Journal of
Clinical Medicine

MDPI

Review

Managing Status Epilepticus in the Older Adult

Stephane Legriel [1,2,*] and Gretchen M. Brophy [3]

1 Medico-Surgical Intensive Care Department, Centre Hospitalier de Versailles—Site André Mignot, 177 Rue de Versailles, 78150 Le Chesnay Cedex, France
2 INSERM U970, Paris Cardiovascular Research Center, 75015 Paris, France
3 Virginia Commonwealth University, Medical College of Virginia Campus, 410 N. 12th Street, Richmond, VA 23298-0533, USA; gbrophy@vcu.edu
* Correspondence: slegriel@ch-versailles.fr; Tel.: +33-139-638-839

Academic Editor: Jane Grant-Kels
Received: 10 March 2016; Accepted: 9 May 2016; Published: 11 May 2016

Abstract: The aim of this systematic review was to describe particularities in epidemiology, outcome, and management modalities in the older adult population with status epilepticus. There is a higher incidence of status epilepticus in the older adult population, and it commonly has a nonconvulsive presentation. Diagnosis in this population may be difficult and requires an unrestricted use of EEG. Short and long term associated-mortality are high, and age over 60 years is an independent factor associated with poor outcome. Stroke (acute or remote symptomatic), miscellaneous metabolic causes, dementia, infections hypoxemia, and brain injury are among the main causes of status epilepticus occurrence in this age category. The use of anticonvulsive agents can be problematic as well. Thus, it is important to take into account the specific aspects related to the pharmacokinetic and pharmacodynamic changes in older critically-ill adults. Beyond these precautions, the management may be identical to that of the younger adult, including prompt initiation of symptomatic and anticonvulsant therapies, and a broad and thorough etiological investigation. Such management strategies may improve the vital and functional prognosis of these patients, while maintaining a high overall quality of care.

Keywords: status epilepticus; anticonvulsant; elderly; older adult; adverse effects

1. Introduction

Status epilepticus (SE) is a major medical condition that is fatal in about 20% of cases [1]. The incidence per 100,000 population has been estimated at 9.9 episodes in Europe and 41 episodes in the US [2]. The aging population and comorbidities associated with this age class make management strategies for SE increasingly important. Unfortunately, these patients received relatively little attention. The aim of this systematic review is to bring a higher awareness to the important aspects of epidemiology, management modalities, and outcome in the older adult population with SE.

2. Materials and Methods

Data reporting in this systematic review of SE in the older adult population is in accordance with the recommendations included in the PRISMA statement. Accordingly, the review question was formulated to respond to the following points of the PICO template: "In older adult patients who experience SE (P), are there any important aspects of epidemiology or management modalities (I), as compared with younger adult population (C), that may explain SE occurrence and outcome (O)?" Given the question being addressed, the retained eligible study designs were randomized and observational, controlled trials of older adult patients with SE.

2.1. Definitions

Status epilepticus was defined according to the the "Guidelines for the evaluation and management of status epilepticus", from the Status Epilepticus Neurocritical Care Society Guideline Writing Committee, as an ongoing clinical and/or electroencephalographic seizure activity lasting at least 5 min, or repeating seizure activity without recovery (return to baseline) between attacks [3]. There is a high variability of definitions of the older adult population across the world; therefore, we used the definition of the World Health Organization definition based on age and distinguishing young-old (65 to 74 years old), middle-old (75–84 years old), and oldest-old (over 85 years old) [4].

2.2. Eligibility Criteria

This review focuses on studies describing and evaluating three types of outcome predictors: epidemiological characteristics, management modalities, and clinical outcomes. Since we were interested in describing particularities of SE occurrence in the older adult populstion and determine outcomes in this population, two types of comparators were used: (1) patients with SE under and ⩾65 years of age, and survivors and non-survivors in the older adult (⩾65 years of age) SE population.

All studies including older adult (⩾65 years) patients who experienced SE were considered for inclusion. Patients with postanoxic SE were excluded from the review process. Prognostic studies in which the neurological outcome was described using either of the following scores, Glasgow Outcomes Scale (GOS) or the modified Rankin Scale (mRS), were included in the review. A favorable outcome was defined as a GOS score of 4 or 5, or a mRS score of 1 to 3. Outcome studies were included if the patients were assessed at hospital discharge, or greater than or equal to three months after discharge, when available.

2.3. Search Strategy

We searched MEDLINE via PUBMED using the following terms: "status epilepticus [MeSH Terms]" and "Aged [MeSH Terms]" or "elderly" or "older". In order to maintain an updated search strategy, we activated an automatic PUBMED alert system from the first article selection to the last search round performed on 18 October 2015. To ensure that all potentially relevant articles were included, the reference lists of relevant review articles and articles selected for inclusion in this review were searched manually for other potential studies.

2.4. Study Selection and Data Extraction

Randomized and observational, controlled trials of adults 65 years of age or older with SE on indexed journals were included. There were no language or date restrictions for the published literature included in this review. Studies were selected and screened by titles and abstracts to identify studies reporting any of the selected interventions and outcomes of focus. Data extraction was performed using a dedicated form. The following data were extracted for each study: first author, publication year, study design, sample size, and primary and secondary outcomes including timing of evaluation.

3. Results and Discussion

Figure 1 is the flow chart of the study selection process. The literature search strategy identified 2259 records from PUBMED. Fifteen additional records were identified through forward search for a total of 2274 records screened. After title and abstract evaluation, 37 articles were considered for full-text analysis. Among them, 21 were excluded because they did not fulfil our inclusion criteria. The remaining 16 articles were considered eligible for this review.

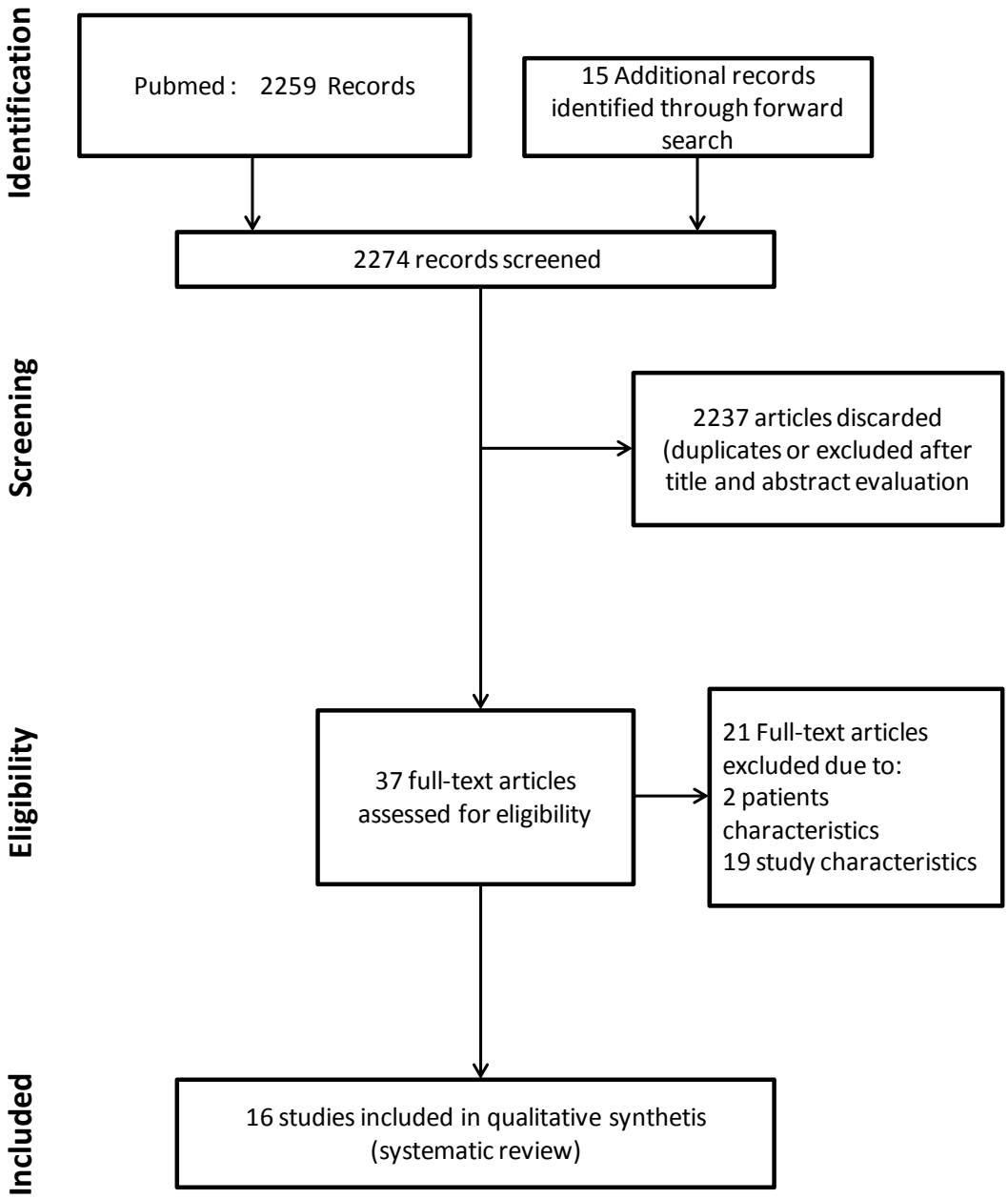

Figure 1. Flow chart of the study selection process.

3.1. What Is the Epidemiology of Status Epilepticus in the Older Adults?

3.1.1. Incidence

The WHO definition of older adults based on age seems to be particularly adapted to the context of epilepsy. A straightforward increase in incidence is effectively noted for every 5 years beyond 60 years old in this pathology [5–7]. The various epidemiological studies performed in populations of North American or European patients with SE report a similar trend, with a cut off after 60 years (Figure 2). Thus, mean annual incidence rate can be estimated to 15.5/100,000 in patients between 60–69 years old, 21.5/100,000 in patients between 70–79 years old, and 25.9/100,000 in patients over 80 years old [8–10].

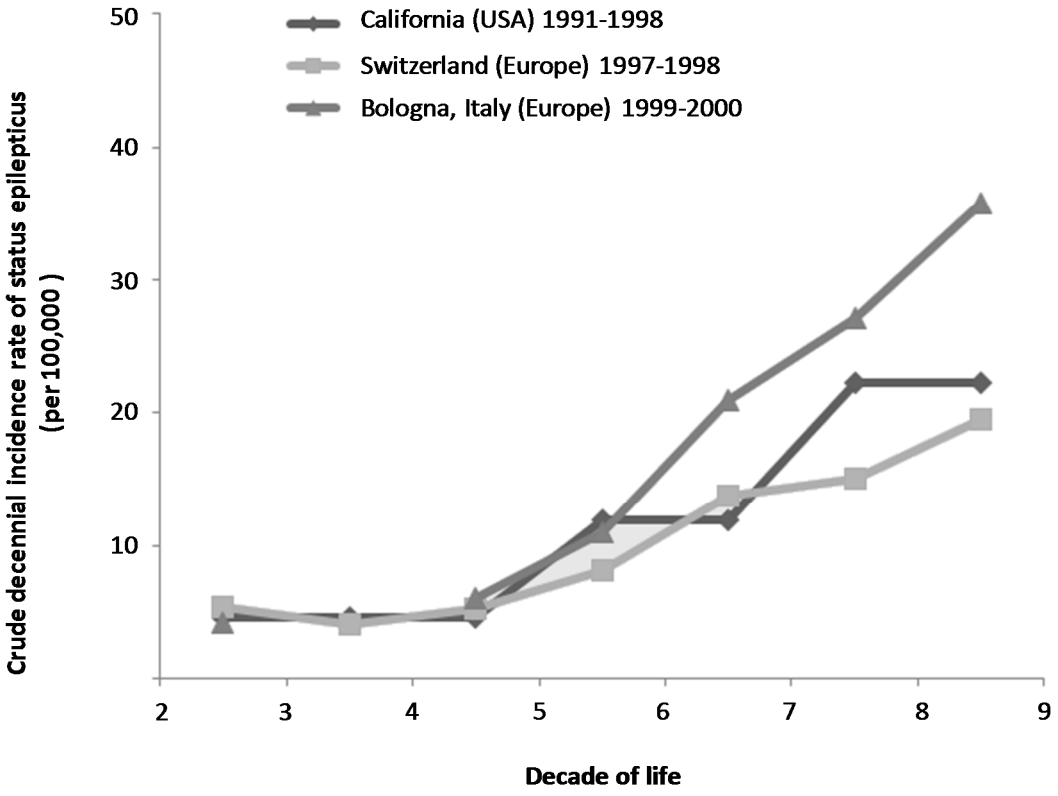

Figure 2. Age-specific crude decennial incidence in patients with status epilepticus in North America and Europe.

3.1.2. Classification

The most widely accepted classification of SE is a pragmatic and operational scheme distinguishing between convulsive status epilepticus (CSE), which is usually easy to recognize on clinical grounds, and nonconvulsive status epilepticus (NCSE), in which the behavioral and/or cognitive changes persist as compared to baseline and where EEG confirmation is mandatory [11]. Subgroups are described within each of these two main categories. Figure 3 illustrates the various subgroups categories as described by the recent report of the ILAE Task Force on Classification of Status Epilepticus [12].

In the older adult population, there is an over-representation of complex partial NCSE [13,14]. In a study involving 63 patients over 70 years of age hospitalized in geriatric medicine for SE, Canouï-Poitrine *et al.* [13] identified 83% of complex partial NCSE, while the remaining 17% patients demonstrated CSE immediately or secondarily generalized SE. The cerebral distribution complex partial NCSE were as follow: fronto-temporal in 74%, temporal in 13%, and frontal and occipital 9% in 4% of cases, respectively [13].

