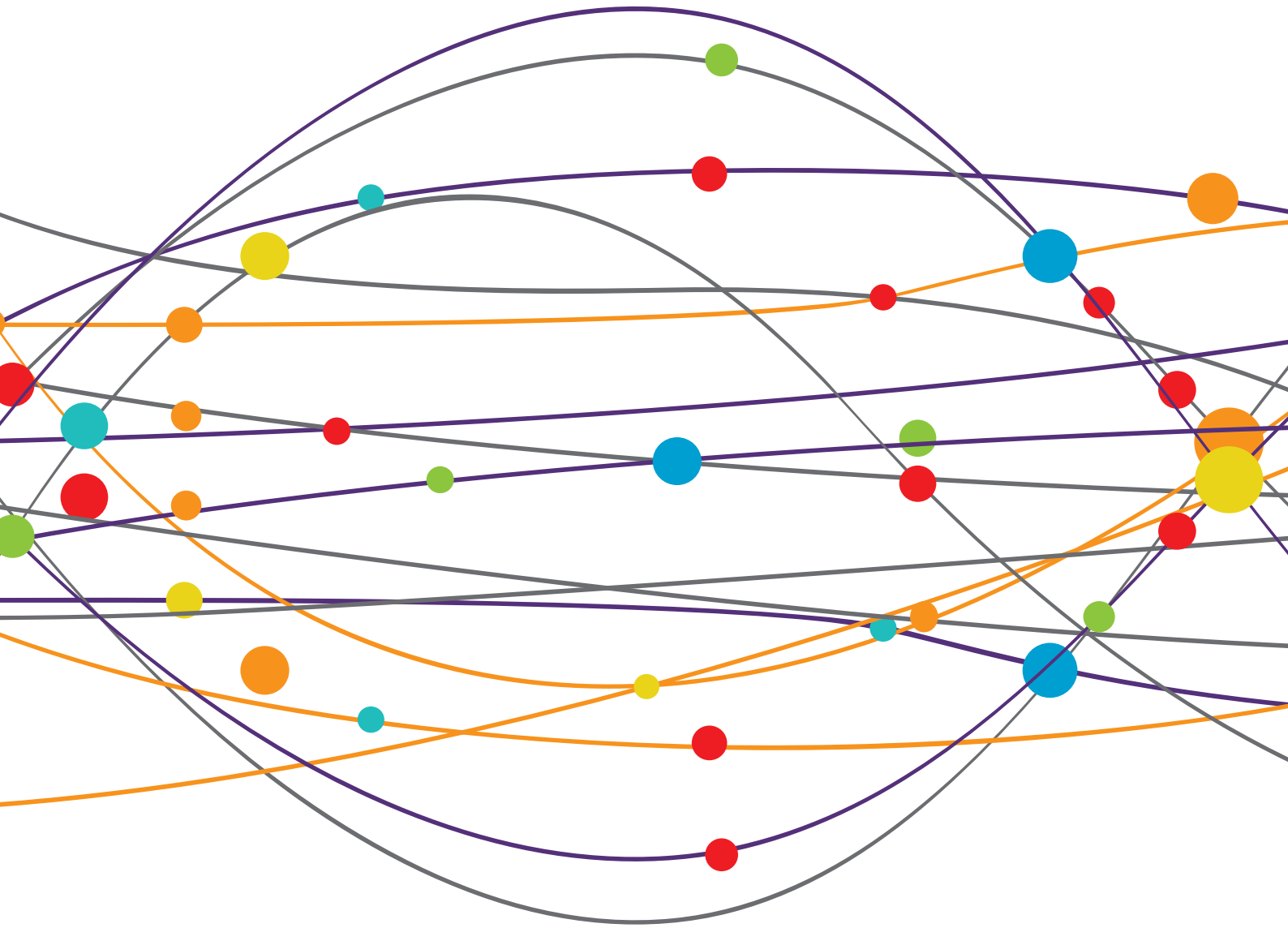
PALLIATIVE CARE IN NEUROLOGY, VOLUME II

EDITED BY: Raymond Voltz, Marianne De Visser and David John Oliver
PUBLISHED IN: Frontiers in Neurology



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ISSN 1664-8714
ISBN 978-2-88974-660-6
DOI 10.3389/978-2-88974-660-6

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PALLIATIVE CARE IN NEUROLOGY, VOLUME II

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Citation: Voltz, R., De Visser, M., Oliver, D. J., eds. (2022). Palliative Care in Neurology, Volume II. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-88974-660-6

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frontiers in Neurology

EDITORIAL
published: 16 February 2022
doi: 10.3389/fneur.2022.840110

Editorial: Palliative Care in Neurology, Volume II

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Keywords: palliative care, neurology, amyotrophic lateral sclerosis (ALS), Parkinson's disease, stroke, glioma, communication, assisted dying

Editorial on the Research Topic

Palliative Care in Neurology, Volume II

Palliative care for people with neurological disease has become more accepted over the years, and there is increasing literature on this area of care. The European Academy of Neurology and the European Association for Palliative Care collaborate closely together to ensure there is involvement in conferences and they developed a Consensus Statement on palliative care for people with progressive neurological disease (1). In 2020, the International Neuro-palliative Care Society started to encourage development of care across the world and in 2021 a truly international meeting was held online (2).

In 2019, Palliative care in Neurology (3) was published, and this has been widely read and referenced. A further Research Topic was opened in 2020 and a wide variety of papers were submitted, and subsequently published. This, it is hoped, will further establish the role of palliative care for neurological patients and encourage further research into this area.

There has been increasing awareness of the palliative care needs of people with Parkinson's disease (PD). Poonja et al. in a retrospective chart review show that people with PD do show variable trajectories of motor function, as measured by the Unified Parkinson's Disease Rating Scale. However, as they approached death, there was a steep increase in the scores, regardless of their previous trajectory. Older patients, over 65 years old, were also found to have shorter prognoses. These results may help in allowing clinicians to be more aware of the changes that occur over time, particularly in considering if the person is declining more quickly and approaching end of life.

Across the world stroke is a major cause of death but the role of palliative care has often been unclear. Reisinger et al. looked at the care of stroke patients, interviewing family members and looking at decision making by the professional team. Palliative care was shown to have a major role in the support of patients and families, with specialist palliative care being integrated early into care planning. Families benefitted greatly from increased communication and support. The collaboration of stroke teams with specialist palliative care services helped in the difficult consideration and discussion of treatment at the end of life, especially if there were ethical or legal issues.

Patients with glioma often do receive palliative care, although as new treatments become available the prognosis has increased and there may be the need for complex decision making about the benefits and risks of treatment (4). Guariglia et al. evaluated the coping styles of patients with

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Specialty section:
This article was submitted to Neurocritical and Neurohospitalist Care, a section of the journal Frontiers in Neurology

Received: *20 December 2021*
Accepted: *11 January 2022*
Published: *16 February 2022*

Citation:
Oliver D, de Visser M and Voltz R (2022) Editorial: Palliative Care in Neurology, Volume II. Front. Neurol. 13:840110. doi: 10.3389/fneur.2022.840110

malignant glioma and their family caregivers. Initially both groups showed a fighting spirit style but at recurrence they were more likely to be fatalistic. Anxiety seemed to correlate with fatalism whereas depression was associated with fighting spirit. The changes over time are important for professional teams, as that they are aware of the need for regular assessment and consideration of the adaptions and defences of patients and caregivers.

Although palliative care has been provided to people with amyotrophic lateral sclerosis [ALS, also known as motor neurone disease (MND)] for many decades and is established within many national and international guidelines (5, 6), the challenges of people with progressive bulbar palsy (PBP), who present primarily with dysarthria and/or dysphagia, are less well-known. Bublitz et al. present a small case series of patients with PBP and show that there is a high symptom burden due to issues with oral secretions and that pulmonary infection is very common at the end of life. This shows that it is very important that these issues are discussed early in the disease progression, in advance care planning (ACP), and oral secretions are managed as effectively as possible, to enable patients to maintain as good a quality of life as possible.

Patients with acute brain injury may not have been considered for palliative care but Voumard et al. have shown that there are discrepancies between the family member's assessment of patients' goal of care compared to the care that was provided-−33% of patients had the goal of care being for comfort whereas only 11% received this care and many received more aggressive treatment. Thus, many patients may be receiving unwanted aggressive treatment, although this may be justified in the very early stages following the injury when the prognosis is very uncertain. However, at 6 months 25% of families were still unaware of the patient's goals of care, showing that it is important to reassess decision making throughout care. Thus, these ongoing and repeated discussions are an important part of ACP, as part of palliative care.

Palliative care is appropriate throughout disease progression and should be available according to need, rather than diagnosis or prognosis. There is increasing discussion of the use of ACP, where people express their wishes for care at the end of life if they are no longer able to make decisions for themselves. Kurpershoek et al. interviewed people with PD and found that the majority of patients preferred their health care professional to start the discussion of ACP, particularly in the early stage of disease. They did wish to know more about the long-term impacts of PD, although this did vary between patients. Meinders et al. present their protocol of a randomised controlled trial of the PD_Pall intervention—consultation with a trained nurse who both supports ACP and care planning and the use of a Parkinson Support Plan workbook, which encourages people to look at the issue at home and document their wishes. This study will help to elucidate the use of ACP and how health care professionals may facilitate patients with PD to think and plan ahead.

How patients with neurological disease start conversations about the disease with professionals at end of life is an important area of research. Genuis et al. report on a scoping review of communication about end of life with ALS patients, which showed very limited evidence. However, there was evidence that important areas were communication skills, together with disease specific information, such as symptom management and the use of assistive devices, in facilitating these discussions. The review also showed the need for more research so that clear guidelines could be developed.

Assisted dying—euthanasia and physician-assisted suicide—are increasingly discussed and becoming more available across the world. This has been the case particularly in neurological disease, and people with diseases such as ALS are often asking, and receiving, an assisted death in areas where this has been legalised. Nuebling et al. have studied the records within a Swiss Right-to-Die organisation and found that people with PD and atypical parkinsonian disorders were overrepresented in the cases of assisted dying. At the time of application, symptoms were commonly immobility, pain, dysarthria, and dysphagia. Atypical parkinsonian patients had a higher symptom burden and were more likely to have been diagnosed with depression. Although 80% of those diagnosed with depression received antidepressants, other symptoms, such as pain, were less well-managed. As this study showed that assisted dying was sought soon after diagnosis, there is the need to provide support for patients from diagnosis—with psychological support for patients and families.

The aim of care for neurological patients is often to support them, and their families, at home. However, admission to hospital may occur, often in an emergency situation. Willert et al. have undertaken a retrospective review of admissions and have shown that the common reasons for admission are seizures, gait disturbances, disturbance of consciousness, pain, and nutritional problems. Palliative care teams were often involved after admission, but often with delays of over 24 h, and the team approach often identified unrecognised psychosocial issues. This highlights the need for early palliative care involvement so that issues can be identified and screening in the emergency department may allow the wider palliative care issues to be picked up and managed appropriately.

The care of people with neurological illness can be difficult at home, particularly if there are cognitive changes. Vaismoradi et al. have undertaken a systematic review of the literature looking at the management of medication by caregivers of people with cognitive disorders. The review showed the importance of the assessment of the patients' needs, the role of the caregivers, and the collaboration of the wider multidisciplinary care team. To ensure safe management of medication the support of the caregivers by the wider multidisciplinary team is essential.

This collection of papers aims to provide a worldwide view of the role of palliative care for people with neurological disease. This is expanding throughout the world, with increasing awareness of the needs of patients and their families. The

development of services will vary, according to the services and specific aspects of every country, but the role of palliative care early in the disease progression and being provided according to need, whether physical, psychosocial, or spiritual, is becoming accepted. People with neurological disease, together with their families and carers, may encounter many complex issues and palliative care may be appropriate and helpful, allowing an improvement and maintenance of quality of life, enabling them to live as full a life as possible until they die.

AUTHOR CONTRIBUTIONS

DO was the main author with contributions, comments, revision, and final version agreed by all the authors. All authors contributed to the article and approved the submitted version.

ACKNOWLEDGMENTS

We would like to acknowledge all the authors who have submitted papers.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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BRIEF RESEARCH REPORT
published: 15 March 2021
doi: 10.3389/fneur.2021.656599

Assisted Suicide in Parkinsonian Disorders

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Background: Due to the high prevalence of suicidal ideation in Parkinson's Disease (PD) and exploratory data indicating a similar prevalence in atypical Parkinsonian disorders (APD), we sought to determine the frequency of assisted suicide (AS) as well as factors driving these decisions in PD and APD.

Methods: Retrospective chart analysis (2006-2012) at a Swiss Right-to-Die organization. Patients with PD and APD who completed AS were analyzed concerning disease state, symptom burden, medication, and social factors.

Results: We identified 72 patients (PD = 34, PSP = 17, MSA = 17, CBS = 4; 7.2% of all AS cases), originating mainly from Germany (41.7%), Great Britain (29.2%), and the US (8.3%). Predominant symptoms at the time of application were immobility (PD/APD: 91%/97%), helplessness (63%/70%), pain (69%/19%), dysarthria (25%/32%), and dysphagia (19%/59%). APD patients generally showed a higher symptom burden and a higher frequency of diagnosed depression (8.8%/28.9%). While most patients with diagnosed depression received antidepressants (80%), other symptoms such as pain (59%) were treated less consistently. Of note, time from diagnosis to application differed greatly between PD (8.5 ± 6.8 years) and APD (1.5 ± 1.3 years, $p < 0.0001$).

Conclusions: In our analysis, Parkinsonian disorders appeared to be overrepresented as a cause of AS considering the prevalence of these diseases. The observation that assisted suicide is sought early after initial diagnosis in APD implies the need for early comprehensive psychological support of these patients and their relatives.

Keywords: assisted suicide [MeSH], progressive supranuclear palsy, multiple systems atrophy, corticobasal syndrome, Parkinson's disease

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Specialty section:
This article was submitted to Neurocritical and Neurohospitalist Care, a section of the journal Frontiers in Neurology

Received: *21 January 2021*
Accepted: *19 February 2021*
Published: *15 March 2021*

Citation:
Nuebling GS, Butzhammer E and Lorenzl S (2021) Assisted Suicide in Parkinsonian Disorders. Front. Neurol. 12:656599. doi: 10.3389/fneur.2021.656599

INTRODUCTION

Parkinson's disease (PD) and atypical Parkinsonian disorders (APD) such as Progressive Supranuclear Palsy (PSP), Multiple Systems Atrophy (MSA), or Corticobasal Syndrome (CBS) impose an immense burden on patients and caregivers. Given the severely limited life expectancy and rapid symptom progression, these diagnoses may lead to existential crises especially in APD, where treatment options are limited to symptom control and based mostly on retrospective case series and anecdotal evidence (1). While single case reports describing assisted suicide (AS) in PD and APD have been published, little is known about the frequency and circumstances of AS in parkinsonian disorders.

Suicidality in general has been extensively studied in PD, especially in the context of deep brain stimulation (DBS) (2). It was discovered that suicidality may be increased during the first year after DBS surgery (3). In contrast, suicide frequencies in the overall PD population appeared not to differ greatly from the general population, although the results of various studies are inconsistent (4–6). Conversely, it was demonstrated that suicidal ideation is highly prevalent in PD (∼30%) (6, 7). In addition, a high frequency of depression was determined in PD patients with a reported prevalence of up to 58% (8, 9).

In contrast, suicidality and especially AS in APD has not been the target of many studies, despite single published cases drawing attention toward this topic (10, 11). In MSA, a prevalence of suicidal ideation of 18.4% was described in a cross-sectional study exploring neuropsychiatric symptoms in 48 patients. A Chinese study exploring causes of death in 138 MSA patients determined a suicide rate of 2.8%. We recently noted a high frequency of suicidality (19%) and death ideation (16%) in a small cohort of PSP patients ($n = 31$) (12). Of note, the authors of one case report describing a patient diagnosed with probable PSP who committed suicide concluded that his course of action was likely due to increased impulsivity rather than depression (13). Furthermore, a large cross-sectional study on forensic autopsies in Japan identified clinically undiagnosed cases of PSP (2.9% of cases) (14). Strikingly, a high number of these cases (37.9%) had committed suicide, although the circumstances of these suicides have not been explored further.

Currently, the legal situation concerning AS is heterogeneous across Europe and a subject of ongoing debate, with physician assisted suicide being legally permitted in Belgium, Luxembourg and the Netherlands, and non-medical Right-to-Die organizations guiding assisted suicide in Switzerland. While the intention of assisted suicide facing a severely disabling and life-limiting condition is accepted as a final act of autonomy in these countries, the situation is complex in the case of parkinsonian disorders. Importantly, concomitant depression is highly frequent in these diseases, and may sometimes be hard to diagnose or treat. Moreover, frontal disinhibition and symptoms of dementia may undermine a patient's ability for informed consent. Lastly, options for symptomatic (pharmacological and non-pharmacological) treatment as well as patient and family support may not be available in certain areas.

Given the lack of knowledge concerning the circumstances of assisted suicide in parkinsonian disorders, we retrospectively analyzed clinical data from a Swiss Right-to-Die organization to determine the number of patients with PD or APD who completed assisted suicide as well as factors potentially driving these decisions. The organization's archives comprised detailed medical and sociodemographic data acquired during the application process. In brief, patients applying for AS are required to undergo two clinical interviews conducted by different physicians, comprising a detailed medical history, physical examination and exclusion of conditions that might interfere with the applicant's ability to consent. Furthermore, current and past medical reports have to be provided. In this process, detailed information concerning alternative treatment options including palliative care is provided by the physicians.

MATERIALS AND METHODS

Retrospective Data Acquisition

The retrospective analysis was conducted at the archive of a Swiss Right-to-Die organization, where unrestricted access was provided to SL and EB. Patients with a clinical diagnosis of PD or APD (PSP, MSA, CBS) who underwent assisted suicide in the years 2006-2012 were identified. Patients with a diagnosis of PD or APD who sought out the organization due to other comorbidities (e.g., malignancies) were excluded. Clinical data was extracted from the archives and anonymized upon extraction. Extracted data included basic demographic information, prior diagnoses, medication, symptom burden as well as circumstances of the application and administration process. If not documented, Hoehn and Yahr scales were retrospectively determined from documented physical examinations.

Statistical Analyses

Numerical data was controlled for normal distribution by D'Agostino and Pearson test, homogeneity of variance was determined by Levene's test. Comparisons of numerical data between APD and PD patients were done by Mann-Whitney *U*-test due to non-normality. Binominal data was compared applying Fisher's exact test. Correction for multiple comparisons was not done given the exploratory nature of the study. $P < 0.05$ was considered statistically significant.

Ethical Considerations

This study was approved by a local institutional review board (application number 17-090) and was conducted in accordance with the Declaration of Helsinki in its most recent revision.

RESULTS

Study Population

We identified 72 patients with a primary diagnosis of PD ($n = 34$), PSP ($n = 17$), CBS ($n = 4$), or MSA ($n = 17$) who committed assisted suicide. These patients made up 7.2% of cases in the investigated time period. Demographic data are summarized in **Table 1**. Countries of origin were Germany (41.7%), Great Britain (29.2%), the United States of America (8.3%), France (5.6%), Canada (4.2%), Switzerland/Spain/Austria (each 2.8%), and Portugal/Czech Republic (each 1.4%). Concerning marital status, 51.4% of the study population were married or in a relationship. 18.1% resided in a nursing home, and the majority of patients (91.4%) was accompanied by family or friends during the assisted suicide. 59.3% (32/54) of the patients with available documentation concerning religious affiliation were members of a Christian denomination, whereas no other religious affiliations could be identified.

Comparison of PD and APD Patients

Compared to PD, APD patients were overrepresented in this study population ($n = 38$; 52.8%) considering the overall lower prevalence of PSP, MSA, and CBS. APD patients were younger and had significantly lower disease durations as compared to PD (see **Table 1**). No differences in gender, marital status, total

TABLE 1 | Demographic analysis, symptoms, and pharmaceutical treatment of the *AS* cohort.

	PSP	MSA	CBS	APD	PD	*p*-value APD vs. PD
Demographic data						
***n* (%)**	17 (23.6%)	17 (23.6%)	4 (5.6%)	38 (52.8%)	34 (47.2%)	
Female gender; *n* (%)	9 (52.9%)	10 (58.8%)	2 (50.0%)	21 (55.3%)	15 (44.1%)	0.479
Age (years); mean(SD)	68.0 (6.4)	64.4 (8.8)	60.7 (11.6)	65.6 (8.2)	72.4 (12.5)	**0.0035**
Married/in relationship; *n* (%)				23 (60.5%)	14 (41.2%)	0.156
Patients without offspring; *n* (%)	4 (13.5%)	5 (29.4%)	1 (25.0%)	10 (26.3%)	13 (38.2%)	0.319
Nursing home resident; *n* (%)	2 (11.8%)	5 (29.4%)	0 (0%)	7 (18.4%)	6 (17.6%)	0.999
Member of a religion; *n* (%)	6 (54.5%) *n* = 11	6 (46.2%) *n* = 13	4 (100%)	16 (57.1%) *n* = 28	16 (61.5%) *n* = 26	0.787
Disease duration (years); mean(SD)	4.7 (1.6)	5.5 (4.4)	4.2 (2.0) *n* = 3	5.5 (3.2) *n* = 37	11.6 (6.9) *n* = 21	**0.00023**
Hoehn and Yahr stage; mean(SD)	4.6 (0.5) *n* = 16	4.3 (0.8)	3.75 (1.5)	4.4 (0.8) *n* = 37	4.1 (1.0) *n* = 33	0.210
Diagnosed depression; *n* (%)	4 (23.5%)	5 (29.4%)	2 (50.0%)	11 (28.9%)	3 (8.8%)	**0.039**
Previous suicide attempt; *n* (%)	3 (17.6%)	2 (11.8%)	1 (25.0%)	6 (15.8%)	4 (11.7%)	0.740
Time from diagnosis to AS application (years); mean(SD)	1.2 (0.9)	2.0 (1.8)	1.3 (0.2)	1.5 (1.3)	8.8 (6.7) *n* = 23	**<0.0001**
Time from application to AS (days); median(range)	127 (21–452)	115 (39–422)	60 (31–94)	105 (21–452)	99 (6–2090) *n* = 23	0.970
Patients accompanied by family and/or friends; *n* (%)	16 (94.1%)	13 (86.7%) *n* = 15	4 (100%)	33 (89,2%) *n* = 37	31 (93.9%) *n* = 33	0.677
Symptoms						
***n* (%)**	17 (24.6%)	16 (23.2%)	4 (5.8%)	37 (53.6%)	32 (46.4%)	
Helplessness	11 (64.7%)	11 (68.8%)	4 (100%)	26 (70.3%)	20 (62.5%)	0.610
Immobility	17 (100%)	15 (93.8%)	4 (100%)	36 (97.3%)	29 (90.6%)	0.330
Dysarthria	17 (100%)	13 (81.3%)	2 (50.0)	32 (86.5%)	8 (25.0%)	**<0.0001**
Dysphagia	13 (76.5%)	8 (50.0%)	1 (25.0%)	22 (59.5%)	6 (18.8%)	**0.0007**
Impaired vision	10 (58.8%)	2 (12.5%)	1 (25.0%)	13 (35.1%)	7 (21.9%)	0.291
Pain	6 (35.3%)	10 (62.5%)	1 (25.0%)	17 (45.9%)	22 (68.8%)	0.0878
Urinary incontinence	1 (5.9%)	9 (56.3%)	1 (25.0%)	11 (29.7%)	6 (18.8%)	0.403
Medication/treatment						
***n* (%)** (patients with available medication)	13 (76.5%)	10 (58.8%)	2 (50.0%)	25 (65.8%)	27 (79.4%)	
L-dopa	3 (23.1%)	4 (40.0%)	0 (0%)	7 (28.0%)	24 (88.9%)	**<0.0001**
Dopamine-agonists	1 (7.7%)	2 (20.0%)	0 (0%)	2 (8%)	8 (29.6%)	0.077
COMT-inhibitors	1 (7.7%)	0 (0%)	0 (0%)	1 (4.0%)	7 (25.9%)	0.051
MAO-B-inhibitors	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (7.4%)	0.491
Amantadine	5 (38.5%)	1 (10.0%)	0 (0%)	6 (24.0%)	6 (22.2%)	0.999
Deep brain stimulation	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (3.7%)	0.999
Antidepressants	10 (76.9%)	2 (20.0%)	2 (100%)	14 (56.0%)	6 (22.2%)	**0.0217**
Neuroleptics	0 (0%)	0 (0%)	0 (0%)	0 (0%)	5 (18.5)	0.0515
Benzodiazepines	4 (30.8%)	2 (20.0%)	2 (100%)	8 (32.0%)	2 (7.4%)	**0.0356**
ACh-esterase inhibitors	0 (0%)	0 (0%)	1 (50.0%)	1 (4.0%)	2 (7.4%)	0.999
Prokinetics	1 (7.7%)	1 (10.0%)	0 (0%)	4 (16.0%)	3 (11.1%)	0.698
Cannabinoids	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (3.7%)	0.999
Analgetics	2 (15.4%)	6 (60.0%)	1 (50.0%)	10 (40.0%)	9 (33.3%)	0.999

Bold values in the right column highlight significant p-values.

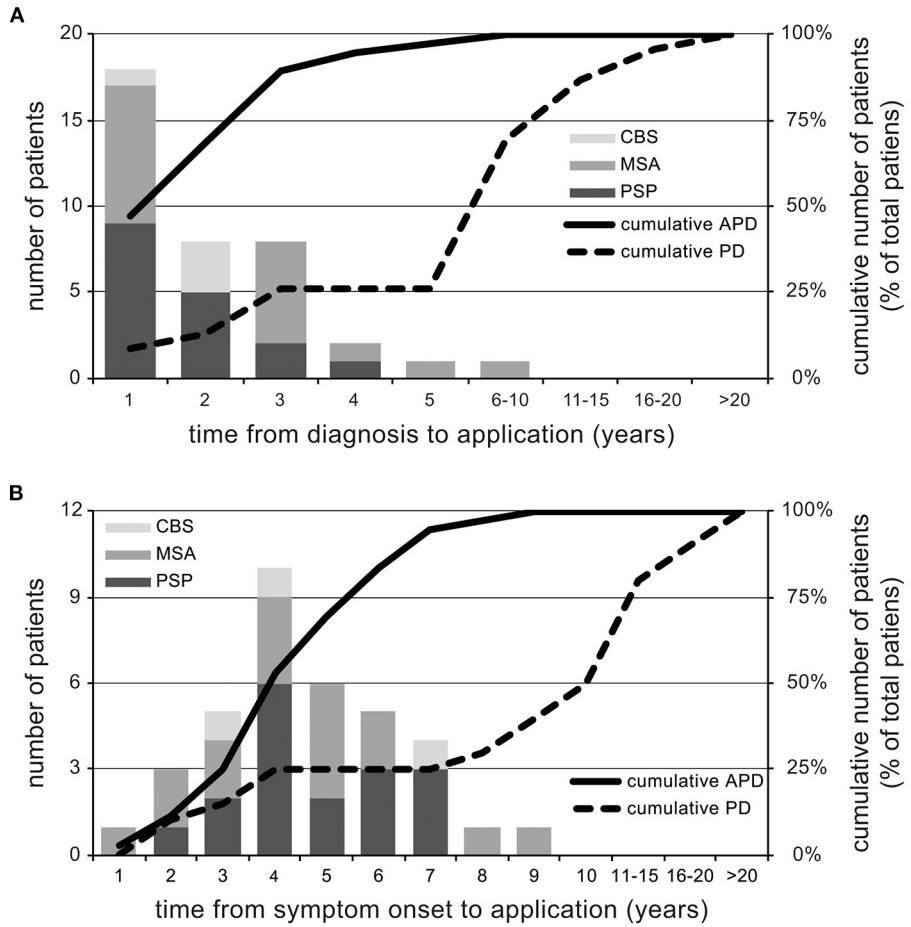

FIGURE 1 | Time to application for assisted suicide. Depiction of the annual application rate for assisted suicide from the time of diagnosis **(A)** and symptom onset **(B)** as well as cumulated percentages of applications for both PD and APD patients. Of note, time from diagnosis to application is markedly reduced in APD as compared to PD.

disability as measured by Hoehn and Yahr scale and nursing home residency was observed (see **Table 1**). Of note, APD patients had a higher frequency of diagnosed depression. The most striking difference to PD patients was a much lower time from diagnosis to application for assisted suicide especially in PSP and CBS. In APD, assisted suicide was applied for within the first year after diagnosis by 47.4% (PSP 52.3%, MSA 47.1%, CBS 25%) of all patients, whereas this was observed in only 8.7% of PD cases (see **Figure 1**).

Symptom Burden and Medication

APD patients generally exhibited a tendency toward higher symptom burden in all disease-associated symptoms except for pain, reaching statistical significance for dysarthria and dysphagia (see **Table 1**). Concerning treatment, it is noteworthy that a high number of patients who had pain documented as a relevant symptom did not receive any pain medication [PD: 75% (15/20); APD: 33% (4/12)]. In contrast, 80% of patients with a diagnosis of depression among those whose prior medication was available had received antidepressants. L-Dopa was used more frequently in PD, whereas more APD patients were prescribed antidepressants and benzodiazepines (see **Table 1**). One PD patient had received deep brain stimulation.

DISCUSSION

Patients suffering from parkinsonian disorders face a wide variety of disabling symptoms. Especially in APD, delays in the diagnostic process and limited knowledge about disease trajectories impose a massive burden on patients and caregivers alike. Once a diagnosis of APD is made, patients have to cope with limited symptomatic treatment options. Although promising novel curative therapeutic strategies such as targeting cerebral deposits of aggregated proteins are currently developed, access to treatment trials is limited, and outcomes are unknown. Hence, applying for assisted suicide may be considered as a last resort of autonomous choice by some patients.

In our study, parkinsonian disorders made up a relevant fraction of total AS applications (7.2%) considering their contribution to overall mortality. In general, neurological

disorders make up a relevant fraction of AS cases in Switzerland, with reported neurological diagnoses varying from ∼12 to ∼47% (15). The broad range of reported neurological diagnoses may in part be explained by the methodology applied, with some studies reporting only the primary diagnosis, whereas others allowed for multiple diagnoses. Some, but not all, studies have reported an increase in the fraction of neurological disorders over time (15, 16). APD cases appeared to be overrepresented as compared to PD patients in this study. Importantly, the time from diagnosis to application for assisted suicide was very short in APD as compared to PD patients. This implies a need for a stronger support network especially for newly diagnosed APD patients.

From our findings, several factors potentially driving a decision for assisted suicide can be discussed. Depression is a factor repeatedly identified as potentially influencing death ideation, with a high prevalence in parkinsonian disorders, possibly highest in PSP and CBS (8, 9, 17, 18). Depression was also highly prevalent in the APD population studied here, where a previous diagnosis of depression was documented in 28.9% of cases, despite the fact that the condition can be difficult to identify in the APD population. Another notable factor identified in our current analysis was a potential discrepancy between symptom burden and medication. A high number of PD patients and (to a lesser extent) APD patients reported pain upon presentation. However, pain medication was documented for only a fraction of these patients. It could thus be argued that insufficient symptom control may be a potential contributor in the decision making process.

Concerning social factors, it was noted that most patients committing assisted suicide were accompanied by family or friends, and less than one fifth of AS cases had lived in a nursing home. In a previous exploratory study, partnership status was not associated with suicidality in PSP (12). However, we have already shown that relatives living with these patients have a high rate of depression, which might influence the patient's decision (19). It is thus possible that the motivation to apply for AS may at least in part originate from a desire not to impose additional burden on spouses and caregivers. Such motives were also noted in another small German cohort (20). These findings may further be explained by the limited access to AS of immobilized patients who do not receive support by spouses or friends, e.g., residents of nursing homes, as it was shown that family members often take on an important role in supporting the decision for AS as well as the organizational process (21).

The current study has several limitations. First, data on patients who committed assisted suicide was collected retrospectively and may thus be incomplete, and correct diagnoses could not be verified by the investigators. This has to be taken into account when drawing conclusions from documented symptoms and medication, and especially when looking at Hoehn and Yahr stages, since these often had to be reconstructed from documented physical examinations. However, we noted that especially documentation of symptom burden was very detailed (both self-reported and caregiver-reported), as was required to prove the patient's high degree of suffering. Furthermore, it has to be considered that in this uniquely vulnerable patient collective, a prospective analysis as the method of choice would face intricate ethical challenges. Second, the investigation was limited to only one of the several Swiss organizations providing AS given its exploratory nature. The observation that almost no Swiss patients applied at the organization most likely reflects the fact that this organization is one of the few providing services to non-Swiss nationals. Thus, the results presented here rather reflect the situation of AS applicants from European countries where AS is not permitted, but not necessarily that of Swiss patients.

In summary, the data presented here prompt physicians to proactively assess a potential need for psychological support after an APD diagnosis is made, and to actively address the wish to hasten death. Thorough assessment and consequent treatment of both motor and non-motor symptoms seems warranted.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because this would jeopardize patient confidentiality. Requests to access the anonymized datasets should be directed to stefan.lorenzl@pmu.ac.at.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethikkommission bei der LMU München. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

GN: study conception, statistical analysis (design, execution), manuscript draft, and approval of the final manuscript. EB: study execution and organization, statistical analysis (design, critical review), critical review of the manuscript, and approval of the final manuscript. SL: study conception and organization, statistical analysis (critical review), critical review of the manuscript, and approval of the final manuscript. All authors contributed to the article and approved the submitted version.

ACKNOWLEDGMENTS

The authors thank Mr. Minelli for granting access to the association's archives.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The handling editor declared a past collaboration with one of the authors SL.

frontiers in Neurology

ORIGINAL RESEARCH
published: 28 July 2021
doi: 10.3389/fneur.2021.683094

Advanced Care Planning in Parkinson's Disease: In-depth Interviews With Patients on Experiences and Needs

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OPEN ACCESS

Edited by:
Benzi Kluger, University of Rochester, United States

Reviewed by:
Roop Gursahani, P. D. Hinduja Hospital and Medical Research Centre, India
Christopher Tarolli, University of Rochester, United States

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Specialty section:
This article was submitted to Neurocritical and Neurohospitalist Care, a section of the journal Frontiers in Neurology

Received: *19 March 2021*
Accepted: *28 June 2021*
Published: *28 July 2021*

Citation:
Kurpershoek E, Hillen MA, Medendorp NM, de Bie RMA, de Visser M and Dijk JM (2021) Advanced Care Planning in Parkinson's Disease: In-depth Interviews With Patients on Experiences and Needs. Front. Neurol. 12:683094. doi: 10.3389/fneur.2021.683094

Introduction: Advance care planning (ACP) is an iterative process of discussing the needs, wishes, and preferences of patients regarding disease-specific and end-of-life issues. There is ample evidence that ACP improves the quality of life and promotes the autonomy of patients with cancer and motor neuron disease who have a high disease burden and shortened life expectancy. In Parkinson's disease (PD) though, knowledge about the experiences and preferences of patients regarding ACP is scarce, despite the major disease burden associated with PD.

Aim: This study aims to explore the experiences, needs, and preferences of PD patients regarding the content and timing of ACP.

Methods: In-depth interviews were conducted with a purposively selected sample of patients diagnosed with PD. Using a semi-structured topic list, the participants were asked about their prospects for a future living with PD and with whom they wanted to discuss this. Qualitative analysis was performed in parallel with data collection using a data-driven constant comparative approach. The transcribed interviews were coded and analyzed by two researchers using MAXQDA software.

Results: Of all 20 patients (13 males; age 47–82; disease duration 1–27 years), most expressed a wish to talk about ACP with a healthcare provider, enabling them to anticipate the uncertain future. The majority of patients preferred their healthcare provider to initiate the discussion on ACP, preferably at an early stage of the disease. Nearly all patients expressed the wish to receive more information regarding the long-term impact of PD, although, the preferred timing varied between patients. They also perceived that their neurologist was primarily focused on medication and had little time to address their need for a more holistic approach toward living with PD.

Conclusion: Our results suggest that PD patients are in need of discussing ACP with their healthcare provider (HCP), even in the early stages of the disease. In addition, PD patients perceive a lack of information on their disease course and miss guidance on available supportive care. We recommend HCPs to inquire the information requirements and preferences of patients regarding ACP regularly, starting soon after diagnosis.

Keywords: Parkinson's disease, advanced care planning, information preferences, physician-patient communication, qualitative analysis

INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disorder with both motor symptoms, such as bradykinesia, rigidity, and tremor, and non-motor symptoms, including autonomic dysfunction and psychiatric manifestations (1, 2). It is difficult to predict how PD will develop in individual patients. As the disease progresses, the motor symptoms generally increase in severity, and patients may additionally experience levodopa-induced dyskinesia, gait impairments, falls, dysphagia, and dysarthria. Moreover, they may develop psychiatric symptoms and/or cognitive impairment. Eventually, the majority of patients will develop dementia (3). Thus, PD patients experience progressive impairments in their day-to-day activities and become increasingly reliant on their caregivers. Eventually, ∼40% will be living in a nursing home (4, 5).

There is growing evidence that *early* integration of palliative care in chronic progressive neurologic disorders improves the quality of life of patients and their significant others (6, 7). Advance care planning (ACP) is an element of palliative care in which the needs, wishes, and preferences of patients regarding disease-specific and end-of-life issues are discussed in an iterative process.

The introduction of advance care planning is possible alongside curative therapies and at any time during the disease course, sometimes even directly after communication of the diagnosis (8, 9). However, in PD, instead of being integrated early, research suggests that, in current practice, ACP generally is not initiated before the progression of symptoms, cognitive decline, or the terminal phase of PD (10).

In amyotrophic lateral sclerosis (ALS) and in non-neurological diseases, mostly cancer, ACP was found to be associated with a higher quality of life, fewer hospitalizations, more compliance with the preferred place of death, and less stress, anxiety, and depression (11, 12). Since PD, like ALS, is a chronic progressive disease associated with substantial morbidity, one can argue that ACP may serve the same purpose in PD patients (13). The timely onset of ACP may be crucial for PD patients as their capacity to express their wishes regarding care may decline due to motor or cognitive impairments (14). Preliminary evidence suggests that half of PD patients prefer to discuss advance directives early in the disease course, whereas, 20% prefer to wait until the disease progresses (15). In practice, palliative care, including ACP, currently seems to be underutilized in PD patients, and neurologists were found to postpone conversations on initiating, withholding, and/or withdrawing treatment in PD until there is significant physical or cognitive decline (16, 17). There is sparse knowledge on the content and optimal timing of ACP in PD (18).

In this study, we set out to obtain insight into the experiences, needs, and preferences of patients with PD regarding ACP at different stages of the disease.

METHODS

A qualitative design using in-depth semi-structured interviews was employed. The study was performed according to the Consolidated Criteria for Reporting Qualitative Research (see **Data Sheet 2**) (19). The institutional Medical Ethics Review Board waived the need for ethico-legal adjudication. All participants gave written informed consent for participation in the study.

Setting

The study was performed at a tertiary referral center for PD and for deep brain stimulation (DBS) treatment, a surgical intervention for advanced PD. Many patients were initially treated elsewhere and were referred for DBS treatment. Patients with DBS often maintain a treatment relationship with the referring neurologist. The PD patients are usually treated by various healthcare providers (HCPs), including neurologists specializing in movement disorders, general neurologists, specialist nurses (regarding DBS and PD treatment), and neurology residents.

Recruitment of Participants

All HCPs at the study site who were involved in the care for PD patients were requested to invite patients treated at the outpatient clinic to participate. The patients were informed that the study focused on communication between patients and their treating HCP about treatment options and the preferences of patients regarding their (future) healthcare. The patients were eligible if they had sufficient command of the Dutch language, had been diagnosed with PD at least 1 year ago, and had no known cognitive impairment. We purposively sampled patients to obtain a broad variation regarding disease duration, age, gender, and disease stage. The eligible patients were contacted by the first author (EK) to further inform them and their significant other about the study. If a patient provided initial oral consent, an appointment was made for the interview.

Data Collection and Analysis

Semi-structured interviews were conducted by the first author (EK), a female graduate medical student trained in qualitative interviewing techniques. The interviews took place at the preferred time and location of the patient, and significant others were allowed to participate in the interview depending on the preferences of the patients. Before the interview started, possible cognitive impairment was assessed by EK as a background characteristic, using the Montreal Cognitive Assessment (MoCA) (20). Other patient characteristics were assessed using a brief self-reported questionnaire, and disease stage was scored according to the Hoehn and Yahr (H&Y) scale, based on data in the electronic patient file (21). The interviews were audio-recorded, subsequently typed-out verbatim, and anonymized by the first author (EK). The transcripts were not returned to the participants.

An interview guide was created in advance by EK and four experienced researchers [two neurologists (JD and MdV) and two psychological researchers experienced with qualitative research (NM and MH)], and it was pilot-tested on two patients prior to the start of the study. The interview guide focused on (1) experiences with advance care planning and (2) preferences in discussing and documenting ACP (for the full topic list, see **Data Sheet 1**). To ensure data-driven analysis, the constant comparative method was employed (22, 23). Analysis was performed in parallel with data collection by three researchers (EK, NM, and MH), using MAXQDA software, version 12 (VERBI software). The interview guide was continuously refined based on the initial analysis. The first five interviews were all independently coded by three researchers (EK, NM, and MH) and subsequently compared and discussed. The subsequent interviews were coded by EK, three of which were double-coded by NM and compared to enhance triangulation. After open coding of all transcripts, the codes were ranked into subcategories that were merged into mutually exclusive categories. Data collection was terminated when saturation was reached, i.e., when three subsequent interviews did not yield any substantial new information (24). Eventually, data were clustered across interviews by EK, NM, MH, JD, and MdV to derive common themes. The patient advocates were requested to provide feedback on the findings in the common themes, which led to some amendments. The original Dutch quotes were translated by a native English speaker.

RESULTS

Twenty-seven patients were contacted by EK, five of whom declined participation. The reasons for declining could not be assessed. Two patients were excluded after the interview because their proficiency in the Dutch language turned out to be insufficient. Twenty patients (13 males and seven females) were included in the study (see **Table 1** for demographics and clinical characteristics). The median age was 63 years (range, 47–82), and the median disease duration was 9 years (range, 1–27). One patient mentioned having had appointments exclusively with a neurologist, while the rest mentioned having been treated by different types of HCPs: neurologists, neurology residents, and specialist nurses. Most patients had moderately severe motor symptoms according to the Hoehn and Yahr scale. Five patients were still working. None of the patients had a severe cognitive impairment, albeit 25% had a MoCA score indicative of mild cognitive impairment (score between 21 and 25). Eleven interviews were held in the presence of the informal caregivers of the patients, who actively took part in the conversation. All interviews were held at the homes of the patients and lasted between 45 and 120 min. Data saturation was reached after 17 interviews.

TABLE 1 | Characteristics of 20 interviewees.

	n	(%)
Gender		
Male	13	(65)
Female	7	(35)
Age (years)		
40–49	1	(5)
50–59	7	(35)
60–69	8	(40)
70–79	2	(10)
>80	2	(10)
Education		
Low (none or primary education)	2	(10)
Middle [(basic) vocational training]	9	(45)
High (research University and University of applied sciences)	9	(45)
Time since Parkinson's disease diagnosis (years)		
1–4	5	(25)
5–9	7	(35)
10–14	5	(25)
15–19	2	(10)
25–29	1	(5)
Cognitive impairment (Montreal cognitive assessment)		
21–25 points (mild cognitive impairment)	5	(25)
26–30 points (no cognitive impairment)	15	(75)
Disease stage (Hoehn and Yahr scale[a])		
Stage 1	2	(10)
Stage 2	4	(20)
Stage 3	12	(60)
Stage 4	2	(10)

[a]*Hoehn and Yahr scale: stage 1, unilateral involvement only, usually with minimal or no functional disability; stage 2, bilateral or midline involvement without impairment of balance; stage 3, bilateral disease—mild to moderate disability with impaired postural reflexes, physically independent; stage 4, severely disabling disease, still able to walk or stand unassisted; stage 5, confinement to bed or wheelchair unless aided.*

Interview Results

Two major themes emerged from the interviews (**Table 2**): first, communication with various healthcare professionals about the diagnosis and advance care planning and, second, communication about the uncertainty of the future disease burden.

TABLE 2 | Themes that emerged from the patient interviews (individual patients raised different topics in the interviews; the major themes are summarized below).

Communication with healthcare provider (HCP) about diagnosis and advance care planning (ACP)
Information provision is considered suboptimal and may be improved by, e.g., a two-tiered diagnostic appointment.
Patients value a healthcare provider with a holistic and empathic approach and who has sufficient knowledge of Parkinson's disease and enough time.
Most patients wish to discuss ACP with their HCP—most with the specialist nurse, some with the neurologist.
Many patients prefer their HCP to explore their willingness to start an ACP conversation.
The preferred timing of the first ACP conversation differs widely.
Communication with HCP about the uncertainty of the disease burden
Patients are concerned about their uncertain future disease burden, they fear becoming demented and losing their (physical) independency.
Many patients find it important to anticipate on the future, mainly regarding practical issues.
The fear patients express of becoming increasingly dependent, makes them consider hastened death.

Communication About Diagnosis and Advance Care Planning

Most patients reported that they did not receive enough information on the consequences of the PD diagnosis. The bad news elicited many questions.

> *(They told me) nothing, absolutely nothing. I remember feeling outraged. I went home thinking: what's next? When will I die? That was my first reaction. I understand you can't cover every single detail during the first consult. You don't listen as well after hearing bad news. But to send someone home without any written information, no booklet or folder … something to read after you've recovered from the initial shock. I thought that was terrible.*
> Respondent 11, female, 56 years old, H&Y stage 3, 14 years since diagnosis

Only a few patients reported having received adequate information about the diagnosis and its consequences, mostly during a separate follow-up appointment in which the neurologist took ample time to discuss all aspects of PD. The patients who reported having had such a follow-up appointment were highly satisfied with its timing, ∼4 to 6 weeks after diagnosis.

