Zeitschrift für
Epileptologie

Z. Epileptol. 2022 · 35 (Suppl 2):S117–S122
https://doi.org/10.1007/s10309-022-00544-2
Accepted: 23 November 2022
Published online: 8 December 2022

Therapeutic options for patients with status epilepticus in old age—English version

Laurent M. Willems[1,2] · Felix Rosenow[1,2] · Adam Strzelczyk[1,2]

[1] Universitätsklinikum Frankfurt, Epilepsiezentrum Frankfurt Rhein-Main und Zentrum für Neurologie und Neurochirurgie, Klinik für Neurologie, Goethe Universität Frankfurt, Frankfurt am Main, Germany

[2] LOEWE Center for Personalized Translational Epilepsy Research (CePTER), Goethe-Universität Frankfurt, Frankfurt am Main, Germany

Abstract

Status epilepticus (SE) is a serious acute condition that requires early and targeted treatment. Especially refractory SE (RSE) as well as superrefractory SE (SRSE) are an interdisciplinary therapeutic challenge even in young subjects. In patients of older age, further relevant aspects have to be considered, which result on the one hand from deviating pharmacokinetics and dynamics and on the other hand from comorbidities, polypharmacy and possible medical treatment limitations or patient preferences. The aim of this article is to review these particular aspects in the context of SE care for patients in older age groups and to highlight potential therapeutic strategies beyond the scope of the current national guidelines. In particular, alternative routes of administration and possible conservative forms of escalation of treatment are discussed, which are of special importance in relevantly premorbid patients in whom intensive medical treatment would further increase the already high mortality of SE in old age. With different parenteral administration forms of benzodiazepines in SE as well as the now well-described use of other antiseizure medications, such as brivaracetam, perampanel, stiripentol, topiramate, and zonisamide in RSE and SRSE, adequate therapeutic options are also available for this vulnerable patient group. Nevertheless, increased attention should be paid to patient preferences and medical ethical aspects in the treatment of SE in older age, especially in view of the per se high mortality.

Keywords
Anti-seizure medication · Epilepsy · Seizure · Limitation of therapy · Drugs

Status epilepticus (SE) is a serious acute condition that requires early and targeted treatment. In patients of older age, some relevant aspects need to be considered that result on the one hand from deviating pharmacokinetics and dynamics, and on the other hand from comorbidities, polypharmacy, and possible limitations of medical treatment or patient preferences. The aim of this article is to present these aspects in the context of SE for patients in older age groups and to highlight potential therapeutic strategies.

Epilepsy and status epilepticus in older adults

In patients in older age groups, epilepsy represents statistically the third most common neurological disorder after dementia and stroke, and the definition of the disorder as such, as well as SE and its treatment stages, does not deviate from the generally accepted norms [23]. Thus, even in older age, a seizure lasting more than 5 min or a series of seizures lasting more than 5 min without adequate recovery of consciousness is referred to as SE [24]. The term "epilepsy in older adults" and likewise that of "SE in older adults" is often used for patients with a first manifestation beyond the age of 60 years and thus

The German version of this article can be found under https://doi.org/10.1007/s10309-022-00525-5.

Scan QR code & read article online

differs in its definition from the current definition of the World Health Organization (WHO), which speaks of "elderly patients" or "older adults" from the age of 65 years [9]. However, due to strong interindividual differences in cognition as well as medical and biological aspects, a pure definition of epilepsy or SE by age measured in years of life does not seem to make much sense, which is why we would like to use the term "older age" as a descriptive synonym in the following.