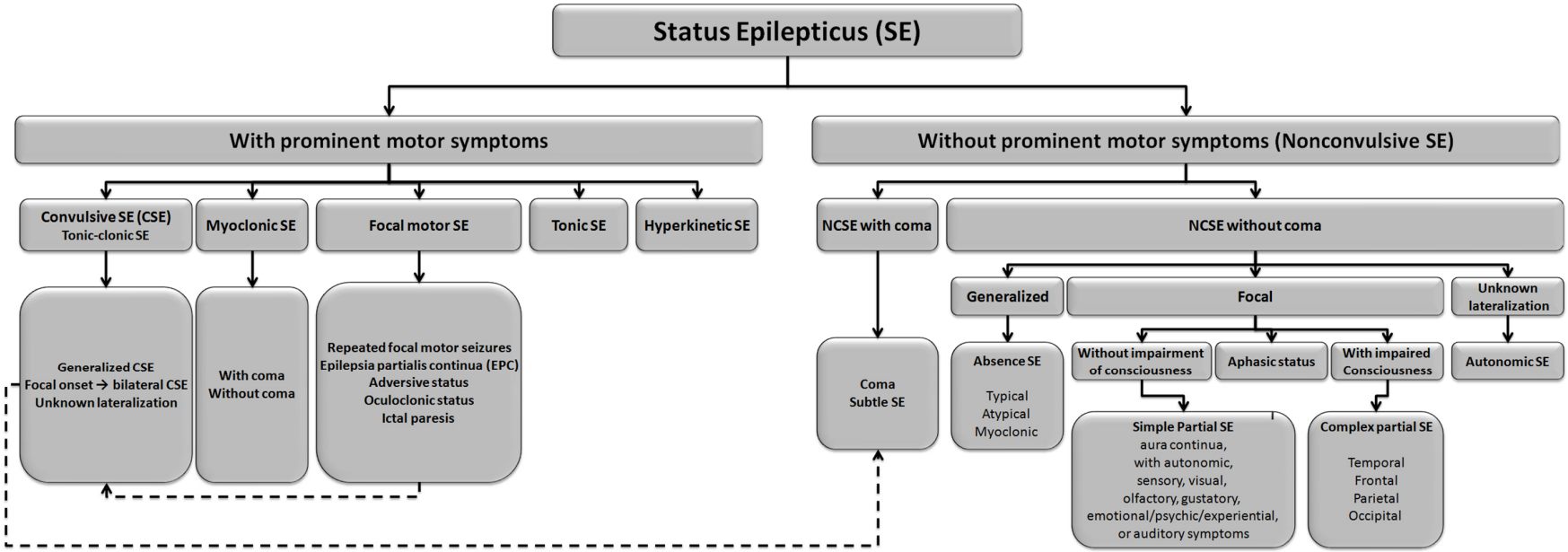

Figure 3. Classification of status epilepticus (adapted from the report of the ILAE Task Force on Classification of Status Epilepticus [12]).

3.1.3. Mortality, Morbidity, and Determinants of Outcome after SE in the Older Adult

Mortality at hospital discharge after status epilepticus increases gradually with age and status epilepticus severity [15,16]. Whereas the mortality rate is about 13% in young adults, it reaches 38% in older adults of 60–79 years old, and was found up to 50% after 80 years [17]. Regarding severity of status epilepticus, mortality has been demonstrated as higher in patients with refractory status epilepticus [18] or super refractory status epilepticus aged over 75 years [19]. Independent predictors of mortality are also particularly marked by age since 65 years old has been identified as a fatal cut off value in several studies [17,18,20–23]. Others factors associated with hospital mortality are related to seizure duration, an underlying CNS structural lesion, *de novo* status epilepticus, intensity of consciousness disorders at scene and refractory status epilepticus [20–22,24,25]. Morbidity is also impacted in older adult survivors after status epilepticus. In a case control study of adults aged over 70 years hospitalized in a geriatric acute care unit, patients who experienced a status epilepticus episode significantly demonstrated functional impairment at hospital discharge than the others, in 85% and 69%, respectively [13].

Finally, long term outcome in patients who initially survived a first episode of status epilepticus is also clearly worse in older adults, demonstrating a 10-year mortality rate of 82% in a population of patients over 65 years *versus* 32% in young adults [26].

3.2. How Should Status Epilepticus Be Managed in the Older Adult Patient?

3.2.1. Diagnosis of Status Epilepticus

The diagnostic strategy of status epilepticus is simple and does not differ in the older adult population. Most forms of CSE do not require EEG confirmation, except myoclonic seizures in particular cases (e.g., drug intoxication, post anoxic status epilepticus). The EEG is essential for the diagnosis of NCSE [27]. The diagnosis is based on the combination of a suggestive context, characteristic EEG patterns, and clinical response to treatment [27–30].

3.2.2. Differential Diagnosis of Status Epilepticus in the Older Adult

In the older adult, the neurosensory manifestations of NCSE deserve special attention, as they may be mistaken for psychiatric disorders (e.g., mood disturbances, cortical blindness, mutism and impaired verbal fluency, echolalia, confabulation, behavioural disorders, dissociative psychosis, and psychosensory disorders). Thus, in this particular population, the first differential diagnosis that should be evoked in case of delirium, stupor, or even coma, is SE [27,28]. It is therefore important to perform an electroencephalogram systematically in this context since it identifies SE in 16% of cases [31].

Conversely, many forms of abnormal motor activity may be confused with convulsive SE (e.g., tetany, neuroleptic malignant syndrome, shivering, drug-induced myoclonus, decerebration posturing, hemiballism, athetosis, and limb shaking in patients with arterial stenosis). Other medical conditions can also mimic SE in the older adult such as syncope, low cerebral blood flow, stroke, migraine, drug intoxication, infections, metabolic disorders, sleep disorders, paroxystic memory disorders, or even dementia [32–34].

Pseudo-seizure is another interesting differential diagnosis. It is defined as paroxysmal motor or behavioral symptoms that simulate SE in the absence of detectable electrical seizure activity or identified brain lesions. Prolonged episodes of pseudo-seizures define pseudo-SE, which mimics SE. The incidence of pseudo-seizure in patients with known epilepsy is about 15% [35]. Of 85 patients with pseudo-seizure, 78% reported at least one episode of pseudo-SE and 27% ICU admission for pseudo-SE. Among the distinctive features of pseudo-SE that have been identified, eye opening and closing may be the best clinical feature for differentiating pseudo-SE from SE. Whereas eye opening is the rule during epileptic seizures (positive predictive value [PPV], 97%), the eyes are closed in most pseudo-epileptic seizures (PPV, 94.3%) [36]. Finally, older patients over 55 years can represent about 10% of all cases of pseudo-seizures. When compared with earlier pseudo-seizures onset, older patients no demonstrated

significant differences in clinical semiology but were less likely associated with antecedent sexual abuse, more likely to have multiple comorbidities and to health-related traumatic experiences " [37].

Errors in diagnosis can also be related to the recording and interpretation of the electroencephalogram. In addition to the artifacts inherent in the EEG recording technique, EEG patterns can be mistakenly ascribed to NCSE including periodic lateralized epileptiform discharges, bilateral periodic epileptiform discharges, generalized periodic epileptiform discharges, and triphasic waves, whose epileptic nature remains widely debated. These patterns should be interpreted with caution based on the clinical setting [30,38].

3.2.3. Predictors of SE Occurrence in the Older Adult

In doubtful cases, the combination of suggestive clinical manifestations and presence of factors frequently associated with status epilepticus in the older adults can reinforce diagnostic suspicion. A previous diagnosis of epilepsy and presence of a chronic neurological disease seem intuitively obvious. A recent study also reported a significant association of SE occurrence with the underlying presence of a dementia (other than neurovascular), an acute medical condition (cardiac, respiratory, or liver), or a dysnatremia [13]. Finally, combining several information sources, the main identified causes in the older adult are dominated by stroke (acute or remote symptomatic), miscellaneous metabolic causes, dementia, infection, hypoxemia, and brain injury (Figure 4) [13,17,39].

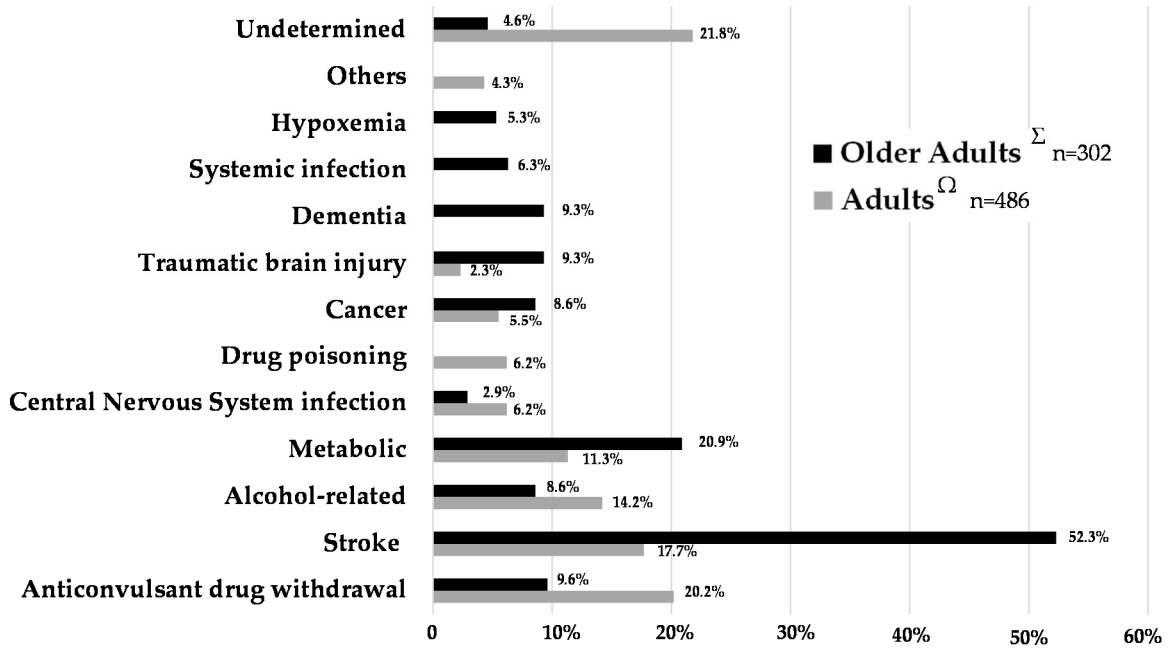

Figure 4. Comparison of causes of status epilepticus in 486 adults and 302 older adult patients. Ω Aminoff [40], Legriel [22] and Legriel [23]; Σ Sung [39], DeLorenzo [41], Canouï-Poitrine [13].

3.2.4. Therapeutic Management of SE in the Older Adult

The paucity of studies dealing with management of status epilepticus in older adults with life threatening complications is an obstacle to the development of treatment strategies supported by a systematic review design. The only focus on this population was provided by Treiman and Walker who published a subgroup analysis from the Veterans study [42]. However, given the incidence of SE in the older adult, the relative contribution of patients aged over 65 years in studies dealing with SE is important, allowing us to consider the extrapolation of their results [43]. Thus, evidence is limited to support the following strategies herein proposed by the authors that are adapted according to guidelines management in the adult taking into account common particularities in the older adults.

Also, the severity of the presentation of SE in older adults requires urgent support based on the recommendations in adults regardless of age, while observing certain precautions and therapeutic choices guided by the context. The initiation of aggressive treatments must be balanced against the expected side effects of these treatments and natural history of the underlying disease treated according to its potential for neurotoxicity [14].

Etiological investigations should be carried out earlier in parallel to symptomatic and anticonvulsant treatment. Anticonvulsive treatment should be administered with progressive therapeutic escalations, taking into account the type of SE and response to prior treatments, with the final objective to definitively control seizure activity in up to 60 min from the onset of SE. Routine monitoring of anticonvulsant concentrations for agents with defined therapeutic targets is highly recommended to guide therapy and reduce the risk of toxicity.

In cases of failure of vital functions, hemodynamic stability should be ensured, particularly as many of the drugs used to treat SE can induce hypotension and/or heart failure. Catecholamine may be needed when using anesthetics in patients with refractory SE. The need for upper airway protection should be evaluated continuously while bearing in mind that the primary treatment goal is seizure resolution with recovery of consciousness. Therefore, an initial phase of coma without life-threatening manifestations is acceptable if not unduly prolonged. Considering endotracheal intubation should be particularly thought in the older adults by weighing the pros and cons. If it is performed, rapid-sequence induction may be preferred using etomidate rather than propofol or thiopental in order to avoid inducing cardiac failure. Succinylcholine can be used, provided there is no evidence of hyperkalemia. Hypoglycemia should be looked for routinely and corrected. If glucose is given, 100 mg of thiamine should be administered concomitantly, most notably when there is evidence of vitamin B1 deficiency. Patients should be routinely evaluated for hyperthermia and metabolic disturbances, which require prompt correction. Metabolic and/or respiratory acidosis should be controlled, and tests for acute renal failure with rhabdomyolysis should be performed. Aspiration pneumonia may complicate the initial consciousness disorders. Patients should be evaluated for injuries such as head injury and shoulder dislocation [44].

3.2.5. Therapeutic Considerations in the Older Adults

In the acute phase of SE, it is important to consider therapeutic particularities related to age because there are changes in the pharmacokinetics and pharmacodynamics resulting in a significant inter-individual variability [45,46]. Thus, older adults are characterized by an alteration of gut or intestinal absorption, but also with an alteration of lipid and water distribution volumes, reducing distribution of medications based on these pharmacological properties. They also demonstrate a decrease in protein binding to albumin, increasing the free fraction of therapeutic agents which can then diffuse more easily beyond the blood brain barrier. Phenytoin and valproate are two anticonvulsants of concern due to approximately 90% protein binding [47]. Older adults also suffer from numerous comorbidities. Thus, respiratory and/or cardiac insufficiency may limit the use of some anticonvulsants. The combination of underlying neurological disorders can make these patients more susceptible to central depressant effects of certain therapeutic agents. Finally, renal or hepatic insufficiency can indicate or incite against particular caution in the use of certain agents (e.g., levetiracetam and renal dysfunction, sodium valproate and hepatic dysfunction) [45,46,48,49].

Older adults exhibit a higher potential for drug interactions given the number of concomitant medications [50]. Thus, one can encounter problems of enzyme induction of cytochrome P450 enzymes and iso IA2, 2B6, 2C9, 3A4/5 and uridine 5′diphospho glucuronosyl tranferases (UGT 1 and 2) (e.g., phenytoin and phenobarbital) that increase hepatic metabolism other treatments [46,51]. It may also pose the problem of inhibition of glucuronidation with cytochrome P450 and CYP2C9 (e.g., valproate) [46,51]. Interestingly, levetiracetam and lacosamide have the important advantage of not causing enzymatic induction or inhibition [48].

In the chronic phase, the relay of these treatments is difficult for some older adult patients [52]. There is a potential long-term use of some enzyme-inducing AEDs, which can impact other medication concentrations during the dose titration phase. It is therefore necessary to titrate anticonvulsant doses slowly and monitor serum concentrations (if available) for efficacy and toxicity. It is also important to simplify therapy as much as possible to improve adherence. Finally, use of newer anticonvulsants that have minimal adverse drug effects and drug-drug interactions should be considered [53].

3.2.6. Treatment Strategies in Status Epilepticus

Anticonvulsant treatments appropriate for the electrical and clinical seizure pattern in the older adult patient should be initiated.

