set the inclusion criteria for age at 65 years or older to recruit a more homogeneous group as PD patients seem to reach the palliative care intervention phase of PD in the age of 65 and older (25).

Cognitive deficits were prominent in all comparable cohorts and were impacting HRQOL, nevertheless the prevalence of cognitive deficits and dementia measured by the MoCA Test was dramatically increased in our group of patients compared to the other cohorts. Hely et al. (24) found 48% of the long time PD patients to be demented, measured by the Mini-Mental State Test, whereas Hassan et al. (13) reported a mean MoCA score of 22.6 in their cohort. In our cohort, the MoCA score was markedly lower with a mean value of 18.4 points. We measured HRQOL with the well-established and validated PDQ-39 form (26). In all comparable cohorts, quality of life is decreased significantly and the reduction is related to the duration of disease (2, 13, 24, 27). Hassan et al. (13) described

TABLE 2 | Palliative care implementation in geriatric advanced Parkinson's disease patients ($n = 76$).

	Yes (%)	No (%)
Advance directive	69.7	30.3
Health-care proxy	68.4	31.6
Actual palliative care	2.6	97.4
Need of information concerning palliative care	72	28
Discussion about end-of-life care in the family	57.9	42.1

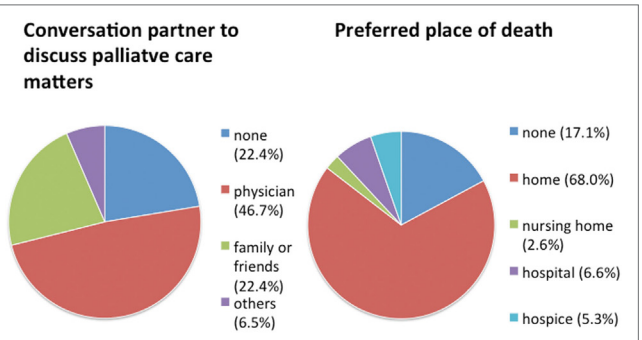

FIGURE 2 | Patients' wishes in regard to palliative care concerning communication partner and place of death. $N = 76$ Parkinson's disease patients.

a decrease of 35.8% in quality of life measured in the PDQ-39, which was less prominent than in our cohort (50.8% and SD 12.4%). Considering the higher mean age, comparably long disease duration and extraordinary high prevalence of cognitive decline, it seems likely for our patients to have markedly decreased HRQOL. In our collective of advanced PD patients, we identified motor symptoms, cognitive decline, depression, hallucinations, anxiety, and impairment in the activities of daily living as main factors significantly correlating with decreased HRQOL. In accordance to other studies motor symptoms, cognitive deficits, depression, and psychiatric symptoms showed the strongest correlation with decreased HRQOL (2, 3, 6, 11, 12, 27). In regard to motor complications of advanced PD patients, the most dominant factor in our study appears to be the amount of off-time per day. We also found off-dystonia to negatively impact HRQOL. Interestingly, dyskinesias did not show a significant correlation with HRQOL in our study. It seems that dyskinesias did not or only mildly impact HRQOL in advanced PD (28–30). Therefore, treatment of motor complications should specially aim to reduce off-time of PD patients in advanced stages.

Former studies in advanced PD did not investigate possible benefits of invasive therapies such as DBS or duodopa pump therapy in a palliative setting, which is why we compared HRQOL in patients receiving DBS or duodopa to patients treated with oral medication only. Despite a previously reported positive effect on quality of life of DBS (31) and duodopa treatment (32) for individual patients, we were not able to show a higher HRQOL in our small DBS and duodopa groups compared to patients receiving oral PD medication only.

By considering comorbidities of advanced PD patients, we found cardiovascular disease and hypertension to be the most frequent systemic diseases in their medical history. Generally, PD patients suffer less often from cardiovascular disease and hypertension (33). PD patients may have a special cardiovascular profile of comorbidities compared to the general population possibly caused by peripheral autonomic disturbances. In the context of palliative care, it is important to notice that the cause of death in PD patients is pneumonia to a huge proportion (34), whereas the frequency of cardiovascular and cerebrovascular causes of death is reduced to values of control populations (33, 35, 36). Therefore, we would expect only a limited effect of cardiovascular disease and hypertension on the HRQOL of our PD cohort.

As shown in our data and by others, HRQOL is dramatically decreased in the palliative intervention phase of PD (13, 24). Palliative care may help to sustain or even improve quality of life in these patients by targeting specific symptoms, especially those determining poor HRQOL (14, 17). Only 2 of our 76 patients received palliative care at all, which is in line with observations of Saleem et al. (15) who also found rare implementation of palliative care in advanced PD patients in the UK. Reason for that might be a lack of awareness of clinical criteria when and how to initiate palliative care in PD (19, 37). In our study, a high number of patients reported the wish to die at home, which is in accordance with previous publications (16, 38). However, neurologists and general physicians may not be fully aware of the increased mortality of PD patients and consequently fail to duly address advance care planning during their consultations (39). It is necessary to encourage patients and their caregivers to discuss EoLC and note life-sustaining treatment orders for

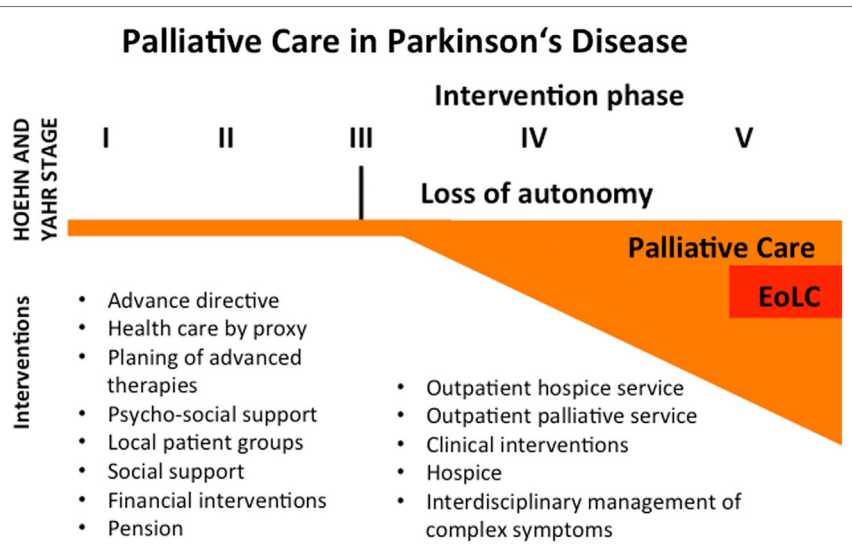

FIGURE 3 | Concept for palliative care in Parkinson's disease (PD). PD is not curable these days, so therapy is symptomatic. Despite a limited palliative aspect in the beginning of the disease course, patients should be encouraged to write an advance directive or health care by proxy. Informed consent should be guaranteed concerning potential invasive therapies in the future. Local patient groups can help to stabilize the patient in many ways. Physicians should focus on the need for psycho-social and financial support and matters of pension. If patients reach Hoehn and Yahr stage 3 or more, they often lose their autonomy and become dependent on others help. In this phase, palliative care interventions should be initiated. These interventions may be the implementation of outpatient services, an interdisciplinary management of complex symptoms, clinical interventions (e.g., i.v. antibiotics for infections, feeding tubes, airway management, palliative sedation), and discharge to a hospice. Even in the palliative intervention phase, the end-of-life care (EoLC) represents only a small proportion of palliative therapies.

better care planning according to their individual wishes (40, 41). In regard to the high prevalence of cognitive decline in our cohort, an early advance care planning is of fundamental importance. Additionally, health care by proxy should be discussed in early course of the disease. In later disease stages, decision-making related to goal of care could be compromised by cognitive impairments (42). For excellent reports of advance directives in patients with dementia in the context of ethical and law issues, see Ref. (43, 44). Clearly, defined clinical criteria indicating a time point for palliative care implementation might help to improve future treatment for advanced PD patients. Richfield et al. have defined possible mile stones for initiation of EoLC such as swallowing problems, recurrent infections, marked decline in physical function, first aspiration pneumonia, cognitive difficulties, weight loss, and significant complex symptoms (37, 45). With occurrence of these symptoms, palliative care interventions are helpful and initiation of EoLC should be evaluated.

Especially in Germany, we are just at the beginning of properly providing palliative care for neurological patients in general. To serve that purpose, it seems constructive to form interdisciplinary teams (e.g., neurologist, palliative care specialist, PD nurse, and social worker) following the model of Miyasaki et al. in Canada (14). Thereby, the awareness of neurologists concerning palliative care in advanced PD could be improved. Considering our data and recent literature (15, 16), we suggest the following model for palliative care in PD (**Figure 3**).

Possible limitations of our study are the monocentric approach with a moderately high number of patients ($n = 76$) as well as the restrictive inclusion criteria defining a severely burdened subgroup of PD patients. Due to the evaluation of numerous patient characteristics and extensive neurological examination, it did not seem feasible to apply additional and more specific questionnaires for depression and anxiety. However, for a general and fast assessment of anxiety and depression, the items of the MDS-UPDRS part I can be used in clinical practice (46). We plan the detailed investigation of this issue in a future study explicitly focusing on depression and anxiety symptoms based on our recent results.

In our study, we found that palliative care is not yet a fixed component of PD treatment which is in line with general observations in German PD patients, although implementation of palliative care in advanced PD can be crucial and is often called for. This characterization of severely diseased PD patients contributes novel clinical data and forms the basis for further trials aiming to improve palliative care implementation in advanced PD patients in order to establish optimal symptom control, sustain quality of life, reduce caregiver burden, and prevent caregiver burnout (10). Our data emphasize the urgent need of palliative care in geriatric advanced PD patients.

ETHICS STATEMENT

We obtained approval from the local Ethics Committee of Hannover Medical School (No. 3123-2016), and patients or their caregivers gave written informed consent.

AUTHOR CONTRIBUTIONS

MK and FW planed the study. AT, MK, LM, LP, and DD recruited the patients. MK, AT, LP, and FW analyzed the data. MK, AT, LM, LP, CS, DD, and FW wrote and corrected the manuscript.

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Alleviation of Psychological Distress and the Improvement of Quality of Life in Patients With Amyotrophic Lateral Sclerosis: Adaptation of a Short-Term Psychotherapeutic Intervention

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Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease that is inevitably fatal. To be diagnosed with a terminal illness such as ALS deeply affects one's personal existence and goes along with significant changes regarding the physical, emotional, and social domains of the patients' life. ALS patients have to face a rapidly debilitating physical decline which restrains mobility and impairs all activities of daily living. This progressive loss of autonomy may lead to a sense of hopelessness and loss of quality of life, which in turn may even result in thoughts about physician-assisted suicide. Here, we would like to propose a psychotherapeutic manualized, individual, semi-structured intervention to relieve distress and promote psychological well-being in ALS patients. This short-term intervention was originally developed for advanced cancer patients. "Managing Cancer and Living Meaningfully (CALM)" focuses on the four dimensions: (i) symptom management and communication with healthcare providers, (ii) changes in self and relations with close others, (iii) spirituality, sense of meaning and purpose and (iv) thinking of the future, hope, and mortality. We suggest to supplement the concept by two additional dimensions which take into account specific issues of ALS patients: (v) communication skills, and (vi) emotional expression and control. This therapeutic concept named "*M*anag*I*ng *B*urden in *A*LS and *L*iving *M*eaningfully (mi-BALM)" may be a further treatment option to help improving quality of life of ALS patients.

Keywords: amyotrophic lateral sclerosis, psychotherapeutic intervention, calm, quality of life, distress

AMYOTROPHIC LATERAL SCLEROSIS (ALS)

Amyotrophic lateral sclerosis represents a rapidly progressing neurodegenerative disease and is characterized by a degeneration of motor neurons (1). ALS affects the upper motor neurons projecting from the cortex to the brainstem and the spinal cord as well as the lower motor neurons projecting from the brainstem or spinal cord to the muscles (1). The initial presentation of ALS varies considerably between patients: while some patients first experience muscle weakness in the

limbs, referred to as spinal onset, others initially suffer from dysarthria and dysphagia, characterized as bulbar onset. Bulbar onset appears in about one-third of patients with ALS and is often associated with emotional lability, which may arise from disconnection of brainstem structures from cortical inhibition (2, 3). Limb-onset weakness accounts for 60% of cases, presents usually asymmetrically and may first develop in either the upper or lower limbs. Apart from weakness, additional symptoms may include spasticity as a sign for upper motor neuron loss, and fasciculations, cramps and muscle atrophy as signs for lower motor neuron loss. Death usually results from respiratory failure which is caused by the loss of nerve supply of the respiratory muscles (3). The average life expectancy of patients with ALS is 2–3 years from the onset of symptoms, while a minority (4%) survive for 10 years or even longer (4, 5). The incidence of ALS is about two cases per 100,000 individuals and the age of onset peaks at 70–74 years (6).

In most cases, ALS appears to develop sporadically, although some patients have a familial disease which is associated with mutations in genes that have a wide range of functions (3). The primary symptoms of ALS are associated with motor dysfunction, such as muscle weakness or dysphagia, but more than 40% of ALS patients additionally develop cognitive or behavioral symptoms in advanced stage of the disease and about 14% of patients present with accompanying frontotemporal dementia (7).

MENTAL BURDEN AND CHALLENGES IN THE PROGRESSION OF THE DISEASE

To be diagnosed with a life-threatening illness, such as ALS, deeply affects one's personal existence and involves a variety of changes in the physical, emotional, and mental-cognitive aspects of a patients' life. At first, ALS patients realize the debilitating physical symptoms due to muscle weakness impairing mobility and autonomy in all activities of daily living (8). A characteristic of ALS is the impairment to communicate verbally due to dysarthria, which means a motor disorder of speech characterized by abnormalities of the articulation and reduced intelligibility of speech. Dysarthria appears in 25–30% of ALS patients as a first or predominant sign in early stage (9) and the potential loss of speech has been rated as one of the three worst aspects of the disease by ALS patients (10). Furthermore, patients suffer from numerous symptoms, including pain, spasticity, difficulty in swallowing, weight loss, and respiratory insufficiency that require intensive treatment by a multidisciplinary care team (11). Among the wide range of symptoms, pain seems to be particularly frequent and to play a major role in affecting the quality of life in ALS patients (12, 13). Moreover, progressive muscle weakness leads to dependence on others like familial caregivers and/or a multiprofessional care team because of immobility (8). Patients have to face mental-cognitive challenges, to adapt to the new life situation and to decide about permanent and invasive medical measures including gastrostomy tube placement and assisted ventilation during disease progress (14). With the respect to the progredient loss of the ability to speak, patients and their related persons have to find new ways of communication, such as computer-based communication devices, such as eye-tracking systems (15). Progressive loss of autonomy and control may lead to severe emotional reactions, including of help- and hopelessness and a complete loss of motivation (16). Regarding potential risk factors for emotional impairments caused by the disease, hopelessness in ALS patients is predicted by the belief that life is determined by forces beyond his or her own control (external locus of control) and a lack of meaning of life, but not by socioeconomic or demographic factors, length or severity of illness, social support satisfaction or spiritual belief (17). Just as hopelessness, depressive symptoms are not related to time since diagnosis, the degree of disability or the progression of the illness (18), but slightly increase with speed of disease progression (19). Depression scores vary considerably between studies and range from 35 to 57% (20–24). Compared to other somatic patient groups including patients with cancer or heart failure, ALS patients most frequently ask for physician-assisted suicide (25, 26). Emotion in ALS patients may be difficult to recognize because emotional expression is frequently altered by the disease. Up to 49% of ALS patients show uncontrollable outbursts of laughter or crying without any appropriate environmental trigger and may be either more pronounced or even incongruent with the underlying emotional state (27, 28). This emotional expression disorder is named "pseudobulbar affect" and poses a problem in correct recognition and interpretation of emotional signs, not only for related persons, but also in therapeutic settings (29).

Taken together, previous research indicates a broad spectrum of physical, emotional, and mental-cognitive challenges for ALS patients (**Table 1**), which all have to be addressed by a multimodal (psycho-)therapy.

FUNDAMENTALS OF PSYCHOLOGICAL INTERVENTIONS IN PALLIATIVE CARE

The high prevalence of mental burden like anxiety and depression, including hopelessness, despair, and demoralization in palliative patients demonstrate the need for effective psychological interventions integrated in palliative care concepts (30). Psychological

TABLE 1 | Specific aspects of amyotrophic lateral sclerosis (ALS) for (psycho-) therapeutic settings.

Specific aspects of ALS for (psycho-)therapeutic settings	
Physical symptoms	– Muscle weakness – Dysarthria
Emotional symptoms/ alterations	– Depression – Hopelessness – Feelings of helplessness – Pseudobulbar affect
Mental-cognitive challenges	– Confrontation with a fatal disease and own end of life – Adaptation to and acceptance of the new life situation – Computer-based means of communication – Decisions about permanent medical measures, including percutaneous endoscopic gastrostomy tube placement and assisted ventilation during disease progress

interventions can address a wide spectrum of objectives in palliative care and together aim to reduce psychosocial distress and maintain quality of life in patients and their caregivers (31). These interventions intend to help the patient and family in coping with the fear of death and dying, managing anxiety, and reducing feelings of isolation, sadness, despair, and depression (32). Other psychological approaches address problems associated with changes of social roles and relationships, increasing dependence on others, the need to adjust to impaired functional status, and existential concerns, such as the search for meaning in life, hope, sense of dignity, grief, and spirituality (32). Clinical psychotherapeutic care for patients with progressing diseases comprises a variety of interventions and techniques, all of which have to be integrated into a multidisciplinary care plan. These include cognitive behavioral therapy, psychodynamic therapy, narrative interventions, relaxation and guided imagery, mindfulness-based interventions, meaning-focused interventions, art therapy, and dignity therapy (33).

Psychotherapeutic Topics and Psychological Needs in Palliative Settings

The "psychotherapeutic work and goals in palliative care settings generally differ in several aspects from psychological interventions for patients with early or curative diseases or physically healthy individuals" (32).

In palliative settings, psychotherapeutic support starts with the diagnosis of the incurable disease. After communication of the diagnosis, patients often need time for reflection and room in which they can express their emotions. Because the delivery and communication of the diagnosis and its consequences is a crucial and emotionally relevant moment for the patient and his/her relatives, a psychologist in the medical team provides the patients with an additional opportunity to express their feelings and fears (34).

Furthermore, the time frame for psychotherapeutic interventions may be limited, especially in the case of ALS patients. Usually, "patients can be see" by the psychotherapist "only a few times, depending on their physical condition, the course of the disease," and the setting (inpatient vs. outpatient). "The limited time has several implications for the development of a trustful and sustainable therapeutic relationship and psychotherapeutic treatment planning" (32). Treatment planning often depends on the stage and course of the disease and always has to be flexible enough to take into account spontaneous changes in the supportive care needs of patients or their caregivers. These and rapid changes in the course of the disease may place high demands on the clinical psychologist with regards to flexibility, empathy, and understanding of the patient's situation (32).

"Treatment planning for patients with serious illnesses must also consider that communication with the patient and caregiver can be hampered by severe health conditions" (32). In ALS patients, poor articulation or even the inability to speak, and, in some cases, cognitive impairment and behavioral changes may significantly affect communication (35).

In addition, communication with the patient and caregiver can be compromised by unclear or divergent perceptions and prognostic awareness about the goals of treatment and the curability of the disease. Prognostic awareness contains multifactorial components, such as awareness of (i) the terminal nature of one's illness, (ii) the purpose of treatment, or (iii) a shortened life expectancy (36). Palliative care patients show a wide range of prognostic awareness, reaching from 0 to 75% (37).

There are multiple reasons why patients report limited or inaccurate prognostic awareness including the lack of information given by physicians, such as incomplete understanding of the information, intentional or unintentional denial to accept the prognosis, and the phenomenon of "double awareness": mixed states of awareness, hope for cure or hope for longer survival, despair or (partly) denial (36, 37).

Having this phenomenon of *double awareness* in mind, "the clinical psychologist is often faced with the difficult task of encouraging patients and caregivers to cope adaptively while promoting acceptance" (32). "Support for coping may focus on maintaining hope and quality of life, and reducing psychological stress. Acceptance may require that patients and caregivers face realistic treatment goals and treatment decisions, which themselves may negatively affect the psychosocial well-being of the patient and the family" caregivers. "The psychologist must be prepared to manage the emotional responses of the patient and the caregiver" and, finally, "clinical psychologists working in palliative care settings must be prepared to deal with" their own emotional reactions caused "by the closeness to death and dying," helplessness, and existential or spiritual questions about the meaning of life and death (32).

INTRODUCTION OF THE PSYCHOTHERAPEUTIC SHORT-TERM INTERVENTION BASED ON CALM IN ALS PATIENTS

A psychotherapeutic short-term intervention has to face the above-mentioned characteristics in treatment of patients with advanced disease. Although psychological interventions are effective in reducing depression and anxiety and improving quality of life, the majority of randomized-controlled trials in physically ill patients are conducted in early stage cancer populations. Thus, data on psychological interventions in palliative care populations including life-threatening diseases other than cancer is scarce. Previous psychological studies in ALS patients have been mostly descriptive (38–40) and a cognitive behavioral therapy study failed because of slow recruitment and low demand for joint patient-caregiver therapy sessions (41).

"Managing Cancer and Living Meaningfully (CALM)" is a manualized, semi-structured, individual psycho-oncological short-term treatment to relieve distress and promote psychological well-being, which has been established by Rodin and colleagues (42, 43). It aims to reduce depression and fears about death and dying, to strengthen communication with the medical treatment team, and to improve the patients' hope and meaning of life. It was developed based on empirical data, clinical observations, and leads back to different theoretical traditions, including relational theory (44), binding theory (45), and existential theory (46). Depending on the individual needs of the patient, CALM is

built up by 3–8 sessions (duration about 45–60 min) over a period of 6 months. The sessions address four dimensions:

1. Symptom management and communication with healthcare providers
2. Changes in self and relations with each others
3. Spirituality, sense of meaning, and purpose
4. Thinking of the future, hope, and mortality

All dimensions are explored with every patient, but the order and extent of each dimension are adapted to the individual needs of the patient.

For ALS patients, we consider it necessary to supplement the concept by two further dimensions based on the specific symptoms and challenges (**Figure 1**):

5. Communication skills
6. Emotional expression and control

Each participant's primary caregiver (e.g., partner, adult son, or daughter) is offered the opportunity to participate in one or more of the therapy sessions, as deemed appropriate by the therapist and with the patient's permission (43). During the course of treatment, different psychotherapeutic principles build the fundament of the therapy (47). One major aspect concerns the authenticity of the therapist and the development of a supportive relationship between therapist and patient. The capacity for mentalization/self reflection of the patient is supported by entertaining the possibility of multiple and complex psychological responses by the therapist to the expression of the patient. This strategy allows the patients to keep hope and accept the reality of their disease in parallel, so that they are able to plan future care and focus on new tasks. Crises due to disease progress and increased burden of symptoms may call for spontaneous changes of therapeutic aims. Therefore, content and timing of the psychotherapeutic sessions have to be adapted to the medical condition of the patient (48).

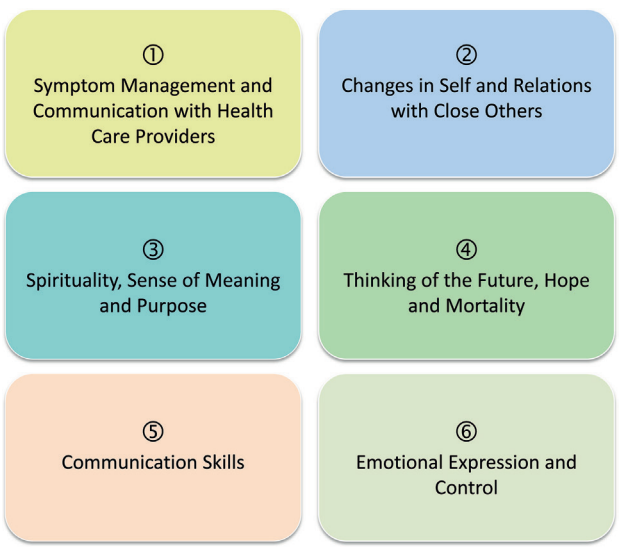

FIGURE 1 | Dimensions of short-term psychotherapy ManagIng Burden in amyotrophic lateral sclerosis (ALS) and Living Meaningfully. Dimensions (1–4) of the short-term psychotherapy managing cancer and living meaningfully with the addition of the dimensions "Communication skills" (5) and "Emotional expression and control" (6) based on the specific symptoms and challenges of ALS patients.

The therapist focuses on the emotional attachment of the patient. In detail, the changes in relationships to others as well as the resulting fears and sadness are explored. A dysbalance of relations is mostly seen in advanced stages of the disease, which results from high levels of dependence and the loss of autonomy (48).

During CALM therapy, the psychotherapist and the patient explore the meanings of the patient's life history, including achievements and failures, as well as the disease itself. Thereby, the whole life trajectory of the patient, his/her aims, experience of suffering, and death/dying play important roles in the therapy. In the therapeutic contact, the therapist can explore how the patient makes sense of his or her situation and may help to facilitate meaning making as an adaptive way to cope with a situation beyond one's control (48).

A pivotal element of the therapy is the willingness of the therapist to reflect his or her own philosophy and sense of meaning, and to face frightening topics such as mortality and suffering in order to encourage the patient to do the same. The therapeutic aim here is to allow the expression of sadness and fear regarding the progress of the disease and the confrontation with mortality, but to simultaneously support hope, courage, and engagement in the current moment (48). The therapist needs to be comfortable with the "non-expert" role and the "unsolvable" existential problems faced by patients with advanced disease.

For ALS patients, we identified the specific additional needs for training of communication skills, because many ALS patients develop a severe dysarthria and need to establish new forms of communication. We suggest a logopedic treatment included in the multimodal therapy of ALS patients to learn new communication strategies, e.g., with communication devices or eye-tracking systems.

In addition, we suggest a specific psychotherapeutic focus on emotional expression and control because of a significant number of ALS patients suffer from depression and/or pseudobulbar affect.

Feasibility and effectiveness of CALM to reduce emotional distress and promote psychological well-being and growth have been tested in qualitative studies and in a Phase 2 trial in patients with advanced cancer (42, 43, 48). In the qualitative studies, no patient-reported risks or concerns have been found (42). Rather, participants described five main benefits of the intervention, which are (i) "a safe place to process the experience of advanced cancer, (ii) permission to talk about death and dying, (iii) assistance in managing the illness and navigating the healthcare system, (iv) resolution of relational strain and (v) an opportunity" to be seen as a whole person "within the healthcare system" (42).

The qualitative results were also supported by quantitative findings: results of the phase 2 trial showed that depressive symptoms and death anxiety decreased significantly under CALM treatment and that spiritual well-being increased in the 3- and 6-month follow-up assessments (43).

Given empirical data on the effectiveness of CALM among cancer patients, this concept might also be useful in patients with other advanced diseases. This might be especially true for patients with ALS, who are, similar to advanced cancer patients, confronted with a mostly fast progressing disease, mortality, and finiteness of life.

Based on the above considerations, we posit that CALM might be an effective psychotherapeutic treatment in ALS patients with the addition of the dimensions "Communication skills" and "Emotional expression and control". To prove applicability and efficacy of this therapeutic concept "mi-BALM" (ManagIng Burden in ALS and Living Meaningfully) for ALS patients, we propose a trial on this semi-structured, individual psychotherapeutic short-term intervention in ALS patients. Demonstration of efficacy of mi-BALM in ALS would fulfill a strong need for improving the physical and psychological quality of life in this patient group and may be beneficially implemented in the interdisciplinary therapy of ALS patients. Having established this therapy, web- or telephone-based forms of this treatment could be developed in order to ensure dissemination of this therapy in patients with advanced stages of diseases or patients from rural areas.

AUTHOR CONTRIBUTIONS

MO, AM, and JC participated in the design of the perspective concept. MO, PE, JC, and AM participated in writing process. MO, PE, and AM participated in the creation of figures and tables. All authors have reviewed the manuscript.

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Associative Increases in Amyotrophic Lateral Sclerosis Survival Duration With Non-invasive Ventilation Initiation and Usage Protocols

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Objective: It is hypothesized earlier non-invasive (NIV) ventilation benefits Amyotrophic Lateral Sclerosis (ALS) patients. NIV typically consists of the removable bi-level positive airway pressure (Bi-PAP) for adjunctive respiratory support and/or the cough assist intervention for secretion clearance. Historical international standards and current USA insurance standards often delay NIV until percent predicted forced vital capacity (FVC %predict) is <50. We identify the optimal point for Bi-PAP initiation and the synergistic benefit of daily Bi-PAP and cough assist on associative increases in survival duration.

Methods: Study population consisted of a retrospective ALS cohort (Emory University, Atlanta, GA, USA). Primary analysis included 474 patients (403 Bi-PAP users, 71 non-users). Survival duration (time elapsed from baseline onset until death) is compared on the basis of Bi-PAP initiation threshold (FVC %predict); daily Bi-PAP usage protocol (hours/day); daily cough assist usage (users or non-users); ALS onset type; ALSFRS-R score; and time elapsed from baseline onset until Bi-PAP initiation, using Kruskal-Wallis one-way analysis of variance and Kaplan Meier.

Results: Bi-PAP users' median survival (21.03 months, IQR = 23.97, $N = 403$) is significantly longer ($p < 0.001$) than non-users (13.84 months, IQR = 11.97, $N = 71$). Survival consistently increases ($p < 0.01$) with FVC %predict Bi-PAP initiation threshold: <50% (20.3 months); ≥50% (23.60 months); ≥80% (25.36 months). Bi-PAP usage >8 hours/day (23.20 months) or any daily Bi-PAP usage with cough assist (25.73 months) significantly ($p < 0.001$) extends survival compared to Bi-PAP alone (15.0 months). Cough assist without Bi-PAP has insignificant impact (14.17 months) over no intervention (13.68 months). Except for bulbar onset Bi-PAP users, higher ALSFRS-R total scores at Bi-PAP initiation significantly correlate with higher initiation FVC %predict and longer survival duration. Time elapsed since ALS onset is not a good predictor of when NIV should be initiated.

Conclusions: The "optimized" NIV protocol (Bi-PAP initiation while FVC %predict ≥80, Bi-PAP usage >8 h/day, daily cough assist usage) has a 30. 8 month survival median, which is double that of a "standard" NIV protocol (initiation FVC %predict <50, usage >4 h/day, no cough assist). Earlier access to Bi-PAP and cough assist, prior to precipitous respiratory decline, is needed to maximize NIV synergy and associative survival benefit.

Keywords: non-invasive ventilation, palliative care, neuromuscular disease, respiratory intervention, survival duration

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder, characterized by loss of motor neurons (1–4) in the spinal cord and brain (5, 6). The median age of ALS onset is 50–60 years (7–10), and half of ALS patients die within 2–3 years of symptom onset (8, 9, 11). The two most common onset modes are limb onset, characterized by extremity weakness or paralysis, and bulbar onset, characterized by speech difficulty and facial weakness; only a small fraction of patients first present with impaired respiration (1, 11–13). Currently, there exists no cure for ALS (12); and the primary marketed ALS etiology-targeted treatment, Riluzole, only extends survival by 1–4 months (14, 15).

Regardless of onset type, patients eventually lose innervation to diaphragm and intercostal muscles, resulting in impaired respiration. In fact, respiratory complications secondary to progressive muscle atrophy are responsible for the majority of ALS patient deaths (11, 13). Assistive interventions, including non-invasive ventilation like bi-level positive airway pressure (Bi-PAP), are commonly prescribed to ALS patients (11, 13, 16–19). In contrast with invasive measures, non-invasive ventilation does not further inhibit swallowing in patients with mild to moderate dysphagia, where at least partial nutrition by mouth is deemed appropriate (20). Moreover, because Bi-PAP is removable, it interferes less with activities, enabling a higher quality of life without the increased risk of pneumonia, a common drawback of invasive ventilation (21). Nonetheless, the impact of Bi-PAP on ALS survival duration has not been examined in a large study population (16), nor is there broad consensus on Bi-PAP usage protocols.

The standard respiratory metrics of forced vital capacity (FVC) and namely percent predicted FVC (FVC %predict), which considers patient age, gender, and height, are the primary metrics used to assess respiratory function in ALS (1). In fact, a recent study found that over 92% of USA and international clinics still use FVC %predict as their primary metric to determine NIV initiation (22). The current USA standard of care dictates a FVC %predict of 50 (i.e., half of the expected FVC value) as the threshold below which Bi-PAP should be initiated in ALS patients (11); this is largely due to USA medical insurances, including Medicare, which require a FVC %predict <50 in order to cover [or pay] for NIV (22). In contrast, internationally, the NIV initiation threshold is highly variable. Many clinics in Europe and Asia begin NIV much earlier, as shown in a recent study examining differences in international standards of care for ALS NIV (22), but over 20% of international clinics actually begin NIV later, well after functional symptoms commence (23). Irrespective, it has long been hypothesized that starting NIV earlier than the <50 FVC %predict threshold could be associated with additional benefits (24, 25), but there has been a lack of data to illustrate this effect in a large-scale study.

While previous work has shown that NIV intervention prolongs life in ALS patients, existent studies are extremely limited by sample size, including well-known studies [e.g., (11, 24, 26, 27)]. The present study has an included sample size four times greater than previous studies. Such a large cohort enables statistically relevant analysis of the ideal FVC %predict threshold for initiating Bi-PAP, the optimal daily Bi-PAP usage time (hours/day), and the evaluation of the adjunctive usage of cough assist for secretion clearance. In fact, cough assist in particular has been highly litigated, particularly in bulbar ALS populations (27–29) where it could carry a higher risk. The goal is to make recommendations regarding NIV (including Bi-PAP and cough assist) initiation and usage that maximize associative survival benefit.

METHODS

A retrospective analysis was performed of a previously collected de-identified data set (30–32) consisting of 1,585 patients seen at a tertiary ALS specialty clinic (Emory University, Atlanta, GA, USA). Metrics for the present study include: baseline visit date (date of first ALS clinic visit); date of patient-reported first ALS symptom onset; onset type (e.g., bulbar, limb, other); existence of co-morbid respiratory conditions; date of initial Bi-PAP prescription; daily Bi-PAP usage time reported at each visit; measured forced vital capacity (FVC) and percent predicted FVC (%predict) at each visit; date of cough assist prescription; cough assist usage at reported at each visit; recorded date of death. Transcription of the original data from the medical records included a quality control check to insure >99% accuracy (30). Internal Review Board approvals were obtained from Georgia Institute of Technology and Emory University.

Patient Inclusion Criteria

Strict data completeness and inclusion criteria were utilized to insure analytical veracity. Only deceased ALS patients with complete clinic and Bi-PAP treatment records for all visits were included. "Non-users" never used Bi-PAP at any point during their disease duration and "users" consistently used Bi-PAP on a daily basis for > 3 months prior to death. Of the 1585 ALS patient

TABLE 1 | Overall cohort characteristics.

	N = 1,585 Patients
Gender	***N (%)***
Male	945 (59.62)
Female	640 (40.38)
RACE	
Caucasian	923 (58.23)
African American	196 (12.37)
Hispanic/Latino	19 (1.20)
Asian	17 (1.07)
Native American	1 (0.06)
Mixed/Other	12 (0.76)
Unspecified	417 (26.31)
ALS ONSET TYPE	
Limb	1098 (69.27)
Bulbar	428 (27.00)
Other/unclassifiable	59 (3.72)
ALS ONSET AGE	
<55 years	509 (32.11)
55–65 years	474 (29.91)
>65 years	602 (37.98)

TABLE 2A | Comparing Bi-PAP users and non-users as a function of onset type.

Usage class	*N* (%)	Median survival months, (IQR)
Bi-PAP Users (all)	403 (85.02)	21.03 (23.97)
Bi-PAP Non-Users (all)	71 (14.98)	13.84 (11.97)
Bi-PAP Users (limb)	252 (53.16)	24.13 (24.47)
Bi-PAP Non-Users (limb)	48 (10.13)	13.5 (11.47)
Bi-PAP Users (bulbar)	139 (29.32)	17.97 (17.93)
Bi-PAP Non-Users (bulbar)	21 (4.43)	14.17 (16.43)

TABLE 2B | Comparing Bi-PAP initiation FVC %predict threshold.

Bi-PAP initiation FVC %predict	*N* (%)	Median survival months, (IQR)
<50%	201 (49.90)	20.30 (22.06)
≥50%	202 (50.10)	23.60 (24.40)
≥60%	141 (34.99)	24.10 (21.80)
≥70%	87 (21.59)	24.13 (22.83)
≥80%	44 (10.92)	25.36 (20.40)
≥90%	23 (5.71)	27.70 (27.43)

TABLE 2C | Comparing Bi-PAP daily usage protocols (hours/day).

Daily Bi-PAP usage protocol	*N* (%)	Median survival months, (IQR)
<4 h/day	29 (7.20)	15.07 (22.97)
4–8 h/day	57 (14.14)	21.17 (18.97)
>8 h/day	123 (30.52)	23.20 (29.90)

charts reviewed (see **Table 1**), 935 patients had a recorded date of death at the time of study data transcription. Of the 935 deceased patients, 461 were excluded because their Bi-PAP usage did not meet the "consistent" usage definition or because they lacked complete records for all clinic visits. The final cohort consisted of a total of 474 patients comprised of 403 Bi-PAP users and 71 non-users (see **Table 2A**). Retrospective enrollment began in 1999 and concluded in 2015. None of the included patients in this study were transitioned to invasive ventilation, Trilogy, or supplemental oxygen.

Bi-PAP Prescription Criteria

Upright FVC %predict was <50; patient-reported new breathlessness or dyspnea regularly impacting sleep or activity; an in-clinic sleep study revealed depressed respiratory function; a pronounced dip (∼20%) in FVC compared to previous clinic visit; the presence of depressed negative inspiratory force (NIF).

Co-morbid respiratory illness (defined below) was not an explicit criterion for Bi-PAP prescription. No distinction was made for this study based on Bi-PAP machine brand name or machine type (e.g., standard Bi-PAP vs. Bi-PAP with Average Volume Assured Pressure Support (AVAPS), the latter which maintains consistent tidal volume).

Threshold for Bi-PAP Initiation

Bi-PAP user group ($N = 403$) was sub-divided based on recorded FVC %predict at the initiation of Bi-PAP prescription. Groups were defined in 10% intervals to ensure adequate sample sizes (**Table 2B**).

Bi-PAP Daily Usage Protocol

Bi-PAP users were divided into the following daily usage time classifications: did not use Bi-PAP; used Bi-PAP <4 h/day; used Bi-PAP ≥ 4 but ≤ 8 h/day, and used Bi-PAP >8 h/day. Analyzed patients had a consistent usage classification constant from Bi-PAP initiation until death ($N = 210$, **Table 2C**).

Cough Assist Usage

Cough assist is an intervention that helps with secretion clearance by placing positive pressure and then quickly switching to negative pressure to induce a natural cough. Patients were classified on the basis of whether they consistently used prescribed cough assist on a daily basis (**Table 2D**), which was defined as at least one cough assist session per day.

Survival Duration Calculation

Survival duration was calculated and compared using two different definitions: (1) time elapsed from the patient's first or "baseline" tertiary ALS clinic visit until death—a definition that has proven to be most reliable for clinical analysis (33, 34); and (2) time elapsed from the patient's first reported symptom or "true onset" until death, a definition preferred for its ease of intuitive understanding but confounded by patient recall

TABLE 2D | Comparison of Bi-PAP and cough assist usage.

Cough assist usage groups	*N* (%)	Median survival months, (IQR)
Bi-Pap (+), Cough Assist (+)	183 (38.61)	25.73 (21.27)
Bi-PAP (+), Cough Assist (–)	218 (45.99)	15.00 (20.77)
Bi-Pap (–), Cough Assist (+)	17 (3.59)	14.17 (10.73)
Bi-PAP (–), Cough Assist (–)	56 (11.81)	13.68 (13.09)
Bi-PAP (±), Cough Assist (+)	200 (42.19)	24.38 (22.32)
Bi-PAP (±), Cough Assist (–)	274 (57.81)	14.87 (18.53)
Bi-PAP (+), Cough Assist (±)	403 (85.02)	21.03 (23.97)

bias or lack of normalization (33, 34). Unless otherwise noted, survival durations (in months) are presented as a median with interquartile range (IQR). While calculations were performed and compared using both definitions of survival onset, the first or "baseline" definition is used for consistency within the text and presented tables and figures, except where otherwise noted.

Temporal Comparisons and Disease Quartiles

In order to better assess how time elapsed since disease start (using both the "true onset" and "baseline" definitions) until Bi-PAP initiation could be associated with survival benefit, the time(s) from from true onset and baseline until Bi-PAP initiation was calculated and compared between different Bi-PAP user groups. Disease quartile comparisons, where a quartile represents each 25% increment from true onset or baseline until death, were calculated. The first quartile represents the first 25%, the second quartile 26–50%, the third quartile 51–75%, and the fourth quartile 76–100% of time elapsed [since true onset or baseline] until death. Bi-PAP initiation within each quartile was compared to determine if time since onset or baseline is a predictor of associative survival benefit.

Antecedent or Co-morbid Respiratory Disease

Patients with confirmed antecedent or co-morbid respiratory conditions, such as COPD, lung cancer, and severe asthma were identified using previously published protocols (31, 32) and separately compared to ALS patients without such disease to identify any possible result-influencing confounds.

ALS Onset Type

ALS patients were classified as either "limb onset," "bulbar onset," or "other/unclassifiable" based on reported first symptoms according to standard published definitions (35). Patients with recorded mixed initial onset symptoms or those that did not clearly or definitively meet the limb or bulbar definition were classified as "other/unclassifiable."

Statistical Analysis

The distribution type was found to be non-normal using a Shapiro-Wilks test. Thus, median survival durations were compared via a Kruskal-Wallis one-way analysis of variance with a significance p-value threshold of 0.05. Additionally, a Kaplan Meier analysis was used to assess probability of survival over time. The present Kaplan Meier plots to visualize survival probability trends from baseline (0 months) to 60 months, a time period where survival differences and samples sizes are largest. Note that the sample sizes of surviving patients beyond 60 months is small.

RESULTS

Cohort Characteristics

Overall selection cohort ($N = 1{,}585$, **Table 1**) characteristics are similar to literature-cited ratios for gender, ethnicity, onset type, and onset age (5, 8, 19, 35). Based on inclusion criteria (see section Methods), 403 Bi-PAP users and 71 non-users were included for analysis. The onset type and onset age distributions of the included patients ($N = 474$) were similar to the overall cohort. Bi-PAP users are further classified by FVC %predict value at Bi-PAP initiation ($N = 403$) and consistent daily Bi-PAP usage time classification (hours/day) from Bi-PAP initiation until death ($N = 210$). Sub-analyses ($N = 474$) were also performed to explicitly examine Bi-PAP users and Bi-PAP non-users on the basis of whether they used cough assist.

Both the "true onset" and "baseline" onset definitions (see section Methods) were initially used to calculate survival duration and other temporal metrics of disease progression. There was no statistical difference in the two definitions when comparing measured differences between sub-populations. Because of the indistinguishable difference on calculated statistical results, the "baseline" definition is used in the presented results and figures given its prior determination as the preferred literature standard for comparing disease progression (33, 34, 36).

Bi-PAP Users vs. Non-users by Onset Type

Table 2A illustrates the breakdown of major classes of Bi-PAP users strictly on the basis of their using Bi-PAP consistently from the time Bi-PAP was initiated until death. The median survival duration for all Bi-PAP users ($N = 403$) was found to be 21.03 months (IQR = 23.97 months), while all non-users was 13.84 months (IQR = 11.97 months). The Bi-PAP users survived significantly longer than non-users ($p << 0.001$), resulting in an average associative survival benefit of 8.19 months, a 52% increase in survival duration. Limb onset Bi-PAP users have a median survival of 24.13 months and bulbar onset Bi-PAP users 17.97 months compared to 13.5 and 14.17 months for limb and bulbar onset non-users, respectively. Thus, the limb onset Bi-PAP users had a 79% associative increase in survival duration whereas bulbar onset Bi-PAP had a 26.8% associative increase in survival duration. 12 Bi-PAP users and 2 Bi-PAP non-users were unable to be classified by onset type (see section Methods).

Forced Vital Capacity Threshold for Bi-PAP Initiation

Table 2B compares survival duration among Bi-PAP users on the basis of percent predicted forced vital capacity (FVC %predict) at Bi-PAP initiation. Historically in the non-invasive ventilation

ALS literature (11, 22), and presently for the sake of Bi-PAP financial coverage by private and/or government medical insurance in the United States, an FVC %predict < 50 is employed as the standard threshold value to initiate Bi-PAP intervention in ALS. The FVC %predict is calculated using expected FVC values for a given patient age, gender, and height (1). A FVC %predict of 50 equates to respiratory function that is only half of the expected value in an equivalent non-diseased patient. An examination of the 50% threshold in ALS Bi-PAP users reveals a significant difference in survival duration between patients initiating Bi-PAP below the FVC %predict threshold of 50 ($N = 201$, median $= 20.30$ months) and those at or above the 50 %predict threshold ($N = 202$, median $= 24.10$ months) at the time of Bi-PAP initiation, with the latter group having a significant 18.7% associative increase in survival duration ($p < 0.01$).

Analyses using higher Bi-PAP initiation FVC %predict threshold values (60, 70, 80, and 90) were explored to determine if earlier Bi-PAP initiation is associated with longer survival duration (**Table 2B**). Increasing the FVC %predict threshold to ≥ 60 ($N = 250$, median $= 24.10$ months) resulted in a significant 18.7% increase in survival duration compared to the standard < 50 FVC %predict threshold ($p < 0.001$). The ≥ 70 FVC %predict group was nearly identical to the ≥ 60 group. However, the ≥ 80 %predict Bi-PAP initiation group ($N = 44$) has a significant 25% associative increase in survival duration ($p < 0.01$) over the standard < 50 FVC %predict threshold group. Those with FVC %predict ≥ 90 at Bi-PAP initiation ($N = 23$) lived an astounding 36.5% longer ($p < 0.01$) than users in the standard threshold (FVC %predict < 50) group.

Assessment of Daily Bi-PAP Usage Protocol

Table 2C compares the daily usage protocols of Bi-PAP users, which includes classes of users that remained on the same daily usage protocol from Bi-PAP initiation until death. 210 of the 403 total Bi-PAP users were included in daily usage protocol analysis due the stipulation that users remain in the same usage protocol classification (hours/day) from Bi-PAP initiation until death. A Kruskal-Wallis comparison of survival duration between patients who consistently used Bi-PAP < 4 h/day ($N = 30$), 4–8 h/day ($N = 57$), and > 8 h/day ($N = 123$) was performed. Statistically significant differences in survival duration between the daily usage groups were only found between the < 4 h/day and > 8 h/day ($p < 0.05$). Overall, these results suggest that while associative survival benefit is present across every Bi-PAP daily usage protocol, maximal associative survival benefit requires > 8 h/day of Bi-PAP usage.

Comparing Bi-PAP and Cough Assist

Table 2D compares the impact of cough assist usage among Bi-PAP users and non-users. Irrespective of Bi-PAP usage, all cough assist users [cough assist (+), Bi-PAP (±); median = 24.38 months] lived significantly longer ($p < 0.0001$) than all patients that did not use cough assist [cough assist (–), Bi-PAP (±); median = 14.87 months]. Among patients that consistently used both Bi-PAP and cough assist [Bi-PAP (+), Cough Assist (+); median = 25.73 months], there is a significant 88% associative increase ($p < 0.0001$) over those that used neither intervention [Bi-PAP (–), Cough Assist (–); median = 13.68 months]. Interestingly, there is a significant difference ($p << 0.001$) between Bi-PAP users who also used cough assist [Bi-PAP (+), cough assist (+); median = 25.73 months] compared to Bi-PAP users who did not use cough assist [Bi-PAP (+), cough assist (–); median = 15.0 months]. However, there was no significant difference ($p > 0.05$) between Bi-PAP non-users who used cough assist [Bi-PAP (–), cough assist (+); median = 14.17 months] vs. those who used neither intervention [Bi-PAP (–), cough assist (–); median = 13.68 months].

Comparing ALSFRS-R Score and Time Elapsed Since Bi-PAP Initiation

Table 3 illustrates the median revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) score at Bi-PAP initiation and the time elapsed (in months) from baseline until Bi-PAP initiation. The ALSFRS-R (33) is series of 12 survey questions with a degree of impairment scale ranging from (4 = normal) to (0 = unable to perform task). The questions predominantly cover activities of daily living that take into account skeletal muscle function, respiratory function, and swallowing ability, where a "normal" total score in a person with no impairment equates to 48 (e.g., 12 x 4 = 48). Bulbar onset Bi-PAP users have a median ALSFRS-R score of 31 at the time of Bi-PAP initiation compared to limb onset Bi-PAP users, which have a median ALSFRS-R score of 25. Bi-PAP bulbar onset patients started Bi-PAP much earlier than limb patients. Time from ALS baseline to Bi-PAP initiation in bulbar onset Bi-PAP users is 5.4 months compared to 10.77 months in limb onset Bi-PAP users. Bi-PAP users in the longer Bi-PAP daily usage (hours/day) categories tend to start Bi-PAP later from ALS onset, although there is no significant difference in daily usage group ALSFRS-R scores at Bi-PAP initiation. Not surprisingly, those patients with better FVC %predict thresholds tend to begin Bi-PAP sooner and have higher ALSFRS-R scores at Bi-PAP initiation compared to patients with lower FVC %predict thresholds at Bi-PAP initiation. There were significant differences ($p < 0.001$) in ALSFRS-R scores between all FVC %predict Bi-PAP initiation threshold sub-groups. There was no significant difference in total ALSFRS-R score at Bi-PAP initiation based on whether Bi-PAP users did or did not use cough assist.