> *The neurologist said to me: I can provide lots of information now. But I'm sure you wish to clear your mind first. So, we made another appointment, 4 weeks later. This appointment took over an hour. He explained everything: the consequences, medication, different perspectives, the Parkinson Association, what my wife could expect. We discussed what kind of outlook to have on life with PD, and how there was more to life than being a PD patient. We covered all sorts of topics. It was very pleasant to divide this over two moments. When they first tell you: "you have PD", your world falls apart. But you don't know to what extent it's falling apart. You're filled with emotions: you're afraid of what you don't know; you're angry. It's good to calm down and do some research before going back to the neurologist (for the second appointment).*
> Respondent 29, male, 54 years old, H&Y stage 3, 12 years since diagnosis

Various types of healthcare professionals were involved in the care of patients, e.g., neurologists, specialist nurses, and general practitioners. A few patients described that their neurologist took time by scheduling a second appointment for a more comprehensive explanation about the diagnosis and associated consequences. However, most patients described the role of the neurologist as that of a technical specialist, with little time available for their patients and only responsible for the diagnosis and PD medication.

> *These conversations with the neurologist are only about the medication. Not about how it is going at home. I had just divorced and I had my two sons, only 11 years old, living with me. Nobody bothered to ask how that was going, and how to anticipate the moment when I would not be able to take care of them any longer.*
> Respondent 12, male, 60 years old, H&Y stage 3, 16 years since diagnosis

They expressed the wish to receive more holistic, empathetic care from the neurologist:

> *(The neurologist provides) a diagnosis and medication. These things are really important. However, in my opinion, something is missing. I mean, like, empathy, or compassion. He shouldn't wash his hands off everything and just refer you to the specialist nurse. A good neurologist understands what it's like to live with PD.*
> Respondent 29, male, 54 years old, H&Y stage 3, 12 years since diagnosis

The specialist nurse was described as caring and empathetic and was reported by the patients to spend more time compared to the consultant neurologist. About half of the patients indicated feeling more comfortable discussing the impact of PD on their lives with their specialist nurse.

> *[The role of the specialist nurse is] further guidance of and support for patients, in what they deal with every day. Also, providing the proper referrals and checking the patient's own environment. How are things at home? Are your relationships suffering? Do you have a job or hobbies that you enjoy doing?*
> Respondent 29, male, 54 years old, H&Y stage 3, 12 years since diagnosis

Some patients perceived that HCPs involved in their care, such as their general practitioner, had little knowledge regarding PD, e.g., about when to refer patients for specialized paramedical care.

> *Well, I have noticed that most healthcare professionals, my GP included, simply have too little knowledge about PD to provide useful information. Both the neurologist and the specialist nurse have no clue where to find this specialized care. That needs improvement. That way, patients don't have to figure everything out by themselves.*

Respondent 28, female, 58 years old, H&Y stage 3, 7 years since diagnosis

Nearly all patients expressed a wish to talk about ACP with their HCPs, enabling them to anticipate the future.

Sometimes I find myself thinking: tell me more about the consequences of PD. At the physical therapist and on television I see patients with PD who are much more disabled than I am. And the neurologist only asks me how it is going right now. He never tells me what to expect regarding the development of PD.
Respondent 3, female, 82 years old, H&Y stage 3, 3 years since diagnosis

A few explicitly preferred to discuss ACP with the neurologist.

If you're asking me what our next step should be, I would like to discuss my future with my neurologist. I think that would make sense.
Respondent 11, female, 56 years old, H&Y stage 3, 14 years since diagnosis

A larger proportion of patients expressed a wish to have such conversations with the specialist nurse.

The neurologist isn't really involved. You only visit him twice a year. He's almost a stranger to me. I would have liked to speak to a specialist nurse who could tell you everything there is to know about all the different regulations and options available for Parkinson's patients in Parkinson's care.
Respondent 2, male, 64 years old, H&Y stage 3, 7 years since diagnosis

Only a few patients thought ACP was not useful.

'It's sort of a self-fulfilling prophecy. You know you'll eventually become stiff, so you feel stiff already. (. . .) It's hard, but I feel that the less pre-occupied I am with the disease, the less I feel its limitations on me. (. . .) I don't like to brood over this. Sometimes I do, of course. And when I do, I become unpleasant and angry.
Respondent 18, male, 58 years old, H&Y stage 3, 11 years since diagnosis

Most patients had discussed issues relating to ACP with their loved ones, whereas, only a few had actually discussed ACP with their HCP.

What if I develop dementia and I am not aware of it anymore. Well, I told my son and husband that I do not want to be left neglected. If I no longer look well-cared for, then I want to be euthanized.
Respondent 3, female, 82 years old, H&Y stage 3, 3 years since diagnosis

Most patients reported that they found it difficult to start a conversation about ACP with their HCP themselves. Instead they would prefer the HCP to initiate this conversation. They emphasized that the HCP should be careful in doing so, exploring whether the patient is willing to discuss these issues.

I think it's fine if the neurologist or the specialist nurse discusses the future. Some patients might back down from this conversation because they're not ready to discuss it yet. Perhaps they (HCPs) should ask how the patient is feeling at that moment. Then, they can continue by asking what should be arranged for you when things get worse.
Respondent 11, female, 56 years old, H&Y stage 3, 14 years since diagnosis

The patients varied in their preferences regarding the ideal timing of ACP conversations. Some reported that they did not want to discuss generic, disease-specific, and end-of-life issues until their PD symptoms worsened.

I'll bring it up when it's necessary. That will give me plenty of time still.
Respondent 24, female, 69 years old, H&Y stage 4, 27 years since diagnosis

Contrarily, some patients preferred to hear about the prognosis and therapeutic or supportive options as soon as possible after the diagnosis. Most patients reported that they would not be bothered if an HCP would attempt to initiate a discussion about ACP early in the disease course.

As soon as possible. It's tough, but at least it's clear. That way, you can arrange everything while you're still thinking clearly. You can't leave it all in the hands of your children. You have to take responsibility.
Respondent 16, male, 57 years old, H&Y stage 3, 16 years since diagnosis

Communication About the Uncertainty of the Future Disease Burden

The second major theme that emerged from the interviews was the uncertainty of the patients about their future disease burden. The patients reported several concerns about the future that they had not been able to discuss with their HCP. They expressed concerns about ending up in a wheelchair or not being able to take care of themselves anymore and thus becoming a burden for their loved ones or having to live in a nursing home. Almost all patients were afraid to become demented.

Yeah, I find myself wondering: what will become of me? What if I will develop dementia … My daughter volunteers at a nursing home for patients with dementia every Sunday. Should I write a euthanasia codicil? Will I remain kind, or will I become a really nasty patient? If that happens, I want it written down somewhere that I do not wish to continue to live.
Respondent 21, female, 56 years old, H&Y stage 2, 1 year since diagnosis

The patients suggested that these important uncertainties about their future disease burden should be addressed in ACP conversations. The patients also reported that ACP conversations should pertain not only to their symptoms but also to the impact of these symptoms on their daily lives. They expressed the wish to get support for activities of daily living, access to

devices, or nursing care for personal hygiene. Other aspects which the patients reported that they wanted to address in ACP conversations were resuscitation, hastened death, and nursing care.

> *The physical care, absolutely. What does it entail? Can your spouse manage? If she can't, you have to make other arrangements. If it were up to me, I would postpone that as much as possible. I would also want euthanasia performed at home, not in a hospital. If the neurologist is clear, you know what to expect of him. They should also write everything down so you can get back to certain topics.*
> Respondent 16, male, 57 years old, H&Y stage 3, 16 years since diagnosis

Many patients who emphasized the importance of anticipating on their future focused on practical issues.

> *Well, practical items like beds, walkers, toilets, stair lifts. I'm trying to get ahead by purchasing these items already before I'm fully dependent on them.*
> Respondent 28, female, 58 years old, Hoehn and Yahr stage 3, 7 years since diagnosis

The patients in our cohort with a relatively short disease duration (i.e., <5 years) and who experienced low symptom burden seemed not to differ in their experiences, needs, and preferences regarding ACP and the uncertainty about future disease burden compared to patients with a more advanced disease.

DISCUSSION

We aimed to explore the experiences, needs, and preferences of PD patients regarding the content and timing of ACP. The findings of our study suggest that nearly all patients desired to discuss ACP with their HCP, even those who had been recently diagnosed and as yet had experienced a relatively low symptom burden. Moreover, the patients perceived a lack of information on their disease course and felt a need for more guidance in finding available supportive care.

Even though, most patients had a desire to discuss ACP with their HCP, only one patient in our sample actually had had such a conversation. The patients generally preferred their HCP to initiate an ACP conversation as they found it difficult to start an ACP conversation themselves. Nevertheless, our group previously showed that neurologists usually do not discuss ACP before the terminal stages of PD. The longstanding relationship between patients and their neurologist in which the focus is on optimizing medical treatment to suppress symptoms may be a barrier for the neurologist to start an ACP conversation (16). This may partially explain why this conversation had not taken place with most patients.

The preferences of the patients regarding the timing of ACP ranged from right after diagnosis to when the disease has progressed. Even those who preferred to discuss ACP later in the disease course still reported that they would not be bothered if the physician would initiate a discussion about ACP at an early stage. These results suggest a discrepancy between the wishes of patients to discuss ACP with their healthcare providers at an early disease stage and their actual experiences.

In contrast to PD, in high-grade glioma and ALS, ACP is initiated directly at diagnosis because of the reduced life expectancy and imminent cognitive impairment, especially in glioma (16). It may well be that the neurologists underestimate the urgency to discuss ACP early in the disease course or to discuss it at all since PD generally initially is well-treatable, and most patients have many years to live after diagnosis. Moreover, the unpredictability of the course of PD possibly contributes to delaying these discussions (20).

That PD patients experience the need for a timely discussion of future care is supported by other studies (13, 15, 25). Evidence regarding the optimal timing of ACP is still scarce. A recently developed tool aimed at timely identifying palliative care needs in PD patients by HCPs may be of practical use (26).

The preferred content of ACP conversations included mostly practical topics, such as support for activities of daily living, access to devices, or home healthcare. Additionally, the patients also expressed their wish to discuss resuscitation and hastened death. Of note is that none of the patients had articulated a wish to be informed about the salient features of advanced PD, such as balance problems, swallowing difficulties, urinary symptoms, or aspiration pneumonia, in an ACP conversation. The patients may not have been sufficiently informed about these issues and therefore had not brought them up. ACP can only be effective if the patient is well-informed not only about the diagnosis and its implications but also about the prognosis (27).

Many patients in our sample indeed felt that they had not received enough information and guidance regarding the course of PD. Since patients with a relatively short disease duration retrospectively reported a lack of provided information as well, one might argue that this need for information is already present shortly after diagnosis. This perceived lack of information by the patient might be multi-causal. Firstly, the information provided may indeed have been insufficient. Additionally, the information may have been provided but forgotten by the patients. Previous research demonstrates the inability of patients to effectively take up additional information directly after receiving a life-altering diagnosis due to the associated stress (28). Moreover, if the information provided to patients throughout their disease course does not match their information needs at that particular moment, they may fail to absorb it. Finally, the reports of the patients during the interviews may have been biased: information that was provided years ago might be inaccurately recalled due to the elapsed time or cognitive decline. Prospective studies are required to further investigate the causes of the perceived lack of information.

Our results do substantiate earlier findings among PD patients and their informal caregivers regarding information preferences—that many patients and their caregivers have a strong need for iterative, tailored information already shortly after the diagnosis (29–31). Additionally, they align with previous findings among patients with chronic progressive neurological diseases, showing that patients highly value participation in the decision-making about treatment and care, which is only possible

if the patient is informed about possible disease progression (8, 13, 15, 32).

Our study has several strengths. Our sample included a wide variation in disease duration, disease severity, and age, which contributes to the validity of our results. The participating patients were also treated by various types of HCPs (e.g., specialist nurse, resident, neurologist, and/or specialist neurologist in movement disorders). The interviews took place at the homes of the patients and were conducted by an independent interviewer, which may have encouraged the patients to openly and critically talk about their experiences and preferences. A thorough analysis was ensured by involving a multidisciplinary team, including two researchers experienced in qualitative research methodology. Several limitations have to be mentioned as well. First, some degree of selection bias may have occurred since the potential candidates for our study were selected by their treating HCP. This might have led to the inclusion of patients with a tendency to express their opinions more explicitly. Five of the 27 eligible patients declined participation, but we could not ask them for their reasons to decline. Besides this, while standard qualitative methods were used for this study, some interviewer bias may have influenced the interview content, selection of themes, and/or presentation of results, yet we minimized bias by using investigator triangulation with a multidisciplinary analytical team (33, 34).

In addition, the patients mentioned having received treatment from different types of HCPs. Most patients had experience with care from one or more neurologists and specialist nurses. Even though, the patients did not explicitly mention this, a substantial proportion likely received treatment from a neurology resident as well since the patients were treated in a teaching hospital.

Additionally, that all patients were included in one medical center may impair the generalizability of the results. Since this was a tertiary referral center for Parkinson's disease, about half of these patients had previously been or were simultaneously treated elsewhere, still ensuring variability in experiences. Finally, not all results can be readily extrapolated internationally as, in the Netherlands, end-of-life considerations, including hastened death, are relatively openly discussed. Conversely, since the results of our study resemble those from earlier publications from the UK and USA regarding the readiness to openly discuss end-of-life issues early on, they seem generalizable at least to western countries with a high socioeconomic status (13, 15, 25).

Based on the results of this study, reporting the experiences and preferences of patients, we first recommend the HCPs to explore the preferences of patients regarding ACP regularly, starting early in the disease trajectory. Second, as a well-informed patient is a prerequisite for an ACP conversation, information provision to patients should be optimized before ACP can be properly implemented in the standard care of PD. For example, one might consider informing PD patients about the diagnosis and consequences of the disease in a two-tiered appointment similar to the process in oncology and ALS since this was shown to facilitate information uptake by the patients in the latter patient groups (8). Communication skills training for HCPs may be crucial to optimize these conversations (10). Additionally, by regularly actively inquiring the need for information by the HCPs regarding prespecified topics, tailored information in both oral and written form can be supplied to PD patients. This may facilitate the information uptake, taking the prolonged disease duration with changing symptoms over time and potential cognitive decline into account.

Finally, to optimize communication about ACP, future research is necessary regarding the following: (1) the communication strategy of neurologists on breaking the bad news of a PD diagnosis and information provision regarding the associated consequences of this diagnosis during the disease course, (2) how the patients and their significant others experience these conversations, and (3) whether the abovementioned recommendations lead to better informed patients.

CONCLUSION

We conclude that PD patients often feel insufficiently informed about their diagnosis, possible future disease evolvement, and future disease burden. Most PD patients wish to discuss ACP with their HCP. The patients varied in their preferences regarding the ideal timing of ACP conversations, yet a substantial part wanted to start shortly after the diagnosis. The interviewed patients expressed the wish that the HCP takes the initiative to start such a conversation. Though future research is needed before ACP can be adequately and efficiently applied in standard care in PD, some recommendations can be made. It seems important to proactively, timely, and iteratively inquire about the needs of the patients for information on the different aspects of the disease. Only then can tailored educational materials be provided at the right time. Finally, it is advised that the HCP regularly verifies the need of the patients to discuss ACP.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available due to the sensitive nature of the full interview transcripts. Requests to access the datasets should be directed to e.kurpershoek@amsterdamumc.nl.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

EK: conceptualization, methodology, formal analysis, investigation, data curation, project administrations, writing-original draft, and writing-review and editing. MH: conceptualization, methodology, formal analysis, data

curation, writing-review and editing, supervision, and providing resources. NM: conceptualization, methodology, formal analysis, data curation, and writing-review and editing. RB: writing-review and editing, supervision, and providing resources. MV: conceptualization, methodology, formal analysis, supervision, writing-review and editing, and providing resources. JD: conceptualization, methodology, formal analysis, supervision, writing–original draft, writing-review and editing, and providing resources. All authors contributed to the article and approved the submitted version.

ACKNOWLEDGMENTS

We thank Natalie LeCouffe for translating all Dutch statements into English.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.683094/full#supplementary-material

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BRIEF RESEARCH REPORT
published: 02 August 2021
doi: 10.3389/fneur.2021.674114

Causes for Emergency Hospitalization of Neurological Patients With Palliative Care Needs

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Background: Acute and unexpected hospitalization can cause serious distress, particularly in patients with palliative care needs. Nevertheless, the majority of neurological inpatients receiving palliative care are admitted *via* an emergency department.

Objective: Identification of potentially avoidable causes leading to acute hospitalization of patients with neurological disorders or neurological symptoms requiring palliative care.

Methods: Retrospective analysis of medical records of all patients who were admitted *via* the emergency department and received palliative care in a neurological ward later on ($n = 130$).

Results: The main reasons for acute admission were epileptic seizures (22%), gait disorders (22%), disturbance of consciousness (20%), pain (17%), nutritional problems (17%), or paresis (14%). Possible therapy limitations, (non)existence of a patient decree, or healthcare proxy was documented in only 31%. Primary diagnoses were neoplastic (49%), neurodegenerative (30%), or cerebrovascular (18%) diseases. Fifty-nine percent were directly admitted to a neurological ward; 25% needed intensive care. On average, it took 24 h until the palliative care team was involved. In contrast to initially documented problems, key challenges identified by palliative care assessment were psychosocial problems. For 40% of all cases, a specialized palliative care could be organized.

Conclusion: Admissions were mainly triggered by acute events. Documentation of the palliative situation and treatment limitations may help to prevent unnecessary hospitalization. Although patients present with a complex symptom burden, emergency department assessment is not able to fully address multidimensionality, especially concerning psychosocial problems. Prospective investigations should develop short screening tools to identify palliative care needs of neurological patients already in the emergency department.

Keywords: emergency hospitalization, palliative care needs, neuropalliative care, emergency department, palliative care, reason for admission, neurological patients

OPEN ACCESS

Edited by:
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Specialty section:
This article was submitted to Neurocritical and Neurohospitalist Care, a section of the journal Frontiers in Neurology

Received: *28 February 2021*
Accepted: *01 July 2021*
Published: *02 August 2021*

Citation:
Willert A-C, Ploner CJ and Kowski AB (2021) Causes for Emergency Hospitalization of Neurological Patients With Palliative Care Needs. Front. Neurol. 12:674114. doi: 10.3389/fneur.2021.674114

INTRODUCTION

After cancer, neurologic conditions are the second most common diagnosis of inpatients receiving specialist palliative care (1, 2). Like the majority of inpatients with other lifetime-reducing diseases and palliative care needs, patients with neurological diseases or complications are predominantly admitted to hospital *via* an emergency department (ED) (3, 4). Acute admission to the ED can cause serious distress in this vulnerable group due to long waiting times, lack of appropriate communication, and insufficient control of symptoms (5). However, ED visits increase with impairment and with decreasing lifetime (6–8). In many cases, they ultimately lead to long hospitalization (7, 9).

An early integration of palliative principles in the trajectory of hospital care is therefore an important aim (10).

Supplementary to disease management in the primary treating department, hospital-based specialist palliative care can be incorporated in the care of patients with life-limiting diseases by consultations of a multi-professional palliative care service. A physician and nurse both specialized in palliative care work alongside and in collaboration with the attending physician. They aim to address symptom management, help to define goals-of-care according to the (alleged) patient will, support patients with advance care planning, and provide psychosocial help for informal caregivers. The multi-professional team approach also includes additional support from social workers, psychologists, physiotherapists, and occupational and speech therapists and pastoral care. To establish a palliative care treatment plan, during the first specialist palliative care consultation an assessment is performed, which evaluates unmet palliative care needs on the physical, social, psychological, and spiritual level.

Specialist palliative care consultation is able to improve symptom burden, patient's and caregiver's satisfaction, and quality of life, and it reduces length of stay and overall healthcare costs (11, 12). Early specialist palliative care consultation is also associated with a lower in-hospital mortality rate compared with late initiation (13). In order to move palliative care "upstream" in the trajectory of in-hospital care, an implementation of palliative care in the ED has been proposed (10). Methods to achieve this goal range from education of emergency physicians in palliative care principles encouraging them as primary providers to implementation of specialist palliative care consultation by a multi-professional palliative care service as secondary providers in the ED (10, 14).

Increasing awareness for palliative care needs in the ED may allow for an early integration of palliative care in hospital. Studies throughout the past decade have mainly concentrated on ED visits of patients with end-stage cancer (7, 15, 16), patients receiving outpatient palliative care (9, 17), seriously ill older patients with complex medical conditions (18), or inpatients who received palliative care consultation after being admitted *via* an ED (3). By contrast, causes for admission of neurological inpatients receiving palliative care have not been studied so far. Here, we studied admission and palliative care needs in a sample of consecutive ED patients in a large university hospital.

METHODS

We studied 130 consecutive patients who had been admitted *via* the ED and subsequently received specialist palliative care consultations by a multi-professional palliative care service in the Department of Neurology, Charité—Universitätsmedizin Berlin, Campus Virchow-Klinikum, between January 2018 and December 2019. Ethical approval was given by the Ethics committee of the Charité—Universitätsmedizin Berlin (EA4/123/19).

Electronic medical records including ED documentation were retrospectively analyzed for age, gender, mode of admission, initial medical triage [Manchester Triage System, MTS (19)], level of consciousness [Glasgow Coma Scale, GCS, (20–22)], chief complaints, documentation of the (alleged) patient will concerning therapy limitations, (non)existence of a patient decree and healthcare proxy or legal guardian, medical imaging, initial treatment (medication), time to admission/time spent in the ED, admitting care units, time until specialist palliative care consultation was initiated, length of stay in the Department of Neurology, and mode of discharge. Time to admission was defined as the time of arrival at the ED to the time point of initial documentation of the receiving ward. Length of stay in the Department of Neurology was defined as the time from admission to the neurological ward to the day of discharge.

From palliative care assessment, routinely conducted by a multi-professional palliative care service at initiation of palliative care in all patients, we extracted the following variables: palliative care symptoms [Minimal Documentation System for Patients in Palliative Care, MIDOS, (23)], pain assessment (visual analog scale from 0 = no pain to 10 = worst pain possible), performance status [Eastern Cooperative Oncology Group, ECOG, (24)], and (non)existence of a patient decree, healthcare proxy, or legal guardian. If patients were not able to communicate, assessment was performed by relatives, proxy, palliative care service, or attending neurologist.

In addition, 14 neurological symptoms were systematically evaluated in reference to the MIDOS-rating scale by the attending neurologist, as they are not included in the routinely conducted palliative care assessment. We also added the items "diarrhea" and specified the item "dyspnea" through adding "dyspnea on resting" and "dyspnea on exertion" and the item "sleep disorder" through adding "difficulties to fall asleep" and "sleep disturbances" in the original MIDOS.

Descriptive statistics was performed *via* IBM SPSS (Statistical Package for the Social Sciences, IBM Corp., Version 23.0, Released 2014. Armonk, NY, USA). Metric data are presented as median (minimum–maximum). For data analysis of MIDOS and additional neurological symptoms, only answered items were included in analysis. Seven cases were excluded due to missing information.

RESULTS

One hundred thirty neurological inpatients (50% female, median age 69 years) who received palliative care after acute hospital admission were identified.

TABLE 1 | Frequent complaints on admission in a minimum of $n \geq 5$ patients.

Chief complaints on admission	*n*	%
Epileptic seizures	29	22,3%
Gait disorder/falls	28	21,5%
Disturbance of consciousness	26	20,0%
Pain	22	16,9%
Nutritional problems/dysphagia	22	16,9%
Paresis	18	13,8%
Confusion	12	9,2%
Aphasia	11	8,5%
Organization of ambulant care/overburdening of family	10	7,7%
Infection	9	6,9%
Shortness of breath	7	5,4%
Nausea/vomiting	7	5,4%
Micturition disturbance	6	4,6%
Weakness	5	3,8%
Dizziness	5	3,8%
Paresthesia	5	3,8%

Mode of Admission and Initial Medical Triage

Sixty-six percent of patients were brought to hospital by ambulance with or without an emergency physician, 11% came by patient transport ambulance, and 11% by other vehicles. For 12% of patients, means of transport was not documented. According to MTS, 45% were classified as requiring "immediate" or "very urgent" medical assessment. Forty-five percent were triaged as needing "urgent" or "standard" medical assessment. Eight percent were not triaged according to MTS, but instead labeled as "handed over from doctor to doctor" and tagged as "stroke" or "trauma." In three cases, triage was not documented.

Level of Consciousness and Chief Complaints on Admission

Level of consciousness was categorized as GCS 13–15 in 58% of patients. Eighteen percent were scored GCS 8–12 and 12% GCS 7 or below. In 12% of patients, a GCS score was not documented. Eight percent of patients required an invasive airway management (intubation or a supraglottic device).

Altogether, 29 different chief complaints could be identified from emergency department documentation, with a median of 2 (1–5) complaints in each patient (**Table 1**). The most frequent reasons for acute admission were epileptic seizures (22%), gait disorder/falls (22%), disturbances of consciousness (20%), pain (17%), nutritional problems (17%), and paresis (14%). Difficulties with organization of care or overburdening of family were only mentioned in 8% (**Figure 1**).

Diagnostics and Therapy

The vast majority of patients received at least one mode of acute diagnostic imaging (88%). Cranial imaging was most frequently performed (60%). Fifty-eight percent received a cranial CT either without or with contrast medium (CM) and/or CT post-CM imaging; 2% had an initial cranial MRI. X-ray (29%) and CT (25%) of other body regions were frequently performed. Only 4% of patients were examined with ultrasound.

In 55% of cases, a medication was administered in the ED: antiseizure medication (19%) and benzodiazepines (14%), analgesics (WHO-I/antipyretics: 18%, WHO-II/III: 8%), antibiotics (17%), and anti-edematous treatment (17%) were initiated most commonly. Even 4% received systemic thrombolysis and/or recanalization as acute stroke treatment.

Documentation of Healthcare Proxy or Legal Guardian, Patient Decree, and Therapy Limitations

In 31% of the ED documentations, we found statements concerning possible therapy limitations according to the (alleged) patient will, (non)existence of a patient decree, and (non)existence of a healthcare proxy or a legal guardian.

The existence of a healthcare proxy or legal guardian was documented in 15% of cases, whereas in 5% it was mentioned that there was none. The presence of a patient decree was documented in 8%; in 5%, it was explicitly noted that no patient decree exists.

The existence of therapy limitations was documented for 12% of patients. In 5%, it was explicitly stated that there are no limitations to therapy. In half of the cases with documented (non)existing therapy limitations, it was specified that the presumed wishes of the patient were considered with the help of family, healthcare proxy, or legal guardian. Two patients were directly quoted concerning their will. In one case, a conflict was mentioned between patient decree and the alleged patient will. In another case, it was documented that the alleged patient will still needs to be evaluated.

Time to Admission, Admitting Care Units, and Diagnosis for Admission

Patients stayed 0.5–20 h (median 5 h) in the ED until they were admitted to a neurological ward (59%), intensive care unit (25%), or other departments (16%).

Primary diagnoses for admission were neoplastic disorders (49%), neurodegenerative disorders (30%), cerebrovascular diseases (18%), or inflammatory autoimmune disorders of the CNS (3%) (**Table 2**).

Time to Initiation of Palliative Care, Palliative Care Needs, and Performance Status

In 63% of patients, it took at least 2 days until specialist palliative care consultation was initiated. In 25% of patients, it took 1 day. Only in 12% of patients were palliative care needs identified on admission.

Symptom assessment after admission revealed that general symptoms and psychosocial problems such as assistance with Activities of Daily Living (ADL, 83%), weakness (71%), difficulties with organization of care (61%), tiredness (59%), or overburdening of family caregivers (53%) were key palliative care needs of at least moderate intensity (**Figure 2A**). Thirty-one percent of patients had experienced pain within the last

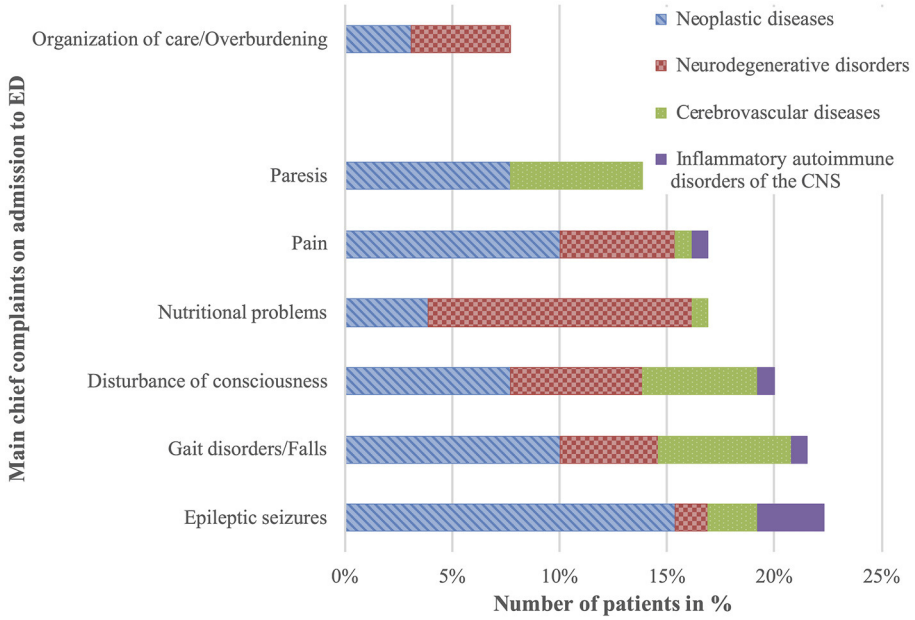

FIGURE 1 | Main chief complaints on admission.

TABLE 2 | Diagnoses.

Diagnosis group	Diagnoses	*n*	%
Neoplastic diseases	Primary brain tumors	22	16,9%
	Secondary brain tumors	30	23,1%
	Other neoplastic diseases	12	9,2%
Neurodegenerative disorders	Amyotrophic lateral sclerosis	17	13,1%
	Parkinson's disease	8	6,2%
	Atypical parkinsonism	4	3,1%
	Dementia	7	5,4%
	Other neurodegenerative disorders	3	2,3%
Cerebrovascular diseases	Ischemic stroke	15	11,5%
	Hemorrhagic stroke	8	6,2%
Inflammatory autoimmune disorders	Multiple sclerosis	4	3,1%

24 h, ranging from 3 to 10 points on the visual analog scale (4–6/10: 21%; 7–10/10: 10%), whereas 14% reported to have pain more than 3 during the assessment (4–6/10: 10%; 7–10/10: 4%). Complementary neurological symptoms were assessed in 73 patients. Difficulties in communication (30% aphasia, 38% dysarthria), nutritional problems for solids (42%) or fluids (38%), and paresis (47%) were the most common moderate to severe neurological symptoms (**Figure 2B**).

Performance status was highly impaired in most patients: 83% were "capable of only limited self-care" or "completely disabled" (ECOG 3 or 4), 17% were "restricted in physically strenuous activity" or "capable of all self-care but unable to carry out any work activities" (ECOG 1 or 2) (24).

Length of Stay and Mode of Discharge

The median length of stay in the department of neurology was 10 days (2–44 days). Forty percent of patients were discharged with further inpatient (palliative care unit or hospice; 12%) or outpatient (home/nursery home with outpatient palliative care supply; 28%) specialized palliative care. Twenty-three percent were discharged without specialized palliative care supply. Twenty-two percent were transferred to other services (e.g., rehabilitation clinics). During their hospital stay, 15% of patients died; 47% while waiting for inpatient or outpatient palliative care.

DISCUSSION

Admission to hospital *via* the ED was triggered by acute events as well as exacerbation of potentially preventable or chronic medical problems.

The level of urgency assigned to the cause leading to admission may indirectly be indicated by means of transport to hospital as well as assessment on arrival. Most neurological patients with palliative care needs arrived by ambulance, a frequent mode of arrival of patients with palliative care needs (3, 9). However, mode of transport may also be influenced by frailty and high functional impairment, a barrier for self-organized arrival (2, 9). A straightforward indicator for acuteness of ED consultation is triage on arrival. More than half of our

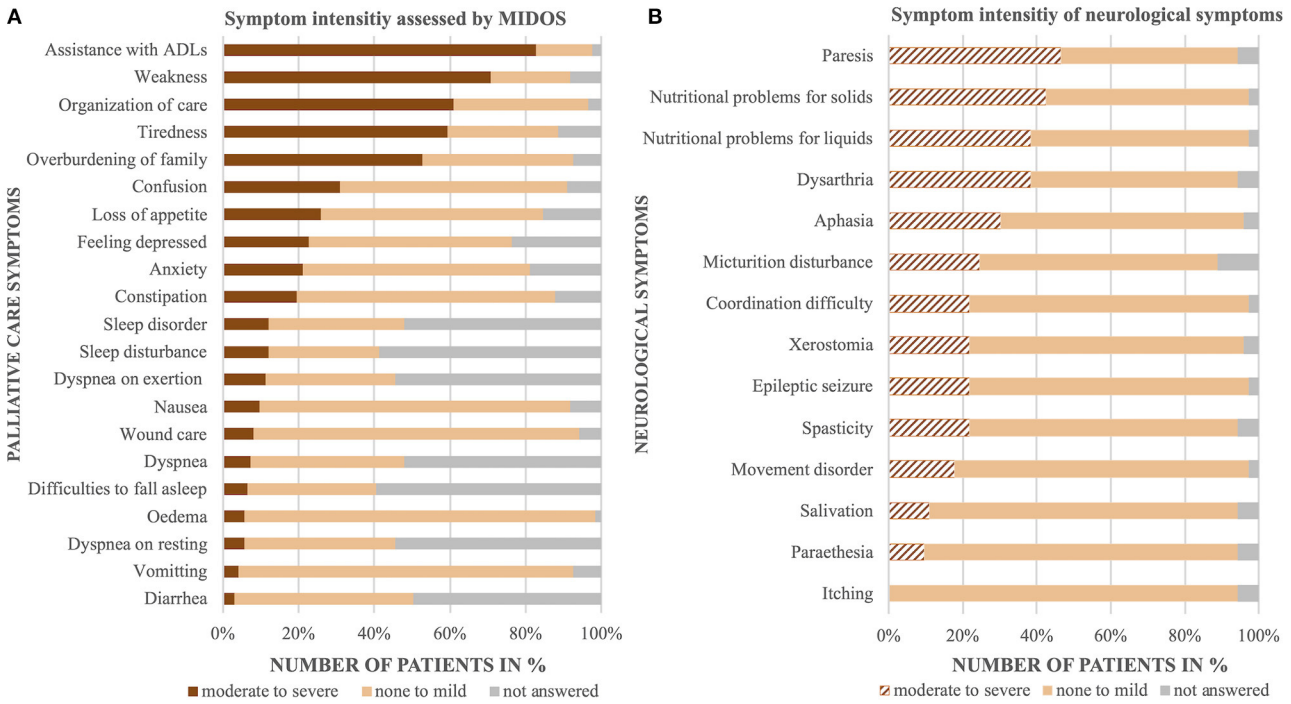

FIGURE 2 | Palliative care assessment. Occurrence and intensity of palliative care symptoms **(A)** and complementary neurological symptoms **(B)**.

patients were assessed to be in need of urgent or immediate medical care or even of continuous monitoring. The proportion of patients needing prompt medical care thus seems slightly higher in neurological patients compared to other patients with palliative care needs presenting to the ED (3, 9). Consequently, it is not surprising that a relevant number of patients were initially admitted directly to the intensive care unit. An admission modality was not often reported in patients with other lifetime-reducing diseases and palliative care needs (7, 25). Frequent and elaborate diagnostics including neuroimaging and body imaging in the majority of patients as well as the variety of administered medications are not as easily conducted in an out-of-hospital setting. Admission to the ED therefore does not seem to be avoidable in all cases, as out-of-hospital treatment would not be equally available.

Patients presented to the ED with epileptic seizures, gait disorders, disturbances of consciousness, paresis, dysphagia, and nutritional problems. Less often, they also reported symptoms from the "classical" palliative spectrum such as pain, shortness of breath, nausea/vomiting, and weakness—symptoms already described in neurological inpatients receiving palliative care (1, 2, 26, 27). Compared to patients at large presenting to the ED, we unsurprisingly see a shift in frequency distribution of neurological chief complaints (28). This certainly reflects the most common diagnoses of neurological patients with palliative care needs: neoplastic diseases (i.e., primary and secondary brain tumors or meningeal carcinomatosis), neurodegenerative disorders, and cerebrovascular diseases.

Chief complaints and symptoms are frequently ambiguous and may be caused both by true neurological emergencies and by persistent deficits that do not require in-hospital treatment. Paresis, epileptic seizure, and disturbance of consciousness may be seen as chief complaints that may require urgent diagnostics and possibly treatment. Epileptic seizures for example are common in older adults as well as cancer patients, and their occurrence is associated with a significant morbidity and mortality (16, 29, 30). First occurrence of epileptic seizures or status epilepticus should lead to neuroimaging and diagnostics. Also, in recurring seizures, reimaging may be needed to exclude tumor progression or complications in primary or secondary brain tumor patients. Although our data do not gather information whether the event was new or reoccurring, seizures may be considered as events that lead to almost unavoidable admission, especially seizures with impaired awareness like tonic–clonic seizures. Even in patients already receiving outpatient palliative care, neurological complications usually require acute hospitalization (25). For example, in patients with sudden onset of paresis due to an ischemic stroke, an immediate ED admission enables treatment options (thrombolysis and/or recanalization) with a chance to prevent major disability, also in palliative care patients.

Other chief complaints like pain, nutritional problems, and gait disorders or falls can be argued to be problems that could also be sufficiently dealt with in an out-of-hospital setting and may therefore be potentially preventable causes for admission. Nevertheless, dysphagia and nutritional

problems are still the most frequent symptoms in hospitalized patients with amyotrophic lateral sclerosis (4). In Parkinson's disease, complications due to falls or reduced ingestion remain common causes for emergency department admissions and hospitalization (31).

A precise documentation of the palliative situation as well as a clearly documented will concerning treatment limitations may help to avoid stressful diagnostics and treatment as well as unnecessary hospitalization. End-of-life discussions also have the potential to reduce the risk of more than one ED visit before death (15). However, in ED documentation information about advance care planning, the (alleged) patient will or healthcare proxy remains sparse (3, 5). This is remarkable, as decisions made in the emergency department often affect the trajectory of in-hospital care. Certainly obstacles such as urgency of the medical situation, lack of an adequate private and calm setting, and lack of knowledge of the complete medical history of the patient are a challenge for healthcare providers, patients and their families (32). However, discussion of goals of care and life-sustaining treatment is essential to conducting treatment in alignment with the patient's will. In neurology and beyond, malignant stroke and massive intracranial hemorrhage are well-acknowledged acute events that initiate serious illness conversations. However, there are also other, disease-specific well-defined "triggers" (33). In neurodegenerative diseases, for example dysphagia and associated nutritional problems are seen as such event-driven milestones to initiate serious illness conversation (33).

Neurological inpatients are known to have specific palliative care needs (1, 2, 27). Our data show that emergency assessment only reveals a small fraction of the full multidimensionality of symptom burden. Reasons for admission display known categories for palliative care patients with other lifetime-reducing diseases: exacerbation of known or occurrence of new symptoms, worsening performance status, and disturbances of consciousness (3, 6, 15, 18). Psychosocial problems like organization of ambulant care or overburdening of family caregivers were rarely obvious as an initial cause of admission. Rather, they became evident during the in-hospital stay in the majority of inpatients and are key palliative care needs of at least moderate intensity. On the other hand, chief complaints presented in the ED like disease-specific problems affecting mobility, nutrition, and communication were consistent with the most common moderate to severe neurological symptoms evaluated by palliative care assessment. Epileptic seizures were frequent chief complaints on admission, but less frequently mentioned as major problems in palliative care assessment later on. A possible explanation might be an already successful establishment or optimization of antiseizure medication.

In the majority of our patients, it took more than 2 days to initiate palliative care. A considerable number of patients were able to be transferred to a palliative care unit, hospice, or outpatient specialized palliative care providers. However, almost half of the patients who died during their hospital stay were waiting for such a transfer. Early identification of palliative care needs and an early decision-making concerning mode of discharge may be important to enable a transfer to further specialized palliative care supply.

Taken together, our results suggest the need for adaption, further validation, and use of a screening tool that could help to increase awareness of unmet palliative care needs of neurological patients in the ED (32–34). The variables we propose to incorporate in such a screening tool would be symptom burden, functional status, and estimated prognosis. Trigger for ED clinicians to apply such screening tool should be a diagnosed or highly suspected, life-limiting primary neurological disease or affection of the nervous system by other life-limiting illnesses. For the variable "symptom burden," we would suggest that the existence of a minimum of two uncontrolled (neurological and/or palliative care) symptoms of at least two different dimensions (physical, social, psychological) should be required, as our patients presented with a median of two chief complaints. For assessment of the variable "functional status," we would suggest using ECOG as a straightforward and well-established tool in palliative care assessment, which has also shown to be associated with prognosis (24, 34, 35). For prognosis estimation, we would incorporate the 12-month "surprise" question (12-SQ), as it has shown to help in assessing the urgency of palliative care integration in oncological as well as neurological patients (34–37).

We believe that such an instrument could help to initiate specialized palliative care consultation as early as possible in the trajectory of in-hospital care.

LIMITATIONS

Firstly, our study focused on patients who were admitted *via* the ED and consequently received palliative care in a neurological ward. Those who were initially admitted solely for end-of-life care are not systematically included, because they do not regularly receive specialized palliative care through our consultation service. In addition, no standardized assessment was performed to decide whether a patient should receive palliative care consultation or not. Patients who were able to be discharged from ED were also not considered in this study. Therefore, we cannot quantify the overall number of patients with neurological chief complaints and palliative care needs who present to the ED.

Secondly, our study is restricted by its retrospective design. ED documentation usually is a brief summary of patients' complaints. Missing information can be either because information was not gathered or because documentation was failed. It also leaves questions like how many patients were already receiving palliative care before being admitted to the ED unanswered—an aspect that definitively should be considered in future, prospective studies.

CONCLUSION

Causes for admission of neurological patients with palliative care needs are broad and include acute events, exacerbation of chronic symptoms, and potentially avoidable problems. Patients already present with complex symptom burden in the ED.

However, ED assessment is not sufficient to display the full multidimensionality especially when it comes to psychosocial problems. Prospective studies should follow to develop short screening tools to identify palliative care needs of patients with chronic neurological diseases at the very beginning: in the emergency department.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Ethics Committee of Charité—Universitätsmedizin Berlin. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

A-CW designed the study, acquired the data, performed the descriptive statistics, and drafted the manuscript. CP provided important methodological advice and revised the manuscript. AK designed the study, acquired the data, supervised the study, and revised the manuscript for intellectual content. All authors contributed to the article and approved the submitted version.

FUNDING

We acknowledge support from the German Research Foundation (DFG) and the Open Access Publication Fund of Charité—Universitätsmedizin Berlin.

ACKNOWLEDGMENTS

We thank all members of the specialized palliative care consultation service for their excellent work and reliable collaboration.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

SYSTEMATIC REVIEW
published: 04 August 2021
doi: 10.3389/fneur.2021.683197

Communication About End of Life for Patients Living With Amyotrophic Lateral Sclerosis: A Scoping Review of the Empirical Evidence

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Background: Communication about end of life, including advance care planning, life-sustaining therapies, palliative care, and end-of-life options, is critical for the clinical management of amyotrophic lateral sclerosis patients. The empirical evidence base for this communication has not been systematically examined.

Objective: To support evidence-based communication guidance by (1) analyzing the scope and nature of research on health communication about end of life for amyotrophic lateral sclerosis; and (2) summarizing resultant recommendations.

Methods: A scoping review of empirical literature was conducted following recommended practices. Fifteen health-related and three legal databases were searched; 296 articles were screened for inclusion/exclusion criteria; and quantitative data extraction and analysis was conducted on 211 articles with qualitative analysis on a subset of 110 articles that focused primarily on health communication. Analyses summarized article characteristics, themes, and recommendations.

Results: Analysis indicated a multidisciplinary but limited evidence base. Most reviewed articles addressed end-of-life communication as a peripheral focus of investigation. Generic communication skills are important; however, substantive and sufficient disease-related information, including symptom management and assistive devices, is critical to discussions about end of life. Few articles discussed communication about specific end-of-life options. Communication recommendations in analyzed articles draw attention to communication processes, style and content but lack the systematized guidance needed for clinical practice.

Conclusions: This review of primary research articles highlights the limited evidence-base and consequent need for systematic, empirical investigation to inform effective communication about end of life for those with amyotrophic lateral sclerosis. This will provide a foundation for actionable, evidence-based communication guidelines about end of life. Implications for research, policy, and practice are discussed.

Keywords: advance care planning, amyotrophic lateral sclerosis, health communication, palliative care, terminal care, review

OPEN ACCESS

Edited by:
David John Oliver, University of Kent, United Kingdom

Reviewed by:
Ambereen Mehta, Johns Hopkins Bayview Medical Center, United States
Nuno Tavares, University of Portsmouth, United Kingdom

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Specialty section:
This article was submitted to Neurocritical and Neurohospitalist Care, a section of the journal Frontiers in Neurology

Received: *20 March 2021*
Accepted: *09 July 2021*
Published: *04 August 2021*

Citation:
Genuis SK, Luth W, Campbell S, Bubela T and Johnston WS (2021) Communication About End of Life for Patients Living With Amyotrophic Lateral Sclerosis: A Scoping Review of the Empirical Evidence. Front. Neurol. 12:683197. doi: 10.3389/fneur.2021.683197

INTRODUCTION

Communication about advance care planning, life-sustaining therapies, palliative care and other options in the last months of life is central to the clinical management of fatal neurological diseases, such as amyotrophic lateral sclerosis (ALS) (1–5). ALS is a degenerative motor neuron disease characterized by progressive motor impairment leading to severe disability and eventual respiratory failure (6). ALS incidence is between 0.6 and 3.8 per 100,000 person-years and its prevalence is 4.1–8.4 per 100,000 persons (7); it is considered a "rare disease" (8). Patients living with ALS confront significant practical and existential losses (9–12) as they contend with an uncertain and variable disease trajectory, a median overall survival of 30 months after symptom onset, and a 5–10% survival rate one decade after diagnosis (13, 14). Accordingly, there is a need for clear and frequent communication with patients and their families over the course of the disease (15).