It is important to remember that a first single seizure with a duration of less than 5 min does not always require emergent treatment, but measures of supportive care and surveillance. Decision to maintain anticonvulsant medication should be more based on presence of risk factors for seizure recurrence rather than older age [54]. This point is particularly important in respect to older adult patients who may have more prolonged adverse effects from anticonvulsant medications.

Once the diagnosis of SE has been made, the first line of treatment (emergent treatment) is to use benzodiazepines. These therapeutics can be administered by intramuscular, rectal, buccal, or intranasal routes when the intravenous route is not available. While intravenous lorazepam was previously considered the first-line treatment of reference, intramuscular midazolam demonstrated equivalence or even superiority in a recent study [55]. Extrapolation of this result to the population of older adult patients is, however, difficult since 80% of patients included were aged less than 60 years. Other agents may be diazepam or clonazepam whose use may be possible through the parenteral or intrarectal route [56–58]. It is important to note that midazolam has also been studied by the intranasal and buccal routes, which is potentially useful in older adult patients in who venous access is sometimes difficult.

One of the key studies in SE compared four anticonvulsants and referring treatments in tonic-clonic SE at generalized overt and subtle stages, with 44% of these patients being greater than 65 years of age [59]. Lorazepam and phenobarbital were both significantly better than phenytoin alone in this study. The results of the analysis by subgroups in the population of patients over 65 years showed an accentuation of efficacy differences described above, while it was not possible to achieve any statistical analysis in this subgroup population. It is also interesting to note that the time to first anticonvulsant treatment was longer in the older adult population, resulting in less efficacy of anticonvulsant treatments, even more pronounced when patients were found at scene in subtle SE (versus overt stage of SE) [42,43].

There are several choices for the second-line (urgent) treatment of SE. Based on the evidence, phenytoin/fosphenytoin or valproate would theoretically be the agents of choice. Levetiracetam and lacosamide are some interesting alternatives to consider, while phenobarbital is generally not a favorable option in older adult patients. Therefore, older adult SE treatment should be guided by the adverse drug effects of available anticonvulsant treatments. Phenytoin/fosphenytoin and lacosamide should be used with caution in patients with cardiovascular comorbidities, while phenobarbital has greater central and respiratory depression. Intravenous phenytoin and phenobarbital also contain a large amount of propylene glycol and may cause hemodynamic instability with rapid infusions. Valproate is contraindicated in cases of liver impairment, and finally lower doses of levetiracetam and lacosamide should be used based on reduced renal function in older adult patients. A recent review recommended levetiracetam dosing adjustment regimen according to creatinine clearance as follows: 500–1000 mg every 12 h in case of creatinine clearance between 50–80 mL/min/1.73 m^2; 250–750 mg every 12 h in case of creatinine clearance between 30–50 mL/min/1.73 m^2; 250–500 every 12 h in case of creatinine clearance <30 mL/min/1.73 m^2 and 500–1000 every 24 h in case of end-stage renal disease. A 250–500 mg levetiracetam supplemental dose is recommended after each dialysis [60]. Lacosamide dosing adjustment regimen would not be necessary if creatinine clearance remains >30 mL/min/1.73 m^2 [61]. In cases of severely impaired renal function, the maximum recommended

dose is 300 mg with dosage adjustments according to creatinine clearance as follows: 150 mg every 24 h in case of creatinine clearance between 15–30 mL/min/1.73 m^2; and 75 mg every 24 h in case of creatinine clearance <15 mL/min/1.73 m^2. A supplemental dose of 25–150 mg (up to 50% of the current dose) of lacosamide is recommended after each dialysis [61]. In addition, dosage adjustments should be considered for lacosamide in patients with mild to moderate hepatic dysfunction. Further reductions should be considered in patients with renal or hepatic dysfunction taking concomitant strong CYP3A4 and/or CYP2C9 enzyme inhibitors. Lacosamide should not be used in patients with severe hepatic impairment [62].

Finally, third line therapies are those of refractory status epilepticus (RSE). They rely on the use of anesthetic agents, namely propofol, thiopental, pentobarbital, or midazolam. Whereas available data are insufficient to prefer one of these anesthetics over another, especially in the population of older adult patients, the particularly half-life associated with thiopental and pentobarbital should discourage use of these drugs as a first choice. Regardless of the drug used, a weight based loading dose should be considered and additional dose titration at 3–5 min intervals under EEG monitoring with the goal of obtaining a burst-suppression pattern with suppression for 5–10 s. Once this goal is reached, a continuous infusion is given to maintain the burst-suppression pattern for 12–24 h. Boluses should be given if the burst-suppression pattern is lost before the pre-specified time; after the boluses, the continuous-infusion dose should be increased gradually. The treatment-discontinuation modalities vary across agents, in relation to the differences in their half-life values. A 20% reduction every 3 h is appropriate with propofol and a 50% decrease every 3 h with midazolam, whereas thiopental and possibly pentobarbital can be stopped with no prior dosage reduction. In patients that are difficult to control, slower withdrawal of RSE treatment should be considered. A loading dose of one or two long-acting antiepileptic agents should be given routinely in combination with the anesthetic agent and continued after anesthesia withdrawal [3].

3.2.7. Etiological Investigations of Status Epilepticus in the Older Adult

In addition to these symptomatic and specific measures, etiological investigations should be promptly performed. Main causes of SE may differ in adult *versus* older adult populations. A rigorous initial clinical examination should be conducted and associated with the realization of diagnostic tests for diagnostic purposes. Hypoglycemia (or hyperglycemia) should be systematically investigated and corrected as well as hyperthermia and possible metabolic disorders (e.g., hypocalcemia, hyponatremia, high uremia, hypomagnesemia, hypoxemia, carbon monoxide, hypercapnia). A blood alcohol assay can be performed. Similarly, the search for subtherapeutic anticonvulsants should be systematically evaluated in the epileptic population. The search for other metabolic disorders (porphyria, thyroid dysfunction) or the search for toxic substances (cocaine, amphetamines, tricyclic/serotonergic antidepressants) will be based on the context [63]. We always raise the possibility of iatrogenic cause (overdose of beta-lactams, quinolones, isoniazid, theophylline, *etc.*). Among toxic causes, we should systematically look at elements associated with posterior leukoencephalopathy. In this same hypothesis, we will look for a hypertensive encephalopathy. Brain imaging is ideally performed on admission to not be disturbed by the initiation of a continuous EEG recording, and in order to enable faster management of mass lesions that need neurosurgical intervention. A brain scan without and with contrast should be routinely performed in the initial management of patients that do not regain consciousness. An MRI may also be considered if all the etiologic diagnosis remains negative.

A lumbar puncture will also systematically be carried out in feverish context, if meningeal stiffness is observed or in immunocompromised patients, and in those whose etiologic remains negative. Given the suspicion of meningitis, encephalitis, or meningoencephalitis, systemic and CSF cultures should be obtained and antimicrobials initiated early and oriented toward suspected microorganisms. If neoplastic meningitis is suspected, lumbar puncture may be repeated up to three times to improve the diagnostic yield [44].

4. Conclusions

The management of SE in older adults requires attention because of increased incidence, some diagnosis difficulties, increased frailty, and a particularly poor outcome. The use of anticonvulsant drugs may be problematic in older adults. It is important to take into account the specificities related to the pharmacokinetic and pharmacodynamics changes: altered lipid and water distribution volumes resulting in lower distribution therapeutic agents involved, altered protein binding causing an increase in circulating serum levels of therapeutic agents normally bound to albumin, multiple comorbidities making it difficult to use certain treatments, and finally drug interactions related to the anticonvulsants with hepatic enzyme inducing or inhibiting properties. Beyond these precautions, the management may be identical to that of the younger adult, associating only prompt initiation of symptomatic and anticonvulsant treatments, and a broad and thorough etiological investigation. Such management strategies could improve the vital and functional prognosis of these older adult patients with SE.

Acknowledgments: No funds or grants were received by the authors to support or cover the costs of publishing this work.

Author Contributions: S.L. conceived, designed, and supervised the trial. S.L. collected, analyzed, and interpreted the data. S.L. and G.B. wrote the first draft of the paper. All authors approved the final version of the manuscript.

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

The following abbreviations are used in this manuscript:

Status Epilepticus (SE)
Glasgow Outcomes Scale (GOS)
Electroencephalogram (EEG)
Modified Rankin Scale (mRS)
Convulsive Status Epilepticus (CSE)
NonConvulsive Status Epilepticus (NCSE)
Positive Predictive Value (PPV)

References

1. Betjemann, J.P.; Lowenstein, D.H. Status epilepticus in adults. *Lancet Neurol.* **2015**, *14*, 615–624. [CrossRef]
2. Chin, R.F.; Neville, B.G.; Scott, R.C. A systematic review of the epidemiology of status epilepticus. *Eur. J. Neurol.* **2004**, *11*, 800–810. [CrossRef] [PubMed]
3. Brophy, G.M.; Bell, R.; Claassen, J.; Alldredge, B.; Bleck, T.P.; Glauser, T.; Laroche, S.M.; Riviello, J.J., Jr.; Shutter, L.; Sperling, M.R.; *et al.* Guidelines for the evaluation and management of status epilepticus. *Neurocritical Care* **2012**, *17*, 3–23. [CrossRef] [PubMed]
4. WHO Indicators for the minimum data set project on ageing: A critical review in sub-saharan africa. Dar es salaam, Tanzania. 21–22 June. In *Epidemiology and Burden of Disease*; WHO: Geneva, Switzerland, 2001.
5. Hauser, W.A. Seizure disorders: The changes with age. *Epilepsia* **1992**, *33* (Suppl. S4), S6–S14. [CrossRef] [PubMed]
6. Wallace, H.; Shorvon, S.; Tallis, R. Age-specific incidence and prevalence rates of treated epilepsy in an unselected population of 2,052,922 and age-specific fertility rates of women with epilepsy. *Lancet* **1998**, *352*, 1970–1973. [CrossRef]
7. Dham, B.S.; Hunter, K.; Rincon, F. The epidemiology of status epilepticus in the united states. *Neurocritical Care* **2014**, *20*, 476–483. [CrossRef] [PubMed]
8. Coeytaux, A.; Jallon, P.; Galobardes, B.; Morabia, A. Incidence of status epilepticus in french-speaking switzerland: (Epistar). *Neurology* **2000**, *55*, 693–697. [CrossRef] [PubMed]
9. Hesdorffer, D.C.; Logroscino, G.; Cascino, G.; Annegers, J.F.; Hauser, W.A. Incidence of status epilepticus in rochester, Minnesota, 1965–1984. *Neurology* **1998**, *50*, 735–741. [CrossRef] [PubMed]

10. Vignatelli, L.; Tonon, C.; D'Alessandro, R.; Bologna Group for the Study of Status Epilepticus. Incidence and short-term prognosis of status epilepticus in adults in Bologna, Italy. *Epilepsia* **2003**, *44*, 964–968. [CrossRef] [PubMed]
11. Walker, M. Status epilepticus: An evidence based guide. *BMJ* **2005**, *331*, 673–677. [CrossRef] [PubMed]
12. Trinka, E.; Cock, H.; Hesdorffer, D.; Rossetti, A.O.; Scheffer, I.E.; Shinnar, S.; Shorvon, S.; Lowenstein, D.H. A definition and classification of status epilepticus—Report of the ilae task force on classification of status epilepticus. *Epilepsia* **2015**, *56*, 1515–1523. [CrossRef] [PubMed]
13. Canoui-Poitrine, F.; Bastuji-Garin, S.; Alonso, E.; Darcel, G.; Verstichel, P.; Caillet, P.; Paillaud, E. Risk and prognostic factors of status epilepticus in the elderly: A case-control study. *Epilepsia* **2011**, *52*, 1849–1856. [CrossRef] [PubMed]
14. Litt, B.; Wityk, R.J.; Hertz, S.H.; Mullen, P.D.; Weiss, H.; Ryan, D.D.; Henry, T.R. Nonconvulsive status epilepticus in the critically ill elderly. *Epilepsia* **1998**, *39*, 1194–1202. [CrossRef] [PubMed]
15. Towne, A.R. Epidemiology and outcomes of status epilepticus in the elderly. *Int. Rev. Neurobiol.* **2007**, *81*, 111–127. [PubMed]
16. Ong, C.T.; Sheu, S.M.; Tsai, C.F.; Wong, Y.S.; Chen, S.C. Age-dependent sex difference of the incidence and mortality of status epilepticus: A twelve year nationwide population-based cohort study in Taiwan. *PLoS ONE* **2015**, *10*, e0122350. [CrossRef] [PubMed]
17. DeLorenzo, R.J.; Towne, A.R.; Pellock, J.M.; Ko, D. Status epilepticus in children, adults, and the elderly. *Epilepsia* **1992**, *33* (Suppl. S4), S15–S25. [CrossRef] [PubMed]
18. Jayalakshmi, S.; Vooturi, S.; Chepuru, R.; Sahu, S.; Surath, M. Aetiology and outcome of generalized convulsive status epilepticus in elderly. *Seizure* **2015**, *29*, 104–108. [CrossRef] [PubMed]
19. Kantanen, A.M.; Reinikainen, M.; Parviainen, I.; Ruokonen, E.; Ala-Peijari, M.; Backlund, T.; Koskenkari, J.; Laitio, R.; Kalviainen, R. Incidence and mortality of super-refractory status epilepticus in adults. *Epilepsy Behav.* **2015**, *49*, 131–134. [CrossRef] [PubMed]
20. Claassen, J.; Lokin, J.K.; Fitzsimmons, B.F.; Mendelsohn, F.A.; Mayer, S.A. Predictors of functional disability and mortality after status epilepticus. *Neurology* **2002**, *58*, 139–142. [CrossRef] [PubMed]
21. Drislane, F.W.; Blum, A.S.; Lopez, M.R.; Gautam, S.; Schomer, D.L. Duration of refractory status epilepticus and outcome: Loss of prognostic utility after several hours. *Epilepsia* **2009**, *50*, 1566–1571. [CrossRef] [PubMed]
22. Legriel, S.; Mourvillier, B.; Bele, N.; Amaro, J.; Fouet, P.; Manet, P.; Hilpert, F. Outcomes in 140 critically ill patients with status epilepticus. *Intensive Care Med.* **2008**, *34*, 476–480. [CrossRef] [PubMed]
23. Legriel, S.; Azoulay, E.; Resche-Rigon, M.; Lemiale, V.; Mourvillier, B.; Kouatchet, A.; Troche, G.; Wolf, M.; Galliot, R.; Dessertaine, G.; *et al.* Functional outcome after convulsive status epilepticus. *Crit. Care Med.* **2010**, *38*, 2295–2303. [CrossRef] [PubMed]
24. Rossetti, A.O.; Hurwitz, S.; Logroscino, G.; Bromfield, E.B. Prognosis of status epilepticus: Role of aetiology, age, and consciousness impairment at presentation. *J. Neurol. Neurosurg. Psychiatry* **2006**, *77*, 611–615. [CrossRef] [PubMed]
25. Sagduyu, A.; Tarlaci, S.; Sirin, H. Generalized tonic-clonic status epilepticus: Causes, treatment, complications and predictors of case fatality. *J. Neurol.* **1998**, *245*, 640–646. [CrossRef] [PubMed]
26. Logroscino, G.; Hesdorffer, D.C.; Cascino, G.D.; Annegers, J.F.; Bagiella, E.; Hauser, W.A. Long-term mortality after a first episode of status epilepticus. *Neurology* **2002**, *58*, 537–541. [CrossRef] [PubMed]
27. Shavit, L.; Grenader, T.; Galperin, I. Nonconvulsive status epilepticus in elderly a possible diagnostic pitfall. *Eur. J. Intern. Med.* **2012**, *23*, 701–704. [CrossRef] [PubMed]
28. Fernandez-Torre, J.L.; Diaz-Castroverde, A.G. Non-convulsive status epilepticus in elderly individuals: Report of four representative cases. *Age Ageing* **2004**, *33*, 78–81. [CrossRef] [PubMed]
29. Walker, M.C. Treatment of nonconvulsive status epilepticus. *Int. Rev. Neurobiol.* **2007**, *81*, 287–297. [PubMed]
30. Beniczky, S.; Hirsch, L.J.; Kaplan, P.W.; Pressler, R.; Bauer, G.; Aurlien, H.; Brogger, J.C.; Trinka, E. Unified eeg terminology and criteria for nonconvulsive status epilepticus. *Epilepsia* **2013**, *54* (Suppl. S6), 28–29. [CrossRef] [PubMed]
31. Naeije, G.; Depondt, C.; Meeus, C.; Korpak, K.; Pepersack, T.; Legros, B. Eeg patterns compatible with nonconvulsive status epilepticus are common in elderly patients with delirium: A prospective study with continuous eeg monitoring. *Epilepsy Behav.* **2014**, *36*, 18–21. [CrossRef] [PubMed]
32. Ferlazzo, E. Confusional status epilepticus in elderly. *BMC Geriatr.* **2010**, *10*, L35. [CrossRef]