In addition to examining time elapsed from baseline until Bi-PAP initiation, we also examined how normalized disease duration quartiles may be associated with Bi-PAP sub-population survival duration. Interestingly, there was no associative difference in survival duration as a function of what disease quartile the patient was in when Bi-PAP was initiated. That is, there was no significant difference ($p >> 0.05$) in survival duration simply based on starting Bi-PAP in the first, second, third, or fourth quartile of the patient's overall disease duration. Thus, neither time since true onset nor baseline onset is a good predictor of when Bi-PAP should be started or a predictor of its overall associative survival benefit. The lack of a correlation with

TABLE 3 | Comparing ALSFRS-R score and time from onset until Bi-PAP intiation.

Bi-PAP user sub-group	Median ALSFRS-R Score, (IQR)	Median time months, (IQR)
Bulbar onset	31 (13)	5.40 (9.79)
Limb onset	25 (12)	10.77 (15.73)
<4 h/day	26 (12)	5.47 (7.89)
4–8 h/day	27 (14)	7.57 (10.25)
>8 h/day	27 (14)	8.68 (12.93)
FVC %predict < 50	22 (13)	9.90 (17.27)
FVC %predict ≥ 50	29 (10)	7.23 (12.34)
FVC %predict ≥ 60	31 (11)	7 (12.29)
FVC %predict ≥ 70	32 (11)	5.57 (10.99)
FVC %predict ≥ 80	34 (13)	5.57 (10.33)

temporal metrics is likely explained by the highly heterogeneous disease courses among patients.

Comparing Bi-PAP Protocol Parameter Combinations

The results discussed above individually evaluated the impact of Bi-PAP protocol parameters (e.g., Bi-PAP FVC %predict threshold, Bi-PAP daily usage threshold (hours/day), and concurrent use of cough assist). Additionally, key combinations of relevant parameters were also assessed based on significance identified upon evaluation of the individual parameters. For the combination assessment, the FVC %predict thresholds included > 80, > 60, and < 50; the daily usage (hours/day) included > 8 and > 0 h/day (e.g., < 4 OR 4–8 h/day); and whether cough assist was used [cough assist (+)] or not [cough assist (−)]. The results, including the sample size of patients using each combination (N), the medians ALSFRS-R score at Bi-PAP initiation, and the medians survival (months) is illustrated for each combination in **Table 4**. The concurrent consistent usage of cough assist has a significant impact irrespective of the other Bi-PAP parameters. In the absence of cough assist [cough assist (−)], the significant differences in median survival durations among the Bi-PAP protocol parameters of initiation FVC %predict and daily usage (hours/day) become even more pronounced. Moreover, there are significant ($p < 0.001$) differences between all > 60 FVC %predict combinations as well as all < 50 FVC %predict combinations. Significant differences in Bi-PAP initiation ALSFRS-R score correlated with the FVC %predict at Bi-PAP initiation; additionally there were significant differences in ALSFRS-R score for all three of the sub-groups who began Bi-PAP at the ≥ 80 FVC %predict threshold.

Based on prior literature (28, 37), we also examined the bulbar patients separately as cough assist was previously questioned as perhaps "not a good idea" in bulbar ALS patients, largely due to potential laryngeal issues. However, in this study cohort, bulbar patients did have an increase in survival duration with cough assist. Bulbar patients who only used cough assist [bulbar, Bi-PAP (−), cough assist (+)] had a median survival duration of 18.14 months, bulbar patients who used both Bi-PAP and cough assist [bulbar, Bi-PAP (+), cough assist (+)] had a median survival duration of 18.6 months, and bulbar patients that had no intervention had a median survival duration of 9.43 months [bulbar, Bi-PAP (−), cough assist (−)]. Thus, cough assist significantly associated with a positive increase in survival duration over no intervention at all. However, the synergistic gains of using Bi-PAP and cough assist in combination were not nearly as pronounced in the bulbar onset group as the limb onset group.

Figure 1 summarizes and compares the significant difference in median survival durations among the optimized Bi-PAP usage + cough assist protocol, standard Bi-PAP + cough assist protocol, standard Bi-PAP without cough assist protocol, and the no intervention protocols. Median survival durations range from 30.8 months (optimized Bi-PAP with cough assist) to just 13.7 months (no intervention).

Comparing Temporal Survival Probability Using Kaplan Meier

Examining median changes, such as median survival, gives a straightforward and meaningful metric to compare different protocols. However, the median, alone, does not always present the whole picture, especially in very heterogeneous populations where the variance, particularly in survival duration, is high. Kaplan Meier analysis is a statistical method that examines survival probability over time. **Figure 2** examines survival probability curves generated from Kaplan Meier analysis for key pairings for the first 60-months (5-years) from baseline. With the exception of **Figure 2F**, each Bi-PAP cohort sub-grouping includes both cough assist users and non-users [e.g., cough assist (±)]. All Bi-PAP users have a higher survival probability than Bi-PAP non-users throughout the 60-months from baseline (**Figure 2A**). The difference in survival among Bi-PAP users and non-users is more stark in limb onset patients (**Figure 2C**) than bulbar onset patients (**Figure 2B**). Bi-PAP initiation FVC %predict threshold (**Figure 2D**) shows a clear trend of associated prolonged increase in survival with higher FVC %predict thresholds, although differences in survival probability are most pronounced between 12 to 36 months from baseline. The difference in using Bi-PAP <4 h/day and >8 h/day are quite stark throughout (**Figure 2E**). Finally, the difference in survival probability among Bi-PAP users who also used cough assist was greatly improved throughout compared to Bi-PAP users who did not use cough assist (**Figure 2F**).

Figure 3 presents a Kaplan Meier survival analysis summary for each individual major sub-group protocol parameter. Again, survival probability is compared from 0 to 60 months from baseline. The two sub-groups that fared comparatively the best were the Bi-PAP users that also used cough assist and the Bi-PAP users who initiated Bi-PAP at an FVC %predict ≥80.

Comparing Benefits of Bi-PAP and Riluzole

For the sake of comparison, we calculated the associative survival benefit of riluzole, the first prescribed ALS-specific treatment, for all included patients with a known date of death. Note that because of the retrospective enrollment end date of this study, the newer ALS drug, edaravone, had not yet been FDA approved for ALS for this United States study population. [Edaravone was not

TABLE 4 | Comparing Bi-PAP usage protocol parameter combinations.

Bi-PAP user sub-group	*N*	Median ALSFRS-R at Bi-PAP initiation Score, (IQR)	Median survival months, (IQR)
≥80 %predict, >8 h/day, cough assist (+)	6	37 (3)	30.8 (22.38)
≥80 %predict, >0 h/day, cough assist (+)	22	37 (12)	24.17 (19.50)
≥80 %predict, >0 h/day, cough assist (–)	30	31 (10)	21.12 (22.46)
≥60 %predict, >8 h/day, cough assist (+)	26	33 (11)	25.85 (32.78)
≥60 %predict, >8 h/day, cough assist (+)	72	33 (10)	25.55 (22.92)
≥60 %predict, >0 h/day, cough assist (–)	69	29 (10)	19.53 (23.50)
<50 %predict, >8 h/day, cough assist (+)	22	20 (8)	29.77 (17.20)
<50 %predict, >0 h/day, cough assist (+)	73	25 (10)	26.03 (15.20)
<50 %predict, >0 h/day, cough assist (–)	116	19 (13)	14.03 (18.34)

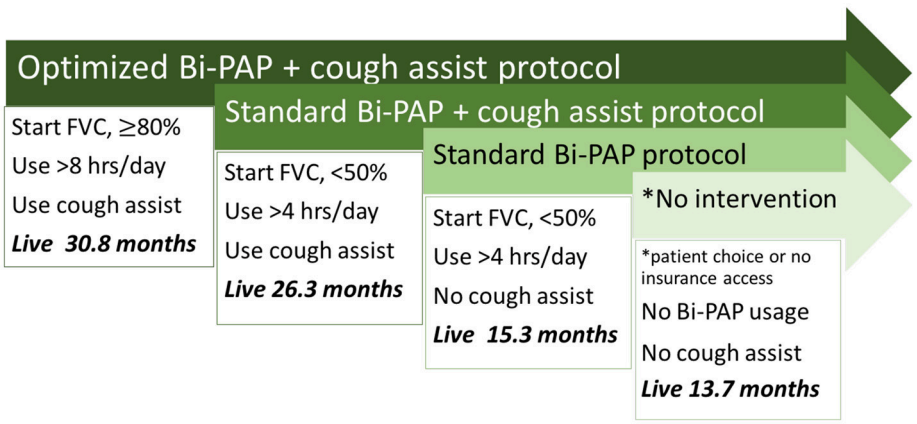

FIGURE 1 | Overview of associative survival duration differences between NIV protocols. There are significant differences in survival duartion among each of the illustrated protocols.

FDA approved in the USA until 2017.]. Thus, comparison data for this cohort was only available for riluzole.

Just under 60% of the 935 patients with a recorded date of death used riluzole at some point during their disease, resulting in a +1.5-month associative increase in survival duration. A +2.4-month associative increase in duration was seen for the 20% of patients who took riluzole throughout their disease course. These associative riluzole survival benefits are similar to previous studies [14, 15]. In contrast, the overall associative survival benefit was +7.4-months for all Bi-PAP users regardless of protocol parameters and +17.1-month for Bi-PAP users on the "optimized" Bi-PAP protocol (started Bi-PAP while FVC %predict ≥ 80, Bi-PAP daily usage > 8h/day, used cough assist). Of course, the riluzole and Bi-PAP cohorts have overlap in that about half of the Bi-PAP patients took riluzole at some point during their disease. Nonetheless, the comparison highlights the additional value of Bi-PAP and cough assist.

Assessment of Possible Confounds

We separately analyzed patients with known antecedent/or co-morbid respiratory illness. Interestingly, the respiratory illness group exhibited a slightly longer, albeit statistically insignificant ($p >> 0.05$), increase in survival duration, which is consistent with previous work (31, 32). Since no significant difference was detected, Bi-PAP usage analyses did not differentiate patients on the basis of antecedent and/or comorbid respiratory illness. Co-morbid or antecedent respiratory patients made up an insignificantly larger percent of Bi-PAP users (15%) compared to non-users (13%).

ALS patients with limb onset and/or a younger onset age tend to live longer, an assertion strongly supported in the literature (35). The impact of onset type in Bi-PAP usage has already been examined in **Table 2A**, **Figures 2**, **3** and in "Comparing Bi-PAP protocol parameter combinations"; these examinations illustrate that, regardless of NIV protocol, bulbar patients do have lesser survival duration although Bi-PAP and/or cough assist usage nonetheless is still associated with a significant increase in survival.

Overall, there was no significant difference in ALS onset age distribution between Bi-PAP users vs. non-users. However, the age distribution of the bulbar Bi-PAP users was significantly older ($p < 0.01$) with 19.42% having an onset age of <55 years, 39.57%

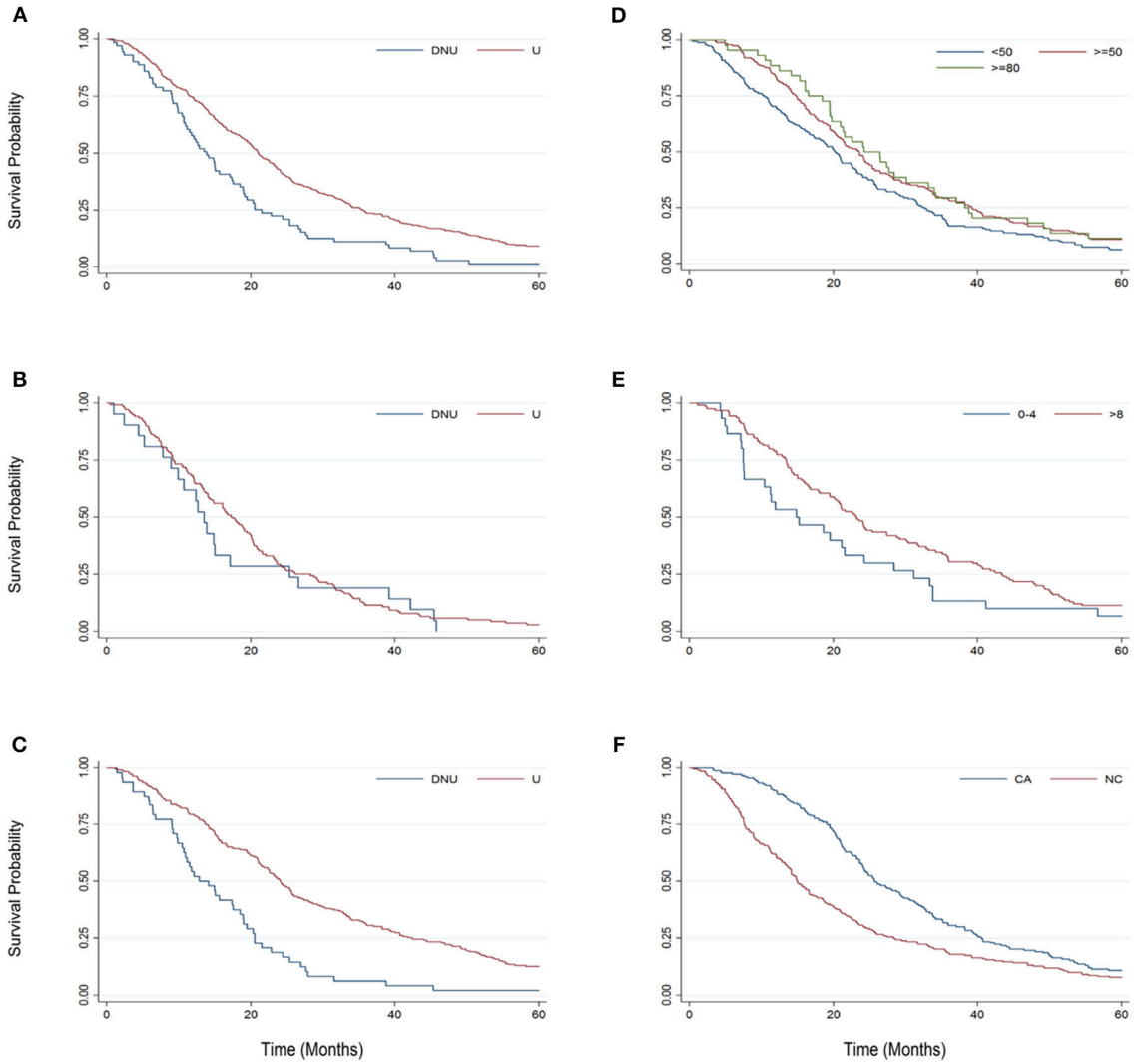

FIGURE 2 | Kaplan-Meier graphs comparing survival probability from 0 to 60 months from baseline for key sub-group pairings. **(A)** Bi-PAP users (U) and non-users (DNU). **(B)** Bulbar onset Bi-PAP users (U) and non-users (DNU). **(C)** Limb onset Bi-PAP users (U) and non-users (DNU). **(D)** BiPAP users classified by the FVC %predict at which they initiated Bi-PAP: <50, ≥50, and ≥80. **(E)** Bi-PAP users classified by their Bi-PAP daily usage time: <4 h/day and ≥ 8 h/day. **(F)** BiPAP users who also used cough assist (CA) or never used cough assist (NC).

with an onset of 55–65 years, and 40.29% having an onset age > 65 years. A previous study has hypothesized that NIV benefit is a function of patient age (38), with older patients benefitting more. However, in the present cohort, there was not a clear correlation of associative benefit solely as a function of patient age.

For additional confounding factors not assessed, please see the *Limitations* sub-section in the Discussion.

DISCUSSION

Our results demonstrate NIV usage, including Bi-PAP and/or cough assist, is associated with significant increases in survival duration. The present study has the advantage of a large sample size (403 Bi-PAP users, 71 non-users, total $N = 474$) compared to previous similar studies, such as that conducted by Kleopa et. al. (70 NIV users, 52 non-users, total $N = 122$) (11), the studies by Bourke et al. (26, 39), which had an enrollment of 15 and 92 subjects, respectively. All of the other NIV studies also had samples sizes of <100 [e.g.,(16, 28, 29, 40)]. The large sample size of the present study provides confidence in the associative survival benefit of NIV. Irrespective of initiation threshold or hours/day usage protocol, Bi-PAP users lived 7.35 months longer, and patients that used both Bi-PAP and cough assist lived 12.05 months longer. In fact, the associative survival benefit of NIV in the present cohort, was 3 to 7 times larger than that of the ALS-specific drug, riluzole. The degree of associative benefit varied as a function of Bi-PAP initiation threshold, hours/day of Bi-PAP

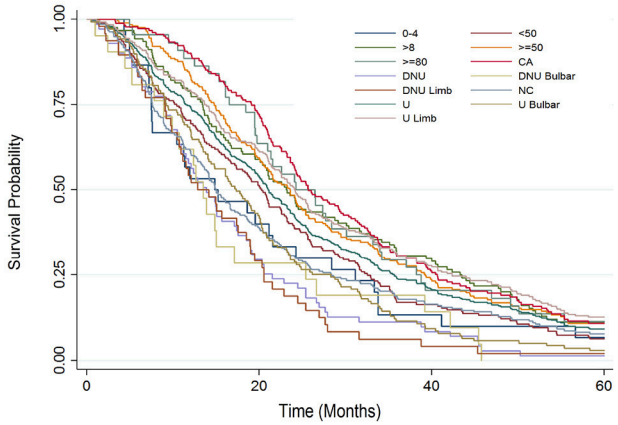

FIGURE 3 | Kaplan Meier survival analysis summary examining surival probability from 0 to 60 months from baseline for each major study sub-group: all Bi-PAP users (U), all Bi-PAP non-users (DNU), all limb onset Bi-PAP users (U limb), all bulbar onset Bi-PAP users (U bulbar), all limb onset Bi-PAP non-users (DNU limb), all bulbar onset Bi-PAP non-users (DNU bulbar), all Bi-PAP users who also used cough assist (CA), all Bi-PAP users who never used cough assist (NC), all Bi-PAP users with <4 h/day of usage, all Bi-PAP users with >8 h/day of usage, all Bi-PAP users who initiated Bi-PAP with a FVC %predict <50 (<50), all Bi-PAP users who initiated Bi-PAP with a FVC %predict ≥50 (≥50), all Bi-PAP users who initiated Bi-PAP with a FVC %predict ≥80 (≥80).

usage, and the daily usage of cough assist (**Figure 1**). Notably, we saw that even bulbar patients, where NIV has been more controversial, had significant increases in survival. Our results support another recent study (29), which also found that bulbar patients benefitted significantly from NIV despite the greater risks with bulbar dysfunction.

Analysis of the FVC %predict threshold reveals that associative survival benefit increases when patients begin Bi-PAP prior to precipitous respiratory decline. Historical literature and current USA medical insurance standards recommend Bi-PAP usage be prescribed to patients only once their FVC %predict falls below 50%, unless a precipitous decline is noted or dyspnea is observed (11, 41). However, other international ALS clinics have certainly promoted earlier non-invasive for several years based on their own clinical observations, which supported earlier non-invasive ventilation paradigms like Bi-PAP (42). The presented analyses showed significant ($p < 0.01$) increases in survival duration for those starting ≥ 60, ≥ 70, ≥ 80, or ≥ 90 FVC %predict when compared to those starting at ≤ 50 FVC %predict. Based on the statistically definitive results of this analysis, we assert that the FVC %predict threshold value for Bi-PAP treatment initiation should be no less than 80%. Moving the Bi-PAP initiation threshold to ≥ 80 FVC %predict results in an associative 25% longer survival duration than the historical standard of < 50 FVC %predict threshold. The sharp increase in survival duration in the ≥ 90 FVC %predict group, a 36.5% longer survival than the standard 50 FVC %predict threshold, warrants further follow-up with a larger sample size.

There will always be discourse on the validity and accuracy of FVC %predict equations, irrespective of parameters used for the predicted calculation. For example, it has been found that some "normal" or non-pathological patients may have a standard FVC %predict that is ± 20% of the predicted [or expected] value with the standard FVC %predict equation (43). Nonetheless, the present study's analysis clearly shows that earlier intervention is associated with longer survival duration in ALS. Thus, even considering a possible ± 20% range on FVC %predict, changing the threshold for Bi-PAP initiation to ≥ 80% of the predicted value is reasonable. Interestingly, negative inspiratory force (NIF) [also known as maximal inspiratory pressure (MIP)] has previously been analyzed being possibly a better metric for determining NIV initiation as it picks up changes earlier, and enables earlier initiation of Bi-PAP in USA clinics where patients may not yet meet the < 50 FVC %predict threshold required for medical insurance to pay for Bi-PAP (44). As noted in the Methods, the adjunctive use of NIF was indeed one alternative way in which patients in the present study's cohort were able to acquire earlier access to Bi-PAP in terms of USA medical insurance coverage.

It is not clear as to why starting Bi-PAP earlier has such a dramatic effect. This study, alone, cannot distinguish between a causal effect vs. an associative effect of optimized NIV protocols with survival duration. One reason for what we refer to as an "associative increase in survival duration" could be a single FVC reading > 50% in the clinic is not indicative of the stress ALS puts on the system, especially during sleep. In fact, all the patients prescribed Bi-PAP with FVC %predict > 50 reported respiratory symptoms or had measurably impaired respiration by adjunctive metrics. Interestingly, only a handful of study patients had a sleep apnea diagnosis prior to their ALS diagnosis. Another possibility is that early Bi-PAP initiation could be prolonging respiratory innervation by insuring adequate oxygenation and taking some stress off of weakened respiratory muscles. Better respiration could also increase quality of life and will to live. Notably, survival was also strongly tied to ALSFRS-R score at Bi-PAP initiation with those with higher scores surviving longer. Additional studies are needed to better ascertain why optimized Bi-PAP protocols, which are typically considered as palliative only, are associated with such stark increases in survival duration. Interestingly, while we did see significant associative increases in survival duration, the use of NIV did not change the slope of respiratory disease decline (data not shown), which was also highlighted in a recent smaller NIV study (40).

While significant associative survival benefit was present across all Bi-PAP daily usage protocol treatment groups (< 4 h/day, 4–8 h/day, > 8 h/day), significant differences between usage protocols was only present between the < 4 h/day and > 8 h/day usage groups. These results compare favorably to the smaller Kleopa et al study (11). The present study supports a standard protocol of > 8 h/day of Bi-PAP usage, which typically translates to using Bi-PAP overnight or during times of sleep. Although it should be noted that the present study does not discriminate on daily or nightly usage but rather total usage in a 24-h period. Bi-PAP usage while sleeping assists in the additional respiratory challenges when laying horizontal and minimizes interference during wakeful activity.

The concurrent daily usage of cough assist (**Table 2D**, **Figures 1–3**) with Bi-PAP has a significant, associative increase in

survival duration, especially in limb onset users. The associative impact of isolated cough assist (without Bi-PAP) is not as profound in limb patients, although the impact of isolated cough assist was more profound in bulbar patients. In all patients, the combination of Bi-PAP and cough assist resulted in an associative increase in survival duration. Thus, there appears to be a highly synergistic effect in clearing secretions with daily cough assist usage combined with daily Bi-PAP usage to assist in respiration. The difference is seen not only in the median survival duration (**Table 2D**), but also in the temporal survival probability as illustrated in Kaplan Meier (**Figure 2**, **3**).

Examining combinations of different Bi-PAP usage protocols reveals that initiation threshold of FVC %predict, daily usage (hours/day), and cough assist usage are all important parameters (**Table 4**). However, as FVC %predict drops, the impact of the other parameters become even more pronounced. While all parameters are important, the combination of median survival duration and temporal Kaplan Meier survival probability suggests that beyond simply consistently using Bi-PAP each day, the order of protocol parameter importance appears to be: cough assist usage, initiating Bi-PAP earlier when FVC %predict is higher (preferably >80), and using Bi-PAP for >8 h/day. The lack of a significant difference in survival duration and Bi-PAP initiation using temporal disease metrics (e.g., time elapsed since onset to determine Bi-PAP initiation) is interesting. In contrast, time since onset is a strong predictor of survival in population-level machine learning prediction and classification models of ALS survival (36).

Limitations and Future Work

Notably, the present study's examination of daily Bi-PAP usage time stipulated that each included patient utilize the same daily usage time protocol from Bi-PAP initiation until death, a criterion that ultimately sacrificed sample size to insure precise categorical comparison. In standard practice, many patients may fall into more than one usage category, as an individual's optimal Bi-PAP usage time is often determined through a trial-and-error process, or Bi-PAP duration is increased as ALS respiratory dysfunction progresses (45). Future work, such as informatics-based analyses (46, 47), is necessary to determine what objective clinical criteria should be used to dynamically determine Bi-PAP usage time as a function of disease stage and patient profile.

FVC was not the only criteria used to prescribe Bi-PAP (see section Methods). However, for many USA medical insurance companies including government-based Medicare, FVC is the primary determining factor for coverage of Bi-PAP. In this USA population, several patients with FVC %predict >50 petitioned insurances via clinician-assisted prior authorizations based on reported symptoms; other respiratory metrics (like NIF) showing impaired function; or sleep studies illustrating respiratory impairment. However, it is possible that personal financial or insurance limitations prevented Bi-PAP access in some cases as not all insurances grant exceptions. A portion of uninsured or denied USA patients are able to personally pay for the Bi-PAP intervention. With the collected data, it was not possible to determine why patients declined to obtain and/or use Bi-PAP even if they met the Bi-PAP prescription criteria stated in the Methods. Other contributors to Bi-PAP patient compliance or refusal of the intervention could be related to depression, will to live, or perceived Bi-PAP side effects (e.g., mask claustrophobia or sleep interference), etc.

Other limitations to the study include the number and types of parameters assessed. In particular, additional assessments of respiratory function could be helpful to find the best metric or combination of metrics for determining NIV initiation. For example, a recent small retrospective study ($N = 87$) by Tilanus et al. found that NIF (also called MIP) and sniff inspiratory nasal pressure (SNIP) were better at identifying the need for earlier NIV (48). Another hotly debated topic is whether FVC %predict should be taken while upright or while laying (22), which should be investigated in greater detail; most USA clinics use the upright metric. Also, additional functional disease progression (e.g., ALSQ40, ALSQ10, bulbar scores, etc.) may be more sensitive than ALSFRS-R, although the ALSFRS-R is still the most widely utilized functional metric. The examination of how NIV impacts quality of life is also important; thus, other quality of life metrics (McGill quality of life scale, neurology quality of life measurement system, etc.) may provide additional insight. Collectively, all of the aforementioned metrics could shed additional light on potential causal or associative reasons why earlier NIV initiation has a significant associative correlation with increased survival duration.

Future work includes not only dynamic NIV assessment with disease progression, but also optimization of specific NIV machine settings, specific Bi-PAP or cough assist machine types, and combined assessment with newer interventional ALS medications like edaravone.

CONCLUSIONS

In summary, as shown in **Figure 1**, we propose that clinician prescriber and/or medical insurance carriers facilitate earlier NIV intervention. In particular, Bi-PAP should be initiated while ALS patients have a recorded FVC %predict $\geq$ 80; Bi-PAP should be used at least 8 h/day; and cough assist should be used daily to assist with secretion clearance. The aforementioned "optimized" NIV protocol can extend life by a factor of up to 2 compared to the standard Bi-PAP protocol and a factor of 2.25 compared to no intervention. The overall conferred survival benefit of optimized NIV protocol is even more impressive than the ALS drug, riluzole. Finally, functional metrics of ALS disease progression (FVC %predict, ALSFRS-R score, etc.) are better predictors of when Bi-PAP should be initiated and of its overall survival benefit compared to temporal metrics of disease progression likely due to highly heterogeneous disease courses and durations in the ALS population.

AUTHOR CONTRIBUTIONS

NK data acquisition, statistical analysis, interpretation, critical review of the manuscript. GC data acquisition, statistical

analysis, critical review of the manuscript. BW conception of study design, data acquisition. CM conception of study design, data acquisition, interpretation of results, drafting of the manuscript.

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Communication Matters—Pitfalls and Promise of Hightech Communication Devices in Palliative Care of Severely Physically Disabled Patients With Amyotrophic Lateral Sclerosis

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Amyotrophic lateral sclerosis (ALS) is the most common motor neuron disease, leading to progressive paralysis, dysarthria, dysphagia, and respiratory disabilities. Therapy is mostly focused on palliative interventions. During the course of the disease, verbal as well as nonverbal communicative abilities become more and more impaired. In this light, communication has been argued to be "the essence of human life" and crucial for patients' quality of life. High-tech augmentative and alternative communication (HT-AAC) technologies such as eyetracking based computer devices and brain-computer-interfaces provide the possibility to maintain caregiver-independent communication and environmental control even in the advanced disease state of ALS. Thus, they enable patients to preserve social participation and to independently communicate end-of-life-decisions. In accordance with these functions of HT-AAC, their use is reported to strengthen self-determination, increase patients' quality of life and reduce caregiver burden. Therefore, HT-AAC should be considered as standard of (palliative) care for people with ALS. On the other hand, the supply with individually tailored HT-AAC technologies is limited by external and patient-inherent variables. This review aims to provide an overview of the possibilities and limitations of HT-AAC technologies and discuss their role in the palliative care for patients with ALS.

Keywords: amyotrophic lateral sclerosis, augmentative and alternative communication technologies, eyetracking, brain-computer-interfaces, quality of life, end-of-life-decisions

INTRODUCTION

Amyotrophic Lateral Sclerosis (ALS) is the most common motor neuron disease. It is characterized by progressive degeneration of upper and lower motor neurons, leading to progressive paralysis, dysarthria, dysphagia and increasing respiratory disabilities. The average survival after diagnosis is 3–5 years and most common causes of death are respiratory failure or dysphagia. Therefore, life-prolonging measures and especially tracheostomy might significantly increase survival (1, 2). As there is still no curative therapy available the main focus is palliative care aiming to improve ALS-patients' individual quality of life (QoL) and support caregivers (3). Moreover, it is reported that multidisciplinary integrated palliative care not only improves QoL but even prolongs survival

(4, 5). On the one hand, physical symptoms such as pain, increasing swallowing and respiratory difficulties and restrictions in activities of daily living can at least be partially controlled by medication and support for everyday life, e.g., by the use of assistive devices. Potentially life-sustaining measures such as percutaneous endoscopic gastrostomy (PEG), non-invasive ventilation (NIV) and tracheostomy with invasive ventilation (TIV) can also improve QoL by controlling feeding problems or dyspnea. However, their initiation needs careful discussion, individualized decisions and patients' explicit and fully informed consent (6–9).

Data is sparse for other countries than Japan, but TIV-rates among ALS-patients seem to increase up to 20% (10, 11). These numbers underpin the relevance of the complex and extremely difficult decision whether or not—and if yes, at which physical or psychological health status—life-prolonging measures should be terminated. The few studies on this subject describe that patients often decide to terminate TIV because of a subjective "loss of meaning in life" and poor QoL (12, 13). At best, this issue should be discussed and considered explicitly in patients' advance care planning after careful discussion (6).

On the other hand and in face of the fatal and progressive nature of the disease, palliative care for people with ALS needs to address not only control of somatic symptoms but also psychological, spiritual and existential aspects. Decision-making over medical care from the time of diagnosis until death is a cyclic process that should be guided by patients' autonomy and care has to be adapted to the changing needs of patients and their families. To meet these needs, intense communication between the affected persons and health professionals is essential (14–16). Communication is further described as crucial to sustain hope and reduce fear in palliative care (17).

Overall, dysarthria occurs in 80–95% of people with ALS at some point in their disease course, making them unable to meet their daily communication needs by means of natural speech (18, 19). We thus aim to provide an in-depth overview of the possibilities of HT-AAC technologies and their influence on, patient care, social life and QoL of severely disabled patients and caregivers, but also of their limitations. On this basis, we discuss the role HT-AAC use in palliative care for patients with ALS.

IMPORTANCE OF HIGH-TECH AUGMENTATIVE AND ALTERNATIVE COMMUNICATION (HT-AAC) TECHNOLOGIES IN ALS

In line with Janice Light's description of communication as "the essence of human life" (20), a qualitative study of McKelvey et al. (21) impressively described the frustration and sadness that patients and their partners experience as speech deteriorates: "That was probably the biggest hurt. She couldn't talk." Patients are often deprived of their ability to judge, experience a lack of control and a change of their social roles. The ability to communicate is strongly associated with patients QoL (22) and communication is seen as crucial for the adaption to terminal diseases such as ALS (23). Therefore, while verbal as well as nonverbal communication abilities deteriorate, augmentative and alternative communication (AAC) strategies and technologies become more and more important. AAC strategies in general are in place to support communication related to a large variety of issues, such as personal and medical care, social interaction and closeness, community involvement and employment, and to express personality and feelings (18, 21).

AAC might be no- or low-tech (gestures, facial expressions, handwriting, topic boards, alphabet boards, and eye-linking partner-supported systems) or high-tech with or without synthesized speech output (e.g., tablets, touchpads, head- or limb-movement-activated microswitch systems). High-tech augmentative and alternative communication (HT-AAC) technologies afford minimal or no head or limb movement and enable complex, caregiver-independent communication as motor abilities decrease (24, 25). Since the decision for TIV increases survival and therefore the length of HT-AAC-use (26) and considering the growing percentage of patients deciding for TIV, the need for HT-AAC will likely grow. The use of (HT-)AAC devices to support communication in different groups of severely disabled patients has been discussed since decades [e.g., (27)]. This review focuses on HT-AAC for severely disabled patients with ALS who depend on multimodal palliative care.

TECHNOLOGY OF HT-AAC EYETRACKING COMPUTER SYSTEMS

The most promising and best-studied HT-AAC devices are eyetracking computer systems (ETCS) which allow cursor control by eye movement. Eye movements are often the least fatiguing (28, 29) if not the only remaining volitional movements that allow communication in ALS (27).

Although the technology that drives eye operated speech generating systems has been modified over the course of the last 40 years, the underlying principles did not change much. All systems use infrared sensitive cameras, mostly based on complementary metal-oxide-semiconductor sensors nowadays and with an active infrared light source to illuminate the eyes. The systems primarily differ in the relative positioning of the infrared light source with respect to the camera lens axis. Systems with an infrared light source located very close to the camera lens axis make use of the bright pupil effect: the infrared light gets reflected on the eye's retina and produces a bright image of the pupil. Conversely, in systems with the infrared lights placed off axis the images received from the camera sensor generate dark pupils. In both systems the infrared light source produces additionally a bright reflection on the cornea (the glint), which is together with the pupil center used to calculate the pupil-glint vector (30, 31). This vector then serves to calculate the Point of Regard on a computer screen and thus can be used to type by

Abbreviations: (HT-)AAC, (high-tech) augmentative and alternative communication; ALS, Amyotrophic lateral sclerosis; BCI, brain-computer-interfaces; CA, classification accuracy; ETCS, eye-tracking computer systems; FTD, frontotemporal dementia; (T)LIS, (total) locked-in-state; NIV, non-invasive ventilation; PEG, percutaneous endoscopic gastrostomy, QoL, quality of life; TIV, tracheostomy invasive ventilation.

means of a gaze sensitive on-screen keyboard or to drive other computer functions.

ADVANTAGES AND PROMISES OF HT-AAC IN PALLIATIVE CARE

Acceptance and Usability of HT-AAC to Restore Communication Ability

Several studies demonstrate the positive impact of ETCS-use for severely disabled people. First of all, acceptance and user satisfaction are reported to be high in ALS and traumatic brain injury (32, 33). Ball et al. (32) found in a study of 50 patients with ALS that 96% of those who were recommended AAC technology due to increasing communication disabilities accepted the device, either immediately or after some delay. The three main reasons for their decision for AAC were maintenance of communication, participation in community and employment. Patients who rejected AAC often suffered from frontotemporal dementia (FTD), which is in line with another study (18).

Patients use ETCS for a variety of activities such as face-to-face-communication—even in groups—e-mail contact, internet access and other computer functions and programs as well as for environment control (24, 34, 35). Regarding the increasing importance of social media, their access by HT-AAC is an additional valuable mean of communication, link to the outside world and thereby supports patients' social networks (36). Thus, HT-AAC can enable social and intellectual stimulation, independent leisure activities and the patients to express even complex thoughts. As AAC allow even severely disabled patients to communicate with less familiar caregivers, they enrich patients' possibilities in choosing communication partners.

Evaluation studies of HT-AAC-use show that once a functioning ETCS could be established, patients use it for several hours each day and report a high user satisfaction, preservation of communicative abilities and subjective indispensability of the device (34, 37). Interestingly, the worse patients' clinical conditions, the higher seems to be their acceptance of HT-AAC (38).

Regain of Social Participation, Psychological Wellbeing and Quality of Life

In an interview study by McKelvey et al. (21) spouses reported that AAC technologies helped to maintain the emotional connection within families. What they additionally valued as a very precious function was that patients—with the help of their next of kin—could discuss philosophical ideas and author "last words" and thoughts to their families. The use of AAC devices even enables psychotherapy for severely disabled patients in order to reduce psychological distress and promote autonomy and self-esteem (39).

Several cross-sectional and two longitudinal studies found a positive association between higher psychosocial wellbeing or QoL and the use of ETCS (25, 34, 38, 40–42). The assumption of a positive effect on Qol is further supported by the findings that HT-AAC-use serves as an active coping mechanism, helps patients to express emotions and personality and to maintain social roles, participation in family and community and even employment (21, 43). These results are confirmed by the first study evaluating the association between QoL and ETCS use in ALS-patients in the locked-in-state (LIS) in a fully caregiver-independent manner by using ETCS-based assessment (44). Patients reported on average a high QoL and the study suggests that ETCS preserve patient autonomy and therefore psychosocial wellbeing particularly by enabling social activities, which patients named as the most important area of life for their QoL. A generally high subjective QoL in ALS has been reported before for less severely affected patients as well as for LIS-patients (45–47). It is discussed that psychological wellbeing might even modify disease course in ALS (48, 49).

Consequently it can be assumed that by enabling patients to stay mentally autonomous and realize their needs in terms of social activities and participation, encouraging successful adaption to the disease and thereby increase psychological wellbeing, HT-AAC might even have disease-modifying effects. This remains to be clarified in longitudinal investigations.

Reduced Caregiver Burden

Caregivers of ALS-patients report low QoL and high burden (50–53), which is especially true for tracheotomized patients and those in LIS (8, 44). The use of ETCS though is associated with reduced caregiver burden, probably by improving patient autonomy and making patient-caregiver-communication more effective (40). An interview-study of 34 family caregivers of ALS-patients reports a very positive attitude toward HT-AAC devices, an increased perception of social closeness and fewer difficulties in providing care due to the AAC-use. These benefits are greater for those with higher AAC technology skill levels (35). Corallo et al. (42) could demonstrate in a longitudinal study of 15 LIS-patients and their caregivers that enabling patients to communicate via HT-AAC reduced caregivers' anxiety and increased their vitality as well as social activity and social role functioning; results that highlight the positive value of HT-AAC supply also for the caregiver themselves.

(Neuro)Psychological Assessment

Another important issue is the use of HT-AAC for neuropsychological assessment, since neuropsychological test procedures usually require at least some motor or verbal skills and therefore become invalid for severely disabled patients. It is known that cognitive deficits affect a great proportion of all-ALS-patients (54) and can compromise their ability to judge and decide over their medical care and life-prolonging measures (see chapter Cognitive and behavioral impairment and its consequences for HT-AAC-use). Promising attempts have been made to develop ETCS-based test procedures of cognitive functioning (55, 56).

IMPACT OF PATIENT AUTONOMY IN PALLIATIVE CARE

The reported findings make clear that enabling complex communication independent of a "translation" by caregivers/next-of-kin and thus patient autonomy is crucial

for the preservation of psychological wellbeing of severely disabled patients. Furthermore, HT-AAC have high implications for end-of-life-issues: First, the possibility to communicate might directly change patients' attitude toward life-prolonging measures, as Fager and colleagues explicitly reported for one LIS-patient equipped with a computerized communication system controlled by minimal head movements: "He was so encouraged [by the regain of his communicative abilities] that, when he entered the hospital with pneumonia, he changed his medical code status from 'do not resuscitate' to 'full code"' (57). In turn, we assume for two of the patients who were recruited for our study (44) but died before the assessment that an earlier supply with ETCS could have changed their decision against life-prolonging measures.

Second, caregiver-independent communication enabled through HT-AAC supply is crucial for assessing the patients' psychological condition and actual will and ensure self-determination of care. Advanced care planning and in general decisions over the medical care for severely disabled patients need a careful discussion of all relevant procedures, advantages and potential risks to ensure self-determination. This is specifically true for decisions to initiate or terminate life-prolonging measures such as PEG, NIV or TIV. It was mentioned above that the patients' self-rated QoL is often relatively high, moreover and importantly it is significantly underestimated by caregivers as well as the general population (52, 58, 59). This is in particular noteworthy for patients in LIS: the average QoL of the 11 LIS-patients in our study, self-rated via ETCS, was 81% while next of kin estimated patients' QoL to be only 63% and thus similarly low as their own self-rated QoL of 54% (44). It is not clarified yet which factors contribute in which extend to this significant discrepancy. However, there has been reported a "response shift" in the evaluation of their QoL by patients toward a higher value of social activities and a lower value of financial aspects, mobility and leisure activities (47, 60, 61); a shift that patients' next of kin are apparently not aware of (44), maybe because it does not happen for them.

Furthermore, in the face of their shorter lifetime some patients gain a "deeper view" and a higher appreciation of life (62).

However, it must also be considered at this point that some patients may suffer a loss of awareness or insight in their situation or a reduced ability to judge it, as executive functioning (63–65) and social cognition including empathy are impaired in a proportion of non-demented patients (66–68); an issue that is further discussed in chapter Cognitive and behavioral impairment and its consequences for HT-AAC-use.

Irrespective of its causes, the contradictory assessment of patients' QoL by patients themselves and caregivers may have tremendous consequences on end-of-life-decisions and thus makes it essential to enable patients to communicate even complex utterances independently of their next-of kin or caregivers. Actually, LIS-ALS-patients themselves confirm that they are able to do so by means of their own ETCS but not without the device (37, 44). It is indispensable that patients' wishes concerning life-prolonging measures are not undermined. This is extremely difficult to assess and ensure, as communication structures in families and between health professionals and patients are hard to grasp anyway, all the more if one partner suffers from severe communication difficulties. We observed one case, in which the patients' wish for TIV probably was circumvented on hospital admission which caused her death (44).

Since the patients' will may change during disease course (12, 69, 70), communication must be enabled at every time point in the progression of the disease and thus even if no head or limb-movement or natural speech is possible. This is emphasized by the fact that a significant proportion or even clear majority of ALS-patients is tracheotomized unplanned, e.g., as an emergency measure, and in a relevant amount of cases without explicit informed consent of the patient (8, 71). As this can obviously be avoided by early, careful and detailed advanced care planning as recommended by Oliver et al. (15), the valid assessment of patients' will has to be striven for at each point of time. It was argued before that this approach will also disburden caregivers from vital decisions for their loved ones in the fear of making them against their actual will. Parallel to ensuring the patient's autonomy, the highly burdened caregivers need to be involved in medical decision making (6, 15) and to receive specialized practical and psychological support (72, 73).

LIMITATIONS AND PITFALLS OF HT-AAC-USE AND-SUPPLY

Nakayama et al. (74) suggested a definition of five stages of communicative abilities of TIV-ALS-patients that is of high value for the prediction of impaired communication: patients who can communicate without any high-tech devices are classified as stage I, patients with communication difficulties that can be overcome by use of HT-AAC technologies to a varying extent as stages II to IV and those who cannot communicate at all as stage V. Predictors identified for the progression from stage I to a higher one and therewith predictors of severely impaired communicative abilities are oculomotor dysfunctions, TIV and full quadriplegia.

This model indicates that despite the diverse possibilities and promising research results by far not all patients suffering from advanced ALS and other conditions that affect communication abilities are supplied with an HT-AAC device or respectively gain a successful restoration of their ability to communicate by means of HT-AAC. Beside the three important reasons for this lack identified by Nakayama et al. (74), there are several more which can be assigned to the three main components of the AAC-acceptance model by Lasker and Bedrosian (75): factors of the user, the environment and the device.

Factors of the User

Eye Pathologies and Eye Movement Dysfunctions

A number of ophthalmologic diseases and oculomotor dysfunctions can complicate ETCS-use. Although oculomotor function is typically spared from the effects of ALS, dysfunctions occur in a proportion of the patients and particularly ophthalmoparesis in those with prolonged survival (74, 76). Certain deficiencies like slowed down saccades or ptosis can be accommodated by some ETCS, but others like eye movement

paralysis as well as further problems such as glaucoma, gaze tiredness or problems to keep the head still can make it difficult or even impossible to use ETCS (34).

While normal astigmatism can be usually very well compensated during the calibration process, more severe and irregular deformations of the cornea may pose a challenge for accurately determining the user's gaze, since this may affect the way the infrared is reflected from the eye. If only one eye is affected, some ETCS allow focusing only on the eye without cataract. Nystagmus, a condition characterized by repetitive, uncontrolled eye movements, is another factor that can make it impossible to use ETCS because nystagmus (a) can impede calibration as a user is not able to hold its gaze still for a prolonged time and (b) even if calibration is possible, users will have difficulties resting their gaze on a button for a long enough period of time. Another condition that can interfere with ETCS use is strabismus. While single eye strabismus can as well be compensated by focusing only on the non-affected eye and eventually applying an eye patch on the other one, alternating strabismus cannot be compensated for by ETCS as it is not possible to determine which eye is directed at any given point in time.

Another frequent obstacle in clinical practice are spurious reflections from glasses since they may, depending on the location of the reflections, interfere with the corneal reflection. Although contact lenses are usually no problem, for hard contact lenses the corneal reflection sometimes happens to lye partly on the circumference of the lense and thus only partly on the cornea.

Electrooculogram-based eye-computer interfaces might overcome a few of the limitations of ETCS since they are not influenced by lighting or the physical conditions of the eyes. However, this method also requires the users' abilities to control their eye-muscles and is moreover less precise than ETCS (77). Microswitch-activated systems that rely on any residual muscular activity can be another option (78).

Irrespective of which HT-AAC device is chosen, there is still the risk that patients progress to a total locked-in-state (TLIS) and thus to stage IV of communication abilities (74), since TLIS is defined as the complete loss of muscle control including the eye muscles and therefore any valid ability to communicate needs (79). This is obviously an extremely burdening situation for caregivers and health professionals. The overall prevalence of TLIS is difficult to determine, but Hayashi and Oppenheimer (80) reported a prevalence in ALS-patients on TIV of 11.4%.

Psychosocial Factors

Certain attitudes and needs are potential reasons for the refusal of HT-AAC by patients. In her qualitative study on the non-acceptance of HT-AAC Murphy (81) reported on this matter that some did not use their device because they desired using their own voice as long as possible. Communicating via a device was perceived as just "not the same." In line with another case study, patients preferred the higher social closeness and the direct interaction of face-to-face-communication (81, 82). Furthermore, patients reported a "shared understanding" in everyday communication with familiar partners that makes HT-AAC devices dispensable. However, referring to the stage model of Nakayama et al. (74), all of these patients were still in stage I, so still able to communicate via speech which often changes as the disease progresses (81). Low-tech and face-to-face-communication—if (still) possible—might be more effective and comfortable for communicating quick needs and for interacting with familiar partners, while sharing detailed information and communication with less familiar partners requires HT-AAC (75, 83). In summary, advantages of different communication modes depend on individual abilities, aims of communication and familiarity of interlocutors.

An additional difficulty is the optimal timing of AAC-interventions, thus the decision at which stage of communication ability or impairment HT-AAC devices are introduced and established. On the one hand, patients and caregivers often don't want to be confronted with predictable deficits before speech becomes intelligible and thus delay the decision about HT-AAC use (18, 84). On the other hand, timely referral not only ensures punctual delivery of the device but also better learning conditions for the patient (14, 18).

Age, education and computer experiences might also influence HT-AAC acceptance. Actually, samples of the reported investigations on ETCS-acceptance and impact on wellbeing (25, 40, 44) were relatively young and highly educated compared to average ALS-patients. However, Caligari et al. (25) found no influence of education and computer experience on ETCS acceptance or benefit. Considering age as a potential factor, Spataro et al. (34) reported regular users to have a younger age of disease onset compared to irregular and non-users.

Cognitive deficits are another important influence factor on the usability of ETCS. While the progression rate of cognitive deficits to a full blown dementia in late stage ALS is not known, up to 10% of ALS patients suffer from FTD at any specific time (54) and cases of the development of severe dementia under TIV are known. Apart from that, studies describe cognitive deficits to be relatively stable over the disease course and observed good cognitive functioning in patients with late-stage ALS (85, 86). Nevertheless, mild to moderate cognitive impairment is highly prevalent in ALS, which is described in depth in chapter Cognitive and behavioral impairment and its consequences for HT-AAC-use.

Factors of the Environment

Supply and Professional Support of HT-AAC-Use

The environmental conditions are probably the most vulnerable aspect of HT-AAC-provisioning for severely disabled people, regarding to begin with the supply of the devices and the continuous individual support to ensure their optimal usability. First, clinicians involved in the care need to be aware of HT-AAC devices and their possibilities and—concerning the mentioned issue of timing of supply—must support the patients' decision process on the use of such devices in an active but also sensitive and properly timed manner. This can be considered a difficult (84, 87) and important challenge, especially in view of the finding that lacking referrals by physicians are a frequent reason for delayed supply with HT-AAC devices (84).