Timely and ongoing discussion about end of life (including advance care planning, technology for symptom management, palliative care, and other end of life options) is particularly important for ALS patients. Therapies introduced for symptom management, such as non-invasive ventilation, may rapidly become life-sustaining, thus changing the natural disease trajectory and making it difficult to predict when a patient is entering the last months of life (16, 17). Further, many patients experience substantial functional communication and cognitive difficulties, which may interfere with communication at later stages of the disease (6). Effective discussions about end of life help alleviate anticipatory fears, especially around choking (6); guide decisions about life-sustaining therapies (18–20); facilitate decisions that are consistent with patients' and families' priorities and needs over time (6, 21, 22); and preserve patient autonomy and dignity (23).

Compounding a complex communication environment and in the ongoing absence of a cure or treatment, ALS is perceived by patients and their families as a "death sentence" (24), "the self under attack" or a "downward journey" (25). This is in contrast to the empowering representation of "fighting" diseases with multiple treatment options, such as many cancers (26, 27). Moreover, increasing discussion and legalization of voluntary assisted death across jurisdictions, including both physician-assisted suicide and euthanasia (28–30), and a focus on ALS in court cases, case studies published in medical journals, and media portrayals of voluntary assisted death (31–35) raises the possibility that this option may become the focus of end-of-life discussions with ALS patients, highlighting the need for effective communication about end-of-life decision-making.

Consensus-based guidelines from Canada, Europe and the United States recommend discussing preferences for life-sustaining therapies and end-of-life care on a regular basis with ALS patients (16, 36, 37). However, guidelines for discussions about end of life with ALS patients have not been published. Communication guidelines have focused on the disclosure of the ALS diagnosis, offering clinicians specific guidance for introducing and discussing the challenges of this rapidly progressing, neurodegenerative disease (36, 38, 39).

Published reviews focusing on quality of care and quality of life (40), end-of-life management (41), and palliative care information needs of ALS patients (42) have also drawn attention to the importance of communication about end of life for people living with ALS. However, there is need for a structured, systematic, and evidence-informed approach to this communication (43). Given the recognition that research evidence is as important in palliative care as it is in other fields of medicine (44), this scoping review investigates the scope and nature of empirical articles on communication about end of life with ALS patients, identifies gaps, and provides a foundation for empirically-based, communication guidelines for discussions about end of life with ALS patients.

METHODS

Identification of Research Question

A team of experts from fields including neurology and health communication were consulted to identify goals and research questions for this scoping review. Identified goals were to understand the empirical evidence base, identify research gaps, determine research opportunities, and provide a foundation for clinically focused communication guidelines. Specifically, the review addressed two research questions: (1) What is the scope and nature of published research on ALS and health communication about end of life? And (2) what, if any, recommendations are made in primary research articles whose central focus is end-of-life communication with patients living with ALS?

Design

Scoping reviews are commonly undertaken when there is a broad question, a range of study designs, no prior knowledge synthesis on the topic, and an interest in identifying gaps and envisaging future research directions (45–48). The methodology used for this review was based on Arksey and O'Malley's five stages for scoping reviews: (i) identify the research question; (ii) develop the search strategy; (iii) apply inclusion and exclusion criteria to select articles; (iv) chart and collate the data; and (v) summarize and report the results (45). In accordance with recommendations for scoping reviews (47, 48), a quantitative, numerical summary analysis, followed by a qualitative thematic analysis of the subset of articles whose central focus was communication in the context of ALS and end of life was conducted. The discussion section completes the summary and reporting stage as it focuses on the meaning and implications of the study findings (47).

Data Sources and Search Strategy

An expert health sciences librarian developed search strategies for the following electronic databases: MEDLINE (Ovid), EMBASE (Ovid), PsycINFO, CINAHL (EBSCO), SCOPUS, Dissertations and Theses Global (Proquest), and Web of Science, and EMB Reviews (Ovid) including Cochrane Database of Systematic Reviews, ACP Journal Club, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials, Cochrane Methodology Register, Health Technology Assessment, and NHS Economic Evaluation Database. The following legal databases

were also searched: Westlaw, Heinonline and the Factiva subcategory "US law reviews and journals." Search algorithms used controlled vocabulary within databases and synonyms for "amyotrophic lateral sclerosis," "end of life," and "health communication." Date or other limits were not applied. Initial searches were completed in October 2015 and updated in January 2018. A second update was conducted in May 2021. At the time of the second update, all the EMB Reviews (Ovid) databases had been replaced by Cochrane Library (CDSR and Central Register of Controlled Trials). The search strategy used for Medline is included as a sample in **Supplementary File 1**; other detailed search strategies are available from the corresponding author.

Application of Inclusion/Exclusion Criteria

Article records, including titles and abstracts, were retrieved and uploaded to bibliographic management software (Endnote 7). For the initial search and 2018 update, four coders removed duplicates and applied the inclusion/exclusion criteria to the article records that met the search criteria. Articles meeting the following criteria were included: (1) reported primary quantitative and/or qualitative empirical data; (2) addressed end of life for people with ALS; (3) discussed health communication; and, (4) were published in the English language. Health communication was defined as per the Medical Subject Headings (MeSH) thesaurus: the transfer of information from experts in the medical and public health fields to patients and the public, and the study or use of communication strategies to inform and influence health-related decisions (49). All coders received training and discrepancies were resolved through discussion to consensus during the training period. Coders then screened 10% of the article records and inter-coder reliability was determined by calculating the Light's kappa coefficient in Microsoft Excel as 0.87. Each coder independently screened one quarter of the remaining records. This same process was followed when assessing the full text articles. Based on 10% of the articles the Light's Kappa coefficient was calculated as 0.81. Two coders completed the 2021 update. The Kappa coefficient was calculated as 0.99 for screening the article records and coding the included full text articles.

Quantitative Data Extraction and Analysis

Based on the research questions and expert input a web-based, standardized data extraction sheet was developed. Each selected article was coded for: bibliographic information, jurisdiction where the study was conducted, research design, study methods, participant population, sample size, quality of life and family burden, discussion of voluntary assisted death, and peripheral or primary focus on health communication. Three trained coders extracted data from the selected full text articles. The calculated Light's Kappa coefficient was 0.74. The Kappa coefficient for the 2021 update was 0.99. Numerical summary analysis was conducted based on the data extracted to a priori categories (47, 50).

Qualitative Analysis and Synthesis

Qualitative, inductive analysis was conducted on the subset of articles that were coded during quantitative analysis as having primary focus on health communication (the "communication subset"). Based on the research questions and expert input, key concepts and themes were identified using an iterative approach. Discussion to consensus was achieved by working through a small sample of articles. One coder coded the communication subset; the second coder coded 10% of the articles. Based on this 10%, the Kappa coefficient was assessed as 0.97 (initial and 2018 update) and 0.94 (2021 update) for the qualitative analysis. NVivo 10 software facilitated data organization and qualitative coding.

RESULTS

Study Screening and Inclusion

Literature searches returned 2,477 unique article records, of which 296 were potentially relevant and eligible for full-text review. Of these, 211 met the review's inclusion criteria for quantitative analysis. (See **Supplementary File 2** for list of included studies). One hundred and ten articles focused explicitly on health communication. These comprised the 'communication subset' and were included in qualitative thematic analysis (**Figure 1**).

Quantitative Analysis of all Articles ($n = 211$)

Distribution of Articles

There was a modest upward trend in publications from 1991 to 2020 (**Figure 2**), with the majority of publications published after 2011 (51%) and peaks in 2014 and 2015. Four articles from the first 4 months of 2021 met the inclusion criteria. The reviewed

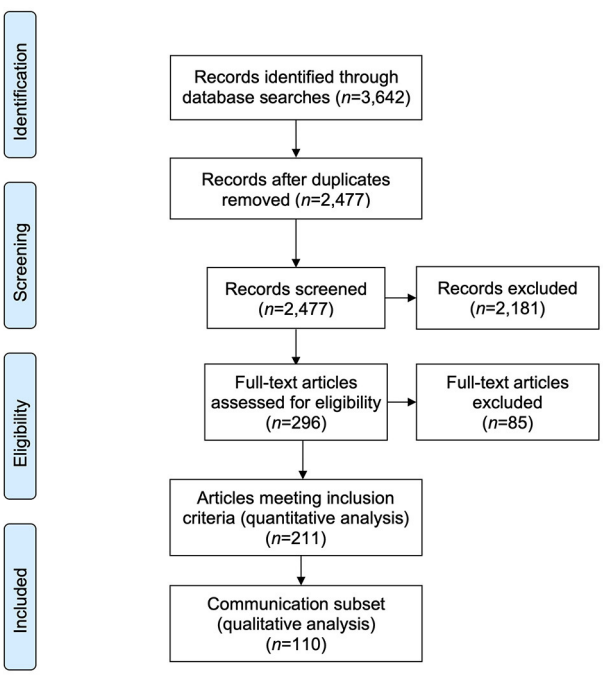

FIGURE 1 | PRISMA flow: Article selection process.

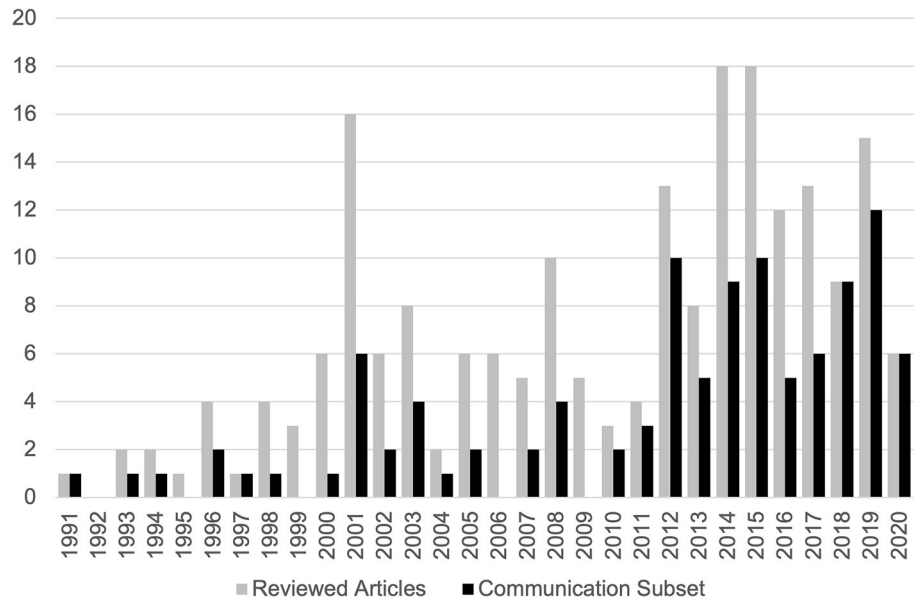

FIGURE 2 | Distribution of reviewed articles and communication subset by year.

TABLE 1 | Distribution by journal title.

Journal title	Reviewed	Communication focus
Neurology	28	4
Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration*	28	13
Journal of the Neurological Sciences	17	9
Palliative Medicine	10	8
Journal of Neurology	8	3
Journal of Pain and Symptom Management	7	3
Palliative and Supportive Care	7	4

**formerly indexed as Amyotrophic Lateral Sclerosis and Other Motor Neuron Disorders (2000–2004) and Amyotrophic Lateral Sclerosis (2005–2012).*

TABLE 2 | Distribution by Web of Science journal subject category.

Journal subject category	Reviewed articles ($n = 211$)
Clinical Neurology-SCIE*	105
Health Care Sciences & Services-SCIE	40
Medicine, General & Internal-SCIE	19
Public Environmental & Occupational Health-SSCI**	19
Health Policy & Services-SSCI	10
Other ($n = 25$ subject categories)	40

** Science Citation Index.*
*** Social Science Citation Index.*

articles ($n = 211$) were published in 84 different journals. Articles in the communication subset ($n = 110$) were published in 60 different journals. Seven journals published more than five reviewed articles each and almost 50% ($n = 105$) of the reviewed articles (**Table 1**). Reviewed articles were primarily published in journals identified by five non-exclusive Web of Science journal subject categories (**Table 2**). Eleven articles were published in journals not indexed by Web of Science.

Article Characteristics

Table 3 summarizes the general characteristics of the included articles ($n = 211$). In addition to the United States, European Union, United Kingdom, and Canada, studies were conducted in Japan, Taiwan, Singapore, Korean, Australia, and Israel. Studies used quantitative, qualitative, and mixed methods. Most included ALS patients or family members, with both groups being included in 69 articles. Study sample sizes ranged from two (a qualitative document analysis) to 1,636 (administrative data analysis). The 42 articles with healthcare professionals as participants included small interview-based studies (<35 participants), larger questionnaire-based studies (>100 participants), and studies that focused on care teams in multidisciplinary clinics.

Quality of Life

Of the 211 articles, 68% ($n = 144$) addressed quality of life (QoL) as experienced by patients ($n = 120$), or the perspectives of family ($n = 41$) and healthcare professionals ($n = 11$) on patients' QoL. These articles addressed the physical domain ($n = 116$), psychological/emotional domain ($n = 104$), social functioning domain ($n = 60$), religious/spiritual domain ($n = 41$), and financial domain ($n = 31$); 107 articles discussed more than one domain.

TABLE 3 | Study characteristics.

Study characteristic	*n* = 211 (%)
Jurisdiction*	
United States	73 (34.6%)
European Union	71 (33.6%)
United Kingdom	23 (10.9%)
Canada	16 (7.6%)
Other	37 (17.5%)
Study design	
Quantitative	132 (62.6%)
Qualitative	55 (26.1%)
Mixed methods	24 (11.4%)
Study methods*	
Quantitative methods	
Questionnaire	112 (53.1%)
Cohort study	39 (18.5%)
Other quantitative methods**	25 (11.8%)
Clinical trial	7 (3.3%)
Case control	7 (3.3%)
Qualitative methods	
Interview	61 (28.9%)
Other qualitative methods**	9 (4.3%)
Document analysis	6 (2.8%)
Focus group	6 (2.8%)
Case study	2 (0.9%)
Participants*	
ALS patients	160 (75.8%)
Family members/informal caregivers	94 (44.5%)
Health care professionals	42 (19.9%)
General population	3 (1.4%)

**Articles from multiple jurisdictions or using multiple methods are included in each relevant category.*

***Articles using quantitative or qualitative methods not included in the data extraction sheet, for example, health economic analysis and chart review.*

Family Burden

The articles ($n = 82$) that addressed family burden addressed burden associated with the psychological/emotional domain ($n = 69$), social functioning domain ($n = 31$), physical domain ($n = 30$), financial domain ($n = 22$), and unspecified domain ($n = 28$); 58 articles addressed more than one domain. Three articles addressed the psychological/emotional burden associated with concerns about familial ALS genetic risk. Sixty-five articles addressed both QoL for patients living with ALS and family burden, and 20 articles identified changes in family dynamics as a factor in patient QoL and/or family burden.

End of Life and Voluntary Assisted Dying

One hundred and twenty-three articles included the views or perspectives of ALS patients, family members, and/or healthcare professionals about end-of-life choices or options (**Table 4**), including palliative care, withdrawal of treatment, palliative sedation, and voluntary assisted death. The majority of articles focused on end-of-life options without discussing voluntary assisted death (60.6%; $n = 77$); 6.5% ($n = 8$) articles focused on voluntary assisted death exclusively.

Quantitative and Qualitative Analysis of the Health Communication Subset ($n = 110$)

Eighty-one articles within the health communication subset ($n = 110$) highlighted the importance of discussions about end of life for people living with ALS. Twenty-eight articles noted the influence of communication on patient care, and 19 noted its influence on the therapeutic relationship between healthcare professionals and patients and/or their families. Fifty-five articles discussed communication about specific end-of-life options; 13 noted voluntary assisted death. Thirty-three articles included discussion of symptom management at end of life, for example, nutritional or respiratory support. Themes identified in the communication subset included communication quality (communication barriers and facilitators) ($n = 81$), difficult conversations ($n = 72$), and functional communication challenges ($n = 45$) (**Table 5**).

Articles that addressed the quality of communication between patients with ALS, families and healthcare professionals noted facilitators ($n = 40$) and barriers ($n = 57$). Facilitators and barriers were characterized not only by communication style, but also by information substance (*what* is communicated) and sufficiency (*enough* information to meet patient need). As might be anticipated, for example, ALS patients and their families valued open and/or "honest" communication with health care professionals (39, 51, 52, 106). In addition, researchers exploring the experiences of ALS caregivers noted that a lack of empathic communication "left the participants feeling shocked, bewildered, angry and devastated" (53). However, this current analysis found that a greater number of articles highlighted the importance of meeting the information needs of patients and families. For example, researchers investigating decisions about life-sustaining treatments reported, "the provision of full information was paramount, which in some cases included providing information in different formats" (54), and neurologists who provided needed or desired information were rated more highly by family caregivers (55). Further, a reviewed study found that ALS patients who "lack communication, information, and clear answers from health providers" experienced "frustration and despair due to a limited life time" (56). Seventeen articles noted seeking information outside the medical system, including online, from interpersonal sources and/or from patient advocacy organizations (18, 51, 54, 57–67, 118, 119, 148).

Of the 72 articles that addressed "difficult conversations," 38 noted avoidance of end-of-life discussions by ALS patients, their families, and/or healthcare professionals. Twenty-four articles focused on communicating an ALS diagnosis. Articles drawing attention to functional communication challenges related to a motor speech disorder ($n = 45$) primarily highlighted the severity of communication impairments ($n = 27$) and strategies to address speech loss ($n = 22$) (**Table 5**).

TABLE 4 | Views represented in articles discussing end-of-life options and/or voluntary assisted death.

n = 123 (%)	ALS patients	Family members	Health professionals	End-of-life options/voluntary assisted death
123	101	39	30	End-of-life options discussed
77	61	29	20	End-of-life options; not voluntary assisted death
38	33	7	9	End-of-life options, including voluntary assisted death
8	7	3	1	Voluntary assisted death; not other end-of-life options

Recommendations

Sixty-seven articles made "actionable" recommendations. These were represented by statements of "how" or "what" should be done to improve communication. Recommendations were thematically analyzed. For example, articles with a thematic focus on improving communication processes (actions and steps needed to communicate effectively) included recommendations for the timing of communication about end of life, potential communication mediums (visual, written, web-based), and collaboration between clinicians.

Recommendations in the analyzed articles focused on improving communication processes ($n = 36$), improving communication style ($n = 21$), and improving or changing the content of information communicated to ALS patients and their families ($n = 21$). The 2021 update resulted in one substantial change: 14 articles from 2018 to 2021 recommended 'more research' whereas only 4 articles between 1991 and 2017 made this recommendation. Fifteen articles noted a need for communication guidelines or standards, and 15 made a range of recommendations for improving the training of health professionals. A small number of articles specifically recommended shared decision-making ($n = 5$), use of decision-making aids ($n = 4$), and the importance of supporting the patient-caregiver relationship ($n = 2$).

Forty-seven articles directed recommendations to health care professionals; 25 did not specify *who* should carry out the recommended action; and 18 articles made recommendations for researchers. Actionable recommendations were also directed toward health systems ($n = 9$), medical educators ($n = 8$), ALS support organizations ($n = 3$), and family members of patients living with ALS ($n = 3$). **Table 6** summarizes analysis of the recommendations found in the included articles.

DISCUSSION

Main Findings of the Scoping Review

This review identified a limited evidence base and lack of comprehensive recommendations for health communication about end of life with ALS patients. Despite increasing discussion and legalization of voluntary assisted death across jurisdictions (28–30) and its implications for ALS patients (30, 149, 150), there has been only a modest increase over time in empirical investigations of communication about end of life for this population. Moreover, most of the reviewed articles addressed end-of-life communication as a peripheral focus of investigation. In keeping with other studies, this review highlights the need for generic communication skills, including empathy and relationship building (151–154). Findings, however, bring attention to the importance of providing substantive and sufficient disease-related information, including information about symptom management and assistive devices, when discussing end-of-life issues. For people living with ALS, decisions about symptom management, for example dyspnea or dysphagia, may change the natural disease trajectory as technologies introduced for symptom management become life-support technologies (16). Recommendations for communication about end of life with ALS patients primarily target health professionals, providing only general suggestions for improving communication rather than specific, actionable guidelines similar to published guidelines for disclosing an ALS diagnosis (36, 38, 39). The following paragraphs discuss the scope of end-of-life, ALS-focused communication research, perceptions of communication quality, unique challenges for discussions of end of life with ALS patients, and a need for "actionable" communication recommendations that might guide effective communication in clinical practice.

The findings in this review highlight the multidisciplinary nature of health communication research and the concomitant challenge of finding a "home" for ALS-related communication research. Although advances with keyword searching and access to multiple databases mitigate some of these challenges, reviewed articles were published across a wide range of journals and were identified by heterogeneous and poorly standardized database subject headings (155–157). This may introduce challenges for clinicians seeking to find ALS-specific, evidence-based guidance for discussing end of life.

Quality of life for ALS patients and, to a lesser extent, family burden has been widely examined in the ALS literature. These themes appear prominently in the current review, with physical and psychological/emotional domains discussed most frequently as related to one another. For example, articles suggested that planning for end of life was influenced by fear of physical symptoms and of being a burden to loved ones (33, 158, 159). Although communication about the physical aspects of end of life may be viewed as a central task for healthcare professionals, findings suggest, unsurprisingly, that psychological/emotional, social, religious, and even financial factors may also be important aspects of end-of-life communication. In addition to the psychological and emotional toll on ALS patients and their families, research demonstrates substantial emotional burden for healthcare professionals caring for people with terminal neurological disease (41). While patient voices were well represented in the review, articles were less likely to examine the perspectives of healthcare professionals. Given the role that

TABLE 5 | Themes identified in the health communication subset.

Themes	*N* = 110 (%)	References
Communication barriers	57 (51.8%)	(18, 19, 39, 51–104)
Insufficient information given about disease and/or assistive devices	31 (28.2%)	(18, 52, 54–58, 60–63, 65–67, 69, 74, 75, 79, 81, 83–85, 87, 89, 90, 92, 96–98, 102, 105)
Lack of options communicated by Health professionals (symptom management and/or end of life)	14 (12.7%)	(51, 55, 58–60, 68, 71, 74, 77, 86, 93, 96, 97, 103)
Health professional is perceived to lack compassion	11 (10.0%)	(18, 53, 55, 64, 70, 73, 84, 88, 97, 102, 103)
Patients and/or family perceives lack of respect or dignity	9 (8.2%)	(53, 55, 56, 59, 60, 65, 88, 102, 103)
Patients and/or family interest in ALS information limits communication	6 (5.5%)	(19, 63, 66, 69, 82, 87)
Patients and/or family experiences negative emotion when communicating with health professional	4 (3.6%)	(61, 70, 71, 88)
Health professional does not have the information to answer question(s)	6 (5.5%)	(65, 70, 72, 91, 98, 103)
Health professional is reluctant to address end of life	9 (8.2%)	(51, 66, 78, 80, 97–101)
Communication is "forced" by an individual or by disease progression	6 (5.5%)	(39, 70, 91, 95, 97, 104)
Communication facilitators	40 (36.4%)	(18, 19, 33, 39, 51, 52, 54–57, 59, 61–63, 68–70, 72, 73, 76, 80, 81, 83–85, 91, 92, 96–98, 103, 106–114)
Health professional is perceived to be friendly or kind	21 (19.1%)	(18, 39, 48, 49, 55–59, 70, 71, 78, 79, 83, 89, 90, 95, 96, 101, 115, 116)
"Sufficient" information given about disease and/or assistive devices	25 (22.7%)	(18, 39, 52, 54, 55, 57, 62, 63, 68–70, 80, 81, 84, 91, 92, 96–98, 103, 111–114, 117)
Access to health professionals, for immediate information needs and ongoing communication or support	16 (14.5%)	(19, 33, 39, 56, 72, 76, 80, 91, 92, 97, 98, 108–110, 112, 114)
Patients and/or family feels satisfied with communication	8 (7.3%)	(18, 61, 63, 73, 85, 91, 92, 103)
Health professional is perceived to be empathetic and/or trustworthy	6 (5.5%)	(55, 59, 80, 81, 97, 103)
Open and/or honest communication	4 (3.6%)	(39, 51, 52, 106)
Patients and/or family feels respected	4 (3.6%)	(39, 70, 91, 107)
Difficult conversations	72 (65.5%)	(18, 19, 33, 39, 51, 52, 54–56, 58, 60, 62–70, 72, 73, 75, 76, 78–82, 87, 89, 92, 93, 93–105, 107–111, 114, 118–137)
End-of-life discussion avoidance	38 (34.5%)	(18, 33, 39, 52, 54, 58, 60, 62–64, 68, 69, 75, 76, 82, 93, 94, 96–100, 103, 107, 109, 114, 118–123, 125, 127, 130, 132, 134, 135)
Timing for difficult conversations	39 (35.5%)	(19, 33, 51, 54, 62, 63, 76, 79, 87, 107, 108, 122, 124, 125, 127, 132, 133, 138)
Delivering bad news, health professionals' perspectives	16 (14.5%)	(69, 73, 80, 81, 87, 93, 94, 97, 99–101, 107, 109, 111, 122, 124)
Health professional reluctance to address prognosis	6 (5.5%)	(69, 87, 93, 97, 107, 109)
Clinical education to prepare health professionals for difficult conversations	13 (11.8%)	(39, 55, 67, 73, 78, 80, 81, 89, 97–99, 128, 130)
Delivering the ALS diagnosis	25 (22.7%)	(18, 39, 53, 55, 57, 60–63, 69, 73, 80–85, 94, 109, 117, 124, 128, 133, 139, 140)
Method for delivering diagnosis	13 (11.8%)	(39, 55, 57, 60, 62, 63, 73, 80, 81, 85, 124, 128, 139)
Badly communicated diagnosis	11 (10.0%)	(18, 53, 55, 60, 61, 73, 81, 83, 84, 117, 140)
Effective communication of diagnosis	5 (4.5%)	(55, 61, 81, 83, 133)
Skilled delivery of diagnosis is important	5 (4.5%)	(55, 73, 81, 94, 109)
Functional communication challenges	45 (40.9%)	(18, 33, 39, 51, 52, 56–58, 63, 64, 67, 71, 76–78, 82, 83, 85, 86, 88, 90, 92–94, 98, 102, 105, 108, 113, 114, 117–119, 127, 132, 134, 138, 139, 141–147)
Severity of communication impairment	27 (24.5%)	(18, 33, 51, 52, 56, 58, 63, 64, 71, 76, 77, 83, 86, 88, 92, 93, 98, 108, 117, 132, 134, 138, 141–145)
Strategies to address speech loss, including AAC	22 (20.0%)	(39, 51, 52, 56–58, 67, 71, 85, 86, 88, 92, 105, 108, 113, 114, 117, 119, 134, 145, 146)
Emotional and social impact of communication challenges	13 (11.8%)	(52, 56, 71, 82, 86, 88, 92, 113, 114, 117, 118, 134, 143)
Impact of devices (e.g., ventilator) on communication	7 (6.4%)	(52, 67, 71, 92, 117, 127, 145)
Effect of AAC on QoL	5 (4.5%)	(52, 67, 71, 88, 94)

TABLE 6 | Actionable recommendations for improving health communication ($n = 110$).

Recommendations (number of articles)	Target group (number of articles)	Examples
Improve communication practices and/or processes (36)	Health professionals (28), Health systems (8), ALS support organizations (2), Family members (2), Unspecified (3)	*Use of advance directives and collaboration with other related practitioners are recommended to enhance communication linked to psychological care and informed consent.* (76)
Improve communication style (21)	Health professionals (17), Medical education (1), Unspecified (3)	*Use language that patients and their families can understand.* (92)
Improve or amend communication content (21)	Health professionals (14), Family members (1), Unspecified (7)	*…fears of "choking to death" are unwarranted. This information should be available to ALS patients at the time when ventilatory options are discussed.* (89)
More research is needed (18)	Researchers (18)	*…qualitative research in this area is needed to fully understand ACP [advance care planning] preferences and practices among patients...* (129)
Communication guidelines or standards needed (15)	Health professionals (4), ALS support organizations (1)„ Medical education (1), Researchers (1), Unspecified (12)	*More widely available guidelines for the provision of gastrostomy and advice on the best way to impart information to patients and caregivers about gastrostomy and NIV appear to be needed.* (125)
Improve health professionals' training (15)	Medical education (8), Health professionals (4), ALS support organizations (1), Researchers (1), Unspecified (7)	*Medical educators must strive to understand their students' perspectives, adapt their teaching so that they impart compassionate and clinically astute end-of-life care practices...* (78)
Facilitate shared decision-making (5)	Health professionals (5), Health systems (1)	*… the patient and caregiver function as a team, and the caregiver should be included in discussions on treatment and care.* (75)
Use decision-making aids (4)	Health professionals (1), Unspecified (3)	*Our study supports the view that PPC [preferred priorities for care] document should also be offered to MND/ALS patients as a standard of care.* (121)
Improve the patient-caregiver relationship (2)	Health professionals (1), Family members (1)	*Caregivers should take care not only of the patient, but also of themselves, in order to offer adequate support to their loved ones.* (60)

healthcare professionals play in discussing end of life with ALS patients, more research on healthcare professionals' perspectives is needed as a step toward developing guidance for end-of-life communication.

Voluntary assisted death, when discussed, was primarily contextualized within an overarching discussion of end-of-life options. Within the communication subset, very few articles noted assisted death. These findings may be an artifact of the lag between legislative changes and empirical investigation. They may also reflect a tendency toward symptom-driven communication rather than end-of-life discussions that are integrated into clinical care. For example, discussions about end of life may occur in tandem with decisions about initiating, continuing, and/or discontinuing life-sustaining interventions such as mechanical ventilation or enteral feeding tubes. Attitudes toward end-of-life options, including voluntary assisted death, vary across regions and cultures (28, 160, 161). With high mobility within populations, increasing attention to the influence of culture and personal beliefs on advance care planning and decisions for people with ALS (41, 118, 120, 162), and increasing access to voluntary assisted death in many jurisdictions (28, 29), the need for patient-centered evidence and communication guidance is increasingly important for sensitive, effective communication about palliative care and end-of-life options.

The integral role of communication for end-of-life care is documented in the palliative care literature (5, 163, 164). Yet, fewer than half of the selected articles focused explicitly on health communication. These articles—the communication subset—indicate that, despite the importance of online disease-related information (165–168) and support (169, 170) for ALS patients, healthcare professionals are critical information sources for patients and their families. This suggests an important role for professionals both in providing information about end of life, and helping people make sense of information from online sources. Although information needs have been identified as an important domain at the time of the ALS diagnosis (61, 165, 171), research is needed to identify and better understand the information that ALS patients and families want and need to make decisions that influence the disease course and end of life. For example, in contrast to cancer patients, life-sustaining interventions such as nutritional and respiratory support are considered "standard of care" for people living with ALS and are positively associated with improved quality of life (172, 173). Communication about accepting or forgoing such interventions is, therefore, particularly relevant to ALS (and, perhaps, other neurodegenerative disorders). It follows that information about the nuances and practicalities of palliative sedation for the withdrawal of such life-sustaining interventions is important for people with ALS and their families.

Many of the communication challenges identified by this review are not unique to people living with ALS. For example, both this review and the palliative care literature identifies healthcare professionals' reluctance to address prognosis and end-of-life discussion avoidance (41, 115, 174, 175); difficulties identifying appropriate times for conversations about end of life (5, 115, 164); and the changing needs of patients (163). ALS, however, presents additional communication challenges. First, findings demonstrate that disclosing an ALS diagnosis is

closely associated with discussions about end of life. Second, throughout the disease course, clinicians must effectively communicate both the chronic and terminal facets of ALS (107). For example, clinicians must guide patients and families through iterative decisions about initiating, maintaining and potentially withdrawing life-sustaining support for nutritional and respiratory needs. Finally, this analysis highlighted functional communication challenges. Almost all ALS patients experience motor speech disorder with disease progression (176, 177). This presents a unique challenge for those seeking to facilitate full and ongoing patient participation in discussions and decisions about end of life.

Thematic analysis makes an important contribution to understanding of the recommendations emerging from the analyzed articles. A small number of themes with specific application were identified (for example, four articles recommended the use of decision aids). However, most recommendations were limited to the specific interventions or gaps in care identified in individual articles and lacked the systematized guidance that is required to operationalize findings for clinical practice. Thematic analysis, however, draws attention to three aspects of communication: processes, style, and the content of communicated information. Findings indicated a primary need for improved communication processes, for example, discussion of end-of-life issues both early and incrementally throughout the disease trajectory (52, 121). Providing substantive information that meets the needs of patients and families was equally important to communication style in the recommendations. These findings draw attention to a need for focused empirical investigation of concrete, evidence-based communication strategies, and the development clinical communication guidelines for discussions about end of life with people living with ALS.

The paucity of focused, end-of-life communication research and the lack of progress in the development of empirically-based communication guidelines for ALS may reflect the tendency for research funding to target marketable interventions and therapies (178, 179). Even among non-profit ALS Societies the overwhelming majority of research funding is directed toward laboratory research, pharmacological interventions, and devices (180–182). Topics such as health communication, which reside at the intersection of Medicine and the Social Sciences, tend to receive limited funding.

Implications for Research, Policy and Practice

Empirically derived data about end-of-life discussions with ALS patients are primarily embedded in broadly focused investigations. Although there was a small increase in empirical articles, systematic investigation of communication about end of life is limited. The scarcity of research focused on communication, and the increasing number of empirical articles recommending more research in this area, may also reflect a need for proven research methodologies, as well as knowledge and expertise, that will address this evidence gap. Clinicians and researchers need to think of novel, patient-oriented methods to investigate both the communication practices of clinicians and the needs of ALS patients for information about end of life, both at the time of diagnosis and throughout the disease course. Investigations should yield specific, actionable recommendations for translation into policy and practice. This will provide a foundation for developing guidelines supporting end-of-life communication between health professionals and ALS patients and their families.

As discussed, findings may reflect policies and practices that direct research funding to marketable interventions and therapies. Despite the importance of these activities, communication is critical to the clinical management of ALS. Policies that promote the funding of communication research will provide a foundation for developing an evidence-base for compassionate, effective, and ethical communication about end of life, as well as evidence-based communication training in educational institutions and via continuing education for health professionals who care for ALS patients.

Finally, this review has implications for medical practitioners. The wide range of journals publishing research in this area of investigation may compromise access for practicing clinicians. Highly ranked journals that are specific to neurology and palliative care should seek to provide a home for this body for research that represents both the science and "art" of medicine. Further, this review draws attention to communication quality as mediated not only by core communication skills, but also by information substance and sufficiency. While emotional connection is important, the clinical expertise and information communicated by health professionals builds trust and "ownership" of care decisions (181, 182).

Clinical discussion of issues related to end of life has substantial impact on care and facilitates compliance with patients' wishes (169). Actionable recommendations and guidance are needed to support clinicians caring for patients with ALS. This is particularly important because ALS specialists and multidisciplinary ALS clinics are concentrated in large urban centers that may become inaccessible with disease progression. ALS patients frequently begin to rely on support from palliative and community physicians at a time when they need expert and nuanced information. Developing a strong empirical foundation and end-of-life communication guidance will support both specialists and non-specialists as they iteratively discuss life-sustaining therapies and end-of-life issues with ALS patients and their families.

Strengths and Limitations

This investigation followed standard methodological recommendations for scoping reviews, as well as Levac et al.'s recommendations to include both numerical summary analysis and qualitative content analytical techniques when summarizing and reporting results (45, 47, 48). Recommendations to consider the review's implications within the broader contexts of research, policy and practice were also followed (47).

A primary strength of this review is the focus on primary research articles. Although many review and commentary articles that may provide insight into end-of-life communication were excluded, this review makes an important contribution by

documenting the paucity of empirical evidence in this area of investigation. Better understanding of the scope and nature of the evidence, both quantitative and qualitative, provides a starting point for systematically addressing evidence gaps. Further, because the review included all empirical articles available in the databases without time restriction, these data meet the study objectives and provide an overarching view of this research area.

There are limitations to this review. Critical appraisal of articles was limited to the application of inclusion/exclusion criteria. For example, articles that did not report primary quantitative and/or qualitative empirical data were excluded. The rigor of research processes within individual studies was not evaluated.Restriction to articles published in the English language presents another limitation. Communication, particularly about end of life, is rooted in cultural expectations and practice. Some of the review's outcomes could, therefore, be an artifact of the language restriction.

Finally, despite the profound impact of legislative changes on end-of-life decisions for ALS patients (68, 122, 150, 183), the heterogenous methods used in the fields of Medicine and Law presented a methodological limitation. Whereas empirical data are central to high quality evidence in scientific fields such as Neurology (184), legal research focuses on doctrinal and comparative analysis of authoritative texts with reasoning and conceptual analysis as an indicator of quality (116, 185). Therefore, articles published in legal journals did not meet study inclusion criteria. Although scoping review methodology facilitates review of articles with varying research designs (45), further methodological development is needed to facilitate review and analysis of high-quality evidence emerging from the disparate research traditions of Medicine and Law.

CONCLUSION

This review demonstrates a small increase in empirical articles discussing end-of-life communication with people living with ALS (1991–May 2021). Most reviewed articles were published in clinical neurology journals. However, the articles were published in large number of different journals with only a small number published in each. Overall, communication about the end of life remains a peripheral part of more broadly focused investigations. This review found that generic communication skills, such as expressing empathy, were important; however, information substance and sufficiency was central to high quality, effective health communication. Recommendations for clinical communication focused on communication processes, style, and content, but lacked systematic guidance. Despite the absence of communication guidelines for end of life, practice recommendations for the management of ALS encourage clinicians to discuss life-sustaining therapies and end of life with ALS patients (16, 36, 37). This review supports these recommendations by highlighting the need for focused, empirical investigation of best practices for end-of-life communication. This will provide a foundation for evidence-based, ALS-specific guidelines for communication about the end of life. Particularly with increasing options at end of life, actionable recommendations and guidance is needed to support ALS clinicians as they iteratively discuss life-sustaining therapies and end-of-life issues with patients and families.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

TB and WJ conceived the original study and developed the design and methods. SC prepared and executed the search strategy. WL and SG screened studies for inclusion and carried out data extraction for quantitative analysis and qualitative data analysis. SG and WL conducted the synthesis with input from TB and WJ. SG drafted the manuscript with contribution from WL, TB, and WJ. All authors contributed to the article and approved the submitted version.

FUNDING

The author(s) disclosed receipt of the following financial support for the research, authorship and/or publication of this article: James and Jeanie Brown ALS Research Fund, Edmonton, Canada.

ACKNOWLEDGMENTS

The authors gratefully acknowledge Mark Bieber, Caitlin Vail, Angela Lee, and Mackenzie Moir for their contributions to data analysis. We are also grateful for funding from the James and Jeanie Brown ALS Research Fund, Edmonton, Canada.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.683197/full#supplementary-material

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frontiers in Neurology

STUDY PROTOCOL
published: 05 August 2021
doi: 10.3389/fneur.2021.673893

Advance Care Planning and Care Coordination for People With Parkinson's Disease and Their Family Caregivers—Study Protocol for a Multicentre, Randomized Controlled Trial

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Specialty section:
This article was submitted to Neurocritical and Neurohospitalist Care, a section of the journal Frontiers in Neurology

Received: 28 February 2021
Accepted: 30 June 2021
Published: 05 August 2021

Citation:
Meinders MJ, Gentile G, Schrag AE, Konitsiotis S, Eggers C, Taba P, Lorenzl S, Odin P, Rosqvist K, Chaudhuri KR, Antonini A, Bloem BR and Groot MM (2021) Advance Care Planning and Care Coordination for People With Parkinson's Disease and Their Family Caregivers—Study Protocol for a Multicentre, Randomized Controlled Trial. Front. Neurol. 12:673893. doi: 10.3389/fneur.2021.673893

Background: Parkinson's disease (PD) is a progressive neurodegenerative disease with motor- and non-motor symptoms. When the disease progresses, symptom burden increases. Consequently, additional care demands develop, the complexity of treatment increases, and the patient's quality of life is progressively threatened. To address these challenges, there is growing awareness of the potential benefits of palliative care for people with PD. This includes communication about end-of-life issues, such as Advance Care Planning (ACP), which helps to elicit patient's needs and preferences on issues related to future treatment and care. In this study, we will assess the impact and feasibility of a nurse-led palliative care intervention for people with PD across diverse European care settings.

Methods: The intervention will be evaluated in a multicentre, open-label randomized controlled trial, with a parallel group design in seven European countries (Austria, Estonia, Germany, Greece, Italy, Sweden and United Kingdom). The "PD_Pal intervention" comprises (1) several consultations with a trained nurse who will perform ACP conversations and support care coordination and (2) use of a patient-directed "Parkinson Support Plan-workbook". The primary endpoint is defined as the percentage of participants with documented ACP-decisions assessed at 6 months after baseline (t1).

Secondary endpoints include patients' and family caregivers' quality of life, perceived care coordination, patients' symptom burden, and cost-effectiveness. In parallel, we will perform a process evaluation, to understand the feasibility of the intervention. Assessments are scheduled at baseline (t0), 6 months (t1), and 12 months (t2). Statistical analysis will be performed by means of Mantel–Haenszel methods and multilevel logistic regression models, correcting for multiple testing.

Discussion: This study will contribute to the current knowledge gap on the application of palliative care interventions for people with Parkinson's disease aimed at ameliorating quality of life and managing end-of-life perspectives. Studying the impact and feasibility of the intervention in seven European countries, each with their own cultural and organisational characteristics, will allow us to create a broad perspective on palliative care interventions for people with Parkinson's disease across settings.

Clinical Trial Registration: www.trialregister.nl, NL8180.

Keywords: Parkinson's disease, palliative care, advance care planning, care coordination, family caregiver

INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disease worldwide, affecting 1–2% of the world population above 65 years of age. The number of people with PD is expected to double from 6.9 million in 2015 to 14.2 million in 2040 (1). On average, people live for 15 years with the disease (2–4). As the disease progresses, people develop a range of motor as well as non-motor symptoms, which typically increase over time. For example, in a European cohort of 692 people diagnosed with late-stage PD and an average disease duration of 15 years, 68% reported off-periods for at least 50% of the day, 82% reported falls, and 92% experienced at least one neuropsychiatric symptom, with apathy, depression, and anxiety most commonly being present (5, 6). Furthermore, around 60% of patients with PD will ultimately develop dementia (7, 8). In light of this complex and multifaceted phenotype, it is understandable that treatment programs are complex, that quality of life becomes progressively threatened, and that informal carers experience considerable distress. However, despite the very high symptom burden at the end of life, end-of-life care in the field of PD often is not aligned with patients' needs and preferences (9, 10). Palliative care is often not introduced: in a cohort of advanced PD patients in Germany, with a mean disease duration of 17 years, 72% of the participants expressed an unmet need for palliative care (11). A large study including ∼125,000 people with PD showed that 43% died in a hospital and only 9.7% in their homes, which is substantially lower compared to the 17% of the general elderly population dying at home. Hospice services were barely utilized, that is, in only 0.6% of the patients (12).

To address these challenges, there is growing awareness of the potential benefits of palliative care for people with PD (13, 14). According to the World Health Organization definition, published in 2012, palliative care is "an approach that improves the quality of life of patients and their families facing the problems associated with life threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual" (15). Advance Care Planning (ACP) is a cornerstone for palliative care, involving the timely identification and definition of goals as well as preferences for future medical treatment and care, discussion of these goals and preferences with family and healthcare providers, and recording and reviewing of these preferences if appropriate (16). There is a vast amount of international evidence, particularly in the field of oncology, on the benefits of palliative care in improving quality of life, increasing satisfaction with care and, for some patients, prolonging life (17–19).

Although the importance of palliative care for chronic neurological conditions has been well-established in the setting of clinical studies (13, 20, 21), in real life, many PD patients do not receive the support they need. Unlike conditions that are life-threatening immediately after diagnosis, the sense of urgency seems to be lacking in a slowly progressive and long-lasting condition like PD. The unpredictable prognosis makes it difficult to define a clear referral cutoff point, which prevents neurologists from appropriately referring patients to specialist palliative care services. Moreover, many physicians lack the communication skills and do not want to take away hope and patience (22). PD patients' acceptance of their symptoms as part of their everyday life, believing that no effective treatments are available, is an important barrier to report non-motor symptoms (23), hampering the recognition of palliative care needs.

Only recently, several studies have explored how palliative care principles should be designed and implemented to effectively support and treat people with PD (24–28). Foremost, effective palliative care requires an individualized approach, and patients should actively be invited to discuss ACP early on in the course of the disease and on a regular basis; palliative care requires skilled professionals who are knowledgeable on both PD and palliative care, and ACP decisions should be clearly documented and shared with relevant services. Finally, given the multidisciplinary

nature of palliative care, care coordination should be an explicit responsibility of the care team (24, 29, 30).

Further studies are needed to evaluate the positive effects of palliative care models across a range of healthcare systems. The current PD_Pal trial was designed to understand the impact of palliative care services for PD, within a wide range of European healthcare systems. An evidence-based intervention will be evaluated consisting of a nurse-led, person-centred palliative care model for people with PD living at home, assisted living situation, or nursing homes. The intervention deals with two major challenges that many people with PD encounter (31, 32):

1. Increasing risk of cognitive and/or communication impairments that hinder the ability to easily discuss or indicate preferences about healthcare and quality of life when the disease advances. Therefore, timely documentation of patients' wishes related to advanced and end-of-life care is essential, but rarely part of standard care.
2. The lack of care coordination during the transition from clinic-based care (focused on adjusting patients' medical treatment to control symptoms) to community-based care (focused on adjusting patients' care and daily living routines to comfortably live with the symptoms that can no longer be completely controlled).