With an incidence of up to 54 per 100,000 people over the age of 60 years—with this figure increasing with age—SE is a common condition that often leads to emergency hospitalization and is associated with a mortality rate of up to 50% [15, 29]. In contrast to young SE patients, in whom this is a rarity, up to one quarter of SE patients beyond 60 years of age develop nonconvulsive SE (NCSE), which is associated with a decrease in vigilance as a leading symptom [14]. Etiologically, SE in older age is predominantly due to structural, neurodegenerative, or systemic causes, such as infections or electrolyte shifts [16]. In general, there is scant evidence for various treatments of SE in older age since larger prospective, randomized, or head-to-head studies are not available. Prospective, randomized study results on the treatment of SE in older age, such as those currently being collected in the German Federal Ministry of Education and Research (BMBF)-funded ToSEE (Treatment of Established Status Epilepticus in the Elderly) study, are currently still lacking [19]. A recent systemic review showed that the functional outcome of established SE in older adults is relevantly worse in the case of a structural or lesional cause compared to a metabolic or infectious etiology, whereas mortality is significantly increased. During hospitalization, complications were more common in older patients, with systemic infections through to sepsis associated with poor outcome, as was the occurrence of renal failure, respiratory insufficiency, and electrolyte disturbances. Similarly, duration of SE of more than 12 h and prolonged intensive care were associated with significantly increased mortality [7, 25]. Also for long-term mortality after SE, age could be identified as an important predictive factor alongside SE duration and semiology and is already applied as a variable in the ACD score (*a*ge at admission, *c*onsciousness level at admission, and *d*uration of SE) in the assessment of clinical prognosis [22].

These findings underscore the fact that rapid treatment escalation according to the current German Neurological Society (DGN) guideline for the treatment of SE in adults with rapid intubation anesthesia, especially in the case of refractory SE (RSE) and super-refractory SE (SRSE), carries high risks for patients of advanced age, and thus other, less invasive treatment options are becoming increasingly important with demographic change [38]. In addition, patients of advanced age present relevant aspects regarding SE therapy due to deviating pharmacokinetics and dynamics, on the one hand, and comorbidities and polypharmacy, on the other. The aim of this article is to present these special features in the care of older patients, to point out relevant risks, and to highlight potential therapeutic strategies.

Special aspects in the treatment of status epilepticus in older age

Pharmacodynamics/kinetics

Aging per se is accompanied by a variety of physiological changes in the body's metabolism that may become apparent in the context of anticonvulsant therapy, particularly due to altered pharmacodynamics and pharmacokinetics. In general, age results in a relative decrease in body fluids with a resulting smaller distribution volume for hydrophilic substances and a relative increase in body fat tissue with a consequent increase in distribution volume, delayed bioavailability, and prolonged half-life of lipophilic substances. While changes in receptor density and sensitivity can lead to a delayed or reduced response, as well as to significant side effects, the pharmacokinetic aspects in particular are highly relevant in the treatment of SE. Here, for example, changes in adsorption, distribution, metabolism, or elimination can lead to inadequately low, but also to toxically high, plasma concentrations. Since both renal and hepatic elimination of xenobiotics decreases with age, it is imperative to monitor renal and hepatic function before starting these drugs as well as during SE treatment and to adjust dosages accordingly if necessary [5].

Comorbidities

Existing comorbidities also often significantly limit the available treatment options in patients with SE in older age when treated according to the guideline. In patients with known liver cirrhosis or severe liver injury, treatment with valproate is formally contraindicated due to the risk of hyperammonemia [17]. In addition, when carbapenems—especially meropenem or ertapenem, as well as to a lesser extent imipenem or doripenem—are taken in the recent history, treatment with valproate is not promising due to various pharmacodynamic and pharmacokinetic mechanisms leading to low, usually subtherapeutic serum levels [18]. For patients with severe cardiac disease, treatment with phenytoin and phenobarbital poses a high risk due to the bradycardic and antihypertensive properties of these drugs, and lacosamide is contraindicated in patients with severe cardiac disease, especially those with higher-grade atrioventricular (AV) block due to the risk of AV block °III [35]. The dose of levetiracetam, although excreted purely renally and not subject to relevant hepatic metabolism, needs to be reduced in the case of renal insufficiency and may cause delirium [10].

Treatment limitations

Over the past few decades, there has been a noticeable increase in the number of patients dealing with their illnesses and their state of health as part of shared decision-making and initiatives to become informed and responsible patients. The number of patients who think about their further treatment and its limits and record this in a living will or through healthcare proxies has also significantly increased recently, which generally also has an impact on the treatment of SE in older age. Fortunately, various oral or parenteral treatment options are now available to patients no longer wishing to receive intensive medical or invasive care. Nevertheless, especially in RSE and SRSE, the question of the ethical justifiability of invasive treatment proce-