Second, funding and availability of devices can be an issue as the health care system of many countries do not or only partially

finance (HT-)AAC devices. The national health system in the United States started reimbursing AAC in 2001, but application is an exhausting and time consuming process (18). As Donegan et al. (88) report, the national health service of Italy started providing ETCS for ALS-patients several years ago because of increasing awareness brought by the research, but this is not consistent practice. For Germany, Funke et al. (89) found as a result of a cohort study on a case management program for ALS-patients that only 61% of AAC devices procured by the treating neurologists were finally delivered to the patients, which might be in fact an overestimation for the general population since the study was conducted in specialized ALS centers. The main cause of failed provision with a HT-AAC device was rejection by the health insurance, followed by rejection by the patient and patient's death. The mean latency of provision was 93 days, a long period of time for people not able to communicate without the device. The authors speculated that especially decisions over expensive assistive devices are guided by financial considerations at the expense of patients' wellbeing (89).

Moreover, provision of HT-AAC devices is not only costly but also difficult to install as they need to be adapted to each individual user. Service providers need to provide training of circa 5 h (24) and ongoing support, trouble-shooting and individual customizing over an extended time period (18, 33). Insufficient training is often reported to be a reason for helplessness and non-use of HT-AAC (33, 75, 81). Caregivers need detailed step-by-step-instructions and intense training too, because they serve as indispensable HT-AAC facilitators (90). AAC success is reported to depend on caregivers concerns, attitudes and awareness (81, 91) and caregivers with higher skills report higher reward (35).

To avoid unequal service provision and optimize the timing of AAC-interventions, regular assessments of patients' communication abilities by trained and independent AAC-experts are recommended (84). At best, an assistive technology clinic as described by Casey (92) is created, combining expertise, time and material resources and the ability to test and individually customize devices. This might also offer a solution for the challenge of optimal timing of AAC-interventions, by allowing patients to get familiar with different technologies and to face upcoming communication problems step by step (14). It is recommended that the communicative abilities of patients suffering from diseases leading to foreseeable disabilities are regularly evaluated by trained health professionals such as speech language pathologists (93). Patients should be referred for AAC assessment when their speaking rate falls below 100 to 125 words per minute or when patient or listener perceive the communication effectiveness as decreasing (18, 94).

Influence of Family Caregivers or Next of Kin

An issue that has not been addressed systematically in the literature until now is that caregivers might experience negative aspects of patients' HT-AAC use. The ability to communicate detailed thoughts and wishes, also with third parties, might lead to increased feelings of burden–especially in combination with a decision pro NIV. This was possibly the case for one patient in a study by Linse et al. (44), in which the family returned the ETCS without stating reasons and despite it was working well and the patient expressed the wish to use it. Evaluating the perceived usefulness of ETCS, next of kin also reported some critical issues, e.g., an increased burden since patients started to use the ETCS (37). Reasons for this higher burden need to be clarified. It is conceivable that it is related to patients' increasing duration and severity of ALS, to the social-communicative or technical requirements raised by the ETCS itself or to the fact that the patient is now able to communicate his wishes that she or he want to be satisfied by the next of kin.

However, family caregivers of severely disabled patients' are in general a highly burdened and overloaded population that has to be considered and supported in the palliative care (15) and in particular concerning patients' supply with HT-AAC. Beside and in connection with the discussed low quality of life and wellbeing of next of kin, it is known that severe diseases like ALS have far-reaching effects on a social system beyond the index patient; and it is therefore essential to study impacts on the caregivers and their perspectives separately from patients' perspectives (89). While HT-AAC technologies can help to prevent the patients' social networks, assuming the role of the caregiver often results in a loss of freedom and of time and energy for self-care as well as in a change of life plans. The size, quality and changes of their personal social network have to be investigated in future to minimize the negative consequences of the disease on family caregivers (95, 96) and in consequence to counteract unfavorable influences on patient's decision, e.g. for or against use of HT-AAC devices.

Factors of the Device

There are also several issues related to the HT-AAC device itself that can hinder its optimal use. Particularly for ETCS, accuracy of older devices can be insufficient and complex calibration and setup procedure can complicate the handling (24). The bad quality of the voice output is another issue occasionally regarded as problematic by patients as well as caregivers (21, 43, 81). Voice banking and voice conversion techniques lead to hope for more personalized speech synthesis in the future (97). However, we are not aware of a single study investigating the value of this voice banking technique. From own experience it can be reported that patients themselves experienced their recorded voice not as their own. In contrast, next of kin do so but have difficulties accepting that this technology device talks with the voice of the patient. Finally, independent of voice banking and concerning the authenticity of the voice, the speech output does not adapt to the content of the words in terms of emotion, thus e.g., joy and crying do not sound differently.

Another technical drawback of the currently used eyetracking technology, independent from individual factors of the patient (e.g., oculomotor dysfunction), is the sensitivity of the infrared light sensitive camera to ambient infrared light, because it immensely reduces the usefulness of the devices in outdoor settings. Only reliable and portable devices that can be adjusted e.g., to a variety of lightning conditions can ensure the use of HT-AAC in different settings (40, 43, 81). Another relevant difficulty in ETCS-use is the "Midas touch problem." It describes the frequent phenomena that the focus of attention is not in

accordance with the users' direction of gaze, which results in non-intended commands like for example a wrong selection of letters (98).

Ideally, switching of access methods (e.g., from touch to joystick to eyegaze) with one device and one easy-to-learn "intuitive" software as well as the setup of different individually tailored features (e.g., internet and mobile phone access, environment control, leisure activities) should be possible with one HT-AAC device. These options would allow to adjust the device to the patients' changing needs and physical abilities and enable communication with different partners in different settings (18, 91). High quality products should be employed as technical problems and learning difficulties reduce the motivation to use HT-AAC even though it is generally wished and needed (38).

COGNITIVE AND BEHAVIORAL IMPAIRMENT AND ITS CONSEQUENCES FOR HT-AAC-USE

As suggested earlier, relevant behavioral and cognitive impairment under the threshold of (frontotemporal) dementia but also caused by frontotemporal dysfunction is a common and critical feature of ALS (99, 100). Guided by FTD-diagnosis though, there is a distinction between (non-dement) ALS with behavioral impairment (ALSbi), with cognitive impairment (ALSci) and with a combination of both (ALScbi) (99).

Cognitive impairment in general is reported to affect between 30 and 40% of the ALS-population (54, 64, 101), although estimations of prevalence vary considerably; an inconsistency that is probably partly explained by the considerable heterogeneity of first those deficits (63, 99) and second of the methods used for their assessment (65).

Nevertheless, impairment is consistently reported for the broad cognitive domains of executive functions, language and memory (54, 63, 64, 102, 103). Recent meta-analyses additionally confirmed deficits in social cognition as another prominent feature of ALS (54, 67). Furthermore, different behavioral changes can be observed in ALS-patients (104).

Concerning consequences for HT-AAC-use, Beukelman et al. (18) interestingly reported for patients with mild cognitive deficits that all who wanted and needed AAC for communication were able to use it. Anyway, in view of the cognitive, linguistic and social demands of communication, the cognitive and behavioral impairments due to ALS must be assumed to have important implications not only for communication ability in general (105) but also by (HT-AAC)-use in particular. This is most obviously for deficits in language comprehension and expression.

Language Impairment

Language function is a very broad domain, but Beeldman et al. (54) analyzed that studies reporting its impairment in ALS often operationalized it as the ability to name objects in Visual Naming Tests, which are used as an important diagnostic tool for aphasia (106, 107). Naming deficits probably based on a general impairment of basal word finding processes seem to be a typical aspect of language dysfunction in ALS (108). The capability to communicate effectively and comprehensible by means of HT-AAC can be further critically aggravated by a lack of comprehension and thus errors concerning semantic, syntax or grammar of language. Such problems were found to affect almost 50% of all ALS-patients (109), already in early disease stages (110) and even when executive functioning is intact (110, 111). They with single word and in particular verb processing (109, 112) and also with continuous speech production in form of e.g., less produced words, shorter utterances, and incomplete sentences (110, 111).

A function especially often reported to be strongly impaired in ALS is (phonemic and semantic) verbal (letter and category) fluency (54, 109, 113). Deficits of fluency in comparison to healthy controls are even present when performance is controlled for patients' reduced motor speed (65, 114). Such deficits can indicate a limited access or principal limitation of the mental vocabulary (115) or a broad semantic deficit (108) and therefore a serious restriction of communication ability.

Although these language function impairments were determined in spoken or written/typed language, they should as well compromise language production by means of HT-AAC devices in terms of comprehensibility, effectiveness, completeness, subjective meaningfulness and value for the recipient. Patients' deficits of language or speech comprehension should hamper communication anyway, irrespective of the means they use for it.

Executive Dysfunctions

Impairments of language function in ALS are reported to be strongly associated with executive dysfunctions (64, 109), some experts even construed them as a pure consequence of the latter (114). Executive function is the most extensively researched cognitive domain in ALS (109) and a population-based study and a meta-analysis confirmed highly prevalent deficits for a variety of standard neuropsychological tests in non-dement ALS-patients (63, 64). A significant lower performance compared to healthy subjects was also found for a complex measure of executive functioning with high ecological validity, controlled for patients' reduced motor speed (65). Generally spoken, executive functions are a group of higher cognitive functions with a crucial role for controlling basal cognitive functions (116) like attention and memory. Hereby, they are necessary for sorted and goal-directed behavior (117) in situations when automated, intuitive or routine behavior is not possible or inadequate (118) and assumed to be of great importance for response initiation and motivation (108). They are therefore obviously important for social interaction and communication (via HT-AAC).

Specific executive functions that are repeatedly reported to be impaired are shifting (114, 119–121) and working memory (114, 122–124), while patients show deficits for explicit measures of inhibition control in some investigations (124) but not in others (121).The high prevalence of verbal fluency deficits is mentioned above, but important again at this point. This is because tasks of verbal fluency and shifting are considered as measures of the executive function of cognitive flexibility and therefore concern the essential interpersonal ability of perspective taking

(117). Since working memory is a precondition of "making sense of written or spoken language whether it is a sentence, a paragraph or longer" [(152), p. 143], deficits of ALS-patients can be assumed to make communication difficult. This is especially true for communication slowed down by HT-AAC-use and for such dealing complex issues. The latter also applies to an impaired ability of (abstract) reasoning which is reported to be common in ALS-patients (65, 125) and a cause of severe language comprehension deficits (126). All these deficits can be suspected to interfere with the ability to judge, which Flaherty-Craig et al. (125) directly assessed through an established cognitive battery and found to be impaired in a clinical relevant extent in 35% of the non-bulbar and over 50% of bulbar-onset-ALS-patients.

Taken together, executive dysfunction common in ALS-patients can be presumed to limit or rule out a clear, stringent, reliable, valid, effective, empathic or purposeful communication that is satisfying for both the patient and interlocutor, even when the patient is cognitively able to operate the AAC device. This high impact is supported by the negative association between subjective executive dysfunction and wellbeing of ALS-patients' caregivers (127).

Social Cognition Deficits

Some of these aspects of successful communication should be importantly influenced by social cognition function as well. This domain includes the abilities to perceive, identify and understand, interpret or attribute social situations and other's cognitive and emotional states and to choose on that basis an appropriate reaction (67, 128, 129); abilities with an obvious importance for successful communication and social interaction and integration Deficits in this domain affect patients with ALSbi and ALSci (67, 99, 130), are associated with executive dysfunctions (67) but also occur in ALS-patients without those (130, 131). The results of a recent meta-analysis even suggests social cognition to be stronger compromised than executive functions (54).

Emotion recognition and Theory of Mind are most frequently studied in ALS-patients (67). Meta analyses report moderate deficits in facial emotion recognition for anger, sadness and disgust (132) and for disgust and surprise, respectively (67)–an inconsistency that can probably be explained amongst others reasons by the heterogeneity of the used measures and of the clinical and cognitive features of the mainly small study samples. A recent study confirmed deficits of correct emotion recognition in face as well as in voice even for ALS-patients with otherwise unimpaired cognitive abilities, but particularly for complex emotion expressions (133). Irrespective of the specific (negative) emotions though, a lacking ability of identifying and consequently attributing them correctly and responding to them adequately can be considered to be very dissatisfying for patient and interlocutor, causing frustration and interpersonal conflicts; all aspects possibly affecting HT-AAC use and validity of QoL measures of locked-in patients which has not yet been studied.

This is just as true for deficits in Theory of mind, a complex concept that includes the ability of perspective-taking (ToM-PT) according to understand other persons' behavior by representing their emotions and cognitions, e.g., thoughts and beliefs (134, 135). In accordance with findings for cognitive flexibility reported above, meta-analyses proved a lower performance of ALS-patients in different measures of ToM-PT compared to healthy controls (67, 132). This finding is confirmed by a recent study for early-stage ALS-patients (136) while again nothing is known yet in very advanced stages. Deficits are repeatedly reported to be more pronounced in ALS with bulbar onset (125, 132, 136, 137) and therefore in the subgroup of patients that is more frequently or earlier dependent of HT-AAC support for communication.

Considering that human behavior is crucially motivated and determined by emotional and social goals (128), the quantity, subjective quality and thereby value of communication can be assumed to suffer under discussed deficits. This is true for the ALS-patients themselves but especially for their next of kin, as the deficits potentially compromise the relationship, intimacy and their wellbeing and quality of life; like it is known to result from ALS-caused changes in behavior, cognition and communication in general (138).

This assumption is importantly supported by findings of changes in social behavior observed by primary caregivers: 70% showed an increased self-centeredness and a reduced interest for the feelings of others persons (139). A study by Fisher et al. (66) further suggests a lack of patients' insight into their social cognition and consequently social behavior impairment and therefore a lack of awareness of its effect on communication and interaction partners, which can be assumed to even increase the burden due to this impairment for the next of kin.

Additionally, the negative impacts of social cognition deficits can be presumed to be strengthened by general characteristics of the disease and of communication via HT-AAC: mimic and gestures are strictly limited, eye contact is not possible while speaking or to say writing, communication is slowed down immensely and the voice output does not transport any emotions.

Memory Impairment

Memory functions have been studied very frequently in ALS and deficits were found by a lot, although not by all studies (99). Focusing their importance for communication ability, immediate (54, 63) and delayed verbal memory are often severely impaired in ALS, also again when controlled for reduced motor speed (54). Recent findings suggest that such deficits are independent from executive dysfunctions (140). Immediate and delayed prose memory (saying recall of stories) as a special type of verbal memory was found to be affected in over 20% of high-functioning ALS-patients (141). In accordance with word-finding and naming-deficits, disturbances in sematic memory seem to affect more than the half of the ALS-population (142).

Behavioral Changes

Despite cognitive deficits–although not independent from them and often hard to distinguish (108)–frontal lobe dysfunction is associated with various significant behavioral changes and neuropsychiatric symptoms in ALS, frequently disinhibition, mood disturbances, and in particular apathy (104, 108, 133, 139, 143–147). Regarding the issue of patient's motivation to communicate, studies by Lillo et al. (124, 143) for example found

significant symptoms of apathy in ALS, particularly a crucially limited motivation in 80% and a significant apathy in about 40% of the 92 enrolled patients (143). These syndromes were reported by caregivers in the questionnaire CBI-R (148), which assesses motivation mainly according to social motivation, e.g., as the motivation to stay in contact with significant others, show affection to them and be interested in their issues and concerns. Therefore, this finding is in accordance and probably directly connected with deficits of social cognition and behavior illustrated before. For other measures, caregivers report a clinical relevant apathy for up 40–60% of the ALS-patients (139, 146, 147). The significance of apathy for communication and social interaction is in accordance with the finding that caregivers and next of kin report a reduced initiation of conversations by the ALS-patients compared to premorbid behavior (66, 146) to show a reduced initiation of conversations. It can be moreover assumed that a lack of motivation up to apathy might especially affect communication by means of HT-AAC, regarding the high effort that is required for training and use of such devices for communication purposes, e.g., choosing every letter of a message via eye movement. Not surprisingly, apathy is strongly associated with caregiver burden (133).

Depressive symptomatology is another factor that must be considered to compromise patients' motivation to communicate. A clinical relevant severity is reported for 30–60% of the ALS-patients (45, 51, 149, 150). Equivalent to dysexecutive syndrome, behavioral changes in ALS are negatively correlated with caregivers' psychological wellbeing (147).

Consequences of Cognitive and Behavioral Dysfunctions for HT-AAC

In summary it can be argued that frequent cognitive and behavioral deficits and impairments in ALS have a negative effect on communication in general and in particular by means of low and high tech AAC. Therefore, they form a mayor challenge for adapting those devices to the individual patient with the aim of maintaining and supporting subjective value of and motivation for communication in both patients and communication partners. Changes in cognitive function should thus be monitored continuously, on the one hand to support this continuous adaption process and on the other hand to prepare patients and next of kins for upcoming challenges and (further) limitations of communication possibilities (91).

In the case of LIS, this objective is particularly challenging and at the same time very important to be achieved. Challenging because it requires motor and speech free tests and thus emphasizes the significance of developing eyetracking-based neuropsychological tests. Important, first because a restriction of direct communication via HT-AAC due to cognitive or behavioral deficits cannot or hardly be compensated by indirect communication in form of, for example, gestures and mimic. Second, because tests suitable for LIS-patients are needed to understand the natural history of ALS; referring to the Braak staging system in particular (151–153), this means to understand whether the progressive pathological involvement of brain structures, including such responsible for cognitive functions especially in late ALS-stages, continues also in the stage of LIS until TLIS. Third, because of the relevance of cognitive impairment for the highly important conclusions from discrepancies between patient's and next of kin's opinion concerning QoL and life prolonging measures. Concerning possible adaptions of HT-AAC devices for communication purposes to cognitive limitations, language dysfunction is–at least for mild to moderate severity–most likely the easiest part to compensate by high-tech devices. (Individualized) word prediction and word and sentence templates can facilitate language production and comprehension. A possible adaption of HT-AAC devices e.g., for LIS-patients with aphasia is the use of a symbol-based interface, which allows patients to express at least basic needs and wants and to control technical devices like TV, radio or lights.

However, deterioration of cognition can make the use of HT-AAC impractical (18), in particular when patients progress into a FTD. It can be additionally assumed that frontal dysfunctions adversely interfere with the patient's motivation as well as the ability to judge the need for using HT-AAC devices for communication, based on a lack of insight e.g., in the non-comprehensibility of the own spoken language. This idea is indirectly supported by data suggesting an association between cognitive and behavioral impairment and low compliance with treatment in ALS (145).

Impaired cognitive and especially high cognitive functions like reasoning and social cognition that might crucially limit the ability to judge play moreover an especially critical or even devastating role when it comes to decisions over life-prolonging measures (108), concerning reliability and validity of such decision in view of the discussed importance of HT-AAC for making them autonomously. This is particularly true when patients' and next of kin's opinions in this matter diverge, considering the consequences of such decisions also for the family and the patient's beloved ones.

The authors believe that it is therefore highly important to clearly diagnose cognitive and behavioral disturbances also in advanced disease stages including LIS. Having a clear diagnosis of dementia or cognitive or social impairment enables the responsible care takers or medical doctors to draw the right conclusions. On the side of the caretaker, this can mean to correctly interpret the patient's unsatisfying (e.g., diminished or non-empathic) communicative behavior, this is to say as a consequence of the disease, which can be relieving. Discussed findings of rejection of ETCS devices by family members and their higher burden after the patient's supply with the communication device (37, 44) support this idea. On side of the caretaker and the attending physicians, drawing the right conclusions might also mean to decide to limit life-prolonging measures. Concerning such decisions with regard to the patient's will, cognitive diagnostic and an earliest possible psychoeducation for patients and next of kin/caregiver about the frequent cognitive and behavioral deficits of ALS is important: first, to emphasize the need to continuously clarify and record this will in written (e.g., in a patient decree), since cognitive impairment might inhibit a reliable or valid decision at some points; second to allow patients and their families to take in

account possible severe cognitive decline in future as an explicit factor for such life-prolonging/ending decisions (e.g., the will to end life prolonging measures in case of FTD or when the patient is not able to communicate via HT-AAC anymore).

BRAIN-COMPUTER INTERFACES

Discussed limitations and shortfalls of ECTS systems as means for communication and environment control raise the question whether there are alternative technological HT-AAC approaches. Brain computer interfaces (BCI) could in theory be one answer, particularly for the mentioned subgroup of (long-surviving) ALS-patients in whom the usability of ETCS is compromised by oculomotor dysfunctions (76), gaze fatigue (154) or the loss of eye movement control in TLIS (155). BCI systems enable e.g., computer operation by voluntary modulation of one's own brain activity which is decoded into commands (e.g., selection of an item) without requiring any motor control (156–158). They are therefore considered a promising communication tool for advanced ALS or LIS-patients, respectively (159–162) and the only remaining option for TLIS-patients (163) or those with severe gaze dysfunction in general (82). It is another advantage over ETCS systems that BCI systems don't require still and strict frontal positioning to the screen (164).

While invasive BCI methods like intracortical electrodes have been primarily studied in animal research (165) and infrequently in tetraplegic patients (166), a number of non-invasive BCI systems has been evaluated in severely paralyzed patients including ALS-patients in (T)LIS (98, 160, 162). The majority of these systems have been developed for spelling or writing or texting (167) which is allowed by selection of letters, words or phrases presented on a screen (98).

In this context, reviews valuate non-invasive BCI based on EEG as a practicable, promising and the most widely used approach (98, 168). Also ALS-studies provide evidence for the principle feasibility of such systems for a relevant proportion of patients. Those BCI devices are based on shifting of particular brain responses measured as EEG-parameters: slow cortical potentials (169–171), sensimotor rhythms (SMR) (155, 172, 173) and the event related potential P3 (164, 173–181).

Communication is one of the BCI-functions that ALS-patients are mostly interested in (182) and with the focus of this review on the importance of communication in palliative care and thus on spelling BCI systems, P3 is the most frequently used and studied EEG parameter (98). The principle of most (P3-)BCI-spelling protocols is the following (98): an e.g., 6×6 matrix of items, usually letters, is presented on a screen and the patient is instructed to concentrate on the target item. Different rows or columns flash rapidly in succession. The P3 can be measured about 300 ms after the item flashes and by averaging the P3-amplitudes following each flash, the target item can be identified [e.g., (173, 175)].

Usual objective evaluation criteria for such BCI are the effectiveness, i.e., classification accuracy (CA) defined as the "percentage of correct target selection" (183) and the efficiency (spelling speed). People with ALS declare a CA-threshold of 90% as satisfying (184). On this basis, all of the 20 ALS-patients in a recent study by Guy et al. (164) achieve a satisfying CA in the simpler task of copying a text ("copy spelling"), although it was lower that 90% for writing a text of their choice ("free spelling"). Anyway, patients reported an overall high user satisfaction (average 8.7 on a 10-point-scale). However and importantly, dysarthria was no inclusion criteria for the study, no subject was defined as (T)LIS and all showed unimpaired gaze control. This is in accordance with a mean CA of 92% reported by Pires et al. (179) for a classical spelling paradigm, whereby they included almost exclusively early-stage ALS-patients with even lower physical disability. A study of more severely motor impaired but also visually unimpaired ALS-patients ($N = 14$) only reported the maximum accuracy: it was circa 96% and did not differ significantly between patients and age-matched controls (175). In a previous study conducted by the same research group, 17 of the 25 enrolled patients achieved a high accuracy (average CA 92%), but an accuracy below 40% for the remaining 8 patients indicates no usability of the BCI for communication; importantly, the latter patients all suffered from some type of visual dysfunction (176).

Overall, however, most studies report for ALS-patients with varying disability-levels and without controlling for visual deficits accuracy-rates that fall significantly below the 90% threshold (155, 170, 172–174, 181, 185). This is in line with the average CA of 73.7 %, reported in a meta-analysis by Marchett and Priftis (183). Although higher spelling accuracy for able-bodied/healthy controls than for patients is reported (186), no evidence for a worse performance in ALS-patients with higher compared to those with lower physical disability is provided by very few studies with a sufficient sample size for analyzing this influence (172, 175, 176). For (T)LIS-patients in particular though, there are only few and only case studies; two of them actually found high and stable effectivity of and satisfaction with a P3-BCI-system for spelling (180) and painting (187), while one reports several unsuccessful trials of implementing a BCI in one patient transferring from LIS to TLIS (163).

An efficacy-related problem that would crucially compromise the BCI-usability in the context of palliative care for patients with such a quickly progressing disease like ALS are the very long training sessions required for reaching outlined accuracies (179). Another practical issue would be the long time that is needed to set up an EEG-BCI (164).

With respect to efficacy in potential future everyday use of BCI arises another main problem: the consistently reported low efficiency of spelling, i.e., in real-life use the slow potential communication speed. While ALS-patients indicate a spelling rate of 15–19 words per minute as satisfying (184)–with a word is standardized to consist of five letters on average (188)–rates in recent P3-BCI-studies range between 2.1 words and 5.0 words (164, 175); and are even much lower (one letter, i.e., about 0.2 words per minute) for EEG-systems using SCR (171) and SMR-modulation (189). This problem is qualified by the patients mostly high satisfaction with BCI though (164, 171)–a finding which supports that speed is less relevant for (T)LIS-patients than the possibility to communicate at all and in a reliable manner (180, 184).

With regard to obligatory decision in palliative care and particularly those regarding life-ending-choices, even a BCI for yes/no-questions could be crucial for these patients without any other possibility to express their needs and decisions– but a very high validity and reliability would be even more essential for this purpose Chaudhary et al. (162) were the first to evaluate a BCI for yes/no-answers in 4 TLIS- or patients transferring from LIS to TLIS, which relies on measuring change in frontocentral hemoglobin. The correct-response rate about 70% is still very unsatisfying although it could be valued as a promising base for further developments. In conclusion of this chapter it is important to note that a lot of the described pitfalls (see chapter Limitations and pitfalls of HT-AAC-use and -supply) and especially those due to cognitive impairment (see chapter Cognitive and behavioral impairment and its consequences for HT-AAC-use) account for BCI use as well.

FUTURE DIRECTIONS

From the reviewed literature it can be concluded that there is tremendous need for further research on the impact of HT-AAC, technical progress of the devices and for an increased awareness of upcoming opportunities and the importance of communication on wellbeing by professionals caring for severely disabled patients and by policy-makers.

Future Technological Developments

A main obstacle for mobile use of ETCS is that they are bound to be used in conjunction with a computer screen. Eyetracking devices are typically mounted at the bottom of the computer screen, on which the user interface, e.g., an on screen keyboard, is displayed. In the near future with advances in augmented and virtual reality, head mounted systems with built in eyetracking capabilities may be applied. In addition to the advantage of being more portable, a see-through display would have the benefit of allowing the user to look at its communication partner and vice versa during conversation. In nowadays systems the computer screen is blocking the line of sight between the two partners, leading to subjectively reduced closeness as described above [e.g., (190)]. In order to reduce the sensitivity of ETCS to adverse lightning conditions, non-infrared based camera approaches may be used in the future, although they have not yet provided the level of accuracy that is needed for good gaze control.

We conclude from the discussed reports that existing (P3-)BCI systems for spelling/communication purposes do not allow and are not suggested for use in standard palliative care of ALS-patients at this point of time, especially in light of patient's quite high expectations on BCI-use (182). Concerning on the one hand patients that are (still) able to use ETCS, this conclusion supports the statement of Marchetti and Priftis (183) that (P3-based) BCIs for spelling still have many disadvantages and no clear advantage that would feature them as an alternative communication tool in daily use. It is however important to note already existing modifications of visual stimuli presentation (174, 179, 185) and technical improvements for existing BCIs (177) that increase their accuracy significantly. Kaufmann and colleagues (185) for example could increase brain responses and consequently CA by integrating well known faces in the matrix in addition to the letters.

Concerning on the other hand ALS-patients that can't use ETCS anymore, BCI systems need to be primarily more effective and secondarily more efficient than they are at the moment, but would be then highly significant for this patient subgroup. Moreover, concerning TLIS-patients as well as the evidence for lower spelling accuracy because of visual problems, there is an indication for non-visual BCIs. Auditory or tactile BCIs exist, but are less widely studied up to now (191, 192). A case study of a LIS-patients found clear superiority of tactile modality (185), while a comparison between a visual and equivalent auditory P3-system indicates the latter as a still less accurate but still promising option for LIS- and TLIS-patients with visual deficits (155). In accordance with that, a LIS-patient with subjectively worsening gaze control expressed in a case study of Käthner et al. (82) his preference for an auditory BCI over ETCS, although the latter showed significantly higher accuracy rates and communication speed.

BCI are therefore an important field of research with regard to the objective to secure self-determination and QoL in every, including the terminal phase of life of patients with most severe disabilities. So far, very few case studies explored BCI usability outside an experimental setting (187, 193). One of these studies though even found evidence for a relevant positive impact of BCI-use for spelling on QoL of a single TLIS-patient (193). Future studies need to examine larger and more samples of (T)LIS-patients in their living environment and everyday life.

The development of inexpensive hard- and software that can be easily adapted to multiple access modes and customized to the patients' individual needs should be a general goal. In the COGAIN ("communication by gaze interaction"; www.COGAIN.org) European Network of Excellence professionals and researchers collaborate toward developing advanced gaze based communication technologies in order to enhance applicability and user satisfaction of the devices and ensure quality control in patient care and research (194).

Health Policy and Attitudes

In addition to ALS and other motor neuron diseases, there is a high potential for HT-AAC to improve care for patients with other acquired neurological conditions that lead to impaired communication abilities, e.g., traumatic brain injury, brainstem impairment, severe chronic aphasia and apraxia of speech, primary progressive aphasia, and dementia (18). Depending on the particular type and extent of communication and/or motor and/or cognitive impairment that are caused by these conditions, different kinds of AAC-systems and functions can be assumed the most useful ones for the patient (e.g., typing vs. eyetracking communication devices; auto-correction function for aphasia patients). Based on an epidemiological approach, Creer et al. (195) estimated the prevalence of people who could benefit from AAC technologies in the UK at 0.5%.

Enabling the individual's optimal communication capabilities should be the standard of care in order to maintain QoL and self-determination in the comprehensive and palliative care for all human beings including severely disabled

patients. The German treatment guidelines for ALS (https: www.dgn.org/leitlinien/3012-ll-18-ll-amyotrophe-lateralsklerose-motoneuronerkrankungen) contain the general information that in case of dysarthria, dynamic AAC technologies with speech output and environment control should be procured. However, the guidelines do not offer detailed recommendations for assessment of communicative abilities for AAC evaluation and supply and do not refer to their value for patients' QoL. Moreover, they are not legally binding.

Furthermore, advance care planning in ALS should explicitly consider the possibility that patients' can reach a disease state in which communication is not possible at all. Advance care planning and power of attorney for caregivers, also including the termination of life-sustaining measures in ALS and other severe neurological disorders, is however a complex issue and thus beyond the focus of this review.

CONCLUSIONS

Usually, the term "palliative care" is not associated with high-technologies, probably because they are supposed to contribute to the dehumanization of medicine and the superiority of survival over QoL. However, HT-AAC devices are not conceived to prolong survival, but to enhance QoL and autonomy for the remaining lifetime which is a core component of palliative care. These HT-AAC devices thus should play an exceptional role in palliative care compared to many other high-tech devices normally used to prolong survival.

HT-AAC have a high potential for improving palliative care for people with ALS and other severe diseases that lead to impaired communication abilities. Several studies convincingly demonstrated that complex and caregiver-independent communication is enabled by HT-AAC, which is crucial for addressing psychological, spiritual, and essential issues in palliative care. Within the current knowledge, the use of HT-AAC respectively the optimization of patients' ability to communicate leads to improved QoL and better wellbeing and enables the maintenance of social roles and intellectual stimulation. Moreover, communication is essential for the prevention of patient autonomy concerning end-of-life care and decisions. The use of HT-AAC can therefore lead additionally to reduced caregiver-burden and strengthen family cohesion, which however needs further independent investigations, also concerning critical issues like barriers of acceptance of the devices.

The technology does also still possess unresolved pitfalls. These can be grouped by different aspects:

(i) Technically, limitations mainly arise from the infrared camera system with respect to distinct light conditions (mainly outside), wearing of glasses and body positioning.
(ii) Disease conditions such as cognitive, e.g. executive or social cognition deficits up to advanced dementia, language impairments including aphasia, but also TLIS or other eye-gaze alterations obviously raise difficulties.
(iii) Critical issues which can be solved more easily are such as barriers of acceptance amongst patients and caregivers, lack of awareness by both health care professionals and politicians/social system and the lack of clear and binding guidelines. The latter is also important to oblige HT-AAC providers to continually support the customer.

Healthcare professionals, technology providers as well as policy makers need a greater awareness of the possibilities but also of possible pitfalls of HT-AAC technologies. They are required to enable timely access to adequate, user-friendly and individually tailored equipment and provide ongoing training, customization and support (14), without letting quality of support suffer at the expense of cost effectiveness. This can be best achieved by individual evaluation of the patients' needs and concerns and by sufficient and continuous training in handling of the devices. It also includes the retraction of HT-AAC devices under certain circumstances, which might be severe dementia, development of significant gaze palsy or TLIS or also the patient's wish to return the device, which should optimally be properly assessed by means of the HT-AAC device.

On the basis of past and future research, detailed and binding guidelines that support patients' supply with AAC devices should be developed in order to ensure effective communication. Patients have to be enabled to make informed decisions for or against any communication support in order to allow the longest period of lifetime with the best possible QoL in accordance with their free will and their individual aims and wishes.

There is tremendous need for further research on the impact of HT-AAC, technical progress of the devices and for an increased awareness of upcoming opportunities and the importance of communication on wellbeing by professionals caring for severely disabled patients and by policy-makers. The consideration of HT-AAC interventions should be embedded as mandatory in multidisciplinary palliative care in order to enable autonomy by ensuring access to the best individually tailored communication strategies and their adjustment to changing needs of patients with ALS.

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All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Death Anxiety and Depression in Amyotrophic Lateral Sclerosis Patients and Their Primary Caregivers

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Background: Given the lethal severity of amyotrophic lateral sclerosis (ALS), the aim of this study was to illuminate the coherence of depression and death anxiety in both ALS patients and caregivers and in how far patients and caregivers are influenced by the mindset of their respective counterpart.

Methods: 30 couples of patients (mean age 60.57; 13 women, 17 men) and primary caregivers (mean age 57.33; 16 women, 14 men) were included into the study. Death anxiety was assessed using the newly developed BOFRETTA scale, depression via Beck Depression Inventory, anxiety by means of State Trait Anxiety Inventory and caregivers' exertion using the Caregiver Strain Index. Patients' impairment was assessed with the ALS functional rating scale.

Results: We found that while death anxiety was related to depression in both patients and caregivers, death anxiety was related to anxiety only in patients. Caregiver strain correlated with both caregiver's depression and anxiety. Moreover, patients' and caregivers' depression, anxiety and death anxiety correlated to the ones of their counterpart.

Conclusion: These results suggest that despite little depressive symptoms in ALS patients the fatal prognosis of the disease takes into account, depression and death anxiety influence each other and might be addressed together in pharmacological and especially psychotherapeutic interventions to the benefit of the patient. Medical professionals should not forget to offer sufficient support to caregivers tending patients affected by depression and death anxiety as they are likely to mirror their patient's feelings.

Keywords: amyotrophic lateral sclerosis, motor neuron disease, ALS-FRS, death anxiety, BOFRETTA, caregivers

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is the most common motor neuron disease with a prevalence of 6 cases per 100.000 persons, whereas the incidence is approximately 1–2 cases/100.000 persons (1). With rapidly progressive degeneration of both first and second motor neuron, ALS has a mean mortality rate of 50% in just 3 years (2). Despite this severe prognosis, clinical depression is less frequent than one might expect (3) with different studies suggesting rates of 9–12% (4–6).

Thus, depression is less common in ALS patients than in patients suffering from other diseases of comparable impact on patients' lives and agility like multiple sclerosis (7) or cancer (8), although death is mostly less imminent in these diseases. Anxiety, e.g., measured with the State-Trait Anxiety Inventory (STAI), amounts to likewise low levels albeit it is much less frequently studied (9). Furthermore, no consistent association between depression as well as other psychopathological impairments and wish to die in ALS patients were found (5, 6, 10). In how far defense mechanisms like denial come into effect here, is unknown. Some studies admit the conclusion that at least in the terminal phase such mechanisms play a role to make the situation endurable since the degree of death anxiety is related to the denial of one's own finiteness (11). The conversion of death anxiety into situational anxiety limits the perception of one's own finiteness and has therefore been stated as a coping strategy (12). Failure of such coping strategies may serve as a catalyst for the formation of mental disorders like depression as pathologic dimensions of death anxiety have been discussed to relate to other mental disorders, e.g., anxiety disorders (13). The few studies touching the subject of anxiety in ALS patients suggest that anxiety in general and thus presumably also death anxiety mostly occur in early stages of the disease and the diagnostic phase and to lesser extent in the course of the disease which is marked by progressive bodily impairment (14–17). It is yet left for speculation whether the little signs of depression and anxiety in the majority of ALS patients, that might appear like acceptance of the disease to outsiders, are a sign of a coping strategy of whatever nature, are caused by the cerebral alterations in cognition and emotion, which take place even in early stages of ALS (18), or have yet another explanation.

Taking into account the rapidly progressing impairment that makes patients dependent on assistance and thus exacts a close daily contact between patient and caregiver, it appears inevitable to evaluate on the one hand in how far and under which circumstances this relation acts protective or may lead to the exacerbation of the surveyed values of depression and anxiety in the patient and on the other hand the effect on the caregiver of the patient's state of mind and vice versa. Studies involving caregivers of ALS patients have shown that a sophisticated evaluation of quality of life, coping strategies, and anxiety are pivotal to develop suitable therapy and relief efforts (15). More than 30% of caregivers of ALS patients have been reported to indicate a marked worsening of their situation with a reduced quality of life (19). A somatic affection of caregivers has likewise been reported several times (18, 20), but this appears to be related more to levels of depression of the relative suffering from ALS (21), which underlines once more the interrelation between caregiver and patient.

Considering the hardly comprehensible reaction of ALS patients to their severe disease in the sense of few depressive symptoms and anxiety, the aim of this study was therefore to further illuminate the ties of depression, anxiety and death anxiety with respect to the setting of a close contact of ALS patient and caregiver.

We hope that our findings will further facilitate the establishment of adequate support measures and therapies for the coping of severe diseases like ALS for patients themselves and their caregivers in the interest of mental health.

MATERIALS AND METHODS

We interviewed a succession of 30 couples of patients and their primary caregivers seen in our outpatient clinic specializing in ALS. The patients, commonly accompanied by their caregiver, are seen at regular intervals of about 3–4 months on average for evaluation of disease development and assistive device need. Inclusion criteria consisted of ALS diagnosis in accordance with revised El Escorial criteria (22) and fluency in German.

Table 1 shows the socio-demographic and clinical data of the 30 patients and their caregivers being included in the study. Most patients were receiving a variety of constant medications including riluzole (80%) agent.

All participants gave written informed consent after the study purpose was explained in detail. The ethics committee of the Medical Faculty of the Ruhr-University Bochum, Germany, approved the study. It was carried out in accordance with the Declaration of Helsinki of 1975.

Clinical Assessment

Severity of depressive symptoms was assessed using the Beck Depression Inventory [BDI; (23)], which generates a score from 0 to 63 with 0–12 indicating no depression, 13–19 mild, 20–28 medium, and $\geq$29 severe depression.

State anxiety was examined using the State-Trait Anxiety Inventory. The score ranges from 20 to 80 with 20–39 indicating low, 40–59 medium, and $\geq$60 high anxiety (24, 25).

The Caregiver Strain Index (CSI) by Robinson (26) on the other hand is a questionnaire with 13 items to be answered with either Yes or No, which depicts the caregivers strain (e.g., due to loss of sleep, changes in private life or bothering behavior). The CSI was only given to the caregivers.

For the evaluation of death anxiety in particular we utilized the BOFRETTA-Scale (27) for the first time, containing 25 statements about attitude toward (10 items) and anxiety for (15 items) death. The scale is based on or taking cue for its modification from Templer's death anxiety scale (28), Lester's death anxiety scale (29) and the question inventory for multi-dimensional evaluation of experience of dying and death [FIMEST; (30)]. To answer the semiquantitative BOFRETTA-scale one can indicate one's accordance with the statements by choosing between "does not apply at all" (1 point), "applies slightly" (2 points), "applies predominantly" (3 points), or "applies mostly" (4 points), amounting to scores from 10 to 40

TABLE 1 | Socio-demographic and clinical characteristics of patients (PAT) and caregivers (CG).

	PAT ($n = 30$)	CG ($n = 30$)	*t*-Test
GENDER			
Female, *n*	13 (43.3%)	16 (53.3%)	
Male, *n*	17 (56.7%)	14 (46.7%)	
AGE			
Mean (*SD*)	60.57 (8.52)	57.33 (9.47)	
Range	44–78 years	38–75 years	
FAMILY STATUS			
Married/with partner, *n*	26 (86.7%)	29 (96.7%)	
Single, *n*	1 (3.3%)	0	
Divorced/widowed, *n*	3 (10%)	1 (3.3%)	
EDUCATIONAL BACKGROUND			
13 years of school, *n*	7 (23.3%)	10 (33.3%)	
10 years of school, *n*	13 (43.3%)	12 (40%)	
9 years of school, *n*	10 (33.3%)	6 (20%)	
Did not graduate, *n*	0	2 (6.7%)	
EMPLOYMENT STATUS			
Employed, *n*	8 (26.7%)	18 (60%)	
Retired, *n*	11 (43.7%)	9 (30%)	
Retired due to ALS, *n*	8 (26.7%)	–	
Unemployed/homemaker	3 (10%)	1 (3.3%)	
Other/did not answer	0	2 (6.6%)	
CLINICAL SCORES			
ALS-FRS mean (*SD*)	32.57 (9.51)	–	
Disease duration (*SD*), Years	2.48 (2.0)	–	
Hours/day spent with caring (*SD*)	–	3.37 (2.85)	
Affection of own health	–	10 (33.3%)	
BDI mean (*SD*)	11.93 (8.40)	8.07 (8.08)	ns
STAIs mean (*SD*)	40.67 (12.5)	45.67 (11.62)	ns
CSI, mean (*SD*)	–	4.67 (3.48)	
BOFRETTA anxiety (*SD*)	25.97 (9.85)	23.5 (8.33)	ns
BOFRETTA attitude (*SD*)	17.43 (3.78)	16.33 (4.05)	ns

ALS-FRS, ALS Functional Rating Scale; BDI, Beck Depression Inventory; STAIs, State-Trait Anxiety Inventory, state subscale; CSI, Caregiver Strain Index; BOFRETTA, Bochumer Fragebogen zur Einstellung zum Tod und zur Angst vor dem Tod (Bochum Questionnaire regarding Attitude toward and Anxiety for Death), subscales anxiety and attitude; ns, non-significant.

for the subscale "attitude toward death" (items number 2, 3, 10, 16, 17, 19, 21–23, 25, and 15–60 for the subscale "death anxiety" (items number 1, 4–9, 11–15, 18, 20, 24). As qualitative analysis, the participant may express personal thoughts or concerns, respectively toward death in two free text columns.

The patient's physical impairment due to the disease was assessed by the ALS functional rating scale [ALSFRS-R; (31)] which reaches from 48 (no impairment at all) to 0 (locked-in syndrome), which is routinely taken in the outpatient clinic.

Statistics

Further statistical analyses of the neuropsychological data were performed using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA). Statistical analyses were performed with appropriate parametric or non-parametric tests (*t*-test and Pearson or Spearman correlation coefficients). Statistical significance was defined as $p < 0.05$. A value of $p < 0.10$ was regarded as statistical tendency.

RESULTS

Patients

The socio-demographic characteristics as well as psychometric scores of the 30 patients interviewed (17 men and 13 women) are summarized in **Table 1**. The patients had a mean age of 60.57 years (*SD* 8.52) and suffered from ALS for 2.48 years (*SD* 2.0) on average. The mean ALSFRS-R was 32.57 (*SD* 9.51).

The mean BDI score amounted to 11.93 (*SD* 8.40), signifying a score which is just still within the non-depressive range. 18 (60%) of the patients interviewed were in the non-depressive range according to BDI, while 9 (30%) had mild, 2 (6.7%) medium, and just 1 (3.3%) patient severe depression.

As for the STAI, the average patient score was 40.67 (*SD* 12.5), lying just inside of the medium anxious range. Nevertheless, the biggest group of 15 patients (50%) showed low signs of anxiety, while 12 (40%) were in the medium range and 3 (10%) in the high range.

When assessed by means of the BOFRETTA death anxiety subscale the average patient score was 25.97 (*SD* 9.85). Taking into account the range from minimum 15 to maximum 60, this is a mean score within the lower third. Anyhow, the maximum score of any patient interviewed was 54. Similar patterns apply to the BOFRETTA attitudes toward death subscale with a possible range from 10 to 40, where we found a mean patient score of 17.43 (*SD* 3.78), thus not particularly negative.

Caregivers

The mean age of the 30 interviewed caregivers (16 women and 14 men) was 57.33 years (*SD* 9.47). For a summary of socio-demographic and psychometric parameters see **Table 1** again.

The average BDI score of caregivers was 8.07 (*SD* 8.08), which is more clearly within the non-depressive range compared to patients. Accordingly, 24 (80%) of caregivers achieved non-depressive scores, while 4 (13.3%) had mild, and each 1 caregiver (3.3%) had medium or severe depression.

45.67 (*SD* 11.62) was the mean STAI score, making it the only parameter caregivers scored higher than patients (though the difference is statistically non-significant). This is within the medium anxious range. 12 (40%) of caregivers showed low, 16 (53.3%) medium, and 2 (6.6%) high signs of anxiety.

BOFRETTA anxiety subscale amounted to 23.5 (*SD* 8.33) on average and BOFRETTA attitude subscale to 16.33 (*SD* 4.05)—both scores likewise within the lower third.

Finally, the CSI resulted in a mean 4.67 (*SD* 3.48), which can be classified on the verge of low to medium third of caregiver strain, given that the scale ranges from 1 to 13. The highest CSI score found in our study was 11. The caregivers spent 3.37 h a day (*SD* 2.85) on average caring for their relative. 10 (33.3%) of caregivers reported an affection of their own health due to caring. Most stated psychic symptoms (stress, difficulties to concentrate

or to sleep, feeling "burnt out," tension) and just two somatic symptoms were stated (dorsal pain, irritable bowel syndrome).

Comparison of Couple Scores

Sociodemographic parameters as well as psychometric scores did not differ significantly between patients and caregivers.

We found various correlations between scores of patients and caregivers (see **Table 2**): Patients' and Caregivers' depression related to the ones of their particular counterpart highly significantly, just like patients' and caregivers' anxiety. While patients' depression did not relate to caregivers' anxiety, patients' anxiety related to caregivers' depression, indicating a specific pattern of reaction on either side to the perceived emotions of one's relative.

While death anxiety of patients and caregivers correlated with each other, this was not the case for attitudes toward death. Besides, patients' death anxiety and caregivers' depression related to each other.

The years of patients has already lived with ALS has no relation to the caregiver's strain. The ALSFRS-R relates negatively to the CSI, thus meaning higher bodily impairment imposes more caregiver strain. Nevertheless, the ALSFRS-R does not relate to caregivers' depression, anxiety, death anxiety, or attitudes toward death.

Psychometric Correlations

Correlations of psychometric and clinical parameters are summarized in **Table 3**.

Anxiety and depression scores correlated highly significantly to each other for both patients and caregivers. Death anxiety correlated with negative attitudes toward death and depression.

In patients, ALSFRS-R correlated negatively to BDI scores. As low ALSFRS-R scores reproduce high bodily impairment due to the disease, this indicates that patients in a worse physical condition are more prone to depression. Anxiety correlated to death anxiety and negative attitudes toward death; negative attitudes toward death correlated to depression.

Taking a closer look at the caregivers, we found that caregiver strain as screened by CSI correlated with depression, anxiety and the amount of hours spent caring per day. The amount of hours spent caring also correlates with depression, while the affection of the caregiver's own health correlates with anxiety.

DISCUSSION

Integrating our findings into the relevant literature, we found rates for depression of patients on similar low levels (4–6), even if only taking into account studies likewise using the BDI to assess depression (9) as different diagnostic tools sometimes lead to varying results. Patients also seem to be not particularly anxious mirroring findings of Vignola et al. (15) for patients a while after diagnosis.

Through ALSFRS-R, we were able to correlate more severe neurological impairment to higher rates of depression, which has also been shown before (5). We could not find a direct relation of neurological impairment to anxiety nor death anxiety in particular. As rates of death anxiety are not high in ALS patients in general according to our findings, one might ascribe it to the fact that views on death are very individual: Just because of increasing health issues, one does not have to become anxious about death as patients might have positive attitudes toward

TABLE 2 | Comparison of couple scores.

Patient score	Caregiver score	Correlation coefficient
BDI	BDI	0.590**
	STAIs	ns
	CSI	0.373*
STAIs	STAIs	0.516**
	BDI	0.708**
BOFRETTA anxiety	BOFRETTA anxiety	0.375*
	BDI	0.466*
BOFRETTA attitude	BOFRETTA attitude	ns
Years with ALS	CSI	ns
ALS-FRS	CSI	−0.629**
	BDI	ns
	STAIs	ns
	BOFRETTA anxiety	ns
	BOFRETTA attitude	ns

*ALS-FRS, ALS Functional Rating Scale; BDI, Beck Depression Inventory; STAIs, State-Trait Anxiety Inventory, state subscale; CSI, Caregiver Strain Index; BOFRETTA, Bochumer Fragebogen zur Einstellung zum Tod und zur Angst vor dem Tod (Bochum Questionnaire regarding Attitude toward and Anxiety for Death), subscales anxiety and attitude; ns, non-significant; *Statistically significant; **Statistically highly significant.*

TABLE 3 | Psychometric correlations.