33. Ramsay, R.E.; Macias, F.M.; Rowan, A.J. Diagnosing epilepsy in the elderly. *Int. Rev. Neurobiol.* **2007**, *81*, 129–151. [PubMed]
34. Veran, O.; Kahane, P.; Thomas, P.; Hamelin, S.; Sabourdy, C.; Vercueil, L. *De novo* epileptic confusion in the elderly: A 1-year prospective study. *Epilepsia* **2010**, *51*, 1030–1035. [CrossRef] [PubMed]
35. Kellinghaus, C.; Loddenkemper, T.; Dinner, D.S.; Lachhwani, D.; Luders, H.O. Non-epileptic seizures of the elderly. *J. Neurol.* **2004**, *251*, 704–709. [CrossRef] [PubMed]
36. Chung, S.S.; Gerber, P.; Kirlin, K.A. Ictal eye closure is a reliable indicator for psychogenic nonepileptic seizures. *Neurology* **2006**, *66*, 1730–1731. [CrossRef] [PubMed]
37. Duncan, R.; Oto, M.; Martin, E.; Pelosi, A. Late onset psychogenic nonepileptic attacks. *Neurology* **2006**, *66*, 1644–1647. [CrossRef] [PubMed]
38. Hirsch, L.J.; LaRoche, S.M.; Gaspard, N.; Gerard, E.; Svoronos, A.; Herman, S.T.; Mani, R.; Arif, H.; Jette, N.; Minazad, Y.; *et al.* American clinical neurophysiology society's standardized critical care eeg terminology: 2012 version. *J. Clin. Neurophysiol.* **2013**, *30*, 1–27. [CrossRef] [PubMed]
39. Sung, C.Y.; Chu, N.S. Status epilepticus in the elderly: Etiology, seizure type and outcome. *Acta Neurol. Scand.* **1989**, *80*, 51–56. [CrossRef] [PubMed]
40. Aminoff, M.J.; Simon, R.P. Status epilepticus. Causes, clinical features and consequences in 98 patients. *Am. J. Med.* **1980**, *69*, 657–666. [CrossRef]
41. DeLorenzo, R.J.; Pellock, J.M.; Towne, A.R.; Boggs, J.G. Epidemiology of status epilepticus. *J. Clin. Neurophysiol.* **1995**, *12*, 316–325. [CrossRef] [PubMed]
42. Treiman, D.M.; Walker, M.C. Treatment of seizure emergencies: Convulsive and non-convulsive status epilepticus. *Epilepsy Res.* **2006**, *68* (Suppl. S1), S77–S82. [CrossRef] [PubMed]
43. Treiman, D.M. Treatment of convulsive status epilepticus. *Int. Rev. Neurobiol.* **2007**, *81*, 273–285. [PubMed]
44. Legriel, S.; Bedos, J.; Azoulay, E. Managing critically ill patients with status epilepticus. In *Intensive Care Medicine*; Springer New York: New York, NY, USA, 2008; pp. 822–836.
45. Elger, C.E.; Schmidt, D. Modern management of epilepsy: A practical approach. *Epilepsy Behav.* **2008**, *12*, 501–539. [CrossRef] [PubMed]
46. Brodie, M.J.; Mintzer, S.; Pack, A.M.; Gidal, B.E.; Vecht, C.J.; Schmidt, D. Enzyme induction with antiepileptic drugs: Cause for concern? *Epilepsia* **2013**, *54*, 11–27. [CrossRef] [PubMed]
47. Birnbaum, A.K. Pharmacokinetics of antiepileptic drugs in elderly nursing home residents. *Int. Rev. Neurobiol.* **2007**, *81*, 211–220. [PubMed]
48. Schmidt, D. Drug treatment of epilepsy: Options and limitations. *Epilepsy Behav.* **2009**, *15*, 56–65. [CrossRef] [PubMed]
49. Verellen, R.M.; Cavazos, J.E. Pathophysiological considerations of seizures, epilepsy, and status epilepticus in the elderly. *Aging Dis.* **2011**, *2*, 278–285. [PubMed]
50. Schmidt, D.; Schachter, S.C. Drug treatment of epilepsy in adults. *BMJ* **2014**, *348*, g254. [CrossRef] [PubMed]
51. Levy, R.H.; Collins, C. Risk and predictability of drug interactions in the elderly. *Int. Rev. Neurobiol.* **2007**, *81*, 235–251. [PubMed]
52. Gidal, B.E. Antiepileptic drug formulation and treatment in the elderly: Biopharmaceutical considerations. *Int. Rev. Neurobiol.* **2007**, *81*, 299–311. [PubMed]
53. Velez, L.; Selwa, L.M. Seizure disorders in the elderly. *Am. Family Phys.* **2003**, *67*, 325–332.
54. Lawn, N.; Kelly, A.; Dunne, J.; Lee, J.; Wesseldine, A. First seizure in the older patient: Clinical features and prognosis. *Epilepsy Res.* **2013**, *107*, 109–114. [CrossRef] [PubMed]
55. Silbergleit, R.; Durkalski, V.; Lowenstein, D.; Conwit, R.; Pancioli, A.; Palesch, Y.; Barsan, W.; Investigators, N. Intramuscular *versus* intravenous therapy for prehospital status epilepticus. *N. Engl. J. Med.* **2012**, *366*, 591–600. [CrossRef] [PubMed]
56. Brigo, F.; Nardone, R.; Tezzon, F.; Trinka, E. Nonintravenous midazolam *versus* intravenous or rectal diazepam for the treatment of early status epilepticus: A systematic review with meta-analysis. *Epilepsy Behav.* **2015**, *49*, 325–336. [CrossRef] [PubMed]
57. Navarro, V.; Dagron, C.; Elie, C.; Lamhaut, L.; Demeret, S.; Urien, S.; An, K.; Bolgert, F.; Treluyer, J.M.; Baulac, M.; *et al.* Prehospital treatment with levetiracetam plus clonazepam or placebo plus clonazepam in status epilepticus (samukeppra): A randomised, double-blind, phase 3 trial. *Lancet Neurol.* **2016**, *15*, 47–55. [CrossRef]

58. Alvarez, V.; Lee, J.W.; Drislane, F.W.; Westover, M.B.; Novy, J.; Dworetzky, B.A.; Rossetti, A.O. Practice variability and efficacy of clonazepam, lorazepam, and midazolam in status epilepticus: A multicenter comparison. *Epilepsia* **2015**, *56*, 1275–1285. [CrossRef] [PubMed]
59. Treiman, D.M.; Meyers, P.D.; Walton, N.Y.; Collins, J.F.; Colling, C.; Rowan, A.J.; Handforth, A.; Faught, E.; Calabrese, V.P.; Uthman, B.M.; *et al.* A comparison of four treatments for generalized convulsive status epilepticus. Veterans affairs status epilepticus cooperative study group. *N. Engl. J. Med.* **1998**, *339*, 792–798. [CrossRef] [PubMed]
60. French, J. Use of levetiracetam in special populations. *Epilepsia* **2001**, *42* (Suppl. S4), 40–43. [CrossRef] [PubMed]
61. Cawello, W.; Fuhr, U.; Hering, U.; Maatouk, H.; Halabi, A. Impact of impaired renal function on the pharmacokinetics of the antiepileptic drug lacosamide. *Clin. Pharm.* **2013**, *52*, 897–906. [CrossRef] [PubMed]
62. Lexicomp online (lexi-drugs online): Lexi-comp, inc., hudson, ohio. Available online: Http://online.Lexi.Com/(loginandsubscriptionrequired) (accessed on 26 April 2016).
63. Taniguchi, G.; Miyajima, M.; Watanabe, M.; Murata, Y.; Sone, D.; Watanabe, Y.; Okazaki, M.; Kobayashi-Kimura, M.; Kato, M.; Onuma, T. Nonconvulsive status epilepticus in the elderly associated with newer antidepressants used at therapeutic doses: A report of three cases. *Epilepsy Behav. Case Rep.* **2015**, *3*, 8–11. [CrossRef] [PubMed]

Journal of
Clinical Medicine

MDPI

Review

Treatment of Established Status Epilepticus

Jessica J. Falco-Walter * and Thomas Bleck

Department of Neurology, Rush University Medical Center, 1725 West Harrison Street, Suite 885, Chicago, IL 60612, USA; tbleck@rush.edu

* Correspondence: Jessica.FalcoMD@gmail.com; Tel.: +1-312-942-5939; Fax: +1-312-942-0251

Academic Editors: Gretchen M. Brophy and Paul M. Vespa
Received: 1 February 2016; Accepted: 19 April 2016; Published: 25 April 2016

Abstract: Status epilepticus is the most severe form of epilepsy, with a high mortality rate and high health care costs. Status epilepticus is divided into four stages: early, established, refractory, and super-refractory. While initial treatment with benzodiazepines has become standard of care for early status epilepticus, treatment after benzodiazepine failure (established status epilepticus (ESE)) is incompletely studied. Effective treatment of ESE is critical as morbidity and mortality increases dramatically the longer convulsive status epilepticus persists. Phenytoin/fosphenytoin, valproic acid, levetiracetam, phenobarbital, and lacosamide are the most frequently prescribed antiseizure medications for treatment of ESE. To date there are no class 1 data to support pharmacologic recommendations of one agent over another. We review each of these medications, their pharmacology, the scientific evidence in support and against each in the available literature, adverse effects and safety profiles, dosing recommendations, and limitations of the available evidence. We also discuss future directions including the established status epilepticus treatment trial (ESETT). Substantial further research is urgently needed to identify these patients (particularly those with non-convulsive status epilepticus), elucidate the most efficacious antiseizure treatment with head-to-head randomized prospective trials, and determine whether this differs for convulsive *vs.* non-convulsive ESE.

Keywords: status epilepticus; established status epilepticus; treatment; antiseizure; phenytoin; levetiracetam; valproic acid; phenobarbital; lacosamide

1. Introduction

Status epilepticus is the most severe and most deadly form of epilepsy. Its annual incidence is 10–41 per 100,000 people. About 5% of adults and 10%–25% of children with epilepsy will have status epilepticus at least once during the course of their lives [1]. The mortality rates in status epilepticus are high: 24%–26% in adults and 3%–6% in children [2], and an overall mortality rate of about 20% [3].

Status epilepticus had previously been defined as continuous seizure activity lasting greater than five min. Some studies used 10 min and other studies used 30 min as a cut-off, depending upon whether there were convulsions or not. Recently the International League Against Epilepsy (ILAE) redefined status epilepticus as ongoing seizure activity due to failure of mechanisms responsible for seizure termination or initiation of mechanisms provoking ongoing seizures causing prolonged seizures after timepoint t_1, and which can have long-term consequences after timepoint t_2, with t_1 and t_2 being 5 min and 30 min, respectively for convulsive status epilepticus, 10 min and 60 min for focal status epilepticus with impaired consciousness, and 10–15 min and unknown for absence status epilepticus (Table 1) [4]. Established status epilepticus is defined as status epilepticus that persists after treatment with a benzodiazepine. Refractory status epilepticus (RSE) occurs when status epilepticus fails to abort after a first line (usually a benzodiazepine) and a second-line antiseizure medication have been given. Time is not part of the definitions for either established or refractory status epilepticus, which are based solely the medications given and persistence of seizures (Figure 1).

Table 1. Definitions of Status Epilepticus.