The objective of this study is two-fold. First, we will determine the effectiveness of a nurse-led, person-centred palliative care intervention for people with PD and their family caregivers compared to care as usual. To evaluate this intervention, we will primarily focus on ACP documentation in the medical files, to demonstrate that relevant end-of-life issues were indeed discussed. Additional outcomes will focus on patients' clinical outcomes, caregivers' quality of life, patients' and caregivers' costs and service utilisation. Second, we will assess the feasibility of the PD_Pal intervention across seven European countries (Austria, Estonia, Germany, Greece, Italy, Sweden and United Kingdom).

METHODS AND ANALYSIS

Study Design

The intervention will be evaluated in a multicentre, single-blinded randomized controlled parallel group design, in seven European countries. Within each participating country, one trial centre will lead the recruitment. Participants will be randomized in a 1:1 ratio to either the intervention or the control group, who will receive care as usual. The intervention will be delivered during the first 6 months after randomisation. Assessments will be performed at baseline (t0), at the end of the intervention phase, that is, after 6 months (t1), and after 12 months (t2) for follow-up (see **Figure 1**).

Participating clinical centres should have at least one movement disorder specialist available. Centres are excluded if they already apply a palliative care model as part of their routine care workflow; if they have detailed palliative care guidelines available with corresponding high-quality practices; and/or if the centre is participating or has participated in a palliative care study in the past 3 years.

Study Population

The intervention targets individuals diagnosed with idiopathic PD or an atypical parkinsonism syndrome, independent of their age.

In order to be eligible to participate in this study, a person should meet all of the following criteria:

1 Meeting the clinical diagnostic criteria for PD, as defined by the Movement Disorders Society (33), or the criteria for an atypical parkinsonism syndrome (34);
2 Hoehn & Yahr $\geq$3 (35);
3 Progressive deterioration in physical and/or cognitive function despite optimal therapy, according to the primary physician;
4 Cognitively able to complete questionnaires and to participate in interviews;
5 Ability to provide written informed consent; and
6 Availability of a family caregiver or informal caregiver, jointly abbreviated as "FC" in the remainder of this article.

Furthermore, persons are excluded from participation if one of the following criteria are met:

1 Inability to communicate independently, with or without supportive communication tools;
2 Unable or unwilling to commit to study procedures;
3 Presence of additional chronic medical illnesses which may require palliative services (e.g., metastatic cancer);
4 Already receiving palliative care or hospice services; and/or
5 Already participating in a clinical study for palliative care.

Having a device-assistant advanced treatment [including deep brain stimulation (DBS), levodopa–carbidopa intestinal gel (LCIG), and continuous subcutaneous apomorphine infusion (CSAI)], or considering one, is not an exclusion criterion. We will identify patients who certainly have complex medical needs and at the same time are still able to commit to ACP conversations and make decision.

The participation of a FC is compulsory. The FC should meet the following criteria:

1 Willing to provide written informed consent;
2 Cognitively able to complete questionnaires and to participate in interviews;
3 Aging $\geq$ 18 years; and
4 Identified by the person with PD as the FC.

Sample Size Calculation

We assume that 5% of the target population will have documented ACP wishes at baseline. The study is powered to show a 20% absolute increase from a baseline of 5% (control group) in the primary outcome measure, that is, documented ACP-decisions, at 6 months, with a power of 0.80, a statistical significance of 0.05 (two sided) and an intraclass correlation coefficient (correcting for clustering within countries) of 0.10, by a Fisher's exact test. With the above assumptions, 74 patients in each treatment group are required. The sample size will be increased to 93 patients in each treatment group for allowing a 25% dropout rate within the 6-month follow-up period for the primary outcome effectiveness evaluation.

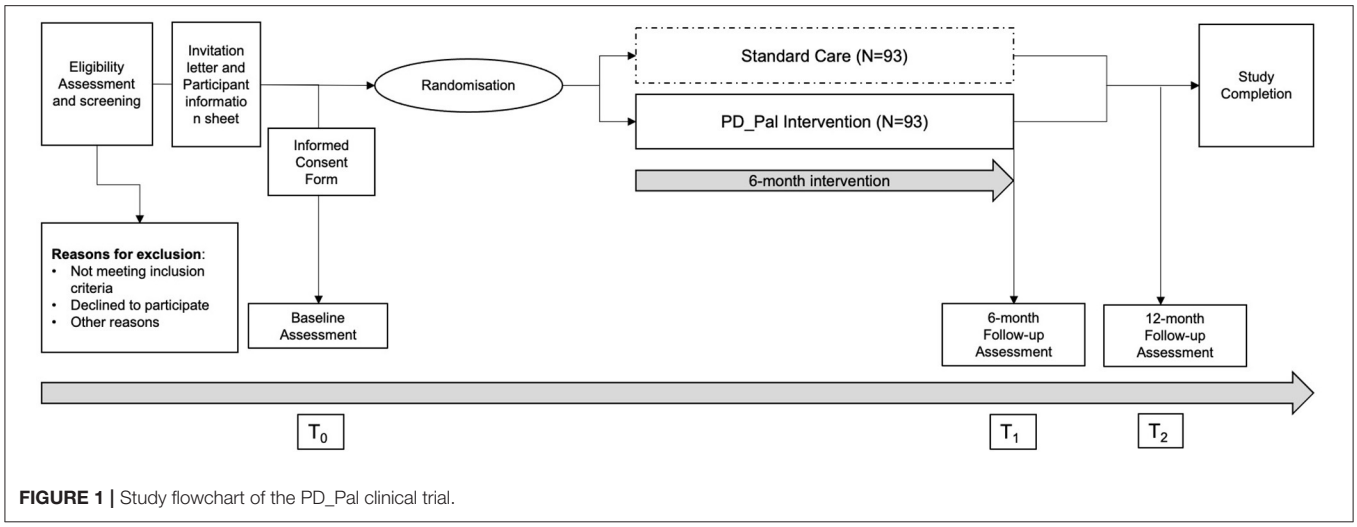

FIGURE 1 | Study flowchart of the PD_Pal clinical trial.

PD_Pal Intervention

The proposed PD_Pal intervention is the result of a systematic approach, where we first explored the views of healthcare professionals and patients on palliative care in the Netherlands (25, 36, 37). Subsequently, these findings were translated into the intervention: trained nurses and a workbook for patients. The specifically trained nurses, labelled as PD_Pal nurses in this study (see below), will be coordinating transmural, integrated, and proactive palliative care, including ACP, through regular conversations with patients and their FC. The conversations are supported with a patient-directed "Parkinson Support Plan—workbook," designed to be used at home by the patient and FC to document their wishes and preferences related to end-of-life care, to prepare and guide the conversations with the PD_Pal nurse. The plan is structured within four steps (**Table 1**). These steps are based on previous theories [e.g., ACP (16)], shared-decision making (38), The Chronic Care Model (39), and empirical studies [e.g., interventions guiding ACP conversations that describe healthcare models or interventions aimed to provide care aligned with patients' needs, values, and preferences on all domains of palliative care, for example, physical, social, psychological, spiritual, and financial (40–43)]. The initial workbook was reviewed by a panel of five Dutch patients and caregivers and subsequently adapted based on their feedback. To make the workbook suitable for the international study, the PD_Pal nurse training started with a critical review of the workbook, and adapted to the national situation, where needed. Given the comprehensive scope of the workbook, the intervention goes beyond the clinical management of PD consequences.

TABLE 1 | Defined steps in the Parkinson support plan.

Step	Aim
1—Individual care plan	Describe current health and caregivers, and identification of current needs related to care and care coordination.
2—Proactive care plan	Identify expected future challenges and care needs per domain (e.g., physical, social, psychological, spiritual, and financial). The leading theme in this step is: "What is needed for good care, now and in the future?" There is also attention for challenges and needs, as experienced by the family caregiver.
3—Quality of life and end-of-life plan	Identify and document the patient's ideas about quality of life, and preferences related to end-of-life care (e.g., surrogate decision maker; life prolonging procedures; and hospital or nursing home admissions).
4—Coordination and revision plan	Discuss and plan how the "Parkinson Support Plan" will be coordinated and reviewed in the future (e.g., contact (newly assigned if not already assigned) care coordinator, update him/her about the plan, and facilitate him/her in consulting a Parkinson expert when necessary; decide when and how the "Parkinson Support Plan" will be reviewed). The PD_Pal nurse and the dyad will allocate the referred to the assigned care coordinator, to guarantee continuity of the integrated palliative care beyond the PD_Pal study.

The PD_Pal Nurse

The PD_Pal nurses are trained to assist the participating patients in taking the four steps of the Parkinson Support Plan. The training consists of (1) face-to-face sessions to develop skills necessary to assist the patient during the intervention, including skills to deal with emotions, and (2) monthly digital coaching sessions with the intervention-coordinator (MMG) where experiences can be discussed. Nurses will be selected based on the following criteria:

1 Previous experience in nursing (preferably on a "Bachelor of Nursing" or comparable level);
2 Experienced in delivering care for people with Parkinson's disease and/or atypical parkinsonism syndromes OR experienced in delivering palliative care;
3 Being able to visit patients at home/at a clinical centre;
4 Able to speak and write in English (training will be held in English);
5 Being able or willing to talk about the end of life; and

6 Open attitude toward (differences in) patients' preferences and values in life.

The delivery of the intervention (e.g., setting, timing, frequency, and content) will be tailored as much as possible to the patient's and FC's preferences and possibilities. Although the duration of the total intervention is tailored to patients' preferences, the study design and timeline mandate the following limits: the first conversation with the PD_Pal nurse should be scheduled up to 4 weeks after randomisation and the last conversation up to 6 months after the randomisation.

The Control Group

Patients in the control arm receive care-as-usual from their neurology and/or home care team. The care-as-usual and the extent to which ACP is part of this care are expected to differ among the participating countries.

Recruitment and Consent

Several methods to reach the target group are employed, building upon the experiences with patient recruitment in the Care for Late Stage Parkinsonism (CLaSP) study (5, 44). First of all, the participating neurology clinics recruit participants from their outpatient and inpatient clinics and registries of patients who have indicated to be interested in research participation. Neurology clinics can only act as a recruitment centre if they do not offer palliative care services themselves. Second, the study centres will contact geriatricians, general practitioners, nursing homes, patient advocate groups, and self-help groups to draw attention to the project and identify and recruit eligible patients. Identified clinicians give written information to patients about the study, and if patients are interested and willing, the clinician completes a standard referral form and sends it to the local research team. The research team will contact the patient by phone, explain the trial, check the eligibility criteria as far as possible in a phone call, and will send the full information package. Patients will have at least 1 week to consider participation. If a patient provides verbal consent to contact their FC, the research team will approach the FC and invite the FC for participation as well, following the same procedure as outlined for the patient.

Patients who are interested in participation, meet the selection criteria, and have provided their initial, verbal consent will be given a first appointment for a screening visit with a study assessor, which could be a physician (neurologist, geriatrician, or psychiatrist), study nurse, or trained researcher. During the screening visit, information about the study will be explained again, and if the participant still agrees, the informed consent form will be signed. Subsequently, eligibility criteria will be verified in the screening visit, before collecting any baseline clinical and demographic data. In case the eligibility criteria can be verified based on a telephone interview and review of the medical records, written informed consent will be obtained without a screening visit. All participants will be able to withdraw their informed consent to parts or to the overall participation at any point in time.

Randomisation, Blinding, and Treatment Allocation

Participants are considered to be enrolled into the study following written informed consent, confirmation of eligibility, and allocation of the participant ID number. After inclusion, a patient will participate in the baseline assessment (t0), after which the patient will be randomized to either the intervention or the control group (1:1) by a computer-generated algorithm embedded within the certified eCRF system. A member of the research team will communicate to the patient and FC the group to which they have been assigned.

The trial is single-blinded, as patients and their FCs cannot be blinded for treatment allocation. Participants are urged not to discuss their allocation status with the blinded study assessor, who is responsible for the data collection. At each visit, the assessor will record to which study arm they think the participant was allocated, which will allow us to assess the efficacy of the blinding.

Study Endpoints

Primary Endpoint

The primary endpoint is defined as the percentage of participants with documented ACP decisions in at least one of the patients' medical records assessed at 6 months (t1) after baseline. We believe it is important to choose an outcome measure that is as close as possible to the intervention. The choice of documentation of ACP decisions as the primary endpoint was prompted by a number of considerations. One of these is that even though discussing ACP is a crucial part of the intervention, such a discussion by itself does not ensure better care, and adequate documentation is therefore a further prerequisite. Another consideration is that this endpoint proved to be sensitive to change in similar interventions targeting other populations (40).

Secondary Endpoints

Secondary endpoints relate to the expectation that patients and their FCs will experience a better quality of life, improved care coordination, and a reduced patient symptom burden and that FC will experience an improved quality of life, in a cost-effective manner.

Other Endpoints

To characterize the population, we will collect demographic and social information from the participants. Furthermore, we will evaluate the feasibility aspects of the intervention and we will document what is needed to tailor the intervention procedures and materials to country-specific characteristics (e.g., differences in language and organisation of care).

In those participants enrolled in the trial who provide a separate consent, wearable sensor data will be collected, by using the PDMonitor system. The PDMonitor system consists of five devices which will be attached to both shanks and wrists and the lower back. Each device contains an accelerometer, a gyroscope, and a magnetometer. The PDMonitor is a CE-marked product, certified as Medical Device class IIa. The system has been validated for PD-related motor-symptoms,

for example, bradykinesia, dyskinesia, tremor, freezing of gait, gait disturbances, postural instability, ON/OFF conditions, and response fluctuations (45, 46). In PD_Pal, data will be recorded during daily living after baseline (t0), and after each follow-up visit (t1 and t2), for five consecutive days (morning to evening) for a maximum of 12 h per day. The data will be used for further validation and exploratory analysis, for example to see if the data can serve as a predictor for the primary and secondary outcomes (e.g., how activity level and severity motor symptoms measured at home are related to the frequency of ACP arrangements, or patients' and caregivers' quality of life).

Assessment Scheme

The baseline assessment (t0) consists of an in-person interview performed by the study assessor. The baseline assessment takes place either in the outpatient clinic setting, at the patient's home, or remotely via a video connection. In addition, the patient and FC complete a set of questionnaires that are self-administered. Within 2 weeks after the baseline assessment, a participant is randomized to either the intervention or the control group. For all participants, two follow-up assessments are thereafter foreseen (t1 and t2). After completion of the t2 assessment, the patient and FC will be invited for an optional semi-structured interview about end-of-life issues. **Table 2** presents all assessments and the instruments that will be used to evaluate the (cost-)effectiveness and feasibility of the PD_Pal intervention.

Statistical Analysis

Primary Endpoint

To evaluate the effectiveness of the intervention, all analyses of endpoints will be done in the intent-to-treat population. The primary efficacy analysis will be to investigate the effect of the PD_Pal intervention on the percentage of patients with documented ACP decisions from baseline to month 6 in the intervention and care-as-usual group. This will be tested by means of the Mantel Haenszel estimate method and by using multilevel logistic regression model, with data clustered within countries and with categorical factors (groups) and baseline characteristics as covariates, in order to test which independent variables (indicators) contribute to the effect of the intervention. The primary analysis will be repeated for the t2 assessment (12 months after randomisation) and also using the per-protocol population to confirm the overall study results. All tests will be performed two-sided, and P-values < 0.05 will be considered statistically significant.

Secondary Endpoints

All secondary study parameters, except for the healthcare utilisation data, will be analysed similarly to the primary outcome parameter, except that for the secondary outcome measures we will correct for multiple testing (Bonferroni adjustments). For the healthcare utilisation data, the primary analysis will be from a health and social care cost perspective, with secondary analyses from a societal perspective.

Gender-Specific Analyses

We will undertake a planned subgroup analysis for the primary outcome measure, separately for women and men.

Other Study Parameters

Information regarding perceived care coordination and feasibility of the intervention will be obtained in optional qualitative interviews. To assure the quality of this multicentre, multinational, multi-language qualitative study, we will build on the lessons learned from the CLaSP trial (62), in which many of the study centres participated, and on recommendations and experiences described in the literature (63).

Software for qualitative analysis will facilitate data storage, coding, searching both within and across sites, and participant groups, retrieving data and recording analytical thinking (e.g., NVivo or AtlasTi). The data are linked with the quantitative data to interpret the change in patients/FCs of the quantitative outcome measures, their clinical significance, and the impact of the intervention at two levels (people and context; processes and tasks), and to identify ways to enhance the intervention and the processes for wider implementation. Quality appraisal is addressed through procedures to ensure systematic and rigorous attention to analysis and reporting.

Data Management

Each investigator will document subject data in his/her own subject files. These subject files will serve as source data for the study. Data collected during this study as recorded on the appropriate source documents will be entered in a web-based electronic data capture (EDC) system specifically developed for the study and provided by the clinical research organisation (CRO) and project partner, Mediolanum Cardio Research (MCR), Milano, Italy. The e-CRFs will be reviewed periodically for completeness, consistency, and query status by the data management personnel of the CRO. Remote monitoring will be regularly performed by the CRO staff in order to oversee the progress of the study, completion, and quality of collected data. The raw sensor data, collected with the PDMonitor devices, and its processed data are uploaded and pseudonymized stored at the PD Neurotechnology's cloud platform.

Harms

All adverse events, adverse reactions, and serious adverse events or reactions that occurred from the signature of the informed consent during the whole study duration will be recorded in the specific section of the e-CRF. Death events due to disease progression will not be considered as serious adverse event (SAE); however, data will also be recorded in a specific section of eCRF. Adverse events will be collected and coded using the most current version of the Medical Dictionary for Regulatory Activities (MedDRA). Each adverse event will be categorized by severity (mild, moderate, severe) and seriousness (serious, non-serious). The investigator will follow up the outcome of any Adverse Events (clinical signs, laboratory values or other, etc.) until the return to normal or consolidation of the patient's condition. In the case of any Serious Adverse Event, the patient will be followed

TABLE 2 | Overview of the assessment schedule and its instruments, to evaluate the (cost-) effectiveness and feasibility of the PD_Pal intervention.

Scales/domains	Instruments	Application at		
		T0	T1	T2
Study rater completed, together with the patient				
Demographics / social data		X		
Motor symptoms	MDS-UPDRS, part III (47)	X		
Non-motor symptoms	MDS-Non-Motor Rating Scale (MDS-NMS) (48)	X	X	X
Cognition	Montreal Cognitive Assessment (MoCA) (49)	X		
Comorbidity	Charlson Comorbidity Index (CCI) (50)	X		
Care coordination	Modified Nijmegen Continuity Questionnaire (mNCQ) (51)	X	X	X
	Interview questions***	X	X	X
Feasibility of the intervention**	Feasibility checklist		X	
(Serious) adverse events	Interview questions		X	X
Study rater completed, together with the FC				
Demographics		X		
Resource utilisation	Resource Utilisation questionnaire (RUD) (52), adapted for PD	X	X	X
[if applicable] Quality of the end-of-life experience of the patient*	Quality of Dying and Death questionnaire (QoDD) (53)		X	X
Questionnaires completed by the patient independently				
Disease-specific symptoms	Edmonton Symptom Assessment Scale for Parkinson's Disease (ESAS-PD) (54)	X	X	
Depression	Beck Depression Inventory (BDI-I) (55)	X	X	
Quality of life	PDQ-39 (56)	X	X	X
Self-rated health	EQ-5D-5L (57)	X	X	X
Palliative-phase symptom severity	Integrated Palliative Care Outcome (IPOS) (58)	X	X	X
Experienced quality of care (including the intervention)	Short Assessment of Patient Satisfaction (SAPS) (59)	X	X	
Experienced involvement in decision making	CollaboRATE (60)	X	X	
Questionnaires completed by the FC independently				
Quality of life	EQ-5D-5L (57)	X	X	X
	PQoL Carer (61)	X	X	X
Study rater competed				
ACP documentation	Chart review	X	X	X
[if applicable] Place of death: preferred and actual	Chart review		X	X
Interview with patient and FC				
Feasibility of the intervention**/***	Interview guide		X	
Experienced quality of care, quality life, and end-of-life issues***	Interview guide			X
Quantitative motor symptom assessment				
Motor symptom assessment***	PDMonitor	X	X	X

in case the patient dies during follow-up; **intervention group only; * Optional element of the study protocol; T0, Baseline after inclusion; T1, 6 months after randomisation (intervention completed); T2, 12 months after randomisation (long-term follow-up).*

up until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized.

DISCUSSION

The awareness of the possible merits of palliative care interventions for people with PD is growing (14, 64). However, we still do not fully understand how to optimally design palliative care models, and little is known about its potential impact for this patient population (13). In 2020, two large randomized controlled trials published the effects of multidisciplinary palliative care teams, with inconsistent results. The first one, conducted in American outpatient clinics, evaluated a multidisciplinary palliative care model for PD patients and their family caregivers. The patients received palliative care support in person or by telemedicine sessions, every 3 months for 12 months. The study showed a modest, but significant improvement in patients' quality of life after 6 months, leaving caregiver burden unchanged. In addition, non-motor symptom burden, motor symptom severity, completion of advance directives, caregiver anxiety, and caregiver burden favoured the

intervention group at 12 months (24). The second study targeted people with long-term neurological conditions, including PD. This UK-based study evaluated a short-term palliative care intervention, using a comprehensive assessment, personalized care planning, case management, and care coordination, and advising existing care providers. The intervention lasted 6–8 weeks, with three distinct sessions for the patient and family caregiver with the multi-professional palliative care teams. After 12 weeks, no change in eight key palliative care symptoms emerged, although the intervention was associated with lower healthcare costs (65).

The PD_Pal intervention takes a different approach: instead of involvement of a multidisciplinary care team, we will assign a dedicated nurse, who will act as the personal case manager for the patient and family caregiver. The nurse will lead the conversations, create a relationship based on mutual trust, and involve other disciplines whenever needed. We deliberately opted for an intervention strategy, which combines specific training of a nurse in relevant areas of knowledge and skills with a prolonged in-depth support intervention for the patients and FCs. Throughout the intervention period, the nurses will join monthly digital meetings to share their experiences and discuss encountered problems and solutions. The Parkinson Support workbook is designed as a strategy to increase active engagement of patients and FCs in the ACP conversations about the future. Furthermore, the intervention is patient-centred and the patients will be deciding what will be discussed and when. None of the (sub)steps within the intervention are obligatory and patients can also add certain care (coordination) issues that are not included in the Parkinson Support Plan. To summarize, the PD_Pal model is advocating active engagement of patients as a key element for effective palliative care interventions (66).

The COVID-19 pandemic has affected the execution of the trial, which was planned to start in February 2020. The pandemic shows the importance of discussing goals of care, and to revisit or establish advance care plans in an early phase of the disease. Furthermore, the pandemic forced us to deploy telehealth solutions for e-consent, e-scales, and e-delivery of the intervention. The original protocol already included an option for teleconsultations for the PD_Pal nurses, as a measure to be inclusive for those patients who would live too far away from the clinical site for regular face-to-face visits. Now we anticipate to use a teleconsultation model as a necessary alternative, leveraging on earlier experiences. A review of 71 studies (67) concluded that, on the positive side, patients generally experience more comfort and control at home, leading to an exclusive digital connectedness between conversation partners. In contrast, professionals can experience reservations about addressing painful truths and emotional topics during teleconsultations as they did not feel sufficiently close. We will therefore strive for a first face-to-face contact between the PD_Pal nurse and the patient, before a teleconsultation solution will be applied. Nevertheless, the pandemic creates a unique opportunity to learn important lessons about the application of telehealth solutions in clinical research.

To conclude, studying the impact and feasibility of the intervention in seven European countries, each with their own cultural and organisational characteristics, will create a substantial body of knowledge about the future of palliative care for people with PD and their family caregivers.

ETHICAL CONSIDERATIONS AND DISSEMINATION

The PD_Pal study design has been developed following the indications contained in the Charter of Fundamental Rights of the European Union. Informed consent will be obtained by each participant as in the Declaration of Helsinki (2013) and in line with ethic committee approval of the protocol. None of the steps within the intervention are obligatory. Patients can indicate they do (not yet) want to discuss or think about certain topics. All participants will be able to withdraw their informed consent to parts or to the overall participation at any point in time. When participants develop cognitive deficits, together with the FC, we will evaluate their ability and willingness to continue participating in the study.

The project results will be disseminated through the MDS Task Force on Palliative Care, the European Association for Palliative Care, the European Academy of Neurology, and the European Parkinson's disease association. In addition, dissemination will be accomplished through scientific publication on national and international journals as well as through participation to scientific and communication events related to the study topics. It is also important that the progress and findings are presented to PD patients and caregivers (usually in regional audiences) and by publishing lay summaries. PD_Pal will support the open-access (OA) initiative. OA literature is digital, online, free of charge, and free of most copyright and licensing restrictions. OA to research articles both in journals ("gold OA") and in repositories ("green OA") is foreseen.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the local ethics committees of all participating study sites (UK: London—Central Research Ethics Committee, REC reference 20/LO/0122, IRAS project ID 271717; Sweden: Etikprövningsmyndigheten, registration number 2020-00032; Austria: Ethikkommission für das Bundesland Salzburg, registration number 1117/2020; Greece: Scientific Council of the University Hospital of Ioannina, Protocol Nr 586/6-8-2020; Germany: Ethics Committee Philipps-University Marburg; study file number 163/19; Italy: Comitato Etico per la Sperimentazione Clinica della Provincia di Padova, protocol number CESC 4840/AO/20; Estonia: Reserach Ethics Committee of the University of Tartu (UT REC), protocols 2971T-16 and 327/M-16). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MM, GG, and MG wrote the initial draft of the manuscript. MM, GG, AS, SK, CE, PT, SL, PO, KR, KC, AA, BB, and MG contributed to the conception of the intervention and design of the evaluation methodology and contributed to the finalisation

of the manuscript and agreed to be accountable for the content of the work. All authors contributed to the article and approved the submitted version.

FUNDING

This work was supported by the PD_Pal project, funded within the EU Framework Programme for Research and Innovation Horizon 2020 (GA n. 825785). PT was additionally supported by Grant PRG957 of the Estonian Research Council. PO and KR received economic support from the Region Skåne, Parkinsonfonden and Åhlens foundation. KR has an additional grant from the Greta and Johan Kock Foundation. AS was supported by NIHR Biomedical Research Council UCL/H.

ACKNOWLEDGMENTS

We thank Anne Harmsen for her support in drafting the manuscript.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer MK declared a past co-authorship with one of the authors CE to the handling Editor.

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frontiers in Neurology

ORIGINAL RESEARCH
published: 18 August 2021
doi: 10.3389/fneur.2021.670567

The Trajectory of Motor Deterioration to Death in Parkinson's Disease

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Background: Motor progression varies even among those with a single diagnosis such as Parkinson's disease (PD) and little is known about the trajectory of motor signs prior to death. Understanding deterioration patterns may help clinicians counsel patients and proactively plan interdisciplinary care, including palliative care. The objective of this study was to examine and describe Unified Parkinson's Disease Rating Scale motor score (UPDRS-III) trajectories at the end of life in PD.

Methods: A retrospective chart review was performed for deceased PD patients who attended the Parkinson and Movement Disorders Program at the University of Alberta for at least 5 years between 1999 and 2018. UPDRS-III scores were recorded for all visits. Trajectory patterns were visualized with Loess curves stratified by sex and age at diagnosis. Piecewise linear models were used to individually model the UPDRS-III scores, and the trajectories obtained were clustered based on their features.

Results: Among the 202 charts reviewed, 84 meeting inclusion criteria were analyzed. The UPDRS-III increased over time regardless of sex and age. Distinct trajectory variations present in PD (e.g., Consistent Deterioration, Stability-Deterioration, Improvement-Deterioration, Deterioration-Improvement-Deterioration) were identified. Twenty-five percent of the patients were classified as Undetermined/Irregular trajectories. In addition, regardless of trajectory type, many patients experienced a steep increase in UPDRS-III approaching death. Those with disease diagnosis after age 65 years had a shorter survival time, compared to PD patients with a younger age of onset.

Conclusion: Our study identified dominant types of motor trajectory in PD that can help clinicians understand their patients' course of illness. This information can help counsel patients regarding the variability in motor deterioration and should alert physicians to recognize a terminal decline. Age of disease onset was correlated with survival time.

Keywords: Parkinson's disease, trajectory, UPDRS, terminal decline, palliative care

OPEN ACCESS

Edited by:
Marianne De Visser, University of Amsterdam, Netherlands

Reviewed by:
Alessandra Splendiani, University of L'Aquila, Italy
Nicola Modugno, University of L'Aquila, Italy

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Specialty section:
This article was submitted to Neurocritical and Neurohospitalist Care, a section of the journal Frontiers in Neurology

Received: *21 February 2021*
Accepted: *26 July 2021*
Published: *18 August 2021*

Citation:
Poonja S, Miyasaki J, Fu X, Camicioli R, Sang T, Yuan Y and Ba F (2021) The Trajectory of Motor Deterioration to Death in Parkinson's Disease. Front. Neurol. 12:670567. doi: 10.3389/fneur.2021.670567

INTRODUCTION

Multiple factors influence the progression and trajectory of Parkinson's disease (PD). Studies on the natural history of PD revealed that despite all advances in the symptomatic management with new pharmacologic agents and technologies for PD, the progression of motor disability is inexorable, adding to patients and caregivers' burden, especially at the end of life (1–3). This encompasses

disability caused by increasing severity of motor signs over time, development of motor complications, and poorly levodopa responsive axial motor signs, including dysarthria, dysphagia, postural instability, and freezing of gait (4, 5). In addition, non-motor symptoms increase in number and severity throughout the course of disease and in particular, neuropsychiatric complications of PD can be burdensome (6, 7).

PD is the most common parkinsonian condition. The prevalence is about 1% in people over the age of 60 years (8), and the reported incidence ranges from 8 to 18 per 100,000 person-years (9). The neuropathological hallmarks of PD are neuronal loss in the substantia nigra, which leads to striatal dopamine deficiency, and intracellular inclusions containing aggregates of α-synuclein (10). Levodopa and other dopamine enhancing agents increase the synaptic dopamine concentration and/or postsynaptic receptor binding, and therefore improve motor symptoms, especially early in the disease course. PD usually carries a better prognosis than the other atypical parkinsonian syndromes (8). Illnesses such as progressive supranuclear palsy, multiple system atrophy, and corticobasal syndrome have less response to treatment and usually progress more rapidly (11, 12). However, although considered a slowly progressive disease, there is marked heterogeneity in PD disease progression. PD motor phenotype is indicative of prognosis. The postural instability/gait difficulty (PIGD) phenotype usually has a poorer response to dopaminergic treatment and a worse prognosis than the tremor dominant phenotype (13).

Since PD is a progressive neurodegenerative condition, and the disease trajectory can vary, it is important to have a better understanding of the patterns of disease course and deterioration in later stages to help clinicians counsel patients and plan interdisciplinary care, including palliative care referrals, accordingly. The objective of this study was to examine and describe UPDRS-III trajectories at the end of life in PD. These data can help patients, families and clinicians understand potential progression trajectories in advanced illness. Since most research has focused on early and mid-stage PD, the end of life has been largely neglected. Following PD patients until their death is unusual in many neurology practices. This data can also help patients, families and clinicians identify terminal motor decline as a trigger for palliative care involvement. More importantly, this study can provide clinicians, patients and families with realistic expectations when making important goals of care decisions.

MATERIALS AND METHODS

Study Subjects

The study population included PD patients followed at the Parkinson and Movement Disorder Program (PMDP) at the University of Alberta between 1999 and 2018, and deceased before 2018. Inclusion criteria included: Diagnosis of PD using UK brain bank criteria (14); followed for at least 5 years. Exclusion criteria included: <5 UPDRS III scores from different years, and no UPDRS-III score in the 2 years prior to time of death and those only had off UPDRS scores. Since we were interested in the trajectory patterns approaching death, five or more assessments and scores recorded close to death were deemed necessary. A flowchart shows original data to the final patient sample (**Figure 1**).

Chart Review and Data Collection

A retrospective chart review was conducted documenting age at diagnosis and visit, sex, UPDRS-III score at each visit, the year of diagnosis, and two time variables documenting post diagnosis time. One variable was time in years from diagnosis to first UPDRS-III assessment in our clinic, and the other was interval between follow up visits and their first UPDRS-III assessment. Levodopa equivalent daily dose (LEDD) (15) was analyzed at initial visit and at time of death for all patients.

Patients were classified into three age groups according to their age at PD diagnosis, <50, 50–64, and ≥65 years. The endpoints of the study were the trajectories of motor deterioration using UPDRS-III score prior to death, stratified by age group and sex.

To identify patterns of individual trajectory, we first visualized individual UPDRS-III score trajectory using spaghetti plots. We then clustered patients based on their trajectory patterns into different categories. Details of these models can be found in the Appendix in **Supplementary Material**. If the standard deviations of the UPDRS-III scores were lower than 2.5 across all visits during follow-up, the patients were considered stable. If the UPDRS-III scores were linearly increasing approaching death, the group of patients was categorized into the linear trajectory group. For linear trajectory, we used a mixed effect model to model the average slope of UPDRS-III score with respect to time prior to death, accounting for age group and sex. For patients who had transition points in their trajectories, we grouped the patients by having either one or two transition points in their trajectory. Separate one-knot or two-knot linear model was fitted to each patient's UPDRS III scores. For fitting a one-knot and two-knot model, we require a minimum of 6 and 8 scores from a patient, respectively. To analyze whether UPDRS-III correlated with LEDD, non-parametric correlation with Spearman rho was performed. All statistical analyses were performed using R Statistical Software (16).

Standard Ethics Approvals

The study was approved by the University of Alberta Health Research Ethics Board (Pro00070137).

RESULTS

Among 202 deceased PD patients, 84 met inclusion criteria (**Figure 1**). Demographic and clinical characteristics of the patients are summarized in **Table 1**. Male to female ratio was 2.42, and 51.2% of the patients were 65 or older at time of diagnosis. The average follow up was 11.4 years among the PD patients, and 64.3% had more than 10 UPDRS-III scores. The median time from PD diagnosis to first assessment was 2 years for the 84 patients (range 0–20 years) (**Table 1**), 9.5 years (<50), 4 years (50–64), and 1 year for ≥65 years age groups. Among all PD patients, the older the patients were at disease onset, the more likely they were to be followed up early in their disease

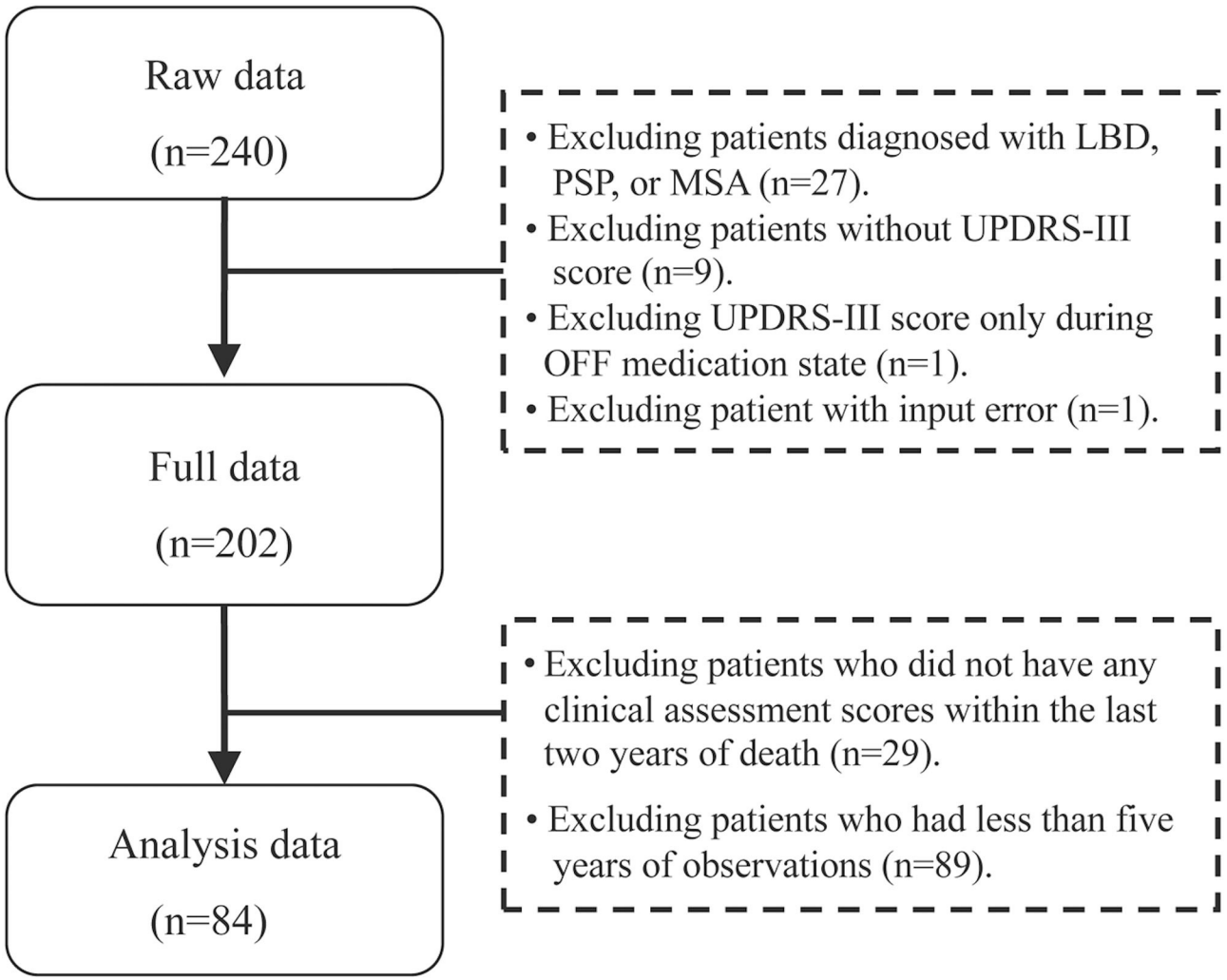

FIGURE 1 | Flowchart of data collection of the patients with Parkinson's disease. Flowchart of final sample of the Parkinson's patients: 84 patients meeting inclusion criteria were analyzed as shown in the flowchart. PD, Parkinson's disease; LBD, Lewy body dementia; MSA, multiple system atrophy; PSP, progressive supranuclear palsy; UPDRS-III, Unified Parkinson's Disease Rating Scale motor score.

course. The LEDD increased from first visit (574.6 ± 485.2 mg) to the time of death (864.1 ± 388.7 mg). However, at both time points, patient's LEDD did not correlate with the UPDRS-III score. In addition, the included and excluded decedents were compared (**Supplementary Table 1**). There was no difference in sex; however, the age of the 84 included patients was younger than the excluded PD patients ($p < 0.01$), and the UPDRS score was 3.4 points higher in the included group at last visit in the included group ($p < 0.05$) (**Supplementary Table 1**). The excluded decedents had a shorter course from diagnosis to death ($p < 0.01$). Given the shorter course, these decedents did not have sufficient observations to be included in the dataset.

Firstly, the spaghetti plots identified patterns of individual UPDRS-III score trajectory, and revealed heterogeneity among PD patients. Based on the trajectory patterns, the patients were grouped into the following categories model: (1) stable, (2) linear, (3) piecewise linear, and (4) irregular (**Figure 2**). In general, the overall trend of UPDRS-III scores was increasing over time as patients approached death regardless of sex and age of diagnosis (**Figure 3**). As there is no appreciative difference between men and women, **Figure 3** shows the Loess curves of the UPDRS-III scores vs. time for the three age groups combining men and women. Five patients (6%) were in the stable group (**Figure 4A**). One-third of the PD patients ($n = 28$) belonged to the linear trajectory group (Consistent Deterioration, **Figure 4B**). Their UPDRS-III scores linearly increased approaching death. In this group, women and men did not have statistically significant different slopes nor did they have different UPDRS-III scores prior to death on average. Age at diagnosis, however, was a predictor for how fast the average UPDRS-III changed. For patients whose age at diagnosis was below 65 years, their average increase in UPDRS-III score was 3.2 per year over their disease

TABLE 1 | Demographic and clinical characteristics of the Parkinson's patients analyzed.

Demographic and clinical characteristics	*N* (%)
Sex	
Male	59 (70.8)
Female	25 (29.2)
Time from diagnosis to first UPDRS-III assessment (years)	
0	21 (25.0)
0–<1	16 (19.1)
1–<5	28 (33.3)
5–<10	12 (14.3)
10–<15	6 (7.1)
>15	1 (1.2)
Age at diagnosis	
<50	6 (7.1)
50–64	35 (41.7)
>65	43 (51.2)
Number of visits	
5–<10	30 (35.7)
10–<15	35 (41.7)
>15	19 (22.6)

course, while the average increase was 2.6 per year for those age at diagnosis was at least 65 years ($p = 0.023$) among the 28 patients in the Consistent Deterioration group. Within the last year of death, the average UPDRS-III scores were 55, 43, and 36 for the three age groups, <50, 50–64, and ≥65, respectively (**Figure 4B**). However, it should be noted that among the three groups, there were only 6 patients in the <50 group.

There were 20 patients who had one transition point in their UPDRS-III trajectories. Three types of motor trajectories were identified (**Figures 4C–E**): (A) stable → increase (Stability–Deterioration, $n = 7$); (B) decrease → increase (Improvement–Deterioration, $n = 9$); and (C) increase → decrease (Deterioration–Improvement, $n = 4$). Most of their transitions (85%) occurred between 2 and 5 years prior to death. Another 10 patients had two transition points, seven of whom had an increase → decrease → increase pattern (Deterioration–Improvement–Deterioration, **Figure 4F**) and three of whom had a decrease → increase → decrease pattern (Improvement–Deterioration–Improvement, **Figure 4G**). A majority (70%) of patients had their 2nd transitions between 2 and 5 years prior to death.

The remaining 25% of the patients did not fit into any of these above patterns and were classified as having "Undetermined/Irregular" trajectories ($n = 21$). Patients in this group tended to have a later age of onset. Summaries of these patterns were given in **Tables 2**, **3**.

There was no difference in post diagnosis life expectancy between men and woman in our study (**Table 4**). In contrast, age of PD diagnosis was associated with survival time. Patients younger than 50 years old at diagnosis had a median survival of 24 years, compared to 8 years in patients >65 years old (**Table 4**).

DISCUSSION

Our retrospective study of PD to death revealed different trajectory patterns (e.g., Consistent Deterioration, Stability-Deterioration, Improvement-Deterioration, Deterioration-Improvement-Deterioration) as assessed by the UPDRS-III. Across the trajectory patterns, the trend of "Decrease" in UPDRS-III before the "Increase" might have been due to initial response to medication initiation or adjustment, and possible introduction of physio/occupation therapy or other multidisciplinary care interventions, resulting in UPDRS III improvement. As PD progresses to late stage, disability progression may relate to a loss of compensatory abilities, widespread Lewy bodies and coexistent pathologies (i.e., vascular, plaques and tangles) (17, 18). Only a small percentage of patients had stable motor function (6%).

Over time, UPDRS-III scores showed a steep increase toward death in many patients. The "terminal decline" in PD could be attributed to changes in levodopa intake (i.e., dysphagia, necessary adjustments due to neuropsychiatric complications, gastrointestinal complications, hospitalization, and nursing home placement with less individualized care) and pharmacodynamic changes with loss of responsiveness to dopaminergic medications. In non-PD elderly, impaired motor function and faster rate of motor decline were associated with increased mortality (19). Lunney et al. has summarized terminal decline into four groups with different duration and shape in the aging population (20): sudden death; terminally-ill (rapid decline until death, i.e., in cancer); organ failure (gradual decline with frequent episodic acute exacerbations); and frailty (chronic disease with slow and gradual decline). Our cohort demonstrated variable patterns that contrast with non-PD elderly including a terminal decline 2–5 years prior to death.

Our findings of variable patterns of motor impairment trajectories confirm clinicians', patients', and families' experience that PD has many presentations, but terminal decline in motor function is common. Rather than the generic, "every patient is different" advice commonly received by PD patients and families, our results may allow clinicians to provide more nuanced information. The pathophysiologic basis for the different trajectories is not clear as we do not have radiographic, pathologic or genetic information. However, our results can be taken as clinical evidence that PD is potentially a spectrum of illnesses rather than a uniform entity and that identifiable patterns do exist (21). Further, our results demonstrate a significant age difference across all trajectory types (**Table 4**), with younger patients having longer survival. This is also valuable information for clinicians, patients and families. Given the difference between those diagnosed prior to age 50 and those diagnosed after 65 years of age, this is significant prognostic information for patients.