Scores		Patient ($n = 30$)	Caregiver ($n = 30$)
		Correlation coefficient	Correlation coefficient
ALS-FRS	BDI	−0.374**	–
STAI	BDI	0.652**	0.676**
STAI	BOFRETTA anxiety	0.510**	ns
STAI	BOFRETTA attitude	0.373*	ns
BOFRETTA anxiety	BDI	0.394*	0.432*
BOFRETTA anxiety	BOFRETTA attitude	0.577**	0.744**
BOFRETTA attitude	BDI	0.414*	ns
CSI	BDI	–	0.409*
CSI	STAI	–	0.412*
CSI	Hours/day caring	–	0.729**
Hours/day caring	BDI	–	0.444*
Own health affection	STAI	–	0.413*

*ALS-FRS, ALS Functional Rating Scale; BDI, Beck Depression Inventory; STAIs, State-Trait Anxiety Inventory, state subscale; CSI, Caregiver Strain Index; BOFRETTA, Bochumer Fragebogen zur Einstellung zum Tod und zur Angst vor dem Tod (Bochum Questionnaire regarding Attitude toward and Anxiety for Death), subscales anxiety and attitude; ns, non-significant; *Statistically significant; **Statistically highly significant.*

death, may it be due to religious beliefs or even judging death as a kind of salvation—patients may become depressed due to the impact the disease has on their daily lives and activities. Many patients are able to find meaning in life despite their disease (14), which makes them able to cope with anxiety and death anxiety better.

We found noteworthy relations of depression, death anxiety and anxiety. While depression and anxiety correlates for both patients and caregivers, death anxiety relates to anxiety and negative attitudes toward death only in patients. This is easily explained taking into account that the own death is more imminent for patients, thus likely more often on their mind, making it a probable central aspect of anxiety. With respect to the fact that depression correlates with death anxiety in both patients and caregivers this circumstance, which may appear self-explanatory at first, gets a therapeutic impact: If death anxiety is present, it forms a sort of continuum with depression and anxiety in patients. Fighting depression, professionals might benefit from broaching the issue of death and death anxiety with the patients affected and giving room to talk about the feelings associated. In the largely agnostic societies in Western Europe, persons so suddenly confronted with the finiteness of their own lives, may ask questions they yet never thought about or pushed away. If the patient is open to it, health care professionals might even think about establishing contact to spiritual counsellors—company which is almost standard in hospices but rather not in ambulant palliative care.

The low rates of depression and anxiety we found in patients also apply to caregivers though anxiety seems to be slightly more widespread in caregivers. Albeit the difference is non-significant, as similar findings occurred in another study (15) the question how to relieve the caregivers from their anxiety becomes ever more important. Since there is no relation to death anxiety according to our data, the anxiety might rather be focused on the current situation: e.g., on the development of the loved one's disease and whether the own person will be able to fulfill the caregiving role further onward. These concerns should thus be tackled with sufficient support in the form of auxiliary means for the patient and perhaps even the hiring of professional nursing services.

A low ALSFRS-R as a measure of disease severity does not relate to caregiver's depression or anxiety, signifying that there are caregivers and patients who cope well despite vast progression of the disease. Nevertheless, caregiver strain derives from the severity of ALS as such, own depression and anxiety and also patient's depression. Notwithstanding, higher caregiver strain does not result in more negative attitudes toward death as we hypothesized.

The striking, highly significant relation of depression, anxiety and death anxiety of patients, and caregivers in our study suggests that the patient-caregiver-relation is of huge importance for coping with ALS. As evident from our data and surely noticeable while conducting the interviews, there were couples of patient and caregivers who found ways to deal with the disease and live merely content despite the changes in their daily lives. Other couples were struggling more. If the patient was depressed, the caregiver was quite likely to mirror these feelings and vice versa. This further underlines the importance of keeping an eye on the patient's surroundings and potentially offering medical or psychotherapeutic assistance to the caregiver as well. Likewise, in psychotherapeutic interventions targeting at depression, the patient-caregiver relation possibly ought to be included into the therapeutic sessions and play a pivotal role.

Limitations of our study include a rather small sample size, though this seems to be universal for ALS research. Methodologically, one may criticize the use of questionnaires not entirely suitable for ALS patients with e.g., BDI asking for weight loss which most likely is not a sign of depression but muscle loss in ALS patients and thus overestimating depressive rates. BDI is a well-established device and ALS-specific questionnaires would have made the comparison to caregivers impossible. Apart from that, some patients were treated with antidepressants.

In conclusion, although depression, anxiety, and death anxiety are not particularly common in ALS patients, we found that they widely correlate with each other and should be addressed altogether. Furthermore, the relation of patient and caregiver and their respective mind-sets play a significant role in coping with the disease and therefore should be considered in medical and psychotherapeutic interventions. After all, even a devastating diagnosis like ALS does not inevitably lead to depression and anxiety—we met many resilient couples who positively deal with their situation and find meaning in life.

ETHICS STATEMENT

The ethical commission of Faculty of Medicine of RUB has approved this study under the correspondence number 15/5384 (23.3.17).

AUTHOR CONTRIBUTIONS

PM-J, MT, and GJ designed this study. MG and UW have performed recruitment and assessment of patients and caregivers. MG and PM-J have analyzed the data and wrote the first draft. All authors have approved the final version. This manuscript is part of the doctoral thesis of MG.

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Access to End-of Life Parkinson's Disease Patients Through Patient-Centered Integrated Healthcare

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Background: Palliative care in Parkinson's Disease (PD) patients considerably differs from palliative care in oncology patients. Integrated care models are a concept to support patients and improve management of PD symptoms. However, it is not known if the access to PD patients at the end of life can be achieved through integrated care models.

Aim: To analyze an integrated model of care for PD patients with the aim to identify if this integrated model of care has access to PD patients at the end of life.

Material and Methods: The Cologne Parkinson's network was designed as a randomized, controlled prospective clinical trial in order to increase quality of life of PD patients. This innovative model of care integrated a neurologist in private practice, a movement disorder specialist of the University Hospital and a PD nurse. Mortality rates of PD patients during the study period of 6 months were registered and compared with mortality rates of the general population of Germany according to the Federal Statistical Office of Germany. The retrospective *post-hoc* analysis was conducted after completion of the initial study at the University Hospital and neurologists' practices in the greater area of Cologne, Germany. Eligible patients had a diagnosis of idiopathic PD and were aged 25–85 years.

Results: Parkinson's Disease patients in this trial had an even slightly lower mortality rate as the general population (1.66 v. 2.1%). These results are contradictory and speak for a substantial proportion of late-stage disease patients, who have not been adequately included in this study or have been better treated within this trial. The mean disease duration of patients in this study was around 6 years which resembles the lower range of the mean disease duration at death of PD patients in general.

Conclusions: The results of our *post-hoc* analysis show, that accessing PD patients in the last phase of their disease is extremely difficult and nearly fails in spite of an integrated care approach. Reasons for poor access and loss of follow-up at the end of life have to be identified and care models for PD patients until the end of life should be developed urgently.

Keywords: Parkinson, palliative care, end-of-life, integrated care, late-stage, network

INTRODUCTION

Despite a significant progress in treatment strategies and modern therapy concepts neurodegenerative diseases like idiopathic Parkinson's disease (PD) or atypical Parkinsonian disorders inevitably lead to progressive motor, neuropsychiatric and non-motor symptoms (1–5). Dementias develops in up to 80% of patients after 20 years (6), depressions in more than 40% of patients and psychotic experiences are frequent in PD patients (7). Reduced mobility implicates higher mortality as in the age-related population, specifically due to infections (pneumonia, urinary tract infections) or falls with consecutive fractures (8). According to a recent meta-analysis, mortality in PD patients is increased in a range of 0.9–3.8. The mean duration until death ranges between 6.9 and 14.3 years, where increasing age and development of dementia were most commonly associated with increased mortality (9).

Palliative care in PD patients considerably differs from palliative care provision in oncology patients, in terms of the models of care, the provision and the duration. The beginning of the palliative phase in PD is still not well defined but according to a recent publication it lasts about 2.2 years for PD patients and 1.5 years for APS before death (10). Currently only occasionally palliative care structures are integrated selectively during the course of the disease. Patients with PD/APS die from infections as a consequence of swallowing difficulties or injuries and fractures as the consequences of falls (11), but hardly ever in hospices and more seldom at home than patients of other oncological diseases (12).

In the last years in the greater area of Cologne, Germany, the Cologne Parkinson's network was designed as a randomized, controlled prospective clinical trial in order to increase quality of life of PD patients. This innovative model of care integrated a neurologist in private practice, a movement disorder specialist and a PD nurse of the University Hospital. In consultation hours at the practices of the neurologists' patients met with the integrated care team and individual neurological treatment plans were designed. The PD nurse visited patients at home regularly every 3 months and could be contacted in between to follow and address patients' Parkinson-related problems. This integrated, multiprofessional, individual and personalized therapy meeting individual needs of patients improved their quality of life, motor functioning as well as non-motor symptoms (13).

This integrated care model included PD patients, who were able to visit a practice of a neurologist. Our retrospective *post-hoc* analysis of the trial's data aimed to detect whether this care model managed to access or follow, respectively, also PD patients at the end of life.

MATERIALS AND METHODS

This study was set up as a randomized controlled prospective clinical study with two arms in the greater area of Cologne in Germany.

The Cologne Parkinson Network (CPN) was established together with movement disorders experts and a PD nurse from the University Hospital of Cologne, Department of Neurology (CE) together with 25 community neurologists.

The trial was conducted between February 2012 (first patient first visit) and July 2015 (last patient last visit) and was approved by the local ethics committee of the medical faculty of the University of Cologne (No. 11-233). For further details of this trial we refer to the published study (13). The study was registered in the German Register for Clinical studies (DRKS00003452).

Briefly, patients were screened for potential involvement [age 25–85 years, exclusion criteria were unstable medical condition as a co-morbidity, major depression (BDI-2 >30 points), severe cognitive decline (PANDA <14 points)] by community neurologists and presented in quarterly Parkinson's consultation hours together with the movement disorders expert and the PD nurse. The time of the consultation was set as needed (up to a maximum of 45 min). Patients were randomized to either a control group (CG) or an intervention group (IG). In the CG, patients were included in the study at the baseline visit in the Parkinson's consultation hour and continued regular German neurological treatment. This included visits at the community neurologists practice about every 3 months (baseline, 3 months, 6 months). Once included, the PD nurse obtained questionnaires and surveyed clinical parameters (e.g., UPDRS III) at baseline and every 3 months. Patients had access to regular physiotherapy, occupational or speech therapy. Access to different medications was the same for both treatment arms.

The IG-treatment additionally included the development of an individual treatment plan, regular home visits of a PD nurse (every 3 months or whenever necessary on short notice) and a telephone hotline. Individual treatment plans were reviewed every 4 weeks and adapted according to individual patients' needs. Furthermore, the PD nurse synchronized the therapeutic pharmacological intervention with the program of speech therapists or physiotherapists. Thus, whenever necessary, rapid therapeutic modifications could be achieved.

Primary outcome parameter was the PDQ-39 to assess quality of life of patients. Changes in mood, motor and

non-motor functioning and cognition (BDI-2, UPDRS III, NMS-Score, PANDA) were evaluated as secondary outcome parameters. Daily medication was converted to the Levodopa equivalence dose according to published conversion rates (14).

Mortality rates of patients during the study period of 6 months were registered and compared with mortality rates of the general population of Germany according to the Federal Statistical Office of Germany (www.destatis.de).

RESULTS

A total of 1,400 patients were screened for eligibility. 300 patients were eligible, included and randomized. Patients were equally randomly assigned to an intervention (IG) and control group (CG). Mean age at baseline was 69.8 ± 8.4 for the IG and 69.9 ± 7.8 years in the CG. 132 patients in the IG and 125 in the CG completed the study, 37 patients dropped out (see **Figure 1** for reasons). Overall, 5 patients deceased during the study period in the IG, which is 1.66% of the total study population ($n = 300$). Reasons for death were heart failure due to myocardial infarction ($n = 3$), hospitalization after femoral neck fracture, secondary aspiration pneumonia and sepsis ($n = 1$) and in consequence of pancreatic cancer ($n = 1$). None of the patients in the CG deceased.

PDQ-39 improved more in IG compared to CG (2.2 points (95% CI −4.4 to 0.1); $p = 0.044$). Likewise, change scores between IG and CG favored IG for UPDRS III ($p < 0.001$, mean change 3.3, 95% CI −4.9 to −1.7) and PD-NMS ($p < 0.001$, mean change 11.3, 95% CI −17.1 to −5.5).

The primary outcome parameter significantly improved in the IG compared to the CG over a 6-month period (2.2 points (95% CI −4.4 to 0.1); $p = 0.044$). The secondary outcome UPDRS improved in the IG after 6 months ($p < 0.001$, mean change 3.3, 95% CI −4.9 to −1.7). The scores of the PD-NMS improved likewise after 6 months in favor of the IG ($p < 0.001$, mean change 11.3, 95% CI −17.1 to −5.5). No changes were detected for the cognition (PANDA) or depressive symptoms (BDI-2). For an overview of baseline characteristics see **Table 1**.

According to the mortality tables of the general population the mean mortality rate for the years 2012–2014 is 2.1% (mean of yearly mortality rates for women/men) for citizen aged 60–80 years (as comparable to the set of the study patients: mean age of patients ± standard deviation) https://www.destatis.de/DE/ZahlenFakten/GesellschaftStaat/Bevoelkerung/Sterbefaelle/Sterbefaelle.html;jsessionid=CC24B4774EDE040EE924FA2B881F0EE9.cae4%22%20/l%20%22Tabellen%22). As such, the group of PD patients in this trial had an even lower mortality rate as the general population (1.66 v. 2.1%).

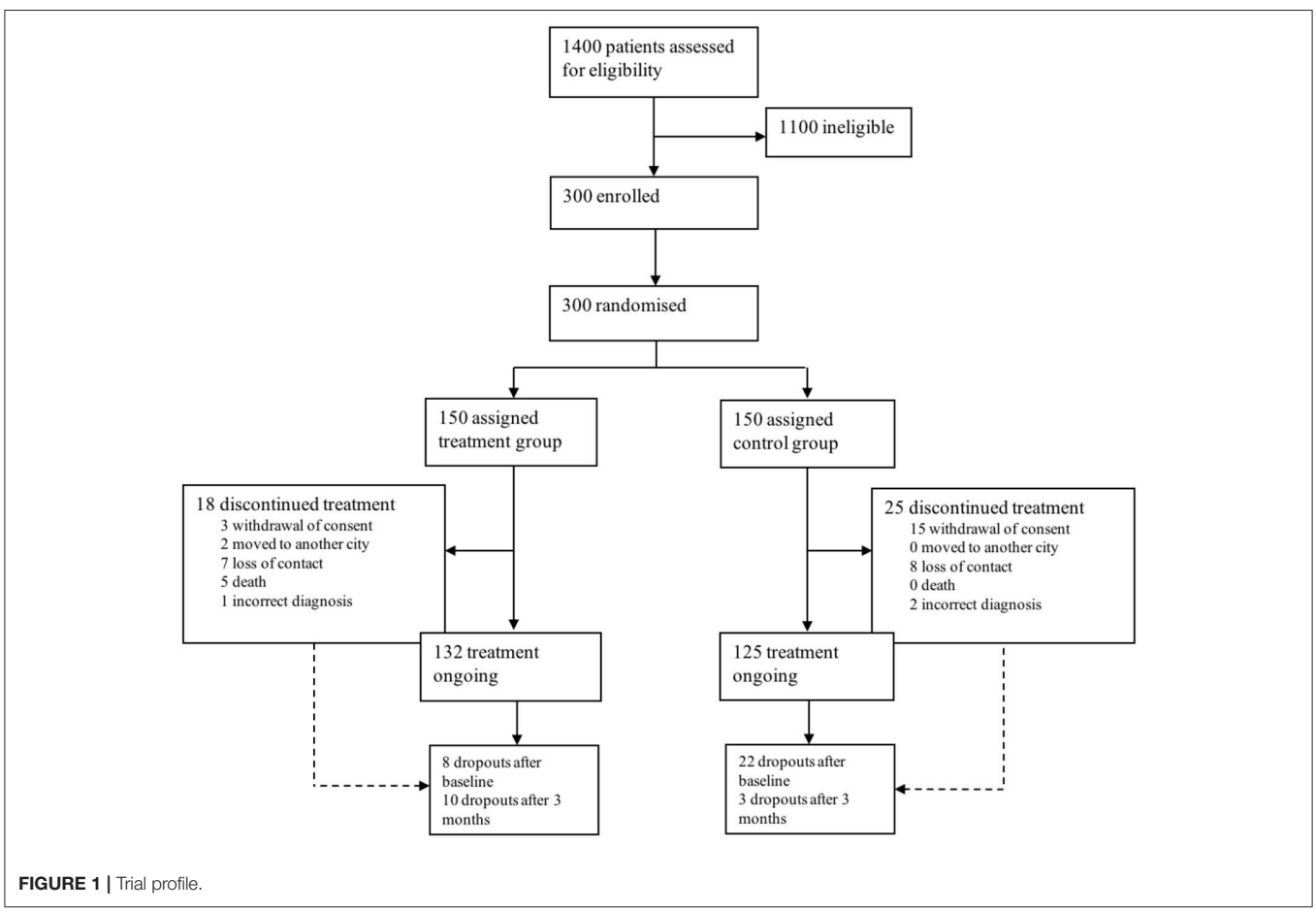

FIGURE 1 | Trial profile.

TABLE 1 | Baseline characteristics IG and CG.

Outcome parameter	Intervention group (IG) Mean and SD	IG *n* =	Control group (CG) Mean and SD	CG *n* =	*p*-value*
Age in years	69.8 ± 8.4	131	69.9 ± 7.8	132	0.924
Women/men		47/85		52/80	0.518
Disease duration/time since diagnosis in years	6.2 ± 6.2	126	5.5 ± 5.2	124	0.716
Hoehn and Yahr stage	2.5 ± 0.8	132	2.6 ± 0.8	125	0.687
Primary Outcome: PDQ-39 Total Score	26.0 ± 14.8	132	27.7 ± 15.6	125	0.407
Subscale mobility	32.1 ± 26.6	132	31.9 ± 24.3	125	0.882
Subscale activities of daily living	27.9 ± 23.6	132	28.9 ± 23.2	125	0.661
Subscale emotional well-being	27.3 ± 20.9	132	31.9 ± 19.6	125	0.072
Subscale stigma	17.4 ± 16.1	132	19.6 ± 20.2	125	0.815
Subscale social support	14.2 ± 19.6	132	14.5 ± 18.7	125	0.561
Subscale cognition	30.9 ± 19.6	132	33.3 ± 21.1	125	0.436
Subscale communication	22.0 ± 18.8	132	2.9 ± 21.1	125	0.927
Subscale bodily discomfort	36.0 ± 23.0	132	39.2 ± 23.4	125	0.266
SECONDARY OUTCOMES					
UPDRS III	28.3 ± 9.1	132	28.0 ± 8.7	125	0.938
PANDA	24.7 ± 3.8	131	24.7 ± 3.5	125	0.795
BDI-2	12.0 ± 8.2	132	12.6 ± 7.3	125	0.266
NMS	53.9 ± 29.6	132	62.3 ± 34.6	125	0.057
Daily LEDD	612.9 ± 431.3	132	612.4 ± 390.6	125	0.659
OTHER					
Medication use in %					
Levodopa	34%	132	34%	125	0.921
Dopamine agonist	30%	132	31%	125	0.885
COMT inhibitor	9%	132	9%	125	0.927
MAO B blocker	16%	132	15%	125	0.862
Amantadin	11%	132	11%	125	0.911
Anticholinergic	0%	132	0.71%	125	0.101
Deep brain stimulation	4%	132	2.8%	125	0.422

**The p-values are from Pearson's chi-square test (nominal data) or Kruskal-Wallis test (at least ordinal data), respectively.*

DISCUSSION

This integrated care model was implemented including various modalities to sustain quality of life in PD patients. The primary and secondary outcome parameters were adequately achieved in this study. Furthermore, this approach may have the opportunity to improve access to PD patients also at the end of life. However, the results of our *post-hoc* analysis show, that accessing PD patients in the last phase of their disease is extremely difficult and nearly fails in spite of an integrated care approach. Reasons for loss of follow-up have to be identified and care models for PD patients until the end of life should be developed urgently. In this study, one major reason for poor access to and loss of follow-up was the missing access to immobile patients. Patients had to get access to neurologists' practices. If they could not turn up at the consultations as they were bed-bound at home or in a nursing home, they could not be included and/or further followed in the study. We are aware, that exclusion criteria like dementia or severe depression are a serious limitation for the inclusion of late stage PD patients. However, this ambitious trial addressed successfully with a highly elaborated integrated care program the various needs of PD patients. We are convinced that not the exclusion criteria were the most limiting factor but immobilization of late stage PD patients played a much more important role.

This cohort showed an even lower mortality than the general German population. Patients in the CG had an even lower mortality rate compared to the IG, albeit a lacking individualized therapy. These results are somewhat contradictory and speak for a substantial proportion of patients, who were not been adequately included in this study as we know that mortality normally increases in PD. Another option for the low mortality rates is an overall improved treatment within this study which lead to a better monitoring process in both treatment arms. Patients in both groups were closely monitored in terms of motor functioning, detection of cognitive decline, depression or further non-motor symptoms. It has been shown that a closer monitoring in clinical trials improves patients outcomes (15). The mean disease duration of patients in this study was around 6 years which resembles the lower range of the mean disease duration at death of PD patients (9). This argues for an overall representative group of PD patients in the late stage of the disease, albeit motor symptoms, daily dosage of levodopa or Hoehn and Yahr stage are moderately expressed.

The time of integrating palliative care is critical, especially as in PD/APS many obstacles and preconceptions have to be overcome. The concept of early integration as described by Shin and Temel for oncology patients (16) targets to routinely assess for pain and other symptoms and regularly inquire about a patient's understanding of his disease and his goals of care. This can provide an extra layer of support for patients and their families by helping with more challenging symptom management, psychosocial support, complex decision-making, advance care planning, and transitions in care (16). This concept can easily be adapted to PD patients in order to integrate specialist palliative care at a disease stage at which patients themselves can still decide on their affairs e.g., with respect to advanced care planning like tube feeding, emergency management, future care in a nursing home vs. staying at home etc.

Specialist palliative care is typically accessible for patients with cancer, albeit a variety of measures to improve access to palliative care for people suffering from incurable non-cancer conditions have been implemented more recently. At least shown for Western Australia, in the last 10 years the proportion of patients with non-cancer conditions getting access to specialist palliative care was increasing about 6%. For PD patients this increase was even bigger with 7.5% (17).

There have been some uncertainties, how patients with non-cancer progressive neurological long-term conditions get access to specialist palliative care. Van Vliet et al. reviewed this issue for the UK and found heterogeneity in service provision and integration between neurology and specialist palliative care services, which varied not only between sites but also between diseases (18). Especially PD patients, less APS, did not frequently benefit from specialist palliative care. This asks for integrated care models, e.g. specialist palliative care could be used as an "add-on" approach to the existing integrated care model of the Parkinson's network if needed. Palliative care would then be provided in addition to neurology care, without taking over.

Overall, not only in the late phase, PD patients show an increased utilization of emergency departments. Gerlach et al. reported that 16–45% of PD patients visit the emergency department at least once per year. Additionally, patients were 1.5 fold more likely to be hospitalized and stayed 2–14 days longer than controls (19). Beside the higher rates of hospitalization, symptom burden increases with progressing disease. This leads to a changing role of spouses toward a full-time caregiver. Spouses and family members who form together with the patients the "unit of care," frequently report to feel isolated and discouraged, without guidance and coordination from healthcare providers and lacking information (20, 21). Finally, they are overstrained after years of supporting and caring for/about the patients. Due to this, a substantial proportion of PD patients dies in hospitals rather than at home or in hospices (12)–even if this is not the preferred place to die for PD patients (22). However, this depends from the symptom burden of patients.

All these findings support the urgent need for advanced care planning (ACP), one important aspect of palliative care. Most of PD patients have not expressed their decisions for proceedings at the end of life. This can include insertion of percutaneous endoscopic gastrostomy (PEG) tube for nutrition as well as the preferred place of death. Overall, reduced (or non-existent) APC in PD patients may lead to an underrepresentation of PD patients in a model of care as presented here. However, APC was not surveyed in this study.

These findings ask for an intensive debate about ACP in PD, as currently it seems not to be adequately addressed during the course of PD. According to Walker, an ACP discussion might "include the individual's concerns, their important values or personal goals for care, their understanding about their illness and prognosis and their preferences for types of care or treatment that may be beneficial in the future and the availability of these" (23). Especially as written ACP are associated with less use of life sustaining treatment, greater use of hospice and less likelihood of hospitalization during end of life phase (24). Furthermore, it was shown, that at least half of PD patients wish to discuss APC early in the course of the disease (25). These findings encourage the implementation of thorough ACP within integrated care structures already at early disease stages.

All these different aspects ask for a further development of the integrated care model, which includes the following principles:

a. Integration of specialist palliative care knowledge at a very early point in the course of the disease with respect on the acceptance of the diagnosis (e.g., once a year from the time of the diagnosis),
b. Implementation of a *clinical liaison/case manager* (e.g., a PD nurse) as a patient advocate, who takes care of the patient during the course of the disease, especially in critical phases of the disease (e.g., high symptom burden, late stage, etc.)
c. Integration of nursing homes, as PD patients in nursing homes are underrepresented in neurological care
d. Integration of general practitioners/family doctors, as they have a closer contact to patients' families and know about changing situations of care,
e. Dovetailing of neurological and specialist palliative care units and outpatient services in order to use knowledge and the best principles of both disciplines.

AUTHOR CONTRIBUTIONS

CE: conception, organization, and execution of the research project, data assessment and data analysis, conception and execution of the statistical analysis, writing and critical review of the manuscript drafts. RD: execution of the research project, data management. JS: execution of the research project, data management, statistical analysis. GF: critical review of the manuscript drafts. LT, RV, and HG: data assessment, critical review of the manuscript drafts. SL: conception of the research project, data assessment, critical review of the manuscript drafts.

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A Pilgrim's Journey—When Parkinson's Disease Comes to an End in Nursing Homes

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Our interdisciplinary mixed-methods exploratory study was aimed at gaining empirical data on the medical and nursing demands of residents who are in a late stage of Parkinson Disease (PD) and are cared for in residential homes in Salzburg (Austria). In earlier studies it has been concluded that symptom burden of late stage PD patients is similar to or even higher compared with oncological patients. However, although all nine residents who took part in our study had severe limitations in performing their daily activities and experienced enormous restrictions in their mobility, they were quite content with their present living situations and did not show significant symptom burden. From the ethnographic family interviews that we conducted the following features emerged: a strong closeness in the family, an improved quality of life when the patients lived in the nursing home and fears about the future. Therefore, we concluded that living in a nursing home that provides for the needs of these patients is the best option for PD patients in the final stages of their disease as well as for their relatives.

Keywords: morbus Parkinson, nursing homes, palliative care needs, ethnographic interview, assessments

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INTRODUCTION

Parkinson's Disease (PD) is the second most frequent neurodegenerative disease worldwide. It is estimated that between seven and 10 million people worldwide are living with PD (1). In Austria approximately 20 000 people live with PD (2). It has been estimated that the number of people who are older than 50 years and are diagnosed with PD will rise considerably from 4.1 to 4.6 million in 2005 to 8.7–9.3 million in 2030 (3). Bach et al. predicted that the number of people who will be affected by PD in 27 European countries, the US and Canada will increase by a factor of 1.6 between 2010 and 2035 (4). It is difficult to estimate the occurrence of PD in the population, as it varies considerably between different publications (5). Between one and two in 1,000 people are affected by PD (5). The average life expectancy of patients who are diagnosed with PD is around 15 years in Europe (6). In people who are 65 years or older the diagnosis of PD is a strong determining factor of long-term institutionalization, even when other chronic conditions and socio-demographic parameters are taken into account (7). Among male patients with PD 30% live in an institution and among female patients even 40 % (7).

The burden of symptoms of late stage PD patients has been described as similar or even higher than of those patients who suffer from oncological diseases (8). It has often been concluded that patients who suffer from advanced stages of PD have substantial unmet palliative care needs (8, 9). Families are often caring for their relatives over a long time period as well as round the clock with considerable personal, financial, social and health sacrifices (10). As the illness progresses and the abilities of the patients are increasingly reduced, the dependency on care rises significantly. At the same time health professionals often loose interest in patients and their families (9). Because medical options decrease and patients are not anymore eligible for pharmacological/medical studies.

Objectives

In the nursing and residential homes in the city of Salzburg and the Salzburg county 4,384 people were being cared for in 2016 (11). Of these, 1,959 were 85 years of age or older (11). The exact number of residents being cared for in the nursing homes in the city of Salzburg and Salzburg county and being diagnosed with PD cannot be given, as there are no valid statistics.

Patients who are in an advanced stage of PD rarely participate in empirical studies (12). In Germany a non-representative study that analyzed death certificates from two different regions, demonstrated a tendency for more and more people dying in nursing homes over recent years: the number of people who died in nursing homes had risen from 12% in 2001 to 19% in 2011 (13).Only few empirical data are available for the care and medical situation of patients in an advanced phase of PD (14). In Salzburg and Salzburg county no data existed about the experience of residents with PD in their last phase of life, nor about their nursing and medical palliative care needs. The experiences of caring relatives are also unknown and their wishes when they are in close contact with their family members who suffer from severe PD and are cared for in a nursing homes. To get answers to these questions, the authors conducted this mixed-methods interdisciplinary, exploratory study.

METHODS

This study was approved by the Ethics Committee of the Salzburg county in November 2016 (415-E/2065/15-2016).

Residents were eligible to take part in our study if they matched our inclusion criteria. They had to be able to give written consent to their participation in the study or be able to instruct a legal attorney to give written consent on their behalf. This was the case for five participants. Another precondition for participation was the diagnosis of an advanced stage of PD (Hoehn and Yahr stage IV and V). At the time our visits and interviews took place, residents had to live in a nursing home either in Salzburg or in Salzburg county. The family member that was also interviewed in this study had to give written consent as well. Before we started with the first visit to a resident, the authors received a contract signed by the municipal authority of the city of Salzburg in which the city allowed the authors to conduct the study in the city's nursing homes. We conducted an exploarive, mixed-methods study.

Instruments

We characterized each patient's situation using established scores. The Hoehn and Yahr scale and the Schwab and England Activities of Daily Living Scale were utilized to check each patient's inclusion criterion: being in an advanced stage of PD (Hoehn and Yahr stage 4 or higher). To assess the resident's severity of symptoms, the authors used the Unified Rating Scale for Parkinsonism (UPDRS). To describe the resident's quality of life the PDQ (Parkinson Disease Questionnaire) and the EQ-5D were used. To test if typical symptoms of the disease were present and to monitor their severity, the authors examined residents with the Edmonton Symptom Assessment System Parkinson Disease (ESAS-PD). To estimate the resident's satisfaction with medical and nursing support we used the patient satisfaction questionnaire short form (PSQ-18). The Charlson-Comorbidity Index Score was used to predict the resident's 10 year mortality. The Supportive and Palliative Care Indicator Tool (SPICT) was employed to detect the resident's palliative care needs and the necessity to develop individual care plans. The resident's family member's psychological situation was appraised by the Zarit Caregiver Burden Inventory (ZBI-22). To gain an insight into the quality of life of the resident's family member insofar as it relates to the experience of dementia, the researchers used the DEMQOL-Proxy-questionnaire.

Furthermore, we used the so-called "surprise question" ("Would you be surprised if this patient died within the next 6 months?") as it is a simple tool which may help to judge estimates of the remaining life time. It is already part of clinical guidelines—e.g., the Gold Standard Framework in the UK.

TABLE 1 | Average and standard deviation of the assessment instruments.

	Average	Standard deviation	Number of residents, who participated = *n*
PDQ	2.54	1.89	8
EQ5D	0.26	0.44	6
GESZ	51.55	40.78	6
ESASPD	1.67	2.65	6
LISK 1	0.89	0.93	5
LISK 2	0.78	0.67	5
PSQ 18	0.36	1.1	1
DEMQOLP	1.24	1.58	5
ZBI	0.26	0.86	2
UPDRS	1.77	1.66	9
Hoehn and Yahr	4.66	0.5	9
Schwab and England	2.66	1.41	9
CCI	0.1	0.70	3
Surprise question			9

TABLE 2 | Recruitment of the nursing home residents.

Participating nursing home	Number of residents	Selected residents who met the inclusion criteria	Number of residents, who were seen by the research team	Number of residents in whom PD Hoehn and Yahr stage 4 or higher could be verified
A (remote, rural area, Salzburg county, privately run)	121	8	8	2
B (remote, rural area, Salzburg county, run by the Austrian red cross)	52	2	2 (1 other resident died before the research team could visit the resident)	1
C (remote, rural area, Salzburg county, run by the local community)	36 (6 day care places)	1	0 (the resident died before the research team could visit the resident)	0
D (City of Salzburg, run by the City of Salzburg)	60	8	4 (4 residents family members were not reachable to ask for study consent/ did not want their resident to participate in the study)	3
E (City of Salzburg, run by the City of Salzburg)	96	6	3 (relatives of 2 residents were not reachable/did not give their consent to their residents participating in the study)	0
F (City of Salzburg, run by the City of Salzburg)	100	5	1 (relatives of 4 residents were not reachable/did not give their consent to their residents participating in the study)	0
G (remote, rural area, Salzburg county, run by the local community)	140	7	4 (2 proxies of attorneys needed more time to decide whether residents should participate in the study: in this time frame 2 residents died; 1 other family members did not give consent to participate in the study)	2
H (remote, rural area, Salzburg county, run by the "Salzburg Hilfswerk")	66	1	1	1
	671	37	23	9

Originally it was developed to provide help with the decision about referral of patients to specialist palliative care treatment. It has been refined to help with the decision about the level of specialist palliative care treatment a patient might need. However, the accuracy of the surprise question, when used as a single assessment tool, varies considerably (15). Therefore, more scientific work is needed to clarify the prognostic accuracy of the surprise question (15). Hence, we intended to find out whether the surprise question can be a helpful tool in identifying patients who might profit from "active total care." This term describes a combination of active treatment and, at the same time, the offer of medicine (and nursing care) which help -managing disabling symptoms and therefore make the time until death worth living (16). The results are shown in **Table 1**.

The authors are aware of the difficulties in exactly predicting death, even when using the "surprise question" (17). Only in fewer than 4% of patients dying in the subsequent year the predicted mortality was above 80% when patients were admitted to the hospital a recent study showed (17).

The authors did intentionally not ask direct questions concerning advanced directives or end-of-life care as the local ethics committee was extremely worried about the study team asking direct questions on death and dying. The big fear was that the authors asking specific question might enlarge residents and family members' worries about their present living situation.

Recruitment

Recruitment has been done in eight different nursing homes (four were located in the city of Salzburg and four in Salzburg county), see **Table 2**. Overall, 15 nursing homes with a total number of 1,478 residents are located in the city of Salzburg. Further 60 nursing homes (3,699 residents) are located in the Salzburg county (18). All nursing homes being either located in the City of Salzburg or in Salzburg county were contacted about the study either via telephone or by Mailing. The recruitment of the nursing home residents is shown in **Figure 1**. Recruitment has been supported by the chief doctor of the nursing homes in Salzburg who selected possible patients; we have distributed posters and flyers describing our study in the nursing homes. To gain extra attention (and possible study participation) of additional residents who were diagnosed with PD and who were not contacted by the chief doctor the flyers and posters were distributed. A message about the start of the study was announced via the electronic newsletter of the Institute

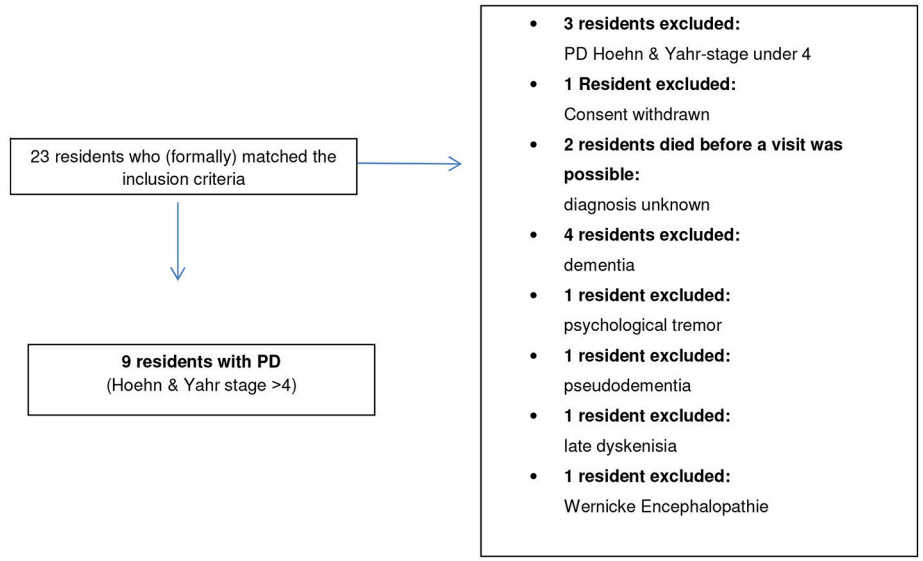

FIGURE 1 | Recruitment.

for Nursing Research and Practice at the Paracelsus Medical University at Salzburg.

A total of 23 residents have been seen by the research team. Our gatekeepers were nursing home doctors, nursing home directors and people who are in charge of the organization of nursing homes in Salzburg and Salzburg county. Nursing home directors tested the criteria for inclusion into the study through their personal and professional nursing experiences and by checking the medical records of the residents that were available at the nursing home. The doctors who are in charge of the nursing homes at the city of Salzburg checked whether the residents who were willing to participate matched our inclusion criteria. The residents were visited in the nursing homes, where they lived by a professor for neurology and palliative care (SL) and by a nursing scientist who is also a nurse (KL). With all nine residents the assessment and the interview took place in the resident's room.

In the second phase of the visit (after completion of the various assessments) the authors invited relatives to participate in ethnographic interviews. This procedure was taken because we first had to confirm the diagnosis of idiopathic PD.

RESULTS

Of the 23 patients reported as idiopathic PD in only nine the diagnosis of PD with a Hoehn and Yahr stage 4 or higher could be verified (see **Figure 1**). Out of these nine patients it was possible to conduct family interviews in the style of ethnographic interviews in five cases.

The median age of the residents suffering from PD was 79.8 years. The socio-demographic data are shown in **Table 3**.

All residents had several comorbidities including polyneuropathy ($n = 2$), high blood pressure ($n = 3$), cerebrovascular diseases ($n = 2$), dementia ($n = 3$), cardiac insufficiency ($n = 1$), chronic lung disease ($n = 1$), gastritis ($n = 2$), spinal stenosis ($n = 1$), blindness ($n = 1$), type II diabetes ($n = 1$), and alcohol addiction ($n = 1$).

The averages and standard deviation of the assessment instruments we used can be seen in **Table 1**.

The research team was surprised by the fact that all residents included in the study were quite satisfied with their living situation, despite being severely impaired by their illness, especially in their overall autonomy. None of the residents had a feeding tube (PEG). Interestingly, one of them had had a PEG but due to intensive nursing care, he got rid of it and started to eat normally again. None of the residents had bothersome symptoms. All residents received a minimum dosage of anti-Parkinson medication (see **Table 4**). The illnesses of the not included residents can be seen in **Table 5**.

As a result of the surprise question, five nurses would be surprised if the residents would die within the next 6 months. Four nurses would not be surprised if the resident would die. All family members would be surprised if their relatives would die within the next 6 months.

We had to exclude 14 patients from our study for several reasons as shown in **Figure 1**. Surprisingly, the 10 residents, who did not match the PD diagnosis, had been treated with classical Parkinson medication. This has been in fact an ethically challenging result of our study. The authors reported this result to the residents, their family members and the nurses working in the residential homes. In four cases the doctor in charge was told about the result. In three cases the responsible doctor in the residential home was told. In several cases, SL gave some alternative treatment advice. Interfering in these cases is extremely difficult, as the researcher (SL) who could not verify the PD-diagnoses is not the doctor in charge, but acted in his role as a researcher.

Qualitative Data

We conducted semi-structured, ethnographic, half-guided family interviews. We performed five interviews with daughters (2), husbands (1), sons (1), and (step-) brothers (1). One planned interview could not be conducted, although the relative (wife) was willing due to a severe speech impairment of the wife. The interviews were recorded and in the following paraphrased. The following features emerged from the interview data

- Strong closeness in the family
- Improved quality of life by living in the nursing home
- Fear about the future
- Feeling of responsibility for the resident, although s/he is being cared for in a nursing home

A positive aspect which emerged through the assessments and the interviews was a remarkable sense of closeness: family members had the feeling of symbiotically belonging to the resident and having the role of advocates, in the sense of caring and protecting the resident's needs who is vulnerable. A resident's half-brother told us about his biggest concern: "I worry whether I visit her enough." Before the interview took place, he told the team that he visits his half-sister who is wheelchair bound and whose reactions and supposed understanding of verbal communication are extremely reduced, every other day.

In another interview situation the husband and his wife seemed to be very much one single person: the wife was enormously reduced in her physical and psychological expression, while the husband was extremely protective and very aware of his role as his "wife's advocate."

The improved quality of life that both parties enjoy when the patient relocated into a nursing home can be illustrated by the following interview quotes. In contrast to any burdens when the patient moved into the nursing home, his/her new living and caring situation in the nursing home has even some beneficial aspects as well. It emerged from the interviews that the main reasons for nursing home treatment were frequent falls at home. Sometimes these falls had severe physical consequences: a resident's wife told us about her husband: "At home, he always fell. One time my son and I could not pick him up. He was too heavy. We had to call the ambulance. At the fall, he lost a tooth.… At home he was on his own and felt lonely; I was still working part-time. I was so worried. Then we moved him to the nursing home. He is much better here. The nurses look after him and cope well with his diabetes. And furthermore, he has something to occupy himself. On this ward lives a lady who enjoys playing cards. So they play cards together. Every day. He enjoys himself."

A son was interviewed about his father's situation. He is completely bedridden and just able to use the words "yes" and "no" seemingly living in his own world: "Father enjoys eating. I think that is the only activity he still enjoys. Nurses care for him extremely well, so there is no burden for me that he lives in a nursing home." "If it were possible to take him in a wheelchair and take a stroll through the park, that would be something I would enjoy tremendously."

A husband used a very colorful picture to illustrate his fears concerning their future: "It all changes so quickly." When asked about his biggest wish he answered: "If my wife's health situation could only improve to the situation it was in 2012, when we celebrated our golden wedding anniversary together."

TABLE 3 | Sociodemographic variables of patients.

	Residents with PD
Total number of residents (*n*)	9
Man (*n*)	4
Woman (*n*)	5
Age (range) (median)	59–94 (79.8)
Hoehn and Yahr stage 4	3
Hoehn and Yahr stage 5	6
Disease duration, years (range) (median)	6–20 (9)
Stay in residential home, years (range)	1–7
Specific anti PD-treatments e.g., deep brain stimulation in the past	1
Regular treatment by a neurologist	2

Caring relatives have the impression that they continue to be "in charge of the elderly relative." Other family members and friends did not keep in contact with the residents. One daughter described this situation as the family was divided. None of the other family members kept in contact or visited her father. That is why she is the only person in her large family who feels that she is in charge of her father's social support and wellbeing. "That the other family members do not care about father's wellbeing has led to rifts within the family. I do not understand why the other family members do not care."

A son told us what annoyed him most was that he from a large family with four other siblings was the only family member who regularly visited his father and felt responsible, including dealing with his financial and legal affairs. He is his legal guardian.

Caring family members seemed to be in a conflicting situation: although they were informed about the actual medical situation and the fact that death was probably to be expected in the near future, all of them hoped that their frail relative might get better. None of the family members expressed the wish that the old and ill relative may have a "good death" and avoid disturbing symptoms as for example dyspnea, fear or pain in the dying phase. When asked about her most important wish, the daughter who told us about the family rifts answered: "When the good fairy comes, she should take Parkinson's Disease away. Without Parkinson's, father would only have the usual symptoms of old age and everything would be fine."

All the wishes about which the caring relatives spoke with the team were optimistic regarding the resident's future. One impressive wish was expressed by a resident's half-brother whose sister had been blind in one eye for the past 5 years and who was bed-bound. She needed complete help in all daily activities (ADLs). When he was asked what he would wish for his half-sister, he answered: "My largest wish is for her eyesight to improve."

A resident's (step-) brother said: "It is like being on a pilgrimage." With this statement he illustrated the ups and downs his sister and he experienced while living with PD, but finally she had reached a state where she wandered to the final destination.

TABLE 4 | Medication of participating residents.

ID-number	Medication against PD							Pain medication		Anticonvulsive, antidepressive, and antipsychotic medication						
	Levodopa (mg)	Entacapone (mg)	Ropinirol (mg)	Pramipexol (mg)	Rasagilin (mg)	Biperidine (mg)	Rivastigmine (mg)	Paracetamol (mg)	Tramadol (mg)	Clonazepam (mg)	Levetiracetam (mg)	Mitrazapin (mg)	Lorazepan (mg)	Milnacipran (mg)	Quetiapin (mg)	Trazodon-hydrochlorid (mg)
5	600			7,65				1,500	300	2	1,000					
9	300											15				
10	500				1								1			
11			12			4	18							25	25	150
18	250			2,62	1											
19	300	400													25	
22	300	200						500				15			50	

TABLE 5 | Illnesses of the not included residents.

Dementia (not specified)	5
Pseudo dementia	1
Late dyskinesia	1
Psychological tremor	1
Wernicke encephalopathie	1
Morbus Parkinson Hoehn and Yahr stage 3	2
Morbus Parkinson Hoehn and Yahr stage 2	1
Unclassified	2

DISCUSSION

The subject of residents who suffer from late stage PD and are cared for in nursing homes is internationally under researched. Only few empirical data are available on residents with PD Hoehn and Yahr stage 4 or higher who are cared for in residential homes [e.g., (19)]. That is why general knowledge on medical and nursing palliative care demands in these patients is limited.

The most important finding of our research has been that although patients who are in a progressive state of PD and are severely disabled, did not seem to have significant physical or emotional burden. Whilst residents were not satisfied with their overall health situation, they were not desperate. Relatives were still emotionally closely connected with the patients and expressed hope and confidence about the progression of the disease and the overall situation of the patients. Participation in our study was not a strain for patients with PD or for their family members. In contrast, we gained the impression that residents and carers, family members as well as nurses, enjoyed being able to contribute to our research.

The residents who participated in our study had been ill on average for 9 years. This is comparable with an earlier study of patients in a community setting in the United Kingdom (UK) (8). However, the residents in our study had a lower quality of life (EQ5D=0.26) compared with the patients who participated in the UK study (8). Although the objectively measured quality of life has been low in our study, the residents were content with their present living situation and seemed to have a much higher "subjectively" experienced quality of life which we could not measure with the instruments we were using. Although all residents in our study were severely limited in their mobility, as they were either bedridden or wheelchair-bound, they did not make a point of it. In another study by Veronese et al. the prevalence of residents experiencing severe mobility problems was 66.7%. Especially people suffering from neurodegenerative diseases have severe constraints on their daily life activities (9). As the illness progresses and mobility becomes even more limited, patients and their family members get used to these limitations (9). If patients are not able to move on their own they are severely affected in their activities and well-being (20). On the other side being bedridden might also be a survival strategy. By lying down patients may gather their strengths to do other things that may be more important to them (20). In this particular

study the findings were comparable to our results. None of the 32 elderly, bedridden patients described their situation as a good one, but they did not appear to suffer from their severe mobility difficulties (20). In our study only one resident, who was assessed H&Y IV and was very aware of his deteriorating physical and cognitive abilities, expressed his unhappiness about his overall situation.

Interestingly, the relatives seemed to have got used to the residents' situations. When we asked them about their wishes concerning the future they articulated a general wish for the patients to "get better again." The ability to move did not seem to be particularly important.

Only two relatives answered the Zarit Caregiver Burden Inventory (ZBI). The very low ZBI- average of 0.26 is due to the fact that the relatives' actual suffering is low because the patient is no longer cared for at home. It might also be an indicator that the nursing care quality in the residential homes in Salzburg and the Salzburg county is high. This result shows a clear contrast to the result of our earlier study where we have recently shown that the ZBI-average is high when PD patients in the advanced stages are cared for at home (14). We have not yet assessed the ZBI factor of nurses in residential homes who care for the PD patients.

The finding that being close to one's family plays an important role for nursing home residents as well as for family members is consistent with other empirical data (21). It has already been shown, how important it is for residents to have close relationships to family and friends. These relationships are the foundation for relational dignity which is an important part of residents' concepts of their dignity (21).

All interviewed family members were convinced that their family members would survive the next 6 months; at the same time relatives were aware of the palliative phase of their family members and seemed to know that they might die sometime in the near future. Relatives of nursing home residents with late stage PD seem to experience highly ambivalent emotions. On the one hand they are very aware of their relatives' health situation as the palliative care phase had already started or was imminent and on the other hand they have optimistic wishes for their relatives' future which are not associated with a wish for a "good death."