ILAE Definitions of Status Epilepticus		
	Time after which if seizures do not terminate patient is considered in status epilepticus (t_1)	Time after which ongoing seizures have long term consequences (t_2)
Convulsive status epilepticus	5 min	30 min
Focal status epilepticus with impaired consciousness	10 min	60 min
Absence status epilepticus	10–15 min	unknown
Other Definitions of Status Epilepticus		
Established statusepilepticus	Status epilepticus that persists after treatment with a benzodiazepine (1st line treatment)	
Refractory status epilepticus	Status epilepticus that persists after a 1st line agent (benzodiazepine) and 2nd lines agent (additional agent such as levetiracetam, phenytoin, valproic acid) have failed	

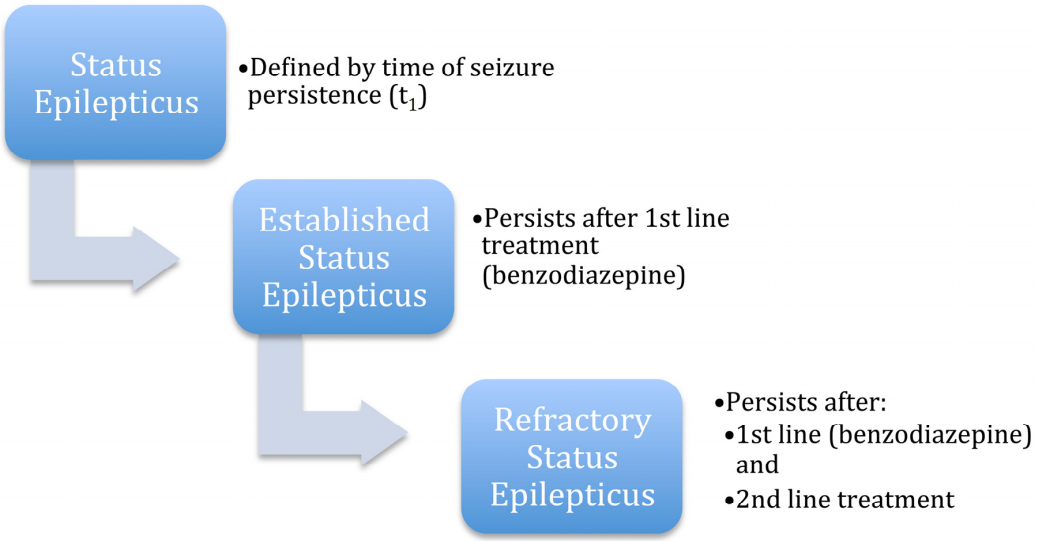

Figure 1. Timeline of the progression of status epilepticus.

The longer status epilepticus persists, the less likely it will resolve spontaneously and the higher the mortality. The higher mortality rates are frequently thought to be due to the underlying cause of the seizures. Prolonged status epilepticus is most often associated with severe brain dysfunction from encephalitis, massive stroke, or large brain tumors in adults [5]. In children, status epilepticus is due to: fever, low anticonvulsant levels, electrolyte imbalances, inborn errors of metabolism, ingestions, CNS infections, bacteremia, and various neuroimaging abnormalities (cortical malformations, trauma, stroke/hemorrhage, tumors, arteriovenous malformations, hydrocephalus) [6].

Our aim in this review is to discuss the pharmacologic treatment of established status epilepticus (ESE) and the current evidence that exists for these treatments. Data sources utilized include MEDLINE and back-tracking of references in pertinent studies. The following search terms were queried: "established status epilepticus", "benzodiazepine AND status epilepticus", "treatment AND status epilepticus", "phenytoin *vs.* phenobarbital in status epilepticus", "phenytoin *vs.* valproic acid in status epilepticus", "phenytoin *vs.* levetiracetam in status epilepticus", "phenytoin *vs.* lacosamide in status epilepticus", "lacosamide AND status epilepticus", "levetiracetam AND status epilepticus", "valproic acid AND status epilepticus", "randomized controlled AND status epilepticus." The abstracts from the resulting studies were reviewed; studies in which benzodiazepines were not administered first were excluded. References in articles that were particularly pertinent were retrieved and reviewed as well.

2. Causes of Ongoing Status Epilepticus

The duration of status epilepticus prior to treatment and the underlying etiology are the most important factors governing whether drugs will stop the seizure activity [7]. When seizures persist for longer periods of time, resistance to antiseizure medications occurs. Some medications are thought to lose their efficacy due to the ongoing seizure activity causing internalization, and therefore loss, of $GABA_A$ receptors from the synaptic membrane. This leads to less inhibition, and thus ongoing seizures. Additionally, seizure activity causes an increase in the number of excitatory receptors (NMDA and AMPA) in the synaptic membrane. These changes explain why medications that increase GABA become less effective, while those that work on NMDA and AMPA receptors are unaffected. Other mechanisms for drug failure in prolonged status are less well understood. Theories exist about seizures causing an increase in cytokines and other proinflammatory markers, as well as of upregulation of drug-efflux transporters such as P-glycoprotein. To date studies have not conclusively shown that either of these mechanisms changes the efficacy of antiseizure medications [8].

3. Pharmacologic Treatment

After a patient has received a benzodiazepine, and their seizures persist, phenytoin or fosphenytoin has been the standard treatment, with fosphenytoin favored in the United States. In Europe it is more common for other antiseizure medications to be given after benzodiazepine failure. Some of the reason for this difference may be due to the higher cost of fosphenytoin in the past, though now phenytoin and fosphenytoin are similar in price. Phenytoin/fosphenytoin has been favored, not because of its proven superiority in treating seizures or status epilepticus, but more because of familiarity with its use as well as its long half-life. More recently it has been proposed that valproic acid, levetiracetam, phenobarbital or phenytoin/fosphenytoin should all be considered for use as the second antiseizure medication following a benzodiazepine [9]. An older clinical practice guideline from the European Federation of Neurological Sciences (EFNS) recommended phenytoin be the standard first-line agent for ESE [10], but more recent clinical practice guidelines from the Neurocritical Care Society and the American Epilepsy Society are ambivalent as to the best agent for ESE [11,12]. There are few controlled, randomized, blinded clinical trials evaluating the different medications available for the treatment of established status epilepticus and no class 1, head-to-head, blinded comparisons of these medications for the treatment of ESE.

3.1. *Phenytoin/Fosphenytoin*

Fosphenytoin and phenytoin's primary mechanism of action is inhibition of sodium channels. Phenytoin is insoluble in water, requiring an alkaline solvent to prevent precipitation. This alkalinity can cause local irritation, thrombophlebitis, compartment syndrome, purple glove syndrome, and tissue necrosis with extravasation [13]. Fosphenytoin is water soluble, enabling it to be given intramuscularly (IM), which phenytoin cannot be. Fosphenytoin has generally been preferred to phenytoin given its better side-effect profile. It can be loaded faster intravenously (IV), has a lower risk of causing arrhythmias, hypotension, and local adverse reactions if extravasation occurs [14]. These benefits are less than was initially claimed as even fosphenytoin causes arrhythmias and hypotension, and the only significant benefit appears to be a lower incidence of purple glove syndrome. While fosphenytoin can be given faster IV, it has the same time to effect on seizures, as it must be converted to phenytoin, which takes about 15 min.

The efficacy of phenytoin for ESE was shown to be 43.1% in a large randomized study for convulsive status epilepticus in adults [15]. A retrospective study in children also demonstrated the efficacy of phenytoin after diazepam failure [16]. A recent meta-analysis pooled data from 22 studies and compared the efficacy of several antiseizure drugs for ESE. Using data from eight studies, the authors noted a mean efficacy of 50.2% for phenytoin in aborting ESE. When compared to the efficacy they found for phenobarbital, valproic acid, and levetiracetam, the efficacy of phenytoin was much

less [17]. Thus, while phenytoin is efficacious, it appears less so than some of the newer antiseizure drugs. Additionally, it has a worse side-effect profile and more drug-drug interactions due to it being a cytochrome P450 inducer. However, it is significantly cheaper than many of the newer antiseizure drugs, which is an important consideration in developing countries and as escalating medical costs become a bigger concern.

Phenytoin and fosphenytoin are dosed by weight, 15–20 mg/kg as an initial loading dose, after which an additional 5–10 mg/kg may be given if the initial dose is insufficient. Two hours after the loading dose a level should be checked, with the goal being a level of 15–20 µg/mL. Giving a loading dose of 1 gm for everyone is not appropriate. Hypotension may still be seen with fosphenytoin; thus, blood pressure and electrocardiographic (EKG) monitoring is needed for these infusions [11,12].

3.2. *Valproic Acid*

Valproic acid, while newer than phenytoin, has been approved by the FDA since the 1960s and is the next best studied. It has multiple mechanisms of action, which include multiple actions on GABA, NMDA-receptor antagonism, and histone deacetylase inhibition [18].

There are several trials that have compared valproic acid to other antiseizure drugs. Valproic acid has been shown to be as effective as, or more effective than phenytoin in two studies, by Gilad *et al.* and Misra *et al.* respectively. Seizures were aborted in 66%–88% of patients with status epilepticus or acute repetitive seizures when they were given valproic acid in these studies. Notably, in both of these studies benzodiazepines were not administered first, as is currently recommended, and phenytoin was likely disadvantaged by its time to onset [19,20]. Agarwal *et al.* compared IV phenytoin to IV valproic acid for ESE refractory to IV diazepam and found that they were equivalent in stopping ESE. The complication rates (hypotension and respiratory depression) were slightly higher in the phenytoin group as compared to the valproic acid group, which was significant [21]. Malamiri *et al.* compared valproic acid to phenobarbital in children who failed a single dose of IV diazepam (0.2 mg/kg) and found no significant difference in achieving seizure control after 20 min, but a significant difference was found for seizure recurrence within 24 h. At 24 h the patients who received phenobarbital boluses and maintenance were more likely to have recurrence of seizures then those who received valproic acid boluses and maintenance doses (37% without recurrence with phenobarbital *vs.* 77% with valproic acid) [22]. Chen *et al.* compared valproic acid to diazepam infusion after initial diazepam administration failed to stop seizures in adults with established generalized convulsive status epilepticus. Both medications were found to be equally efficacious, at 50% and 56% response rates, respectively. Notably, there were more complications (hypotension, need for artificial ventilation, and vasopressor support) for the patients who received the midazolam infusion [7]. Finally, the meta-analysis discussed above by Yasiry and Shorvon pooled data from eight studies on valproic acid, and showed an efficacy of 75.7% in aborting ESE. This was the highest efficacy of any of the medications reviewed [17]. From reviewing the above studies valproic acid is clearly at least as effective as phenytoin in aborting ESE.

Of note, valproic acid is a cytochrome P450 inhibitor, thus interacting with many other medications, similar to phenytoin. While it is less cardiotoxic than phenytoin, it is not free of adverse effects, most notably hepatotoxicity, thrombocytopenia, hyperammonemia, and acute hemorrhagic pancreatitis [13]. This agent is particularly problematic in patients with inborn errors of metabolism, such as ornithine carbamyltransferase deficiency.

Valproic acid is administered as 20–40 mg/kg IV over 10 min, and an additional 20 mg/kg can be given over 5 min if the patient is still seizing. The goal blood level is 100 µg/mL, and can be drawn immediately after the loading dose has been administered. Maximum dose of 3 gm. Cardiac complications are not an issue with valproic acid [11,12].

3.3. Phenobarbital

Phenobarbital aborts seizures primarily by enhancing GABAergic inhibition and secondarily by inhibiting sodium currents. It has been more extensively used in developing countries and in the pediatric population, though there are surprisingly few head-to-head studies looking at its efficacy.

As discussed above, Malamiri *et al.* compared IV valproic acid to IV phenobarbital in children after diazepam failure and found no difference initially in efficacy, but a higher recurrence of seizures in the phenobarbital group at 24 h [22]. Yasiry and Shorvon found an efficacy of 73.6% in their meta-analysis, which included just two papers, looking at 42 patients in total [17].

In developing countries, where cost is paramount, phenobarbital use is more common. Being a cytochrome P450 inducer, it interacts with many medications and has a worse side effect profile, with a propensity to cause hypotension, sedation, and respiratory depression, particularly with rapid infusion [13]

Phenobarbital should be given as a bolus of 10–20 mg/kg IV at a rate of 50–100 mg/minute, up to a total amount of 700 mg in seven min. Patients must have their respiration and blood pressure monitored while they are receiving the bolus [11].

3.4. Levetiracetam

Levetiracetam is a pyrrolidone derivative and piracetam analog. Its precise mechanism of action is unknown; it binds to synaptic vesicle protein 2A (SV2A) [18], but how this may affect seizures is presently unclear.

While there are not any head-to-head, prospective trials of levetiracetam, it appears to be as effective as valproic acid and other antiseizure drugs in the data that currently exist for ESE [23]. Knake *et al.* performed a retrospective study in which they found that levetiracetam controlled 16/18 patients in ESE [24]. Yasiry and Shorvon found an efficacy of 68.5% in their meta-analysis of eight studies. This was less than the efficacy of phenobarbital and valproic acid, but greater than that of phenytoin [17]. However, Alvarez *et al.* questioned whether levetiracetam is as efficacious for ESE. In their retrospective comparison of levetiracetam, valproic acid, and phenytoin, each medication failed to abort ESE in 48.3%, 25.4%, and 41.4% of patients, respectively. Thus, levetiracetam was significantly less efficacious than valproic acid and phenytoin [25].

Unlike the medications discussed above, levetiracetam has a significantly better adverse effect, interaction, and safety profile. It does not affect the cytochrome P450 enzymes. Its IV formulation is slightly more expensive than phenytoin.

Levetiracetam is given as 2.5 gm over 5 min or 1–4 gm IV over 15 min. A maximum of 4.5 gm can be given. Levetiracetam has the advantage of not causing many adverse reactions and also not interacting with other medications. It does accumulate in patients with renal dysfunction, however, and maintenance doses must be reduced in this setting [11,12].

3.5. Lacosamide

Lacosamide aborts seizures by selectively enhancing the slow inactivation of voltage-gated sodium channels [18]. While it only came to market in 2008, its high rate of off-label use for refractory status epilepticus is likely due to its availability in the IV form, which has been available since 2009.

There are no studies specifically looking at lacosamide in ESE, and only a handful looking at its efficacy in SE (19 studies, 10 single case-reports and 9 case-series) looking at a total of 136 patients. These studies showed an overall success of aborting status of 56%. The most common side effects were mild sedation and hypotension [13,26]. Yasiry and Shorvon were able to obtain additional data from the authors of the studies published, which resulted in only four patients qualifying as receiving lacosamide for ESE. Thus they concluded that there was insufficient data at this time [17]. A randomized trial of lacosamide and fosphenytoin (TRENdS) for NCSE is still being analyzed, but

it was stopped prematurely due to difficulty recruiting patients. This study may elucidate where lacosamide fits into treatment, but it will likely be under-powered [27].

The most commonly used bolus dose is 400 mg IV, followed by a daily dose of 200–400 mg given in divided doses [11].

4. Future Directions

While the medications discussed above all appear to have some evidence for halting status epilepticus that is resistant to benzodiazepines alone, there are no class 1, head-to-head, blinded comparisons of these medications for the treatment of ESE. To address this lack of evidence, the Established Status Epilepticus Treatment Trial (ESETT), is currently enrolling patients. This study will compare the efficacy of fosphenytoin, levetiracetam, and valproic acid. Patients who are greater than two years of age, with witnessed generalized tonic–clonic activity that is ongoing in the emergency room for over five min and who have failed to respond to benzodiazepines will be enrolled. The benzodiazepine may have been given in divided doses and may be given prior to arrival or in the hospital. The benzodiazepine doses acceptable as first line are: diazepam 10 mg IV, lorazepam 4 mg IV, midazolam 10 mg IV or IM if they are over 40 kg. For patients less than 40 kg they must have received lorazepam 0.1 mg/kg IV, midazolam 0.3 mg/kg IV or IM. Patients meeting the inclusion criteria will be randomized to one of three arms: fosphenytoin at 20 mg/kg, levetiracetam at 60 mg/kg or valproic acid at 40 mg/kg. The medications will be formulated so they will all infuse over 10 min. Patients will be assessed for seizure resolution as well as for hypotension and arrhythmias. ESETT plans to enroll up to 795 patients, but interim analyses will be performed at 400, 500, 600 and 700 patients, to assess for a higher success rate or of a failure of any of the medications [28–30].