Table 1 Guideline-based stepwise treatment of status epilepticus in adults

Stage	Classification	Active ingredient	Initial dosage	Note/repeated administrations
I	Impending status epilepticus	Lorazepam i.v.	0.1 mg/kg	Max. 4 mg/bolus[a]
		Diazepam i.v.	0.15–0.2 mg/kg	Max. 10 mg/bolus[a,b]
		Clonazepam i.v.	0.015 mg/kg	Max. 2 mg and 1 mg/bolus[a]
		Midazolam i.v.	0.2 mg/kg	Max. 10 mg/bolus[a,c,d]
II	Established status epilepticus	Levetiracetam i.v.	60 mg/kg	Max. 4500 mg in 10 min
		Valproate i.v.	40 mg/kg	Max. 3000 mg, max. 10 mg/kg/min
		Fosphenytoin i.v.	20 mg/kg	Max. 150 mg/min[d]
		Phenytoin i.v.	20 mg/kg	Max. 50 mg/min
		Phenobarbital i.v.	15–20 mg/kg	Max. 100 mg/min
		Lacosamide i.v.	5 mg/kg	Over 15–30 min
R	Refractory status epilepticus (RSE)	Midazolam i.v.	Bolus 0.2 mg/kg	Maintenance dose 0.1–0.5 mg/kg/h[e]
		Propofol i.v.	Bolus 2 mg/kg	Maintenance dose 4–10 mg/kg/h[e]
		Thiopental i.v.	Bolus 5 mg/kg	Maintenance dose according to symptoms[e]
IV	Super-refractory status epilepticus (SRSE)	Thiopental anesthesia Ketamine anesthesia Volatile anesthesia IV steroid pulse Plasmapheresis/immunoadsorption IV immunoglobulins	–	–

Modified from Rosenow et al. 2020 [24]
[a]If necessary, repeat once after 5 min
[b]If i.v. access is not available or cannot be established, rectal administration possible
[b]If i.v. access is not available or cannot be established, intranasal or buccal administration possible
[c]For body weights < 40 mg max. 5 mg/bolus
[d]Currently not available in Germany, Austria, or Switzerland
[e]Over at least 24 h, dose control according to EEG findings

Table 2 Alternative routes of administration and dosage of benzodiazepines in the acute treatment of status epilepticus

Substance	Route of administration	Initial dose	Maximum dose	Half-life
Midazolam	Buccal Intranasal (i.n.) via MAD	10 mg 5 mg	20 mg 20 mg	3–4 h
Lorazepam	Sublingual (s. l.)	1–2.5 mg	5 mg	12–16 h
Clonazepam	Oral p.o. via NGS	0.5 mg	3 mg	30–40 h
Diazepam	Rectal as rectiole/enema Intranasal (i.n.) via MAD	10 mg 10 mg	20 mg 20 mg	20–100 h

Modified from Schubert-Bast et al. 2019 [28]
MAD mucosal atomization device/nasal atomizer, *NGS* nasogastric probe

dures is a central aspect in determining the therapeutic concept [38].

Practical consequences for routine treatment

According to the current DGN guideline on the treatment of SE in adults, treatment in older age should also be based on the now established stepwise concept. This concept distinguishes early SE, established SE, RSE, and SRSE, depending on the response to drug therapy, and is shown in **Table 1** [24]. In the following, specific aspects related to patients in older age are discussed for each treatment level and their evidence—if available—is presented.

Basic treatment

Even in patients in older age, the administration of benzodiazepines represents the basic treatment of any SE. Contrary to the general therapeutic recommendation "start low, go slow" in geriatric patients, an adequate, sufficiently high dosage of first-line therapy should always be observed in the treatment of SE, since a dosage that is too low can promote a refractory course. An evaluation of the ESETT study (Established Status Epilepticus Treatment Trial) showed that diazepam, midazolam, and lorazepam were not dosed according to guidelines in a considerable proportion of the benzodiazepine administrations studied. While only about 20% of patients were underdosed with diazepam, the rate of incorrect dosing was significantly higher for lorazepam and midazolam at approximately 80% and 90%, respectively [26]. User concern about respiratory deterioration was discussed as one of the main reasons for this [27]. However, especially for patients with preexisting respiratory diseases such as chronic obstructive pulmonary disease (COPD) or obstructive sleep apnea syndrome, the administration of benzodiazepines seems to lead to relevant respiratory depression, meaning that deviation from the recommended dosages may be necessary in such cases [36, 37]. According to the literature, however, the administration of benzodiazepines is safe per se [8], especially since the risk of secondary cardiopulmonary deterioration appears to be significantly higher with placebo compared to adequate benzodiazepine therapy [2]. In any event, continuous cardiopulmonary monitoring should be ensured in order to detect and address cardiac and respiratory problems at an early stage [24]. In the palliative setting or in patients with treatment limitations in terms of i.v. medication, benzodiazepines can be administered via