Details on PD motor progression were not well-documented with validated rating scales in the pre-levodopa era (22, 23). The introduction of dopaminergic agents improved motor function and disability in PD, but did not translate to reduced mortality in a 10-year multicentered study (24). These investigators reported that if advanced PD was defined by the appearance of axial symptoms and dementia, both bromocriptine and levodopa

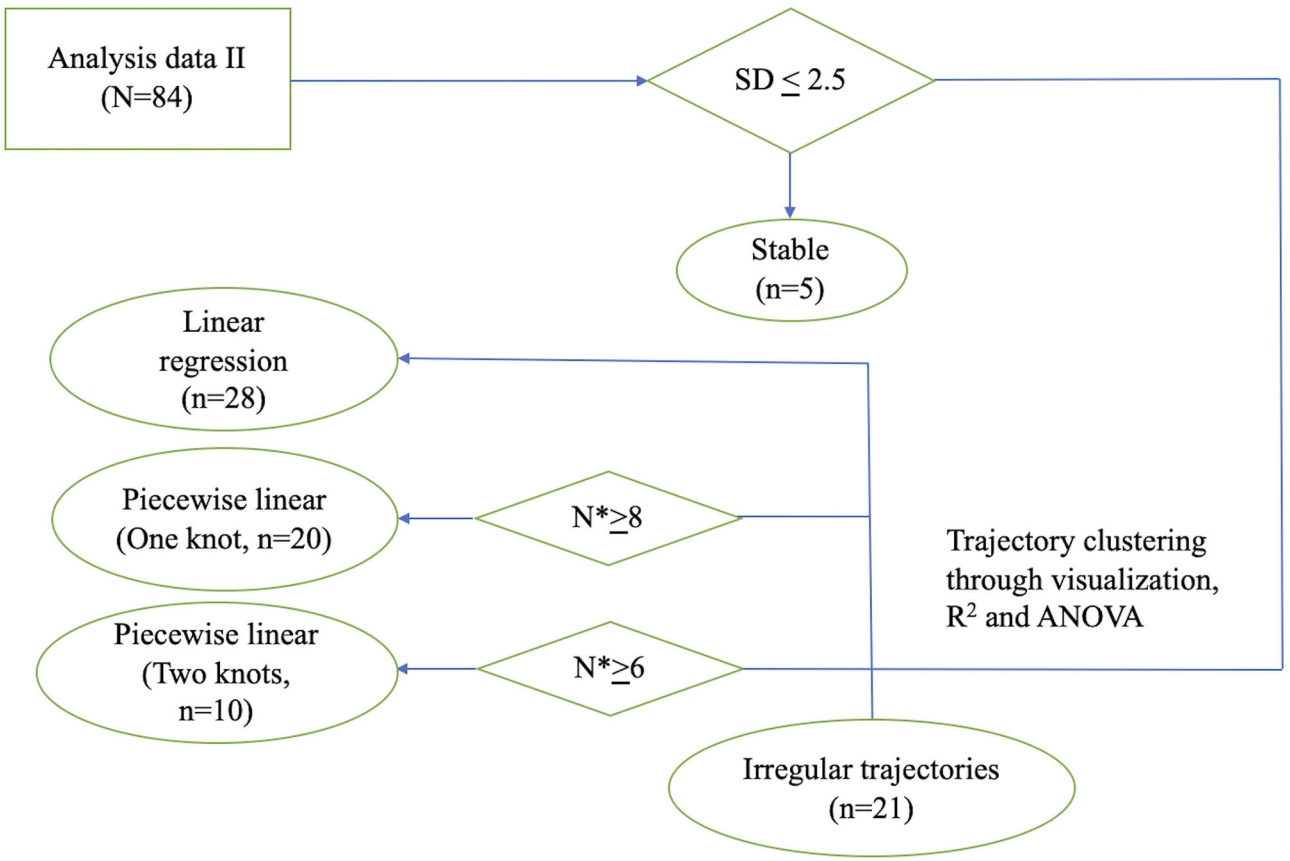

FIGURE 2 | Flowchart illustrating the process of individual model fitting. Flowchart illustrating the process of individual model fitting for the 84 PD patients (*n*: number of patients; *N**: number of observations per patient). SD, standard deviation; ANOVA, analysis of variance.

groups progressed at a similar rate. In addition, current medical and surgical therapies have not been shown to significantly alter the progression of the underlying neurodegeneration process in PD (4, 5). PD trajectories are complicated by phenotypic heterogeneity, diagnostic inaccuracy, and confounding factors including age and comorbidities (25). Further, recent genetic advances bring into question whether PD as the phenotype is indeed a single illness (21). Many placebo-controlled trials defined the rates of progression of motor dysfunction using the Unified Parkinson's Disease Rating Scale (UPDRS II and III) within the first 2–5 years of PD diagnosis (26–28). The rate of progression decreases with longer follow-up of 4 (29) and 8 years (30). This is consistent with previous clinical cross-sectional studies (23, 31, 32). The non-linear progression of PD motor impairment with steeper declines earlier in the disease may be due to an exponential decline of neuronal cell counts in the substantial nigra (33).

PD increases mortality compared to age-matched non-PD (34, 35). It is the 14th leading cause of death in the US (36). In a large population-based study, Beyer et al. indicated that age, UPDRS scores, and Hoehn and Yahr stage at baseline were greater in those who died during the follow-up period compared to the survivors (35). However, no longitudinal changes were collected during the follow-up. Our work provides importance evidence that terminal decline is a feature of PD, with later age of diagnosis associated with much shorter survival (10 years with diagnosis after 65 years of age vs. 24 years with diagnosis before age 50) (**Table 4**). This is valuable prognostic information for clinicians, patients, and families. In late stage disease, motor features seemed to become less responsive to dopaminergic therapy. Therefore, for those over 65 years of age at time of diagnosis, consideration of early implementation of palliative care principles of care would be appropriate. In the setting of motor complications, earlier rather than later DBS may be indicated given the relatively less progressive and long course especially in young onset (diagnosis before age 50) patient population (37, 38).

We did not observe any differences in disease trajectory between men and women as patients approached death. Previous longitudinal and cross-sectional studies of sex differences in PD progression yielded mixed findings. A longitudinal, observational study with 4,679 PD patients indicated that no significant differences between men and women were observed after 1 year of follow-up (39). However, baseline characteristics were different with women being significantly older than male participants in their study. A large clinical trial found no difference between male and female PD patients who were on

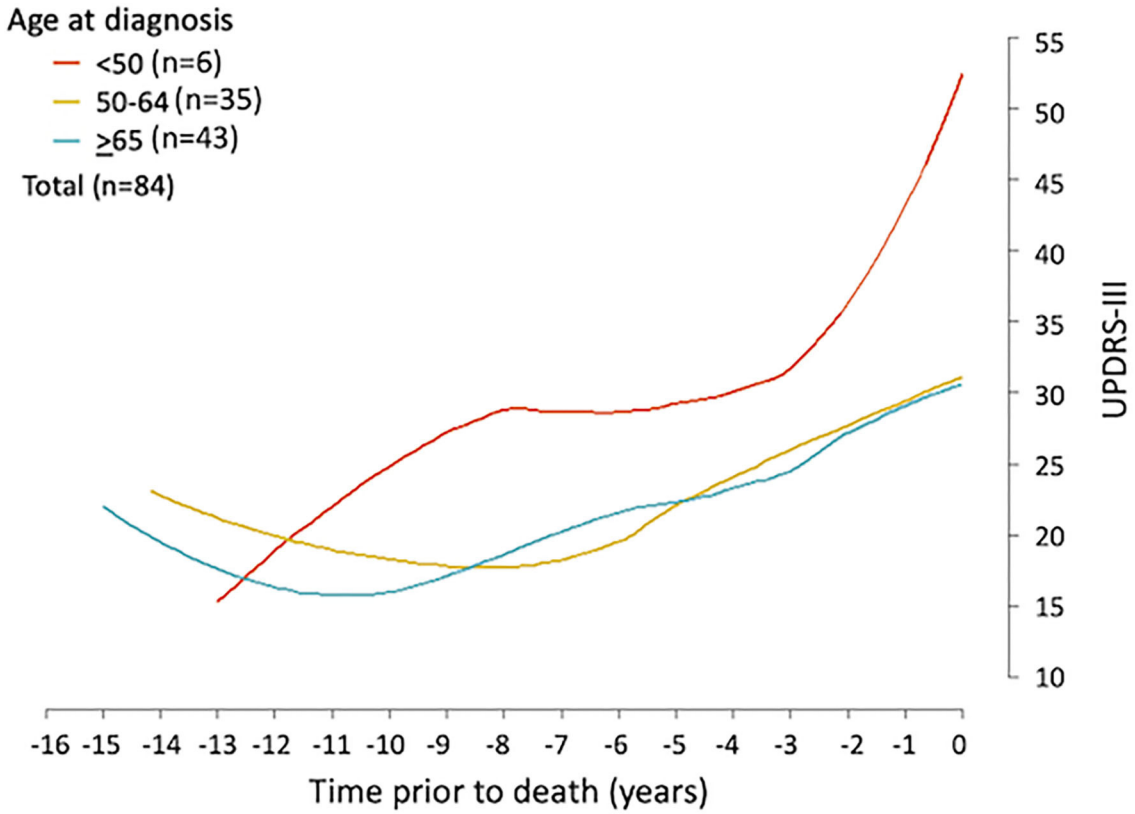

FIGURE 3 | UPDRS-III trajectory prior to death among Parkinson's patients. Loess curves were estimated using UPDRS-III scores from PD patients ($n = 84$) stratified by age at diagnosis, <50, 50–64, and ≥65 years. The figure shows the loess curves of the UPDRS-III scores vs. time for the three age groups combining men and women.

similar treatment regimens before enrollment during early stages of disease (40). In contrast, faster clinical decline was reported in men compared to women in another study (41). However, baseline clinical features between male and female patients were not analyzed in this study.

Consistent with our findings that patients older than 65 had shorter survival time, a previous systematic review using cluster analysis identified PD subtypes: young age (≤40 years old) at onset with slow disease progression, and old age (≥70 years old) at onset with rapid disease progression (13). A long term follow up study showed an increase hazard ratio for mortality of 1.40 for every 10-year increase in age (42). Similarly, older age at onset was a predictive factor for more rapid motor progression, nursing home placement, and shorter survival time (43), and was associated with progression of non-levodopa-responsive symptoms (44).

In our study, within the Consistent Deterioration group (**Figure 4B**, $n = 28$), age at diagnosis was associated with terminal UPDRS-III score. The older patients (≥65) had a lower UPDRS-III score toward death. However, it is hard to conclude that this observation represents the true natural history since it is only restricted to the Consistent Deterioration group with linear trajectory, as well as restricted to the end of life period instead of the entire survival period. In addition, we have only 6 patients belonging to this group whose age of onset was <50 years. It should be noted that, in young onset patients, we have missed years of follow up between age of onset and age at first assessment. The six individuals showed linear trajectory for the duration of analysis. However, to study the true pattern of progression in the patients with young age of onset, further studies, using larger sample sizes, are needed to use nature age as the time axis. Therefore, for patients diagnosed at younger age, the pattern of trajectory could potentially change to a different profile.

For those living with PD, planning for future needs especially in late stage is important. Our identification of terminal motor decline, similar to that in non-PD elderly, can provide a signpost for clinicians to inform patients and especially family members of the arrival of a new stage of illness. Terminal decline of UPDRS III can provide families with a sign that is easy for them to grasp and appreciate. Clinicians who identify terminal decline in their patients can use this information to guide a discussion regarding patient and caregiver needs and the potential benefits of palliative care involvement. Activating palliative care can engage the holistic philosophy that may relieve burdensome symptoms that accompany terminal decline such as pain, shortness of breath, caregiver burden, dysphagia, and

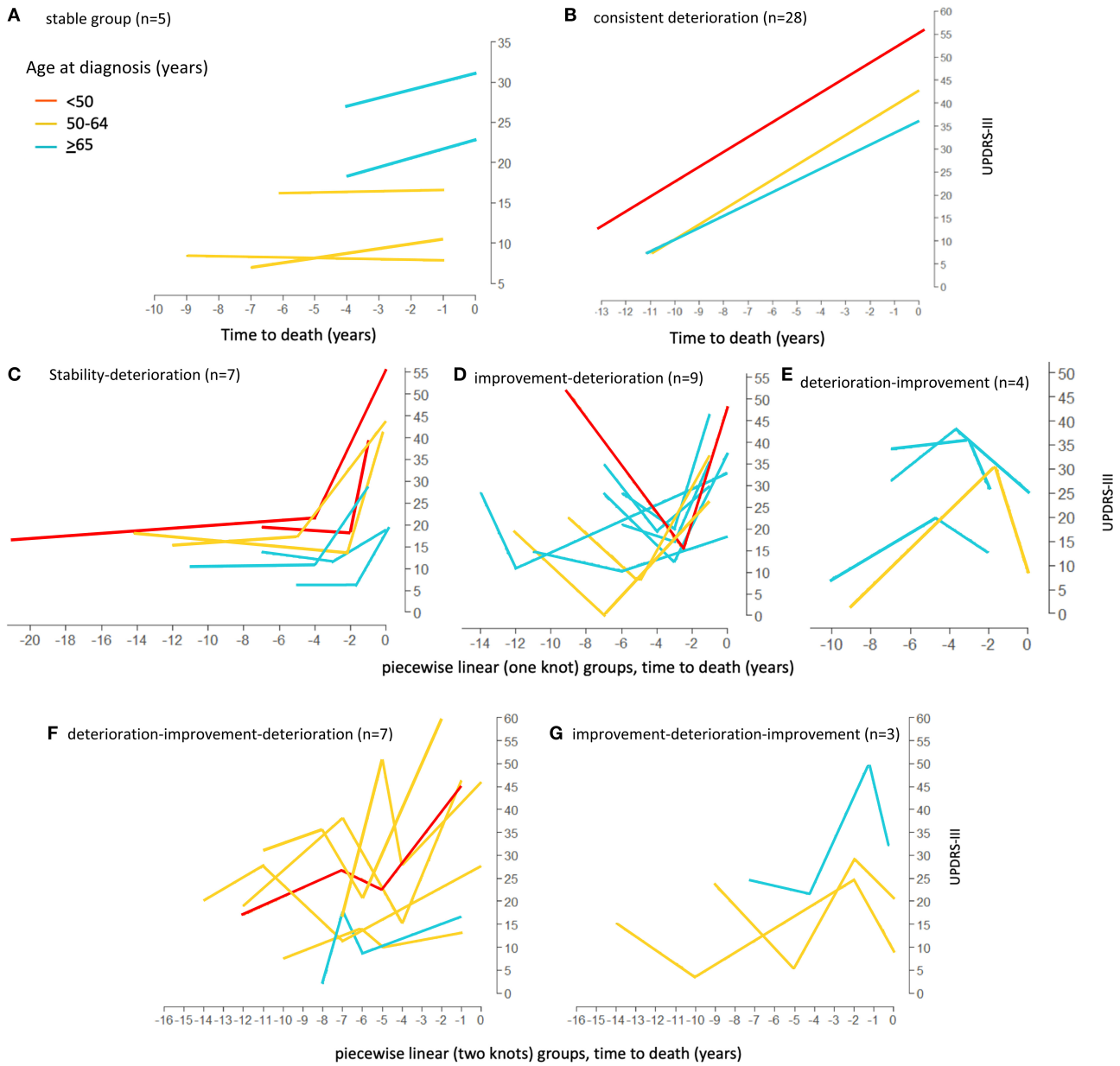

FIGURE 4 | Loess curves of UPDRS-III scores for Parkinson's patients with model fitting. Loess curves were visualized on time prior to death for the 84 Parkinson's patients analyzed. The curve was stratified by age at diagnosis, <50, 50–64, and ≥65 years. The individual model fittings are: **(A)** stable group, $n = 5$. **(B)** linear trend (Consistent deterioration) group (lines represent the average pattern for each age group), $n = 28$. **(C–E)** fitted trajectories for piecewise linear (one knot) groups. **(C)** Stability-Deterioration ($n = 7$); **(D)** Improvement-Deterioration ($n = 9$); and **(E)** Deterioration-Improvement ($n = 4$). **(F,G)** fitted trajectories for piecewise linear (two knots) groups. **(F)** Deterioration-Improvement-Deterioration ($n = 7$); **(G)** Improvement-Deterioration-Improvement ($n = 3$). PD, Parkinson's disease; UPDRS-III, Unified Parkinson's Disease Rating Scale motor score.

delirium (2). Furthermore, this information can help counsel patients with advanced disease to dispel the notion that PD has a constant rate of motor deterioration and educate about realistic expectations for the future. Our results can act as a trigger to help engage patients and caregivers in multidimensional shared decision-making discussions and make well-informed and thoughtful care decisions based on PD progression. The novel statistical approach to analyze disease trajectory resulting in distinct patterns is also clinically relevant. The modeling approach takes into account within patient score correlation, allowing teasing out the effect of age group and sex on the linear trend of the longitudinal scores. Due to limited sample size in some patterns of trajectory, we were unable to use statistical models to identify when change point(s) occur prior to death on average. We described and summarized our observation of individual trajectories instead (**Figures 4A,C–G**) and **Tables 2**, **3**.

TABLE 2 | Trajectory characteristics of the Parkinson patients (time prior to death, $n = 84$).

(A) Change in UPDRS-III.

Trajectory characteristics	*n* (%)	Change in UPDRS-III (points per year), Median (range)
Stable[a]	5 (6.0)	NA
Consistent deterioration	28 (33.3)	3.2[1], 2.6[2]
Piecewise linear (one knot)		
Stability – Deterioration	7 (8.3)	0.05 (−0.5, 0.3)7.25 (2.9, 21.9)
Improvement – Deterioration	9 (10.7)	−3.77 (−8.8, −0.9)10.6 (2.2, 18.9)
Deterioration – Improvement	4 (4.8)	2.85 (0.5, 3.9)−8.59 (−17.1 −5.1)
Piecewise linear (two knot)		
Deterioration – Improvement – Deterioration	7 (8.3)	2.5 (1.5, 16.9)−9.0 (−39.9, −4.1)10.9 (5.0, 27.5)
Improvement – Deterioration – Improvement	3 (3.6)	−2.9 (−1.0, −4.5)10.5 (5.6, 12.5)−12.25 (−27.6, −10.2)
Irregular/Undetermined	21 (25.0)	NA

(B) Transition time, time prior to death (years).

Trajectory characteristics	*n* (%)	Transition 1 Median (range)	Transition 2 Median (range)	Age at diagnosis (years) Median (range)
Stable[a]	5 (6.0)	NA	NA	60.5 (56, 75)
Consistent deterioration	28 (33.3)	NA	NA	68 (43, 80)
Piecewise linear (one knot)				
Stability – Deterioration	7 (8.3)	−3 (−5, −1.7)	NA	63 (47, 70)
Improvement – Deterioration	9 (10.7)	−4 (−12, −2.5)	NA	70 (48, 81)
Deterioration – Improvement	4 (4.8)	−3.35 (−4.7, −1.7)	NA	67 (61, 75)
Piecewise linear (two knots)				
Deterioration – Improvement – Deterioration	7 (8.3)	−7 (−11, −5)	−5 (−7, −4)	56 (45, 67)
Improvement – Deterioration – Improvement	3 (3.6)	−5 (−10, −4.3)	−2 (−2, −1.3)	64 (61, 73)
Irregular/Undetermined	21 (25.0)	NA	NA	63 (52, 76)

[a]Patients with standard deviation <2.5; [1]Fixed effects slope for age group (<50 and 50–64 years); [2]fixed effects slope for age group (≥65 years).

There are some limitations of the current study. Since the study was a retrospective chart review, other aspects of importance in advanced PD such as cognitive, other non-motor features, comorbidities and quality of life measures were not examined. Nevertheless, the UPDRS-III is used widely to reflect PD motor disability and is a main outcomes measure in many symptomatic trials (45, 46). However, it is possible that the UPDRS-III does not completely reflect true functional status of patients or progression rate at higher levels of disease severity. UPDRS-III scores may not be reliable in advanced disease due to a ceiling effect (47). We did not perform subgroup UPDRS III score analysis (tremor-dominant or PIGD) as previous studies have done (27, 28, 48, 49). Due to the long-time frame of data collection, the new MDS-UPDRS was not used. Our dataset was small as we limited ourselves to decedents with "complete" data. We acknowledge that additional patterns of change may be possible with large sample size. It is also important to note that 25% of our PD patients could not be classified into a pattern – this may be due to inability of patients to fully participate in examination or other factors not controlled for in a clinical setting. Our criteria for inclusion could have excluded older patients who were unable to be assessed in the clinic within 2 years prior to death, given the age difference between the included and excluded decedents. Similarly, with lack of the UPDRS-III in the final 2 years, the excluded group had a slightly lower UPDRS-III score at last assessment. In addition, in order to analyze the trajectory, we excluded the patients with <5 years of visit, which likely led to the shorter disease duration in the excluded group. However, this does not refute the observed patterns in the terminal motor trajectory in the PD patients with more complete data.

Future prospective studies of motor progression, non-motor symptoms, cognitive and neurobehavioral symptoms and the impact of comorbidities are needed to better characterize the totality of PD progression. While our retrospective study has provided a framework for counseling PD patients and caregivers, future prospective studies including reliable metrics that assess global function, including motor, non-motor, and activities of daily living, can further categorize disease trajectory and provide more accurate and holistic information.

Despite these limitations, our results outline four main types of motor progression in the years leading to death (Consistent Deterioration, Stability-Deterioration, Improvement-Deterioration, Deterioration-Improvement-Deterioration) and that, regardless of motor progression, terminal motor decline with a steep increase in UPDRS III

TABLE 3 | Summary of the trajectory types in relation to sex and age of onset of Parkinson's disease.

Trajectory characteristics	Sex, *n* (col%)		Total *n* (col%)
	Male	Female	
Stable	3 (5.1)	2 (8.0)	5 (6.0)
Consistent deterioration	19 (32.3)	9 (36.0)	28 (33.3)
Stability – Deterioration	5 (8.5)	2 (8.0)	7 (8.3)
Improvement – Deterioration	5 (8.5)	4 (16.0)	9 (10.7)
Deterioration – Improvement	3 (5.1)	1 (4.0)	4 (4.8)
Deterioration – Improvement – Deterioration	6 (10.2)	1 (4.0)	7 (8.3)
Improvement – Deterioration – Improvement	2 (3.4)	1 (4.0)	3 (3.6)
Irregular/Undetermined	16 (27.1)	5 (20.0)	21 (25.0)
Total *n* (row %)	59 (70.2)	25 (29.8)	84 (100)

Trajectory characteristics	Age at diagnosis*n* (col%)			Total *n* (col%)
	<50	50–64	≥65	
Stable	0 (0)	3 (8.6)	2 (4.6)	5 (6.0)
Consistent deterioration	2 (33.3)	8 (22.8)	18 (41.9)	28 (33.3)
Stability – Deterioration	2 (33.3)	2 (5.7)	3 (7.0)	7 (8.3)
Improvement – Deterioration	1 (16.7)	2 (5.7)	6 (14.0)	9 (10.7)
Deterioration – Improvement	0 (0)	2 (5.0)	2 (5.4)	4 (4.8)
Deterioration – Improvement – Deterioration	1 (16.7)	5 (14.3)	1 (2.3)	7 (8.3)
Improvement – Deterioration – Improvement	0 (0)	2 (5.7)	1 (2.3)	3 (3.6)
Irregular/Undetermined	0 (0)	12 (34.3)	9 (20.9)	21 (25.0)
Total *n* (row %)	6 (7.1)	35 (41.7)	43 (51.2)	84 (100)

TABLE 4 | Survival time post diagnosis for the Parkinson's patients.

Characteristics	*n* (%)	Median (IQR)	Range
Sex			
Male	59 (70.2)	11 (8–17)	(5–30)
Female	25 (29.8)	13 (9–18)	(5–22)
Age at diagnosis groups (years)			
<50	6 (7.1)	24 (19–27)	(18–30)
50–64	35 (41.7)	15 (12–18)	(6–26)
≥65	43 (51.2)	10 (7–11)	(5–20)

The survival time of the parkinsonian syndromes in relation to sex and age of the patients. Survival time, survival from time of diagnosis in years. IQR, interquartile range.

was seen in many patients approaching death. Those with diagnosis after age 65 years had shorter survival times. Our study provides knowledge of dominant trajectory types in PD that can help clinicians understand their patients' course of illness. This information can help counsel patients with advanced disease to identify triggers of declining function and potentially may be used for hospice enrolment criteria or involvement of palliative care.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of Alberta Health Research Ethics Board. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

SP: statistical analysis – review and critique and manuscript – writing of the first draft and review and critique. JM: research project – conception, organization, execution, statistical analysis – design and review and critique, and manuscript –

review and critique. XF: research project – execution and statistical analysis – execution and review and critique. RC: research project – conception, organization, execution, statistical analysis – review and critique, and manuscript – review and critique. TS: research project – execution, statistical analysis – execution and review, and manuscript – review and critique. YY: statistical analysis – design and review and critique and manuscript – review and critique. FB: research project – conception and execution, statistical analysis – review and critique, and manuscript – writing of the first draft and review and critique. All authors contributed to the article and approved the submitted version.

FUNDING

JM received funding from the Parkinson Foundation Parkinson Outcome Project, the University of Alberta Hospital Foundation, and Dennis and Doreen Erker Fund. RC received funding from the Canadian Consortium on Neurodegeneration in Aging (CCNA FRN CNA137794). He also received funding from Axovant for a clinical trial in Dementia with Lewy Bodies. YY's research is supported by NSERC (RGPIN-2019-04862). FB received funding from Natural Science Foundation of China (NSFC 81871322, 2018), Mates Foundation for Parkinson's Research, and Kaye fund. She received funding from the Canadian Consortium on Neurodegeneration in Aging (CCNA FRN CNA137794).

ACKNOWLEDGMENTS

We thank all individuals who contributed in the study. We acknowledge Drs. Jennifer McCombe, Ted Roberts, Tom Nowacki, Oksana Suchowersky, Naheed Rajabali, and W. R. Wayne Martin who cared for the patients in the Parkinson and Movement disorders Program, University of Alberta, Canada.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.670567/full#supplementary-material

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frontiers in Neurology

ORIGINAL RESEARCH
published: 01 September 2021
doi: 10.3389/fneur.2021.709132

Coping Style in Glioma Patients and Their Caregiver: Evaluation During Disease Trajectory

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Background: Patients with glioma have a poor prognosis and, in a short period of time, have to deal with severe forms of disability, which compromise their psychological distress and quality of life. The caregivers of these patients consequently carry a heavy burden in terms of emotional and patient care. The study aims to evaluate the coping strategies of patients and their caregivers during the course of the disease in order to frame the adaptation process in a rapidly progressing pathology.

Methods: A prospective study on 24 dyads of patients affected by malignant glioma and their caregivers was conducted between May 2016 and July 2018. Questionnaires designed to identify the coping style (MINI-MaC Scale) and psychological distress (HADS scores) and assess QOL (EQ-5D) were administered at two time points: at first lines of treatment and at disease recurrence.

Results: Patients and their caregiver structure adaptive coping strategies during the disease: a coping style oriented toward a fighting spirit prevails at baseline (Mini-Mac Mean 3.23); fatalism prevails at recurrence (Mini-Mac Mean 3.03). Psychological distress affects the coping style expressed: high levels of anxiety symptoms were found to be significantly associated with a coping style oriented toward anxious preoccupation, helpless–hopeless, and fatalism; low depressive symptoms were inversely correlated with fighting spirit coping style. Patients' and caregivers' perceptions of quality of life were correlated between them and with performance status assessed by clinicians. In a dyadic perspective, the adaptation of a member of the couple varies as a function of the other partner's coping style.

Conclusions: Our data are in line with previous literature on cancer patients, demonstrating that coping style is not a persistent dimension of personality, but can change depending on the situation. Despite the disease rapid course, patients and their caregivers can structure adaptive and functional defenses to manage the disease.

Keywords: coping style, glioma, dyadic model, distress, quality of life, palliative care

OPEN ACCESS

Edited by:
Marianne De Visser, University of Amsterdam, Netherlands

Reviewed by:
Rainer Spiegel, University of Basel, Switzerland
Nicolai Goettel, University of Florida, United States

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Specialty section:
This article was submitted to Neurocritical and Neurohospitalist Care, a section of the journal Frontiers in Neurology

Received: *13 May 2021*
Accepted: *21 July 2021*
Published: *01 September 2021*

Citation:
Guariglia L, Ieraci S, Villani V, Tanzilli A, Benincasa D, Sperati F, Terrenato I and Pace A (2021) Coping Style in Glioma Patients and Their Caregiver: Evaluation During Disease Trajectory. Front. Neurol. 12:709132. doi: 10.3389/fneur.2021.709132

INTRODUCTION

Patients diagnosed with glioma have a poor prognosis and, despite increased treatment options, a limited survival (1–3). Fear about death, rapid physical decline, disease burden, difficult medical decisions, and desire for information about the disease induce, both patients and caregivers, to define adaptive strategies to deal with the disease burden. According to Lazarus' transactional approach to stress (4), coping can be defined as "constantly changing cognitive and behavioral efforts to manage specific external or internal demands that are appraised as taxing or exceeding the resources of a person." Coping may be organized into five categories: fighting spirit, cognitive avoidance, anxious preoccupation, helpless–hopeless, and fatalism (4, 5). Coping strategies are considered a determinant factor in the process of emotional adaptation to the disease and may influence health-related quality of life (HRQoL) perception and psychological status in cancer patients (6–8). According to the theoretical model (4), coping strategies may change over time in different stages of the disease and are influenced by several factors, such as quality of life, cognitive function, different psychological distress features, clinical condition, and disease awareness (8–10). In addition, an analysis of coping strategies should take into account the dynamic interplay between partners, such as the dyad made by the patient and his/her main caregiver (11). The origin of the stress, the goals, the appraisals, and the coping strategies of each individual and patient/caregiver dyads need to be considered.

Several studies have evaluated coping styles in cancer patients, focusing both on individual and relational (dyadic) coping; however, brain tumor (BT) patients require a special approach due to the particular trajectory of the disease, the very poor prognosis, and the presence of cognitive and behavioral changes induced by the tumor in the brain. Malignant gliomas present a median survival of 17–36 months, and, despite aggressive treatments, the majority of patients will experience disease recurrence during the first years after diagnosis (EANO Guidelines) (12).

In this prospective, longitudinal study, we hypothesize that despite the short course and the aggressive nature of the disease, patients are still able to find adaptive strategies and change their coping style in relation to factors previously identified in the literature: quality of life, distress, and relational structure.

PATIENTS AND METHODS

A prospective study on 24 dyads of patients affected by newly diagnosed malignant glioma and their caregivers was conducted at IRCCS Regina Elena Cancer Institute in Rome between May 2016 and July 2018. The inclusion criteria were patients with newly diagnosed high-grade glioma, who were subjected to first-line treatment (surgery, radiotherapy, chemotherapy) without serious cognitive impairments that compromised the ability to understand and respond to questionnaires. All patients received a comprehensive clinical evaluation including psychological assessment, cognitive functions evaluation, and quality-of-life measurements. All caregivers were patients' relatives. Coping style, quality of life, and anxiety and mood were assessed at baseline, after diagnosis, and at the recurrence of the disease. All subjects provided written informed consent. The sociodemographic and clinical characteristics were collected using medical records. All patients included in this study were preliminarily assessed with the Italian version of the Mini-Mental State Examination (MMSE) (13, 14) and did not show relevant cognitive deficits. Patients' and caregivers' characteristics are shown in **Table 1**.

TABLE 1 | Patients' and caregivers' characteristics.

Characteristics	Patients, *n* (%)	Caregivers, *n* (%)
Histology:	Glioblastoma 22 (92)	
	Anaplastic astrocytoma 2 (8)	
Evaluated at baseline	24	24
Evaluated at recurrence	8	8
Age in years, median (min–max)	58 (31–76)	
Males/females	14/10 (58/42)	7/17(29/71)
Patients educational level	Elementary 3 (12)	
	Lower secondary 5 (21)	
	Upper secondary 9 (38)	
	Graduate 7 (29)	
Baseline Karnofsky, median (min–max)	90 (70–100)	
Karnofsky at follow-up, median (min–max)	70 (60–100)	
baseline MMSE, median (min–max)	30 (25–30)	
MMSE at follow-up, median (min–max)	28 (24–30)	

Assessment Tools

Styles of coping of patients and caregivers were evaluated using the Mini-Mental Adjustment to Cancer (Mini-MAC) scale (15).

The Mini-MAC is a revised version of the widely used Mental Adjustment to Cancer scale (15), developed for measuring mental adjustment to cancer in a general cancer population. The Mini-MAC has five domains: Fighting Spirit (FS; four items); Helpless–Hopeless (HH; eight items); Anxious Preoccupation (AP; eight items); Fatalism (FA; five items); and Cognitive Avoidance, (CA; four items). It is composed of 29 questions relating to the five coping strategies. The items are rated on a four-point Likert scale ranging from "Definitely does not apply to me" (1) to "Definitely applies to me" (4) and measures the patients' experiences at present. A higher score represents a higher endorsement of the adjustment response. The domains can be scored separately through simple addition. Since the domains consist of a different number of items, we also calculated mean scores by dividing the sum by the number of items.

The Hospital Anxiety and Depression scale was used to evaluate the level of distress both in patients and in caregivers (7, 16). The questionnaire comprises seven questions for anxiety and seven questions for depression. For both scales, scores <7 indicate absent anxiety/depression; scores between 8 and 10

indicate a mild level of anxiety and depression; scores between 11 and 14 indicate a moderate level of anxiety and depression; and scores between 15 and 21 indicate severe-level anxiety and depression.

Patients' quality of life was assessed using the Italian version of the EuroQol-5D (EQ-5D) questionnaire, obtaining a patient's self-evaluation and a caregiver's evaluation of the patient's health status (17). The questionnaire has two components: health state description and evaluation. In the description part, health status is measured in terms of five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. In the evaluation part, the respondents evaluate their overall health status using the visual analog scale (EQ-VAS). Patients' performance status was assessed by clinicians using the Karnofsky scale.

Questionnaires and interviews were handed out on paper by two psychologists (LG and SI).

Statistics

Descriptive statistics were calculated for all variables of interest. Continuous variables were reported through means and their relative standard deviations, while categorical variables were synthetized with frequencies and percentage values. All continuous variables were tested for normality. The non-parametric Spearman's rank correlation coefficient was used to evaluate the correlation between the different categories of copying. Statistical significance was considered when p-value ≤ 0.05. All analyses were carried out with SPSS v 21.0.

RESULTS

Between May 2016 and July 2018, 24 patients affected by malignant glioma and their respective main caregivers were assessed during the first cycle of adjuvant chemotherapy (baseline). Patients and caregivers were recruited at Neuro-Oncology Department of Regina Elena Cancer Institute in Rome, Italy. The first evaluation was 4.3 months after diagnosis, on average (range 1.6–6.7 months). Eight patients and their respective caregivers were reassessed after a recurrence of glioma, on average 12.1 months after diagnosis. At recurrence, 16 patients were not evaluable due to disease progression with severe neurocognitive impairment (10 patients) or lost at follow-up (6 patients).

The average interval between the first and second evaluations was 7.3 months (range 4–13 months). Main caregivers were spouses ($n = 18$), sons ($n = 4$), or parents ($n = 2$). Patients' and caregivers' characteristics are demonstrated in **Table 1**.

Patients' Coping Styles

Baseline

At baseline, at group level, patients reported higher scores in the domain of FS (mean 3.23; SD 0.82) and CA (mean 3.05; SD 0.51). The domains of FA (FA mean 2.77, SD 0.82) and AP (AP mean 2.29, SD 0.71) reached a slightly lower average score. Detailed Mean Score values are described in **Table 2**.

At the individual level, most frequent coping strategies resulted in CA (18 patients, 75%) and FS (17 patients, 70%).

TABLE 2 | Results of assessments at baseline and recurrence in patients and caregivers.

	Baseline ($n = 24$)		Recurrence ($n = 8$)	
	Mean (SD)	**Min–max**	**Mean (SD)**	**Min–max**
Patients				
FS	3.23 (0.82)	1.75–4.00	2.90 (0.68)	1.75–3.75
HH	1.84 (0.57)	1.00–3.38	2.06 (0.42)	1.50–2.75
AP	2.29 (0.71)	1.13–3.50	2.47 (0.61)	1.88–3.38
FA	2.77 (0.82)	1.40–4.00	3.03 (0.64)	2.40–4.00
CA	3.05 (0.51)	2–4	2.53 (0.66)	1.75–3.50
Caregivers				
FS	2.93 (0.64)	1.50–4.00	2.90 (0.42)	2.50–3.75
HH	1.83 (0.55)	1.00–3.38	2.00 (0.53)	1.25–2.88
AP	2.90 (0.62)	1.75–4.00	2.89 (0.44)	2.25–3.63
FA	2.65 (0.58)	1.40–3.60	2.85 (0.30)	2.40–3.20
CA	2.84 (0.70)	1.25–4.00	2.56 (0.40)	2.00–3.00

FS, fighting spirit; HH, helpless–hopeless AP, anxious preoccupation; FA, fatalism; CA, cognitive avoidance.

However, 33% of responders displayed a predominant coping style in the domain of FA and 25% in the domain of AP (**Figure 1**).

High levels of anxiety symptoms measured with the Hospital Anxiety and Depression (HAD) scale at baseline were found to be significantly associated with a coping style oriented toward anxious preoccupation (baseline: Rho $= 0.618$, $p = 0.001$), while low depressive symptoms were inversely correlated with fighting spirit coping style, although this finding did not reach a full statistical significance (Rho $= -0.398$, $p = 0.054$).

Patients' self-perception of a high quality of life, measured with EQ5 VAS, was directly correlated with FA (Rho $= 0.727$, $p = 0.041$). There was no statistically significant correlation between age, sex, educational level, and adopted coping style; in the same way, no statistically significant correlations were observed between the functional status measured by the Karnovsky scale and the coping styles adopted.

Recurrence

A longitudinal evaluation was possible only in eight patients and their caregivers due to early disease progression, cognitive deficits, or patients lost at follow-up. At recurrence, at a group level, patients evaluated reported higher scores in the domain of FA (mean 3.03; SD 0.64) and FS (mean 2.90; SD 0.68). The domains of CA (mean 2.53; SD 0.66) and AP (mean 2.47; SD 0.61) reach a slightly lower average score (**Table 2**).

At an individual level, patients evaluated showed a higher score in the domain of FS (60%) and FA (60%). Avoidance coping style was present in 50% of patients (**Figure 2**).

At recurrence, a high score of anxiety symptoms was associated with a coping style oriented toward the domains of HH (Rho $= 0.789$, $p = 0.020$), AP (Rho $= 0.895$, $p < 0.003$), and FA (Rho 0.821, $p = 0.012$). The presence of depressive symptoms was found to be associated with a coping strategy predominantly in the domain of HH (Rho $= 0.867$, $p = 0.005$) and AP (Rho

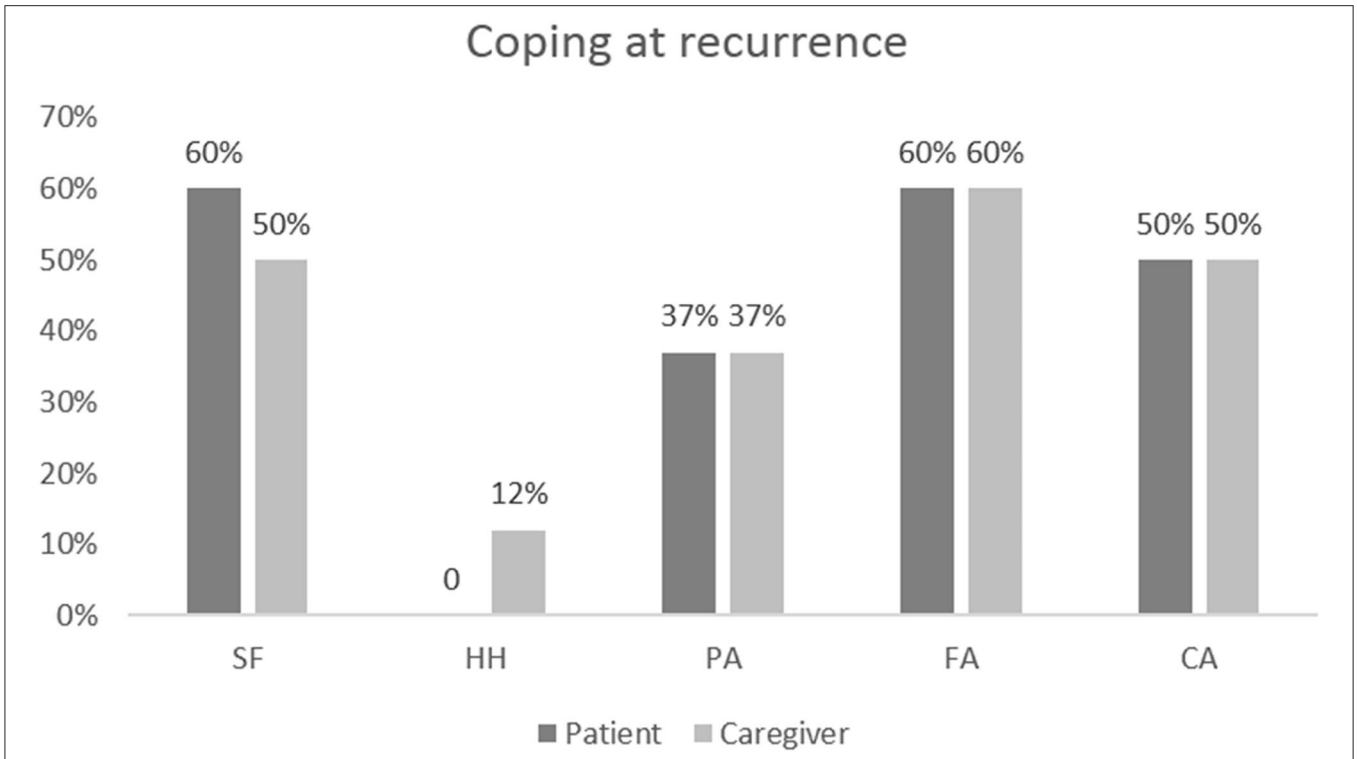

FIGURE 1 | Results of coping assessments at baseline in patients and caregivers at the individual level.

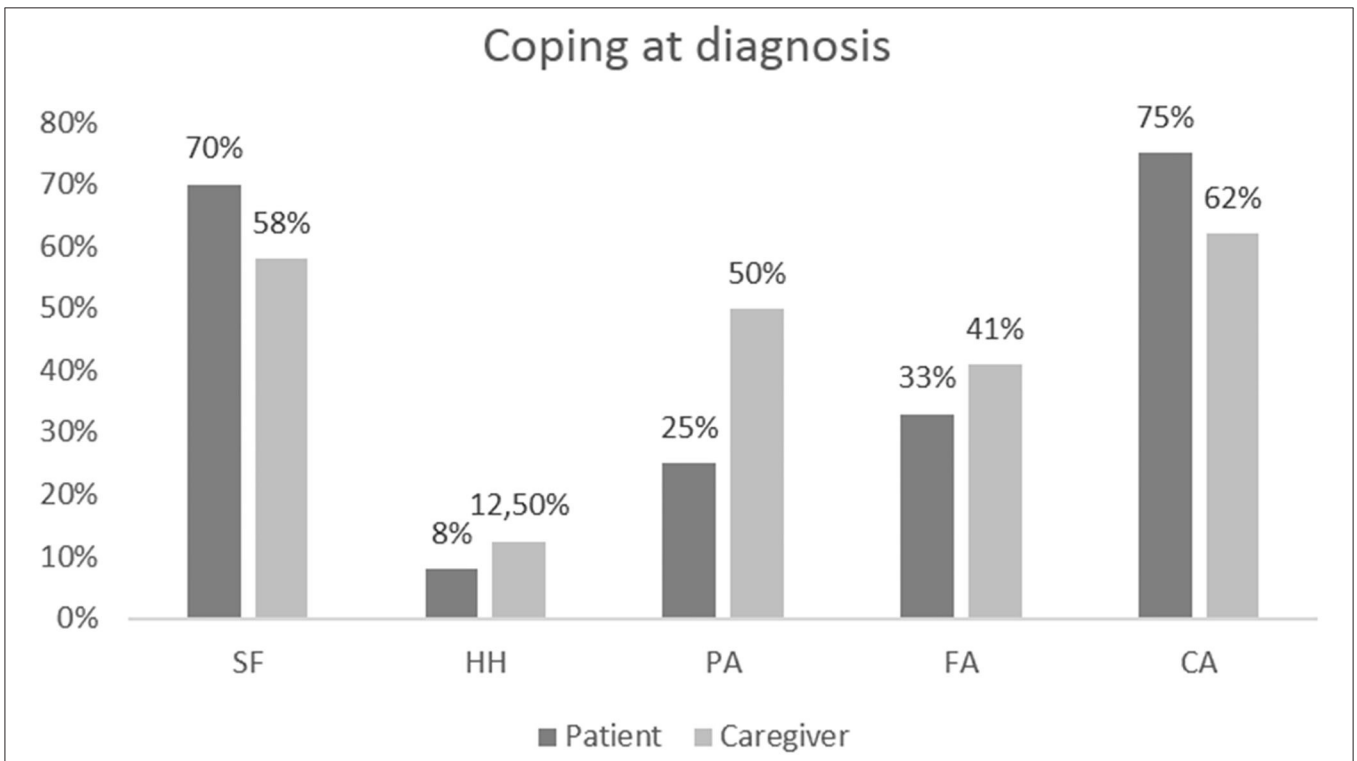

FIGURE 2 | Results of coping assessments at recurrence in patients and caregivers at the individual level.

= 0.957, $p < 0.001$) and inversely correlated with FS (Rho = −0.845, $p = 0.008$). At recurrence, patients' self-perception of low quality of life was correlated with anxious preoccupation coping style (Rho = −0.780, $p = 0.022$).

Caregivers' Coping Styles

Baseline

At baseline, at the group level, caregiver coping style analysis showed a higher score in the domain of FS (mean 2.93; SD 0.64) and AP (mean 2.90; SD 0.62). The domains of CA (mean 2.84; SD 0.70) and FA (mean 2.65; SD 0.58) reached a slightly lower average score. Detailed mean score values are described in **Table 2**. At the individual level, 54% of caregivers presented a coping style predominantly oriented toward the domain of fighting spirit and avoidance, and 50% showed a high score in the domain of anxious preoccupation. HAD score measures in caregivers at baseline showed that low levels of anxiety and depression were associated with a coping style oriented toward a fighting spirit (Rho = −0.586, $p = 0.003$ for anxiety and Rho = −0.691, $p < 0.001$ for depression); high levels of anxiety were associated with a coping style oriented toward anxious preoccupation (Rho = 0.456, $p = 0.025$); and high levels of depression were associated with AP (Rho = 0.480, $p = 0.018$) and HH (Rho = 0.581, $p = 0.003$). Perception by the caregiver of a low patient quality of life at baseline was correlated with HH (Rho = 0.484, $p = 0.016$) and with AP (Rho = 0.619, $p = 0.001$). On the contrary, perception of a better patient quality of life was correlated with FS (Rho = 0.747, $p = 0.033$) and inversely correlated with HH (Rho = −0.926, $p = 0.001$).