An important result was the strong feelings of uncertainty about the future. Many relatives expressed these worries in the interviews. In a qualitative study that explored PD patient's palliative needs (22). The main theme was the strong feeling of uncertainty and worry about the future (22). In this aspect our interviews are consistent with prior results (22).

The observation that family members "who are in charge of the resident" felt abandoned by the other family members or former friends of the resident has already been made in another study (9). Interestingly, being abandoned applies also to professionals: e.g., neurologists who do not care anymore about the elderly patients deteriorating (9).

Several residents had been diagnosed with PD years ago. However, this diagnosis could not be verified by the PD specialist (SL). All these residents had been treated with classical anti-Parkinson medication.

An idea to take some tension from not being able to verify a former PD-diagnosis and the n being stuck in the difficult situation of unclearness which doctor to confront with the "wrong" diagnosis—often having been diagnosed by a trusted GP- using the social constructivism method might help (23).

The research literature strongly suggests that people in advanced phases of PD should be looked after by a neurologist (12). As residents are no longer mobile enough, to travel and seek diagnosis and treatment by a neurologist, outreach neurologist services are strongly advised (12). Treatment by a neurologist leads to improved survival, fewer PD-related hospitalizations, lower health-care costs and greater patient satisfaction. Residents are also healthier, therefore it is extremely advisable to enable more PD-patients who are cared for in nursing homes, to have the benefits of getting medical treatment by neurologists as long as possible (24).

It is known that PD patients who are treated by a neurologist have an additional 6 years of survival compared with patients, who are looked after by family doctors or geriatricians (25). It has also been investigated that nursing home residents cared for by a neurologist are in better general health: they have lower rates of dementia, hip fracture, congestive heart failure, diabetes, ischemic heart disease, and stroke/TIA (25). To draw a reverse conclusion: residents who are not medically treated by a neurologist have a higher risk of suffering from comorbidities and the probability of an earlier death.

Taking the global shortage of neurologists (especially of those being experts in movement disorders) into account, specially qualified nurses might be a solution in ensuring a good medical and nursing care of residents having to live in nursing homes (26, 27). In some countries (e.g., Sweden) especially qualified PD-nurses take over an expert position in continuing medical and nursing care throughout the disease trajectory and offering a high amount of professional competency (27). It might be possible to qualify nurses according to the Swedish model and let these nurses care medically—in specific aereas- for affected residents. With this model the care of PD-residents might improve as less residents with wrong PD-diagnosis might be medically treated as having PD.

The authors had the impression that a high proportion of the residents' present quality of life was due to the caring and responsible work of the nurses and other carers who work at the Salzburg residential homes. The researchers were deeply impressed by the dedication of the nurses and the positive atmosphere in the nursing homes. The nurses were calm, lively and devoted.

The most important result of our study was that good palliative care is based on considerate nursing care and on minor and timely medical supplementation. This result confirmed the result of the study by Masel et al. (28). One of the main results of this study was that attentiveness and symptom management are important for PD patients (28).

Furthermore, reliable and validated PD and palliative care assessment instruments could not be adequately used in patients' late stages. Therefore, it was not possible to use classical, advanced statistical tests for analyzing data.

Based on our results it seems to make sense to triangulate methods when exploring patients' needs who are in an

advanced phase of PD. With the validated assessment instruments experienced neurologists are able to verify the patients' illness stage. If one needs a more in- depth view of the experiences of patients and their relatives, qualitative methodology is essential. Combining interviews and observations with established assessment tools will lead to even more insights into the situations of the residents.

AUTHOR CONTRIBUTIONS

KL: research project organization and execution, manuscript writing of the first draft; SL: research project conception and execution, statistical analysis design, manuscript review and critique; JO: funding; PL: manuscript review.

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Dementia and Parkinson's Disease: Similar and Divergent Challenges in Providing Palliative Care

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Dementia and Parkinson's disease are incurable neurological conditions. Patients often experience specific, complex, and varying needs along their disease trajectory. Current management typically employs a multidisciplinary team approach. Recognition is growing that this team approach should also address palliative care issues to optimize quality of life for patient and family caregivers, but it remains unclear how palliative care is best delivered. To inspire future service development and research, we compare the trajectories and conceptualization of palliative care between dementia and Parkinson's disease. Both Parkinson's disease and dementia are characterized by a protracted course, with progressive but fairly insidious development of disability. However, patients with Parkinson's disease may experience relatively stable periods initially but with time, a wide range of debilitating symptoms develops, many of which do not respond well to treatment. Eventually, dementia develops in most Parkinson patients, while motor disability develops in many dementia patients. In both diseases, symptoms such as pain, apathy, sleeping problems, falls, and a high caregiver burden are prevalent. Advance care planning has benefits in terms of being prepared before the disease progresses into a stage with communication problems or severe cognitive impairment. However, for both conditions, the protracted disease trajectories complicate conceptualization of palliative care through different stages of the disease, with pertinent questions such as when to offer what interventions pro-actively. Given the similarities and differences, we should develop palliative approaches that are partially generic and partially disease-specific. These should be integrated seamlessly with disease-specific care. Substantial research is already being performed on dementia palliative care. This may also inform the further development of palliative care for Parkinson's disease, including an evaluation of palliative interventions and services.

Keywords: end of life care, hospice care, palliative care, health services, nervous system diseases

INTRODUCTION

Palliative care has been developed to improve quality of life, mostly for patients with incurable cancer (1, 2). However, equity of access to palliative care involves access on the same footing for patients with other incurable diseases. This does not mean that palliative care is, or should be, the same across these diseases. On the contrary, to optimally tailor care to individuals, the contents of palliative care, and how, when and where it is delivered, can and in fact should differ between diseases.

Along the trajectory of chronic-progressive and incurable neurological diseases such as dementia or Parkinson's disease (PD), various complex needs arise, some of which are disease-specific. Palliative care promotes quality of life in the face of *any* life-threatening, or progressive, incurable illness (3, 4). To optimize it for individuals, however, a good understanding of disease-specific aspects of palliative care is helpful, i.e., a conceptualization of what palliative care entails exactly for a specific disease.

Epidemiology of Dementia and Parkinson's Disease (PD)

Dementia and PD are both diagnosed frequently and increase mortality (5, 6). Perhaps dementia is perceived more so as a memory problem and a disease of old age, but the incidence of dementia and PD in younger age is similar. In the Netherlands, for dementia, the incidence per 1,000 person-years is 0.4 among those aged 60–64 (7), and for PD, it is 0.3 (ages 55–65) (8, 9). Dementia incidence patterns, however, show a much steeper increase with age; mounting to 27 per 1,000 person-years for those 85 and over, compared to 4 for PD over 85. In view of similar mortality (6), therefore, the prevalence of dementia in the general population is much higher than prevalence of PD (8–11). However, adjusted for age and other factors, 6-year mortality in PD is higher than in Alzheimer's dementia (6). Age adjustment is relevant also as it shows that comorbid disease may be equally prevalent for Alzheimer's–a main type of dementia–and PD across the same age groups (12).

Comparing Trajectories and Conceptualization of Palliative Care for Dementia and PD

The two disease trajectories may overlap partly as dementia is a frequent manifestation of PD. Mild cognitive impairment may already present upon diagnosis of PD (13). Importantly, it is independently associated with lower quality of life (14). Across studies, typically about a quarter of patients with PD have dementia (15, 16), but ultimately, most develop dementia (15–17).

A clear conceptualization of palliative care in chronic-progressive diseases is important for the development of healthcare systems that facilitate the integration of a palliative approach (18). Therefore, in this article we compare the disease trajectories of dementia and PD in as far as relevant for the conceptualizations of palliative care. We do not include atypical Parkinsonian disorders such as multiple system atrophy because these warrant a special approach with earlier palliative care (19). We first provide background on where we are by describing how palliative care for dementia and PD developed.

Palliative Care in Dementia

The first evaluated palliative care program specific to dementia was described in 1986 (20). The volume of research has grown exponential after 2000 (21, 22). There are few randomized controlled trials, and therefore, there is still little evidence on effectiveness (23, 24). However, many western countries have funded observational studies resulting in numerous publications describing patient, family and professional caregiver needs (25, 26).

Research specific to dementia is important because the course of the disease is highly variable and uncertain. Because of the progressive dementia, patients themselves often cannot remain involved in decision making. Also, health services and changes such as transfer to a hospice, do not necessarily represent optimal care for people with dementia (27). Palliative care in dementia needed a clear conceptualization, and the European Association for Palliative Care (EAPC) along with experts agreed to a distinct concept in terms of eleven domains, different from "usual" palliative care (28).

Palliative Care in Parkinson's Disease

Palliative care for people with PD and their caregivers has progressed over the last 10 years but it is still an upcoming field. Evidence of effects is limited (17, 29, 30) but trials are underway (31). Qualitative studies on palliative care needs (32–34) and natural history studies (35–37) have indicated that the needs of people with advanced PD are complex. Awareness of the potential benefit of palliative care is growing, but we know little about useful components (17, 29). To the best of our knowledge, there is no clear conceptualization of the specifics of palliative care in PD.

DIFFERENCES AND SIMILARITIES

We highlight key similarities and differences between the trajectories and perceptions of the disease, and treatment and care for people with dementia and PD based on recent literature. The comparator is a population without the disease, sometimes matched or adjusted for differences such as age or co-morbidities.

The Disease Trajectories

With both diseases, the diagnosis may be delayed due to gradual onset with a-specific symptoms after which burdensome symptoms develop, while the disease duration is highly variable (**Table 1**, items a and b). Burdensome symptoms that decrease quality of life often include rather unspecific symptoms such as pain and depression. Clearly, PD is distinct from dementia as it is characterized by its motor symptoms, such as bradykinesia, rigidity, and tremor. Symptomatic treatments are available and with the right therapeutic approach, the course of PD typically includes an initially relatively stable phase.

For PD patients, loss of functional ability (item c) occurs with symptoms that are largely unresponsive to treatment speech

TABLE 1 | The course of dementia and Parkinson's disease: items relevant to palliative care.

Course of the disease, items	Dementia	Parkinson's disease
a. Diagnosis, duration, and staging	Symptoms may occur long before diagnosis of dementia. Onset is usually after age 65, but when before, duration is usually longer, and the number of life years lost is greater (5). Survival of dementia patients is highly variable between individuals and across studies with median or mean survival generally being between 3 and 12 years from diagnosis (5, 38, 39) About half may die before reaching an advanced stage of dementia when decision making and ADL functioning are severely impaired (40) and the large majority does not reach a stage in which they are totally dependent in ADLs, incontinent, bedridden, and mute (41). Definitions of severe or advanced dementia generally comprise criteria for cognition combined with criteria for behavior and function including ADL (42–44)	Prodromal symptoms, such as depression, constipation and Rapid Eye Movement (REM) sleep behavior disorder may occur long before diagnosis (45–47). Progression and survival in Parkinson's disease is highly variable, and mean duration of the disease until death ranges between 7 and 14 years (48). Patient populations are heterogeneous and complex and therefore the clinical course is variable (49). Given enough time, the disease is suggested to progress through five phases: prodromal, stable, unstable, advanced, and late-stage disease (50). However, consensus on demarcation of later stages is lacking (51, 52)
b. Symptoms (physical, psychological, social, and spiritual) and caregiver issues	Pain, agitation and shortness of breath are highly prevalent and burdensome symptoms, and pain and shortness of breath increase toward the end of life (44, 53) while agitation and other symptoms such as apathy may increase during the course of the illness in community-dwelling people (54), but may stabilize or decrease at the end of life (in nursing home populations) (44, 53) Agitation and behavioral symptoms of dementia prevalence rates vary widely but develop at some point in most people with dementia (55, 56). They add greatly to caregiver burden (57). In particular depression often compromises quality of life (58). Regarding spirituality, recent studies show that people with dementia may understand through remembrance of early life experiences (59, 60)	Diagnosis is based on motor symptoms; bradykinesia, tremor, and rigidity (61). Parkinson's disease affects physical, emotional and psychosocial aspects of life (62, 63). Compared to motor symptoms, non-motor symptoms, such as pain, depression, fatigue, psychotic phenomena are more important in terms of quality of life (64, 65) and they may be under recognized (66, 67) Cognitive deficits in Parkinson's disease may be present already at diagnosis and affect quality of life (14). There is significant impairment in executive functions such as poor planning and problem solving capacities. Up to a majority may develop dementia ultimately (15–17) Caregiver burden increases when patients reach advanced stages due to increasing disability, and also with the appearance of symptoms such as hallucinations, depression and falls (68)
c. Functioning	Progressive impairment is related to a decline in cognitive and physical functioning. There is a continuous decline in functioning, e.g., first dependency in IADL occurs, followed by ADL dependency (69). There are also various personality changes with different types of dementia; for example, apathy more commonly develops with Lewy body dementia compared with Alzheimer's disease (70, 71)	The disabling nature of Parkinson's disease increasingly hinders daily activities and social participation (72). Disease progression leads to impairments at different levels of body functions, limitations in a wide variety of ADL and IADL functioning and in a severe stage, disability, and social embarrassment occurs
d. Cause of death	Dementia is often not mentioned as a cause of death in death certificate studies, in particular when patients are younger, have mild dementia and a non-Alzheimer type of dementia (73). Immediate causes of death are often pneumonia and cardiovascular problems (73, 74) also in autopsy studies [e.g., (75, 76)]; more often so compared to people with no dementia	Parkinson's disease was not reported as the underlying or contributory cause of death on more than 53% of death certificates (77). There is a significant increase in deaths from pneumonia, dementia and other infections (78, 79)
e. Prediction of mortality	Strong predictors of mortality are functioning (ADL dependency), nutritional status or intake (80) and male gender including in acutely ill patients (81, 82). Higher age and various co-morbid conditions also relate to increased mortality. Dementia stage, however, is not a strong predictor of mortality in nursing home residents with dementia (83, 84) as a fatal pneumonia or food and fluid intake problem also occur before the advanced stage. Similarly, a late stage on the Functional Assessment Staging (FAST) scale has no predictive value (85). Of note, the available prognostic scores do not identify many at risk of death within a particular timeframe, although they can identify a reasonably sizeable group of people at low risk of mortality, within, e.g., 6 months	Strong predictors of death in people with Parkinson's disease are age, dementia, pneumonia, infections and falls (6, 79, 86–89). Other studies also found male gender, comorbidity, axial features and motor and therapy-related complications to predict mortality (90, 91). Both motor complications and non-motor symptoms were associated with mortality at 4 years in a recent study in patients with Parkinson's disease and no dementia (91)

problems, postural imbalance and cognitive deterioration; (51, 92) or with symptoms that may worsen due to treatment (psychosis, orthostatic hypotension) (51). Other reasons for functional deterioration are age-related comorbid disease (92) and under-treatment of symptoms (93, 94), which also happen with dementia. With dementia, loss of motor or functional ability often relates to progressive cognitive dysfunction.

Defining a severe or advanced stage of the disease (item a) has been recognized as important for palliative care in case of dementia (42–44). For PD, the most widely used measure to define disease stage is the Hoehn and Yahr scale (51, 52, 95).

However, it selectively focuses on motor function. A recent consensus study defined key factors for diagnosing advanced PD including, for example, ADL impairment, and dementia (96).

The stage of dementia is often being perceived as relevant for palliative care although there is no consensus how exactly (28). Also, it is not a particularly strong predictor of mortality among those with moderate or severe dementia, despite sensitive measures; this may be related to uncertainty as to in what stage acute problems such as pneumonia develop or different resilience among long-term survivors (**Table 1**, items d and e) (74, 83, 84). Similarly, a late stage on the Functional Assessment Staging (FAST) scale has shown no predictive value (85), but practice lags behind, still promoting it for prognostication in dementia (97). ADL dependency, on the other hand, is a strong predictor of mortality in dementia (44, 80, 81). In contrast, it may not predict mortality in PD well (98). In PD, dementia or cognitive impairment independently predicts mortality (6, 35, 99).

Pneumonia is a relatively frequent cause of death in dementia and in PD (74, 78, 81). However, well-known problems in coding practice include dementia being grossly underreported on the death certificate (73), also in those with PD (78). Similarly, PD often goes unreported (79).

The overlap between PD and dementia is significant as up to a majority of patients with PD eventually develop dementia (9, 16, 17), due to spreading of Lewy bodies. Because of initial stability and uncertainty as to whether patients develop severe cognitive problems or die before, PD may be perceived as an even more protracted disease course than the dementias.

Conceptualization of the Diseases, Needs, and Interventions

Both dementia and PD are incurable and progressive diseases with often complex problems and needs, for which tailored interventions are available (**Table 2**, items a–d). For dementia, experts agree that "recognizing its eventual terminal nature is the basis for anticipating future problems and an impetus to the provision of adequate palliative care" (28). Some advocate *advanced* dementia to be a terminal disease to support eligibility for palliative care. However, as about half of dementia patients never reach an advanced stage (**Table 1**); (40), it may be a late trigger to initiate palliative care. There is no consensus, however, at which stage palliative care in dementia should start (153, 154).

For PD there are no curative treatments either, but the success of dopaminergic replacement therapy and deep brain stimulation has enabled the majority of patients to live independently with a relatively low symptom burden for the first 10 years after diagnosis-when they live up to a decade (48). This may contribute to PD generally not being recognized as an illness for which a palliative approach may be helpful (155, 156). A US patient and caregivers council recommends palliative care to be available from diagnosis of PD (138). This is also the ideal of the European Parkinson's Disease Association (EPDA) (157) although they emphasize that when to start palliative care is an individual decision.

Patients with dementia may have a number of needs in the four domains of palliative care (physical, psychological, social and spiritual) in addition to specific needs for a peaceful, familiar environment, and practical support (104–106). Typically, complex, multifaceted interventions could address needs. Psychosocial needs may be pronounced in young-onset dementia (onset under age 65) (158, 159). Patient advocacy organizations recognize the importance of high-quality end-of-life and palliative care in the advanced stages (132–134).

To measure symptom burden, specific tools are available (**Table 2**, item e). For dementia, these typically involve proxy (caregiver) report. Quality of care and dying assessment tools specifically developed for dementia show the best psychometric properties (129). For PD, there are adapted versions of generic tools (118, 160). Regardless, effective use of tools and implementation of complex interventions requires multidisciplinary communication and team work (161).

Place of death varies by country (**Table 2**, item f). Patterns are similar for dementia (120, 121) and PD (124), with dying in nursing homes being common in many western countries except Southern European countries with more frequent home death, while hospital death is more common in Asian countries, France and Hungary. In the UK, a trend of decreasing hospital death and increasing nursing home death has been observed in dementia (162). However, continuity of care may be problematic across countries, with nursing home or hospital admissions at the end of life in people with dementia and PD (122–124, 163). Also, with PD, specific knowledge of the disease is often suboptimal among nursing staff in nursing homes, while upon admission, neurologists often stop seeing patients with PD, with communication of neurologists with primary care being suboptimal too (93, 94).

"Person-centered care, communication and shared decision making" was among the most important domains of palliative care in dementia according to experts around the world, and it was prioritized for research (28). Advance care planning (ACP) is a special form of ongoing communication about preferred future health care (**Table 2**, items g and h). Researchers and policy makers are increasingly interested in researching and implementing ACP, and some beneficial effects have been documented in dementia (23, 139, 140). However, there are numerous barriers such as patient and family expecting the physician to start it while physicians may not prioritize such anticipatory care. Also, while many appreciate discussions, not all would like to decide about future treatment (126, 164). Similar barriers might exist in PD (141). In a synthesis of studies, interview studies have shown physicians to be hesitant in discussing progression of the disease in early disease stages as they fear to diminish hope (17). Also patients indicate a conflicted need as they reported both a wish for more information on disease progression and death, and fear to receive the information ("an information tension") (17).

Family caregivers usually have information and support needs in regards to proxy decision making and how to best care for their loved one (28, 165) (**Table 2**, item i). They may experience a magnitude of stress in caregiving and pre-grief in dementia (145) and PD caregiving (150). In dementia, anticipatory grief in response to compounded serial losses is common, and stress in caregiving preceding physical death may be equal to or greater

TABLE 2 | Conceptualization of the disease, needs of patients and family caregivers, and interventions.

Items about conceptualization, needs and care	Dementia	Parkinson's disease
a. Treatment of the disease	No curative treatment is available. Some drugs such as Donepezil may improve cognition and behavior of people with Alzheimer's disease. It may not deserve labeling it as disease modifying drugs; essentially this is palliative medication because they do not slow the progression of, nor cure the disease (100)	No curative or neuroprotective agents are available. A wide range of treatment strategies are available for symptom reduction, often requiring specific Parkinson's disease expertise. Available treatments are pharmacological (e.g., dopaminergic replacement), as well as rehabilitative (e.g., physiotherapy, occupational therapy) (101)
b. Conceptualization of the disease as a terminal disease	Recognizing dementia as a terminal disease may help providing adequate palliative care (28). However, about half of family caregivers and nursing staff do not perceive it as a terminal disease or a disease you can die from (102, 103)	To our best knowledge, there is no research that examines perceptions about Parkinson's disease as a terminal disease
c. Patient's needs in an advanced stage	In advanced dementia, needs may relate to the four domains of palliative care (4), additionally, to (practical) support, and important environmental needs such as a peaceful environment (104–106). Familiarity of environment, routines and people around who know the patient and can interpret the behavior is also important (27, 107)	Prizer et al. (108) add financial needs to needs in the four domains of palliative care and find that patients and families report fewer needs in the financial and spiritual domains; on average, as these needs are more variable between individuals than needs in the other domains. Patients preferred individualized care to address psychosocial issues, adjustment to illness (particularly at diagnosis and with progression), non-motor symptom control, and advance care planning as an adjunct to usual care (109) and it is also perceived as a social need (108). Patients and family caregivers in Canada found that they are not receiving enough information about diagnosis and prognosis (33)
d. Interventions to address needs in particular in an advanced stage	Non-pharmacological treatment of symptoms such as agitation is first choice (28, 100). Because symptoms are easily missed and causes are not always easily identified, systematic assessment and treatment (such as in the stepwise STA OP! or STI intervention) is needed (110). Also regular special programs (such as Namaste Care) (111) to connect with people in the advanced stage in a peaceful atmosphere are needed when they cannot participate anymore in regular activities such as those offered in nursing homes Familiar rituals and music may be recognized until late stages of the dementia and therefore it is important to know religion or spiritual orientation (28, 59). Furthermore, spiritual, and faith practice may help cope with the disease, to find meaning in life, and they relate to wellbeing (59, 60)	Interventions are typically multifaceted and require specialist knowledge, therefore intervention programs have focused on enhancement of multidisciplinary collaboration and education of professionals (e.g., the expert network of ParkinsonNet). Evidence of effectiveness is becoming available, for example occupation therapy, physiotherapy and integrated multidisciplinary care (112–114). An international guideline in palliative care for people with PD includes recommendations for specific late-stage problems (115). However, no study has focused specifically on addressing palliative care needs
e. Assessment tools	Tools specific to dementia are needed for the assessment of pain, distress and behavior (116, 117). There are over 30 pain observation tools available (116) and there are also inventories for multiple symptoms that, in contrast, include pain as a single item such as the Integrated Palliative care Outcome Scale for Dementia (117)	There are symptom assessment tools adapted from generic tools that could identify specific palliative care needs in PD, such as the Palliative care Outcome Scale Parkinson disease (POS-PP) and the Edmonton Symptom Assessment System Parkinson's Disease (ESAS-PD) (49, 118, 119)
f. Place of death and continuity of care	In western countries, people with dementia in a moderate or severe stage are often admitted to a residential or nursing home which is also the most common site of death in most western countries. However, comparing several studies, home death was more common in Southern European countries and Mexico, and hospital death in (developed) Asian countries (120). Japan, for example, refers patients with dementia with behavioral problems to psychiatric inpatient care and people may die there (121). Continuity of care in the last year of life with dementia is problematic also in western countries including in the US and Finland (122, 123)	A substantial proportion of deaths with PD occur in a hospital, although there is wide variation between countries. A study in 11 countries showed that hospital death was most prevalent in France, Hungary and South Korea, whereas nursing home death was most common in New Zealand, Belgium, USA, Canada and Czech Republic; and home death in Mexico, Italy and Spain (124). Patients with PD had more physician consultations and more emergency department visits per year compared to patients without PD (125)

(Continued)

TABLE 2 | Continued

Items about conceptualization, needs and care	Dementia	Parkinson's disease
g. Communication, decision making and the patient's perspective	Due to increasing cognitive problems, communication with people with dementia changes. Apprehension of risk changes and health numeracy decreases; patients are often not involved in treatment decisions (126, 127). Shared decision making models need an extended preparatory phase to first examine perceptions of the need for a decision (128) Palliative care or comfort care is often, but not always preferred for nursing home residents with dementia from the perspective of patient and family caregiver, in different countries (107, 129, 130). In a hypothetical situation of advanced dementia, most older people would opt for comfort care in a study in rural areas (131). Patient advocacy organizations have issued recommendations for end-of-life and palliative care in the advanced stages of dementia (132–134)	Dissatisfactory communication with professionals is one of the most common complaints of patients with PD (109, 135). Treatment of the disease is mainly driven by the clinician (136) In a hypothetical end-of-life situation the majority of proxies of patients with advanced PD would choose comfort care as the goal of treatment (137). A US patient and family caregiver council advocates palliative care to be available from diagnosis (138)
h. Advance care planning (ACP)	ACP often does not start until the late stage when the patient cannot be involved anymore. It is not always clear whose responsibility it is, there are multiple barriers including patients rather living by the day, and there may be discontinuity of information with a change of setting of care (126). However, in view of the cognitive decline, ACP is preferably started early (28). There is also evidence of effectiveness to increase advance decision making, family satisfaction with it, and other outcomes (23, 139, 140)	Many patients want information on prognosis early in the disease. Patients' preferences regarding communication and timing of end-of-life discussions vary (141). A full ACP process may be perceived as lowering mood in an early stage the disease, and should therefore be tailored to the stage of the disease and individual preferences (135). Only a few patients with PD who died in a UK hospital had had end-of-life care discussions which were documented (142)
i. Care for families	Family caregivers usually need support and care themselves including support in proxy decision making, long before the dying phase (28). Caring for a person with dementia is often highly burdensome especially when behavioral symptoms such as agitation and sleep disturbance develop (143). In addition to higher caregiver burden, there are fewer positive caregiving experiences, even at the end of life (144) Pre-grief often occurs with the decline of the patient, especially among spouses (145). Psychosocial interventions may decrease pre-grief (146)	Family dynamic change (30, 68, 147–149), loss of autonomy, economic strain and social isolation are part of the caregiver burden Pre-death grief was a significant finding in family caregivers of patients with advanced PD and was associated with a patient's cognitive decline (150). In a review (151) of 30 studies about interventions to support caregivers only one psychosocial intervention was shown to significantly decrease psychosocial problems and need for help (152). Interventions that embrace psycho-educational skills such as problem solving, goal setting and cognitive restructuring can bring benefit (29)

than stress in bereavement. Roland et al. (166) found caregiving experiences and stressors to be similar between caregivers care for a patient with dementia, PD, and PD and dementia.

Disease-Specific Palliative Care and Practice

Disease-specific palliative care is needed; services and tools taken uncritically from cancer palliative care have shown to not fit well with dementia and require adaptation or even redevelopment from scratch (27, 167, 168). Palliative care specialists, however, may not know enough about the specifics of dementia and PD. In addition to suboptimal access to palliative care (17) access *to disease-specific* multidisciplinary care for PD may be suboptimal (93, 169, 170).

Clearly, better integration of disease-specific and palliative care expertise is needed. To establish dementia-specific palliative care, the EAPC therefore recommends collaboration between disease-specific (dementia) and palliative care (28). In the UK there are initiatives for outreach with specialist dementia palliative care to support the familiar care team (27, 171, 172).

Regarding PD, the provision of palliative care is widely advocated (17, 29, 32, 173). A special task force of the International Parkinson & Movement Disease Society is dedicated to improving palliative care in PD (29, 174). A mapping exercise in the UK showed service provision to vary across regions, and services for PD were not well-integrated with palliative care (175). There are some patchy examples of integration of expertise from a palliative care department with a neurology department (176). Patients and family caregivers found they lacked knowledge about palliative care services. Only few patients received care from a palliative care service and coordination of care was poor (33, 147, 148). The need for palliative care, including early in the disease trajectory, has been emphasized by a collaborative statement from the EAPC and the European Academy of Neurology (EAN) (177).

Among dementia care specialists, providing palliative care early is controversial (154, 171). Soon after diagnosis, palliative care can start in the form of ACP if patient and family caregiver are willing to talk about the future (28). Waiting until an advanced stage means many will never receive palliative care,

mortality having been predicted inaccurately so patients die well before palliative care issues could be addressed. Establishing criteria to restrict access to US hospice care to those closest to the end of life has been subject of considerable research [e.g., (82, 85)]. Prediction research consistently shows we can identify those likely to survive accurately, but not, or very few of those likely to die. Needs may differ with more advanced dementia though, and ideally, a needs-based approach is adopted (176). Similarly, for people with PD, triggers for palliative care (98) and access to US hospice care have been sought using a mortality prediction approach (178). For example, a BMI less than 18.5, accelerated weight loss and reduction of dopaminergic medications was suggested for referral to US hospice care (178).

There is a lack of awareness about palliative care being applicable to dementia both among the general public and health care professionals, and this is perceived as a major barrier to improve palliative care, for example by Dutch and British physicians (179). Nursing staff may feel that they lack competencies to deliver high-quality palliative dementia care (Bolt et al., under review). Also, in PD, professionals may feel uncertain about the palliative care they deliver and often experience a lack of education and competence in this field (155, 156, 180, 181).

CONCLUSION

Substantial research is being performed on dementia palliative care. Much has happened since early descriptive research in dementia compared symptoms and treatment with cancer [e.g., (182)], and introduced a hospice model of care (20). The research has culminated into a clearer definition of what palliative care should entail with dementia and into some understanding of its effects. Comparisons with other diseases are now available regarding a variety of aspects (e.g., a higher caregiver burden compared with cancer (183), symptoms compared with various other chronic-progressive diseases (184), or specific problems described in subgroups with both dementia and cancer (185–188). Nevertheless, it is still unclear what is important at what stage and how to best incorporate individual preferences, for example regarding discussions about future care.

PD follows an even more protracted course which complicates a clear definition and there is no agreed-upon, evidence-based, disease-specific conceptualization of palliative care. Even more varied multidisciplinary expertise may be needed including also dementia care expertise (in addition to PD disease-specific care, palliative care and generic long-term care for older people). More specific tools may also be needed, for example, application of pain observation tools in PD dementia should consider that facial expressions indicating pain are distinct [e.g., less eye narrowing but similar upper lip raising (189)], to avoid possible underreporting in Parkinson's disease compared with Alzheimer's disease (190).

The combining of various expertise requires clear roles and inter-professional collaboration which is challenging in the face of uncertain disease trajectories (191). However, integration of palliative care has shown to improve process outcomes and patient and caregiver outcomes in cancer and chronic-progressive disease (192). Integration should take place at the clinical (patient) level but also, for example, through relationships between professionals and between organizations and in the wider system (193). For this, multidisciplinary networking and teams sharing expertise

BOX 1 | Basic recommendations for practice of palliative care based on similarities and divergences between progressive neurological diseases and available evidence*.

1) Do not wait with bringing palliative care to the table until a late or terminal stage of the disease. Although it seems an obvious and safe choice to limit to a late stage, it may be too late to involve the patient or to implement a palliative care treatment plan. With PD, there is often opportunity to speak about palliative care when cognitive problems are still mild or absent. With dementia, it is difficult to predict who will die already before the late stage, while many will, with unmet palliative care needs. Therefore, discussion of palliative care before a moderate stage is recommended.
2) Improving awareness, among all involved, of the progressive course of the disease supports a shared understanding of the disease, implications for death and dying and what it means for the individuals involved. This will be helpful in identifying and addressing palliative care needs.
3) Common causes of hospital admissions include pneumonia, sepsis, and falls. Physicians could discuss these scenarios as a starting point to establish patients' views and preferences regarding invasive therapies and the benefits of a palliative care approach.
4) Elicit preferences of patient and family and the preferred style with regard to talking about future care and end-of-life scenarios. Address any information needs, and a step-wise approach with discussions continued later on may avoid feelings of being overwhelmed.
5) The course of the disease is uncertain, whereas *change* is. All members of a care team should help identify and discuss subtle changes in symptom and caregiver burden early.
6) Palliative care is an approach in which intervening is still possible even if active treatment of the disease or its complications is not possible or when other treatment is being withheld. It can be a potent adjunct to usual care but it should be well-integrated, also at a system level. As opposed to being *uni*form, straightforward, hassle free fix, "*multi*" is the important term in this: *multi*faceted interventions targeted to the individual in a context of *multi*disciplinary collaboration between generalists and disease and palliative care specialists.
7) Tools to identify needs and a change in the patient's condition (physical, psychosocial, spiritual, caregiver needs) should be sufficiently *specific* to the disease while a context or setting *specific* system should be in place to support its continued use (for example, a systematic approach to managing pain, behavioral symptoms, autonomic dysfunction, sleep dysfunction or motor fluctuations/dyskinesias sustainably implemented in long-term or acute care).
8) Pre-grief with progressive decline of the patient and prolonged social isolation are common. Psychosocial support is needed in different phases to empower patients and family caregivers to cope with both chronic stressors and crises.

*We inferred this general and more disease-specific guidance from the items on course of the diseases and conceptualizations in **Tables 1**, **2**, acknowledging that these are only a couple of key recommendations and that evidence is limited. Also, this guidance should be refined and fit the local context when implemented. For more detailed guidance for clinical practice, we refer to the recommendations as part of the European Association for Palliative Care (EAPC) dementia white paper (28) and guidelines from the Irish Palliative Care in Parkinson's Disease Group (115).

is important, supported more formally by shared guidelines and pathways (194).

Sawatzky et al. (18) describe three reasons how a clear conceptualization of palliative care in chronic-progressive disease may be helpful: (1) earlier recognition ("upstream") of needs, (2) to promote adaptation of palliative care knowledge and expertise for unique disease profiles, (3) to operationalize a palliative approach through integration into systems and models of care that do not specialize in palliative care. Such conceptualization is promoted by looking at similarities with other diseases with more established palliative care models, but also taking a closer look at divergences, such as the initial stable phase in PD and how this should affect palliative care services. It raises the question whether ACP is an integral part of palliative care, or could precede it, also for dementia considering ambiguity around early palliative care. This resonates with recommendations of Temel et al. (195) for "early" palliative care to depend on the type of cancer; with low symptom burden, waiting until a change in health status or emergency room admission may be a reasonable approach.

For palliative dementia care, it has been helpful to also consider how it differs from "usual" dementia care, for example, by a highly proactive approach. Such understanding of what needs to be changed in practice facilitates the integration of a palliative approach in dementia care so that ultimately, the integrated care becomes the standard (196). With Kluger et al. (29), we believe that palliative care in PD will benefit from a clearer conceptualization.

Although probably not directly suitable as entry criteria for palliative care, research on prognostic factors in PD may be helpful. For example, ADL dependency strongly predicts mortality in older people and in dementia (80, 81, 85), probably covering cognitive and physical impairments and other risk factors. In contrast, it may not predict mortality in PD well (98), perhaps because motor function declines early; some dependency therefore occurs earlier than in dementia. Further, we agree that more work is needed regarding assessment of needs–including spiritual needs, development of assessment and educational tools and interventions for patient and caregiver support (29, 108).

Although we could not compare directly, we hope that our review contributes to an emerging understanding as to what elements of palliative care with neurological conditions are disease-specific and which are more general. We acknowledge that the brevity of the review did not allow more depth regarding aspects of the disease and care in different types of the diseases or forms of parkinsonism which need further research. More could be written about possible implications such as how to organize disease-specific palliative care in a cost-effective manner. We recognize a need for basic guidance for clinical practice which we offer in **Box 1**, awaiting high-quality trials and other research we need to build refined evidence-based practices that optimally serve individuals with neurological disease.

AUTHOR CONTRIBUTIONS

JS, HL, and DH: manuscript development, manuscript writing, and manuscript authorization; BA, MG, JH, BB, RK: manuscript writing and manuscript authorization.

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Supportive Care Needs in Glioma Patients and Their Caregivers in Clinical Practice: Results of a Multicenter Cross-Sectional Study

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Objective: Supportive care needs in glioma patients often remain unrecognized, and optimization in assessment is required. First, we aimed at assessing the support needed using a simple structured questionnaire. Second, we investigated the psychosocial burden and support requested from caregivers.

Methods: Patients were assessed at three centers during their outpatient visits. They completed the Distress Thermometer (DT; score $\geq$ 6 indicated significant burden in brain tumor patients), the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-C30+BN20, and the Patients' Perspective Questionnaire (PPQ) that assessed psychosocial distress as well as support requested and received by patients for specific domains (e.g., family, doctor, and mobile care). In each subgroup, patients' caregivers were assessed simultaneously by a questionnaire developed for the study. Multivariate backward logistic regressions were performed for investigating predictors of patients' request for support.

Results: Assessments were conducted for 232 patients. Most patients (82%) had a high-grade glioma and a mean age of 52 years (range 20–87). The male to female ratio was 1.25:1. According to the PPQ results, 38% (87) of the patients felt depressed; 44% (103), anxious; and 39% (91), tense/nervous. Desired support was highest from doctors (59%) and psychologists (19%). A general request for support was associated with lower global health status ($p = 0.03$, odds ratio (OR) = 0.96, 95% CI: 0.92–0.99) according to EORTC QLQ-C30. Most of the assessed caregivers ($n = 96$) were life partners (64%; $n = 61$) who experienced higher distress than the corresponding patients (caregivers: 6.5 $\pm$ 2.5 vs. patients: 5.3 $\pm$ 2.4). When patients were on chemotherapy, caregivers indicated DT $\geq$ 6 significantly more frequently than patients themselves ($p = 0.02$).

Conclusion: Our data showed that glioma patients and their caregivers were both highly burdened. The PPQ allowed us to evaluate the psychosocial support requested and perceived by patients, detect supportive care needs, and provide information at a glance. Patients in poorer clinical condition are at risk of having unmet needs.

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The caregivers' burden and unmet needs are not congruent with the patients' need for support. In particular, caregivers of patients on chemotherapy were more highly burdened than patients themselves.

Keywords: supportive care needs, palliative care, glioma, brain tumor, self-assessment

INTRODUCTION

The prognosis in high-grade glioma patients remains poor, and supportive care needs should be addressed in a timely manner. The requirement for psychosocial support and early palliative has not only become a focus of (neuro-) oncological research (1–5), but is also incorporated in guidelines for the provision of care for these patients (6, 7). Application of patient-reported outcomes (PROs) has become essential in assessing the patients' quality of life and their needs, distress, and psychosocial burden, as well as supportive care needs (8). Recently, it has been shown that monitoring symptoms via PRO measures can be very helpful for cancer patients and even influence survival (9, 10).

Palliative and end-of-life care are still partially neglected topics in current neuro-oncological outpatient care. Seibl-Leven et al. reported recently that palliative care in glioblastoma patients is either not provided at all, or not in a timely fashion, leading to a shortage of services for patients and caregivers (11). Adequate assessment of unmet needs, early integration of palliative care and timely end-of-life-care planning should be implemented as clinical routine (12).

As glioma patients suffer from neurocognitive deficits caused by both the disease itself and the treatment (13–15) they may not always be able to answer PRO questionnaires. Furthermore, as reported by our group and others, patients undergoing chemotherapy or in a poor clinical condition may be missed by PRO assessment; however, at the same time, they are those who could particularly benefit from early supportive care (5, 16–18). Therefore, we believe it is of utmost importance to adequately identify glioma patients in need of supportive care.

Caregivers face challenging situations as well, sometimes even more so than glioma patients. The neurological, psychological and cognitive symptoms of patients with gliomas represent significant challenges to their caregivers: Not only do they have to cope with the diagnosis of the family member, with the therapy and the knowledge that they will finally lose their partner or parent or child, but also accept changes in roles, relationships, social isolation, financial restriction and sooner or later, have to take care of the partner or family member day and night (19–23).

Therefore, the aims of our study were to (1) Assess support received and needed by patients and (2) Assess support needed by patients' caregivers.

PATIENTS AND METHODS

Patients

During April 2015 to June 2016, patients at three German neuro-oncological centers were approached during their outpatient visits and asked to participate in the study. Inclusion criteria were diagnosis of glioma WHO grades II–IV regardless of disease stage (initial diagnosis or recurrent disease), absence of aphasia impairing communication or consent to the study, and given informed consent. Patients were asked to complete several PRO measures. Furthermore, demographic and clinical data were recorded in a database.

PRO Measures Used

Distress Thermometer (DT)

The DT is a self-reporting screening instrument developed by the National Comprehensive Cancer Network to evaluate psychological distress on a visual analog scale (0–10 points). A problem list with 40 items is included for patients to indicate the area of concern (family, financial, and physical) (24). Studies have proven its acceptance in oncological patients, and the German version for brain tumor patients was first evaluated by Goebel and Mehdorn (25). A score $\geq$6 indicates significant burden in brain tumor patients.

European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core Module for Cancer Patients Accompanied by the Brain-Specific Module (EORTC QLQ-C30 + BN20)

The EORTC QLQ-C30 is a widely accepted questionnaire applying a 4-point Likert scale to evaluate cancer patients' quality of life. Five functional, three symptom, and six single-item scales as well as the global health status are investigated (physical, role, emotional, social, and cognitive functioning; fatigue, nausea and vomiting, pain; dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Its validity and reliability have been proven in numerous clinical studies, and it is available in 85 languages. The additional module for brain tumor patients (BN20) consists of 20 questions specifically assessing their symptoms (3 neurological deficit scales, 1 future uncertainty scale, treatment and disease-related symptoms) (26, 27). The EORTC scores were calculated according to the user manual (28). Each scale is scored from 0 to 100, with higher scores indicating better functioning for functional scales and worse symptoms for symptom scales. In our regression and correlation analyses, we used the global health scale (GHS) as the primary endpoint.

The Patients' Perspective Questionnaire (PPQ)

The "Patients' Perspective Questionnaire" (PPQ) is a questionnaire assessing patients' current status of support received, its subjective benefit and further needs. It was adapted for brain tumor patients based on a questionnaire used by Singer et al. (29). They applied several versions, whereas in our study we combined them into one questionnaire, added

questions and items of probable interest to glioma patients according to the authors' experiences. This resulted in one questionnaire comprising three parts: Part I: The first 9 items assessed psychosocial distress (sad /worried /angry /tense /hopeful /burdened by disease/ burdened by other problems/ sufficiently supported/ sufficiently informed) by 5-step Likert-scales (scoring from 1 = not at all to 5 = very much) and if support was requested by the patient with regard to the respective item ("I need support for.…": yes/no). The latter questions were considered for the general request for support if one or more item was answered with "yes." The next 10 items (Part II) assessed support provided and its subjective benefit on a 5-step Likert scale (scoring from 1 = support was not helpful at all to 5 = support was very helpful). The last 7 items (Part III) recorded support requested currently by the patients (from doctors, psychologist, social worker, and so on) with dichotomous answer possibilities (yes/no). Further support currently requested by any profession or next of kin was considered positive if one or more answers were "yes." The questionnaire is provided as **Supplement 1**.

The Questionnaire for the Caregivers/Caregivers' Perspective Questionnaire (CPQ)

In order to provide a questionnaire for glioma patients' caregivers in line with the PPQ with regard to structure and practicability, we combined elements and items after conducting a literature search and using an expert panel in the study group. We first applied it as a pilot study in family members volunteering during an information-sharing event for brain tumor patients. According to their anonymous feedback, the questionnaire was adapted with respect to wording, font size and item specification. The final version of the questionnaire is provided as **Supplement 2**.

Part I assessed the psychological distress on a visual analog scale (0–10 points) according to the DT applied to patients. Further, possible problem-items were provided similarly to the DT item list with dichotomous choices with regard to practical, family or emotional problems (24). In part II, we incorporated two questions with regard to quality of life and global health with Likert scales scoring from 1 to 7 according to the items 29 and 30 of the EORTC QLQ-C30 questionnaire (26). Finally, part III provided a list of items recording the support requested by caregivers (psychologists, social care, doctor, physiotherapy, dietician, self-help, friends, family members, palliative care). The questionnaire further included a question if an explanation of any term in the questionnaire was needed (**Supplement 2**).

Patients' and Caregivers' Assessment

Patients completed the DT, EORTC QLQ-C30+BN20 and the PPQ by themselves. Further, patients were asked directly by the attending neuro-oncologist during the patient-doctor consultation if they would like support by a psychologist. Neuro-oncologists also indicated and recorded their own assessment with regard to patients' unmet psycho-oncological needs independent of the assessment by questionnaires after having obtained the current medical history.

In a subgroup, patients' caregivers were assessed simultaneously by the CPQ developed for the study.

Statistical Analysis

Demographic and tumor-related data, as well as Karnofsky-Index, were analyzed descriptively. Explorative Spearman's rho correlations between DT score as well as GHS and general request for support or request for support by doctors were performed.

Multivariate logistic regressions were performed with regard to "request for support in general" as well as "request for support by doctors" and "by other health care professionals." Clinical and demographic factors probably influencing request for support were selected content driven by the authors as follows: sex (male/female), living situation (alone/in relationship), educational level (university degree/no university degree), WHO grade (low-grade/high-grade glioma), Karnofsky-Index (continuous variable, score 0–100), on chemotherapy (yes/no), GHS (continuous variable, EORTC QLQ-C30, score 0–100), DT score (continuous variable, score 0–10), surgery for recurrent disease (yes/no), and age (continuous variable, 25–85). The statistical analyses were performed using SPSS version 22 (IBM Corp., Armonk, NY).

Ethics

The study was performed in accordance with national law, institutional ethical standards, and the Declaration of Helsinki after approval of the study protocol by the local ethics committees (Mainz, Germany and Ulm/Günzburg, Germany [No: 837.349.15 (10117)]. All patients provided written informed consent prior to data assessment.

RESULTS

Patients

Two hundred and thirty-two patients were assessed and 84% of the patients had a high-grade glioma. Mean age was 52 years (range 25–85). Male to female ratio was 1.25:1. Most of the patients were in a relationship and 30% ($n = 71$) had a higher education level. Mean Karnofsky-Index was 79 and 52% of the patients were on chemotherapy during assessment. Further details are provided in **Table 1**.

Patients' Perceived and Requested Support According to the PPQ

We observed that 38% (87) of patients felt depressed (indicated ≥ 3 on the Likert scale), 44% (103) were anxious and 39% (91) were tense/nervous. Fifty-nine percent (138) reported to be adequately informed about the disease and therapy and 77% (180) of the patients felt sufficiently supported (**Table 2**).

Patients' support was reported to be highest from family (75%) and doctors (e.g., physician or attending neuro-oncologists, 68%). Only 13% were supported by psychologists. The support was mostly reported as helpful with highest mean scores being that of family and friends (mean score > 4), followed by doctors, outpatient care services and physiotherapists.

TABLE 1 | Clinical and demographic data of the patient sample and results of the psychosocial assessment using the Distress Thermometer (DT; score ≥ 6 indicated significant burden in brain tumor patients), the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-C30+BN20, and the Patients' Perspective Questionnaire (PPQ).

Variable	Patients $n = 232$ (100%)
AGE IN YEARS	
Mean (SD; min, max)	52 (14; 20, 87)
Sex, n (%)	
Male	129 (56)
Female	103 (44)
LIVING SITUATION, *n* (%)	
Single	49 (21)
In relationship	75 (72)
Unknown	8 (7)
EDUCATION LEVEL	
University degree	71 (30)
No university degree	151 (66)
Unknown	10 (4)
WHO-GRADE, *n* (%)	
LGG (WHO I°+II°)	35 (16)
HGG (WHO III°+IV°)	190 (84)
TUMOR LOCALIZATION I, *n* (%)	
Frontal	99 (43)
Temporal	57 (25)
Parietal	31 (13)
Occipital	12 (4)
Other	17 (8)
Unknown	16 (7)
ONGOING CHEMOTHERAPY, *n* (%)	
Yes	111 (48)
No	121 (52)
SURGERY FOR RECURRENT TUMOR, *n* (%)	
Yes	57 (25)
No	140 (60)
Missing	35 (15)
KARNOFSKY-INDEX	
Mean (SD, range)	79 (16; 40–100)
TIME SINCE DIAGNOSIS IN MONTHS	
Mean (SD, range)	42 (54; 4–288)
Median	19
VALUE OF DISTRESS-THERMOMETER*	
Mean (*SD*, range)	5.0 (2.5; 0.0–10.0)
< 6 (*n*, %)	126 (54)
≥ 6 (*n*, %)	95 (41)
Missing	11 (5)
SELECTED EORTC QLQ-C30 AND EORTC QLQ-BN20 SCORES, MEAN (*SD*)	
C30 Global Health Status/QoL	57.4 (23.0)
C30 Physical functioning	68.8 (30.1)
C30 Role functioning	57.3 (36.4)
C30 Emotional functioning	60.4 (28.0)
C30 Cognitive functioning	58.3 (32.7)
C 30 Social functioning	54.3 (35.9)
C 30 Fatigue	46.3 (32.0)
C 30 Pain	23.4 (28.0)
BN20 Future uncertainty	43.9 (29.9)
BN20 Motor dysfunction	25.0 (27.1)
BN Communication	31.7 (32.4)
BN Headache	29.7 (32.2)

LGG, low grade glioma; HGG, high grade glioma.

Desired support was highest from doctors (59%) and psychologists (19%) as well as from dieticians (15%, **Table 2**).