Table 3 Alternatives to drug escalation for refractory or super-refractory status epilepticus

Substance	Mechanism of action	Initial dose	Maximum dose	Dosage interval	Dosage forms
Brivaracetam[a]	SV2A ligand	100–200 mg	200 mg/day	–10–10	i.v., p.o. (tablet, oral solution)
Perampanel[a]	Antagonist at the AMPA receptor	8–12 mg	12 mg/day	–00–01	p.o. (tablet, suspension)
Stiripentol[a]	Modulator at the $GABA_A$ receptor	2000–3000 mg	4000 mg/day	–10–10	p.o. (tablet, suspension)
Topiramate[a]	Na channel blocker, antagonist at the AMPA receptor, modulator at the $GABA_A$ receptor	400 mg	400 mg/day	–10–10	p.o. (tablet, suspendable)
Zonisamide[a]	Na channel blocker, Ca channel blocker	300 mg	600 mg/day	–10–10	p.o. (tablet, suspension)

In alphabetical order, modified from Willems et al. 2020 [38]
[a]Not approved for the treatment of status epilepticus in adults (individual off-label use)

alternative routes. Buccal midazolam, rectal diazepam, or intranasal midazolam or diazepam by means of a MAD (mucosal administration device) nebulizer has proven effective in clinical and preclinical applications [13]. For midazolam, there is also the option of subcutaneous administration [4, 20]. An overview of the different routes of administration of benzodiazepines as well as their dosage is shown in **Table 2**.

Established status epilepticus

If treatment is unsuccessful after potentially repeated administration of benzodiazepines, intravenous anticonvulsants are used in accordance with the current guidelines (**Table 1**; [24]). Due to the lack of interaction with other drugs, good tolerability, and lack of hepatic metabolism, the SV2A ligand levetiracetam has become established in escalation therapy of SE recently. Due to the circulation-depressing effects of phenytoin and phenobarbital, the administration of which also requires central venous access, these drugs are increasingly receding into the background as therapeutic options in the treatment of SE in general as well as in older age. Moreover, induction of the hepatic cytochrome P450 system with relevant effects on potential other drugs diminishes the use of these agents in patients with preexisting polypharmacy. Valproate has a high potential for interaction, particularly in the case of polypharmacy, again due to marked interaction with the hepatic cytochrome system, especially the P450 enzymes, CYP4B1, CYP2C9, CYP2A6, CYP2B6, CYP2C19, and UDP-glucuronyltransferase. Treatment with carbapenems such as meropenem or ertapenem, and to a lesser extent imipenem or doripenem, results in a dramatic decrease or lack of increase in serum valproate levels due to various pharmacokinetic and pharmacodynamic mechanisms. Contrary to the common assumption that this interaction is due to an increased hepatic metabolization of valproate by P450 enzymes, the cause of the drop in valproate levels is multifactorial and can by no means be explained by the hepatic cytochrome system alone. Causes include inhibition of intestinal absorption of valproate, reduced bacterial hydrolysis of glucuronidated valproate due to a carbapenem-induced reduction of the intestinal microbiome, inhibition of the erythrocytic multidrug resistance receptor 1 (MDR-1) with subsequently increased intracellular storage of valproate, as well as direct inhibition of glucuronyl hydrolase and increased conversion of the glucuronidated form into free valproate [18, 34]. Levetiracetam can be rapidly administered as a short infusion, and dose adjustment to renal function is necessary when creatinine clearance is below 80 ml/min/1.73 m^2 (see product information). Currently, the multicenter ToSEE study underway in Germany is directly comparing the efficacy and safety of valproate and levetiracetam in patients of older age [19]. The SV2A ligand brivaracetam, which can be administered as a bolus, also appears to be safe and effective in SE therapy [1, 30, 31, 39]. Lacosamide is mentioned as another sodium channel blocker in the current SE guideline as an alternative; however, especially in patients with higher-grade AV block or severe heart disease, there is also a relative contraindication [24]. Nonetheless, lacosamide is increasingly used in modern SE treatment due to its rapid titratability compared to phenytoin and phenobarbital [3, 32, 33].

