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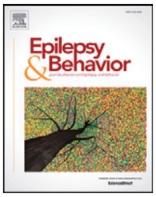

Review

Management of prolonged epileptic seizures and status epilepticus in palliative care patients

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ABSTRACT

Prolonged seizures and status epilepticus (SE) are relevant problems in palliative care. Timely recognition and effective early treatment with first- and second-line antiepileptic drugs (AEDs) may prevent unnecessary hospitalizations. Seizures should be recognized and addressed like any other symptom that causes discomfort or reduces quality of life. Use of alternative AED administration routes (buccal, intranasal, or subcutaneous) may offer possibilities for effective and individualized AED therapy, even during the last days of life. In hospice or home care, however, also intravenous treatment is possible via vascular access devices for long-term use. Aggressive unlimited intensive care unit (ICU) treatment of refractory SE in palliative patients is mostly not indicated. At worst, intensive care can be futile and possibly harmful: death in the ICU is often preceded by long and aggressive treatments. Metastatic cancer, old age, high severity of acute illness, overall frailty, poor functional status before hospital admission, and the presence of severe comorbidities all increase the probability of poor outcome of intensive care. When several of these factors are present, consideration of withholding intensive care may be in the patient's best interests. Anticipated outcomes influence patients' preferences. A majority of patients with a limited life expectancy because of an incurable disease would not want aggressive treatment, if the anticipated outcome was survival but with severe functional impairment. Doctors' perceptions about their patients' wishes are often incorrect, and therefore, advance care planning including seizure management should be done early in the course of the disease.

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1. Background

Status epilepticus (SE) is an abnormally prolonged epileptic seizure that may cause long-term neurologic complications [1]. The International League Against Epilepsy has defined two critical time points during seizure, t_1 and t_2; seizures that continue beyond t_1 are prolonged and seldom cease spontaneously. After t_2, neuronal death or injury may occur [1]. Emergency treatment of SE should be started at t_1, which is at 5 min in tonic–clonic seizures and at 10 min in focal impaired awareness seizures [1]. The recommended first-line treatment is benzodiazepine administration [2]. Other antiepileptic drugs (AEDs) are used intravenously as a second-line treatment.

In refractory SE, the patient is usually treated in the intensive care unit (ICU) with general anesthesia as the third-line treatment [3]. The 1-year mortality in ICU-treated refractory SE is 23%, and an additional 29% show neurologic deficits; however, in the elderly, the mortality rises rapidly to 60–80% [4]. The patient outcome can be improved by facilitating early and effective treatment with AEDs [5]. Early treatment shortens hospital stay and reduces the risk of being admitted to the ICU with refractory SE [6].

The perceived boundaries between active treatment and palliative care in neurology are often not as well-defined as they are for many nonneurologic diseases. Some authors suggest that palliative care in specific neurologic diseases describes the whole process of treatment, whereas others associate the term palliative care only with the end-of-life (EOL) setting. There are several conditions where management of SE should be evaluated from the palliative care perspective. These include not just end-stage cancer, such as primary brain tumors and cerebral metastases, but also other conditions associated with dismal prognosis (e.g., severe ischemic stroke, intracerebral hemorrhage, neurodevelopmental and neurodegenerative diseases, and nonneurological conditions such as terminal liver, kidney, or respiratory failure) [7]. Patients may also suffer from multiple comorbidities simultaneously or from overall frailty [8]. These conditions carry an increased risk for epilepsy and epileptic seizures as well as for SE. It is assumed that the mortality of SE in the palliative care population is higher than

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that in the general population, but apart from the influence of age and comorbidities, as yet there are no data available to support this.

In palliative care as in general care, the management of prolonged seizures should be initiated as early and effectively as possible. In refractory SE, it is especially important to balance the benefit and harm caused by the treatment and critically adapt the usual treatment guidelines accordingly. However, there is increasing tendency to admit patients in the last stages of life to hospitals and ICUs. Death in the ICU is often preceded by long and aggressive treatments [9,10], whereas specific management protocols of SE in palliative care are lacking. In this article, we review the decision-making processes and practical recommendations for the management of SE in palliative care.

2. Process of palliative care

2.1. Definition of palliative care

According to the World Health Organization, palliative care is an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness. Palliative care focuses on the prevention and relief of suffering by means of early identification, assessment, and treatment of pain and other physical, psychosocial, and spiritual problems [11].

Palliative care provides relief from pain and other distressing symptoms with neither the intention to hasten nor postpone death. Palliative care is applicable in the early course of an illness in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy, and it includes those investigations needed to better understand and manage distressing clinical complications.