Patients' Requested Support in Comparison to DT, GHS, and Clinical Condition

Patients requesting support according to the PPQ generally showed higher DT scores (according to DT, $p = 0.006$, $r_s = 0.20$), lower GHS (according to EORTC QLQ-C30, $p < 0.001$, $r_s = -0.34$), and lower Karnofsky indices ($p = 0.03$, $r_s = -0.18$). The request for support was further associated with patients' wish for psychological intervention when asked directly ($p = 0.03$, $r_s = 0.27$), and the neuro-oncologist's clinical assessment of patients' unmet needs ($p = 0.001$, $r_s = 0.24$).

Factors Associated With Current Requested General Support According to the PPQ

With regards to the request for support in general, we observed that patients reporting "lower GHS" were at higher risk for unmet needs ($p = 0.03$, odds ratio (OR) = 0.96, 95% CI: 0.92–0.99), as assessed by logistic regression analysis (step 5). Patients "living alone" indicated higher request for support; however, this was not significant. Educational level, WHO grade, Karnofsky-Index, on chemotherapy, DT score, surgery for recurrent disease and age were not significantly associated with the request for support in general.

Factors Associated With Current Requested Support by Doctors According to the PPQ

Logistic regression analyses revealed that "living situation/not in partnership" was associated with request for support by doctors according to the PPQ (living situation/in partnership $p = 0.01$, OR = 0.06, 95% CI: 0.01–0.53). Further, we observed a tendency of patients "on chemotherapy" to wish for greater support; however, this was not significant. Request for support from physicians was not significantly associated with educational level, GHS, sex, WHO grade, Karnofsky-Index, DT score, surgery for recurrent disease and age.

TABLE 2 | Results of assessments in 232 patients using the PPQ.

Item	Do you feel…? (Mean on Likert scale*)	Support requested (*n*, %)
PART I: MOOD AND WELL-BEING		
Sad/depressed	2.3 (1.2)	37 (16)
Worried/anxious	2.5 (1.2)	36 (16)
Angry	2.0 (1.2)	28 (12)
Tense/nervous	2.3 (1.2)	33 (14)
Hopeful	3.3 (1.2)	25 (11)
Burdened by disease	2.9 (1.3)	44 (19)
Burdened by other problems	2.2 (1.3)	27 (12)
Sufficiently supported	3.9 (1.3)	33 (14)
Sufficiently informed	3.5 (1.3)	49 (21)
Profession	**Received support (*n*, %)**	**If yes, how helpful? (Mean on Likert scale#)**
PART II: RECEIVED SUPPORT		
Doctor	157 (68)	3.9 (1.0)
Outpatient care/palliative services	46 (20)	3.8 (1.1)
Physiotherapist	54 (23)	3.6 (1.3)
Social service	27 (12)	3.4 (1.6)
Psychologist	31 (13)	3.3 (1.6)
Pastor	11 (5)	2.9 (1.7)
Dietician	12 (5)	2.8 (1.4)
Support group	4 (2)	2.3 (1.6)
Family	174 (75)	4.5 (0.9)
Friends	156 (67)	4.2 (1.0)
Profession	**Requested support (*n*, %)**	
PART III: REQUESTED SUPPORT		
Doctor	137 (59)	
Outpatient care/palliative services	31 (13)	
Social service	26 (11)	
Psychologist	43 (19)	
Pastor	10 (4)	
Dietician	34 (15)	
Support group	23 (10)	

*In part I, patients indicated their psychological well-being and mood as well as satisfaction and unmet information needs. In part II, patients indicated received support and rated how helpful the support was. In part III, patients indicated by which profession he/she needed support. *Likert scale 1–5 with 1 = not at all and 5 = very much. #Likert scale 1–5 with 1 = not at all helpful and 5 = very helpful.*

Factors Associated With Current Requested Support by Any Health Care Profession According to the PPQ

With regard to request for support by any health care profession, logistic regression revealed that "living situation/not in partnership" as well as "university degree" were associated with wish for support by any health care profession according to the PPQ; "living situation/in partnership" was protective ($p = 0.01$, OR = 0.076, 95% CI: 0.10–0.57), whereas having "university degree" posed a higher risk ($p = 0.04$, OR = 7.86, 95% CI: 1.10–56.08). There was no significant association between requested support from any health care profession and sex, GHS, WHO grade, Karnofsky-Index, on chemotherapy, DT score, surgery for recurrent disease and age.

The Caregivers' Burden

In a subgroup of 96 patients, their caregivers completed the CPQ. Patients' age in this subgroup was 56 years (*SD* 14.8, range 19–84). Most of the caregivers (64%, $n = 61$) were life partners.

Caregivers' DT mean was higher than the DT mean of the corresponding patients (caregivers: $DT = 6.5$, $SD = 2.5$ vs. patients: DT mean = 5.3, $SD = 2.4$). Similarly, a DT score ≥ 6 was reported more frequently by caregivers (55%, $n = 53$) than patients (47%, $n = 37$). Simultaneously, according to the CPQ, caregivers were highly burdened: 48% indicated to be anxious, 54% were sad and 70% reported concerns/worries. Practical problems were mostly problems with insurance or financial problems (24%), mobility and transport (38%) and working situation (25%). The changes in relationship (32%) and problems in interactions with spouse or life partner (28%) were frequently reported. Further results are presented in **Table 3**.

When patients were on chemotherapy, caregivers indicated DT $\geq$ 6 significantly more frequently than the patients themselves (patients: 33%, $n = 13$ vs. caregivers: 59%, $n = 23$, $p = 0.02$, Fishers' exact test).

Caregivers' Requested Support

Twenty-eight percent ($n = 26$) of caregivers indicated a moderate and 14% ($n = 13$) a poor quality of life (mean of all assessments QoL: 4.4, and global health: 4.7 on a Likert scale 1–7). Requests for support came mostly from family (26%), doctors (24%), psychologists (15%), physiotherapists (15%) as well as social service (13%). **Table 3** presents results in more detail.

DISCUSSION

In our study, we were able to apply the PPQ to glioma patients and assess support received and needed by patients as well as evaluate the accompanying caregivers by a study-specific questionnaire in a subgroup of patients. We found clinical and demographic factors (e.g., GHS, living situation, and university degree with regard to education) to be associated with higher wish for support, either global or support by a specific profession. Caregivers were even burdened more highly and needed support as well.

Patients and Required Support

In our sample of glioma patients, we observed that the male to female ratio, general conditions expressed by the Karnofsky-Index and the high rate of high-grade gliomas (HGG) represented patients seen by neuro-oncologists in outpatient settings in general. However, as we did not assess the percentage of patients refusing the assessment, we are unable to reflect on the reasons for refusal (e.g., the assessment comprising three questionnaires might not have been well-accepted and probably

TABLE 3 | Results of assessments in 96 caregivers using the self-developed questionnaire.

PART I: DISTRESS AND PROBLEMS	
Distress mean (SD; median)	6.5 (2.5, 6)
Problems with…	***n* (%)**
Child Care	11 (11)
Housing situation	10 (10)
Insurance/finance	23 (24)
Mobility/transport	36 (38)
Working/education	24 (25)
Interaction with children	10 (10)
Interaction with life partner	27 (28)
Interaction with parents	12 (13)
Depression	12 (13)
Anxiety	46 (48)
Nervousness	45 (47)
Sadness	52 (54)
Worries	67 (70)
Changes in relationship	31 (32)
PART II: QUALITY OF LIFE	
Quality of Life of caregiver*	4.4 (1.5)
Global health of caregiver*	4.7 (1.4)
PART III: REQUESTED SUPPORT	
Profession	***n* (%)**
Psychologist	14 (15)
Social service	12 (13)
Doctor	23 (24)
Outpatient care	13 (14)
Physiotherapist	14 (15)
Pastor	4 (4)
Dietician	10 (10)
Self-help group	4 (4)
Family	25 (26)
Palliative services	8 (8)
Request for further explanation of terms	3 (3)

In part I, caregivers indicated their distress and problems. In part II, caregivers indicated their quality of life and health status. In part III, they indicated by which profession he/she needed support.

** Likert scale 1–7 with 1 = extremely poor and 7 = very good.*

too demanding). Seibl-Leven et al. reported a relatively high refusal and drop-out rate in their field study (11). Further, in a previous study by our group, we observed that patients refusing an assessment or dropping out of an observational study were more often with recurrent diseases, poorer clinical condition and harbored more often a glioblastoma (18, 30). Therefore, we should take into account that a certain percentage of patients probably with unmet needs may have been missed by our assessment and assume that we observed a selection of glioma patients, leading to a lower generalizability of the results.

In general, high burden and a strong wish for support for certain mental/emotional states (e.g., worries and depression) were indicated by the patients using the PPQ, which was also reflected by the fact that higher DT scores were associated with more frequent requests for support. This is in line with other studies and emphasizes how demanding comprehensive care for glioma patients is (2, 11, 31–34).

Interestingly, 15% of the patients required support by dieticians. While rarely addressed by neuro-oncologists, this aspect should be taken into account when planning supportive care for glioma patients as they frequently suffer from dysphagia in the final phase of the disease (35, 36).

Although many patients suffered from depression, worries and sadness, only 13% were supported by psychologists and 20% by outpatient/palliative care services, and only 19% and 13% required support from these respective professions. One reason for this finding could be that patients felt stigmatized when they experienced psychological problems and hesitated to ask for and accept support. Doctors rarely refer patients proactively for psychosocial support or palliative care timeously. Ideally, the treatment team is multidisciplinary from the very beginning of the disease trajectory. Even if the patients are not healed, this team can still support the patients together (5, 7, 36). This is also strengthened by the fact that according to the findings from the PPQ in our study, many patients and caregivers required general support as well as support from doctors relatively often. As we did not define the specialist disciplines (e.g., neurologist, family doctor or oncologist) in the questionnaire, it remains difficult to interpret this high percentage. It may probably include other disciplines: Patients might hesitate to indicate the need of psychological support; however, they might prefer to indicate support by doctors. The high rate of required support by doctors compared to other disciplines could be further due to the timing of the assessment. All patients were assessed prior to the appointment. Thus, potentially relevant questions were not addressed. Patients participating in this study may have attempted to be a "compliant patient" which may have introduced a certain bias in our study. This is also a possible explanation for the finding that patients rated the support by doctors as "helpful" in part II of the PPQ.

Patients seemed to be not well informed. This is of concern and needs to be considered seriously, and as already reported by other studies on patient-doctor consultations in (neuro-) oncology, improvement in communication skills is required (37). Glioma patients suffer from neurocognitive deficits and comprehension can be impaired (38, 39). Further, due to the lack of data and effective treatment options for patients with recurrent gliomas, patients may feel that they are under-informed and hope for new therapeutic options (40).

Distress, GHS and Request for Clinical Support

We found a correlation of elevated DT, higher burden of patients and request for clinical support. Furthermore, the wish of patients when asked directly and the assessment of attending neuro-oncologists were both associated with request for general support. It is well known that doctors' views are not always congruent with the patients' views with regard to psychosocial distress and unmet needs (2). However, our data show that if there is no time for an extensive psychosocial

assessment or patients are unable to complete questionnaires during the routine clinical visit, a higher level of distress directly indicated by the patient on a visual analog scale (which should be feasible for most of the patients) may signal unmet needs. Of note, the doctor in charge has to find out during the consultation the reasons for the distress and the areas of unmet needs. In our opinion, a routinely implemented question on distress during the consultation could draw attention to the patients' problems and initiate support whenever another type of screening (e.g., with questionnaires) is not possible.

Factors Associated With Required Support

We observed several clinical and demographic factors to be associated with required support. As also shown by others, patients in poor general condition (as perceived by themselves and expressed in our study by GHS) require greater support (34, 41).

In times of increasing social isolation, it seems to be an important finding of our study that patients living alone were at risk of higher unmet needs. Attending neuro-oncologists and physicians should consider the social situation of patients in order to initiate support timeously, particularly as patients with gliomas (as well as their families) are at risk for social isolation *per se* (42, 43).

Interestingly, patients with higher educational level longed for more support by any health care profession than did other patients. Possibly, they may have been better informed than the others or needed further support to deal with information obtained by themselves (e.g., via the internet). Presumably, all patients deal intensively with the poor prognosis, the clinical deficits, the neurocognitive impairment and psychological burden; however, those with higher education verbalize their questions better than the others. Although our analyses have to be regarded as exploratory, we observed similar results as others and the factors could serve as features signalizing patients with unmet needs to the doctors in charge (22, 34).

Caregivers' Burden

As in other studies, the caregivers of our patients reported high distress, even higher than that of the patients (1, 2, 22, 23). Our caregivers were mostly life partners accompanying their relative to the consultation. It is well known that in glioma patients, family problems occur due to role changes, or changes in relationships. Demanding financial situations and practical issues also lead to tremendous burden in caregivers along the disease trajectory—reflected in our data as well (e.g., 70% of the caregivers reported to be worried). Hence, special screening for caregivers is required using instruments such as our questionnaire which was well accepted. When patients are on chemotherapy, neuro-oncologists should take into account that mostly caregivers organize the family life, take care of the patients and are in charge when patients suffer from side effects. In order to relieve caregivers, early integration of palliative care, outpatient services, social services and interdisciplinary treatment (during ongoing tumor-specific therapies) are required (44–47).

Caregivers' Requested Support

Although caregivers reported high burden, only a minority wished for support by any profession. This may be partially due to functional coping strategies [e.g., high expectation of self-efficiency (20)] as well as feelings such as shame and fear about being unable to manage. These hinder caregivers to requesting and/or accepting "external help." Some patients may also refuse outpatient care services as they do not like to accept the help of people they do not know and wish to stay at home in the final phase as well (36). This could lead to an enormous burden for caregivers when not supported by outpatient palliative care, which is the task of the doctor in charge (mostly physicians and neuro-oncologists) to initiate in a timely and sensitive way (45).

Strengths and Limitations of the Study

Of note, this is the first study that applied the two questionnaires in glioma patients and caregivers simultaneously in a multicenter study, with both questionnaires found to be useful for clinical and research purposes. However, the study does have several limitations.

The study required patients to be fit enough to complete several questionnaires. Therefore, patients in advanced stages of the disease and with cognitive deficits were not included, even though they might be the ones with the highest level of distress and need for supportive care. Shorter assessments are required for such patients. The study was a cross-sectional study and did not investigate the course of needs and distress during the disease trajectory. PPQ and CPQ were not validated instruments; therefore, the results should be interpreted with caution. Furthermore, the patient population was in a heterogeneous disease stage and current treatment. However, this can also represent a certain benefit as the results translate well to the general outpatient population seen at neuro-oncological centers. The content-driven selection of probable influencing clinical and demographic factors with regard to requested support for explorative correlation and logistic regression analyses reduced the statistical strength.

CONCLUSION

Our data show that glioma patients are highly burdened, and doctors play a crucial role in initiating these patients' psychosocial care and support. The PPQ allows us to evaluate the support requested and perceived by the patients, to detect supportive care needs and provide information at a glance. We observed clinical factors (e.g., when patients live alone in relation to support by doctors, lower GHS with regard to general requested support) and demographic factors (e.g., living alone or higher educational level with regard to support by any profession) that are possibly associated with unmet needs.

Of note, the patients' needs do not always reflect the caregivers' situations. Especially, caregivers of patients on chemotherapy are more burdened than patients themselves. Therefore, either using a questionnaire or questioning during consultation, regular assessment of relatives/caregivers accompanying the patient is required.

AUTHOR CONTRIBUTIONS

MR contributed to the conception and design of the study and wrote the first draft of the manuscript. DM, HL, EW, and MD assessed the study data and organized the data base. MR and DM developed the questionnaire for caregivers. CW, FR, and SS contributed to the conception and design of the study and edited the manuscript. JC contributed to the conception and design of the study, performed the statistical analyses, and edited the manuscript. All authors contributed to revision of the manuscript, read and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2018.00763/full#supplementary-material

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Palliative Care for Stroke Patients and Their Families: Barriers for Implementation

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Stroke is a leading cause of death, disability and is a symptom burden worldwide. It impacts patients and their families in various ways, including physical, emotional, social, and spiritual aspects. As stroke is potentially lethal and causes severe symptom burden, a palliative care (PC) approach is indicated in accordance with the definition of PC published by the WHO in 2002. Stroke patients can benefit from a structured approach to palliative care needs (PCN) and the amelioration of symptom burden. Stroke outcome is uncertain and outlook may change rapidly. Regarding these challenges, core competencies of PC include the critical appraisal of various treatment options, and openly and respectfully discussing therapeutic goals with patients, families, and caregivers. Nevertheless, PC in stroke has to date mainly been restricted to short care periods for dying patients after life-limiting complications. There is currently no integrated concept for PC in stroke care addressing the appropriate moment to initiate PC for stroke patients, and the question of how to screen for symptoms remains unanswered. Therefore, PC for stroke patients is often perceived as a stopgap in cases of unfavorable prognosis and very short survival times. In contrast, PC can provide much more for stroke patients and support a holistic approach, improve quality of life and ensure treatment according to the patient's wishes and values. In this short review we identify key aspects of PC in stroke care and current barriers to implementation. Additionally, we provide insights into our approach to PC in stroke care.

Keywords: stroke, palliative care, palliative care needs, family, next-of-kin, caregiver burden, early integration, palliative care indication

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INTRODUCTION

Stroke has all the characteristics of a disease consistent with the mandate of palliative care (PC) as defined by the WHO in 2002 (1): (a) PC addresses patients with life-threatening diseases, regardless of individual prognosis; stroke shows a 1-year mortality of 30–40%, it is the second leading cause of death worldwide. Its global burden of disease is continuously rising (2, 3); (b) PC addresses quality of life (QoL) as primary outcome parameter. QoL is severely impaired following stroke. There is evidence that stroke patients and families suffer from anxiety and decreased self-worth; they feel that they lack information, have difficulty sharing feelings and emotions. This was the result of an assessment six weeks after stroke. After six months and one year, respectively anxiety remained prominent for both patients and next-of-kin (4); (c) PC assesses and ameliorates symptom burden (SB) in various dimensions. SB is severe in stroke patients, comprising somatic, social, psychological, and spiritual aspects (5, 6).

In a neuro-critical care unit setting with mostly stroke patients, two thirds of patients and families reported PC needs (PCN) (7).

Integration of PC in treatment of stroke has been demanded repeatedly and data points to its beneficial effect (4, 8). PC can reduce SB after stroke (9) and shorten the length of hospital stay (10). PC correlated with longer time of survival after acute stroke (11) in parallel to its effects in cancer and dyspnoae patients (12–14).

Integration of PC in stroke care has been required by various professional societies (15, 16). In consequence, Creutzfeldt and Holloway demanded that stroke specialists must be able to deliver primary palliative care, comprising (1) patient- and family-centered care, (2) prognosis estimation, (3) development of appropriate goals of care, (4) awareness of end-of-life implications for common stroke decisions, (5) assessment and management of symptoms, (6) experience with palliative treatments at the end of life, (7) care coordination, including referral to PC or hospice, (8) fostering personal growth for patient and family, (9) ensuring the availability of bereavement resources if death is anticipated and (10) participation in quality improvement and research (15). Still, less than one in 15 stroke patients receive PC, whereas more than half of stroke patients die within 12 months or remain severely impaired with unknown SB and PCN (8, 17). Despite the need of a comprehensive approach, Ackroyd and Nair state that PC is still mainly integrated to co-manage the last days of life and to help with the determination of treatment goals (18). We identified crucial topics for PC in stroke and barriers to its timely and adequate implementation.

The Right Time for Palliative Care Involvement

Laymen and health care specialists alike may view the term palliative care (PC) as related to giving up curative or life-prolonging treatment and essentially on the patients themselves (19, 20). Accordingly, stroke specialists often consider PC applicable only in the phase of dying (4) or in the certain case of a poor prognosis (11), and may even equate PC with a decision against any treatment at all (21). In a qualitative study with 33 health care professionals specialized in stroke, only one participant understood that prognostic uncertainty may persist after the introduction of palliative care (4).

Indication for PC changes over the course of a disease (22). In cancer patients, PC is part of a comprehensive treatment concept, which is implemented in parallel with anticancer therapy as an integrated approach (23). If curative treatment has been unsuccessful over the course of the disease, patients will eventually no longer benefit from anticancer therapy and PC will be offered exclusively (22). Incurable cancer progresses gradually and impacts overall health. In stroke, the course of the disease is different: an acute onset—if not instantly lethal—is followed in most cases by a chronic rehabilitation period (**Figure 1**). In acute stroke, PC involvement is often initiated to support care of the dying (18), but in the chronic stage of stroke, PCN may remain high, increase, or reappear (9). For post stroke patients, treatment is focused on rehabilitation, secondary prevention, and care management, but PC needs (PCN) are neither regularly screened for nor routinely treated (9, 24). Especially patients with cognitive and communicative impairments found it difficult to get access to services and equipment and often felt abandoned. This impression was reinforced once health care professionals decided that they had reached a stable plateau and curative and rehabilitation offers were withdrawn (4). Conversely, many doctors will refrain from offering PC to address mental, social, and spiritual SB at this stage, as they fear such measures would be understood as a signal of abandonment (11).

Structured screening programs can help to overcome this barrier and Creutzfeldt has suggested the use of a "Palliative care needs checklist" to screen for PCN, as seen below:

- *Does this patient have pain or distressing symptoms?*
- *Does the patient and/or their family need social support or help with coping?*
- *Do we need to readdress goals of care or adjust treatment according to patient-centered goals?*
- *What needs to be done today?* (25).

Therapeutic Goals and Communication

Stroke may lead to severe loss of function. Whether loss of function causes "unacceptable" circumstances of living differs subjectively. In a mixed method investigation, some stroke patients with rather severe disabilities accepted their disability and some with less severe disabilities felt discontented up to the point to claim that death would have been preferable (4). Interviews with stroke patients, next-of-kin and formal caregivers revealed that thoughts of death were common, but were not addressed with formal caregivers, who hope for good recovery even in cases with death as a possible outcome. Staff admitted to be overoptimistic in order to motivate patients, especially when encouraging them to participate in physical therapy (4).

Communicating therapeutic goals and possible outcomes truthfully can help to avoid vast discrepancies between experiences and expectations (26). The further patients' and families' experiences deviate from communicated goals and expectancies, the lower their satisfaction and overall QoL will be (27–29). Uncertainty of prognosis is a main stressor for families of stroke patients (30). Informal caregivers often feel that advance planning for both recovery and deterioration would help to address this issue (4).

Defining therapeutic goals after acute stroke faces various challenges. Decisions must be based both on medical evidence and on patients' personal preferences (30). Stroke occurs as a sudden and unexpected life event often with severe impact on all aspects of life including cognition and communication.

Abbreviations: AD, Advance Directives; CSI, Carer Strain Index; DALYs, Disability Adjusted Life Years; EQ5D, Quality of Life Questionnaire; GBD, Global Burden of Disease; HRQOL, Health Related Quality of Life; PC, Palliative Care; PCN, Palliative Care Needs; POS, Palliative Outcome Scale; QoL, Quality of Life; SB, Symptom Burden; SPARC, Sheffield Profile for Assessment and Referral to Care.

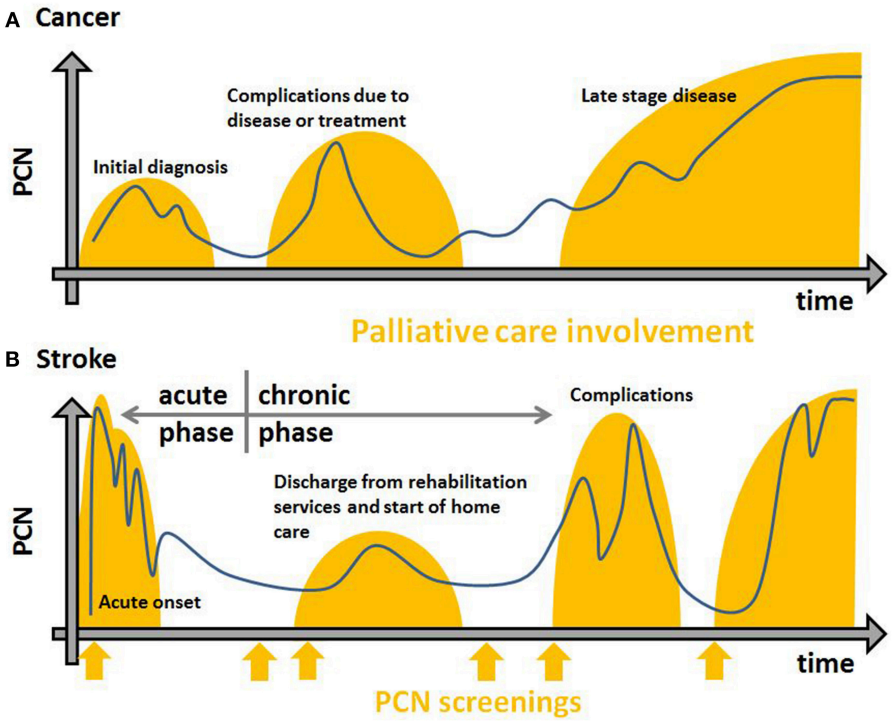

FIGURE 1 | Exemplary trajectories of chronic diseases **(A)**, e.g., cancer, heart failure, moto-neuron disease, Parkinson's disease and acute diseases **(B)**, e.g., stroke in terms of PCN (y-axis) over time (x-axis). The blue lines are possible courses of SB over time. Orange orbs show PC involvement. Initiation in a timely fashion to achieve best results is based on regular standardized screenings for PCN (orange arrows).

Living wills can be helpful here, but they are not always available. Therefore, determining the will of the patient, when communication and/or decision-making capacities have been lost, is particularly challenging and often relies on narratives by proxies. Limitations in experience, resources, and self-perceived qualification present additional barriers for health care professionals to successfully elicit the patient's point of view (11, 15, 31). Families describing their loved ones are likely to remember them as having been healthier and more autonomous than they actually were (recall bias) (30). In consequence, treatment outcomes may appear unfavorable although they are in accordance with the patient's life as it was. Also, perception of patients on favorable outcomes may change and we know QoL of patients to improve in the course of disabling diseases (32–34) and to be better than the QoL healthy participants expect when imagining to experience comparable circumstances (35). For example, most healthy persons said they would decide against hemicraniectomy facing the odds of disablement in case they had a severe stroke (36), whereas most people having been treated by hemicraniectomy after stroke would make the same choice again being given the same situation (37). Weighing values of future outcomes is directly influenced by perception of loss and gain based on the current status. Kahneman coined the term "losses loom larger than gains" (38), describing that a loss is felt more intensely than a possible gain, as is the case with imagining a new life situation when the focus lies on loss of function (speech, mobility, autonomy) in contrast to perceived values (gaining rehabilitation, social participation, and life) (30, 39). This psychological phenomenon has to be addressed by health care specialists when discussing treatment options in stroke.

PC involvement is often initiated to elicit goals of care together with the patient, the family and the stroke care team and also to support advance care planning. In a large retrospective series, PC involvement was found to triple advance directives (AD) while standard stroke care achieved an increase by 50% (7). In addition, AD exceeds mere planning for sudden deterioration, as it also serves to communicate therapeutic alternatives as well as to encourage and systematize quality care for severely ill patients (16). As therapeutic contacts will become less frequent after discharge from clinics and rehabilitation facilities, stroke patients can profit from AD through improvement of long term care.

Identification of Palliative Care Needs

Palliative care needs (PCN) are common and substantial after stroke (15, 24, 25, 40, 41). Both patients and families report lower health-related quality of life (HRQOL) after stroke (9, 15). Certain populations are especially at risk for inadequate amelioration of SB, including very young and old patients as well as patients with impaired communication skills (42).

Data points to the fact that short term PCN in the last days of life are different from PCN among stroke survivors, with only few studies shedding light on long-term SB.

Several studies have investigated PCN in stroke patients with a focus on the last days of life. Here, most common somatic symptoms are dyspnoea (30%), pain (25–30%, mostly central post-stroke pain, hemiplegic shoulder pain, and spasticity induced pain), xerostomia (20%), constipation (20%), sadness (35–50%), anxiety (25%), and fatigue (50%) (6, 9, 43, 44). Although burdensome symptoms are sporadically recognized by stroke specialists, there is a lack of awareness and attention. Symptoms are attributed to stroke as part of the natural course rather than being viewed as treatable distress (43, 45, 46).

A structured approach is needed to identify PCN after stroke, but no appropriate tool has been developed so far (6). The Sheffield Profile for Assessment and Referral to Care (SPARC) has been proposed as a screening tool to identify patients who may profit from PC (40) and was successful in regards to acceptance and feasibility in a roll-out trial with 135 patients with various diseases (47). Whereas, SPARC covers PCN extensively, it contains 45 items and is challenging for patients with cognitive impairment. It has not been validated in patients with communication impairment, although elderly patients and those with impaired communication skills are in increased danger of untreated SB after stroke (42). The Palliative outcome scale (POS) is a validated and multidimensional assessment tool. POS comprises 11 items and addresses SB in somatic, psychological, social, and spiritual dimensions. Additionally, POS allows for multicenter comparison and thereby supports research endeavors. POS is widely accepted and has been adapted for multiple sclerosis and Parkinson's disease, but not for stroke.

Place of Death

Stroke causes severe restrictions in terms of autonomy and self-care. The level of professional care after stroke is high and many people remain in hospitals and rehabilitation clinics for a considerable length of time (48). When discharged, many are transferred to nursing homes, even though most persons wish their homes to be the place of care and their place of death (49). Within 1 year after stroke, about two thirds of patients die in a hospital and only one in ten dies at home. Death in hospices was not specifically recorded (50). Only 10–12% of all deaths were found to be unexpected. For only 6% of patients who died in a hospital, their place of death corresponded to their explicit will. In contrast, 39% of patients who died in nursing homes and 78% of patients who died at home had expressed wishes to die there (50).

Caregiver Burden

A mixed-methods study showed that stroke is a major life crisis for patients as well as for next-of-kin (4). Stroke has a severe and sudden effect on physical, behavioral, and psychological functions, impacting all social interactions (51). Family members were unsure whether they were "doing the right thing" and were confused by health care professionals who expressed controversial narratives of good recovery vs. accounts of disability and death (4). Uncertainty of prognosis and possibility of a second stroke contributed to the strain especially strongly (30). Next-of-kin reported severe burdens on social structures (21, 52) and anxiety, partially due to lack of information, and emotional distress remained severe up to 1 year after the stroke (4).

Additionally, as most stroke patients die in a hospital (50), next-of-kin may be restricted in spending time with the patient through hospital regulations and logistic challenges, which increases caregiver burden. For patients who die in palliative and hospice care, next-of-kin report less posttraumatic stress disorder and facilitated grieving (53) as well as higher satisfaction with end-of-life care (54).

For next-of-kin in a mixed population, including mainly cancer patients, the burden is effectively alleviated by involvement of PC services (55). Especially in a multidimensional approach, PC improves quality of care significantly; main topics of significant improvement are: religious/spiritual beliefs, adequate support in dealing with one's own feelings, feelings after the possibility of death has been addressed, referral to psychosocial support for family, assessment of emotional/spiritual needs, support of the family's self-efficacy, and mild to strong confidence within families to know what to expect as well as what to do when the patient would die. Data shows that burden and need of support of next-of-kin increases if patients' cognitive functions are impaired (56–58). Uncertainty of outcome leads to a rise in burden for next-of-kin and patients (59). Both factors of increased burden for next-of-kin are highly prevalent in stroke patients. Although informal care giver burden is of great significance for both the individual (60) and society (61, 62), screening tools and instruments to assess informal caregiver burden in stroke are needed (63) as well as systematic research into suitable interventions (64).

OWN EXPERIENCES AND CONCLUSION

The appropriate point-of-time to integrate PC is a main challenge in implementing PC, especially for stroke patients and their families. PC has its origins in end-of-life care for cancer patients, which was reflected in the WHO technical report series of 1990 (65). Much has changed in favor of patients. Today, PC is understood as an integrated service which works in conjunction with other medical specialties in order to improve QoL and ameliorate SB regardless of prognosis in case of any life-threatening disease (1, 23, 66). By systematic and early integration of PC several beneficial effects have been found, e.g., reduction of SB and depression, increase of QoL, satisfaction of next-of-kin, and likelihood of survival in cancer patients (12–14). PC has been of increasing importance in neurology (20, 67), but it integrates more easily in some subspecialties, e.g., moto-neuron diseases, Parkinson's disease, and multiple sclerosis than in others like stroke (30) as the clinical course of stroke is fundamentally different from that of the aforementioned (**Figure 1**).

The main barrier of integration of PC in stroke is the obsolete idea of PC as being invariably joined with both definite and poor prognoses and automatic withdrawal of stroke care. Even health professionals still confuse these aspects (68). This is paralleled in the case of other vascular diseases like heart failure. In congestive heart failure, the foremost barrier for integration of PC the incorrect perception of PC being prognosis-dependent and requiring suspension of life-prolonging treatment (19). A suggestion on how to move from "prognostic paralysis to active total care" is to focus on patients who "reasonably might die" rather than patients who "will die in the next six months" (69, 70), as is also reflected in the surprise question "Would I be surprised if my patient were to die in the next 12 months?" (71). If the answer to the surprise question is "no," a detailed PCN screening is necessary. Whether the time span of 12 months that has been validated in cancer patients can be paralleled to the course of disease in neurological non-cancer patients has not yet been researched.

We endorse Creutzfeldt's proposition of the PCN checklist (25). However, as it has neither been standardized nor validated, it may still be difficult for a stroke specialist to apply the PCN checklist in practice. A standardized and structured approach will be necessary to screen for and identify PCN.

Integrated pathways of care have proven to increase quality of care for stroke patients and for patients in hospice and palliative care, respectively (72–74). Still, an integrated PC approach has not yet been implemented in stroke care. Beyond initial and acute evaluation, regular assessments are crucial to ensure the identification of stroke patients who develop PCN later in the course of their disease due to complications, deterioration, and increasing distress in informal caregivers (21). Existing PC screening instruments, which are mostly derived from research on cancer patients' PCN, do not reflect specific SB of patients with chronic illnesses. For some neurological entities, adaptations of such screening tools have been developed, e.g., POS for Parkinson's disease and multiple sclerosis.

We have implemented a structured approach for stroke patients, based on a questionnaire which is sent to patients or next-of-kin within 6 months after discharge. The questionnaire constitutes a self-assessment tool which screens for PCN in four domains (physical, mental, social, spiritual) and has been validated for PC patients (75) and neurological outcome measures such as modified Rankin Scale and Barthel index. In addition, we address spasticity-associated pain and discomfort as specific and treatable symptoms. We use 20 pictures showing spastic postures of extremities and 16 questions aiming at symptoms related to post-stroke spasticity. The questionnaire is designed for self-assessment or assessment by proxy and the evaluation of its content is based on cumulative scores (76, 77).

Our approach aims at the first months after discharge with a focus on post-stroke spasticity. To ensure a holistic approach to PCN after stroke, future research is urgently needed to identify and quantify stroke-specific parameters and develop appropriate intervals for PCN screening in the late phase of stroke.

In order to deliver PC to stroke patients and their families, more needs to be known of stroke-specific PCN. Stroke-specific PCN may be treated differently from similar symptoms in cancer care. Post-stroke pain, for example, is a common symptom, but management stemming from cancer pain might not be the most efficient way to ameliorate this pain. Opioids may reduce alertness and worsen constipation (78), whereas focal interventions like injections with botulinum toxin may help more in case of spasticity with significantly less adverse side effects (79).

PC addresses both the patient and the family. Next-of-kin are severely burdened by a rapidly changing situation in life, changes of the patient's functional and psychological status, and responsibilities in home care. Cancer-focused research showed that targeted interventions to increase QoL for the patient do not automatically lead to an increase of QoL of their family (80, 81). Therefore, it is necessary to develop this tailored support for caregivers (82).

Defining appropriate therapeutic goals and discussing alternatives are necessary steps in all phases of stroke. Next-of-kin are fraught with uncertainty by contradictory narratives simultaneously aiming at a good outcome and describing catastrophic development in dual presentation (4, 83). Uncertainty is a main factor of distress (30), but may be ameliorated decisively by addressing it openly and engaging in a transparent and meaningful dialogue about possible outcomes and therapeutic goals (4, 27, 38). To openly discuss the uncertainty of health outcomes with patients, families, and formal caregivers is a key competence in PC (70). AD may yield an appropriate platform to initiate this discourse with the added benefit to ensure patients' wishes in further course of the disease. To achieve this goal, further education of health care specialists on communication skills is needed. An open discussion on therapeutic goals may foster a trusting relation with patients and their families.

In the future, more research and more openness on both sides—palliative care specialists and neurologists—is needed to better understand PCN of stroke patients and their families and to assess how to ameliorate stroke-specific SB. Early detection and tailored interventions may prevent exacerbation of symptoms, reduce the involvement of emergency services and thereby health costs, prolong patients' lives, reduce suffering, increase QoL for patients and families, and allow patients to remain and possibly to die at home in care of their loved ones.

AUTHOR CONTRIBUTIONS

TS: concept, first draft, and final version. RK: essential input and formative evaluation. CO: concept, essential input, formative evaluation, and final version.

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The "Surprise Question" in Neurorehabilitation—Prognosis Estimation by Neurologist and Palliative Care Physician; a Longitudinal, Prospective, Observational Study

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Background: The 12-months "surprise" question (12-SQ) for estimating prognosis and the need for integrating palliative care (PC) services has not yet been investigated for neurological patients.

Objective: Test the value of the 12-SQ on a sample of neurorehabilitation patients.

Methods: All patients newly registered in the Department of Neurorehabilitation, Dr. Becker Rhein-Sieg-Clinic (8/2016-03/2017) were asked to participate. The treating neurorehabilitation physicians (NP) and an external consulting PC physician (PCP) independently estimated patients' prognosis using the 12-SQ; while symptom burden was independently assessed using the standardized palliative outcome measurement HOPE-SP-CL, a set of additional neurological issues, and ECOG. Follow-up with consenting patients 12 months later was via telephone. Descriptive and inferential statistics were utilized in data analysis.

Results: Of 634 patients, 279 (44%) patients (male: 57.7%, female: 42.3%; mean age: 63 ± 14) (or, alternatively, their legal representative) consented and were assessed at baseline. Per patient NP and PCP both answered the 12-SQ with "Yes" (164), with "No" (42), or had different opinions (73). The "No" group displayed the highest symptom burden on all three measures for both disciplines. Overall, PCP scored higher (i.e., worse) than NP on all measures used. Follow-up was possible for 236 (drop-out: 15.4%) patients (deceased: 34 (14.4%), alive: 202 (85.6%)). Baseline scores on all measures were higher for deceased patients compared to those still living. Prognostic characteristics were: *sensitivity:* NP 50%, PCP 67.6%; *specificity:* NP 86.1%, PCP 70.3%, $p < 0.001$; *positive predictive value:* NP 37.8%, PCP 27.7%; *negative predictive value:* NP 91.1%, PCP 92.8%; *area under the curve:* NP 0.68, PCP 0.69; *success rate:* NP 80.9%, PCP 69.9%,

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$p = 0.002$. Regression analysis indicated that age, dysphagia and overburdening of family (NP answering the 12-SQ), dysphagia and rehabilitation phase (PCP answering the 12-SQ) were associated with increased likelihood of dying within 12 months. Without the 12-SQ as relevant predictor, age, dysphagia and ECOG were significant predictors (NP and PCP).

Conclusion: Combining the 12-SQ with a measurement assessing PC and neurological issues could potentially improve the 12-SQ's predictive performance of 12-month survival and help to identify when to initiate the PC approach. Clinical experiences influence assessment and prognosis estimation.

Keywords: surprise question, neurorehabilitation, palliative care, observational study, prognosis, outcome measurement

INTRODUCTION

For predicting the point at which to introduce palliative care for incurable cancer patients the German national S3 palliative guideline[1] recommends using the 12-months "surprise" question (12-SQ) (Would you be surprised if your patient would die within the next 12 months?). A "No" response (i.e., a poor prognosis) indicates that the assessor considers it a possibility that the patient could die within the next 12 months and, thus, palliative care should be initiated promptly.

The various disease entities to which the SQ has been applied thus far include cancer (1–5), chronic obstructive pulmonary disease (COPD) (6), nephrological diseases (7–13), as well as pediatric palliative care (14), intensive care (15), emergency care (16, 17), and in elderly care (17–19). The SQ has yet to be applied to neurological care where patients are characterized by different disease trajectories compared to other disease entities, especially cancer patients. Prognosis estimation is therefore challenging (20) and a suitable prognostic instrument would aid in estimating lifespan and indicating when best to initiate the palliative care approach for these patients.

A recent systematic review and meta-analysis revealed that the SQ it is not an ideal diagnostic tool for predicting one-year mortality, especially among non-cancer patients (21). Rather, the use of additional parameters seems warranted (22, 23).

Thus, in addition to the 12-SQ, supplementary assessment tools focusing on patients' symptom burden were employed for this study. Typical palliative care assessment tools, including the German Hospice and Palliative Care Evaluation initiative (HOPE= HOspiz- und PalliativErhebung) (24) and the internationally used palliative outcome scale (POS) (25, 26) were developed for patients suffering from later stage cancer diseases. This is not surprising, as presently, palliative and hospice care structures primarily care for advanced cancer patients[2] (27, 28), although the portion of cancer patients has slightly decreased (95% in 2005 vs. 76% in 2017 (see[2]) with respect to other disease entities such as neurological conditions, COPD, nephrological diseases or chronic heart failure (see[2]). For example, patients cared for in German palliative and hospice care structures suffering from nervous system diseases represented 4.8% in 2017 compared to only 0.8% in 2005 (see[2]). Despite this slight increase in the number of neurological patients in German palliative and hospice care, the current, rather small, percentage is still astonishing considering the great number and variety of neurological diseases, among them long-term neurological conditions (LTNC) which present with a high symptom burden. Given these cases are mostly incurable, symptom relief, and enhanced quality of life are the leading therapeutic goals in treating these patients, according to the World Health Organization (WHO)[3]. Using a combined neurorehabilitation and palliative care approach, neuropalliative rehabilitation for LTNC is on the way to becoming integrated into care in the UK (29–31), in contrast to Germany. Symptoms and complaints among neurological and cancer patients are in part fairly similar but may differ in their manifestation and certain issues clearly transcend those of cancer patients, presenting distinct challenges for such patients (32–40). Therefore, the neurorehabilitation study population was characterized utilizing a combination of a standard palliative care assessment tool (HOPE including ECOG) and an additional list of items representative for neurological disease entities as revealed from longstanding clinical experience, literature (32–40) and a previous study on glioblastoma (41). In addition to using the 12-SQ, this detailed characterization can help to identify further prognostic criteria of neurological patients, which may lead to improved prognostic accuracy of the 12-SQ, an approach in accordance with other studies commending additional tools other than the 12-SQ to predict mortality (22, 23).

Abbreviations: 12-SQ, twelve-months "surprise" question; PC, palliative care; NP, neurorehabilitation physicians; PCP, palliative care physician; HOPE= HOspiz- und PalliativErhebung, German Hospice and Palliative Care Evaluation initiative; HOPE-SP-CL, HOPE symptom and problem checklist; ECOG, Eastern Cooperative Oncology Group; POS, palliative outcome scale; COPD, chronic obstructive pulmonary disease; LTNC, long-term neurological conditions; WHO, World Health Organization; ROC, receiver operating characteristics; PPV, positive predictive value; NPV, negative predictive value; AUC, area under the curve; FDR, false discovery rate; SPSS, Statistical Package for the Social Sciences; SD, standard deviation; ADLs, activity of daily living; OR, odds ratio.

[1]http://www.awmf.org/uploads/tx_szleitlinien/128-001OLl_S3_Palliativmedizin_2015-07.pdf (accessed 29.05.2018)

[2]https://www.hope-clara.de/download_1/ (accessed 29.05.2018)

[3]http://www.who.int/cancer/palliative/definition/en/ (accessed 29.05.2018)

The objective of this study was to investigate prognostic criteria for neurological patients. For the first time, the suitability of the 12-SQ for neurological patients was prospectively investigated, combining it with an assessment merging palliative care and neurological issues.

Patients were recruited from among those newly registered at a neurorehabilitation clinic providing care to a broad range of neurological disease entities. An important secondary goal was to examine whether the professional background—being a neurorehabilitation physician (NP) or being a palliative care physician (PCP) with no neurology background—played a role in assessment and prognosis estimation. This is a critical issue as a consultant palliative care service is not typically integrated in neurorehabilitation clinics and NP and their teams must make decisions on their own. On the other hand, the PCP might also care for neurological patients but only a small percentage of them are trained in neurology. Thus a complementary approach suggests itself, one that includes the professional assessment of both, NP and PCP.

In Summary, Aims of the Study Were

Primary Objective

Is the 12-SQ suitable for prognosis estimation with neurological patients?

Secondary Objectives

Does prognosis estimation depend on the physicians' background (NP vs. PCP)?

How is the study population characterized and assessed by both, NP and PCP?

How are the patients who died within this 12 month period actually characterized? Can factors be deduced which would help estimate the prognosis of these patients alone or in combination with the 12-SQ?

MATERIALS AND METHODS

Study Design

This is a longitudinal, prospective, observational study. The recruitment period encompassed August 10, 2016–March 10, 2017. The follow-up period extended until March 10, 2018; 12 months later.

Study Participants

All newly admitted patients (permitted age range 18–100 years, all genders) then in treatment at the Dr. Becker Rhein-Sieg-Klinik, Department of Neurorehabilitation (phase B, C, D; a German classification system characterizing type and intensity of neurological rehabilitation) during the recruitment period were enrolled in the study after providing their informed written consent (or alternatively via their legal representative). The local ethics committees of the North Rhine Medical Chamber and of the University Hospital of Cologne approved the study (#16–118).

Data Collection

For quality assurance and to enable a patient-oriented care post-hospital discharge at the Dr. Becker Rhein-Sieg-Klinik, department for neurorehabilitation, an estimation of prognosis using the 12-SQ and an assessment of symptom burden was implemented into the clinical routine.

"Surprise"-Question

At time of admission, treating NP - neurologists with additional neurorehabilitation expertise, but no specialist training in palliative care—as well as an external consulting PCP—with no neurological training—responded independently to the 12-SQ. The PCP visited the Department of Neurorehabilitation once a week.

Assessment of Symptom Burden

Concurrently to answering the 12-SQ, both NP and PCP also independently assessed the symptom burden of the neurological patients utilizing the core documentation of the German Hospice and Palliative Care Evaluation initiative (HOPE), the HOPE symptom and problem checklist (HOPE-SP-CL) (24) including the Eastern Cooperative Oncology Group (ECOG) Performance Status scale. The HOPE-SP-CL consists of 17 items and assesses symptoms and problems representative for cancer patients in palliative care (24). Single items are scaled using a 4-point grading scale (0 = none, 1 = mild, 2 = moderate, 3 = severe) (possible total score: 0–51) (24). The ECOG Performance Status scale is a 5-point grading scale ranging from 0 (normal activity) to 4 (care-dependent, totally confined to bed).

A list of symptoms which might be of special importance for neurological patients who have or might develop palliative care needs was added to account for the particularities of the neurological patients' symptom burden (32–40). This "neuro supplement" was derived from clinical experience and existing literature (32–40). Augmenting this was a preliminary study (41) on assessing palliative care issues utilizing standardized outcome measurements (HOPE-SP-CL (24, 42), the POS (palliative outcome scale) (25, 26) as well as an open interview part which included symptoms not covered by these assessment tools. The neuro supplement scale derived from this comprises 13 items. Following the HOPE-SP-CL scale, single items of the neuro supplement are scaled using a 4-point grading Likert scale (0 = none, 1 = mild, 2 = moderate, 3 = severe) (possible total score: 0–39). All 3 scales (HOPE-SP-CL, ECOG, neuro supplement) combined in this study result in a possible total score ranging from 0 to 94.

Follow-Up

Twelve months after answering the 12-SQ, patients (or alternatively their legal representative) were contacted via telephone by NP (ME) or PCP (AK) to find out whether patients were still alive.

Statistical Analysis

Distribution of age, gender, rehabilitation phase, main, and secondary diagnoses, results from the clinical assessment (12-SQ-answer, HOPE-SP-CL, ECOG, neuro supplement) were

analyzed descriptively to characterize the study population at baseline.

The classification of patients was done in two separate steps. First, we used each physician's independent response to the 12-SQ, assigning patients to either the "Yes" group or the "No" group. Next, we combined the physicians' responses and allocated patients into three individual groups. Those who were given a good prognosis by both physicians were classified into the 12-SQ "Yes" group, those given a poor prognosis by both physicians were categorized as the 12-SQ "No" group, and those with contrary ratings were classified as the 12-SQ "Discordant"-group. This classification into three groups allowed us to characterize the study population (statistical details below) when the consensus of both physicians was used (secondary objective).

Prior to all analyses, the Kolmogorov-Smirnov Test was applied to assess normality for all relevant variables.

To investigate whether the 12-SQ can be used as a prognostic indicator for neurological patients (primary objective), the predictive power of the 12-SQ was determined using receiver operating characteristics (ROC) curves to assess sensitivity (proportion of patients who died within 12 months and were given a poor prognosis), specificity (proportion of patients who survived over 12 months and were given a good prognosis), positive predictive value (PPV, proportion of poor prognoses correctly predicting death within 12 months), negative predictive value (NPV, proportion of good prognoses correctly predicting survival over 12 months), and the area under the curve (AUC, function of both sensitivity and specificity measuring the predictive accuracy). Similarly, we examined the success rates of both physicians; defined as percentage of correct predictions accounting for all possible outcomes. The differences in prognostic accuracy proportions between the NP and PCP were assessed with the McNemar χ^2 test as appropriate (secondary objective) (43).

Group differences of demographic and clinical data were tested with the Mann-Whitney-U test and the Kruskall-Wallis test (for two and three groups, respectively) for continuous measures and a χ^2 test for dichotomous measures. *Post-hoc* tests were corrected for multiple comparisons using the false discovery rate (FDR) at $p < 0.05$ (44).