Even in established SE, other enteral or parenteral administration of anticonvulsants may be used as part of a palliative treatment concept or when limiting the desired therapies. For levetiracetam, there is evidence from single-case reports for subcutaneous administration [6, 21]; levetiracetam, lacosamide, valproate, and perampanel are also available as oral solutions and can be administered via nasogastric or percutaneous gastric tube [38]. Off-label treatment with other oral anticonvulsants should also be considered, particularly in patients who do not wish to be treated in an intensive care setting or in whom such treatment is not justifiable from a medical ethical point of view, even if this is unlikely to achieve rapid breakthrough of SE. The evidence for oral therapies in SE has recently been investigated in a systematic review; the levels of evidence, routes of administration, and the respective starting and maintenance doses are presented in **Table 3** [38]. Brivaracetam can be used, which also binds to the presynaptic SV2A receptor and has shown a treatment response in 27–54% of patients in studies. Comparably good responses have also been shown for perampanel in 16–100% of cases in case reports or retrospective analyses [38, 39]. There is less evidence for the use of the $GABA_A$ receptor modulator stiripentol, which is only approved as an add-on treatment in Dravet syndrome; in the three studies published to date, a treatment response was observed in 60–100% of patients [38]. The therapeutic benefit of topiramate, which mediates its effect by modulating sodium channels as well as AMPA and $GABA_A$ receptors, has been demonstrated in retrospective and prospective studies, with response rates ranging from 16 to 100%. For zonisamide,

data are available from a retrospective study showing a therapeutic effect in 16% of cases [38]. The evidence for a steroid pulse, the administration of magnesium, or the use of a ketogenic diet cannot be generally recommended based on the respective evidence, but should be weighed up and evaluated on an individual basis [24, 38].

Refractory and super-refractory status epilepticus

If initial treatment with benzodiazepines fails and there is no response to level 2 anticonvulsants, analgesia with the aim of EEG seizure suppression or a burst-suppression pattern should be attempted for at least 24 h in the case of RSE according to the guideline. In line with the current guideline, midazolam or propofol should be used in the first instance, with the maintenance dose depending on the individual EEG response and cardiopulmonary stability [24]. If seizure activity cannot be interrupted or recurs after discontinuation of sedation, the patient has SRSE, for which there are no evidence-based treatment recommendations, but there are reports on the use of volatile anesthesia with isoflurane or thiopental or ketamine [24]. Furthermore, a ketogenic diet or steroid pulse may be considered in individual cases. A large Finnish registry study showed that mortality in RSE and SRSE correlates with age as well as with poor previous condition. Therefore, in RSE patients of older age, one must carefully consider in each individual case whether and, if so, in what way intensive medical therapy with anesthesia and artificial ventilation is reasonable and compatible with the presumed will of the patient [12]. In addition to the escalation levels in RSE already mentioned in the section "Established status epilepticus" (◘ **Table 2**), there are individual case reports on the use of oral ketamine without intubation anesthesia in NCSE, which, however, is currently not available in oral form in Germany [40]. Thus, as with the use of ketamine in RSE in children, which is established in some centers, its administration in patients of advanced age would also be conceivable [11].

Practical conclusion

In summary, the pharmacotherapy of SE in patients of older age is a challenge since, in addition to individual factors such as prior medication, preexisting disorders, and general condition, the verbally communicated or written will regarding treatment restrictions increasingly limits the choice of therapy. Therefore, it is necessary in many cases to deviate from the guideline-based treatment and resort to alternative medications, therapeutic approaches, or routes of administration. Fortunately, different options can be used in this context, albeit with low evidence, that enable adequate treatment of SE in almost all escalation stages, including in multimorbid or treatment-limited patients of advanced age. Despite these options, patient-centered care with advancing age should be the focus of treatment, especially in view of the high mortality for RSE and SRSE in this particular patient population.