Additionally, the Emergency Treatment with Levetiracetam or Phenytoin in status epilepticus in Chidren (EcLiPSE) Trial is currently enrolling patients. This study will compare the efficacy of levetiracetam and phenytoin in children. This study is being conducted at multiple centers in the United Kingdom. Patients must be 6 months to 18 years of age, with convulsive status epilepticus (generalized tonic–clonic, generalized clonic, or focal clonic) that is ongoing and has failed to respond to first line treatment. First line treatment is defined as a benzodiazepine of any sort by any route or rectal paraldehyde. Patients meeting the inclusion criteria will receive either levetiracetam 40 mg/kg (up to a maximum of 2500 mg) IV over 5 min or phenytoin 20 mg/kg (up to a maximum of 2000 mg) IV over 20–40 min (rate dependent upon dosage). Patients will be assessed for time to visible seizure cessation as well as whether an additional agent was required, if intubation or ICU admission was needed, and for any complications. They plan to enroll 340 patients. The study began enrolling patients in 2014 and is expected to finish in March of 2019 [31,32].

Until these trials are complete, the studies discussed above provide the best evidence for management of ESE. While phenobarbital was proposed by Betjemann and Lowenstein as a second line agent after benzodiazepine failure, ESETT and EcLiPSE will not address the efficacy of phenobarbital. Lacosamide has also been proposed as a second line agent, but there are minimal data on its efficacy in ESE and it also will not be included in ESETT or EcLiPSE.

The vast majority of the patients included in the studies discussed above had convulsive status epilepticus. In some of the studies patients with non-convulsive status epilepticus (NCSE) were specifically excluded, and in other studies they were included, but their numbers were small and the studies were not powered to make conclusions about this subset. The percentage of individuals with NCSE in intensive care units is estimated to be up to 20%, but there is little data about the best treatment for these individuals. While there is convincing evidence that ongoing generalized convulsive seizures is damaging, particularly after 30 min, there is little evidence to indicate that non-convulsive status epilepticus causes similar damage. There is even some evidence to indicate that being overly aggressive with more sedating AEDs is detrimental, particularly in the elderly. As a result, many interventionalists feel a less aggressive treatment approach to non-convulsive status

epilepticus is appropriate [18]. Whether the subset of NCSE should be treated differently in regard to ESE is unclear, and further studies will need to be completed.

5. Conclusions

The current evidence supports the use of valproic acid, levetiracetam, phenobarbital, or phenytoin all as treatments for ESE. There is insufficient data to support the use of lacosamide at this time. Valproic acid appears to be slightly more efficacious in a handful of the studies discussed, but until ESETT is completed any of these medications could arguably be considered equivalent. Additionally, given the adverse effect profile of each medication, for a given patient, one agent may be preferable. Overall there is a definite need for prospective controlled randomized trials for ESE.

Conflicts of Interest: Thomas Bleck receives salary reimbursement from Sage Therapeutics for service as the DSMB chair of clinical trials of allopregnenolone for super-refractory status epilepticus. Jessica Falco-Walter has no conflicts of interest.

References

1. Shorvon, S.D. *Status Epilepticus: Its Clinical Features and Treatment in Children and Adults*; Cambridge University Press: Cambridge, UK, 1994; p. 27.
2. Jallon, P. Mortality in patients with epilepsy. *Curr. Opin. Neurol.* **2004**, *17*, 141–146. [CrossRef] [PubMed]
3. Logroscino, G.; Hesdorffer, D.C.; Cascino, G.; Hauser, W.A.; Coeytaux, A.; Galobardes, B.; Morabia, A.; Jallon, P. Mortality after a first episode of status epilepticus in the United States and Europe. *Epilepsia* **1997**, *46*, 46–48. [CrossRef] [PubMed]
4. Trinka, E.; Cock, H.; Rossetti, A.; Scheffer, I.; Shinnar, S.; Shorvon, S.; Lowenstein, D. A definition and classification of status epilepticus—Report of the ILAE Task Force on Classification of Status Epilepticus. *Epilepsia* **2015**, *56*, 1515–1523. [CrossRef] [PubMed]
5. Abend, N.S.; Bearden, D.; Helbig, I.; McGuire, J.; Narula, S.; Panzer, J.A.; Topjian, A.; Dlugos, D.J. Status Epilepticus and Refractory Status Epilepticus Management. *Semin. Pediatr. Neurol.* **2014**, *21*, 263–274. [CrossRef] [PubMed]
6. Riviello, J.J.; Ashwal, S.; Hirtz, D.; Glauser, T.; Ballaban-Gil, K.; Kelley, K.; Morton, L.D.; Phillips, S.; Sloan, E.; Shinnar, S. Practice Parameter: Diagnostic assessment of the child with status epilepticus (an evidence-based review). *Neurology* **2006**, *67*, 1542–1550. [CrossRef] [PubMed]
7. Chen, W.B.; Gao, R.; Su, Y.Y.; Zhao, J.W.; Zhang, Y.Z.; Wang, L.; Ren, Y.; Fan, C.Q. Valproate *versus* diazepam for generalized convulsive status epilepticus: A pilot study. *Eur. J. Neurol.* **2011**, *18*, 1391–1396. [CrossRef] [PubMed]
8. Löscher, W. Molecular mechanisms of drug resistance in status epilepticus. *Epilepsia* **2009**, *50* (Suppl. 8), 19–21. [CrossRef] [PubMed]
9. Betjemann, J.P.; Lowenstein, D.H. Status Epilepticus in adults. *Lancet Neurol.* **2015**, *14*, 615–624. [CrossRef]
10. Meierkord, H.; Boon, P.; Engelsen, B.; Göcke, K.; Tinuper, P.; Holtkamp, M. EFNS guideline on the management of status epilepticus in adults. *Eur. J. Neurol.* **2010**, *17*, 348–355. [CrossRef] [PubMed]
11. Brophy, G.M.; Bell, R.; Classen, J.; Alldredge, B.; Bleck, T.P.; Glauser, T.; LaRoche, S.M.; Riviello, J.J., Jr.; Shutter, L.; Sperline, M.R.; *et al.* Guidelines for the Evaluation and Management of Status Epilepticus. Neurocritical Care Society Status Epilepticus Guideline Wiriting Committee. *Neurocrit. Care* **2012**, *17*, 3–23. [CrossRef] [PubMed]
12. Glauser, T.; Shinnar, S.; Gloss, D.; Alldredge, B.; Ayra, R.; Bainbridge, J.; Bare, M.; Bleck, T.; Dodson, E.; Garrity, L.; *et al.* Evidence-Based Guidline: Treatment of Convulsive Status Epilepticus in Children and Adults: Report of the Guideline Committee of the American Epilepsy Society. *Epilepsy Curr.* **2016**, *16*, 48–61. [CrossRef] [PubMed]
13. Trinka, E.; Höfler, J.; Laitinger, M.; Brigo, F. Pharmacotherapy for Status Epilepticus. *Drugs* **2015**, *75*, 1499–1521. [CrossRef] [PubMed]
14. Ogutu, B.R.; Newton, C.R.; Muchohi, S.N.; Otieno, G.O.; Edwards, G.; Watkins, W.M.; Kokwaro, G.O. Pharmacokinetics and clinical effects of phenytoin and fosphenytoin in children with severe malaria and status epilepticus. *J. Clin. Pharmacol.* **2003**, *56*, 112–119. [CrossRef]

15. Treiman, D.M.; Meyers, P.D.; Walton, N.Y.; Collins, J.F.; Colling, C.; Rowan, R.; Handforth, A.; Faught, E.; Calabrese, V.P.; Uthman, B.M.; *et al.* A comparison of four treatments for generalized convulsive status epilepticus. *N. Engl. J. Med.* **1998**, *339*, 792–798. [CrossRef] [PubMed]
16. Brevoord, J.C.; Joosten, K.F.; Arts, W.F.; van Rooij, R.W.; de Hoog, M. Status Epilepticus: Clinical Analysis of a Treatment Protocol Based on Midazolam and Phenytoin. *J. Clin. Neurol.* **2005**, *20*, 476–481.
17. Yasiry, Z.; Shorvon, S. The relative effectiveness of five antiepileptic drugs in treatment of benzodiazepine-resistant convulsive status epilepticus: A meta-analysis of published studies. *Seizure* **2014**, *23*, 167–174. [CrossRef] [PubMed]
18. Wasim, M.; Husain, A. Non-Convulsive Seizure Control in the Intensive Care Unit. *Curr. Treat. Options Neurol.* **2015**, *17*, 1–9. [CrossRef] [PubMed]
19. Gilad, R.; Izkovitz, N.; Dabby, R.; Rapoport, A.; Sadeh, M.; Weller, B.; Lampl, Y. Treatment of status epilepticus and acute repetitive seizures with i.v. valproic acid *vs.* phenytoin. *Acta Neurol. Scand.* **2008**, *118*, 296–300. [CrossRef] [PubMed]
20. Misra, U.K.; Kalita, J.; Patel, R. Sodium valproate *vs.* phenytoin in status epilepticus: A pilot study. *Neurology* **2006**, *67*, 340–342. [CrossRef] [PubMed]
21. Agarwal, P.; Kumar, N.; Chandra, R.; Gupta, G.; Antony, A.R.; Garg, N. Randomized study of intravenous valproate and phenytoin in status epilepticus. *Seizure* **2007**, *16*, 527–532. [CrossRef] [PubMed]
22. Malamiri, R.A.; Ghaempanah, M.; Khosroshahi, N.; Nikkhah, A.; Banarian, B.; Ashrafi, M.R. Efficacy and safety of intravenous sodium valproate *versus* phenobarbital in controlling convulsive status epilepticus and acute prolonged convulsive seizures in children: A randomized trial. *Eur. J. Paediatr. Neurol.* **2012**, *16*, 536–541. [CrossRef] [PubMed]
23. Zheng, F.; Du, C.; Wang, X. Levetiracetam for the treatment of status epilepticus. *Expert Rev. Neurother.* **2015**, *15*, 1113–1121. [CrossRef] [PubMed]
24. Knake, S.; Gruener, J.; Hattemer, K.; Klein, K.M.; Bauer, S.; Oertel, W.H.; Hamer, H.M.; Rosenow, F. Intraveous levetiracetam in the treatment of benzodiazepine refractory status epilepticus. *J. Neurol. Neurosurg. Psychiatry* **2008**, *79*, 588–589. [CrossRef] [PubMed]
25. Alvarez, V.; Januel, J.; Burnand, B.; Rossetti, A.O. Second-line status epilepticus treatment: Comparison of phenytoin, valproate and levetiracetam. *Epilepsia* **2011**, *52*, 1292–1296. [CrossRef] [PubMed]
26. Höfler, J.; Trinka, E. Lacosamide as a new treatment option in status epilepticus. *Epilepsia* **2013**, *54*, 393–404. [CrossRef] [PubMed]
27. Husain, A. Lacosamide in status epilepticus: Update on the TRENdS study. *Epilepsy Behav.* **2015**, *49*, 337–339. [CrossRef] [PubMed]
28. Cock, H. Established Status Epilepticus Treatment Trial (ESETT). *Epilepsia* **2011**, *52*, 50–52. [CrossRef] [PubMed]
29. Bleck, T.; Cock, H.; Chamberlain, J.; Cloyd, J.; Connor, J.; Elm, J.; Jones, E.; Lowenstain, D.; Shinnar, S.; Silbergleit, R.; *et al.* The Established Status Epilepticus Trial 2013. *Epilepsia* **2013**, *54*, 89–92. [CrossRef] [PubMed]
30. Kapur, J. Established Status Epilepticus Treatment Trial (ESETT). NIH Research Portfolio Online Reporting Tools (RePORT). Project Number: 1U01NS088034-01. Available online: https://projectreporter.nih.gov/project_info_description.cfm?projectnumber=1U01NS088034-01 (accessed on 21 April 2016).
31. A Pragmatic Randomized Controlled Trial of Intravenous Levetiracetam *versus* Interavenous Phenytoin in Terminating Acute, Prolonged Tonic Clonic Seizures Including Convulsive Status Epilepticus in Children, the EcLiPSE Study: Emergency Treatment with Levetiracetam or Phenytoin in Status Epilepticus. National Institute for Health Research (NHS). NIHR HTA Reference Number: 12/127/134. Available online: http://www.nets.nihr.ac.uk/projects/hta/12127134 (accessed on 21 April 2016).
32. Emergency Treatment with Levetiracetam or Phenytoin in Status Epilepticus in Children (EcLiPSE)—An Open Label Randomized Controlled Trial. National Institute for Health Research (NHS). NIHR HTA Reference number: 12/127/134. Available online: http://www.nets.nihr.ac.uk/__data/assets/pdf_file/0014/123350/PRO-12-127-134.pdf (accessed on 21 April 2016).

Journal of
Clinical Medicine

MDPI

Review

Comparison of Intravenous Anesthetic Agents for the Treatment of Refractory Status Epilepticus

Michael E. Reznik [1], Karen Berger [2] and Jan Claassen [1,*]

[1] Department of Critical Care Neurology, Columbia University Medical Center, New York, NY 10032, USA; mr3513@cumc.columbia.edu
[2] Department of Pharmacy, Weill Cornell Medical Center, New York, NY 10065, USA; kab9098@nyp.org
* Correspondence: jc1439@cumc.columbia.edu; Tel.: +1-212-305-7236; Fax: +1-212-305-2792

Academic Editors: Gretchen M. Brophy and Paul M. Vespa
Received: 13 April 2016; Accepted: 16 May 2016; Published: 19 May 2016

Abstract: Status epilepticus that cannot be controlled with first- and second-line agents is called refractory status epilepticus (RSE), a condition that is associated with significant morbidity and mortality. Most experts agree that treatment of RSE necessitates the use of continuous infusion intravenous anesthetic drugs such as midazolam, propofol, pentobarbital, thiopental, and ketamine, each of which has its own unique characteristics. This review compares the various anesthetic agents while providing an approach to their use in adult patients, along with possible associated complications.