The key objectives of the treatment of chronic diseases include improving the quality of life by eliminating or alleviating symptoms and extending life expectancy. As the disease progresses, however, it is inevitable that the expected lifetime of the patient becomes limited, and he/she will die, as there is no curative treatment available for the disease. When a serious illness is diagnosed as fatal and there is no possibility for recovery, it is time to move on to EOL care. The duration of EOL care can last from a few days to several weeks. Palliative care is provided along with curative or life-prolonging treatments and extends to the family's bereavement period (Fig. 1). Hospice provides palliative care with a focus on terminally ill patients no longer seeking curative therapies, and it is expected that patients will have 6 months or less to live.

2.2. Advance care planning

Decisions regarding the available therapeutic options should be shared, and care should be planned anticipating situations that will be faced in the final stage of life. This is known as advance care planning (ACP). Advance care planning enables patients to define their preferences and expectations from therapeutic options; it is a process that helps adult patients of any age or any health condition to understand and share their personal values, life objectives, and preferences in terms of future healthcare [13]. Advance directives (ADs) are an essential part of ACP; ADs include the presence of a living will, do-not-resuscitate order, do-not-hospitalize order, medication restriction, or feeding and hydration restriction in the case of future loss of competence. Given the possibility that the patient will become incompetent regarding EOL decision-making in the late stages of their illness, it is important to discuss the subject at a relatively early stage. If the patient has epilepsy, seizure management should always be included in the ACP.

To a certain extent, ADs presume an unrealistic control over the future. It is not possible to fully predict acute exacerbations, making ADs difficult to adopt and sometimes misleading. Patient wishes may also vary over time and according to the different phases of the diseases [14]. Patients change their minds, particularly as illness progresses and especially after experiences in the hospital. For this reason, advance care plans should be reviewed periodically and whenever the patient has a change in health status. Patients can revise their care plan and ADs at any time. A surrogate decision maker should be identified for all patients if possible because loss of decisional capacity is common.

Treatment of seizures in the EOL phase is an essential topic in the context of ACP. Information can be provided on the occurrence and risks of seizures in the EOL phase, which may reduce distress in both patients and caregivers. In addition, alternative methods of administering AEDs can be discussed early in the disease trajectory. This may subsequently lead to better seizure control in the EOL phase and prevention of hospitalization [15].

Advance care planning could facilitate timely and adequate amelioration of symptoms in the EOL phase by discussing possible options in different medical situations. This may in turn result in higher satisfaction with care, better quality of life, and lower levels of anxiety and depression in both patients and their caregivers. Adequate care also may help to decrease caregiver burden, which is high in the EOL phase [16].

2.3. Evaluation of prognosis and medical futility

The word futility is derived from the Latin word *futilis*, meaning leaky or falling out of the desired end through intrinsic defect, and hence, it implies uselessness or worthlessness. In critical care, futility is generally considered as the condition when a patient receives treatment that will have no beneficial effect in terms of both duration and quality of life; there may be a physiological effect, but this will not correspond to benefit for the patient [17]. Futile intensive care has been defined as “interventions that prolong life without achieving an effect that the patient can appreciate as a benefit” [18].

One of the major barriers to the definition and acceptance of medical futility and potentially inappropriate treatments is the medical community's struggle with prognostication. Uncertainty often exists regarding the prognosis that is delivered to patients and their families. Even the best and updated severity-of-illness scores and the associated risk predictions that accurately predict the mean mortality for groups of patients cannot predict with certainty the fate of an individual patient [19]. Therefore, an individual assessment is always mandatory when estimating the usefulness of intensive care.

Nevertheless, it is helpful to be aware of the factors strongly influencing patients' capacity to benefit from intensive care. Factors that are known to be associated with increased mortality of intensive care patients in general are the severity of acute illness, age, overall frailty, functional status before hospital admission, and presence of comorbidities [8,20–23]. The strongest risk factors for increased hospital mortality are heart or liver failure and hematological malignancy [23]. A metastatic cancer strongly increases the probability of death [24]. The length of the preceding hospitalization is associated with prognosis of ICU patients: those admitted to the ICU directly from the emergency department or the operating theater have a substantially better prognosis than those who have already been hospitalized for weeks [23].