Corresponding address

Laurent M. Willems
Universitätsklinikum Frankfurt, Epilepsiezentrum Frankfurt Rhein-Main und Zentrum für Neurologie und Neurochirurgie, Klinik für Neurologie, Goethe Universität Frankfurt
Schleusenweg 2–16, 60528 Frankfurt am Main, Germany
laurent.willems@kgu.de

Declarations

Conflict of interest. L.M. Willems declares that there were no conflicts of interest in the preparation of the article as defined by the recommendations of the International Committee of Medical Journal Editors. F. Rosenow discloses honoraria from Arvelle Therapeutics, Eisai GmbH, GW Pharmaceuticals, UCB medical. He has also received or is receiving research funding from the DFG, BMBF, EU, as well as the Hessian Ministries of Science and of Arts and of Social Affairs and Integration. A. Strzelczyk discloses honoraria or research support from Arvelle Therapeutics/Angelini Pharma, Desitin Arzneimittel, Eisai, GW (Jazz) Pharmaceuticals, Marinus Pharmaceuticals, Precisis, UCB, UNEEG medical, and Zogenix.

No studies on humans or animals were conducted by the author for this article. For the studies listed, the ethical guidelines stated therein apply in each case.

The supplement containing this article is not sponsored by industry.

References

1. Aicua-Rapun I, Andre P, Rossetti AO et al (2019) Intravenous brivaracetam in status epilepticus: correlation between loading dose, plasma levels and clinical response. Epilepsy Res 149:88–91
2. Alldredge BK, Gelb AM, Isaacs SM et al (2001) A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus. N Engl J Med 345:631–637
3. Bauer S, Willems LM, Paule E et al (2017) The efficacy of lacosamide as monotherapy and adjunctive therapy in focal epilepsy and its use in status epilepticus: clinical trial evidence and experience. Ther Adv Neurol Disord 10:103–126
4. Bennett J, Nichols F, Rosenblum M et al (1998) Subcutaneous administration of midazolam: a comparison of the bioject jet injector with the conventional syringe and needle. J Oral Maxillofac Surg 56:1249–1254
5. Borchelt M (2005) Important aspects of geriatric pharmacotherapy. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 48:593–598
6. Feddersen B, Remi J, Noachtar S et al (2017) Epileptische Anfälle und Status epilepticus bei Palliativpatienten. DNP 18:50–59
7. Guterman EL, Betjemann JP, Aimetti A et al (2021) Association between treatment progression, disease refractoriness, and burden of illness among hospitalized patients with status epilepticus. JAMA Neurol 78:588–595
8. Guterman EL, Sanford JK, Betjemann JP et al (2020) Prehospital midazolam use and outcomes among patients with out-of-hospital status epilepticus. Neurology 95:e3203–e3212
9. Hochbaum M, Kienitz R, Rosenow F et al (2022) Trends in antiseizure medication prescription patterns among all adults, women, and older adults with epilepsy: a German longitudinal analysis from 2008 to 2020. Epilepsy Behav 130:108666. https://doi.org/10.1016/j.yebeh.2022.108666
10. Hwang ES, Siemianowski LA, Sen S et al (2014) Levetiracetam: an unusual cause of delirium. Am J Ther 21:e225–228
11. Ilvento L, Rosati A, Marini C et al (2015) Ketamine in refractory convulsive status epilepticus in children avoids endotracheal intubation. Epilepsy Behav 49:343–346
12. Kantanen AM, Kalviainen R, Parviainen I et al (2017) Predictors of hospital and one-year mortality in intensive care patients with refractory status epilepticus: a population-based study. Crit Care 21:71
13. Kay L, Merkel N, von Blomberg A et al (2019) Intranasal midazolam as first-line inhospital treatment for status epilepticus: a pharmaco-EEG cohort study. Ann Clin Transl Neurol 6:2413–2425
14. Knake S, Rosenow F, Vescovi M et al (2001) Incidence of status epilepticus in adults in Germany: a prospective, population-based study. Epilepsia 42:714–718
15. Kortland LM, Alfter A, Bahr O et al (2016) Costs and cost-driving factors for acute treatment of adults with status epilepticus: a multicenter cohort study from Germany. Epilepsia 57:2056–2066
16. Leppik IE (2018) Status epilepticus in the elderly. Epilepsia 59(2):140–143
17. Lind J, Nordlund P (2019) Intravenous use of valproic acid in status epilepticus is associated with high risk of hyperammonemia. Seizure 69:20–24
18. Mancl EE, Gidal BE (2009) The effect of carbapenem antibiotics on plasma concentrations of valproic acid. Ann Pharmacother 43:2082–2087
19. Muller A, Schmiedeknecht A, Mende M et al (2020) Treatment of established status epilepticus in the elderly—a study protocol for a prospective multicenter double-blind comparative effectiveness trial (ToSEE). BMC Neurol 20:438