To determine independent predictors of 12-month mortality (secondary objective), binary logistic regression analyses were performed for both NP and PCP. In addition to the 12-SQ, age, gender, main and secondary diagnoses, frequency of secondary diagnoses, rehabilitation phase, HOPE-SP-CL single items, neuro supplement single items and the ECOG score were included in the model. A univariate regression was constructed first. Resulting predictors with a p-value of < 0.1 were then included in the multivariable regression. To determine which variables best predicted 12-month mortality in the presence and absence of the 12-SQ, we selected statistically significant predictors of the multivariable regression (at $p < 0.05$) for the final model and compared their prognostic accuracy indices to those of the 12-SQ as a stand-alone predictor.

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) software (v. 25, Inc, Chicago, IL).

RESULTS

Study Participation and Follow-Up

From August 10, 2016 through March 10, 2017, 634 patients were admitted to the Dr. Becker-Rhein-Sieg-Clinic Nümbrecht, Department of neurorehabilitation (**Figure 1**). Of this total, 137 (21.6% of 634) could not be included into the current study due to the restricted personnel resources and tightly packed clinical routine processes. Another 218 (34.4% of 634) patients had incomplete data, i.e., either the patients (or alternatively their legal representative) did not give their informed written consent or the physicians' assessment was not attainable because of the demanding clinical routines of the physicians or patients. The remaining 279 patients were independently assessed by both NP and PCP who concordantly estimated 164 (58.8%) patients with a good prognosis (both 12-SQ "Yes") and 42 (15.1%) patients with a poor prognosis (both 12-SQ "No"). 73 (26.2%) patients were estimated discordantly (one, either NP or PCP, answered 12-SQ "Yes", while the other responded "No"). A total of 43 out of 279 (equaling a drop-out rate of 15.4%) patients (or alternatively their legal representative) could not be followed-up due to unattainability via the phone (**Figure 1**). Complete data sets were obtained from 236 patients (37.2% of 634).

Characteristics of Study Participants at Baseline

Demographic information of the included 279 patients can be found in **Table 1** (male: 57.7%, female: 42.3%, male/female ratio: 1.4; mean age: 63 $\pm$ 14). Main diagnoses were grouped into 15 categories, secondary diagnoses were divided into seven groups (**Table 1**). Distribution of secondary diagnoses were as follows: 19.6% had no secondary diagnosis, 33.8% had secondary diagnoses in one category, 25.5% in two categories, 14.7% in three categories, 5.8% in four categories, and 0.7% in five categories, respectively (**Table 1**).

Characteristics of study participants at baseline as assessed by NP and PCP, respectively, utilizing HOPE-SP-CL, neuro supplement, and ECOG are presented in **Table 2**. Patients were given a higher score on all three measures when assessed by the PCP (all p-values < 0.025), except for feeling depressed and anxiety in the "No" group.

Significant group differences (12-SQ "Yes" by both NP *and* PCP; 12-SQ "No" by both NP *and* PCP; 12-SQ "Yes"/"No" NP and PCP discordant) were found for all but the following characteristics: pain, feeling depressed, anxiety, tension, symptoms of intracranial pressure, epileptic seizures, spasticity (all p-values < 0.031). As expected, *post-hoc* analyses showed that patients in the "No" group were evaluated with a higher symptom burden than patients in both the "Yes" and the "Discordant" group, and patients in the "Discordant" group were evaluated as worse than patients in the "Yes" group.

Characteristics of Deceased and Surviving Patients as Assessed at Baseline

Of the 115 patients assessed "No" on the 12-SQ by at least one discipline (**Figure 1**) 26 had died within the year. At the 12 months follow-up a total of 34 patients had died (also

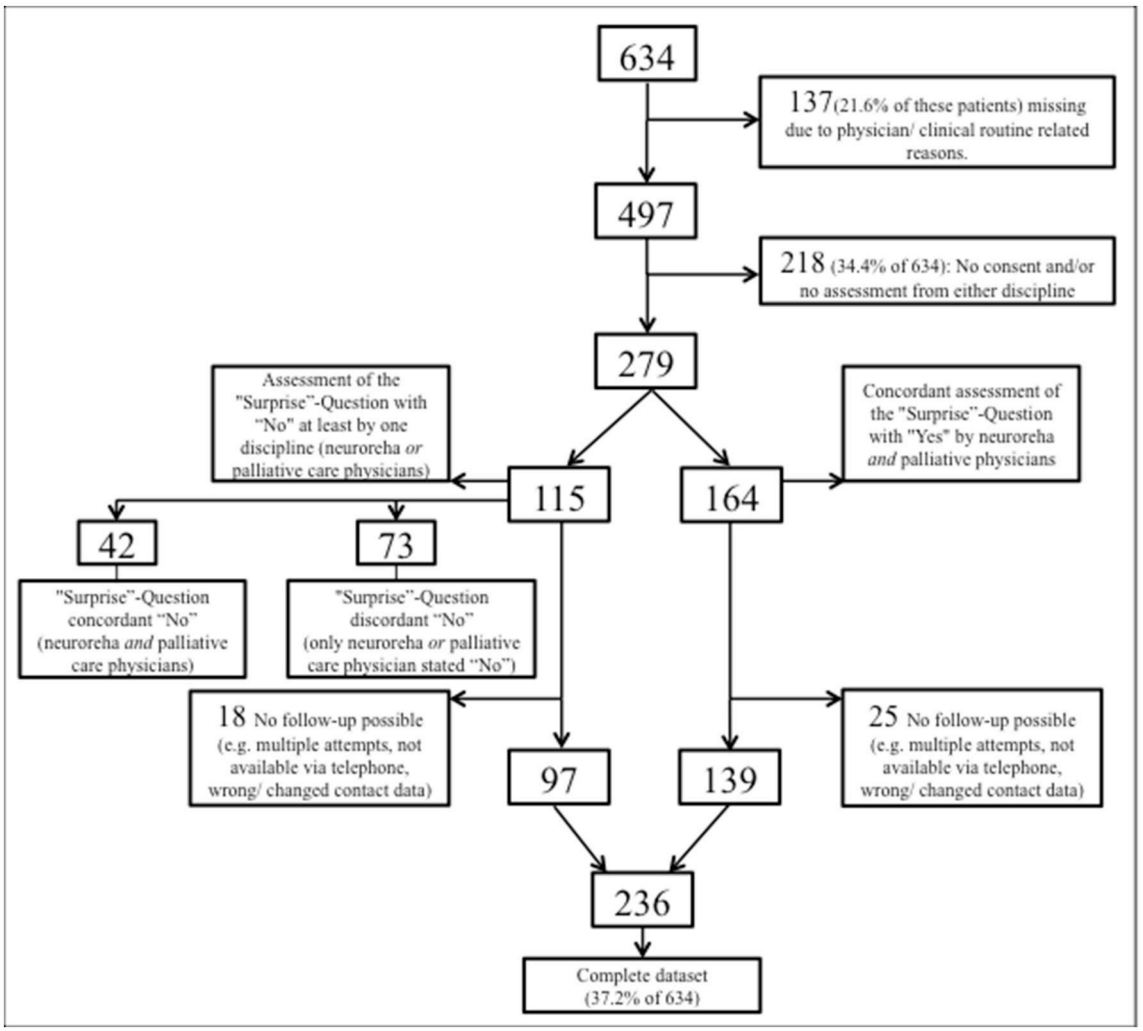

FIGURE 1 | Flow-chart of study participation and follow-up.

encompassing eight patients estimated as "Yes" at baseline on the 12-SQ).

Table 3 summarizes the characteristics and differences of patients still alive at the time of 12-month follow-up ($N = 202$, 85.6%) and those deceased after 12 months ($N = 34$, 14.4%). The deceased were significantly older, more often in Rehabilitation phase B, less often in Rehabilitation phase D, and suffered significantly more often from malignancies (except for primary brain tumors) (all p-values < 0.001). With regards to our clinical outcome measures, deceased patients were evaluated with a higher symptom burden compared to patients still alive after 12 months (all p-values < 0.030) (**Table 3**).

Prognosis Estimation

Comparison of prognosis estimation via 12-SQ as diagnostic tool revealed an increased number of good prognoses (12-SQ "Yes") compared to poor prognoses (12-SQ "No") for both PCP ($p < 0.001$) and NP ($p < 0.001$). The PCP estimated more patients with a poor prognosis (12-SQ "No") ($N = 95$) than did the NP ($N = 62$) ($p = 0.008$). Also, he offered a worse clinical assessment of patients compared to the NP. This difference is statistically significant for the total sample, the concordant "Yes" group and the discordant "Yes (NP)/No (PCP)" group (each $p < 0.001$) (**Table 4**).

Prognostic accuracy indices for both disciplines are summarized in **Table 5**, the corresponding frequency distribution can be found in **Tables 6–7**. Sensitivity of the 12-SQ as stand-alone predictor was poor. While we observed a higher sensitivity for responses of the PCP relative to treating NP, this difference did not achieve statistical significance. In contrast, specificity of the 12-SQ was significantly higher when estimated by NP compared to PCP [$\chi^2_{(1,N=194)} = 14.58, p < 0.001$]. There were no statistically significant differences between physicians for PPV, NPV, or AUC.

The combined "yes" and "no" success rate was high, with a significant difference between NP and PCP [$\chi^2_{(1,N=236)} = 9.47$,

TABLE 1 | Characteristics of study participants at baseline.

Study participants	***N* = 279**	
Age mean (SD)	63 (14)	
Gender Male	161 (57.7%)	
Female	118 (42.3%)	
Main diagnoses	Ischemic stroke	131 (47.0%)
	Neurodegenerative disorders	29 (10.4%)
	Primary intracerebral hemorrhage	24 (8.6%)
	Infection of CNS	21 (7.5%)
	Multiple Sclerosis	14 (5.0%)
	Brain injury	13 (4.7%)
	Critical illness polyneuropathy	11 (3.9%)
	Spinal canal stenosis	10 (3.6%)
	Primary brain tumors	9 (3.2%)
	Subarachnoid hemorrhage	4 (1.4%)
	Slipped disc	4 (1.4%)
	Subdural hematoma	3 (1.1 %)
	Epilepsy	2 (0.7%)
	Dementia Syndrome	2 (0.7%)
	Hypoxic brain injury	2 (0.7%)
Secondary diagnoses (categories)	Cardiovascular diseases	184 (65.9%)
	Bronchopulmonary diseases	57 (20.4 %)
	Other internal diseases	92 (33.0) %
	Neurological and psychiatric diseases	37 (13.3 %)
	Infectious diseases	19 (6.8 %)
	Diseases of the musculoskeletal system	19 (6.8 %)
	Malignancies (except for primary brain tumors)	17 (6.1 %)
Rehabilitation phase	Phase B	25 (9.0%)
	Phase C	107 (38.4%)
	Phase D	147 (52.7%)

SD, standard deviation.

Comments on main diagnoses:

Primary brain tumors encompassed: Glioblastoma, Astrocytoma, Meningioma

Neurodegenerative disorders encompassed: Parkinson's disease, atypical Parkinsonian's syndromes, multiple system atrophy, amyotrophic lateral sclerosis.

Comments on secondary diagnoses:

Cardiovascular diseases encompassed: Coronary heart disease, heart failure, arterial hypertension, peripheral arterial occlusive disease, cardiac arrhythmia, heart valve diseases

Bronchopulmonary diseases encompassed: pneumonia, chronic obstructive pulmonary disease, asthma

Other internal diseases encompassed: Obesity, nutritional deficiencies, liver failure, kidney failure, diabetes mellitus and other metabolic disorders

Neurological and psychiatric diseases: Depression, psychoses, anxiety disorders, intelligence defects, e.g. post-early childhood brain damage, dementia syndrome, organic brain syndrome, multiple sclerosis, typical and atypical Parkinsonian's syndromes, polyneuropathies of various origins, epilepsy, dizziness of unknown origin, restless legs

Infectious diseases encompassed: Pneumonia, urinary tract infections (including renal infections), hepatitis, thyroiditis, Lyme disease, abscesses, herpes zoster, human immunodeficiency virus

Diseases of the musculoskeletal system encompassed: fractures, osteoporosis, rheumatism, degenerative changes of the musculoskeletal system.

Rehabilitation phases B, C, D (German classification system characterizing type and intensity of neurological rehabilitation):

Phase B (early rehabilitation): There are still considerable disorders of consciousness; the ability to cooperate is severely restricted. Intensive medical treatment may be required.

Phase C (subsequent rehabilitation): High nursing need. The aim is intensive mobilization (sit up, straighten up, positioning, joint mobilization).

Phase D (medical rehabilitation): Early rehabilitation phase is completed and possibility of actively participating in rehabilitation measurements. The aim is free walking, performing care independently and regaining everyday competence).

$p = 0.002$] (**Table 5**). The success rate for the "Yes" group was also significantly higher for NP relative to PCP [$\chi^2_{(1,N=236)} = 17.80$, $p < 0.001$]. Conversely, the success rate for giving a poor prognosis did not differ between physicians.

Regression analysis showed that age ($p = 0.015$), dysphagia ($p = 0.006$), and overburdening of the family ($p = 0.036$) were associated with an increased likelihood of dying at 12 months when the NP responded to the 12-SQ (**Figure 2**, **Table 8**). Overall classification was 80.3% accurate.

When patients were assessed by the PCP, the overall predictive accuracy of the model was 79.9%. Response to the 12-SQ ($p = 0.014$), dysphagia ($p = 0.041$), and rehabilitation phase ($p = 0.014$) were statistically associated with 12-month mortality. Patients in the "No" group were 3 times more likely to die than patients in the "Yes" group. Rehabilitation phase also predicted the likelihood of dying at 12 months with patients in phase B registering as 7.3 times more likely to die than patients in phase D ($p = 0.005$), and patients in phase C being 2.8 times more likely to die compared to patients in phase D ($p = 0.041$) (**Figure 3**, **Table 9**).

Without the 12-SQ as relevant predictor, age (NP: $p = 0.038$; PCP: $p = 0.026$) and dysphagia (NP: $p = 0.012$, PCP: $p = 0.029$) remained significant predictors, irrespective of the physicians' medical background. In addition, for both the NP and the PCP, an increased ECOG score was significantly related to an increased risk of dying (NP: $p = 0.003$; PCP: $p = 0.005$) (**Figures 2–3**, **Tables 8**, **9**). When assessed by the PCP, the model showed 86.9% overall classification accuracy, which increased to 89% when assessed by the NP.

DISCUSSION

According to literature search this is the first study investigating prognosis estimation using 12-SQ and assessment of palliative care symptoms supplemented by neurological items, as rated by NP and PCP, respectively, in a sample of neurorehabilitation patients.

Prognosis estimation in this patient group proved challenging when utilizing 12-SQ as a single tool, which was reflected in poor prognostic accuracy indices, found also for other non-cancer diseases (21, 23). However, in our study, answering 12-SQ "No" pointed to physicians' expectation of poor prognosis as both treating NP as well as the PCP evaluated the 12-SQ "No" group consistently with the highest symptom burden. Overall, treating NP assessed patients better (meaning lower scores on the utilized measures) than the PCP. A potential explanation might be the clinical background of assessors with PCP primarily caring for the potential of general deterioration and the end of life and the NP being more concerned with recovery and restitution. Seemingly combined expertise might be needed for a balanced and accurate estimation.

In our study, accurate prediction for patients at increased risk of dying was especially low for NP. Accordingly, the NP demonstrated higher accuracy for predicting whether patients would still be alive after 12 months compared to PCP. Our results suggest the use of "12-SQ2": "Would I be surprised if this patient

TABLE 2 | Assessment of patients' symptom burden (HOPE-SP-CL, ECOG, neurological symptoms) by neurorehabilitation physician (NP) and palliative care physician (PCP), respectively, for the patients who were concordantly estimated to have a good prognosis (NP and PCP, *both* answered 12-SQ with "Yes"), for the patients who were concordantly assessed as having a poor prognosis (neurologist and PC physician, *both* answered 12-SQ with "No") and for the patients whose prognosis was discordantly estimated by neurologist and palliative care physician (NP answered 12-SQ with "No" and PCP with "Yes" and vice versa, respectively).

Symptom	Assessor	12-SQ "Yes" (NP and PCP) *N* = 164 mean (SD)	*p*-value	12-SQ "No" (NP and PCP) *N* = 42 mean (SD)	*p*-value	12-SQ "Yes"/ "No" (NP, PCP discordant) *N* = 73 mean (SD)	*p*-value	*p*- value group comparison[#]
HOPE-SP-CL								
Pain	NP	0.75 (0.92)	**0.015**	0.90 (0.96)	0.743	0.55 (0.78)	0.019	0.191
	PCP	0.95 (1.17)		0.83 (1.08)		0.82 (1.18)		
Nausea	NP	0.05 (0.25)	**0.003**	0.31 (0.68)	0.414	0.15 (0.49)	0.310	**0.001***
	PCP	0.17 (0.52)		0.45 (0.80)		0.23 (0.54)		
Vomiting	NP	0.03 (0.21)	0.046	0.26 (0.59)	0.868	0.11 (0.46)	0.885	**<0.001*/*** **
	PCP	0.08 (0.35)		0.29 (0.60)		0.12 (0.41)		
Dyspnea	NP	0.07 (0.30)	**<0.001**	0.33 (0.65)	0.018	0.19 (0.52)	**0.003**	**0.003***
	PCP	0.32 (0.66)		0.67 (0.85)		0.47 (0.88)		
Constipation	NP	0.25 (0.57)	**0.022**	0.64 (0.79)	0.834	0.41 (0.68)	0.114	**0.002*/****
	PCP	0.38 (0.73)		0.69 (1.00)		0.60 (0.96)		
Weakness	NP	0.91 (0.77)	0.053	1.83 (0.85)	0.130	1.23 (0.95)	0.059	**<0.001*/**/*** **
	PCP	1.06 (0.99)		2.05 (1.01)		1.45 (0.96)		
Loss of appetite	NP	0.24 (0.55)	0.489	0.98 (1.00)	0.878	0.68 (0.90)	0.449	**<0.001*/****
	PCP	0.27 (0.63)		1.02 (1.26)		0.79 (1.09)		
Tiredness	NP	0.74 (0.69)	**0.010**	1.33 (0.90)	0.127	1.18 (0.84)	0.241	**<0.001*/****
	PCP	0.98 (1.00)		1.64 (1.19)		1.32 (0.86)		
Wound care	NP	0.11 (0.44)	0.498	0.45 (0.80)	0.637	0.26 (0.67)	0.911	**<0.001*/****
	PCP	0.13 (0.48)		0.48 (0.83)		0.26 (0.65)		
Assistance with activity of daily living [ADLs]	NP	0.55 (0.82)	0.041	1.76 (1.03)	0.763	1.30 (1.08)	0.878	**<0.001*/****
	PCP	0.67 (0.97)		1.81 (1.27)		1.29 (1.21)		
Feeling depressed	NP	0.45 (0.70)	0.537	1.07 (1.02)	**<0.001**	0.63 (0.86)	0.104	0.045
	PCP	0.48 (0.78)		0.43 (0.77)		0.44 (0.76)		
Anxiety	NP	0.40 (0.62)	**0.009**	0.88 (0.99)	**0.002**	0.53 (0.77)	0.071	0.379
	PCP	0.55 (0.75)		0.31 (0.60)		0.36 (0.61)		
Tension	NP	0.45 (0.58)	0.144	0.83 (0.92)	0.017	0.66 (0.79)	0.054	0.416
	PCP	0.52 (0.72)		0.40 (0.70)		0.45 (0.69)		
Disorientation/ Confusion	NP	0.06 (0.29)	**0.025**	0.64 (0.79)	0.926	0.34 (0.79)	0.941	**<0.001*/**/*** **
	PCP	0.13 (0.48)		0.67 (1.07)		0.34 (0.75)		
Organization of care	NP	0.13 (0.45)	**<0.001**	0.81 (0.99)	0.033	0.45 (0.83)	**0.009**	**<0.001*/****
	PCP	0.34 (0.62)		1.17 (1.08)		0.88 (0.91)		
Overburdening of family	NP	0.19 (0.54)	0.129	0.64 (0.91)	0.156	0.36 (0.81)	0.014	**<0.001*/****
	PCP	0.25 (0.49)		0.88 (0.97)		0.70 (0.83)		
Other symptoms	NP	0.00 (0.00)	0.317	0.07 (0.34)	1.000	0.00 (0.00)	0.180	**0.031***
	PCP	0.01 (0.08)		0.07 (0.46)		0.05 (0.37)		
HOPE total score	NP	5.41 (4.02)	**<0.001**	13.74 (9.07)	0.679	9.18 (7.69)	0.035	**<0.001*/**/*** **
	PCP	7.30 (5.64)		13.86 (7.14)		10.47 (6.07)		
NEUROLOGICAL ISSUES								
Symptoms of intracranial pressure	NP	0.09 (0.37)	0.906	0.07 (0.34)	1.000	0.04 (0.26)	1.000	0.290
	PCP	0.09 (0.37)		0.07 (0.34)		0.04 (0.26)		
Epileptic seizures	NP	0.10 (0.41)	0.039	0.14 (0.47)	0.783	0.23 (0.68)	0.161	0.790
	PCP	0.16 (0.52)		0.17 (0.66)		0.15 (0.52)		
Sensory disturbances (sensory organs)	NP	0.48 (0.77)	**0.004**	0.86 (0.98)	0.247	0.79 (0.82)	0.509	**<0.001*/****
	PCP	0.65 (0.92)		1.10 (1.14)		0.85 (0.92)		

(Continued)

TABLE 2 | Continued

Symptom	Assessor	12-SQ "Yes" (NP and PCP) $N = 164$ mean (SD)	*p*-value	12-SQ "No" (NP and PCP) $N = 42$ mean (SD)	*p*-value	12-SQ "Yes"/ "No" (NP, PCP discordant) $N = 73$ mean (SD)	*p*-value	*p*- value group comparison[#]
Sensation deficit (skin)	NP	0.77 (0.85)	**<0.001**	1.24 (0.98)	0.355	0.96 (0.84)	0.121	**0.027***
	PCP	1.05 (1.02)		1.40 (1.19)		1.14 (0.99)		
Motor disturbances	NP	1.09 (0.94)	**<0.001**	1.90 (0.85)	0.168	1.41 (0.94)	0.035	**<0.001*/*****
	PCP	1.37 (1.02)		2.10 (1.12)		1.63 (1.15)		
Dysphagia	NP	0.07 (0.34)	**0.001**	0.74 (0.99)	0.084	0.34 (0.75)	0.435	**<0.001*/**/*****
	PCP	0.19 (0.50)		0.98 (1.22)		0.41 (0.86)		
Spasticity	NP	0.20 (0.56)	**<0.001**	0.62 (1.04)	0.061	0.37 (0.83)	0.523	0.572
	PCP	0.38 (0.78)		0.36 (0.79)		0.32 (0.69)		
Vegetative disturbances	NP	0.24 (0.59)	**0.008**	1.00 (1.01)	0.942	0.51 (0.86)	0.114	**<0.001*/**/*****
	PCP	0.37 (0.74)		1.00 (1.15)		0.71 (1.11)		
Neuropsychological disorders	NP	0.26 (0.58)	**<0.001**	0.81 (1.07)	**0.001**	0.60 (0.92)	**<0.001**	**<0.001*/****
	PCP	0.66 (0.84)		1.45 (1.19)		1.26 (1.14)		
Quantitative disturbance of consciousness	NP	0.04 (0.30)	**<0.001**	0.48 (0.94)	**<0.001**	0.21 (0.62)	**<0.001**	**<0.001*/****
	PCP	0.29 (0.57)		0.90 (1.01)		0.53 (0.71)		
Symptoms of delirium	NP	0.02 (0.17)	0.084	0.38 (0.73)	0.432	0.23 (0.68)	0.892	**<0.001*/****
	PCP	0.06 (0.35)		0.29 (0.74)		0.21 (0.50)		
Change in personality	NP	0.09 (0.36)	**<0.001**	0.64 (0.96)	0.355	0.34 (0.73)	0.072	**<0.001*/****
	PCP	0.39 (0.65)		0.79 [0.98)		0.52 (0.77)		
Loss of autonomy	NP	0.38 (0.67)	**<0.001**	1.31 (1.16)	**<0.001**	0.93 (1.10)	**<0.001**	**<0.001*/**/*****
	PCP	0.80 (0.86)		2.02 (1.07)		1.58 (1.15)		
Neuro total score	NP	3.89 (3.16)	**<0.001**	10.19 (7.81)	**0.001**	7.05 (6.56)	**<0.001**	**<0.001*/****
	PCP	6.46 (4.05)		12.62 (8.44)		9.41 (5.88)		
ECOG	NP	1.28 (0.84)	**<0.001**	2.64 (1.10)	0.065	1.96 (1.02)	**0.001**	**<0.001*/**/*****
	PCP	1.52 (0.95)		2.93 (0.92)		2.33 (0.97)		
Total score	NP	9.30 (6.14)	**<0.001**	23.93 (16.12)	0.122	16.23 (13.51)	**0.001**	**<0.001*/**/*****
	PCP	13.76 (8.5)		26.48 (14.19)		19.88 (10.48)		

Numbers represent mean [standard deviation (SD)] and are reported here for ease of interpretation instead of median [range]. However, due to the skewed distribution of the data, non-parametric tests were applied to detect statistically significant differences. Values in bold are significant at $p < 0.05$ (FDR-corrected).

[#]If significant group differences were found (Kruskall-Wallis test), a post-hoc test was applied (FDR-corrected at $p < 0.05$).

"yes" vs. "no", **"yes" vs. "discordant", *"no" vs. "discordant".*

12-SQ, "surprise" question; PCP, palliative care physician; NP, neurorehabilitation physician; SD, standard deviation; ADLs, activity of daily living.

is still alive after twelve months?" (45) for physicians with a background in neurology or a combination of the original 12-SQ and the 12-SQ2, which has been piloted in a sample of general practitioners (45, 46).

Significantly, the 12-SQ was not originally developed for an accurate prognosis in the prediction of death, but to identify patients in need of palliative care (1–19). In specialties such as neurorehabilitation the implementation of the 12-SQ in combination with a palliative care assessment into the clinical routine—as in our study—might help sensitize healthcare professionals toward palliative care issues like initiating conversation on advanced care planning or prognosis or integrating additional services like palliative and hospice care services if needed. Currently, this approach is not yet well recognized in German neurorehabilitation and integrative prognostic studies may serve to help change this, an eventual consequence which would be beneficial to both patients and the caregivers involved in neurorehabilitation. The need for such a multi-disciplinary neuropalliative rehabilitation approach has already been highlighted and recommended in the UK's National Service Framework for Long-term (Neurological) Conditions (29–31) but has not been consistently pursued in neurorehabilitation in Germany so far.

In a recent study, the 12-SQ was combined with further clinical parameters to better identify patients with palliative care needs and aid in prognosis estimation (22). Our study corroborates the importance of bringing in additional clinical assessments to the 12-SQ, i.e., HOPE-SP-CL, neuro supplement,

TABLE 3 | Characteristics of patients deceased after 12 months ($N = 34$) and those still alive ($N = 202$).

	Still alive after 12 months $N = 202$ (85.6%)	**Deceased after 12 months $N = 34$ (14.4%)**	***p*-value**
Age mean (SD)	62 (13.7)	70.9 (13.1)	<0.001*
GENDER [%]			
Male	57.5	58.8	0.879
Female	42.5	41.2	0.879
REHABILITATION PHASES [%]			
B	4.0	26.5	<0.001*
C	37.0	52.9	0.081
D	59.0	20.6	<0.001*
MAIN DIAGNOSES [%]			
Ischemic stroke	48	32.4	0.256
Primary intracerebral hemorrhage	7.5	20.6	0.040
Primary brain tumors	2	11.8	0.011
Critical illness polyneuropathy	2.5	8.8	0.115
Neurodegenerative disorders	10.5	8.8	0.905
Infection of CNS	8.5	5.9	0.647
Subarachnoid hemorrhage	1.5	2.9	0.555
Subdural hematoma	1.5	/	0.561
Multiple Sclerosis	5	2.9	0.720
Epilepsy	0.5	2.9	0.245
Dementia	1	/	0.681
Hypoxic brain injury	0.5	/	0.377
Slipped disc/spinal canal stenosis	2	/	0.475
CATEGORIES OF SECONDARY DIAGNOSES [%]			
Cardiovascular diseases	64	61.8	0.240
Other internal diseases	32	35.3	0.747
Bronchopulmonary diseases	18	26.5	0.221
Malignancies (except for primary brain tumors)	4.5	23.5	<0.001*
Neurological and psychiatric diseases	12	8.8	0.232
Infectious diseases	5	8.8	0.092
Diseases of the musculoskeletal system	7.5	5.9	0.786

(Continued)

TABLE 3 | Continued

ASSESSMENT RESULTS AT BASELINE (HOPE, NEURO SUPPLEMENT ECOG) MEAN [SD]			
	HOPE score t0 Survivors $N = 202$ (85.6%)	**HOPE score t0 Deceased $N = 34$ (14.4%)**	***p*-value**
HOPE			
Pain	0.83 (0.91]	0.74 (0.74)	0.810
Nausea	0.16 (0.39)	0.16 (0.47)	0.394
Vomiting	0.09 (0.32)	0.12 (0.35)	0.834
Dyspnea	0.23 (0.46)	0.50 (0.63)	0.004*
Constipation	0.37 (0.61)	0.63 (0.74)	0.030*
Weakness	1.11 (0.79)	1.63 (0.92)	0.001*
Loss of appetite	0.39 (0.64)	0.93 (0.95)	<0.001*
Tiredness	0.97 (0.70)	1.43 (0.75)	0.001*
Wound care	0.12 (0.34)	0.37 (0.63)	0.002*
Assistance with activity of daily living [ADLs]	0.83 (0.92)	1.66 (1.11)	<0.001*
Feeling depressed	0.49 (0.63)	0.66 (0.66)	0.080
Anxiety	0.48 (0.59)	0.51 (0.56)	0.564
Tension	0.50 (0.55)	0.58 (0.59)	0.427
Disorientation/Confusion	0.16 (0.42)	0.53 (0.80)	0.002*
Organization of care	0.37 (0.54)	0.44 (0.61)	<0.001*
Overburdening of family	0.31 (0.48)	0.72 (0.73)	<0.001*
Other symptoms	0.003 (0.04)	0.10 (0.36)	<0.001*
HOPE total score	7.41 (4.86)	12.15 (7.72)	<0.001*
NEURO SUPPLEMENT			
Symptoms of intracranial pressure	0.08 (0.27)	0.01 (0.09)	0.161
Epileptic seizures	0.11 (0.42)	0.21 (0.54)	0.146
Sensory disturbances (sensory organs)	0.64 (0.78)	0.87 (0.75)	0.044
Sensation deficit (skin)	0.95 (0.79)	1.41 (0.87)	0.005*
Motor disturbances	1.35 (0.91)	1.87 (0.96)	0.004*
Dysphagia	0.18 (0.42)	0.79 (1.06)	<0.001*
Spasticity	0.29 (0.57)	0.38 (0.71)	0.592
Vegetative disturbances	0.38 (0.67)	0.90 (1.05)	0.003*
Neuropsychological disorders	0.60 (0.72)	1.16 (1.01)	0.002*
Quantitative disturbance of consciousness	0.22 (0.39)	0.57 (0.79)	0.003*
Symptoms of delirium	0.07 (0.25)	0.21 (0.45)	0.015*

(Continued)

TABLE 3 | Continued

	HOPE score t0 Survivors *N* = 202 (85.6%)	HOPE score t0 Deceased *N* = 34 (14.4%)	*p*-value
Change in personality	0.27 (0.41)	0.63 (0.76)	0.005*
Loss of autonomy	0.78 (0.78)	1.60 (1.05)	<0.001*
Neuro total score	5.97 (3.65)	10.62 (1.18)	<0.001*
ECOG	1.66 (0.88)	2.66 (1.09)	<0.001*
Total score	13.39 (7.57)	22.76 (14.15)	<0.001*

Numerical scores are given as mean [standard deviation]. They are reported here in lieu of medians [range] for ease of interpretation. As the data is not normally distributed, statistical group differences were analyzed with non-parametric test (FDR-corrected at $p < 0.05$) as directed by the data. Numerical scores for each item are presented here as mean score from both the PCP and NP.

**$p < 0.05$ (FDR-corrected)*

SD, standard deviation; 12-SQ, "surprise" question; PCP, palliative care physician; NP, neurorehabilitation physician; ADLs, activity of daily living.

TABLE 4 | Prognosis estimation of NP and PCP.

	N	Total score+ given by NP median [range]	Total score+ given by PCP median [range]	*p*-value
Total	279	10 (1–74)	15 (1–58)	<0.001*
12-SQ **concordant "Yes"** (NP: 12-SQ "Yes", PCP: 12-SQ "Yes") (concordant estimation of good prognosis)	164	8 (1–41)	13 (1–54)	<0.001*
12-SQ **concordant "No"** (NP: 12-SQ "No", PCP: 12-SQ "No") (concordant estimation of poor prognosis)	42	18.5 (2–65)	25.5 (2–58)	0.122
12-SQ **discordant** (NP: 12-SQ "No", PCP: 12-SQ "Yes")	20	18.5 (3–74)	22.5 (2–50)	0.737
12-SQ **discordant** (NP: 12-SQ "Yes", PCP 12-SQ "No")	53	11 (1–33)	19 (3–47)	<0.001*

+Total score, sum of HOPE-SP-CL total score; Neuro supplement total score and ECOG.

**Indication for significant differences*

12-SQ, 12-months "surprise" question; NP, neurorehabilitation physician; PCP, palliative care physician.

TABLE 5 | Prognostic accuracy indices, 95% confidence intervals are displayed in brackets.

	Neurorehabilitation physician	Palliative care physician	Significance
Sensitivity	50% (0.32–0.67)	67.6% (0.50–0.83)	NS
Specificity	86.1% (0.81–0.91)	70.3% (0.64–0.77)	<0.001
PPV	37.8% (0.27–0.50)	27.7% (0.22–0.34)	NS
NPV	91.1% (0.88–0.94)	92.8% (0.89–0.96)	NS
AUC	0.68 (0.57–0.79)	0.69 (0.59–0.79)	NS
Success rate ("Yes")	73.7%	60.2%	<0.001
Success rate ("No")	7.2%	9.7%	NS
Success rate (combined)	80.9%	69.9%	0.002

PPV, Positive predictive value; NPV, negative predictive value; AUC, area under the curve; NS, not significant.

TABLE 6 | Frequency table for prognosis estimation by the neurorehabilitation physician.

	Deceased	Living
12-SQ "No"	17	28
12-SQ "Yes"	17	174

TABLE 7 | Frequency table for prognosis estimation by the palliative care physician.

	Deceased	Living
12-SQ "No"	23	60
12-SQ "Yes"	11	142

ECOG, diagnoses, age, gender, rehabilitation phase, to establish a broader basis for estimation of prognosis and palliative care needs.

With the help of the additional data we were able to identify several items (HOPE-SP-CL as well as neuro supplement as well as ECOG) which were scored significantly higher at baseline (meaning worse) for the group of patients who died after 12 months compared to those still alive. This speaks in favor of these measurements being suitable to assess patients' deteriorating general health condition. Moreover, the regression identified three factors (age, ECOG, dysphagia) which might help to predict one-year mortality in our sample of neurorehabilitation patients. These three factors are all reasonable indicators for a worsened overall condition. As anticipated, increased age is a risk factor for dying, even more so when seriously ill. Second, an increasing ECOG score in patients indicates decreasing, i.e., worse, functionality in all daily activities. Lastly, dysphagia has been identified as a critical prognostic factor in neurological patients, especially those suffering from stroke and neurodegenerative disorders (20, 47, 48). In the rehabilitation setting mortality risk increased by a factor of 13 for patients suffering from dysphagia (47). Depending on subtypes, patients suffering from progressive supranuclear palsy or multiple system atrophy died 2–24 months after developing severe dysphagia (48). Potential reasons for dysphagia being associated with a poor prognosis might be the development of serious complications like aspiration pneumonia (20, 47, 48).

As the 12-SQ is a commonly used tool for estimation of prognosis—even if poor when used as the only instrument—and for initiating palliative care in cancer and non-cancer patients (1–19), we investigated whether adding further clinical

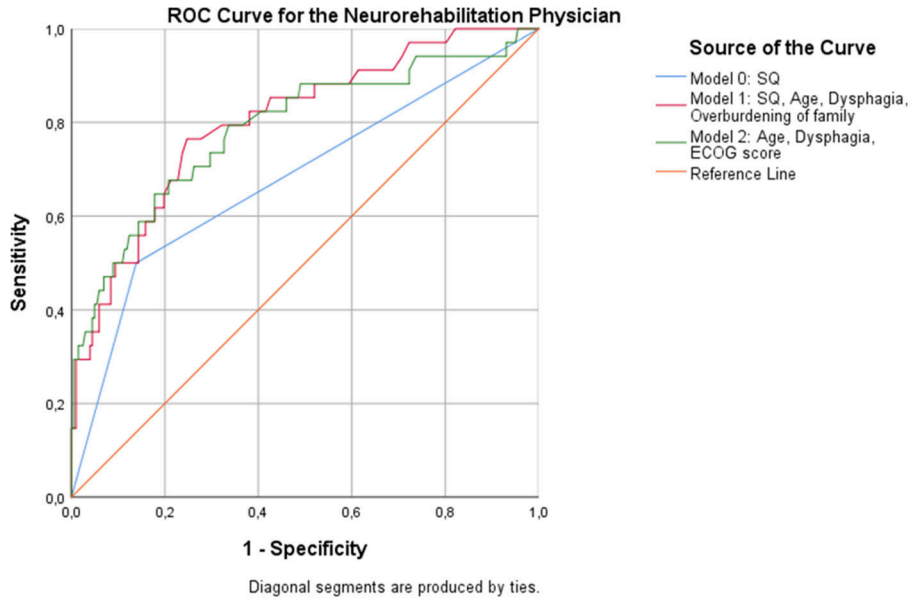

FIGURE 2 | ROC curves showing the trade-off between sensitivity and specificity for all significant predictors after multivariable regression with (Model 1) and without (Model 2) the NP's response to the 12-SQ. Classification accuracy is higher for both models compared to the 12-SQ as stand-alone predictor (Model 0), though these differences did not reach statistical significance.

TABLE 8 | Binary logistic regression to predict 12-month mortality as assessed by the neurorehabilitation physician.

	Predictor	OR	AUC (one for each model)
Model 0	12-SQ (reference: "Yes")	6.21 (2.84–13.58)	0.68 (0.57–0.79)
Model 1	12-SQ (reference: "Yes")	2.00 (0.75–5.33)	0.80 (0.72–0.89)
	Age	1.05 (1.01–1.09)	
	Dysphagia	2.54 (1.3–5.0)	
	Overburdening of the family	1.97 (1.05–3.7)	
Model 2	Age	1.04 (1.00–1.08)	0.79 (0.69–0.88)
	Dysphagia	2.39 (1.21–4.71)	
	ECOG score	1.90 (1.24–2.92)	

95% confidence intervals are displayed in brackets.
OR, odds ratio; AUC, area under the curve; 12-SQ, 12-months "surprise" question; ECOG, Eastern Cooperative Oncology Group.

characteristics to the 12-SQ would improve the overall predictive power. Again, our results indicate that age and dysphagia, as well as rehabilitation phase and overburdening of the family in combination with the 12-SQ have great prognostic value in estimating prognosis and thus identifying patients in need of palliative care. These two additional factors can be interpreted similarly to the ECOG: Patients in rehabilitation phases C and B suffer from a more serious illness with decreased functionality compared to phase D and "overburdening of family" also indicates patients' health deterioration. It is well known that as patients' health condition worsens, family caregivers physically and psychologically reach their limits (49–52).

LIMITATIONS

Of our initial sample of 634 patients only 236 (37%) could be included and later followed up. This proportion is quite good for a palliative care study, but generalizability remains limited as we were unable to present a full data set. Moreover, study participants attending rehabilitation phase B (i.e., seriously ill patients) were represented to a lesser degree than patients in rehabilitation phase C or D. One potential reason might be the increased difficulty in obtaining consent (seriously ill, legal representative, etc.). Of the 236 included and followed-up patients 14% died within one year. Despite similar incidences of death reported in other studies investigating the 12-SQ (21) this is a moderate to small fraction complicating the interpretation of prognostic accuracy indices. The neurorehabilitation population investigated was quite heterogeneous. Group sizes of the different main diagnoses groups were unequal ranging from 47% (ischemic stroke, largest group) to 0.2% (epilepsy, dementia syndrome, and hypoxic brain injury, respectively) and thus, a sound subgroup analysis was not possible. At least from results of this study, we cannot conclude whether the 12-SQ and identified risk factors may be of differing predictive accuracy with respect to special disease entities s (e.g., ALS representing a progressive disorder vs. ischemic stroke normally representing a monophasic illness). One caveat to the interpretation of our results is that various NPs (each time the respective treating NP) evaluated the patients while there

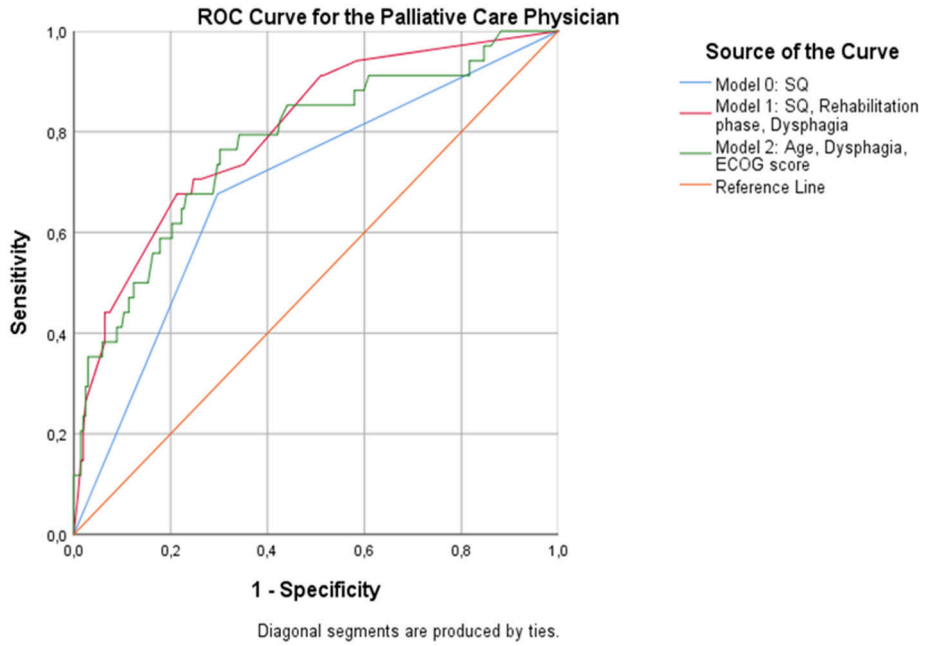

FIGURE 3 | ROC curves showing the trade-off between sensitivity and specificity for all significant predictors after multivariable regression with (Model 1) and without (Model 2) the PCP's response to the 12-SQ. Classification accuracy is higher for both models compared to the 12-SQ as stand-alone predictor (Model 0), though these differences did not achieve statistical significance.

TABLE 9 | Binary logistic regression to predict 12-month mortality as assessed by the Palliative Care Physician.

	Predictor	OR	AUC (one for each model)
Model 0	12-SQ (reference: "Yes")	4.95 (2.27–10.79)	0.69 (0.59–0.79)
Model 1	12-SQ (reference: "Yes")	2.95 (1.25–6.97)	0.80 (0.72–0.88)
	Rehabilitation phase (reference: phase D)		
	Rehabilitation phase B	7.32 (1.83–29.26)	
	Rehabilitation phase C	2.78 (1.04–7.39)	
	Dysphagia	1.61 (1.02–2.54)	
Model 2	Age	1.04 (1.00–1.07)	0.78 (0.69–0.87)
	Dysphagia	1.61 (1.05–2.47)	
	ECOG score	1.87 (1.21–2.88)	

95% confidence intervals are displayed in brackets.
OR, odds ratio; AUC, area under the curve; 12-SQ, 12-months "surprise" question; ECOG, Eastern Cooperative Oncology Group.

was a single, external, consulting PCP assessing the patients, so that systematic assessment bias for the PCP could not be averaged out. That clinical background influenced 12-SQ estimation was also apparent amongst the rather large group of patients who were discordantly judged using the 12-SQ (26.2%) thereby reducing the number of unambiguously assigned patients.

CONCLUSION

Prognosis estimation of neurological patients is challenging and thus, identifying the right point in time to integrate the palliative care approach for neurological patients remains difficult. Implementing an assessment tool into the care of these patients - in the current study with a sample of neurorehabilitation patients - combining the 12-SQ with palliative care and neurological items might improve predictive performance of 12 months survival and thus identify an appropriate, sufficient time to initiate the palliative care approach and services if needed. Factors improving predictive accuracy (with and without the 12-SQ) were rehabilitation phase, dysphagia, age, overburdening of family and ECOG. Professional background influences assessment and prognosis estimation.

AUTHOR CONTRIBUTIONS

ME, HG, RV, AK, and IB planned the study. ME and AK recruited and assessed patients. KD, AK, IB, and HG analyzed the data. HG, KD, AK, ME, IB, and RV wrote and corrected the manuscript.

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BRIEF RESEARCH REPORT
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Telemedicine in Palliative Care: Implementation of New Technologies to Overcome Structural Challenges in the Care of Neurological Patients

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Telemedicine provides a possibility to deal with the scarcity of resources and money in the health care system. Palliative care has been suggested to be appropriate for an increasing number of patients with neurodegenerative disorders, but these patients often lack care from either palliative care or neurology. Since palliative care means a multidisciplinary approach it is meaningful to use palliative care structures as a basis. There exists no systematic access to neurological expertise in an outpatient setting. A successful link of two existing resources is shown in this project connecting the Department of Neurology of an University Hospital with specialized outpatient palliative care (SPC) teams. A videocounselling system is used to provide expert care for neurological outpatients in a palliative setting.

Methods: A prospective explorative single arm pilot trial was implemented to provide a mobile telesystem for 5 SPC teams. The opportunity was given to consult an expert in neuropalliative care at the specialized center in the hospital (24/7). Semistructured interviews were conducted with the physicians of the SPC teams after a trial duration of 9 months.

Results: Our data provides strong evidence that the technical structure applied in this project allows a reasonable neurological examination at distance. Qualitative interviews indicate a major impact on the quality of work for the SPC teams and on the quality of care for neurological patients.

Conclusion: The system proves to be useful and is well accepted by the SPC teams. It supplies a structure that can be transported to other disciplines.

Keywords: neurological, telemedicine, neuropalliative care, specialized outpatient palliative care team, videoconsultation

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BACKGROUND

A multidisciplinary palliative care approach improves patient's quality of life and symptoms in advanced neurological diseases (1). End of life care in neurological diseases is often challenging since disease trajectories are less predictable compared to cancer patients (2). Furthermore, either the palliative care expertise might be lacking in neurologists or the neurological expertise be missing in palliative care experts (3).

Outpatient Palliative Care services are a multidisciplinary approach with a network around the core team. A specialized outpatient palliative care (SPC) support which enables patients to stay at home is currently seen as the most appropriate form of palliative care. Usually, the neurological expertise is lacking in SPC teams which makes it difficult to handle patients with either neurological diseases or neurological symptoms. In most countries no regulated approach to a neurological consultant in an outpatient setting is established.

Owing to the increased awareness of the benefits of palliative care for non-cancer patients, telemedicine might provide a solution to cope with the growing requirements in the health care system. It enables the provision of expert medical opinion over long distances and can transport the support to virtually any place. It offers the opportunity to enhance quality and capacity of medical care (4). Especially in rural areas a lack of experts due to a lack of human resources could be overcome by providing expertise via telemedicine. It gives the possibility to monitor patients with advanced illnesses at home (5).

Here we describe an established system that provides the opportunity to consult an expert in neurology/neuropalliative care via a teleconference app.

METHODS

Study Design

A single center, multi-site, non-randomized trial was conducted at a Bavarian Neurological Medical Centre with expertise in neuropalliative care. Five teams were equipped with a mobile telesystem to consult an expert in neuropalliative care at the specialized center (24/7). The mobile telesystem allows a videoconsultation between the patient at home and the medical center. Patients had to meet the following criteria: (1) to be attended by one of the five selected specialized outpatient palliative care teams with a (2) diagnosis of a neurological disease or having a cancer diagnosis suffering from neurological symptoms. Ethics were approved by University Ethics committee (Nr. 17-068) and the study was registered at the DRKS.

Each team selected has been equipped with a mobile teleconsultation device consisting of a mobile phone with a high resolution camera (Samsung Galaxy S6) supplemented by a mobile WIFI router and a small tripod (see **Figure 1A**). Additionally, a WIFI router which offers the opportunity to generate a wireless LAN, has been supplied.

The videoconference software (MEYDOC®) is installed on the mobile device as an app. The acquired software ensures high data integrity providing a point to point communication with authenticated endpoints, the server is used only for call control procedure and an end to end encryption is used. The teleconsultation equipment at the medical center consists of a laptop with the videoconference software installed.

Intervention

Teleconsultations are held on demand. When the outpatient team identifies a symptom which is difficult to control, a call is made to the expert medical center for an appointment.