In Finnish ICU patients aged 80 years or over, a poor premorbid functional status (defined as need for assistance in activities of daily living or inability to climb stairs) doubled the odds of death within a year [25]. Perhaps surprisingly, living at home instead of in nursing facilities was only weakly associated with survival. A plausible explanation is that even people with poor functional status can live at home with the help of their families or outpatient healthcare systems. Living in institutional care is a factor associated with poor long-term prognosis [26], but living at home does not necessarily mean a good long-term prognosis. Ferrante et al. [27] found that over 50% of elderly patients with critical illness died within 1 month or experienced significant functional decline over the following year, with particularly poor outcomes in those who had high levels of premorbid disability.

A total of four prognostic scores for SE have been proposed to date: the Status Epilepticus Severity Score, the Epidemiology-Based Mortality Score in Status Epilepticus (EMSE), the modified Status Epilepticus Severity Score, and the Encephalitis Nonconvulsive Status Epilepticus

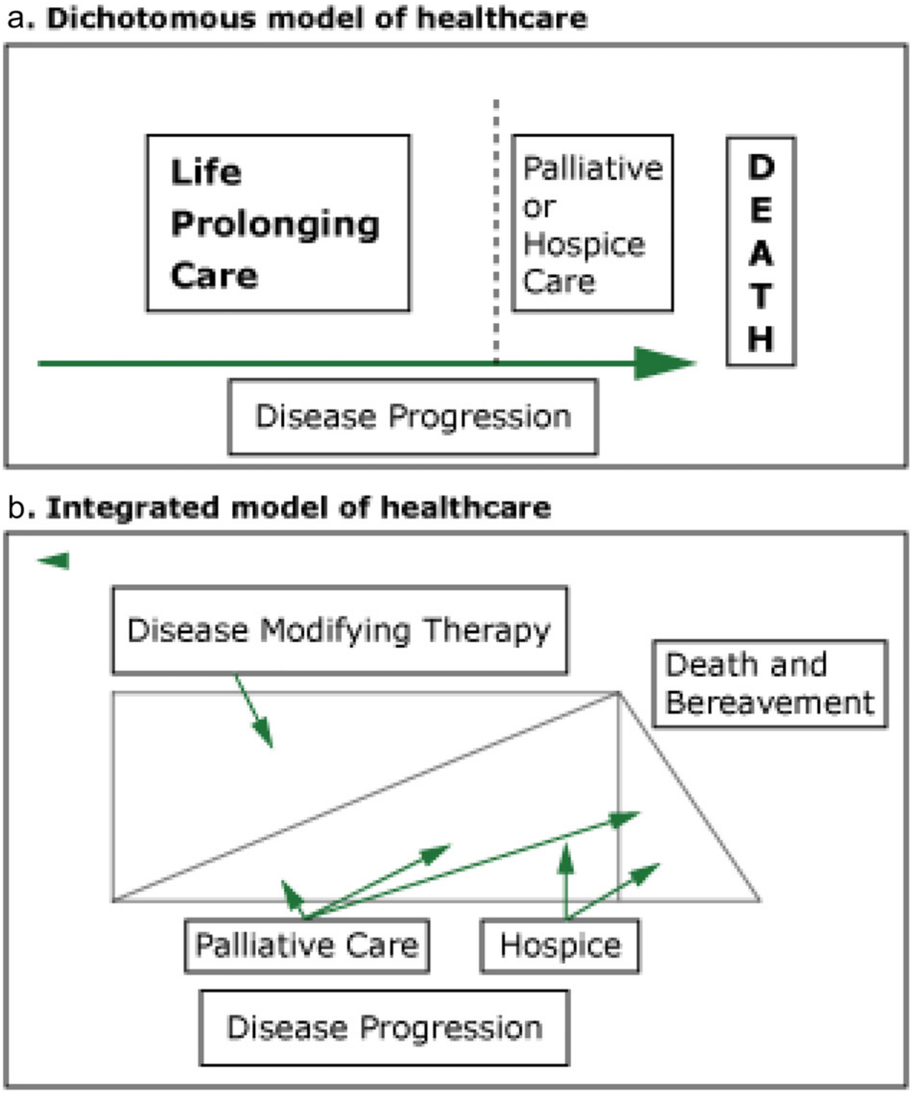

Fig. 1. Models of palliative care. a) The traditional model shows an acute transition from life-prolonging (curative) treatment to hospice care. b) In the revised model, palliative care is already integrated from diagnosis alongside life-prolonging (curative) treatment and becomes increasingly important over time. This trajectory model also includes family bereavement. Adapted from the National Consensus Project for Quality Palliative Care clinical practice guidelines (http://www.nationalconsensusproject.org) [12].