20. Pecking M, Montestruc F, Marquet P et al (2002) Absolute bioavailability of midazolam after subcutaneous administration to healthy volunteers. Br J Clin Pharmacol 54:357–362
21. Remi C, Lorenzl S, Vyhnalek B et al (2014) Continuous subcutaneous use of levetiracetam: a retrospective review of tolerability and clinical effects. J Pain Palliat Care Pharmacother 28:371–377
22. Roberg LE, Monsson O, Kristensen SB et al (2022) Prediction of long-term survival after status epilepticus using the ACD score. JAMA Neurol 79:604–613
23. Rohracher A, Trinka E (2021) Epilepsy in the aged : challenges in diagnostics and treatment. Z Gerontol Geriatr 54:395–408
24. Rosenow F, Weber J (2020) Status epilepticus im Erwachsenenalter, S2k-Leitlinie. In: Deutsche Gesellschaft für Neurologie (ed) Leitlinien für Diagnostik und Therapie in der Neurologie. Thieme, Stuttgart
25. Sadeghi M, Eshraghi M, Akers KG et al (2020) Outcomes of status epilepticus and their predictors in the elderly—a systematic review. Seizure 81:210–221
26. Sathe AG, Tillman H, Coles LD et al (2019) Underdosing of benzodiazepines in patients with status epilepticus enrolled in established status epilepticus treatment trial. Acad Emerg Med 26:940–943
27. Sathe AG, Underwood E, Coles LD et al (2021) Patterns of benzodiazepine underdosing in the established status epilepticus treatment trial. Epilepsia 62:795–806
28. Schubert-Bast S, Strzelczyk A (2019) Therapie des akuten konvulsiven Anfalls und Status epilepticus im Kindesalter. Z Epileptol 32:116–125
29. Strzelczyk A, Ansorge S, Hapfelmeier J et al (2017) Costs, length of stay, and mortality of super-refractory status epilepticus: a population-based study from Germany. Epilepsia 58:1533–1541
30. Strzelczyk A, Klein KM, Willems LM et al (2016) Brivaracetam in the treatment of focal and idiopathic generalized epilepsies and of status epilepticus. Expert Rev Clin Pharmacol 9:637–645
31. Strzelczyk A, Steinig I, Willems LM et al (2017) Treatment of refractory and super-refractory status epilepticus with brivaracetam: a cohort study from two German university hospitals. Epilepsy Behav 70:177–181
32. Strzelczyk A, Zollner JP, Willems LM et al (2017) Lacosamide in status epilepticus: systematic review of current evidence. Epilepsia 58:933–950
33. Sutter R, Marsch S, Ruegg S (2013) Safety and efficacy of intravenous lacosamide for adjunctive treatment of refractory status epilepticus: a comparative cohort study. CNS Drugs 27:321–329
34. Sutter R, Ruegg S, Tschudin-Sutter S (2015) Seizures as adverse events of antibiotic drugs: a systematic review. Neurology 85:1332–1341
35. Trinka E, Hofler J, Leitinger M et al (2015) Pharmacotherapy for status epilepticus. Drugs 75:1499–1521
36. Vozoris NT (2014) Do benzodiazepines contribute to respiratory problems? Expert Rev Respir Med 8:661–663
37. Wang SH, Chen WS, Tang SE et al (2018) Benzodiazepines associated with acute respiratory failure in patients with obstructive sleep apnea. Front Pharmacol 9:1513
38. Willems LM, Bauer S, Jahnke K et al (2020) Therapeutic options for patients with refractory status epilepticus in palliative settings or with a limitation of life-sustaining therapies: a systematic review. CNS Drugs 34:801–826
39. Willems LM, Bauer S, Rosenow F et al (2019) Recent advances in the pharmacotherapy of epilepsy: brivaracetam and perampanel as broad-spectrum antiseizure drugs for the treatment of epilepsies and status epilepticus. Expert Opin Pharmacother 20:1755–1765
40. Yeh PS, Shen HN, Chen TY (2011) Oral ketamine controlled refractory nonconvulsive status epilepticus in an elderly patient. Seizure 20:723–726