Recurrence

At recurrence, caregiver coping style analysis showed a higher score in the domains of FS (mean 2.90, SD 0.42) and AP (mean 2.89, SD 0.44). The domains of FA (mean 2.85, SD 0.30) and CA (mean 2.56, SD 0.40) reached a fairly high average score. Detailed mean score values are described in **Table 2**.

At the individual level, 62% of caregivers presented a coping style predominantly oriented toward the domain of FS and FA; 50% presented a coping style oriented toward AP; 37% toward CA (**Figure 2**).

At recurrence, low levels of anxiety were associated with an FS coping style (Rho = −0.907, $p = 0.002$).

Dyadic Coping

Analyzing the interconnection between patient and caregiver dyad, at baseline, 58% of couples show complementary coping styles: patients with HH have caregivers with AP (Rho 0.431, $p = 0.036$); patients with FA have a caregiver with an FS (Rho = 0.462, $p = 0.023$); and patients with FS have a caregiver with HH (Rho = −0.434, $p = 0.034$).

However, 42% showed symmetrical coping: an FS and a HH coping in the patient was significantly correlated with the same style of coping in the caregiver (Rho = 0.539, $p = 0.007$ and Rho = 0.448, $p = 0.028$, respectively). At recurrence, among the eight dyadic couples examined, 80% showed symmetrical coping: HH coping in the patient was significantly correlated with the same coping style in the caregiver (Rho = 0.813, $p = 0.014$). However, 20% of dyadic couples showed a complementary coping: patients with AP have caregivers with HH (Rho = 0.809, $p = 0.015$). An inverse weak correlation was found between avoidance style in the patient and in the caregiver (Rho = −0.716, $p = 0.046$), which means that when a member of the couple uses avoidant coping, the other is unable to use the same strategy (**Figure 1**).

Concerning the quality-of-life evaluation, our results show that at baseline, patients' and caregivers' perceptions of patients' quality of life were correlated (Rho = 0.725, $p < 0.0001$). Also at recurrence, the patient health status self-assessment was correlated with the caregiver evaluation (EQ-VAS: Rho = 0.753, $p = 0.031$). Quality of life, as assessed both by patient and by caregiver, was correlated with performance status assessed by clinicians (Rho = −0.546, $p < 0.006$; Rho = −0.642, $p < 0.001$).

DISCUSSION

Brain tumors represent a devastating disease and the poor prognosis, and the short history of disease renders this tumor quite different with respect to other cancers. Our prospective, longitudinal study is aimed to evaluate how BT patients and their caregivers organize the response to stress utilizing strategies to manage the disease and related symptoms.

Our results show that, both at baseline and recurrence, patients' coping strategies are not strongly polarized but showed many different styles facing the new situation. However, most BT patients initially face the disease either with a fighting spirit or by a defensive cognitive avoidance style; after recurrence, many patients maintained a fighting spirit but the cognitive avoidance coping style boils down to fatalism.

Despite the aggressiveness of the disease and the poor prognosis, during first-line treatment, most of the patients can display functional coping strategies, such as FS, which favors active participation and adherence to treatment; in addition, CA style preserves the individual from excessive exposure to distress. On the other hand, HH, which is considered the most dysfunctional style of coping, is the least expressed at baseline evaluation. The functional coping strategies are also preserved at disease recurrence but with a progressive adherence to the reality: CA is replaced by FA.

The caregivers' coping strategy initially face the patient's disease with an FS or by an AP style and seem to maintain the same adaptation strategy at disease recurrence.

Concerning the correlation between coping style and anxious/depression and HRQOL, our data show that, both at baseline and recurrence, in patients and caregivers, high levels of anxiety/depression and low perception of HRQoL were significantly associated with a higher score on the HH and AP domains. In addition, higher levels of anxiety and depression observed in caregivers at baseline were correlated with a higher score in the domain of AP.

These data confirm previous evidence of a strong association of anxious and depressive symptoms with coping strategies (9, 10, 18). Similarly, our data confirm previous observations on cancer patients, showing that perceptions of HRQoL correlate with coping strategies (9, 10, 18). However, probably due to the small sample size, in our study, a significant correlation between HRQoL and coping style was observed only between EQ5 VAS score, a visual analogical scale and, therefore, with a greater

degree of approximation, and coping style oriented toward AP and HH domains, mainly in caregivers' perception.

Our data are in line with previous literature on cancer patients, demonstrating that coping style is not a persistent dimension of personality, but can change depending on the situation. In addition, patients' and caregivers' reactions could be different, although a mutual influence was present, according to a dyadic model.

Few studies have examined the patient/caregiver interaction model in BT. Other studies in cancer patients have reported that the relation of one partner's coping to adjustment varies as a function of the other partner's coping style (19).

The theoretical model of dyadic coping describes coping change not only based on each one's resources but also on the couple relationship that engendered a mutual influence and consistency (19). When coping is considered in a dyadic perspective, in some cases patients and caregivers assume a symmetrical attitude and provide the same coping response to the disease, establishing a supportive relationship; in other cases, patients and caregivers assume a complementary attitude: one of the two members assumes a style of coping that is contrary to the other, establishing a compensative relationship (19).

In the early period of the disease, one subject takes charge of facing reality letting the other keep in a defense attitude (i.e., when the disease is faced with AP by the caregiver and with an FS by the patient).

At recurrence, the couple most frequently maintains similar coping strategies and reinforce each other (i.e., when the disease is faced with FA or CA from both). Our data show a consistent difference between the baseline assessment and that at disease recurrence: at baseline, 42% of couples express a symmetrical relationship between the coping styles, while at the recurrence of the disease, the percentage achieves 80%. Therefore, during the course of the disease, couples progressively settle on the expression of the same coping style.

Although the results of the longitudinal assessment are limited by the small number of patients/caregivers receiving a follow-up evaluation, our results show that, after a few months since baseline assessment, there is a modification of coping strategies observed at disease recurrence with a shift toward AP and FA, probably related to a higher score of anxious/depression and perception of lower quality of life. This aspect represents probably the main difference between BT and other cancer patients due to the rapid deterioration of clinical conditions and a short time to recurrence in neuro-oncological patients.

The results of our study provide important insights into coping strategies adopted by patients with malignant gliomas and their caregivers along the disease trajectory.

Considering the short life expectancy of malignant glioma patients and their care needs throughout the disease trajectory, coping strategies should be considered as a key component in the management of BT patients. Patients' coping styles have an important influence in critical aspects of care such as communication of diagnosis and prognosis, discussion with patients and their caregivers about the goal of treatments, early introduction of palliative care, and advanced planning of patients' preferences concerning the end-of-life treatment and issues.

Despite the well-recognized importance to improve patient–clinician communication about illness and prognosis and early integration of palliative care in the trajectory of disease of BT patients, recent studies on prognostic awareness and preferences for prognostic communication in BT patients reported that some BT patients wish that prognosis was discussed in greater depth and earlier in the disease course, but others do not want to discuss prognosis fully, especially when the discussion is experienced as deleterious to maintaining hope (20). In addition, in a qualitative study on preferences for information about prognosis, comprehension of information, and satisfaction with information, 50% of participants preferred to receive "all information" while the remainder wanted only "important" or "critical" information (21).

According to recent studies in advanced cancer, the coping style adopted may strongly influence patients' prognostic awareness and patients' availability to participate in prognosis discussions (10).

Moreover, patients' prognosis awareness fluctuates longitudinally through disease and treatment courses. Considering the strong interaction between patients' coping strategies and critical issues related to communication and early integration of palliative care, additional studies on timing and ways of discussing prognosis and goals of care in this population are needed.

The most important limits of this study are the small sample size and the small number of dyadic couples receiving a longitudinal assessment. Moreover, the inclusion in this study of patients without cognitive deficits may lead to a selection bias with the exclusion of patients with lower performance status.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LG and AP contributed to the conception and design of the study. LG, SI, VV, AT, and DB administered the questionnaires and assessed patients. FS and IT performed the statistical analysis. All authors contributed to the manuscript revision, read, and approved the submitted version.

ACKNOWLEDGMENTS

Editorial assistance was provided by Laura Brogelli and Aashni Shah (Polistudium, Milan, Italy).

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

SYSTEMATIC REVIEW
published: 03 September 2021
doi: 10.3389/fneur.2021.694572

Needs Assessment of Safe Medicines Management for Older People With Cognitive Disorders in Home Care: An Integrative Systematic Review

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OPEN ACCESS

Edited by:
David John Oliver, University of Kent, United Kingdom

Reviewed by:
Benjamin Aaron Emanuel, University of Southern California, United States
Hossein-Ali Nikbakht, Babol University of Medical Sciences, Iran

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Specialty section:
This article was submitted to Neurocritical and Neurohospitalist Care, a section of the journal Frontiers in Neurology

Received: *13 April 2021*
Accepted: *21 July 2021*
Published: *03 September 2021*

Citation:
Vaismoradi M, Behboudi-Gandevani S, Lorenzl S, Weck C and Paal P (2021) Needs Assessment of Safe Medicines Management for Older People With Cognitive Disorders in Home Care: An Integrative Systematic Review. Front. Neurol. 12:694572. doi: 10.3389/fneur.2021.694572

Background and Objectives: The global trend of healthcare is to improve the quality and safety of care for older people with cognitive disorders in their own home. There is a need to identify how medicines management for these older people who are cared by their family caregivers can be safeguarded. This integrative systematic review aimed to perform the needs assessment of medicines management for older people with cognitive disorders who receive care from their family caregivers in their own home.

Methods: An integrative systematic review of the international literature was conducted to retrieve all original qualitative and quantitative studies that involved the family caregivers of older people with cognitive disorders in medicines management in their own home. MeSH terms and relevant keywords were used to search four online databases of PubMed (including Medline), Scopus, CINAHL, and Web of Science and to retrieve studies published up to March 2021. Data were extracted by two independent researchers, and the review process was informed by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Given that selected studies were heterogeneous in terms of the methodological structure and research outcomes, a meta-analysis could not be performed. Therefore, narrative data analysis and knowledge synthesis were performed to report the review results.

Results: The search process led to retrieving 1,241 studies, of which 12 studies were selected for data analysis and knowledge synthesis. They involved 3,890 older people with cognitive disorders and 3,465 family caregivers. Their methodologies varied and included cohort, randomised controlled trial, cross-sectional studies, grounded theory, qualitative framework analysis, and thematic analysis. The pillars that supported safe medicines management with the participation of family caregivers in home care consisted of the interconnection between older people's needs, family caregivers' role, and collaboration of multidisciplinary healthcare professionals.

Conclusion: Medicines management for older people with cognitive disorders is complex and multidimensional. This systematic review provides a comprehensive image of the interconnection between factors influencing the safety of medicines management in home care. Considering that home-based medicines management is accompanied with stress and burden in family caregivers, multidisciplinary collaboration between healthcare professionals is essential along with the empowerment of family caregivers through education and support.

Keywords: aged, cognitive disorder, dementia, caregivers, family, home care services, medication therapy management, Alzheimer disease

INTRODUCTION

Cognitive disorders consist of several neurological conditions such as dementia and its most common subtype (70% of cases) Alzheimer's that influence the memory, cognition, thinking, behaviour, and functional ability to perform activities of daily livings. Age has been introduced as a strong risk factor for the development of cognitive and memory disorders (1). Given that 23% of the total global burden of diseases can be attributed to disorders among older people (≥60 years), neurological disorders are considered one of the leading contributors (6.6%) to disease burden in this age group (2).

Demographic transition has resulted in a significant increase in the elderly population, bringing degenerative neurological diseases including cognitive and memory disorders. Nowadays, 50 million people live with dementia worldwide, and the number will most likely rise to about 150 million by 2050 (3). As the matter of economic impact, the global estimation of the costs of dementia treatment and care has been US $957.56 billion in 2015, which will reach US $2.54 trillion in 2030 and US $9.12 trillion in 2050 (4). The devastating impact of cognitive and memory disorders on caregivers and family members should be added to this economic burden (3, 5). However, the burden of neurological disorders has been seriously underestimated by traditional epidemiological and health statistical methods that take into account only mortality rates rather than disability rates (6).

Family Caregiving for Older People With Cognitive Disorders

Cognitive and memory disorders are multifactorial and complex healthcare conditions (7). According to the World Health Organisation (WHO) Ministerial Conference on Global Action Against Dementia in 2015, improvement of the quality of care delivered to these patients has been stated as a priority given its significance to the reduction of the global burden of these disorders in both individual and social levels (8). There is a huge gap in the workforce required to provide care to patients living with long-term illnesses and behavioural health issues (9). Therefore, development of community-based care initiatives, families' partnership, and consideration of institutional care as the last care resort have been emphasised for developing sustainable and high-quality care provision to these patients (10).

Family caregivers have the crucial role in the provision of long-term care and support to patients (11). Involvement of family members in designing and developing transitional care programs from hospital to own home and provision of support and education influences their commitment for collaboration (12, 13). Rapid and inappropriate transition of care including brief discharge plans, referral to the general physician or a primary caregiver without the full engagement of families have been shown to lead to insufficiencies in hospital-to-home transitions (14). New approaches to care planning for older people with cognitive disorders should include families and informal caregivers (15). However, the caregivers of patients with cognitive disorders often experience moderate or high levels of care burden that impacts their health, well-being, life satisfaction and resilience (16–18). Therefore, family caregivers need interaction and collaborative relationship with healthcare providers in the process of care transition to their own home leading to more patient-centred care (19, 20).

Medicines Management in Home Care

Patients with cognitive disorders experience non-cognitive and psychotic symptoms, behavioural disturbances, and mood changes, which cause many challenges for both the patient and their caregivers (21). Poorer cognition and behavioural and psychological symptoms, impairments in performing activities of daily living, and burden of caregiving that accompany cognitive disorders increase the risk of admission to nursing homes (22). Therefore, the use of medications for symptoms' treatment among patients with cognitive disorders is associated with the improvement of functional and cognitive outcomes, fewer admission to nursing homes and hospitals, and the overall mortality (23, 24).

It has been shown that more than 40% of older people with cognitive disorders regularly use psychotropic medications such as antidepressants and cognitive enhancers (25). However, the rate of medication adherence among these older people ranges from 10.7 to 38% (26), which increases the risk of rehospitalisation after care transitions from hospital to own home (24). Therefore, family caregivers have the central position to perform home-based medicines management. The burden and distress of care in family caregivers should be reduced to improve the quality and safety of the medication process (11, 27, 28).

Previous reviews so far have concentrated on dementia home care by family caregivers and have not elaborated and

specified the needs of family caregivers in home-based medicines management (29–31). Given the lack of integrated knowledge to inform the needs assessment of medicines management for older people with cognitive disorders who receive care from their family caregivers in their own home, this systematic review of international literature aimed to find the answer to the following question: What are the requirements of safe medicines management for older people with cognitive disorders by family caregivers in home care?

MATERIALS AND METHODS

Design

The systematic review of international literature was carried out as an explicit method for collating and synthesising relevant empirical knowledge and giving a comprehensive answer to the research question (32). Since criteria for conducting meta-analysis or meta-synthesis could not be met on this research topic, an integrative review approach was chosen to include all empirical studies with qualitative and quantitative designs and to develop a comprehensive understanding of the healthcare problem through the creation of a connexion between numeric and narrative findings (33). The PICO statement was used for framing the review question, as follows: P: family caregivers of older people with cognitive disorders; I: medicines management in own home; C: requirement of medicines management identified by stakeholders; and O: safety of the medication process.

Search Process

After the review protocol was developed and agreements on its details were reached by the authors, four online databases that mainly covered health sciences' literature were searched: PubMed (including Medline), Scopus, CINAHL, and Web of Science. It was aimed to retrieve all empirical studies without any limitation in the language and year of publication up to March 2021.

Inclusion criteria were all empirical studies with both qualitative and quantitative designs that involved the family caregivers of older patients with cognitive disorders in medicines management in own home and were published in peer-reviewed journal. On the other hand, reviews, commentaries, discussions, conference proceedings, letters to editor, and empirical studies on medicines management in acute and long-term healthcare settings were excluded.

The authors' previous experiences with conducting research on medicines management and the care process for older people with long-term mental health issues as well as a pilot search in general databases helped with identifying appropriate keywords. Also, a librarian in the affiliated university was approached to ensure the accuracy of keywords and database selections. Therefore, all probably relevant keywords and MeSH terms were identified and were used to build search phrases for conducting the search in titles, abstracts, and articles' contents using the Boolean method and the related operators (AND, OR). Cross-referencing from articles' bibliographies and a manual search in well-known journals that published relevant studies helped with improving the search coverage.

The titles and abstract of retrieved studies were carefully screened by the authors, and full texts were read to identify relevant studies to our review topic. However, decisions on the inclusion or exclusion of studies based on the inclusion criteria were through holding discussions by the authors.

Quality Appraisal and Risk of Bias Assessment

Two authors (MV and SB-G) were made blind to studies' authors, journal name, and institution and independently evaluated the quality of each study using quality appraisal tools. They held discussions to share the evaluation results and to decide the inclusion and exclusion of each study.

The modified Consolidated Standards of Reporting Trials (CONSORT) was used for the appraisal of the methods and results sections of interventional studies. Studies with scores $\geq$70% of the highest score of the CONSORT checklist were judged as high quality, 40–70% as moderate quality, 20–40% as low quality, and $<$20% as very low quality (34).

The modified Newcastle–Ottawa Quality Assessment Scale was applied (35) for the quality appraisal of observational studies in terms of the selection of participants, comparability of the study, and assessment of outcomes. Scores above 6, 3–5, and below 3 were interpreted as high, moderate, and low quality, respectively.

The Critical Review Form—Qualitative Studies (Version 2.0) was used for assessing qualitative studies (36). It assessed studies in terms of purpose, justification of research, theoretical and philosophical perspectives for the design, method, sampling, data collection, data analysis, rigour, and conclusions and implications. Scores 1–6, 7–11, and 12–18 were interpreted as low, moderate, and high quality, respectively.

The ROBINS tool in non-randomised studies of interventions and observational studies was used for assessing the risk of bias (37), which has been recommended by the Cochrane (32). Five domains of (i) assessment of exposure, (ii) development of outcome of interest in case and controls, (iii) selection of cases, (iv) selection of controls, and (v) control of prognostic variable in cross-sectional studies; seven domains of (i) selection of exposed and non-exposed cohort, (ii) assessment of exposure, (iii) presence of the outcome of interest at the start of the study, (iv) control of prognostic variables, (v) assessment of the presence or absence of prognostic factors, (vi) assessment of outcome, and (vii) adequacy of follow-up for cohort studies; and also six domains of (i) bias in random sequence generation, (ii) bias in allocation concealment, (iii) bias in blinding of participants and personnel, (iv) bias in blinding of outcome assessment, (v) bias in incomplete outcome data, and (vi) bias in selective outcome reporting for interventional studies were used for the assessment. Accordingly, the authors' judgment for risk of bias was categorised as "low risk," "high risk," and "unclear risk" for interventional studies and high risk, low risk, and probability yes or no risk of bias for observational studies.

Data Extraction and Knowledge Synthesis

Data from the selected studies were extracted independently by two authors (MV and SB-G) using an extraction table. The data

TABLE 1 | The result of search and article selection process.

Search keywords	Databases	Total in each database	Selection based on title	Selection based on abstract	Selected based on full text	Selection based on quality appraisal and risk of bias assessment
(medication OR drug OR medicines OR "medicines management" OR "medication management") AND (old* OR elder* OR aged* OR senior*) AND (dementi* OR alzheimer* OR "cognitive impairment*") AND (family OR spouse* OR partner* OR "family care*" OR "family nursing" OR caregiver* OR "informal care*" OR "non-professional care*" OR partner*) AND (home* OR domestic OR "home health nursing*" OR "home nursing*")	PubMed (including Medline)	123	16	11	7	7
	Scopus	274	6	3	0	0
	CINAHL	409	5	0	0	0
	Web of Science	432	49	4	4	4
	Backtracking references of selected articles	3	3	3	1	1
	Total	1,241	79	21	12	12

were exported into the categories of author's name, publication year, country, design, sample size and setting, findings, and conclusion of home-based medicines management with the involvement of family caregivers.

The studies identified for this review had many variations in terms of aims, research structures, and methodological considerations. Therefore, a meta-analysis of findings could not be performed; and the review findings are presented narratively, which was informed by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (38).

RESULTS

Search Results and Selection of Studies

The comprehensive search on the online databases and backtracking of references led to retrieving 1,241 studies (**Table 1**). After duplicates and irrelevant studies were deleted based on independent title screening and abstract reading by two authors (MV and SB-G), 21 studies were chosen for full text reading (**Figure 1**). They were carefully read, and their contents were checked against inclusion criteria, of which 12 studies fully met the criteria and were entered into full-text quality appraisals and risk of bias assessment.

Quality Assessment and Risk and Bias Assessment

The full texts of 12 articles were assessed in terms of methodological quality and risk of bias. The quality assessment of the included studies has been presented in **Supplementary Tables 1–4** and **Supplementary Figures 1–3**. Nine studies were classified as high quality (39–47) and three as moderate quality (48–50), and no study had low quality.

The studies mostly were judged as having low risk of bias for the evaluated domains (**Supplementary Figures 1–3**). Accordingly, all cross-sectional studies (40, 41, 48, 50) had a low risk of bias in the assessment of exposure and development of outcome of interest. However, two-thirds of them had probability high risk of bias in selection of case and controls, and half of them had high risk of bias in control of prognostic variable.

There was one cohort study (49) that had low risk of bias for adequacy of follow-up of cohorts, assessment of outcome and exposure, and assessment of the presence or absence of prognostic factors. However, it had high risk or probable high risk of bias in the selection of exposed and non-exposed cohorts, control of prognostic variable, and presence of outcome at start of study.

In interventional studies, all studies (39, 42, 46) had a low risk of bias in the reporting of selective outcomes, incomplete outcome data, and random sequence generation. However, two-thirds of them had a high risk or unclear risk of bias in the blinding of personnel, participants, and outcome assessment. In addition, all of them had an unclear risk in the allocation concealment.

Therefore, all studies ($n = 12$) were included in the data analysis and knowledge synthesis given their acceptable methodological structure and relevance to our review topic.

Characteristics of Selected Studies

The general characteristics of the selected studies have been presented in **Table 2**. They were published between 2006 and 2017, indicating that the search process encompassed a decade research on this topic. They involved 3,890 older people with cognitive disorders and 3,465 family caregivers.

Four studies were conducted in the United States (40–42, 48), three studies in the United Kingdom (43–45), three studies in Germany (46, 49, 50), and two studies in Australia (39, 47).

The studies had variations in methodologies including cross-sectional studies (40, 41, 48, 50), randomised clinical trials (39, 42, 46), cohort (49), and qualitative studies (43–45, 47).

The studies aimed to assess for skills and adherence to home-based medicines management (40, 43–48), interventions to

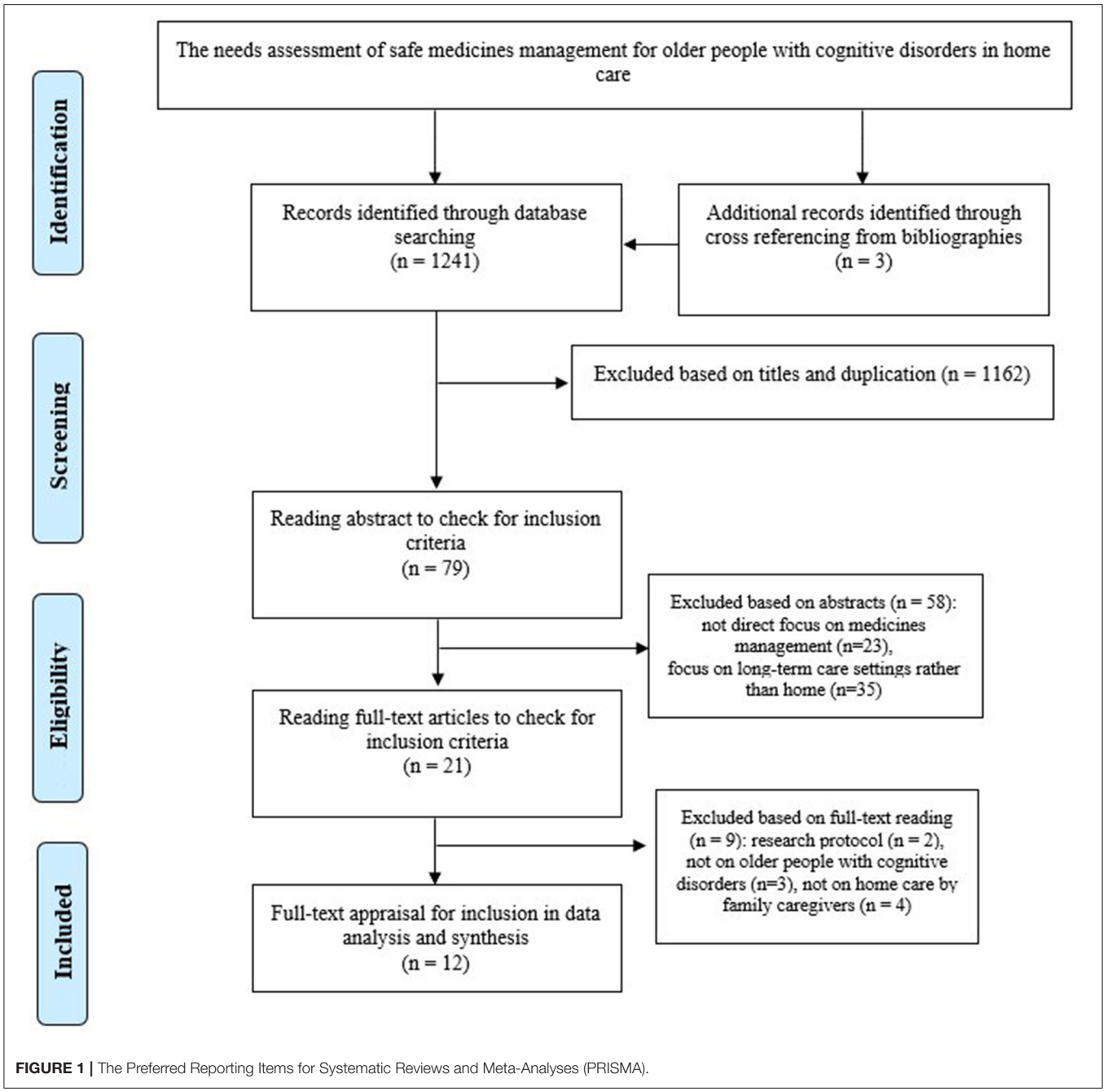

FIGURE 1 | The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

support family caregivers (39, 42), and inappropriate medication use and drug-related problems (41, 49, 50).

Needs Assessment of Safe Medicines Management in Home Care

The older people participating in the studies suffered from dementia and had various levels of cognitive impairment from mild to severe. Also, the mean number of medications taken by them in home care was between a minimum of 4.9 and a maximum of 10, indicating over-medication and polypharmacy, respectively. Overall, their adherence to medications was low; and therefore, all older people needed and received support for medicines management from family caregivers in home care. Family caregivers were taken as responsible and were involved in all interventions related to home-based medicines management including dispensing, preparation, administration, follow-up, and monitoring the effects and side effects of medications (**Table 3**).

Older People's Dependence on Family Caregiving in Their Own Home

Family caregivers were mentioned to be in the best position to accurately assess the ability and performance of older people with cognitive impairment to manage medications and to ensure

that the safe level of adherence to the medication regimen was achieved (45, 48, 49). They tried to improve older people's independence in medicines management as much as possible and enhance their confidence in self-care. Older people tried to learn about medications and remember regimen using the visual recognition of medications, linking medications' taking to life routines, memory aids as board notices, and dose administration aids (47). However, they were unable to perform the medication process safely (45, 48, 49). They showed worse functions in medicines management tasks, including timing, dosing, preparation and naming medications, and medication intake, due to forgetfulness and administration of medications (48, 49). They also relied heavily on their family caregivers to regularly supply their medications given that no such a care option was available by healthcare providers in home care (47). Therefore, family caregivers were on the duty of older people care between 16 and 24 h a day on average for the provision of support (40), which influenced the quality and safety of the medication process. The greater the level of cognitive impairment and awareness deficit, the greater the support for the preparation and administration of medications was needed. Consequently, those older people who received more support in their activities of daily living from their family caregivers had greater adherence to medications than those who received less support (48).

Family Caregivers' Concerns and Strategies for Medicines Management

Medicines management was mentioned as a complex process that required adopting routines. Family caregivers had no structurally defined role and did not receive education and support to perform medicines management tasks. Insufficient problem-solving skills, poor cognitive and memory function, and co-morbidities in family caregivers who had to manage their own medications at the same time enhanced the burden of care and the possibility of medication errors (40, 47). Also, caregivers' age was associated with deficiency in medicines management in terms of knowledge of medications and how to carry out the medication process (40). Additionally, the emotional burden of care encompassed having the obligation to take responsibility of the medication process for someone else and prioritising others' health on their own health (43). In this respect, decision making by family caregivers on the administration of sleep medications to older people to promote rest in family caregivers created an ethical challenge as it counterposed the health needs of family caregivers and those of older people who needed advocacy (44).

Taking medication at different times of the day and supply of medications were main challenges from family members' perspectives (43). Family caregivers were responsible for monitoring supplies from various prescriptions and timely refilling medications. Therefore, changes in prescriptions were added to the burden of care regarding taking correct medications (45).

Medication administration also enhanced their anxiety and care burden given the possibility of error during filling the dosette box. They tried to prevent medication errors by undertaking the task when they felt fresh and had more readiness to perform complex caring tasks (45, 47). Missed doses because of older people's reluctance to take medications were another concern. To overcome this barrier, they tried to inform older people and share information with them to involve them in decision making regarding medications to feel control over their own medications (45). However, adherence was difficult, as not all older people could understand the significance of taking medications, because of the complexity of regimens and not all medications taken regularly had a visible impact on their symptoms (43, 47). Explaining the reason for the administration of medications for relieving visible signs and symptoms reduced older people's resistance to adherence (44, 47). Regular and frequent visits and reminders *via* phone calls by those family caregivers who did not live with older people ensured that medications were taken timely (45).

Family caregivers felt frustration over the ineffectiveness of medications on improving the behaviour and memory of older people (43). They monitored the effectiveness and side effects of medications through observing older people's behaviour such as being tired and accordingly made judgments (45). They also were worried about taking over the tasks of medicines management and communicating routines to other family members or healthcare providers in emergency situations and hospitalisation. They used their mobile phones and created a backup of the list of medications and asked another family member to save it (47).

Medicines Management Issues in Home Care

Rapid changes in cognitive abilities, complexity of medications, side effects of medications, and transition of care to the hospital and then back to own home hindered family caregivers in undertaking home-based medicines management safely (47). Also, insufficient use (21%) of healthcare services such as physiotherapist, occupational therapist, and speech therapy indicated inadequate or limited access to such services, which in turn led to overreliance on medication use for relieving health issues (46). About 55% of caregivers made at least one medication error, and an average of three deficiencies in medication was reported by 92.3% of them. Medication reconciliation identified 56% medication errors in terms of wrong time, forgetting to take the medication, losing pills, refilling prescriptions, mixing medications inappropriately, discontinuing medications without consultation, not taking medication on an empty stomach, and dumping pills into water (40). In another study, administration and compliance issues (60%), all potential drug-related interactions (17%), inappropriate selection (15%), dosage (6%), adverse drug events (2.5%), inappropriate time of application (40%), inappropriate combinations and interactions with moderate severity (35%), lack or outdated medication list (25%), inappropriate medication (23%), forgetting to take medications (18%), inadequate storage of medications (44%), and inappropriate storage as poor traceability, being exposed to moisture or light, and being scattered around the house (41%) were reported (50).

In addition to donepezil and other cognitive-enhancing drugs such as cholinesterase inhibitors and anticholinergic drugs, older

TABLE 2 | General characteristics of selected studies included to data analysis and knowledge synthesis.

Author, year, country	Aim	Methods	Sample and settings	Outcome measurement	Main finding	Conclusion	Quality appraisal
Cotrell et al. (2006), USA	To investigate the cognitive status of patients, skills for medicines management, adherence to medications, and amount of help received from family caregiver	Cross-sectional	27 (male/female) older people (>65 years) with Alzheimer's and 20 (male/female) healthy older people, dyad caregivers as spouse, children, and other relatives in home care	Complexity of the medication regimen, behaviour of adherence using pill counts, predicated adherence, medicines management tasks, prediction of task, awareness discrepancy	Acceptable level of adherence to medications but ineffectiveness of some strategies by family caregivers to ensure sufficient adherence	The need to adopt additional strategies by family caregivers for medicines management	Moderate
Brodaty et al. (2009), Australia	To examine the effect of a 3-month psychosocial counselling intervention focused on symptoms, emergencies, and managing difficult behaviours for the family caregivers of older people with Alzheimer's taking donepezil (5–10 mg daily) on their admission to the nursing home and mortality	Randomised controlled trial: 2 years' treatment and up to 8.5 years' follow-up	155 intervention and control (male/female) older people (>70 years) with Alzheimer's and their (male/female) family caregivers (>70 years) as dyad in home care in Australia, the United Kingdom, and the United States	Time to admission to the nursing home and death, concurrent medications and related adverse events, the older people's physical health	Similar nursing home placement and mortality in the intervention group, but Australians admitted earlier	Variations in healthcare, nursing home systems, and affordability of care influence on admission to the nursing home more than other factors	High
Lau et al. (2010), USA	To investigate the association between medication use and potentially inappropriate medication use among older people with and without dementia	Retrospective cross-sectional	4,518 (male/female) older people (≥65 years) with (n = 2,665) and without dementia (n = 1,853) living with the family as spouse, partner, family, relative, or friend	Potentially inappropriate medication use, as those medications should be avoided among elderly people, number of prescription medications used excluding *pro re nata* (PRN) and over the counter (OTC)	Increased risk of inappropriate medication use and polypharmacy	The need to evaluate the necessity and appropriateness of medications in home care to reduce the risk of admission to the nursing home	High
Erlen et al. (2013), USA	To describe the characteristics of family caregiving for medicines management in home care for older people with impaired cognition	Cross-sectional	91 dyads (male/female) of older people (80 years)—family caregivers (67 years) who were spouse/non-spouse	Sociodemographic and health-related characteristics, health literacy, working memory, source of stress, older patients' aggressive/disruptive behaviours and caregiver's reactions, self-confidence, depressive symptoms, perception about problem solving, social support resources, medicines management	Caregivers' demographic characteristics, cognitive abilities, psychological condition, and perception influence caregiving in home	Significance of the family caregiver's demographic and health-related characteristics in medicines management in home care	High
Fiss et al. (2013), Germany	To investigate the frequency of potentially inappropriate medications taken by older people with dementia cared by family caregivers in comparison with healthy older people	Cohort	342 older people (≥80 years) consisting of 111 (female/male) with dementia and 231 (female/male) healthy ones	Sociodemographic and health-related variables, cognitive impairment, home medicines review, identification of potentially inappropriate medications for older people, and potentially inappropriate for those with dementia	20% older people with dementia had potentially inappropriate medications; number of medications (1–4) was a risk factor for it	Receiving <5 medications and support in home care protected against potentially inappropriate medications. Systematic medication review in home care should be established	Moderate
While et al. (2013), Australia	To explore the perspectives of older people with dementia and their family carers regarding medicines management and compare them with those of healthy older people	Grounded theory	8 older people with dementia and 9 family caregivers (spouse and child)	Self-medicines management of prescribed and non-prescribed medications in home care and the family member support	Life routines and established caring strategies can enable older people with dementia to perform self-medicines management. Family members can support independence in medicines management	Family caregivers are responsible for medication safety in home care, but their stress and the burden of care should also be considered	High

(Continued)

TABLE 2 | Continued

Author, year, country	Aim	Methods	Sample and settings	Outcome measurement	Main finding	Conclusion	Quality appraisal
Poland et al. (2014), UK	To identify the perspectives of family caregivers of older people with dementia about medication management in home care	Thematic analysis	9 family caregivers (spouse and child)	Priorities, benefits, and side effects of medications, adherence, prescription and administration, medication review, communication with healthcare staff	Use and administration of medications, communication issues, responsibility and accountability, medications' risks, and benefits	Lack of appropriate support for medicines management and need to empower them to directly become involved in care	High
Smith et al. (2015), UK	To explore the experiences of family caregivers about how to make medicines management more responsive to the needs of older people with dementia	Framework analysis	9 (male/female, 45–86 years) family caregivers (spouse and child) and 5 older people with dementia (male/female, 81–93 years)	Activities related to medicines management and problems experienced by caregivers	Complexity of care and decision making for medicines management, medication supplies, adherence to the regimen, and access to healthcare providers, obtaining information and advice, older people's autonomy	Need for strategies to reduce burden of care through training and support	High
Thyrian et al. (2016), Germany	To analyse the various aspects of dementia care including medicines management for older people in own home after receiving multi-professional and multimodal individualised care to improve dementia care at home	Cluster randomised controlled trial	516 older people (≥70 years) and their family caregivers as dyads: intervention ($n = 348$), control (168)	Medication review on antidementia drugs (donepezil, rivastigmine, galantamine, memantine, and their combinations) and antidepressants, as well as OTC: compliance, adverse effects, administration of medications, potentially inappropriate medications as the risks of adverse events outweigh benefits	About 26% received antidementia medications and 14% received antidepressants	Complexity and multivariate identity of home care and	High
Lingler et al. (2016), USA	To examine the effect of a problem-solving intervention for improving medicines management among the caregivers of older people with dementia	Randomised controlled trial	76 older people and their family caregivers (spouse and child) as dyads: intervention ($n = 37$) and control ($n = 39$)	Medicines management practise and deficiencies	Reduction of medication problems 2 months after the intervention	Effectiveness of raising awareness of significance of medication safety	High
Maidment et al. (2017), UK	To explore the key challenges of medicines management from the perspectives of older people with dementia and their family caregivers in home care	Framework analysis	11 family caregivers (male/female), 4 older people with dementia (male), 16 healthcare providers (male/female)	Practical issues and challenges of medicines management	Responsibility for medicines management, emotional burden of care, obtaining support	Need for coordinated and continuous support for family caregivers, medication review, improving the role of community pharmacists in home care initiatives	High
Wucherer et al. (2017), Germany	To identify the prevalence and type of drug-related problems and associated factors among older people with dementia in home care after the implementation of collaborative dementia care management	Cross-sectional	446 (>79 years) older people with dementia (male/female), family caregivers (n = not specified)	Medication assessment: medication history (prescription and OTC), compliance, adverse events, administration of medication	1,077 drug-related problems were found; 93% had at least one problem with administration and compliance, drug interactions, medication selection	Association between the number of medications and medication problems	Moderate

TABLE 3 | Medicines management and the need of older people with cognitive disorders to receive support in their own home.

References	Level of cognitive impairment	Mean number of medications taken by older people	Adherence to medications	Older people's need to receive help for medicines management from family caregiver	Areas of need to support for home-based medicines management by family caregivers
Cotrell et al. (48)	Mild–moderate	Not specified	17–100%	Yes	Checking and setting up pill box, timing, dosing, naming and preparation of medications, administration of medications
Brodaty et al. (39)	Moderate–moderately severe	Not specified	Not specified	Yes	Dosage, preparation and administration of medications, assessing effectiveness of medications, concurrent medications use, alcohol–medication interaction, adverse events
Lau et al. (41)	Very mild–severe	4.9	Not specified	Yes	Not specified
Erlen et al. (40)	Moderate	10	Acceptable level	Yes	Supply, storage, timing, being reminded to take medications, mixing, administration of medications
Fiss et al. (49)	Mild and suspicious	6.8	No	Yes	Preparation and administration of medication
While et al. (47)	Not specified	Not specified	Yes	Yes	Filling dosette box, dosage, supply, administration of medications, monitoring side effects, tracking medications and renewal
Poland et al. (44)	Not specified	Not specified	Not specified	Yes	Preparation, mixing, medication administration based on the older people's need, communicating medication-related issues to healthcare providers, deciding on the discontinuation of medications, monitoring effects and side effects
Smith et al. (45)	Various	7	Low level	Yes	Supply, refill, filling dosage box, timing, monitoring effects and side effects, communicating with healthcare providers
Thyrian et al. (46)	Mild	Not specified	Not specified	Yes	Preparation and administration of medication
Lingler et al. (42)	Mild	10	Low	Yes	Pharmacy pickup, storage, pillbox, medication administration (OTC) over the counter medications, receiving support from local pharmacist, backup list for someone else to administer medications, discarding discontinued medications, changing medications
Maidment et al. (43)	Not specified	Not specified	Low	Yes	Supply, timing, administration of medication, deciding on the discontinuation of medications
Wucherer et al. (50)	Mild–severe	>5	Low	Yes	Storage, timing, medication list preparation, administration

people took many medications for cardiovascular, nervous, digestive, and respiratory disorders; osteoporosis; joint pain; and mental and psychiatric health issues (45, 46, 49, 50). Taking more medications was associated with more medication deficiencies and errors in home care (40). Therefore, over-medication as taking many medications at the same time and polypharmacy as taking more than five medications increased the risk of potentially inappropriate medications use and were considered safety concerns. They potentially worsened behavioural and psychological symptoms and made the family caregivers worried about medications' effectiveness and side effects (41, 47, 49, 50). Increasing the total number of medications increased the risk of potentially inappropriate medication use, as follows: five to six medications, 6.44 times; and seven to eight medications, 12.6 times (41).

The presence of co-morbidities including hypertension, incontinence, depression, and anxiety in these older people increased potentially inappropriate medication use, as 15% of older people had at least one potentially inappropriate medication use with the following medications: oral oestrogens (14%), muscle relaxants and antispasmodics (14%), fluoxetine (13%), short-acting nifedipine (11%), and doxazosin (7%) (41). In another study by Thyrian et al. (46), about 19.3% had one, 2.3% two, and 0.2% three potentially inappropriate medications. In the study by Fiss et al. (49), 27% received potentially inappropriate medications, and 20% received medications that

were contraindicated in these patients including antidepressants (mostly amitriptyline), hypnotics (zolpidem), and anxiolytics (diazepam). In the study of Wucherer et al. (50), 92.8% had at least one drug-related problem, 64% had one to three drug-related problems, and 27% had four to seven drug-related problems. Also, 8% of older people received medications with a high dosage, and 6% reported adverse drug events related to a prescribed medication. The most frequently prescribed potentially inappropriate medications were antidepressants, benzodiazepines, and analgesics. On the other hand, the appropriate use of Fybogel as a laxative for relieving constipation as a minor health issue reduced physical and emotional distress among older people (44).

Both polypharmacy and potentially inappropriate medication use enhanced the risk of falls (72%) and adverse drug effects considering that these older people were sensitive to cognitive impairments induced by medications including confusion, nightmare, agitation, and depression, which enhanced the risk of admission to the nursing home (41, 49, 50). Given the cost of admission to nursing homes and the reported survival rate in there in the United Kingdom and Australia, the safety of home care in the hands of family caregivers depended on care supervision by healthcare professionals to monitor the effects and side effects of medications and help with resolving medication-related issues that were beyond the abilities of family caregivers (39).

Support for Medicines Management in Home Care

Listening to family caregivers' concerns and provision of verbal and written information at their understanding were important, but more assistance with problem solving for managing medications in home care was required (40, 43). Physicians, pharmacists, nurses, older people, and family caregivers should coordinate medication-related care, as it created the feelings of safety, confidence, and assurance in home care (46, 47). Coordinated actions from various healthcare providers such as compliance packs prepared by pharmacists and support by nurses with *pro re nata* (PRN) medications specifically were needed (43). Family caregivers needed a structured list to keep track of medications when renewal was needed, and authorisation of prescription could be granted *via* phone calls. Inconsistencies in collaboration by healthcare providers led to frustration and stress (44, 45, 47). Also, absence of the medication list contributed to the high number of administration and compliance problems (50). For example, home visits by the nurse or social worker along with telephone calls to support the family caregivers' role in medicines management in terms of preparation, administration, and follow-up reduced the number of problems and deficiencies in medicines management in terms of dropping or losing pills, forgetting to take medications, dosage issues, and wrong times of medication administration (42).

Medication review by healthcare professionals was required to reduce the complexity of the medication regimen, leading to changes in medications and replacing them with those that could be administered with fewer doses and administering times, which consequently could improve adherence (43). A home-based medication review on prescribed and over-the-counter (OTC) medications not only improved medication compliance but also enhanced appropriate storage of medications (50). It should go beyond asking the patient about taking and not taking medications and should encompass dosage, effects, and side effects of medications (40, 43, 50). It could help with rectifying the misperception in family caregivers who deprescribe and stop medication could endanger the quality of life of loved ones (43, 44). The result also should be shared with other healthcare providers to enable care coordination and reduce the burden of sharing complex information by families and older people (43).

Considering the effect of progression of cognitive impairment on learning and developing skills for the medication process, family caregivers should be involved in the hospital discharge plan and be informed of changes in the medication regimen. Family caregivers could influence older people's beliefs and preferences to take medications and adhere to the medication process and were able to monitor and report medications' side effects (45, 47).

A supportive carer–healthcare professional relationship was needed to improve their knowledge about medications and enhance their power and feeling of control. Family caregivers felt despair in communicating medication-related issues and getting support from healthcare providers, as they felt that healthcare providers put all responsibility of care on their shoulder and did not advise about the practical aspects of medicines management (44, 47). Given that older people with cognitive impairment were unable to communicate their needs, family caregivers wanted to learn about identifying older people's needs to medications through observations and interpretation of behavioural clues (44).