Diazepam Resistance Imaging Tracheal Intubation score. The first three were developed to predict mortality before hospital discharge, and the last one predicts functional outcome 3 months after hospital discharge [28]. Epidemiology-Based Mortality Score in Status Epilepticus, which includes etiology, comorbidity, age, and electroencephalography (EEG) data, also predicts functional outcome in refractory SE [29].

The predominant factor influencing the outcome of SE is the underlying cause/disease [5]. Thus, in patients with advanced disease and a poor prognosis, SE may be a terminal event. In ICU-treated refractory SE, Kantanen et al. [30] showed that the 1-year mortality of the patients was associated with higher age, severity of organ failure, and poorer premorbid functional performance (Fig. 2).

Whether a critically ill patient should or should not be offered life-supporting treatment in the ICU is arguably the most important decision that is regularly made on behalf of a patient; deciding not to admit somebody may mean that their death is inevitable. Admission to the ICU allows critically ill patients access to life-saving treatments, but this care involves invasive, distressing, and possibly harmful interventions.

Given the burden of aggressive treatments in the ICU and the limited prognosis for many critically ill patients, admission to an ICU is not appropriate in all cases. Clinicians must assess whether less invasive care might achieve the same goals, whether the burdens of ICU care outweigh any potential benefits, and if palliative care is in the best interests of the patient. However, determining who will and will not benefit from ICU care is not always easy. Many of the patients considered for ICU admission are too ill to make decisions for themselves, and clinicians must therefore make difficult practical and ethical assessments when discussing with the family about balancing the benefits and burdens of ICU care. Table 1 describes primary criteria for considering the need for a palliative care assessment at the time of admission.

There is no generally accepted process for deciding who should be given care in the ICU. In some situations, later withdrawal of care is considered as preferable to initial withholding of treatments [32]. The idea is to allow the patient a trial of therapy, sometimes referred to as a time-limited trial [33]. Importantly, if it is decided that a trial of therapy should be conducted, time limits and targets for the trial must be set in advance, and if treatment goals are not met by the allocated time, treatment should be withdrawn according to the plan [32]. Good communication with the family is particularly important in this situation to ensure that the purpose of the trial is clearly understood. This highlights the importance of defining the intention of SE treatment and the goals of care with surrogate decision makers early in the patient's presentation [34].

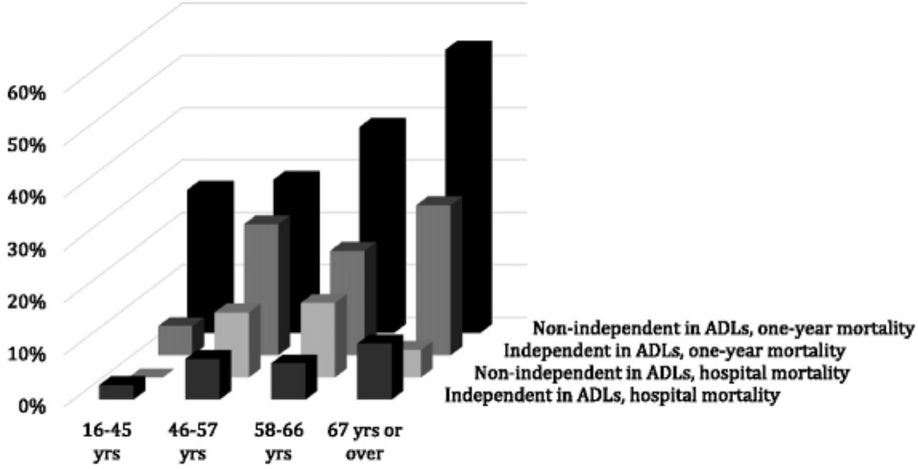

Fig. 2. One-year mortality of patients with ICU-treated refractory SE was associated with higher age and poorer premorbid functional performance. ADL = activities of daily living. Figure adapted with permission from Kantanen et al. [30].

2.4. Patients' preferences

Physicians have traditionally acted paternalistically on behalf of their patients; however, contemporary biomedical ethics recommend that physicians should not take this role alone. Instead, the patients' preferences should be respected. Unfortunately, physicians may not know what their patients want done in the event of serious illness. Hamel et al. [35] studied 4556 adults who had one of several illnesses associated with an average 6-month mortality rate of 50% and who stated a preference about care. For 25% of the patients, physicians stated that they were unaware of the preferences. When the physician had a perception about the patient's wishes, it was incorrect in more than one-third of cases; the physician had a correct understanding of the patient's preferences in only 45% of cases. For 19% of patients, the physician incorrectly believed that the patient wanted care focused on comfort instead of prolonging life, and for 12%, the physician mistakenly believed that the patient wanted care focused on prolonging life. Increased age of the patients increased the probability that physicians would erroneously believe that patients did not want life-extending care.