Keywords: status epilepticus; refractory status epilepticus; IV anesthetics

1. Introduction

Refractory status epilepticus (RSE) is defined as ongoing seizures that cannot be controlled with first- and second-line agents and has an incidence ranging from 9% to 43% [1–6]. Some patients fail to respond to third-line therapy, and are considered to have super-refractory SE (SRSE), the true incidence of which is unknown. Both of these are associated with progressively-increasing morbidity and mortality, and expert guidelines advocate early initiation of intravenous anesthetic agents to maximize the chance of seizure cessation while minimizing the risk of long-term sequelae [7]. Despite guideline recommendations, the optimal approach to management remains controversial due to a lack of evidence from high quality clinical trials. The most commonly used continuous infusion intravenous anesthetics (cIV-AEDs) include midazolam, propofol, and pentobarbital, though the use of ketamine has also been increasingly described. (Note that outside the U.S., thiopental, rather than pentobarbital, is often the barbiturate of choice, especially in Europe.) This article provides an overview of their use in adult patients and the available clinical evidence. A summary of their pharmacologic properties is provided in Table 1.

Table 1. Pharmacology of Commonly Used CI Anesthetics for RSE.

	Mechanism of Action	Metabolism	Active Metabolite	Half-Life (Hours)	Half-Life Considerations	Drug Interactions	Examples of Drug-Drug Interactions	Adverse Reactions
Midazolam	GABA agonist	Hepatic	1-hydroxy-midazolam (renally eliminated)	2–7	Duration prolonged in renal failure and with extended duration of use	CYP 3A4 substrate	Phenytoin and phenobarbital (CYP 3A4 inducers) → lower midazolam concentrations	➢ Hypotension ➢ Respiratory depression
Propofol	GABA agonist; NMDA antagonist properties	Hepatic	N/A	0.5–7	Duration may be prolonged with extended duration of use	N/A	N/A	➢ Hypotension ➢ Respiratory depression PRIS ➢ ↑ Triglycerides
Pentobarbital	GABA agonist; Barbiturate	Hepatic	N/A	15–50	Duration may be prolonged with extended duration of use	CYP 2A6 inducer	Valproate (decreases barbiturate metabolism) → May increase pentobarbital concentrations Lamotrigine (CYP 2A6 substrate) → pentobarbital lowers lamotrigine concentrations	➢ Hypotension ➢ Respiratory depression ➢ Paralytic ileus ➢ Immune suppression ➢ Hepatic/pancreatic dysfunction ➢ ↓ Body temperature ➢ Propylene glycol toxicity
Ketamine	NMDA antagonist	Hepatic	Norketamine (hepatically eliminated)	2.5	N/A	CYP 2C9 & 3A4 substrate	Phenytoin and phenobarbital (CYP 2C9 inducers) → lower ketamine concentrations	➢ Hypertension ➢ Hypersalivation ➢ Hallucinations ➢ Emergence reaction

PRIS = propofol-related infusion syndrome.

2. Approach to cIV Anesthetic Use

Most practitioners using cIV AEDs aim for a goal of seizure suppression or burst suppression, but even more aggressive management including suppression of all background activity has been proposed. [7] This has not been investigated in a systematic way, as the heterogeneous nature and relative rarity of the disease process makes conducting large randomized controlled trials challenging (as evidenced by the difficulty in enrolling patients in the only RCT attempted to date [7,8]). Often, total seizure suppression cannot be achieved without inducing a therapeutic coma with a burst-suppression pattern on electroencephalography (EEG) or, at times, even a completely isoelectric EEG. A meta-analysis of cIV-AEDs for RSE found that titration of treatment to EEG background suppression was associated with a significantly lower frequency of breakthrough seizures than titration to seizure suppression, but was also associated with a significantly higher frequency of hypotension; meanwhile, neither titration goal nor choice of anesthetic infusion (between propofol, midazolam, and pentobarbital) was associated with a change in overall outcome [9].

There is also no consensus on the optimal duration of anesthetic infusions for RSE, though guidelines traditionally recommend seizure control for 24–48 h, followed by a gradual wean of the infusion [7]. Seizures that occur during weaning of the anesthetic are labeled as withdrawal seizures, though there may also be later SE recurrence. Both of these necessitate resumption of the anesthetic infusion, potentially at a higher dose and/or addition of another antiepileptic. It is important to keep in mind that, while RSE carries a significant risk of poor outcome, multiple retrospective studies and case series have shown the possibility of meaningful functional recovery even when SE resolution required weeks or months, suggesting that there is no clear duration of SE or number of failures to wean IV anesthetic infusions that should be considered futile [10–14].

Note that there is even less agreement in treating SRSE, when cIV-AEDs fail to control seizures. The management of SRSE is outside the scope of this review, but combination therapy involves adding another treatment that is often non-pharmacologic, like hypothermia [15] or ketogenic diet [16], to ongoing treatment with cIV-AEDs. A relevant point worth noting, however, is that the use of hypothermia leads to a decrease in overall metabolism, which may lead to an increase in the half-life of the IV anesthetics referenced here.

3. Benzodiazepines: Midazolam

Midazolam administered as a continuous infusion has been a preferred treatment for RSE since the 1990s, with multiple case series and meta-analyses describing its successful use [9,15–20]. Its popularity stems from its favorable properties, including a fast onset (1–5 min) and relatively short half-life (in the range of 1–6 h) when used as a bolus or short-term infusion [21,22]. It also does not contain propylene glycol, unlike lorazepam and diazepam, which obviates any concern for toxicity from propylene glycol accumulation. Propylene glycol has been associated with hypotension, in addition to more severe cardiac dysfunction and metabolic acidosis, though midazolam itself can cause hypotension.

Note that although midazolam has a relatively short half-life after a single dose, case reports have demonstrated a significantly increased half-life after prolonged infusion, due to an increased free fraction and volume of distribution and accumulation of its active metabolite, leading to a longer than expected time to awakening after stopping an infusion [23,24]. Prolonged infusion can also lead to tachyphylaxis, necessitating progressively higher doses to achieve the same effect. Midazolam cIV causes respiratory depression, requiring intubation for the duration of therapy.

As with other benzodiazepines, midazolam potentiates the inhibitory action of gamma-aminobutyric acid (GABA) via binding to the gamma-subunit of the GABAA receptor [19]. It undergoes hepatic metabolism via hydroxylation from CYP 3A4 and 3A5, which forms the active metabolite 1-hydroxymidazolam that is renally excreted [25]. As a cytochrome P450 substrate, levels of midazolam are affected by AEDs and other medications that are inducers or inhibitors.

When using midazolam for RSE, a loading dose of 0.2 mg/kg at 2 mg/min is recommended, with repeated boluses of 0.2–0.4 mg/kg [7] until seizures have stopped. A continuous infusion should

be started at 0.05–0.2 mg/kg/h and titrated up to 2 mg/kg/h as required, although rates as high as 2.9 mg/kg/h have been described [26]. Fernandez *et al.* compared high- and low-dose midazolam treatment protocols (if needed, as high as 2.9 mg/kg/h and 0.4 mg/kg/h, respectively) and found that the group treated under the high dose protocol had fewer withdrawal seizures after weaning off the midazolam infusion and had a significantly lower discharge mortality with no difference in hospital complications (aside from a higher incidence of hypotension, which did not affect outcome). However, though the study showed that these higher doses were probably safe, the median maximum doses in the high- and low-dose groups were 0.4 mg/kg/h and 0.2 mg/kg/h, respectively, with only half of the patients in the high-dose protocol group receiving doses higher than 0.2 mg/kg/h; meanwhile patients in the high-dose protocol also received treatment earlier, suggesting that an overall more aggressive approach to treatment may be more effective. Unfortunately, there have been no prospective trials comparing midazolam infusions to other cIV anesthetics for the treatment of RSE.

4. Propofol

For many, propofol is a practical alternative to midazolam as the third-line agent anesthetic of choice for RSE, chiefly because of its ultra-fast onset and rapid clearance even, in many cases, after extended infusion. Its half-life after a high-dose prolonged infusion is about 10 min for the first phase, although subsequent phases may take hours to days [27]. This property is due to the drug's high lipid solubility, allowing it to cross the blood-brain barrier and redistribute to peripheral tissues rapidly, where it also tends to accumulate after prolonged infusions [28,29]. Its most frequent side effects are hypotension, which often requires the use of vasopressors for the higher doses that are utilized in RSE, and respiratory depression, though it may also cause bradycardia. Hypertriglyceridemia is also common given its formulation as a lipid emulsion, and significantly elevated serum triglycerides (*i.e.*, exceeding 400 mg/dL) should prompt consideration about alternative therapy. More seriously, propofol carries with it the major caveat of an uncommon but life-threatening adverse effect known as propofol-related infusion syndrome (PRIS), which was initially described in children, but has also been associated with prolonged infusions as in those used for RSE [30]. This is manifested as severe metabolic acidosis, rhabdomyolysis, renal failure, and circulatory collapse, and has been attributed to mitochondrial dysfunction that leads to a mismatch between energy supply and demand [31]. Prolonged use of propofol should, therefore, prompt routine monitoring of lactate, creatine kinase, triglycerides, and potassium. Due to the risk of PRIS and reported case reports of fatal events, propofol is not routinely recommended in pediatric patients and is contraindicated for use in young children [7].

Despite this risk, multiple case series [16,28,31,32] and a meta-analysis [9] appear to show that its complication rate and efficacy is comparable to other cIV anesthetics used for RSE. (Interestingly, there have also been some case reports about seizure-like phenomena occurring during propofol use, primarily in the anesthesia literature and especially during induction and emergence, however this appears to be a rare occurrence [33]). Again, prospective data is limited, aside from a small prospective trial comparing propofol with pentobarbital that was only able to enroll 24 patients [8].

Propofol's mechanism of action involves modulating GABAA receptors; in addition, however, it also acts on sodium and calcium channels, and likely also has an antagonistic effect on NMDA receptors [26,34]. Its metabolism is primarily through hepatic glucuronidation with subsequent renal excretion, though a significant portion is also metabolized by cytochrome P450 isozymes. However the redistribution of propofol from blood into tissues is much more rapid than from peripheral compartments back into the blood, so clearance is also highly dependent on the total volume of distribution.

Propofol for RSE is typically given as a loading dose of 1–2 mg/kg followed by a continuous infusion, which can range from a starting rate of 20 mcg/kg/min up to as high as 200 mcg/kg/min (though infusions higher than 80 mcg/kg/min should be used cautiously due to the risk of PRIS) [7]. Propofol is formulated as a lipid emulsion and has a caloric value of 1.1 kcal/mL which should be accounted for when calculating nutritional requirements.

5. Barbiturates: Pentobarbital and Thiopental

Until the advent of propofol and midazolam infusions, barbiturates were the agents of choice for treating RSE. Traditionally, pentobarbital has been the barbiturate used in the U.S., while thiopental is more commonly used in Europe. In current practice, though, barbiturates are typically reserved for the management of RSE that fails to respond to midazolam and/or propofol, also known as super-refractory SE (SRSE). Though the class of medications has a long history of successful use [4,9,35–42], a host of major side effects limit its appeal given the other available options. These side effects include severe hypotension (often necessitating the use of vasopressors) and overall cardiovascular depression, respiratory depression, paralytic ileus, lowering of core body temperature, immune suppression, and a potential risk for pancreatic and hepatic dysfunction. The IV formulation of pentobarbital (but not thiopental) also contains propylene glycol, leading to a risk of propylene glycol toxicity with prolonged infusions.

In their favor, however, are several studies that suggest a possible benefit over other cIV-AEDs. A meta-analysis of 28 studies comparing midazolam, propofol, and pentobarbital infusions for RSE suggested that treatment with pentobarbital was associated with a significantly lower frequency of short-term treatment failure, breakthrough seizures, and changes to a different continuous infusion [9]. In a more recent single-center retrospective study, episodes of RSE in which barbiturates were used were associated with EEG burst suppression or complete suppression significantly more frequently than episodes in which they were not given. However they were also associated with significantly longer hospital stays for surviving patients, while mortality and likelihood of returning to clinical baseline at discharge did not differ significantly compared to propofol or midazolam [4]. Another recent single-center retrospective study confirmed these findings, and also found that weaning from pentobarbital appeared to be more successful (with lower incidence of withdrawal seizures) when phenobarbital was added before weaning [42]. Finally, a previously-mentioned, small randomized trial comparing pentobarbital with propofol showed comparable mortality and return to clinical baseline between the two, along with similar rates of infection and hypotension, though pentobarbital was associated with a significantly longer duration of mechanical ventilation [8].

Both pentobarbital and thiopental exert their effects via binding to the GABA receptor and prolonging the duration of opening of the associated chloride channel (as opposed to the increased frequency of opening caused by benzodiazepines), enhancing its inhibitory effects [43]. Since both barbiturates are highly lipophilic, they quickly distribute into the central nervous system, allowing for a fast time to onset for pentobarbital (15–20 min), and an ultra-fast time to onset for thiopental (30–60 s). However this may also result in deposition into peripheral tissues and saturation of metabolic pathways even after relatively short infusions, leading to nonlinear metabolism and a long half-life (ranging from 15 to 60 h for pentobarbital, and 11 to 36 h for thiopental) [44–47]. They both also have a tendency toward autoinduction which typically takes days to occur, as well as numerous drug interactions. Both pentobarbital and thiopental are hepatically metabolized; the main metabolite of thiopental is pentobarbital. Both pentobarbital [48] and thiopental [49] are highly protein-bound in plasma, ranging from 60% to 90%.

When used for RSE, pentobarbital is administered as a loading dose of 5–15 mg/kg, with an additional 5–10 mg/kg as needed to obtain the desired effect (infused at a rate $\leqslant$ 50 mg/min); a continuous infusion is started at a rate ranging from 0.5 to 5 mg/kg/h [7]. Thiopental is administered as a loading dose of 2–7 mg/kg (infused at a rate $\leqslant$ 50 mg/min), with additional doses of 1–2 mg/kg as needed, followed by a continuous infusion at a rate of 0.5–5 mg/kg/h. Therapeutic monitoring of pentobarbital levels may be useful for patients where brain death is considered, but should not be used to guide therapy for RSE. As mentioned in the retrospective study above, it may also be preferable to start phenobarbital in anticipation of weaning pentobarbital, to potentially reduce the risk of withdrawal seizures [42].

6. Ketamine

Ketamine has emerged as a more recent addition to the arsenal of cIV-AED treatment for RSE, primarily due to its alternative mechanism, though current evidence only supports its use in conjunction with other anesthetics. As opposed to the agents mentioned above, all of which act on the GABA receptor, ketamine is an antagonist on the N-methyl D-aspartate (NMDA) receptor, thereby inhibiting glutamate activity. It has a very high lipid solubility leading to a fast onset and extensive distribution, with an elimination half-life of around 2–3 h. Metabolism is primarily hepatic, with oxidation via the cytochrome P450 system (especially CYP3A4) predominantly into the active metabolite norketamine, which is then glucuronidated and excreted in urine and bile [50].