Knowledge of medications was important; and family caregivers preferred to discuss with healthcare providers about rationale for prescription and the balance between the benefits, side effects, and harms of medications. They needed to be empowered to be able to monitor and report the effect of the medication regimen, side effects, and adverse drug reactions (44, 47). The role of family caregivers in the control of medication use and making decisions on their continuance of use was unclear, as no healthcare provider was accessible to monitor medications for pain relief, hypertension, osteoporosis, diabetes, and eye problems as well as PRN medications (44). Family caregivers proactively sought information about medications through reading packages, searching the internet, and making phone calls to healthcare providers regarding the type of medication, dosage, and related side effects (45). However, medication packaging was not helpful given difficulties in understanding and the multiple use of medications. Information should be simplified based on culture and language abilities and be interpreted to become appropriate to information-seeking needs particularly for the most common side effects and how to make decisions on them in the absence of access to expert knowledge (43–45).

A summary of the review findings regarding the needs assessment of safe medicines management for older people with

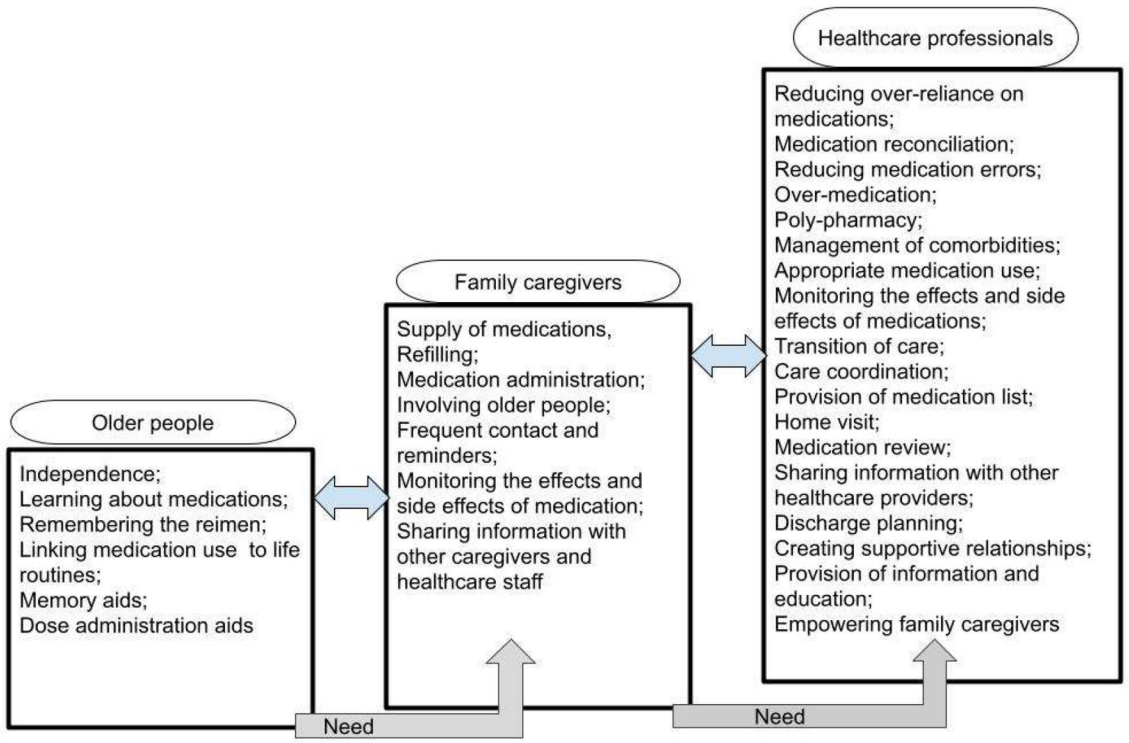

FIGURE 2 | The needs assessment of safe medicines management for older people with cognitive disorders who are cared by their family caregivers in own home.

cognitive disorders who are cared by their family caregivers in their own home is presented in **Figure 2**.

DISCUSSION

This systematic review with an integrative approach helped with removing the gap of knowledge and enhanced our understanding of needs assessment of home-based medicines management for older people with cognitive disorders who were cared by their family caregivers. The review findings indicated the areas of needs of older people with cognitive disorders and their family caregivers in home care and what the role of healthcare professionals could be to help with safeguarding medicines management.

Older people with cognitive disorders preferred to remain independent as much as possible and to gain more control over their own medications. Family caregivers complied with older people's preferences, but progression of the disease and memory issues were barriers to retain independence. Therefore, the burden of medicines management was put on the shoulder of family caregivers who themselves needed support to manage medications for their own underlying health conditions and to reduce care stress. Collaborative strategies for medication management depend on the disease stage, and physical and mental capacity of older people as well as collaboration inputs by family caregivers (51). According to the statement by the United Nations (UN) and the WHO, facilitation of access to rehabilitation and palliative care is considered an ethical responsibility of healthcare systems. Also, healthcare professionals have the duty to alleviate pain and suffering among older people with physical, psychosocial, or spiritual sources irrespective of the curability of the disease (52). Any intervention aiming at the reduction of frailty among older people enhances benefits for individuals, families, and the society as they experience less cognitive or functional decline and have lower mortality rates (53). Family caregivers take different roles during the care process as caregivers, welfare enhancers, facilitators, apprentices, and minimisers/managers of suffering. They carry out many tasks and are responsible for the continuity of care and making decisions at the end of life (54). In the caregiving relationship, burden, resilience, needs, and rewards are interrelated (55). Female and male caregivers take on different tasks, which come with gender-specific care burden and health-related concerns. Sex- and gender-based analyses regarding caregiver's burden are limited. In terms of preparedness, being female and cohabiting with the patient have been associated with a higher level of preparedness to take over the caregiver's role (56). All caregivers achieve lower scores on physical and mental health measures than the general population (57). Studies assessing caregiver's burden have found higher burden or care-related distress among female caregivers as well as significantly higher levels of depression in female caregivers compared with their male counterparts. In terms of mental health, women report two times higher depression, but there have been suggestions within the international literature that men's experiences of depression may manifest with symptoms that are not currently

included in traditional depression scales. In terms of physical health, female caregivers experience better sleep quality and significantly less co-morbidity, but male caregivers demonstrate biomarkers for increased thrombosis and inflammation risk (58). Prolonged grief disorder is predicted by the poor physical and mental health status before bereavement (57). Caregiver's health impacts the patient's quality of life and dying. Caregiver's capacity and preparedness for the provision of care can ensure quality of life, care, and death for older patients with memory disorders. Caregiver's fair-to-poor health status can predict non-elective hospital visits as well as hospital death (59).

Despite the family caregivers' crucial role, safety of the medication process could not be fully preserved, and medication errors and non-adherence to the medication regimen were reported in home care. The full compliance with the safety initiatives of home-based medicines management needed the support of healthcare professionals. Healthcare professionals should reduce over-reliance on medications; prevent medication errors; manage over-medication, polypharmacy, and inappropriate medication use; and monitor the effects and side effects of medications. Safety of medicines management in home care required that healthcare professionals coordinate discharge planning and care transition, attend home visits, and share information between other healthcare providers involved in home care. Moreover, a supportive and professional family caregiver–healthcare relationship with an emphasis on considering family caregivers' concerns, their education, and empowerment to safely perform the medication process was needed. The accepted perspective is that older people with cognitive impairment living in the community need coordinated and flexible care process (60–62). An early integration of holistic palliative care approaches that encompass medicines management initiatives into home care should be included from the beginning of the illness (63, 64). *The Lancet*'s call for action specifies "as the world population ages, comorbidity also increases, a shift from a health system centred in medical specialties to person-centred care is required." This call also includes the provision of education and support to family caregivers, whose role in providing the best care for people with memory disorders should not be overlooked (65).

The heterogeneity of the studies included in this systematic review in terms of methods and aims hindered conducting a meta-analysis. Also, a few studies were retrieved during the search process, indicating the insufficient number of empirical studies. Nevertheless, this review provides an overview of international knowledge about home-based medicines management for older people with cognitive disorders by their family caregivers and aspects that should be investigated in future studies. Clinical trials are needed to improve our understanding of the effect of home-based medicines management interventions with the participation of family members on the quality and safety of care. Equally significant are the realist evaluations of any medicines management initiatives or educational activities, which provide a framework for understanding how the context and underlying mechanisms affect the pattern and outcome of the selected intervention.

CONCLUSION

This integrative systematic review demonstrated that medicines management in home care was systematically overlooked adding to caregiver's burden and endangering the safety of older people. Family caregivers' abilities in the provision of care to older people with cognitive impairment could not cover all aspects of home-based medicines management. Therefore, the burden of medicines management in home care can be reduced through sharing the responsibility of safeguarding medicines management between family caregivers and healthcare professionals to be able to safely respond to older people's care needs.

Healthcare professions involved in home care are expected to proactively assess and meet older people's needs for safe medicines management in home care and relieve the great amount of stress and burden experienced by family caregivers. Consideration of family caregivers' concerns, continuous communication with them and provision of information about medications, discussion about medicines management strategies, empowerment of older people with memory disorders and their caregivers through education, and multidisciplinary collaboration have been emphasised.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

MV and PP: conceptualisation. MV, SB-G, and PP: data curation, formal analysis, investigation, and methodology. MV and SB-G: project administration, resources, and software. MV, SB-G, SL, CW, and PP: writing—original draught, writing—review, and editing. All authors have read and agreed to the published version of the manuscript.

FUNDING

This work has been partially funded by the European Union's Horizon 2020 research and innovation programme under Grant Agreement No. 825785. The funder played no role in the design of the study or collection, analysis, interpretation of data, or the writing of the manuscript.

ACKNOWLEDGMENTS

Nord University, Bodø, Norway, covered the processing charge to this article.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.694572/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 17 September 2021
doi: 10.3389/fneur.2021.710783

Goal-Concordant Care After Severe Acute Brain Injury

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Background: Patients with severe acute brain injury (SABI) lack decision-making capacity, calling on families and clinicians to make goal-concordant decisions, aligning treatment with patient's presumed goals-of-care. Using the family perspective, this study aimed to (1) compare patient's goals-of-care with the care they were receiving in the acute setting, (2) identify patient and family characteristics associated with goal-concordant care, and (3) assess goals-of-care 6 months after SABI.

Methods: Our cohort included patients with SABI in our Neuro-ICU and a Glasgow Coma Scale Score <12 after day 2. Socio-demographic and clinical characteristics were collected through surveys and chart review. At enrollment and again at 6 months, each family was asked if the patient would prefer medical care focused on extending life vs. care focused on comfort and quality of life, and what care the patient is currently receiving. We used multivariate regression to examine the characteristics associated with (a) prioritized goals (comfort/extending life/unsure) and (b) goal concordance.

Results: Among 214 patients, families reported patients' goals-of-care to be extending life in 118 cases (55%), comfort in 71 (33%), and unsure for 25 (12%), while care received focused on extending life in 165 cases (77%), on comfort in 23 (11%) and families were unsure in 16 (7%). In a nominal regression model, prioritizing comfort over extending life was significantly associated with being non-Hispanic White and having worse clinical severity. Most patients who prioritized extending life were receiving family-reported goal-concordant care (88%, 104/118), while most of those who prioritized comfort were receiving goal-discordant care (73%, 52/71). The only independent association for goal concordance was having a presumed goal of extending life at enrollment (OR 23.62, 95% CI 10.19–54.77). Among survivors at 6 months, 1 in 4 family members were unsure about the patient's goals-of-care.

Conclusion: A substantial proportion of patients are receiving unwanted aggressive care in the acute setting after SABI. In the first days, such aggressive care might be justified by prognostic uncertainty. The high rate of families unsure of patient's goals-of-care at 6 months suggests an important need for periodic re-evaluation of prognosis and goals-of-care in the post-acute setting.

Keywords: neuropalliative care, severe acute brain injury, goal-concordant care, shared decision-making, palliative care

OPEN ACCESS

Edited by:
Raymond Voltz, University Hospital Cologne, Germany

Reviewed by:
Karin Diserens, Centre Hospitalier Universitaire Vaudois (CHUV), Switzerland
Raffaele Ornello, University of L'Aquila, Italy

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Specialty section:
This article was submitted to Neurocritical and Neurohospitalist Care, a section of the journal Frontiers in Neurology

Received: *17 May 2021*
Accepted: *13 August 2021*
Published: *17 September 2021*

Citation:
Rutz Voumard R, Dugger KM, Kiker WA, Barber J, Borasio GD, Curtis JR, Jox RJ and Creutzfeldt CJ (2021) Goal-Concordant Care After Severe Acute Brain Injury. Front. Neurol. 12:710783. doi: 10.3389/fneur.2021.710783

BACKGROUND

To provide goal-concordant care means to provide medical care that honors a patient's individual goals and values, and to align medical treatments with those goals-of care (1, 2). Recent studies suggest that prior documentation of preferences to limit life-sustaining treatment may reduce the likelihood of being admitted to an ICU in the last 6 months of life (3). Studies of the past decade have also shown that such values and goals can be difficult to assess prior to an illness and to translate into relevant goals-of-care (4, 5).

When patients are admitted to the hospital with severe acute brain injury (SABI), which includes stroke, traumatic brain injury and hypoxic-ischemic encephalopathy after cardiac arrest, they typically lack decisional capacity and rarely have had their goals-of-care previously documented. Consequently, their family members or other surrogate decision-makers are tasked to work with clinicians to make treatment decisions based on the patients' presumed goals (6). Treatment decisions in the acute setting of SABI often concern high-stakes decisions around whether to focus medical care on survival, including the use of life-sustaining treatment (LST) such as mechanical ventilation, artificial nutrition or hydration, or to focus on comfort, which may mean limiting LST and allowing the patient to die a more natural death (7, 8). Given the substantial uncertainty regarding both the patients' prognosis and their presumed goals-of-care, LST is often administered as a time-limited trial in order to gain a better understanding of the patient's trajectory, prognosis, and likely goals over a defined period of time (9, 10). Consequently, at the end of a period of a time-limited trial, the continued use of LST has to be re-evaluated (11). Prognostic uncertainty typically persists for months after SABI and can challenge ongoing decisions in the acute care and post-acute care setting (12).

Using a cohort of patients with SABI, the objective of this study was therefore to assess (1) patients' presumed goals-of-care as assessed by family members in the acute setting; (2) the frequency of family-assessed goal-concordant care and the patient and family characteristics associated with family-assessed goal-concordant care; and (3) whether and how these goals have changed 6 months later.

METHODS

Study Design and Participants

The SuPPOrTT* study is a prospective, observational, single-center cohort study that aims to better understand the needs of patients and family members after SABI. Patient participants were aged 18 years and older and hospitalized in the Neuro-ICU for SABI. We defined SABI as stroke (ischemic stroke, intraparenchymal hemorrhage, subarachnoid hemorrhage), hypoxic-ischemic encephalopathy after cardiac arrest (HIE), or traumatic brain injury (TBI). Our definition also included a Glasgow Coma Scale of 12 or less at enrollment after day 2. Eligible family participants were aged 18 years and older and spoke English adequately to complete surveys. For patients to be eligible, family members must have been available in person or by phone. Family member participants were primarily the surrogate-decision maker or, with the surrogate-decision maker's permission, the next close family member or friend, including spouse/partner, adult child, parent, sibling, or other close relative. After agreement of the clinical team in charge of the patient, family members were approached in person at the bedside or by phone and invited to participate in the study. The protocol was approved by the ethical review board of the University of Washington (STUDY 00003393).

Abbreviations: The acronym SuPPOrTT stands for the 4 questions we asked clinicians and family members: - Do the patient or family require social, spiritual or emotional **Su**pport? - Does the patient have **P**ain or other distressing symptoms? - Does the family have concerns about **P**rognosis or treatment **O**ptions? - Do we need (**re**-)address goals-of-care or **T**arget **T**reatment to patient-centered goals?

Outcomes

We were interested in three outcomes that were assessed through family surveys: (a) family assessment of patients' prioritized healthcare goals at enrollment; (b) the family-perceived priorities of the actual care that the patient was receiving at the time of enrollment; and (c) family assessment of patients' prioritized healthcare goals 6 months after SABI. We asked one family member per patient to state the patient's goals-of-care by using the following question that was adapted from the landmark Support study (13) (question a): "If your loved one were able and had to make a choice today, would he/she prefer a plan of medical care that focuses on extending life as much as possible, or would he/she want a plan of medical care that focuses on comfort, and would limit life-saving treatments?" Three response options were offered: (1) efforts to extend life as much as possible, (2) limit life-saving treatment and focus on comfort, or (3) unsure what they would choose. We then asked the family about the type of care they felt their family member was currently receiving, using the same three response options (question b). When care received was consistent with family-assessed goals-of-care (a = b), we considered the care to be goal concordant. Six months after enrollment, the first question was repeated verbatim in the follow-up survey that we sent to families of survivors by mail or email.

Patient and Family Characteristics

To evaluate factors associated with each family-assessed prioritized healthcare goal as well as predictors of goal concordance at enrollment, we retrieved patient clinical and socio-demographic data retrospectively through the electronic health records (EHR), and families filled out a sociodemographic questionnaire regarding personal data. Patient characteristics included age; gender; race/ethnicity; disease category; clinical severity described with the APACHE score, and neurological severity described with Glasgow Coma Scale score (GCS). Family self-reported characteristics included age; gender; race/ethnicity; relationship to patient; level of education.

Analysis

Data were collected using Research electronic data capture (REDCap) (14). Differences between demographic and other patient and family characteristics by prioritized healthcare goals were assessed for statistical significance using Kruskal-Wallis

TABLE 1 | Patient and Family characteristics.

	Participants $n = 214$
Patient age, mean (SD)	58.0 (18.9)
Patient gender, female, *n* (%)	96 (45%)
Patient race/ethnicity, non-white or hispanic, *n* (%)	67 (31%)
GCS at enrollment, mean (SD)	7.3 (2.6)
APACHE*at enrollment, mean (SD)	15.9 (4.4)
Disease category, *n* (%): - stroke	129 (60%)
- Traumatic brain injury (TBI)	65 (30%)
- Hypoxic-ischemic encephalopathy (HIE)	20 (9%)
Family age, mean (SD)	50.9 (16.1)
Family gender, female, *n* (%)	138 (64%)
Family race/ethnicity, non-white or hispanic, *n* (%)	62 (34%)
Family education < 4yr college degree**, *n* (%)	116 (58%)
Family relationship—spouse/partner	66 (31%)
- Mother/father	31 (14%)
- Son/daughter	75 (35%)
- Sister/brother; other	42 (19%)

Sample excludes subjects without a response to goals of care (n = 7).
**APACHE (acute physiology and chronic health evaluation score): unknown for 34 patients (total), 21 all efforts, 6 comfort, 7 unsure.*
***Family education: unknown for 15 patients (total), 7 all efforts, 5 comfort, 3 unsure.*

tests for continuous and ordinal variables and Fisher's exact tests for nominal variables. We used multivariate regression to examine how patient and family characteristics were associated with (1) each prioritized end-of-life goal (extending life, comfort, unsure; using nominal regression) and (2) goal concordance (using logistic regression). Multivariate models were constructed by starting with age and race as covariates regardless of significance, then putting in additional covariates one at a time using a forward selection algorithm until no remaining covariates could provide sufficient improvement, setting a threshold of $p<.05$ to enter. All statistical testing was two-sided, with no *post-hoc* adjustments for multiple comparisons given the exploratory nature of this study.

Alluvial diagrams were used to visualize the relationship between prioritized goals vs. care received, and between prioritized goals at enrollment vs. at 6 months, and constructed using RAWgraphs (15).

RESULTS

Of the 222 patients enrolled in our SuPPOrTT study, families answered the goal concordance questions for 214 in the acute setting at a mean of 5.1 (SD 2.9) days after admission (**Table 1**). The majority of these 214 patients were non-Hispanic White ($n =$ 147, 69%) and male ($n = 118$, 55%), with a mean age of 58 years (SD 18.9). Most patients had suffered a stroke ($n = 129$, 60%), with 30% suffering TBI ($n = 65$), and 9% HIE ($n = 20$). Family members included spouses ($n = 66$, 31%), adult children ($n = 75$, 35%), parents ($n = 31$, 14%) or siblings and others ($n = 42$, 19%), and a majority of them were white ($n = 142$, 66%) and female (n = 138, 64%) with a mean age of 50.9 years (SD 16.1).

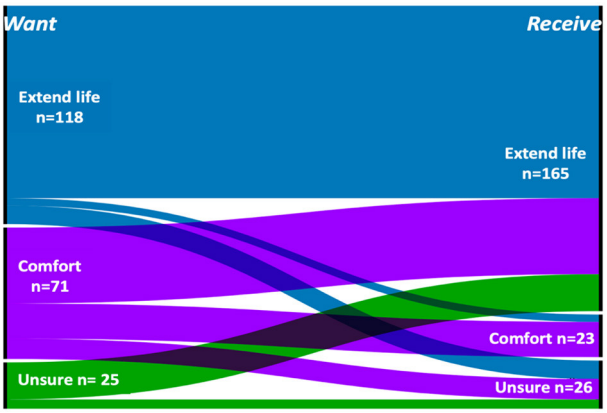

FIGURE 1 | Alluvial diagram illustrating Goal concordance at enrollment. Families were asked what goals of care the patient would prioritize ("Want," left boarder) and what type of care the patient was receiving at that time ("Receive," right boarder); $n = 214$.

Prioritized Goals-of-Care and Goal Concordance

For these 214 patients with SABI, family members' assessment of patients' goals-of-care was extending life in 118 cases (55%); comfort in 71 (33%); and family members were unsure for 25 patients (12%). Goal concordance, meaning that the care the family assessed the patient was receiving was consistent with the care their family member assessed them as wanting, occurred in 104/118 (88%) of the patients presumed to want "extending life" and in 19/71 (27%) of those presumed to want "comfort." Most of the families who were "unsure" of the patient's goals-of-care thought the patient was receiving "extending life" (20/25, 80%) while all others (5/25, 20%) were unsure of the focus of care the patient was receiving (**Figure 1**).

Overall, patients who were presumed to prioritize extending life compared to those presumed to prioritize comfort were younger (mean age 55.7 vs. 62.3 years), less likely to be non-Hispanic White (62 vs. 83%) and had lower clinical disease severity (mean APACHE score 14.9 vs. 17.6). Patients for whom family members reported they were unsure about patient priorities had a mean age of 56.3, 60% were non-Hispanic White, and mean APACHE was 15.4. After adjusting for potential confounders, race and clinical disease severity remained significantly associated with prioritized end-of-life values. Non-white patients had a 68% lower odds of prioritizing comfort vs. extending life (odds ratio, OR, 0.32, 95% confidence interval, CI, 0.14–0.73), and for every one-point increase in the APACHE score (=higher clinical severity), the odds of prioritizing comfort vs. endorsing extending life increased by 17% (OR 1.17, 95% CI 1.08–1.28; **Table 2**).

After adjusting for significant covariates via forward selection, the only significant association with goal concordance was having a family-assessed goal of extending life at enrollment (OR 23.62, 95% CI 10.19–54.77). We also found a trend suggesting a possible association with goal concordance in patients who were older after accounting for race and goals-of-care (see **Table 3**).

TABLE 2 | Determinants of presumed prioritized healthcare goals at enrollment ($n = 214$).

Covariate	Multivariate analysis; $n = 214$				
	P overall	Comfort (vs. extending life)		Unsure (vs. extending life)	
		OR	95% CI	OR	95% CI
Age (per 10yr increase)	0.331	1.13	0.94–1.37	0.95	0.73–1.24
Non-white (vs. white)	**0.014**	**0.32**	**0.14–0.73**	0.45	0.13–1.51
Female (vs male)	0.407				
GCS (per 1pt increase)	0.826				
APACHE (per 1pt increase)	**0.001**	**1.17**	**1.08–1.28**	1.05	0.93–1.19

Statistical significance by nominal regression. Multivariate model started with age/race, then added subsequent factors by forward selection ($p < 0.05$).
P-values in gray indicate significance if the effect were added to the final multivariate model.
Bold indicates statistically significant ($p < 0.05$).

TABLE 3 | Determinants of goal concordance at enrollment ($n = 214$).

Covariate	Multivariate analysis; $n = 214$		
	P	Concordance (vs. Discordance)	
		OR	95% CI
Age (per 10yr increase)	0.066	1.23	0.99–1.54
Non-white (vs. white)	0.394	1.49	0.60–3.72
Female (vs. male)	0.838		
GCS (per 1pt increase)	0.084	0.88	
APACHE (per 1pt increase)	0.492		
Disease category	0.075		
TBI (vs. stroke)	0.056	0.39	
CA (vs. stroke)	0.087	0.28	
Goal all efforts (vs. comfort)	**0.003**	**23.62**	**10.19–54.77**

Statistical significance by binary logistic regression.
Multivariate model started with age/race, then added subsequent factors by forward selection if $p < 0.05$.
P-values in gray indicate significance if the effect were added to the final multivariate model.
Bold indicates statistically significant ($p < 0.05$).

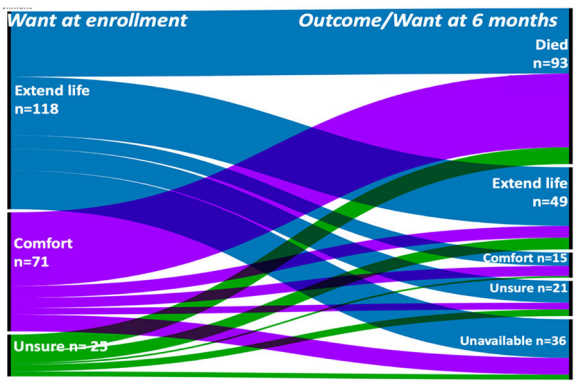

FIGURE 2 | Alluvial diagram illustrating Change in prioritized goals over time. Families were asked what goals of care the patient would prioritize at enrollment ("Want at enrollment," left boarder) and 6 months later ("Outcome/Want at 6 months," right boarder). At 6 months, we had 85 survivors, 93 decedents and 36 non-respondents.

Six-Month Outcomes

Of the 214 patients, 76 (36%) died in hospital and 17 more died over the ensuing 6 months. Six-month outcome was unavailable for 36 (26%), leaving 85 long-term survivors for whom family-assessed goals-of-care were available at a mean of 148 days (standard deviation, SD 43) after enrollment. These survivors had a mean age of 52 years (SD 18), a slight majority were non-Hispanic white (61%), male (55%) and had suffered a stroke (58%), TBI (36%) or HIE (6%). At this follow-up, family-assessed goals-of-care prioritized extending life for 58% of survivors (49/85), comfort for 18% (15/85), and family members were unsure of the patients' priorities for 25% (21/85). **Figure 2** shows the distribution of goals at enrollment and at 6 months. Taking into account small numbers, multivariate regression suggested a significant association of age, ethnicity and disease category with prioritized healthcare goals at 6 months (**Table 4**). Compared to prioritizing life extension, the odds of prioritizing comfort was 1.6 times higher with every 10-year increase in age, and 4.8 times higher in patients with TBI compared to stroke. The odds of being unsure about goals (vs. prioritizing extending life) was three times higher for non-white patients compared to white patients.

DISCUSSION

In our cohort of 214 patients in the first week after severe acute brain injury (SABI), just over half of families felt that

TABLE 4 | Determinants of presumed prioritized healthcare goals in the post-acute setting (148 days after enrollment).

Covariate	Multivariate analysis; n = 85				
	P Overall	Comfort (vs. extending life)		Unsure (vs. extending life)	
		OR	95% CI	OR	95% CI
Age (per 10yr increase)	**0.044**	**1.58**	**1.07–2.32**	1.05	0.73–1.52
Non-white (vs. white)	0.118	0.96	0.24–3.90	3.07	1.01–9.36
Female (vs. male)	0.845				
Disease	**0.033**				
TBI (vs. stroke)		**4.84**	**1.21–19.34**	0.52	0.12–2.27
CA (vs. stroke)		—	—	2.16	0.30–15.51

Statistical significance by nominal regression.
Multivariate model started with age/race, then added subsequent factors by forward selection ($p < 0.05$).
P-values in gray indicate significance if the effect were added to the final multivariate model.
Cell counts are too small to allow complete estimation for disease "CA vs. Stroke."
Bold indicates statistically significant ($p < 0.05$).

their loved one would prioritize extending life as much as possible. However, those family-assessed goals matched the family-reported care received for only 65% of patients. Life-sustaining treatment (LST) is often the default in hospital-level acute care unless a patient has specifically requested otherwise (13, 16). In the acute setting of SABI that is characterized by a high degree of prognostic uncertainty, national US guidelines even recommend "aggressive" therapy for those without advance directives to the contrary (17). Most families in our study report receiving care focused on extending life, regardless of goals, and goal concordance was accordingly more likely for patients who prioritized extending life. A presumed priority of comfort was more likely when patients were clinically sicker (by APACHE score), which may be related to their higher risk of mortality, although we do not know what information the family was given on the patient's chance of survival or recovery.

Our observation that non-Hispanic whites were more likely to prioritize comfort needs to be interpreted with caution as it was only significant for the comparison with "extending life" but not with "unsure." We also did not collect detailed socio-economic characteristics, religious or cultural beliefs which might further confound this association. The observation is consistent with the literature that suggests higher prevalence of prioritizing aggressive care at the end-of-life in non-white compared to white patients and requires further research (18, 19).

One in four patients in our study may have been receiving unwanted aggressive care in the acute setting. It is possible that LST was provided with the mutual understanding of a time-limited trial, whereby family and clinicians have agreed on a period of aggressive interventions to see if the patient improves according to outcomes consistent with the patient's presumed goals-of-care (10, 20). In that case, this relatively high prevalence of aggressive care may be ethically justified as long as the prognostic uncertainty persists and as long as the time-limited trial is brought to a conclusion.

Future studies are needed to better understand the framework of goal concordance specifically in the setting of a time-limited trial after SABI. The possible associations of age, disease severity, and disease category also require further investigation. Goal concordance in older patients may be because they are more likely to have voiced their own goals prior to SABI, as described for the US population (21). Lower severity of SABI may account for more prognostic uncertainty leading to a trial of LST even in a patient who eventually might prioritize comfort. The trend toward a higher likelihood of goal concordance in patients with stroke could be related to the disease category itself, but also to the subspecialty of their medical providers (i.e., stroke neurologists vs. neurosurgeons or intensivists).

Six months after the acute event, a large proportion of family members were unsure of the patient's priorities. Given that SABI survivors are at high risk of re-hospitalization, these findings suggest important missed opportunities for improved communication between SABI survivors, their families and clinicians, even long after the event. Periodic re-evaluation of patient-centered goals and intentional conclusions to time-limited trials should be a routine part of post-SABI clinic visits (12, 22).

Our findings need to be considered in the setting of several important limitations. First, the single center design may limit generalizability of results. However, our center is the only comprehensive stroke and level 1 trauma center for a five-state region and is an academic county hospital serving wide variety of patients which may mitigate this limitation. Second, most of the patients were non-Hispanic white, and small numbers of non-white patients preclude analyses of separate minority races. Third, because patients were unable to communicate their own wishes or perspectives, we relied on families to provide substituted judgment. This does, however, reflect clinical practice where, if patients are unable to participate in decisions, goals-of-care are determined by family surrogates. Of note, only 22 (10%)

of our patients had some type of pre-SABI advance directives documented in the EHR of which only half ($n = 9$) indicated any treatment preferences.

CONCLUSION

The observed high prevalence of patients potentially receiving unwanted aggressive care after SABI may be justified in the acute setting as long as prognostic uncertainty exists and provided it is in the context of a well-implemented time-limited trial. The high prevalence of families who are unsure of their loved one's goals of care 6 months after SABI suggest missed opportunities in communication between clinicians, families and patients as well as missed opportunities for completion of time-limited trials in the post-acute setting. More research is needed to better understand goal concordance in both the acute and post-acute care setting in the context of a time-limited trial of life-sustaining treatment.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation available to sincere requests.

ETHICS STATEMENT

The protocol was approved by the ethical review board of the University of Washington (STUDY 00003393). The ethics committee waived the requirement of written informed consent for participation.

AUTHOR CONTRIBUTIONS

RR and CC: obtained funding and drafting of the manuscript. CC, RJ, and JC: supervison. JB: statistical analysis. RR, JB, JC, and CC: acquisition, analysis, or interpretation of data. RR, JC, RJ, and CC: concept and design. All authors critically revised the manuscript for important intellectual content.

FUNDING

RR was supported by a grant of the Swiss National Science Foundation (P400PM_186732). CC received funding from a career development award from the National Institute of Neurological Disorders and Stroke (K23 NS099421). The researchers' funders had no role in the design, data analysis, interpretation or writing of the manuscript. All co-authors had full access to all the data in the study and had final responsibility for the decision to submit the publication.

ACKNOWLEDGMENTS

We would like to thank Wesley Plinke, Allison Kunze, Nathan McLaughlin, Erik Risa, and Dr. Kim Matsumoto for assistance with data collection.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer, KD, declared a shared affiliation, though no collaboration, with three of the authors, RR, GB, and RJ to the handling editor.

frontiers in Neurology

ORIGINAL RESEARCH
published: 22 September 2021
doi: 10.3389/fneur.2021.683624

Involvement of Specialist Palliative Care in a Stroke Unit in Austria—Challenges for Families and Stroke Teams

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Purpose: Severe stroke poses vast challenges. Appropriate goals of care according to individual preferences and values have to be developed under time restrictions—often impeded by limited ability to communicate and the need for decisions by surrogates. The aim of our study was to explore the decision-making process and the involvement of specialist palliative care in the acute phase of severe stroke.

Methods: Twenty patients suffering from severe ischemic stroke treated in an Austrian acute inpatient stroke unit were included in a prospective study. Their families were interviewed with a questionnaire (FS-ICU 24), which covered satisfaction with care and decision-making. With a second questionnaire, decision-making processes within the stroke team were investigated.

Results: A palliative approach and early integration of specialist palliative care in severe ischemic stroke results in individualized therapeutic goals, including withholding therapeutic or life-sustaining measures, especially in patients with pre-existing illness.

Conclusions: Family members benefit from understandable and consistent information, emotional support, and a professional team identifying their needs. Stroke unit professionals need skills as well as knowledge and strategies in order to make decisions and provide treatment at the end-of-life, when there may be ethical or legal issues. Close cooperation with specialist palliative care services supports both treatment teams and families with communication and decision-making for patients with severe ischemic stroke.

Keywords: early integration, patient care planning, family satisfaction, FS-ICU 24, decision making, ethics, severe stroke, specialist palliative care

OPEN ACCESS

Edited by:
David John Oliver, University of Kent, United Kingdom

Reviewed by:
Mary Beth Morrissey, Fordham University, United States
Peter Eastman, Barwon Health, Australia

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Specialty section:
This article was submitted to Neurocritical and Neurohospitalist Care, a section of the journal Frontiers in Neurology

Received: *21 March 2021*
Accepted: *09 August 2021*
Published: *22 September 2021*

Citation:
Riesinger R, Altmann K and Lorenzl S (2021) Involvement of Specialist Palliative Care in a Stroke Unit in Austria—Challenges for Families and Stroke Teams. Front. Neurol. 12:683624. doi: 10.3389/fneur.2021.683624

INTRODUCTION

Stroke is a leading cause of death and disability worldwide. Despite a decline in incidence and mortality in recent years, the prevalence of stroke increases due to a growing and aging population. Therefore, stroke will remain a major concern globally (1).

American and Canadian professional societies recommend palliative care as an integrated part of stroke care (2, 3). When stroke affects activities and quality of life and reduces life expectancy,

patients and their families should have comprehensive access to palliative care from the moment of diagnosis and throughout the entire course of the illness, particularly in the presence of progressive chronic comorbidities or preexisting palliative care goals (3).

In severe stroke, families are confronted with an acute onset and the victim's devastating decline in function and cognition—often accompanied by loss of verbal communication skills. Prognosis on the course and outcome is often unclear. Anxiety and depression among stroke patient's family members are common (4) and the related emotional burden is also measurable 1 year after the incident (5).

In this situation, preference-sensitive decisions need to be made. Advance directives are rare and patient's autonomy is often determined via proxies who base their opinion on previously expressed wishes of the patient or give advice in the best interest of the patient (6). Although decision-making can entail enormous emotional burden, caregivers want to be involved (7, 8). However, the surrogate's decisions can be influenced by culture and religion, cognitive biases (3), as well as by her/his own wishes and values (9).

Decision-making, alignment of treatment with the patient's goals, emotional support for families, and the basics of symptom management are core elements of palliative care and should be routine aspects of care for anyone caring for stroke patients and their families (3).

The aim of our study was to assess whether the approach of having early and close cooperation with specialist palliative care (SPC) services has an impact on stroke patient's families sense of satisfaction. Furthermore, we intended to evaluate decision-making in the context of limiting life-sustaining therapies (LST) in severe stroke.

METHODS

Patients with severe ischemic stroke admitted to the acute stroke unit of Barmherzige Schwestern in Ried im Innkreis, a secondary/tertiary care hospital in Austria, Europe, between June 2019 and February 2020 were studied.

Inclusion criteria were severe ischemic stroke (modified Rankin Scale $\geq$4 after acute therapy or no therapeutic options), age $\geq$18 years, contact to a palliative care team during hospital stay, and visit by family member(s) during stroke unit stay.

The palliative care team, including a palliative care physician and nurse, was involved following the decision of the treating physician, without the use of predefined triggers for referral.

Data about patients were collected prospectively during the study period and data on the role and involvement of the palliative care team retrospectively using patient's medical charts. Data analyses were descriptive in nature.

For the study of stroke patients' relatives, the questionnaire FS-ICU 24 was used. This questionnaire is available in German and assesses family satisfaction with care and decision-making in a critical care setting (10). The researcher contacted them in person or via telephone within 1–4 weeks after the patient's discharge from the stroke unit. As the study involved older participants, the survey was carried out on paper. Questionnaires were handed out, sent by mail or e-mail. If necessary, a reminder (e-mail or telephone call) was sent after 4 weeks. Questionnaires were handed in within 2 weeks to 2 months after the stroke unit stay.

The second part of the survey studied the stroke team's approach to limiting LST in all their patients, mostly stroke victims. In November and December 2019, team members (12 physicians and 20 nurses) were questioned via an electronic questionnaire based on a questionnaire previously used by Jox et al. in German intensive care units (ICU) (11). Participants were approached by e-mail. To maximize the response rate, an e-mail reminder was sent after 2 weeks.

The study was approved by the local ethics commission on June11, 2019.

RESULTS

Patient Characteristics

A total of 427 patients with ischemic stroke were treated in this stroke unit in 2019. We identified 20 patients who received SPC during the 9-month-long study period, representing 5% of all patients admitted.

Patient characteristics can be found in **Table 1**.

The mean PREMISE score, which predicts mortality within the first week after admission to a stroke unit (12) was 8 ($\pm$2) for all reviewed patients. This would imply a 19% mortality within the first week.

Therapies and complications can be seen in **Table 2**. It also shows that all patients had therapy limitations, introduced step by step during the stay. Due to the severity of stroke and concurrent reduced consciousness and/or comorbidities such as dementia, 17 patients (85%) were incapable of making decisions on their own. Two patients refused intensive care measures and cardiopulmonary resuscitation (CPR); one referred to her advance directive where she had refused CPR. Two patients (10%) had an advance directive.

Most patients were transferred from the stroke unit. Overall, 60% died during the hospital stay.

SPC consultation took place 3 days ($\pm$3 days; mean $\pm$ SD) after stroke and, in 95% of cases, was conducted face-to-face. In one case, only telephone contact was made. On average, two contacts ($\pm$2; mean $\pm$ SD) occurred during the hospital stay. The palliative care physician was involved in all and the palliative care nurse in 35% of cases. The focus of palliative care contact was primarily on the assessment and therapeutic advice in symptom management (70%), assistance in transfer to SPC services (65%), communication and support for families (55%), and decision-making (30%).

Family Questionnaire

Seventeen out of 20 (85%) family members completed the questionnaire; 59% ($n = 10$) were female, and 41% ($n = 7$) male. Their mean age was 59 years (42–72 years); 47% ($n = 8$) were

Abbreviations: CPR, cardiopulmonary resuscitation; DNR, Do Not Resuscitate; ICU, intensive care unit; LST, life-sustaining therapy/therapies; SPC, specialist palliative care.

TABLE 1 | Patient characteristics.

	Mean ± SD	%, (*n*)	
Age, years	83 ± 9		
65–74		15 (3)	
75–84		35 (7)	
≥85		50 (10)	
Gender female		55 (11)	
Ethnicity		100 (20)	Caucasian
Stroke location		90 (18)	Anterior circulation
		10 (2)	Posterior circulation
Etiology		50 (10)	Cardioembolic
		25 (5)	Macroangiopatic
		20 (1)	Microangiopatic
		20 (1)	Unknown
mRS[a] premorbid	3 ± 1		
mRS admission	5 ± 0		
NIHSS[b]	15 ± 6		
Comorbidities		80 (16)	Cardiac diseases
		55 (11)	Atrial fibrillation
		45 (9)	Dementia
		40 (8)	Heart failure
		20 (4)	Diabetes
		10 (2)	Heart attack in history
		5 (1)	Cancer
		5 (1)	Hemodialysis
		5 (1)	Smoking
PREMISE score (12)	8 ± 2		

[a] *mRS, modified Rankin Scale.*
[b] *NIHSS, National Institute of Health Stroke Scale.*

TABLE 2 | Therapies and course of illness.

		%, (*n*)	Time (days) Mean ± SD
Therapies			
	Intravenous thrombolysis	60 (12)	
	Thrombectomy	5 (1)	
	Craniectomy	0	
	Tracheotomy	0	
	PEG[a] insertion	0	
Complications			
	Infection + antibiotics	35 (7)	
	Hemorrhage total	30 (6)	
	Hemorrhage after iv thrombolysis	42 (5)	
Decision making			
	Capable of decision making	15 (3)	
	Advance Directive	10 (2)	
Therapy limitations			
Do Not Resuscitate (DNR)-*time till*		100 (20)	1 ± 2
Do Not Escalate (DNE)-*time till*		70 (14)	4 ± 7
Comfort Terminal Care (CTC)-*time till*		55 (11)	5 ± 8
Stay			
	Stroke unit		3 ± 3
	Hospital stay surviving		22 ± 11
	Hospital stay deceased		11 ± 11
Referral from stroke unit			
	Neurologic ward	45 (9)	
	Palliative care unit	45 (9)	
Death			
	Stroke unit	10 (2)	
	Overall deaths	60 (12)	
	Death after thrombolysis	58 (7)	

[a] *PEG percutaneous endoscopic gastrostomy.*

daughters, 24% ($n = 4$) sons, 18% ($n = 3$) siblings, and 12% ($n = 2$) had other relationships to the patients; 36% ($n = 5$) had been involved as family members of a stroke patient before.

Care for the patient (concern and caring, pain, breathlessness and agitation management); skills and competencies of the stroke unit team (physicians and nurses); care for family members themselves (consideration of needs, emotional support, coordination of care, concern, and caring); and information (frequency, ease of getting, understanding, honesty, completeness, and consistency) were rated excellent, very good, or good by most participants. Most of them were also satisfied with the amount of care the patient received (see **Figure 1**).

Most participants felt included and supported in decision-making and had the feeling of control over the care their family member received (see **Figure 2**). The vast majority of the relatives (14 out of 16 participants) felt that the time for addressing concerns and questions during decision-making was adequate; two participants (13%) would have needed more time.

Team Questionnaire

The stroke team was questioned about their approach to limiting LST; 18 out of 32 team members (56%) completed the survey; 59% ($n = 10$) were nurses and 41% ($n = 7$) were physicians.

57% of the physicians reported needing to deal with the topic of limiting LST at least once a week, and 43% 1–2 times per month.

When asked "*What were the most common LST withheld from your patients and thus no longer stopped the patient's death?*" physicians and nurses reported that CPR or mechanical ventilation was often withheld. None of the participants reported forgoing artificial hydration. Regarding artificial nutrition, the perceptions of nurses and physicians differed: nurses reported withholding artificial nutrition in 30% and physicians in 86% of cases (**Figure 3**).

When questioned about the decision-making process concerning limiting LST, physicians and nurses alike reported the involvement of the patient's family. The decisions were made cooperatively by the physician's team rather than by senior doctors individually. Physicians reported that nurses were involved in 71% of cases, whereas nurses themselves felt involved only in 40% (**Figure 4**). Satisfaction with decisions (physicians 100%, nurses 90%) and communication (physicians 100%, nurses 80%) was high in both professional groups.