Whether or not it makes sense to initiate intensive care depends on the outcomes that can and are likely to be achieved. When doctors ask about a patient's preferences, the probability of different outcomes may not always be presented. However, anticipated outcomes do heavily influence these preferences. Fried et al. [36] studied 226 persons aged 60 years or over who had a limited life expectancy because of cancer, congestive heart failure, or chronic obstructive pulmonary disease. The study participants were asked whether they would want to receive a given treatment if the outcome without treatment was specified as death. For a low-burden treatment with the restoration of current health, 99% of respondents would want the treatment. Given the same anticipated outcome, the proportion of respondents who wanted treatment decreased as the burden of treatment (length of hospital stay, amount of testing, and invasiveness of interventions) increased. If the anticipated outcome was survival but with severe cognitive impairment, 89% of the participants would not choose treatment.

Table 1
The primary criteria for considering the need for a palliative care assessment at the time of admission according to Weissman and Meier [31].

A potentially life-limiting or life-threatening condition *and* …
Primary criteria[a]
The “surprise question”: *You would not be surprised if the patient died within 12 months or before adulthood*
Frequent admissions (e.g., more than one admission for the same condition within several months)
Admission prompted by difficult-to-control physical or psychological symptoms (e.g., moderate-to-severe symptom intensity for more than 24 to 48 h)
Complex care requirements (e.g., functional dependency; complex home support for ventilator/antibiotics/feedings)
Decline in function, feeding intolerance, or unintended decline in weight (e.g., failure to thrive)

[a] Primary criteria are global indicators that represent the minimum that hospitals should use to screen patients at risk for unmet palliative care needs.

3. Recognition of epileptic seizures in palliative care

The recognition of epileptic seizures in palliative patients is ideally made at the patient's place of care without hospital admission [8]. Accuracy is best if the clinician is in direct dialog with the eyewitness [14]. Recording of the seizures with smartphone videos while testing the patient in a similar manner as during seizures in video-EEG monitoring units is also a very useful method of providing the relevant data regarding symptoms to the clinician responsible for the diagnosis and treatment decisions. If the patient is hospitalized and especially if more aggressive treatments are planned, EEG, laboratory, and imaging diagnostics should be used to verify diagnosis.

Diagnosing nonconvulsive SE in the palliative care setting can be challenging. If there is no possibility for EEG-based diagnosis, probationary therapy with benzodiazepines is a reasonable approach. While continuous EEG monitoring is a vital tool for SE in the ICU, ongoing EEG monitoring in dying patients who transition to EOL care may engender medical interventions that are not symptom based and therefore unnecessary EEG-monitoring should be avoided [34].

4. Therapy of status epilepticus in palliative care and hospice

4.1. First-line treatment

As in other settings, most of the seizures in palliative patients are self-limiting, and acute administration of AEDs is not indicated after every seizure. After abnormally prolonged seizures (>5 min) or seizure clusters, the first step of treatment is the administration of benzodiazepines. In the out-of-hospital setting, the treatment can start with buccal or intranasal midazolam, or it can start with intramuscular midazolam or rectal diazepam [2]. Nonintravenous benzodiazepines can also be given by family members or by care providers and can be kept at the patient's bedside as the seizure frequency increases towards the EOL [15]. In the hospital setting, intravenous lorazepam or diazepam are the most effective ways to stop early SE [2]. Early start of the effective therapy increases the chance of seizure termination, and therefore, general treatment protocols should be adapted for first- and second-line intravenous SE therapy in the palliative care situation (Table 2).

4.2. Second-line treatment

In established SE (lasting 10–60 min), possible medications include intravenous phenytoin/fosphenytoin, levetiracetam, brivaracetam, lacosamide, or valproate [2] (Table 2). If intravenous use is not possible, there is also some evidence for subcutaneous and rectal use of AEDs. Although these are off-label recommendations, they are valuable options and better than leaving the patient without any treatment.

Seizure management during the EOL phase is often hampered by swallowing difficulties or an impaired consciousness, which eventually occur in most patients during the last days before death [7,34,37]. If patients are not able to swallow oral AEDs, they need alternative administration routes to prevent subtherapeutic AED serum levels.