Depending on the acuteness of the problem the teleconsultation usually is scheduled within the next 1 to 5 days. Generally, the teleconsultations can be scheduled beforehand. However, emergency calls are possible (24 h/day). The screen to screen contact is built up between the patient's home and the specialist in the medical center. The hospital-based neurological team consists of two neurologists (one having major expertise in neuropalliative care). A physician or a nurse of the specialized palliative outpatient team is involved by joining the video consultations at the patient‘s home.

For data analysis we have used a mixed methods approach. Quantitative data: We have documented personal data of the patients, the neurological diagnosis, main neurological symptoms, and the technical quality of the teleconsultation (ranking by the physicians at the medical center on a NRS 1-5). For qualitative analysis we have used a semistructured interview guide (see **Table 1a**).

After a trial duration of 9 months the researchers conducted five semi-structured ethnographic interviews with the leading physician of each specialized palliative care team. The interviews were recorded, transcribed and anonymized. They were subjected to a pragmatic thematic analysis of the content conducted by CW and KL.

RESULTS

Specialized Outpatient Palliative Care Teams–Selection and Characterization

We asked seven SPC teams in Bavaria to participate. Finally, five teams agreed to participate (One team never answered the proposal. The other team already had the support of a neurologist.) The teams covered an area of about 7,250 km^2 (ranging from 317 to 2,370 km^2) with a population density ranging from 113 inhabitants per km^2 to 4,713 inhabitants per km^2, employing from two to 5.4 physicians. In the five participating teams the specializations consist of anaesthisiologists (9), general practitioners (6), internists (7), and one geriatrician. In one team a neurologist stepped in during the ongoing trial.

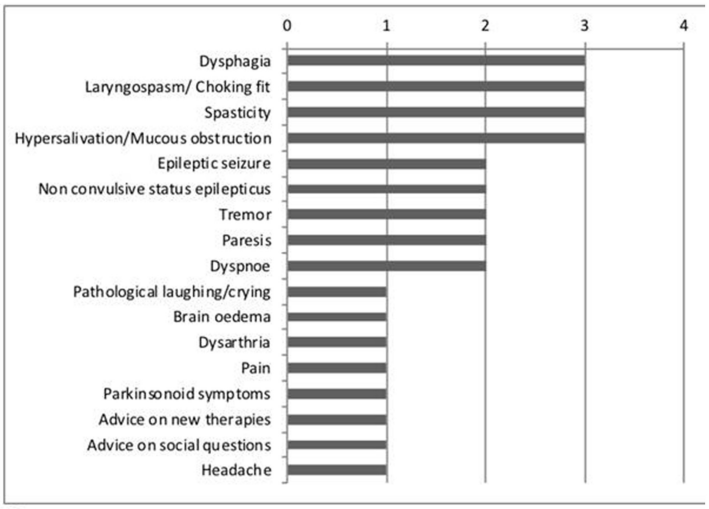
Technical Feasibility

The first 26 videoconsultations were evaluated for their technical quality. A stable connection with a satisfactory quality of the visual and acoustic components even in rural areas is feasible using the dual phone card solution and the mobile wireless LAN router (NRS 2). In two cases problems occurred with the audio line. In some cases the pre-existing wireless LAN of the patient‘s home was utilized. Redialling was sometimes necessary to establish the connection. However, in every case a teleneurological consultation with sufficient quality to determine the acute problems and to make a neurological assessment was possible.

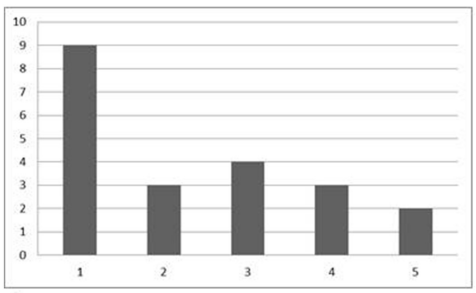
Quantitative Data

Until March 2018, 37 teleconsultations were held concerning 21 patients. Eleven of the consultations were conducted via telephone, 26 consultations via videoconference. **Figure 1B**

A



C



B

FIGURE 1 | (A) Teleconsultation device consisting of a mobile phone, a small tripod and a mobile WIFI router; **(B)** Number of patients co-supervised per SPC team (team 1 to 5 on the x axis); **(C)** Frequence of symptoms discussed in the consultations.

shows the number of patients co-supervised per team varying from nine to two patients. In 48% of the cases a re-consultation was conducted with up to 4 follow up consultations for one patient. Fourteen of the 21 patients were cared for by the SPC for neurological disorders. The other seven patients had an internal or oncological diagnosis and neurological symptoms. Half of the patients suffered from motor neuron disease, three of them from glioblastoma. The other four had Parkinson's disease, Progressive supranuclear palsy, a non-convulsive status epilepticus and unclassified dementia. **Figure 1C** shows the main neurological symptoms discussed in the video and telephone consultations from all of the 21 patients. The leading symptoms were dysphagia, hypersalivation, laryngospasm, spasticity, and epileptic seizures or non-convulsive status epilepticus.

Qualitative Data

A positive impact of the telemedical project for the teams and the patients is the core tenor of the interviews. The SPC teams perceived that the patients highly accepted a neurological telemedical visit. Recommended therapy procedures, discussed in the teleconsultation often led to efficient symptom control thereby improving patient's quality of life, as perceived by the SPC teams.

TABLE 1a | Interview guide.

Questions
1) How did you handle neurological problems prior the participation in the trial?
2) Did the project influence your job satisfaction?
3) Did the project modify your daily job activity? If yes, how did it change your work?
4) How do you estimate your knowledge concerning neurological problems prior to and post-trial participation?
5) Did you have problems with the technology, which were the most disturbing ones?
6) Did you think there was a problem with the patient's acceptance of the telemedical system?
7) Do you have any suggestions for the next trial stage?
8) Miscellaneous

Even if there has been no improvement with the suggested treatment, the fact that everything possible was done by consulting a specialist, has been significant enough to have a positive effect on the patient's satisfaction. Physicians experience an obvious increase in the satisfaction with the quality of their work. SPC teams feel safer having a neurological

TABLE 1b | Quotes of the semistructured interviews.

Patient's acceptance of the neurological telemedical screen to screen visit	"…if we inform patients that we want to consult a neurologist, who is unable to come in person but joins us via a videoconference, patients are actually enthusiastic"(interview C, line 57–58)
	"…they rather thought this was a really good idea and were excited, because when suffering from ALS or MS they no longer manage to visit the resident neurologist."(interview D, line 192–194)
Symptom control by recommended therapy	"Patient X… she lived quite a long time with a significant increase in mobility and was very satisfied and extremely thankful." (interview C, line 15)
The fact that everything possible was done by consulting a specialist	"patients are highly satisfied also because they feel comprehensively cared for." (interview A, line 41)
Satisfaction with the quality of their work increases in the SPC teams	"where a new neurological symptom supervenes … and I feel incapable of making the right diagnosis and initiating the accurate therapy … it is really brilliant for this."(interview C, line 34–37)
	"in other cases there were fewer consequences (*therapeutically*), but we got certainty"(interview C, line 11–12)
Clear structures make it easier to discuss neurological problems	"if we have a reasonable initial suspicion" (interview C, line 23–24).
	"It was extremely helpful, we may never have solved such questions" (interview D, line 125–126).
The visual component is a key feature of the system	"… asking you without inhibitions, and not only calling and describing, but really displaying, having you with us in the living room (*via camera*)" (interview D, line 26–27).

telemedical background. There was no clear structure in handling neurological/neuropalliative questions in any of the teams prior to the participation in this trial. Strategies used before the telemedical application included asking the residential neurologists or the nearest neurological department, reading books and making treatment decisions on their own. Therefore, using the telemedical application even these structures for the teams have been improved. The project changed the awareness of neurological symptoms, it resulted in a faster consultation. It has been highly acknowledged to have a contact person with neuropalliative care expertise. To further point out: a key feature of the telemedical approach with a huge significance is the visual component of the consultation.

Suggestions for technical improvement were a bigger display for the videosystem at the patient's side and the request for a timely fixed consultation hour beyond the videoconsultations, for short discussions concerning neurological symptoms or medications (quotes of the interviews are listed in **Table 1b**).

DISCUSSION

In this small pilot study we have been able to show for the first time that telemedical support for SPC teams with a focus on neurological patients or neurological symptoms in oncology patients is technically feasible and supports the team's treatment. It enables the teams to get rapid access to neurological and neuropalliative care expertise without losing contact to the patient. Until now, there was no clear structure in the teams in dealing with these issues which often caused troubles since neurological expertise is usually only available during hospital treatment. However, since patients with progressed neurological diseases are usually bedridden and have severe communication problems they are frequently difficult to transport to a hospital or even a palliative care unit. Telemedical consultation therefore enabled the patient to stay at home and the SPC team to be the primary provider of care using expert opinion on demand. This also strengthened the relationship between the patient and the SPC team.

Patients with a neurological diagnosis are seldom cared for by SPC teams. Due to the growing awareness of the usefulness of a multidisciplinary palliative approach in progressive neurological conditions, we suggest a growing number of neurological patients in the specialized outpatient teams. The telemedical project offered clearly defined consultance structures which also improved the quality of work and job satisfaction of the SPC teams. The interviews with the physicians report a high acceptance of the telemedical application by the patients. It is important to point out that in some cases where we couldn't add much to symptom control, only the patient's awareness of comprehensive medical care brought benefit to the patient. To get an unbiased view of patient's acceptance further interviews with the patients and caregivers have to be performed. The offered system, especially because of the possibility of a visual way of appraisal, yields more safety in the care for neurological palliative outpatients. Furthermore, the system is small, easy to carry and it stands out due to a simple application.

Since this is a pilot trial, the number of patients is too small for statistical analysis. Not surprising is the fact that half of the patients with a neurological diagnosis cared for by SPC teams suffer from ALS. This is one of the few neurological diagnoses where the need and the benefit of a palliative support is already comprehensively proven (7). Therefore, the main symptoms discussed in the videoconsultations were pseudohypersalivation, laryngospasm/choking fits, dyspnoea, and spasticity.

The concentration on neurological and neuropalliative care questions and the encompassed needs in a palliative situation proves successful. A comprehensive palliative care approach can be difficult to provide via telemedicine as shown in a telemedical approach for pediatric palliative care (6). Further application might provide access to specialist in cardiac or pulmonary care (8).

The system we offer works even in rural area. The technical construction (two mobile cards and the WIFI router) is stable enough even with a low bandwidth. As a future task, we are currently preparing to include more SPC teams as we have seen that based on the amount for videoconsultation we can provide our knowledge to an even larger number of teams. The suggested improvements (bigger display of the videotool and a consultation hour) will be implemented.

In conclusion, the qualitative interviews suggest that expert neurological and neuropalliative consultation is helpful in SPC teams concerning patients quality of life and the quality of work for the SPC teams. Our telemedical approach offers technical components which are easy to handle and have stable communication lines even in remote areas. The telemedical "home visitation" of a specialized neurologist has been well accepted by the teams. It provides an easy and effective way of symptom discussion and treatment evaluation. Further research is needed to explore telemedical applications in palliative care consultations.

ETHICS STATEMENT

Ethics committee Ludwig Maximilians University Munich. 17-068, 6.6.17. Written informed consent was obtained from all participants in this study.

AUTHOR CONTRIBUTIONS

CW and SL are the Researchers in the Project. The Project was initiated by SL and CW was part of the Project from the beginning. KL and CW evaluated the qualitative Research part.

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MINI REVIEW
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Practical Management of Epileptic Seizures and Status Epilepticus in Adult Palliative Care Patients

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In terminally ill patients, paroxysmal or episodic changes of consciousness, movements and behavior are frequent. Due to ambiguous appearance, the correct diagnosis of epileptic seizures (ES) and non-epileptic events (NEE) is often difficult. Treatment is frequently complicated by the underlying condition, and an approach indicated in healthier patients may not always be appropriate in the palliative care setting. This article provides recommendations for diagnosis of ES and NEE and treatment options for ES in adult palliative care patients, including aspects of alternative administration routes for antiepileptic drugs such as intranasal, subcutaneous, or rectal application.

Keywords: palliative care, epilepsy, epileptic seizures, end of life, status epilepticus, non-convulsive status

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INTRODUCTION

Patients may require palliative care for several conditions. These are not only end stage systemic cancer including primary brain tumors and cerebral metastases, but also ischemic stroke, intracerebral hemorrhage, neurodegenerative diseases, and non-neurological conditions such as terminal liver, kidney, or respiratory failure. Many of these carry an increased risk for epilepsy and epileptic seizures (ES) or non-epileptic events (NEE, defined as paroxysmal or episodic changes of consciousness, movement and/or behavior) (1–4).

Both ES and NEE present an important challenge in the already complex interaction with palliative patients. Differential diagnosis and treatment can be difficult. Events are not always witnessed by professionals and even if so, focal seizures with reduced awareness and automatisms can be mistaken for delirium or agitation (5). If patients are found in a state of impaired consciousness, several reasons are possible, too, such as a postictal state, non-convulsive status epilepticus (NCSE), dehydration, metabolic dysfunction, or new intracerebral pathology such as ischemic stroke or hemorrhage. In elderly patients who are increasingly represented among palliative patients, event duration as a distinguishing feature is less useful than in young patients due to longer lasting postictal periods of impaired consciousness or focal neurological deficits (4, 6). The ability of patients to report subjective symptoms which might facilitate differentiation can be reduced in palliative patients.

Treatment with antiepileptic drugs (AEDs) including benzodiazepines requires careful consideration in palliative patients since they may have prolonged sedative effect. This can even obscure the diagnosis (7, 8). Nevertheless, if patients are confirmed to have epilepsy, anticonvulsive treatment is usually indicated, however, in palliative patients in particular the burden of side effects has to be balanced against the benefit of reduction of seizure frequency and severity (9). In palliative care side effects can be especially strong due to drug-drug interactions, impaired metabolism and systemic comorbidities (9–11). Cognitive or sedative side effects can rob palliative patient's

remaining autonomy and negatively affect quality of life. Reliable routes of AED administration (which need to maintain constant blood level) is a particular challenge in patients with dysphagia and/or impaired consciousness.

The following sections provide recommendations for the differential diagnosis of ES and NEE and for treatment of ES in patients under palliative conditions.

DIAGNOSTICS

Semiology

Seizure semiology, the description of ictal signs and symptoms, is the most important diagnostic tool in epileptology. Characteristic semiological elements and their sequence can be used to ascertain the epileptic etiology of seizures (or NEE in turn) and to guide further diagnostic and treatment (12).

Since studies on seizure semiology in the palliative care setting are lacking, findings in elderly patients may be a helpful approximation. In a prospective study comparing young and elderly epilepsy patients, Stefan et al. found less clonic elements and a higher proportion of non-convulsive status epilepticus in elderly patients. In the light of more differential diagnoses, this leads to frequent misdiagnosis in particular in first manifestations of seizures (4, 13, 14).

Sheth et al. described that in elderly patients with ictal confusion the correct diagnosis was made only late (31 ± 30 h, range: 1–140) (14). Patients often appeared bewildered, had impaired attention and concentration, or had impairment of goal-directed action. Speech was reduced to simple semiautomatic phrases or gestures. Subtle ictal manifestations included a subtle gaze preference and low amplitude fragmentary myoclonic jerks, typically in the face, eyelids, or hands, and at times associated with hand automatisms.

Studies assessing symptoms in palliative care patients tend to report a relatively small prevalence of ES, but impaired consciousness of unspecified cause is very common with occurrences in up to 90% of cases (15). This discrepancy might indicate a high number of unrecognized seizures. Therefore, ictal or post-ictal states should be considered an important differential diagnosis of unexplained drowsiness.

As patient's descriptions may have limitations owing to their level of consciousness, the observer's description is frequently the only available source of information for physicians (16). Subtle semiologies are often not recognized and therefore remain unreported. Witnesses of seizures may use misleading descriptions of what they saw (17–19). And in palliative care patient's symptoms may often appear less "textbook-like" than in healthier patients. Therefore, every attempt should be made to get as close as possible to the actual semiology of the event.

Abbreviations: ES, epileptic seizure; NEE, non-epileptic event; AED, Antiepileptic drugs; NCSE, non-convulsive status epilepticus; EEG, Electroencephalography; CT, Computed tomography; CK, Creatine Kinase; SE, status epilepticus; GTCS, generalized tonic clonic seizure; QoL, Quality of life; ICU, intensive care unit; SQ, subcutaneous; IV, intravenous; IM, intramuscular; LEV, levetiracetam; LTG, lamotrgin; BRV, brivaracetam; PB, phenobarbital; VPA, valproic acid; LCM, lacosamide; TPM, topiramate; CBZ, carbamazepine; NG, nasogastric; PEG, percutaneous endoscopic gastrostomy.

Beniczky et al. reported that accuracy in diagnosis is higher when resulting from a dialogue between physician and patients or witnesses, respectively, compared to when symptoms are only reported (20). Recording characteristic episodes by smartphone videos is a valuable aid, too. To document the level of consciousness patients should be addressed verbally in the video sequence as recommended for video-EEG monitoring (21).

Technical Examination

Ideally, in palliative patients the diagnosis will be made at the patient's place of care without hospital admission. Yet, in some instances electroencephalography (EEG) may be required to make the correct diagnosis. In particular the diagnosis of NCSE is facilitated by EEG (22–24). EEG patterns of NCSE can be highly variable and sometimes difficult to distinguish from encephalopathy, and clinically suspected NCSE without typical EEG pattern are common (25). Sometimes only the combination of EEG and time limited treatment trial (see below) clarifies the situation. Since NCSE can fluctuate prolonged EEG recording can be necessary (26).

The diagnostic value of short term (routine) EEG in palliative care is difficult to rate, because EEG in elderly patients (and probably in palliative patients, too) rarely shows normal findings, instead focal slowing with or without epileptic discharges is frequent (27). Absence of epileptic discharges, on the other hand, does not exclude epilepsy.

If EEG shows clear epileptiform discharges, the risk for seizure recurrence is considerably higher and the diagnosis of epilepsy might be made after only one seizure [practical definition of epilepsy; (28)]. However, EEG readers should be aware that the combination of a NEE and an overinterpreted EEG (e.g., mistaking sleep signs as epileptiform discharges) may lead to a misdiagnosis and avoidable use of AED. Therefore, before application of EEG the clinical assessment of the event in question is of paramount importance.

MRI is the most sensitive imaging method regarding epileptogenic lesions (29). In palliative patients with new-onset seizures, imaging could in fact reveal brain metastases, meningeosis, brain tumor progression, or stroke or verify metastases of already diagnosed systemic cancer (10). Yet, in patients in palliative setting MRI only needs to be performed if recognition of brain pathology had therapeutic consequences. Computed tomography (CT) may be less sensitive for the above pathologies, but will reveal most of the relevant reasons, like gross tumors or brain edema, and is much less time consuming and less of a burden for the patients. Therefore it might be more adequate in these patients.

Laboratory testing has some relevance in the differential diagnosis of ES and NEE. The focus is, however, more on detecting conditions that mimic ES such as dysglycaemia, electrolyte imbalance, hyperammonemia, anemia rather than on verifying epileptic seizures. Postictal creatine kinase (CK) elevation in serum is helpful only after generalized tonic clonic seizures (GTCS), but in palliative patients the reliability of CK elevation after GTCS is unknown due to often reduced muscle mass. CK in general can be substantially lower in the elderly (30).

Serum prolactin measurement has no use in the palliative care setting.

Measuring AED blood levels is useful in cases when drug intoxication is part of the differential diagnosis [e.g., valproic acid (VPA) intoxication vs. NCSE], but this is rare and regular blood sampling should be avoided in the palliative setting.

In case of doubt concerning semiology based differential diagnosis and the application of technical examinations it might be helpful to get the opinion of an epileptologist though undoubtedly, in some cases a precise diagnosis might remain impossible.

Antiepileptic Therapy

Seizures interfering with Quality of life (QoL) should be treated, though anticonvulsive treatment *per se* should not impair QoL. We propose the following principles to guide anticonvulsive treatment in epilepsy patients in the palliative care setting:

Respecting Patient Resources and Wishes

Brom et al. found 93% of the patients in the palliative setting prefer to share responsibility with their physician in clinical decision making (31). Because cognitive problems may hamper communication and thus shared decision-making as brain diseases progress, advanced planning is crucial (15).

Target Levels of QoL

Treatment regimes should be chosen to protect or improve activities of everyday life that are important to the individual patient (e.g., not accepting daytime sleepiness for complete seizure freedom).

Considering the Current and Future Requirements of Therapy

Avoiding interactions with medications used to control other symptoms (e.g., steroids, palliative chemotherapy) (10) and between AED themselves.

Ensuring Practicality

Choosing application forms easily applicable by the patients themselves, family and caregivers. Since disease progress and/or symptom fluctuations can make swallowing of tablets or capsules difficult temporarily or permanently, treatment plans should enable flexibility in this respect to avoid acute withdrawals.

The threshold for seizure medication cessation in the end of life-setting should vary according to the kind of pre-existing epilepsy (low threshold for single post-stroke seizure a year ago vs. high threshold for long-standing structural epilepsy.) However, this is a highly individual decision in all cases, even if comprehensive medical records are available and may be approached using a shared decision making process involving the patient and caregivers.

Acute Management of Seizures and Convulsive Status Epilepticus

As most epileptic seizures are self-terminating, there is no need to apply acute anticonvulsive treatment during or after every seizure. This accounts for a first in lifetime seizure in palliative patients, too. The rationale behind this is that, in addition to postictally impaired consciousness and a potential acute seizure cause, AED, in particular benzodiazepines, may impair consciousness—sometimes for days. Acute administration of AED in palliative patients should thus be restricted to status epilepticus (SE) or series of seizures.

While the current definition of status epilepticus applies to palliative epilepsy patients (32), not all treatment recommendations can be transferred.

Patients should be acutely treated when a generalized seizure lasts longer than 5 min (so-called continuous seizure activity, or early SE) or two or more seizures occur without regaining pre-ictal level of consciousness in between events (32, 33). Choice of treatment of SE will depend on the patient′s location: hospital, hospice, or home care.

In either setting, the first step of treatment (0–10 min) is administration of benzodiazepines. Due to its pharmacokinetic characteristics (e.g., long antiepileptic effect conditional on slow redistribution in the body fat), lorazepam is often preferred as initial treatment of SE (33). Alternatively, midazolam has been proven equally effective (34).

Formal recommendations for starting doses in a palliative situation do not exist, but application of lower doses of benzodiazepines, if necessary repeated, may be preferable over the initial application of the maximum recommended dose. Future research should address if in the specific setting of palliative patients, the initial application of non-sedating, easily applicable fast acting AED such as levetiracetam (LEV) or brivaracetam (BRV) may prove advantageous.

Hospital Setting

Intravenous status therapy and even intensive care treatment can be reasonable acknowledging that early beginning of treatment increases the chance of seizure termination (35). Therefore, first steps of in-hospital treatment of SE in the palliative situation can be adopted from the general treatment recommendations for SE (**Table 1**). In established SE (10–60 min), intravenous drugs [e.g., phenytoin/fosphenytoin, valproate (VPA), LEV, phenobarbital (PB)] are most commonly used, although there is no class I evidence for choosing one over the other (33). Among those VPA, LEV, and lastly additional lacosamide (LCM) seem to be effective and safe alternatives (33).

The idea of palliative care is to balance noninvasive treatment and avoiding delays in optimal (but invasive) therapies (e.g., deduced from ICU treatment of patients with cancer: "unlimited ICU support for a limited time period"), respecting the patient's wishes (36). Knowing refractory and super-refractory SE are treated with anesthetics with a markedly lower success rate and a high morbidity and mortality (33, 37), it seems difficult to apply these principles to the palliative care setting. In some cases "palliative sedation" using benzodiazepines (or alternatively propofol) might alleviate symptoms even if epileptic activity persists.

Hospice/Home Care Setting

In SE in children, intranasal or buccal midazolam or lorazepam or IM- midazolam have been found to be at least equally effective as the IV or rectal form (34, 38–43). Although data in adults are

limited (34, 44) the differences among various non-intravenous routes are likely to be small. The non-IV application forms of benzodiazepines can be administered by family members or carers and are thus a valuable tool in the therapy of SE in a hospice or home care setting where the IV-route is typically not available (**Table 1**) (45).

In patients with recurrent episodes of prolonged seizures or SE, benzodiazepines should be administered as early as possible to shorten the seizure.

Addressing practical issues, lorazepam has been shown to be stable at room temperature (20–25°C) for at least 0.8 months (46). Although it showed some chemical degradation after 60 days, the concentration of the active metabolite remained at acceptable levels. Midazolam was found to be stable for 60 days (47). Therefor these medications can be kept at the patient's bedside to allow fast administration if necessary. This is of particular relevance as seizure frequency increases in the last weeks of life (48).

TABLE 1 | Administration routes and characteristics of antiepileptic drugs relevant for palliative care.

AED	Daily Dose	Special consideration for palliative care	IV	Liquid solution	Suspension	Tablet
Brivaracetam (BRV)	50–200 mg	Mild CYP3A4 metabolism. Probably no clinical relevant interactions	+	+	–	+
Carbamazepine (CBZ)	600–2000 mg	Dizziness, nausea, ataxia Effective for neuralgic pain (200-400 mg/d), decreases: VPA, TPM, LTG, neuroleptics, antimycotic agents, antidepressant drugs, steroid level Increases: diazepam level and effective CBZ- Metabolite Is decreased by: PHT Is increased by: Theophyllin, Cisplatin	–	+	+	+
Eslicarbazepine (ESL)	800–1600 mg (max. 1200 mg when combined with other AED)	Dizziness, gait disturbance, ataxia, hyponatremia Is decreased by: PHT, CBZ Increases: PHT	–	–	–	+
Gabapentin (GBP)	900–3000 mg	Sedation (especially in combination with opioids), therapy of neuropathic pain (900 mg/d) Is increased by: morphine	–	+	+	+
Lacosamide (LCM)	100–600 mg (max. 400 mg when combined with other AEDs)	Dizziness No relevant interactions	+	+	+	+
Lamotrigine (LTG)	100–300 mg	Tremor, sedation (rare), sleep disturbance„ mood stabilizing effect. Very slow titration necessary Is decreased by: CBZ, PHT Is increased by: VPA	–	–	+	+
Levetiracetam (LEV)	1000–3000 mg (−4000 mg off-label) mg	Sedation (rare), psychiatric side effects No relevant interactions	+	+	+	+
Oxcarbazepine (OXC)	900–2400 mg	Dizziness, nausea, ataxia (less often when the slow release form is used), hyponatraemia	–	+	+	+
Perampanel (PER)	4–12 mg	Dizziness, somnolence Is decreased by: CBZ, OXC, TPM Decreases: CBZ, OXC, VPA	–	–	–	+
Phenytoin (PHT)	200–350 mg	Dizziness, allergy. Potentially complicated titration Decreases: steroid level	+	–	+	+
Pregabalin (PGB)	150–600 mg	Sedation. No relevant interactions Anxiolytic effect.	–	+	+	+
Topiramate (TPM)	50–200 mg	Sedation, fatigue, lack of appetite, weight loss, paraesthesia, speech disturbances No relevant interactions	–	–	+	+
Valproate (VPA)	1200–2400 mg	Tremor, encephalopathy, mood stabilizing effect. Enzyme inhibition (leading e.g., to increased toxicity of chemotherapy).	+	+	+	+

Non Convulsive Status Epilepticus (NCSE)

Samala et al. noted that in terminally ill patients, successful treatment of NCSE can restore the ability to communicate, facilitate goals of care discussion and positively impact QoL (49). Lorenzl et al. shared this opinion in lining out that the most notable effect of treating NCSE was regaining the ability to communicate (50). Because NCSE is potentially responsive to therapy, treatment should be considered in all patients and started as soon as (50) possible.

As outlined above, diagnosing NCSE or SE in the palliative care setting can be challenging. Drislane et al proposed to include the response to anticonvulsant as a diagnostic criteria, in addition to the semiological and EEG features discussed above (51). Therefore, probatory therapy seems to be a reasonable approach in the palliative setting, given that a prolonged confusional state following a GTCS might in fact be due to ongoing NCSE and a history of epilepsy is a risk factor for this condition as well.

The initial treatment of NCSE does not differ from the approach outlined for GCSE outlined above. The first step should be the administration of a benzodiazepine followed by LEV, LCM, or VPA, if necessary. In a palliative situation, these drugs may be administered orally, sublingually, via an NG or PEG tube, or subcutaneously [(50), **Table 2**].

Application Forms of AEDs

Dysphagia is a common symptom in neurological and oncological patients (15, 52). Independent of the underlying disease, swallowing might be affected by a reduced level of alertness, inattention, and muscular weakness. Therefore, it is helpful if an AED can be administered as an oral liquid, subcutaneously, or rectally.

Subcutaneous AED Application

Subcutaneous (SQ) administration of LEV has been shown to be safe and effective as a continuous infusion via a syringe driver (250–4000 mg/d, dosage equal to prior oral route), or intermittent bolus diluted in 100 ml 0.9% sodium chloride every 12 h over 30 min. In 20 prospectively examined patients, 7 showed seizure activity under SQ administration, leading to an increase of the SQ dose or addition of a benzodiazepine (53). Rémi et al. identified 20 patients treated with SQ LEV without adverse reaction at the infusion. In 16 patients (80%), no further seizures were noticed or SE was terminated (54).

Moreover, Rémi et al. described one patient receiving SQ LCM. According to the former oral dosage, 200 mg of the undiluted LCM solution over 10 min SQ twice a day was administered and well tolerated. Serum levels were in the recommended range and their course comparable to oral administration (55).

Rectal AED Application

The rational of rectal antiepileptic administration is avoidance of hepatic first pass effect due to rectal venous drain. Anderson et al. suggest rectal administration to be feasible for short term administration of carbamazepine (CBZ), lamotrigine (LTG), LEV, PB, topiramate (TPM), and VPA (56).

Birnbaum et al. found compressed LTG to be rectally absorbed and well tolerated in 12 healthy adults (57). Chewable dispersible

TABLE 2 | Proposal for (convulsive) SE treatment in palliative care [partially taken from (33)].

		Hospital	Hospice/home care	Outcome
Stage 1 5–10 minutes	Early phase Premonitory SE, Impending SE	Lorazepam IV 0.05 mg/kg max. 2 mg/minute, if necessary repeat after 5 minutes	Midazolam buccal or intranasal 0.2 mg/kg (5–10 mg) or Lorazepam buccal or intranasal 0.05 mg/kg or 10 mg IM-midazolam Repeat if necessary	better
Stage 2 10–30 minutes	Established SE	Levetiracetam 30-60 mg/kg IV max. 500 mg/minute, if necessary repeat after 10 minutes and/or additional lacosamide 5 mg/kg IV in 15 minutes *Alternative stage 2:* Valproate 20-30 mg/kg IV max. 10 mg/kg/minute, if necessary repeat after 10 minutes	*In absence of IV route:* 1000–2000 mg levetiracetam in 100 ml 0.9% sodium chloride over 30 minutes SQ if necessary additional: 200 mg lacosamide over 20 minutes SQ Repeat if necessary, or repeat benzodiazepine administration	
Stage 3 30–60 minutes	Refractory SE: SE, that continues despite stage I/II treatment, subtle SE, stuporous SE	midazolam bolus 0.2 mg/kg IV, continuously 0.1–0.5 mg/kg/h or propofol bolus 2 mg/kg IV, continuously 4–10 mg/kg/h	consider palliative sedation	
Stage 4 >24 h	Super refractory SE: SE, that continues despite treatment with anesthetics >24 h	consider palliative sedation	consider palliative sedation	worse

LTG was tested likewise in 12 healthy adults but was not absorbed to the same extent compared to oral administration (58).

Conway et al. showed TPM to be absorbed to a similar extent as the oral dosage when administered rectally in 10 healthy adults (59).

Stockis et al. monitored pharmacokinetic data during targeted delivery of LEV to the colon (60). Systemic bioavailability after application in the ascending colon was comparable to oral administration. This suggests that LEV may be administered rectally (56).

VPA has been shown to be highly absorbed (80%) after rectal administration in healthy adults. Its peak serum concentration was ∼30% lower and achieved 2.1 h later when compared to oral intake (3.1 vs. 1 h) (61). Multiple studies and case series demonstrate its clinical practicability and effectiveness (61–65).

It is important to note that many of these recommendations, although widely used, are off-label, and patients and caregivers should be informed accordingly.

CONCLUSION

ES are a relevant clinical problem in a palliative care setting that may affect the patient's QoL. They thus require adequate supportive care and treatment. Timely recognition and adequate out of hospital management may prevent unnecessary hospital admissions for uncontrolled seizures (66). In line with the general philosophy of palliative care, seizures should be addressed like other symptoms that may cause discomfort or reduce QoL. The patient's wishes and needs should shape the anticonvulsant therapy as early as possible. Careful use of alternative AED administration routes can lead to a very individualized and practical therapy regime even in the last days of life. Seizure recognition, acute management, drug administration, and possible side effects are all areas where caregivers might benefit from education and training (3, 15).

What outstanding questions should be addressed by future research in this area? Randomized or controlled studies will be difficult to conduct in palliative care settings. Future research to improve seizure management should include pharmacokinetic studies on alternative administration routes combined with respective case series; descriptive studies on seizure semiology in the terminally ill; and studies on service provision regarding transdisciplinary communication.

AUTHOR CONTRIBUTIONS

WG wrote the first draft of the manuscript. All authors (WG, SP, TW, US, and JW) revised the manuscript critically and approved the final version.

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CASE REPORT
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Improvement of Restless Legs Syndrome Under Treatment of Cancer Pain With Morphine and Fentanyl

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Restless-Legs-Syndrome (RLS), also known as Willis-Ekbom disease, is a sleep- and rest related disorder characterized by the unpleasant urge to move the legs. Pharmacological therapy is mainly based on dopamine-agonists and delta-2-alpha calcium channel ligands. Also, randomized-controlled-trials (RCTs) reported effectiveness of oral oxycodone (in combination with naloxone), and intrathecal opioids have also been administered for this indication. In the case reported here, a patient with advanced pancreatic cancer was referred to an acute palliative care unit for the treatment of cancer-related pain. Yet, in thorough exploration of her symptom burden, the patient reported that she felt her quality of life had been predominantly limited by symptoms other than cancer pain. Her medical history and neurological examination revealed that these symptoms were most obviously caused by severe RLS. In the years before, pharmacological therapies with dopamine-agonists and delta-2-alpha calcium channel ligands were initiated, but failed to relieve the RLS. In the palliative care ward, intravenous morphine was successfully titrated to treat her cancer pain. Concurrently, the patient also experienced almost complete relief from her RLS-symptoms and an increase in quality of life. The amelioration of her RLS-symptoms continued after morphine therapy was switched from intravenous to oral administration. Even after the patient was dismissed to home care and opioid rotation to transdermal fentanyl, symptom control of RLS remained excellent. To our knowledge, this is the first report of successfully treating RLS with intravenous and oral morphine. Since morphine is more easily available worldwide and the cost of morphine therapy is substantially lower compared to oxycodone/naloxone, comparisons to morphine may be an intriguing option for future RCTs.

Keywords: restless-legs-syndrome, Willis-Ekbom disease, treatment, morphine, oxycodone, transdermal fentanyl

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INTRODUCTION

Restless-Legs-Syndrome (RLS), also known as Willis-Ekbom disease, is a sleep- and rest related disorder characterized by unpleasant sensations in the legs and the urge to move the legs, which may reduce the symptoms (1). RLS is a common disease with a reported prevalence of 5–10% in European and North American adults, with 2–3% experiencing moderate-to-severe symptoms (2). Women are affected twice as frequently as men (2).

If non-pharmacological interventions fail to relieve symptom burden, common pharmacological interventions include dopamine-agonists or an alpha-2-delta calcium channel ligand as first-line therapy (3). Unfortunately, after initial amelioration of symptoms many patients (50–70% over a period of 10 years) treated with dopamine-agonists experience worsened symptoms under ongoing medication, a process called augmentation (4). Therefore, other therapy options are needed to help these patients.

As a second-line approach, opioids have been used in clinical practice for years, but only a few placebo-controlled randomized trials have been conducted to prove their effectiveness. A recent phase III trial showed reduction of RLS-symptoms when patients were treated with oxycodone/naloxone (5), but there are some concerns of attrition bias due to high drop-out rates (6). An older study investigated the monotherapy of oxycodone without naloxone showing similar beneficial effects on symptom burden (7).

Several retrospective studies implicate other opioids -for example methadone (4, 8) and tramadol (9)- to reduce RLS-symptoms. Additionally, intrathecal morphine was administered successfully to treat RLS-patients (10–12). However, to our knowledge so far there are no published reports on orally or intravenously administered morphine in the treatment of RLS.

CASE REPORT

A 75-year-old woman was admitted to our palliative ward with abdominal pain, nausea, and vomiting. The patient had been diagnosed with metastatic pancreas carcinoma with one singular liver metastasis 18 months before. She had received first- and second-line chemotherapy regimens; the latter had been stopped due to severe side effects. Two months prior to admission, when MRI scans revealed progressive disease, and together with her medical oncologist, the patient decided against continuing chemotherapy. Instead, symptom oriented, palliative care was chosen without any further antineoplastic therapy.

The patient had been suffering from RLS for 12 years already, with moderate to strong symptoms [Numerical Rating Scale (NRS): 6-10/10] mostly in the evening and at night. The family history regarding RLS was not investigated. She reported symptom alleviation by long walks (up to several hours long), and rigorous tennis playing, both of which she could no longer accomplish because of the progressive cancer related fatigue. Twelve years ago, her neurologist started treating RLS with levodpa, but after initial improvements in symptom control, symptoms began worsening again due to augmentation. Five years later, the patient was started on a transdermal application of the dopamine-agonist rotigotine (4 mg/d), but this treatment could not reduce RLS-symptoms satisfactorily. The patient reported that a trial of pregabalin was discontinued because of side effects (dizziness) and oxycodone was stopped because of nausea and vomiting. Thereafter transdermal rotigotine (4 mg/d) was continued with little effect until admission to our palliative care unit.

To assess RLS-symptom burden and pain we used the 11-NRS, an established tool to assess pain and commonly used in the palliative care setting, where 0 = no pain and 10 = worst possible pain (13). We used the NRS to semi-quantify RLS-symptom intensity, because it is well-known by staff while other assessment tools specifically designed for RLS are not established. When using the NRS for the assessment of RLS-symptoms, we asked the patient: how severe are your RLS-symptoms right now (0 = no RLS-symptoms, 10 = worst possible RLS-symptoms)?

Upon initial admission, she reported abdominal cramps (NRS 8/10). Her temperature and blood pressure were normal with a heart rate of 100 bpm. The abdomen was distended, but soft with normal bowel sounds. The patient reported ubiquitous abdominal tenderness. The rest of the physical examination was normal. Initial laboratory testing included elevated gamma-glutamyl transferase at 194 U/l (reference range, <40 U/L), lactate dehydrogenase at 364 U/L (reference range, 135–214 U/l) and C-reactive protein at 42 mg/l (reference range, <5 mg/l). Bilirubin and lipase levels were normal. The peripheral-blood count was normal. An abdominal ultrasound dismissed possible bowel obstruction, hepatic cholestasis, and gall bladder abnormalities, but revealed a significant amount of ascites, which is why percutaneous ascites drainage was performed (3.5l). Cell counts in the ascites fluid revealed elevated neutrophils/μl indicating spontaneous bacterial peritonitis. Calculated antibiotic treatment was started with tazobactam/piperacillin.

The patient also received intravenous fluids, analgesics (oral metamizole) and antiemetics (dimenhydrinate, ondansetrone). At day 5 after admission the abdominal pain exacerbated. Symptomatic analgesia with intravenous morphine (20 mg/d) was initiated. Pain management was excellent after 1 day with a NRS of 0-3/10. Unintendedly, the patient also reported almost complete symptom relief regarding her RLS (**Figure 1**), which had not occurred for her in years. After nausea and vomiting had resided, analgesics, including morphine were given orally. Still, pain management and the symptom control of RLS-symptoms remained steady. According to the patient's wish, she was discharged 13 days after admission. Three days later, she was re-admitted with increasing abdominal pain. Without our knowledge, her general practitioner had rotated morphine to transdermal fentanyl (25 μg/h). While pain control was insufficient, RLS-symptoms remained adequately controlled with this opioid therapy. After re-admission we discontinued transdermal fentanyl and re-initiated intravenous morphine therapy, which once again achieved excellent pain relief. Paracentesis revealed an increasing neutrophil count in the ascites. Considering her incurable, advancing and metastatic disease and good symptom control under analgesia, the patient declined antibiotic treatment and died a little more than 1 week later.

DISCUSSION

We report a case of a patient with advanced pancreatic cancer, treated with intravenous and oral morphine for cancer

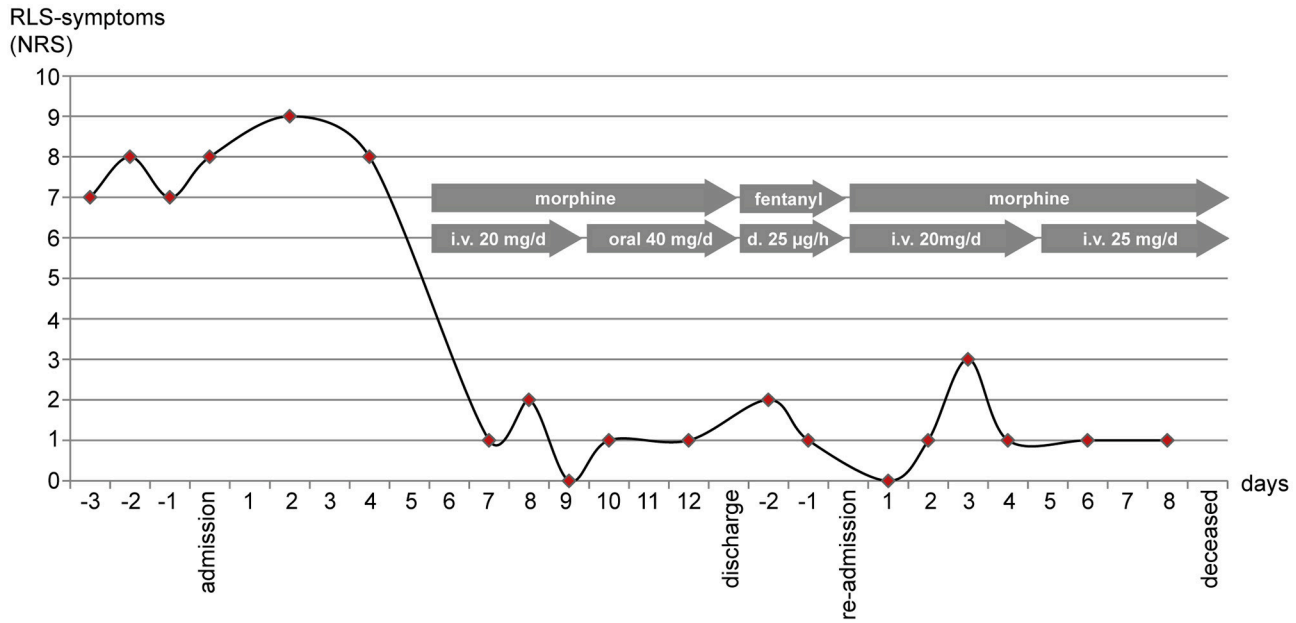

FIGURE 1 | RLS-symptoms (the urge to move the legs) were measured using the numerating rating scale (NRS) once per day in the evening. After initiation of intravenous (i.v.) morphine (day 5) NRS-scores dropped. Scores remained low after switching morphine to oral administration, after rotation to transdermal (d.) fentanyl, and after continuing intravenous morphine when the patient was re-admitted to the hospital.

pain, who experienced markedly reduced symptom burden of her RLS-syndrome. While there are several publications reporting successful use of intrathecal morphine (10–12) and oral methadone and tramadol (4, 8, 9) in RLS, to our knowledge this is the first report showing amelioration of RLS-symptoms by morphine administered intravenously and orally and by transdermal fentanyl.

A systematic review by Trenkwalder et al. on association of RLS with certain diseases could not identify increased prevalence in malignant disease, although MEIS1, the RLS gene most strongly associated with RLS risk in GWAS studies, is a transcription factor with implications in leukemia and neuroblastoma (14). To our knowledge, no association with malignant disease has been reported so far. As in our patient, RLS symptoms occurred years before diagnosis of the malignant disease and no other typically RLS-associated condition was present. We therefore assume that she was suffering from primary (idiopathic) RLS. Still, a neoplastic origin from so far unidentified anti-neuronal antibodies (secondary RLS) cannot be excluded. The late onset of RLS in our patient might favor secondary disease, which is seen later in life than idiopathic disease (15).

The pathophysiology of RLS is poorly understood. Three main pathways seem to be involved: iron metabolism, dopaminergic dysfunction, and the central opioid system (16). Why are opioids effective in treatment of RLS? Cell culture experiments in iron-deficient conditions show that dopaminergic cells from the substantia nigra are protected from apoptosis by the delta-opioid peptide enkephalin (17). Furthermore, post mortem analyses of human brains showed reduced antibody staining against beta-endorphine and met-enkphalin in RLS patients when compared to controls, possibly involving the mu-opioid receptor subtype in the pathogenesis of RLS (18). At a morphological level, dendritic spines, which are small membranous protrusions at the dendrites proposed to be the cellular basis for learning and memory, may be involved in the pathogenesis of RLS (19, 20). Activation of ubiquitously clustered mu-opioid-receptors in excitatory synapses by morphine invoke morphological changes in dendritic spines and decreased expression of glutamate receptors (21). This may as well-contribute to the beneficial effect of opioids on RLS symptoms.

Our patient had previously been treated with the dopamine agonist rotigotine and levodopa. According to the practice guidelines, second line therapy should include delta-2-alpha calcium channel ligands such as gabapentin (level A recommendation) or pregabalin (level B) (22, 23). In our patient, pregabalin had caused dizziness and was discontinued. Some years before, her neurologist had treated our patient with oxycodone/naloxone (2 × 5 mg/2.5 mg/d; daily oral morphine equivalent dose of 15–20 mg), which had also not led to improvement of the RLS symptoms. Notably, the oxycodone/naloxone dose had not been increased stepwise, as it is suggested by the phase III trial (5). During her stay on our palliative care unit our patient was titrated up to 20 mg intravenous morphine daily dose (daily oral morphine equivalence of 40–60 mg), which is the equivalent dose of the fentanyl dose that relieved her RLS symptoms but around 200–300% the daily morphine equivalent when oxycodone/naloxone was tried unsuccessfully. This could explain why our patient

had not experienced any benefits from oxycodone/naloxone concerning the RLS symptoms. We assume that opioid equivalents known from treatment of pain are also applicable to the treatment of RLS. This is not necessarily the case, because there might be other mechanisms involved during opioid-action in RLS. For example, several downstream targets of the mu-receptor are known (24). However, it is unknown, exactly which downstream targets are involved in mediation of mu-receptor activation in the treatment of RLS. These targets could be different in pain and RLS causing different equivalence dosages. In Europe, oxycodone/naloxone (Targin®) is approved for treatment of RLS after failure of dopaminergic therapies. No prospective RCTs have investigated the effectiveness of other opioids. Our patient experienced markedly reduced RLS-symptoms after initiation of analgesia with morphine, regardless of application route (intravenous or oral), and transdermal fentanyl. Interestingly, RLS symptom burden remained low after the patient's general practitioner switched oral morphine to transdermal fentanyl therapy. This indicates that in addition to oxycodone, morphine and other opioids may have beneficial effects on RLS-symptoms. RCTs with comparison of other strong opioids are warranted to investigate this intriguing option: morphine is more readily available worldwide and therapy costs of morphine are substantially lower compared to oxycodone/naloxone.

A concern in the long-term use of opioids is addiction. While opioids are well-established in treatment of cancer-pain, in chronic pain their use is controversial and should only be considered under certain precautions (25). There is no data investigating the issue of addiction when opioids are used for RLS. Therefore, opioid use in RLS-patients should be monitored closely to reduce potential abuse. Possible reversible causes of RLS-refractoriness (such as low iron stores) and other therapeutic options (such as pharmacological combination therapy, non-pharmacologic and complementary approaches) should be considered before prescribing opioids (26, 27). Although opioid use disorder could be a relevant problem in RLS-patients, we know that long-term use of opioids in "low" dosages (<100 mg/d morphine or equivalent) has significantly lower risks than the use of high dosages (26, 28). Additionally, a recent study found increased rates of invasive pneumococcal pneumonia in patients receiving opioid therapy (29). In the cohort study of Wiese et al. the authors hypothesize that this finding may be caused by the immunosuppressant effects of opioids, but confounders and other risks of bias cannot be excluded. Nevertheless, these findings and the debate about the current "opioid epidemic" emphasize the need for thorough risk-benefit appraisal for each individual patient before initiating opioid therapy for RLS (30).

CONCLUDING REMARKS

A patient with advanced pancreatic cancer experienced pronounced and sustained amelioration of RLS-symptoms by intravenous and oral morphine therapy and due to transdermal fentanyl therapy. In the literature no case reports or studies of oral or intravenous morphine or transdermal fentanyl against RLS could be identified. As morphine is more readily available worldwide and therapy costs of morphine are substantially lower compared to oxycodone/naloxone, randomized clinical trials are warranted to investigate the role of morphine in the treatment of RLS. Yet, in the non-palliative care population, thorough individual risk-benefit appraisal should be conducted for every patient before initiating opioid therapy due to safety issues concerning misuse (addiction) and potential immunosuppression.

ETHICS STATEMENT

The patient provided verbal and written consent for use of the patient's personal health information in this case report.

AUTHOR CONTRIBUTIONS

CB and JG wrote the manuscript. CB prepared the figure, and GB and KJ edited the final manuscript.

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