Of physicians, 14% felt insufficiently trained and insecure in situations dealing with limiting LST, whereas of nurses,

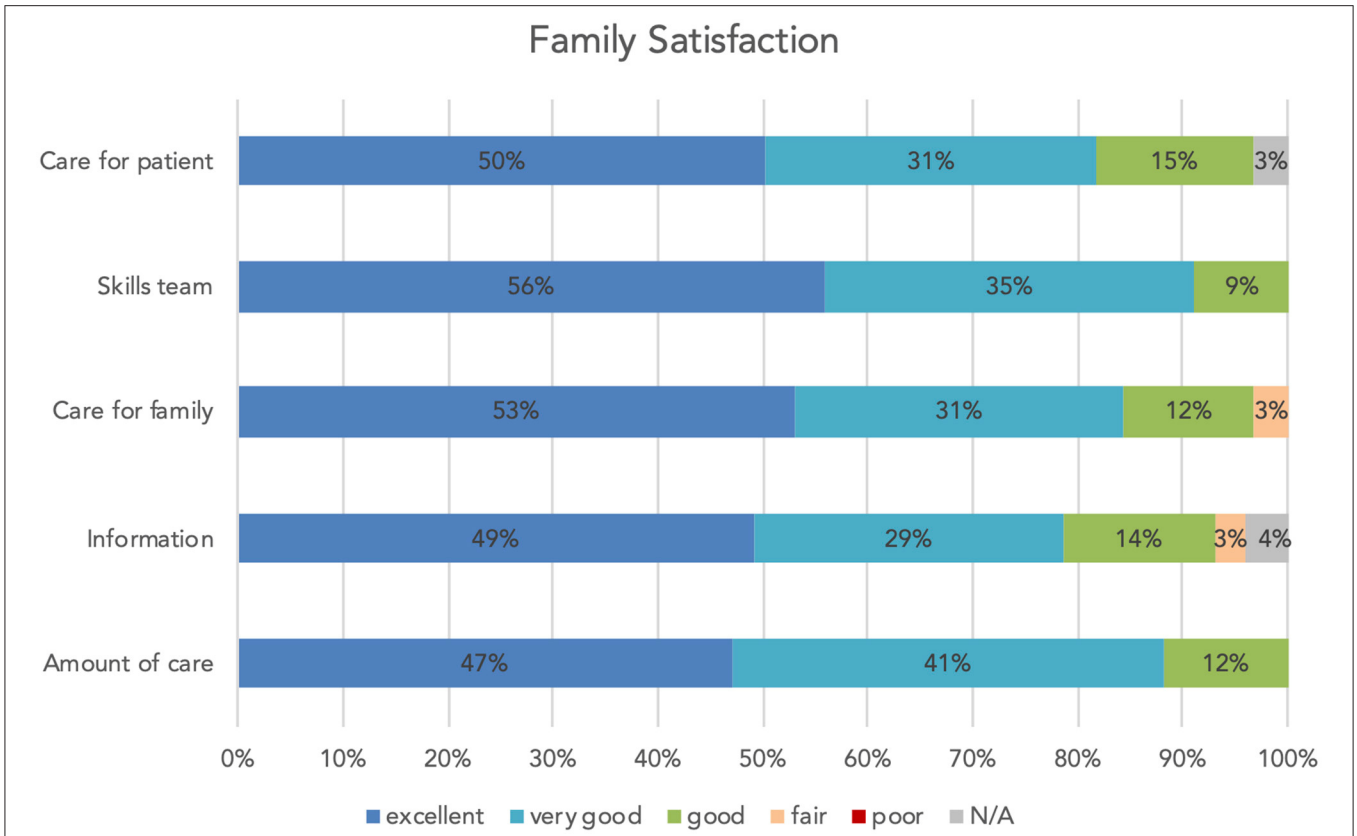

FIGURE 1 | Family satisfaction: care for the patient (concern and caring, management of pain, breathlessness and agitation), skills team (physicians and nurses), care for family (consideration of needs, emotional support, coordination of care, concern and caring), information (frequency, ease of getting, understanding, honesty, completeness and consistency), amount/level of care patient received.

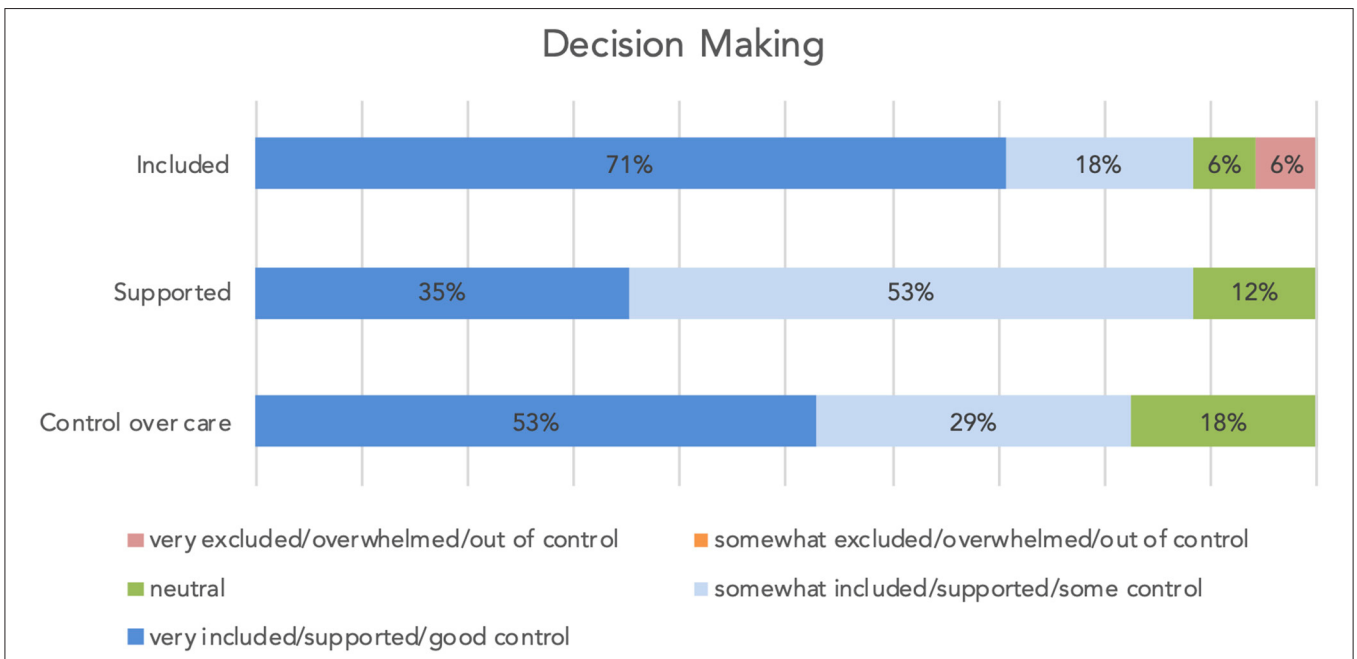

FIGURE 2 | Decision making: included in the decision process, supported during the decision process, control over the care the patient received.

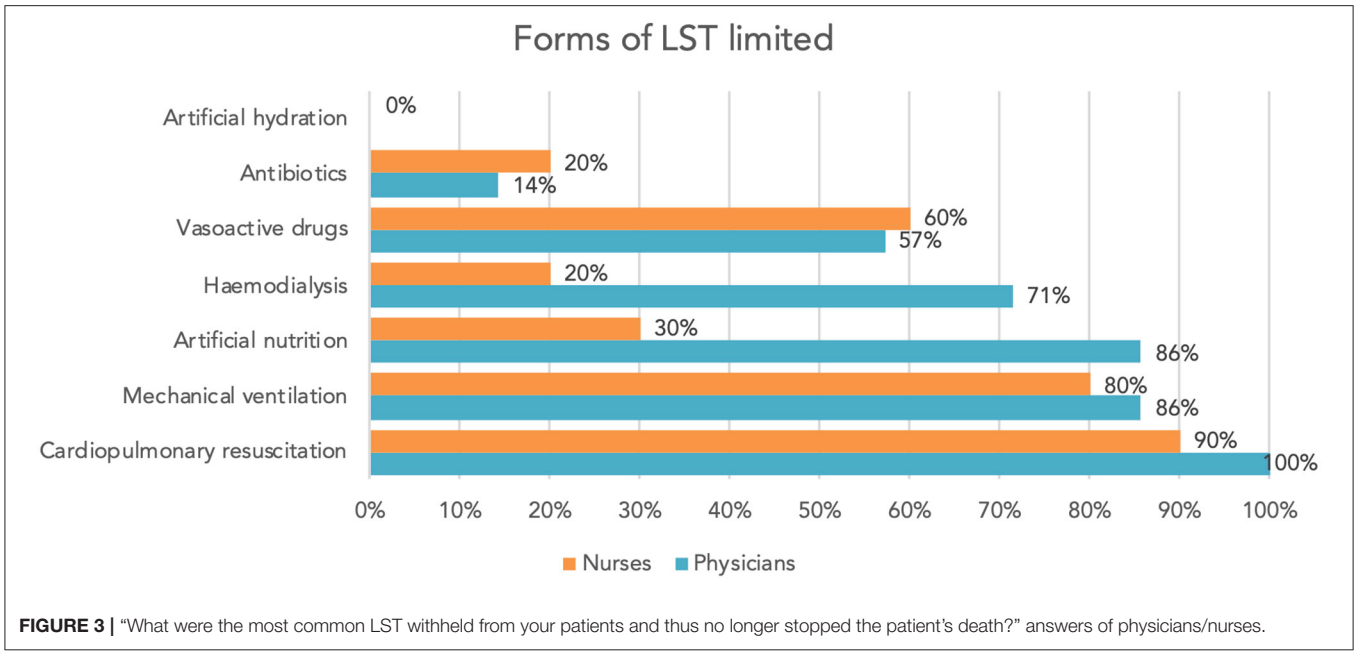

FIGURE 3 | "What were the most common LST withheld from your patients and thus no longer stopped the patient's death?" answers of physicians/nurses.

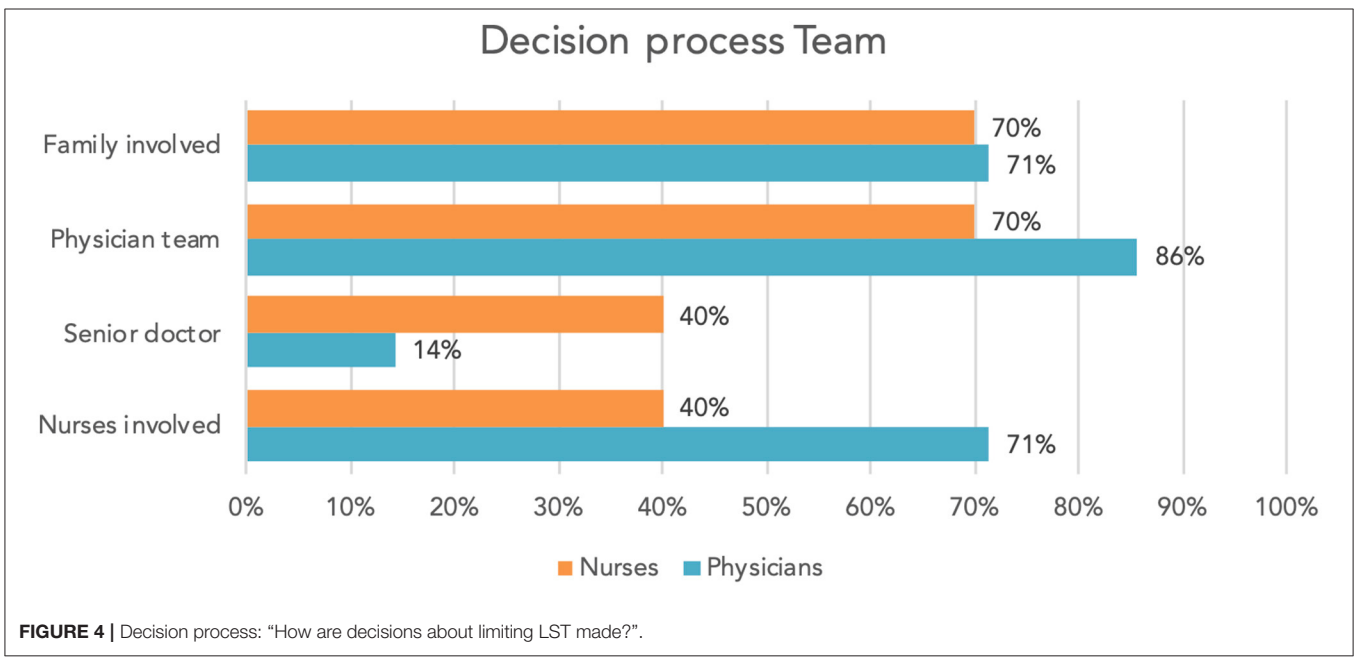

FIGURE 4 | Decision process: "How are decisions about limiting LST made?".

30% felt insufficiently trained and 10%, insecure. Both groups reported communication with the patient and/or the family challenging. In addition, physicians reported ethical and legal concerns (**Figure 5**).

Whereas, all involved physicians reported raising the issue of advance directives with patients or relatives, the rate stood only at 50% among the nurses questioned.

Overall, the topic of limiting LST was considered important by both physicians and nurses (100% each) and their need for information proved high (physicians 100%, nurses 90%).

DISCUSSION

Current recommendations for stroke management in German-speaking countries (Austria, Switzerland, Germany) do not cover palliative care. Our small study is the first evaluation of SPC in stroke patients in Austria. Albeit having been a monocentric and small trial (stroke unit of Barmherzige Schwestern in Ried), we were able to gain some insights into palliative care service for stroke patients. We identified that out of all stroke patients, 4.6% received SPC. This number is consistent with data from the USA

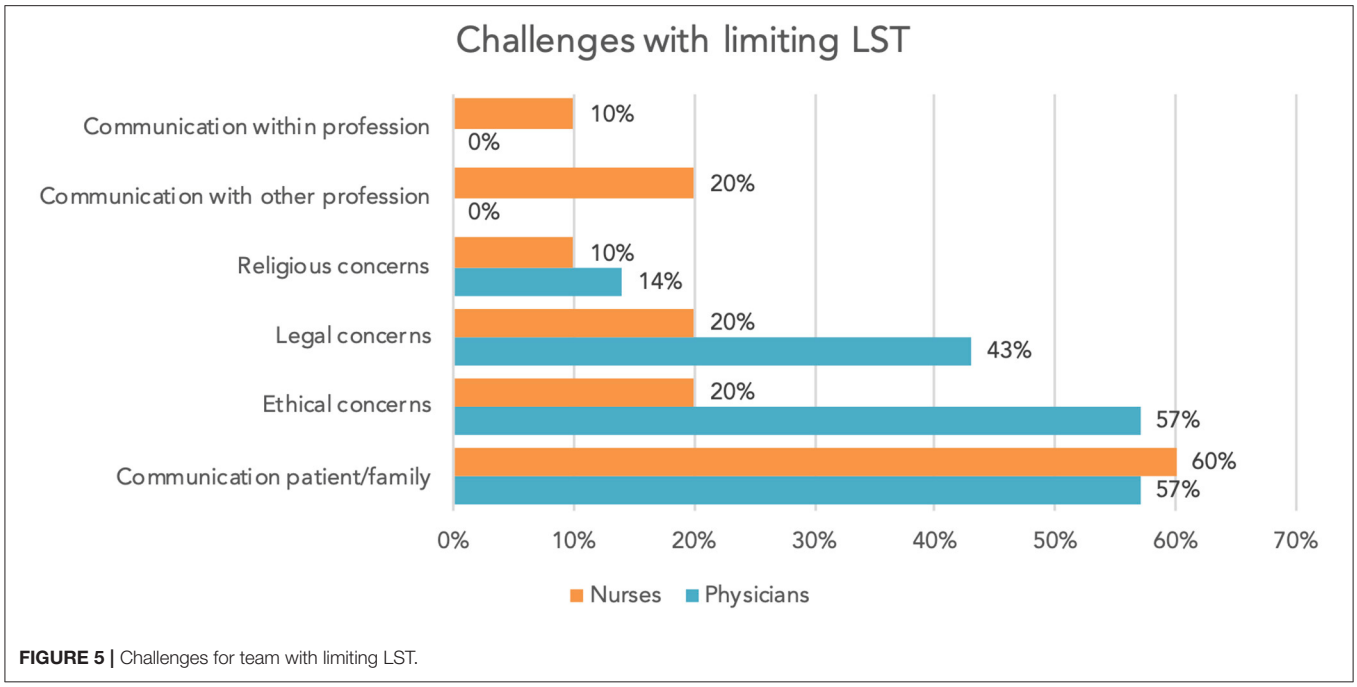

FIGURE 5 | Challenges for team with limiting LST.

(13), but considerably lower than in Australia where 11.4% of all stroke patients received SPC (14).

Patient Characteristics and Treatment

The patient's average age was 83 (±9 years; mean ± SD) and 65% of them needed preliminarily care. They suffered from severe stroke (mean modified Rankin Scale 5); 80% had cardiac comorbidities and in 45% dementia had been diagnosed before admission for acute stroke. In Canada and the United States, palliative approach is especially recommended for these patients, who have been hit by a severe stroke affecting daily functioning, life quality, and life expectancy as well as having existing significant comorbidities (2, 3).

Acute stroke care is a highly standardized procedure. Data from the USA show that even for patients who were transferred to hospice or died, initial therapy was applied in a timely manner and with high adherence to stroke process measures (15). This is again comparable with our data. Although our study population would have profited less from intravenous thrombolysis due to their age, existing comorbidities and preliminary need for care, intravenous thrombolysis was administered in 60% of cases.

The death of 12 patients in our study occurred on average 11 (±11) days after admission and 6 days after setting the therapy goal to comfort terminal care. The mean PREMISE score predicting mortality within the first week after admission to the stroke unit (12) was 8 (±2), which would imply a mortality of 19% within the first week. Since 25% ($n = 5$) of our patients died within this period, the usefulness of this score can be seen, even in this small sample. The prognostic accuracy of the PREMISE score in patients with acute ischemic stroke has been also demonstrated in a larger cohort in Greece (16). Therefore, its use might prove a valuable indicator for the need of palliative care support. However, the value of prognostic models has not been established for post-stroke end-of-life treatment decisions (3).

Decision-Making

In severe stroke, prognosis is frequently unclear, as patients suffer acute neurological deterioration and are often unable to communicate and make decisions for themselves. In this setting, clinicians and families frequently need to make treatment decisions. Shared decision-making is an approach where patients, families, and clinicians consider patient's values and preferences alongside the best medical evidence and cooperate to make the best decision for a given patient in a specific scenario. This approach can be applied to every decision within stroke care (17).

In our sample, only three patients were capable of making decisions for themselves and all of them refused intensive care measures and CPR.

Two patients (10%) had preexisting advance directives on admission, which is average for Austria where about 8% of over 70-year-olds have an advance directive (18). Although the relevant law was established in Austria already in 2006, some medical professionals are still insecure about the completion and application of advance directives (18) and avoid the topic. Enhanced knowledge (19) and the role of decision-maker could be the reasons why advance directives were addressed by all of physicians but only by 50% of the nurses who participated in our research.

Due to the severity of stroke or preexisting comorbidities, for example, dementia, most decisions in our research were surrogate decisions. Decisions about limiting LST were reported

to having been made in cooperation between the physician's team and the patient's family. Families were satisfied with the information provided and felt included and supported in the decision-making process.

In this research, physicians stated that in 71% of cases, nurses were involved in the decision-making process. Nurses themselves, however, felt being involved in only 40% of cases. Our data did not reveal the reasons for this disparity. Although the involvement of nurses in end-of-life decision-making for patients with acute stroke influences neurologist's intensivist practice and behavior and may help them (20), nurses are rarely involved because of the lack of awareness, knowledge, and time as well as hierarchical reasons (11, 21). On the other hand, nurses are highly involved in executing these decisions. This might be identified as a relevant risk factor for burnout in ICU personnel (22). At the same time, overall satisfaction with decisions and communication concerning limitation of LST was high in both professions in this team.

Limiting Life-Sustaining Therapies

As treatment restrictions are independently associated with mortality (23), decisions on withholding or withdrawal of life-sustaining treatments should be taken with great caution (6). Yet, this highly demanding procedure is common in intensive care units. Physicians feel confronted with the topic more frequently than nurses.

All of our patients had individual therapeutic goals with directives for gradual forgoing of treatment completed at an early stage. Despite these time pressures on decisions concerning therapeutic goals, 88% of the questioned family members stated that they had adequate time to have their concerns addressed and questions answered during the decision-making process; 88% of the questioned family members were completely satisfied or very satisfied with the level or amount of health care provided to their family member.

In our research, CPR proved the most limited form of LST mentioned by nurses and physicians. All of our analyzed patients had a Do Not Resuscitate order. In general, 18% of in-hospital cardiac arrest patients survive to discharge and age over 70: altered mental status, need for assistance in every day activities, and admission for medical non-cardiac diagnosis are considered to be in strong correlation with the failure to survive to discharge (24). Evidence for the outcome of CPR in stroke patients is lacking, yet forgoing CPR in stroke is common (25). 35% of the sample received antibiotic therapy and thus it would seem that the restriction of CPR was considered differently to other LST (3).

In the researched setting that does not offer mechanical ventilation, forgoing ventilation was reported more often than in ICUs (11). In contrast, withdrawing mechanical ventilation is regarded more difficult since it is associated with legal and ethical concerns (26) and needs highly specialized palliative care for sufficient symptom control.

Stroke patients are prone to malnutrition, dehydration, and aspiration pneumonia due to dysphagia, impaired consciousness, perception deficits, and cognitive dysfunction. When dysphagia is considered prolonged, percutaneous endoscopic gastrostomy (PEG) is recommended (27) but it is also associated with persisting impairment of swallowing and mobility and a mortality of 66% after 2 years (28). Decisions about nutrition can be highly emotional for families and can result in conflicts with treatment teams (29). Forgoing PEG placement and artificial nutrition is more frequent in stroke patients admitted to palliative care (13, 30) and was reported by 86% of the physicians questioned in our research. Nurses reported the limitation of artificial nutrition less frequently than doctors (30 vs. 86%), as shown in previous research (31).

Although forgoing artificial hydration in dying patients is recommended when no benefits are expected (32), all team members stated that hydration is never withheld. This has been also documented in previous reports (30). Some countries or cultures consider hydration as a basic measure that cannot be withheld (32). As well as personal beliefs, religious and cultural considerations have an important role in this decision.

Our data show that the topic of limiting LST is important for nurses as well as physicians and the need for information is high. Compared to data from German ICUs (11), our staff felt less insecure about applying LST, felt better trained, and had less fears for legal consequences. Ethical policies and consultations implemented in our hospital appear to facilitate decision making (11).

To structure, de-emotionalize, and make decisions on limiting LST reproducible for others, standardized documentation is recommended (11, 33). Whereas, German ICU personnel stated that 32% of cases would have no written documentation about Do Not Resuscitate orders (11), the implemented form for documentation of resuscitation status was used in every patient analyzed. For further steps of forgoing therapy (Do Not Escalate DNE, Comfort Terminal Care CTC), our hospital has no standardized documentation protocols, leading to reduced documentation on these.

Palliative Care in the Stroke Unit

Palliative care needs of patients with severe stroke and their families are high requiring complex decision-making, aligning treatment with goals and symptom control (3). Uncertain prognosis, communication, and quality of life are specific issues for palliative care in the Neuro-ICU (34). Frequently, family members are the main recipients of SPC (35).

In the researched setting, the focus of SPC consultations was mainly on the assessment and therapeutic advice in symptom management, followed by assistance in transfer to SPC services.

Assistance in discussing and clarifying care goals is a common indication for palliative care consultations (34, 35). Indeed, in palliative care consultations a lot of time is spent on discussing prognosis, family's understanding of prognosis, and exploring patient's and family's values, whereas neurologists and intensivists are in charge of prognostication (35). Interestingly, in our sample, assistance in discussing and clarifying goals was part of the consultations in only 30% of cases. The limited availability of the SPC team, who are available only during day time working hours, may have influenced the neurologists to develop palliative care skills. Further research is needed to look at this area.

SPC services are often used when the care team believes that issues regarding the withdrawal of LST are the focus of a patient's

management (34). Our data shows that in the context of limiting LST, communication with patients and/or their families was the biggest challenge for stroke unit professionals. As shown before (35), communication and support for families were a frequent part of SPC consultations in the researched setting.

Limitations

Our study has several limitations, above all, the single-center trial and, thus, the small number of patients as well as team members. Expanding it to other Austria stroke units would give a better overview about clinical practice and the level of integration of palliative care in the country.

Creutzfeldt et al. demonstrated that a brief palliative care needs screening tool had the potential to improve care for patients and their families (36, 37). In our research, the involvement of SPC was based on individual decisions, which, according to a recent survey (34) was the preferred way of access also among US neurointensivists. With the chosen approach, some patients and families with palliative needs may not have been identified.

Our sample included only Caucasian people, which reflects the ethnic structure in our region.

CONCLUSION

Although palliative care is a recognized part of stroke care (38) this is the first study in Austria to examine an approach with early and close cooperation with SPC services, resulting in setting patient-centered therapeutic goals early in the acute phase of severe stroke. While acknowledging the small sample size, families' satisfaction with the care delivered to the patients, including the level or amount of health care, was high. Similarly, families were highly satisfied with decision-making processes as well as with information and support received. Furthermore, we could gain information about team decision-making process, especially concerning limiting LST, in the context of acute stroke care.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics committee of Krankenhaus Barmherzige Schwestern Ried im Innkreis. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

RR and SL contributed to conception and design of the study based on former research by KA. RR organized the database, performed the statistical analysis, and wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

ACKNOWLEDGMENTS

We thank all patients and relatives as well as the nurses and physicians who participated in this trial. Thanks also to Prof. Dr. Ralf Jox for providing us his questionnaire about limiting life-sustaining treatment.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The Handling Editor declared a past co-authorship with one of the authors, SL.

frontiers in Neurology

ORIGINAL RESEARCH
published: 24 September 2021
doi: 10.3389/fneur.2021.700103

Palliative Care Challenges of Patients With Progressive Bulbar Palsy: A Retrospective Case Series of 14 Patients

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Progressive bulbar palsy (PBP) is a form of motoneuron disease and is widely classified as a subtype of amyotrophic lateral sclerosis (ALS) with a shorter time of survival and female predominance. In this retrospective case series of 14 patients with PBP, we focus on challenges in palliative care for this patient cohort, including symptom control, gastrostomy, non-invasive ventilation, and end-of-life phase. We show that rapid physical decline at the end of life is associated with bronchopulmonary infection and excessive oral secretion leading to a high level of symptom burden. Early and regular advance care planning discussions with a focus on oral secretion management with patients and caregivers are crucial.

Keywords: amyotrophic lateral sclerosis, progressive bulbar palsy, palliative care, oral secretion management, end-of-life

OPEN ACCESS

Edited by:
David John Oliver,
University of Kent, United Kingdom

Reviewed by:
Guillermo Solorzano,
University of Virginia, United States
Gabriel Rodriguez,
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Specialty section:
This article was submitted to Neurocritical and Neurohospitalist Care, a section of the journal Frontiers in Neurology

Received: *25 April 2021*
Accepted: *25 August 2021*
Published: *24 September 2021*

Citation:
Bublitz SK, Weck C, Egger-Rainer A, Lex K, Paal P and Lorenzl S (2021) Palliative Care Challenges of Patients With Progressive Bulbar Palsy: A Retrospective Case Series of 14 Patients. Front. Neurol. 12:700103. doi: 10.3389/fneur.2021.700103

INTRODUCTION

Early integration of palliative care is an important task when treating patients with amyotrophic lateral sclerosis (ALS) (1, 2). ALS is a progressive neurodegenerative disease with a high symptom burden, and in the majority of cases, ALS leads to paralysis of the limbs, impaired speech, swallowing, and ventilatory failure. The rapid progression of the disease and the question of whether or not to include life-prolonging therapies, such as feeding tube placement or ventilatory support, should be a stimulus for early discussion regarding therapeutic limitations and advance care planning (ACP).

ALS and motoneuron disease (MND) are generic terms for a range of different phenotypes defined by a varying involvement of spinal and bulbar upper and lower motoneurons (3). Progressive bulbar palsy (PBP), or bulbar phenotype, is defined as bulbar onset with dysarthria and/or dysphagia, tongue wasting, fasciculations, and no peripheral spinal cord involvement for the first 6 months after symptoms onset (3). The median survival time in bulbar phenotype patients is shorter than in other subgroups (3, 4).

An analysis of a large Italian ALS population found a correlation of the bulbar phenotype with older age and women being more affected than men (5). Expansions in the gene *C9orf72* were related to a significant increase of the bulbar phenotype, and patients with bulbar phenotype had an increased risk of developing cognitive impairment and were more likely to develop frontotemporal dementia (FTD) (5). Recent diffusion tensor imaging (DTI) data showed the same microstructural involvement in both PBP and ALS, supporting the hypothesis of a phenotypic spectrum of the same

disease (6). However, the discussion of whether PBP might be seen as a subgroup within a spectrum of ALS or as a distinct entity continues (7).

This paper presents a retrospective case series of PBP patients in palliative care, including symptom control, course of the disease, and end-of-life phase in a relatively homogenous group of patients.

METHODS

This is a retrospective case series of patients with PBP in palliative care, which was conducted from September 2017 till January 2021. During this time, 91 ALS patients were treated at our hospital as in-patients and out-patients. Patient records were analyzed regarding demographic and clinical data, medication, course of the disease, and end-of-life phase.

PBP patients were identified according to the diagnostic criteria for PBP (3, 8). All patients ($N = 14$) showed isolated bulbar onset with dysarthria and/or dysphagia, tongue wasting, fasciculations, and no peripheral spinal involvement for the first 6 months after symptom onset. Of the 14 patients, 1 was male. Four patients are still alive; one is currently on invasive ventilation *via* tracheostomy.

RESULTS

Demographic data of the 14 PBP patients are shown in **Tables 1A,B**. The median age at the time of symptom onset was 68.5 years. The time between symptom onset and diagnosis varied between 3 and 16 months. Ten out of the 14 patients have died, with a median survival time from symptom onset until death of 27.5 months. In 11 patients, PBP manifested with isolated dysarthria, 1 patient (No. 4) noticed swallowing problems and burning of the tongue as the first symptom, and 2 patients (Nos. 3 and 13) reported dysarthria and dysphagia as having occurred together. Eight patients developed weight loss in an early phase of the disease, within the first 6 months: Nos. 1, 2, 3, 7, 9, 10, and 13.

The duration of isolated bulbar symptoms was longer than defined by Chio et al. (3), and the median time until first spinal symptoms (muscle weakness of limbs, spasticity of limbs) were documented was 24 months. One patient did not develop any spinal symptoms until death (No. 13) and two of the surviving patients still have no spinal symptoms (Nos. 12 and 14). All patients took riluzole in a standard dosage.

Symptomatic Treatment

Saliva/Drooling, Thick Mucus

Sialorrhea was the most challenging symptom in all 14 patients (see **Table 1A**). Anticholinergic drugs (scopolamine and amitriptyline) were recommended to all patients. Initially, these showed an effect on drooling in most patients. Two patients refused medication against sialorrhea despite severe drooling due to a lack of belief in the effectiveness of medication (Nos. 7 and 12). The scopolamine patch had to be terminated due to acute cognitive alterations in one patient (No. 4). Another patient taking amitriptyline developed circulatory problems (No. 5). Four patients received injections of botulinum toxin into salivary glands (Nos. 1, 6, 8, and 11). The only patient who received radiotherapy after initial therapy with botulinum toxin did not show satisfying results with both treatments (No 8). Another patient was considered for radiotherapy (No. 6), but this was not feasible because the patient was not able to lie flat for long enough to tolerate the procedure.

The majority of patients (9 out of 14) developed thick mucus later in the disease, which did not respond well to anticholinergic drugs. In seven patients, a mechanical insufflator/exsufflator device to loosen thick mucus was introduced, but was not tolerated by three patients (Nos. 6, 8, and 13).

Interventions

Gastrostomy

A total of 11 (Nos. 1–6, 8, 9, 10, 11, and 13) of the 14 patients with severe dysphagia and/or weight loss underwent placement of a feeding tube, percutaneous endoscopic gastrostomy tube (PEG). Median time from onset of diagnosis until PEG placement was 21 months (range, 5–27 months). Only one patient (No. 7) did not decide on feeding tube placement, despite several discussions on this topic and severe dysphagia and weight loss. Patient No. 10 died suddenly 4 days after PEG placement in the hospital without signs of acute infection. Median survival time after gastrostomy was 7 months (range, 0–15).

Non-invasive Ventilation (NIV), Invasive Ventilation

In six patients (Nos. 1, 2, 4, 5, 6, and 10), NIV was started when symptoms of nocturnal hypoventilation occurred. For patient No. 3, NIV was initiated in acute ventilatory insufficiency during bronchopulmonary infection and this patient died 1 week later. All other patients (Nos. 1, 2, 4, 5, 6, and 10) who started NIV did not tolerate this well, and the causes for NIV intolerance are described in **Table 1B**. Only one patient (No. 5) was able to use NIV for 3–4 h per night but did not tolerate NIV in the second half of the night due to severe dryness of the mouth. Later, this patient underwent tracheostomy and is still, to our knowledge, receiving invasive ventilation. The circumstances that led to tracheostomy could not be clarified.

One patient (No. 8) actively decided against initiating NIV. The other six patients have not (yet) developed symptoms of nocturnal hypoventilation or shown hypercapnia in arterial blood gas analysis.

End-of-Life Phase and Place of Death

Six out of 10 patients died in the hospital, three of them on an intensive care unit (ICU), two on a neurological ward, and one on a palliative care ward. Three patients died in hospice care. Only one patient died at home 3 weeks after discharge from a palliative care ward (see **Table 2**). Four patients died in the context of bronchopulmonary infection and subsequent ventilatory insufficiency (patient Nos. 3, 8, 9, and 13). The combination of excessive oral secretion and ventilatory insufficiency, without clinical signs of infection, was central in the end-of-life phase of four patients (Nos. 1, 2, 4, and 6). Patient No. 1 declined rapidly due to excessive oral secretion. She was admitted to an ICU and non-invasive ventilation was attempted, but due to

TABLE 1A | Demographic and clinical data of patients with progressive bulbar palsy.

Patient no.	Age at onset (years as range)	Time symptom onset to diagnosis (months)	First symptom	Significant early weight loss	Time onset to first spinal symptoms (months)	PEG placement (time from onset) (months)	NIV initiation (time from onset) (months)	Treatment efforts against sialorrhea	Mechanical insufflator/ exsufflator device initiated	Death (time from onset) (months)
1	60–65	12	Dysarthria	Yes	30	24	24 Not well-tolerated and rarely used due to sialorrhea	Scopolamine had little effect, Mestinon no effect, Amitriptyline resulted in unpleasantly dry mouth. Botulinum toxine mediocre effect on drooling, thick mucus persistent.	Yes	31
2	50–55	4	Dysarthria	Yes	23	21	23 Not well-tolerated due to siallorrhea	Pirenzepine and Scopolamine showed no effect	Yes	29
3	70–75	15	Dysarthria + dysphagia	Yes	18	16	30 Initiated on ICU 1 week prior to death	Amitriptyline	No	30
4	80–85	6	Burning of tongue, dysphagia	No	12	21	21 Not tolerated when tested due to constriction of pharyngeal muscles on exspiration	Scopolamine lead to cognitive alteration, Amitriptyline to daytime tiredness	No	27
5	56–60	10	Dysarthria	No	30	19	16 Regular use max. 3–4 h/night, in the second half of the night severe dryness of the mouth	Amitriptyline lead to circulatory problems. Scopolamine showed mediocre effect on drooling.	No	TIV
6	70–75	12	Dysarthria	No	24	22	22 Not tolerated when tested due to constriction of pharyngeal muscles on exspiration	Scopolamine showed little effect on drooling, thick mucus persistent. Atropine lead to cognitive alteration. Botulinum toxine mediocre effect. Radiotherapy not feasible due to orthopnoea	Yes, but not tolerated	37
7	70–75	11	Dysarthria	Yes	28	No PEG	No indication	Scopolamine and Amitriptyline discussed several times, patient decided against medication	No	28

(Continued)

TABLE 1A | Continued

Patient no.	Age at onset (years as range)	Time symptom onset to diagnosis (months)	First symptom	Significant early weight loss	Time onset to first spinal symptoms (months)	PEG placement (time from onset) (months)	NIV initiation (time from onset) (months)	Treatment efforts against sialorrhea	Mechanical insufflator/ exsufflator device initiated	Death (time from onset) (months)
8	66–70	3	Dysarthria	No	23	17	Decided against NIV	Scopolamine initially with good effect, later severe skin irritation. Amitriptyline mediocre effect. Botulinum toxine and Radiotherapy without satisfying effect.	Yes, but not tolerated	25
9	66–70	10	Dysarthria	Yes	17	14	No indication	Scopolamine initially effective	Yes	20
10	66–70	16	Dysarthria	Yes	24	27	24 Not well-tolerated when tested due to constriction of pharyngeal muscles on exspiration	Scopolamine started 1 month before death	Yes	27
11	66–70	11	Dysarthria	No	28	23	n.a.	Scopolamine lead to skin irritation. Botulinum toxine with mediocre effect.	No	n.a.
12	76–80	7	Dysarthria	No	n.a.	n.a.	n.a.	Scopolamine discussed, patient hesitant.	No	n.a.
13	80–85	5	Dysarthria + dysphagia	Yes	None	5	No indication	Scopolamine started 1 month before death	Yes, but not tolerated	7
14	50–55	15	Dysarthria	No	n.a.	n.a.	n.a.	Scopolamine currently with good effect on drooling.	No	n.a.

NIV, non-invasive ventilation; TIV, tracheostomy invasive ventilation; n.a., not applicable; Age at onset was given as a range in order to avoid indirectly identifying data of patients.

TABLE 1B | Demographic data and timeframe of interventions of patient cohort with progressive bulbar palsy.

	Median (range)	
Age at onset (years)	68.5 (53–80)	$n = 14$
Time to diagnosis (months)	10.5 (3–16)	$n = 14$
First spinal symptoms (months since onset)	24 (12–30)	$n = 12$
Gastrostomy placement (months since onset)	21 (5–27)	$n = 11$
Survival time after gastrostomy (months)	7 (0–15)	$n = 9$
NIV initiation (months since onset)	23 (16–30)	$n = 7$
Death (months since onset)	27.5 (7–37)	$n = 10$

collapsing pharyngeal muscles, this was not effective, and like Patient No. 3, invasive ventilation was not attempted as this was not in accordance with their expressed wishes. Patient 7 died due to severe traumatic brain injury after a fall on the stairs at home. She underwent emergency intubation, but invasive ventilation was withdrawn when the patient's will was communicated by her family. Patient 10 died 4 days after PEG tube placement without signs of acute infection, probably due to increasing hypercapnia because of postinterventional immobility. NIV had been trialed but had not been tolerated and therefore had been terminated 3 months before, when the physical decline had begun following an episode of pneumonia. Patient No. 13 died in the context of bronchopulmonary infection despite intravenous antibiotic treatment, possibly due to asphyxia. An autopsy was not performed on these two patients.

Symptom control in the terminal phase was successful in all patients for whom this information could be retrieved (Nos. 1, 3, 4, 6, 8, and 9; see **Table 2**). Most received morphine either intravenously or subcutaneously; patient No. 3 also received midazolam intravenously. Patient No. 2 was transferred to a palliative care ward in her home town and we were not able to retrieve further information about her. Patient Nos. 4 and 6, who died in hospice care, were treated with oral morphine.

DISCUSSION

In our analysis of a retrospective case series of 14 patients with progressive bulbar palsy (PBP), the special needs of this patient group can be seen, together with the role of palliative care. PBP patients may stay independent in self-care and mobility but have many symptoms, and medical interventions can lead to specific challenges.

The median time of survival and female predominance was similar to the characteristics defined by others (3, 5). A median survival time after feeding tube placement of 7 months was comparable to data of a large prospective cohort study (9). Gastrostomy should be openly and early discussed with PBP patients, but studies show that gastrostomy feeding prevented weight loss in only half of ALS patients, and in those who gained weight, the clinical benefit was unclear (9). Moreover, airway secretion accumulation is a major risk factor and increases the perioperative risk by 2.6 (10). In our view, the decision for gastrostomy feeding should be based on the assessment of quality of life. Caregiver burden due to gastrostomy feeding is not high, as PBP patients remain autonomous for a longer period before paresis of the limbs may limit self-care.

Excessive oral secretion, which frequently worsens after feeding tube placement, is a major burdensome symptom in PBP patients and a challenge to manage. Therefore, symptomatic treatment of this symptom must be attempted before PEG insertion and especially during the healing process. First-line therapies are anticholinergic substances, such as scopolamine or amitriptyline. Alternatively, sublingual application of atropine eye drops or glycopyrrolate can be considered, which is available for subcutaneous or oral application (11). Botulinum toxin A injections into salivary glands is available as second-line therapy for sialorrhea (12).

PBP patients may not tolerate non-invasive ventilation (NIV) as well as ALS patients with limb phenotype, and this has been included in treatment guidelines (12). Only one of our patients tolerated NIV for more than 3–4 h. This may have been due to several aspects: excessive saliva and/or thick mucus is a major issue of distress in this cohort, which often cannot be treated with satisfying results and impairs usage of ventilation masks; muscular weakness of the pharynx leads to constriction mainly in exsufflation which cannot be technically compensated. The risks and complications of NIV should be openly discussed with patients before initiation of NIV to prevent frustration. For clinicians, the anticipation of potential obstacles when initiating NIV in ALS patients is very important in order to ensure that NIV is able to provide effective help and is acceptable to the patient. In addition to optimizing secretion management, Baxter et al. (13) recommend the following when initiating NIV: easily accessible in-person advice, the use of humidifiers and alternative mask interfaces, and discussing the potential benefits of NIV in detail with patients.

In our experience, only very few patients with progressive bulbar palsy decide to undergo tracheostomy if this aspect is discussed as part of ACP in the course of the disease. Only one of our patients underwent tracheostomy and is still, to our knowledge, under mechanical ventilation. This patient, however, has been lost to follow-up and we do not know under which circumstances tracheostomy was performed. She now lives in a specialized respiratory care facility.

Recognizing the end-of-life phase in PBP patients can be challenging, as they often maintain a relatively high functional status with mild to moderate limb paresis. However, PBP patients deteriorate quickly, and to avoid unwanted hospitalizations and to ensure adequate palliative care at the end of life, this phase has to be identified in a timely manner. The implementation of specific triggers predicting the end-of-life phase can help to increase palliative care input and prepare patients and caregivers. Studies to assess the value of triggers for palliative care involvement in neurological patients have shown that the number of triggers increases rapidly in the last 6 months of life (14, 15). Hussein et al. identified key factors that seemed to influence the deterioration of neurological patients in the last 6 months of life in particular: decline in physical function, weight loss and respiratory symptoms, recurrent infections and cognitive impairment, and aspiration

TABLE 2 | Terminal phase of PBP patients.

Patient no.	Place of death	Circumstances of dying	Symptom control in terminal phase
1	ICU	Ventilatory insufficiency, excessive oral secretion. NIV non-efficient due to collapsing pharyngeal muscles, no signs of infection. No invasive ventilation according to patient's will.	Morphine i.v.
2	Palliative care ward	Ventilatory insuffiency and excessive oral secretion	No information
3	ICU	Progressive ventilatory insufficiency, bronchopulmonary infection treated with antibiotics 1 week prior. NIV, no invasive ventilation according to patient's will	Morphine, Midazolam i.v.
4	Hospice care	Ventilatory insufficiency, excessive oral secretion	Morphine p.o.
6	Hospice care	Ventilatory insufficiency and excessive oral secretion	Morphine p.o.
7	ICU	Severe traumatic brain injury after domestic stair fall 1 day before. Invasive ventilation terminated according to patient's will.	No information on medication used
8	Hospice care	Ventilatory insufficiency. Bronchopulmonary infection treated with antibiotics twice (8 and 6 weeks prior to death) on Neurology ward, then transfer to palliative care ward, then transfer to hospice for the last 3 weeks.	Morphine s.c.
9	At home	Ventilatory insufficiency. Bronchopulmonary infection and antibiotic therapy on neurological ward 5 weeks prior to death, then transfer to palliative care ward. Stabilization during the 2 weeks on palliative care ward and decision not to treat further infections with antibiotics. Died 3 weeks after discharge from palliative care ward due to recurrent bronchopulmonary infection.	Morphine s.c.
10	Neurology ward in hospital	Sudden death, 4 days after PEG placement. Possibly due to hypercapnia, NIV not tolerated. 4 months prior first pulmonary infection and NIV initiation	Sudden death
13	Neurology ward in hospital	Severe thick mucus accumulation, bronchopulmonary infection, 4 days of i.v. antibiotics, patient died suddenly probably due to asphyxia	Morphine p.o. against nightly cough attacks

ICU, intensive care unit; i.v., intravenously; p.o., per os.

(15). Triggers that indicate the end-of-life phase in ALS in general have been established by expert consensus and include swallowing problems, recurrent pulmonary infection, marked decline in functional status, cognitive difficulties, weight loss, and significant complex symptoms (2, 16). In PBP, however, some of these symptoms may have been seen earlier in the disease course. In this patient group, rapid decline began in the context of bronchopulmonary infection in at least five patients, and excessive oral secretion could be recognized in all these patients prior to the pneumonia. Therefore, we consider the time of first pulmonary infection to be a crucial point toward the end-of-life phase in patients with PBP, as was seen in early studies (14).

Communication with patients with PBP and their caregivers should take these issues into account, and we wish to emphasize that ACP conversations with patients and families are crucial—as it is with all ALS patients (17). In particular, pseudohypersalivation and associated bronchopulmonary infection as risk factors have to be discussed thoroughly with patients and relatives. The difficulties, or even inability, to communicate verbally as the disease progresses have to be taken into account. In an acute care setting, many patients will not be able to participate in end-of-life discussions to the extent that they would like to. Risks and benefits of life-sustaining interventions, such as emergency intubation, tracheostomy, and gastrostomy tube should be discussed early and regularly.

As we have shown in our patient group, PBP is often associated with a rapid and often not foreseeable decline, and therefore, it can be challenging to care for these patients at his or her own home. Only 1 of the 10 deceased PBP patients died at home, much less than expected according to older data, where ∼50% of German ALS patients died at home (18). Moreover, five patients died in an acute setting on a Neurology ward or ICU. High symptom burden at the end of life and rapid decline seem to be more pronounced in this ALS subgroup. Therefore, this group of patients should be involved in ACP early and remain in frequent contact with specialized nurses and physicians (19). It is important to inform patients and relatives and prepare them for an increase in symptom burden, and there may be effective treatment. Anticipatory prescription of on-demand medication, such as morphine for the treatment of dyspnea (20), and early involvement of palliative care services can avert emergency hospitalization and enable dying at home.

A limitation of our study is the small number of patients, the retrospective design, and incomplete information for some patients. Furthermore, we do not have any pathological or genetic data of our patients.

It is important to recognize that patients with PBP form a subgroup of ALS with distinct features. Due to short survival time and possible impairment of decision-making capacity, early and accurate information of patients and caregivers are highly important. Possible rapid deterioration at the end of life should also be kept in mind as an additional challenge in palliative care.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

SB collected and analyzed patient data and wrote the manuscript. CW, AE-R, KL, PP, and SL participated in discussions on results and reviewed the manuscript. All authors contributed to the article and approved the submitted version.

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The handling editor declared a past co-authorship with one of the authors, SL.

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