Phenobarbital, carbamazepine, valproate, lamotrigine, and levetiracetam can be given rectally without the need for dose adjustments [38,39]. Some drugs can be given subcutaneously, including benzodiazepines, phenobarbital, levetiracetam, and lacosamide [40,41]. If levetiracetam is used to prevent seizures when there is no licensed alternative route available, it is recommended to use levetiracetam alone in a syringe driver, not to exceed 2000 mg in one 30 mL syringe driver, and to monitor for site reaction and seizure activity [41].

To continue AED treatment after SE, AEDs may also be given as an oral liquid via a nasogastric or percutaneous endoscopic gastrostomy tube. In hospice or home care, however, intravenous treatment is usually possible via vascular access devices intended for long-term use [42], which is recommended in situations where the patient experiences recurrent or even prolonged seizures. Seizures should be treated with the same level of importance as pain, anxiety, or restlessness in EOL care, and adequate use of intravenous AEDs provides relief to these symptoms better than other alternative routes.

4.3. Treatment of refractory and super-refractory status epilepticus

As a general guideline, refractory SE can be treated with a propofol or midazolam-based 12-hour anesthesia in the ICU [2]. However, aggressive unlimited ICU treatment of super-refractory SE in palliative patients is mostly futile because of the high mortality and morbidity of the condition. Palliative sedation may be considered if no other forms of treatment can be used to make the patient's condition tolerable. Palliative sedation induces a state of decreased awareness by the administration of sedative medications (usually midazolam) to alleviate the symptoms, even if epileptic activity persists or the patient is not in the ICU [43]. For patients at the EOL, palliative sedation is a last-resort measure to alleviate severe symptoms that are refractory to other forms of treatment. It is most commonly utilized for pain, dyspnea, or delirium, but it can also be used for seizures. The intent of palliative sedation is to relieve the burden of otherwise intolerable suffering for terminally ill patients. Midazolam is given subcutaneously (s.c) as a continuous infusion with a syringe pump, 10 mg to 20 mg over 24 h, and additional midazolam is given 5 mg s.c. hourly, as required; then the dose is titrated according to the patient's needs, e.g., to 10 to 60 mg over 24 h [44]. In frail patients, lower doses may be advisable.

Table 2
Protocol for treatment of status epilepticus in palliative care (modified from [2,7]). More options for treatment in the text. IV = intravenous, SC = subcutaneous.

		Hospital	Hospice/home care
Stage 1 5–10 min	**Early phase** Premonitory SE	Lorazepam IV 0.05 mg/kg Repeat if necessary	Midazolam buccal or intranasal 0.2 mg/kg Repeat if necessary
Stage 2 10–60 min	**Established SE**	Phenytoin/fosphenytoin IV Levetiracetam/-brivaracetam IV Valproate IV Lacosamide IV	Levetiracetam SC/IV Lacosamide SC/IV Brivaracetam IV Valproate IV
Stage 3 >60 min	**Refractory SE**	In selected cases one trial of propofol or midazolam Anesthesia at ICU	Consider palliative sedation
Stage 4 >24 h	**Superrefractory SE**	Consider palliative sedation	Consider palliative sedation

5. Conclusion

In summary, prolonged seizures and SE are relevant problems in palliative care. Timely recognition and effective early treatment with first- and second-line AEDs may prevent unnecessary hospitalizations. Seizures should be addressed like any other symptom that causes discomfort or reduces quality of life. Use of alternative AED administration routes may offer possibilities for effective and individualized AED therapy, even during the last days of life. Advance care planning could significantly improve multiple outcomes, including rates of completion of ADs, the likelihood that clinicians and families understand and comply with the patient's wishes, hospitalization at the EOL, use of intensive treatments at the EOL, enrollment in hospice, and the likelihood of dying in the preferred place. The primary goal of care should be the preservation of dignity, minimization of suffering, and restoration of a less medicalized care environment. A multidisciplinary approach involving expertise of palliative care, critical care, and neurology is recommended for dying patients with SE.

List of abbreviations

ACP	advance care planning
ADs	advance directives
AEDs	antiepileptic drugs
EMSE	Epidemiology-Based Mortality Score in Status Epilepticus
EOL	end-of-life
ICU	intensive care unit
SE	status epilepticus

Declaration of interest

RK received grants from the Academy of Finland and the Saastamoinen Foundation; speaker's honoraria from Eisai, UCV, and Orion; and honoraria for the membership of advisory board from Eisai, Fennomedical, GW Pharmaceuticals, Sage Therapeutics, Takeda, and UCB. MR has nothing to declare.

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