Its side effect profile is also generally favorable, as it is not associated with cardiac depression and hypotension as with the other IV anesthetics, but instead induces a positive sympathetic response, sometimes leading to drug-induced hypertension. Note, however, that in certain patients these cardiac effects may be detrimental, especially in those with coronary disease or significant cardiomyopathy. Prior studies had raised concern about the risk of increased intracranial pressure, but more recent studies show no changes in intracranial pressure with the use of ketamine [51,52]. Though it has potent anesthetic and analgesic properties, ketamine is not typically associated with respiratory depression, although hypersalivation may become an issue. Meanwhile, patients who regain consciousness after ketamine is stopped may experience psychiatric emergence phenomena, including agitation, confusion, and psychosis.

Though experience with ketamine for RSE is more limited than with the other cIV-AEDs, a number of case reports and case series detail its use [51,53–63]. Both a multi-center retrospective study by Gaspard *et al.* [51] and a meta-analysis that included it, along with 22 other studies [63], showed that ketamine appeared to contribute to seizure control in RSE for approximately 57% of adult patients—however, outcomes and more detailed information for most of these patients in the meta-analysis was not available. In the study by Gaspard *et al.*, ketamine was thought to be likely primarily responsible for seizure control in 32% of RSE episodes, while early response to ketamine was also associated with a significantly improved mortality rate. Of note, because ketamine is often started only after other anesthetic drugs have failed, there remains the possibility that its efficacy may be higher if introduced earlier.

There has been significant variation in reported dosing, but median loading doses appear to be in the range of 1–2 mg/kg, with a continuous infusion ranging anywhere from 1 to 10 mg/kg/h, based on the cited reports. Importantly, in almost all cases, ketamine was initially added to at least one other cIV-AED with subsequent weaning of other anesthetics; evidence is lacking as to its potential efficacy as a stand-alone cIV-AED. In the meantime, expert opinion suggests that it be preferentially used in conjunction with another anesthetic, preferably one with GABAergic action.

7. Controversies of Prolonged Anesthetic Use

Aside from the adverse effects listed above for individual anesthetic agents, prolonged anesthetic use comes with its own set of possible repercussions, and these have become more widely recognized. This has led to controversy about whether or not treatment of RSE with cIV anesthetic drugs may actually worsen outcomes, as suggested by several recent observational studies.

Kowalski *et al.* [64] found that anesthetic use predicted poor outcome and death in SE, with patients receiving these drugs having a three-fold relative risk of poor outcome compared to those who did not (though no attempts were made in this study to adjust for possible confounders). A study by Sutter *et al.* [65] showed that patients receiving anesthetics had four times more infections during SE and a nearly three-fold relative risk for death, despite attempts being made to account for possible confounders, such as SE duration and severity, other antiepileptic drugs used, and degree of overall critical illness. Marchi *et al.* [66] echoed these findings in a larger study that was also adjusted for possible confounders, with a subgroup analysis that also showed the association with poor outcome was strongest in patients with more benign SE subtypes (*i.e.*, absence, simple partial, or even complex

partial SE). This may be deceiving, however, as such SE subtypes are rarely treated with cIV-AEDs by experienced practitioners, and their inclusion may have been responsible for any significant findings in the study.

Above all, perhaps the biggest criticism of these studies is that, even with attempts made to account for confounding factors, there was likely some degree of inherent bias in prescribing anesthetic agents to patients who were likely more ill, in ways that could not necessarily be captured by the authors' analyses. Though they do raise valid questions about the possible harms associated with cIV-AEDs, caution should be used in interpreting these studies in such a way as to meaningfully affect clinical practice, at least until high-quality prospective evidence becomes available. Meanwhile, the general intensive care literature has raised awareness of another issue, suggesting that sedation, in general, especially in higher doses, appears to be associated with higher incidences of cognitive dysfunction, as described in a recent meta-analysis [67].

8. Conclusions

RSE carries with it a high morbidity and mortality regardless of treatment, though more aggressive management aimed toward early seizure cessation may improve outcomes. Multiple anesthetics have been shown to be effective in treating RSE, each with their own pros and cons but, unfortunately, there is not yet strong evidence from prospective trials to guide specific management with regards to choice of anesthetic and duration of treatment. Until such trials do exist, current clinical practice guidelines allow for flexibility in choice of anesthetic, so that the decision can be tailored to each individual case.

Author Contributions: All authors contributed to drafting and revising the manuscript.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Treiman, D.M.; Meyers, P.D.; Walton, N.Y.; Collins, J.F.; Colling, C.; Rowan, A.J.; Handforth, A.; Faught, E.; Calabrese, V.P.; Uthman, B.M.; *et al.* A comparison of four treatments for generalized convulsive status epilepticus. Veterans affairs status epilepticus cooperative study group. *N. Engl. J. Med.* **1998**, *339*, 792–798. [CrossRef] [PubMed]
2. Mayer, S.A.; Claassen, J.; Lokin, J.; Mendelsohn, F.; Dennis, L.J.; Fitzsimmons, B.F. Refractory status epilepticus: Frequency, risk factors, and impact on outcome. *Arch. Neurol.* **2002**, *59*, 205–210. [CrossRef] [PubMed]
3. Holtkamp, M.; Othman, J.; Buchheim, K.; Meierkord, H. Predictors and prognosis of refractory status epilepticus treated in a neurological intensive care unit. *J. Neurol. Neurosurg. Psychiatry* **2005**, *76*, 534–539. [CrossRef] [PubMed]
4. Rossetti, A.O.; Logroscino, G.; Bromfield, E.B. Refractory status epilepticus: Effect of treatment aggressiveness on prognosis. *Arch. Neurol.* **2005**, *62*, 1698–1702. [CrossRef] [PubMed]
5. Novy, J.; Logroscino, G.; Rossetti, A.O. Refractory status epilepticus: A prospective observational study. *Epilepsia* **2010**, *51*, 251–256. [CrossRef] [PubMed]
6. Sutter, R.; Marsch, S.; Fuhr, P.; Ruegg, S. Mortality and recovery from refractory status epilepticus in the intensive care unit: A 7-year observational study. *Epilepsia* **2013**, *54*, 502–511. [CrossRef] [PubMed]
7. Brophy, G.M.; Bell, R.; Claassen, J.; Alldredge, B.; Bleck, T.P.; Glauser, T.; Laroche, S.M.; Riviello, J.J., Jr.; Shutter, L.; Sperling, M.R.; *et al.* Guidelines for the evaluation and management of status epilepticus. *Neurocrit. Care* **2012**, *17*, 3–23. [CrossRef] [PubMed]
8. Rossetti, A.O.; Milligan, T.A.; Vulliemoz, S.; Michaelides, C.; Bertschi, M.; Lee, J.W. A randomized trial for the treatment of refractory status epilepticus. *Neurocrit. Care* **2011**, *14*, 4–10. [CrossRef] [PubMed]
9. Claassen, J.; Hirsch, L.J.; Emerson, R.G.; Mayer, S.A. Treatment of refractory status epilepticus with pentobarbital, propofol, or midazolam: A systematic review. *Epilepsia* **2002**, *43*, 146–153. [CrossRef] [PubMed]
10. Drislane, F.W.; Blum, A.S.; Lopez, M.R.; Gautam, S.; Schomer, D.L. Duration of refractory status epilepticus and outcome: Loss of prognostic utility after several hours. *Epilepsia* **2009**, *50*, 1566–1571. [CrossRef] [PubMed]

11. Cooper, A.D.; Britton, J.W.; Rabinstein, A.A. Functional and cognitive outcome in prolonged refractory status epilepticus. *Arch. Neurol.* **2009**, *66*, 1505–1509. [CrossRef] [PubMed]
12. Legriel, S.; Azoulay, E.; Resche-Rigon, M.; Lemiale, V.; Mourvillier, B.; Kouatchet, A.; Troche, G.; Wolf, M.; Galliot, R.; Dessertaine, G.; *et al.* Functional outcome after convulsive status epilepticus. *Crit. Care Med.* **2010**, *38*, 2295–2303. [CrossRef] [PubMed]
13. Hocker, S.E.; Britton, J.W.; Mandrekar, J.N.; Wijdicks, E.F.; Rabinstein, A.A. Predictors of outcome in refractory status epilepticus. *JAMA Neurol.* **2013**, *70*, 72–77. [CrossRef] [PubMed]
14. Kilbride, R.D.; Reynolds, A.S.; Szaflarski, J.P.; Hirsch, L.J. Clinical outcomes following prolonged refractory status epilepticus (PRSE). *Neurocrit. Care* **2013**, *18*, 374–385. [CrossRef] [PubMed]
15. Parent, J.M.; Lowenstein, D.H. Treatment of refractory generalized status epilepticus with continuous infusion of midazolam. *Neurology* **1994**, *44*, 1837–1840. [CrossRef] [PubMed]
16. Prasad, A.; Worrall, B.B.; Bertram, E.H.; Bleck, T.P. Propofol and midazolam in the treatment of refractory status epilepticus. *Epilepsia* **2001**, *42*, 380–386. [CrossRef] [PubMed]
17. Claassen, J.; Hirsch, L.J.; Emerson, R.G.; Bates, J.E.; Thompson, T.B.; Mayer, S.A. Continuous eeg monitoring and midazolam infusion for refractory nonconvulsive status epilepticus. *Neurology* **2001**, *57*, 1036–1042. [CrossRef] [PubMed]
18. Ulvi, H.; Yoldas, T.; Mungen, B.; Yigiter, R. Continuous infusion of midazolam in the treatment of refractory generalized convulsive status epilepticus. *Neurol. Sci. Off. J. Ital. Neurol. Soc. Ital. Soc. Clin. Neurophysiol.* **2002**, *23*, 177–182. [CrossRef] [PubMed]
19. Fernandez, A.; Lantigua, H.; Lesch, C.; Shao, B.; Foreman, B.; Schmidt, J.M.; Hirsch, L.J.; Mayer, S.A.; Claassen, J. High-dose midazolam infusion for refractory status epilepticus. *Neurology* **2014**, *82*, 359–365. [CrossRef] [PubMed]
20. Kumar, A.; Bleck, T.P. Intravenous midazolam for the treatment of refractory status epilepticus. *Crit. Care Med.* **1992**, *20*, 483–488. [CrossRef] [PubMed]
21. Denzel, D.; Burstein, A.H. Midazolam in refractory status epilepticus. *Ann. Pharmacother.* **1996**, *30*, 1481–1483. [PubMed]
22. Naritoku, D.K.; Sinha, S. Prolongation of midazolam half-life after sustained infusion for status epilepticus. *Neurology* **2000**, *54*, 1366–1368. [CrossRef] [PubMed]
23. Bodmer, M.; Link, B.; Grignaschi, N.; Kummer, O.; Ruegg, S.; Haschke, M.; Krahenbuhl, S. Pharmacokinetics of midazolam and metabolites in a patient with refractory status epilepticus treated with extraordinary doses of midazolam. *Ther. Drug Monit.* **2008**, *30*, 120–124. [CrossRef] [PubMed]
24. Riss, J.; Cloyd, J.; Gates, J.; Collins, S. Benzodiazepines in epilepsy: Pharmacology and pharmacokinetics. *Acta Neurol. Scand.* **2008**, *118*, 69–86. [CrossRef] [PubMed]
25. Bebin, M.; Bleck, T.P. New anticonvulsant drugs. Focus on flunarizine, fosphenytoin, midazolam and stiripentol. *Drugs* **1994**, *48*, 153–171. [CrossRef] [PubMed]
26. Kanto, J.; Gepts, E. Pharmacokinetic implications for the clinical use of propofol. *Clin. Pharmacokinet.* **1989**, *17*, 308–326. [CrossRef] [PubMed]
27. Bailie, G.R.; Cockshott, I.D.; Douglas, E.J.; Bowles, B.J.M. Pharmacokinetics of propofol during and after long term continuous infusion for maintenance of sedation in icu patients. *Br. J. Anaesth.* **1992**, *68*, 486–491. [CrossRef] [PubMed]
28. Stecker, M.M.; Kramer, T.H.; Raps, E.C.; O'Meeghan, R.; Dulaney, E.; Skaar, D.J. Treatment of refractory status epilepticus with propofol: Clinical and pharmacokinetic findings. *Epilepsia* **1998**, *39*, 18–26. [CrossRef] [PubMed]
29. Iyer, V.N.; Hoel, R.; Rabinstein, A.A. Propofol infusion syndrome in patients with refractory status epilepticus: An 11-year clinical experience. *Crit. Care Med.* **2009**, *37*, 3024–3030. [CrossRef] [PubMed]
30. Vasile, B.; Rasulo, F.; Candiani, A.; Latronico, N. The pathophysiology of propofol infusion syndrome: A simple name for a complex syndrome. *Intensive Care Med.* **2003**, *29*, 1417–1425. [CrossRef] [PubMed]
31. Parviainen, I.; Uusaro, A.; Kalviainen, R.; Mervaala, E.; Ruokonen, E. Propofol in the treatment of refractory status epilepticus. *Intensive Care Med.* **2006**, *32*, 1075–1079. [CrossRef] [PubMed]
32. Power, K.N.; Flaatten, H.; Gilhus, N.E.; Engelsen, B.A. Propofol treatment in adult refractory status epilepticus. Mortality risk and outcome. *Epilepsy Res.* **2011**, *94*, 53–60. [CrossRef] [PubMed]
33. Walder, B.; Tramèr, M.R.; Seeck, M. Seizure-like phenomena and propofol: A systematic review. *Neurology* **2002**, *58*, 1327–1332. [CrossRef] [PubMed]

34. Orser, B.A.; Wang, L.Y.; Pennefather, P.S.; MacDonald, J.F. Propofol modulates activation and desensitization of gabaa receptors in cultured murine hippocampal neurons. *J. Neurosci. Off. J. Soc. Neurosci.* **1994**, *14*, 7747–7760.
35. Rashkin, M.C.; Youngs, C.; Penovich, P. Pentobarbital treatment of refractory status epilepticus. *Neurology* **1987**, *37*, 500–503. [CrossRef] [PubMed]
36. Van Ness, P.C. Pentobarbital and eeg burst suppression in treatment of status epilepticus refractory to benzodiazepines and phenytoin. *Epilepsia* **1990**, *31*, 61–67. [CrossRef] [PubMed]
37. Lowenstein, D.H.; Aminoff, M.J.; Simon, R.P. Barbiturate anesthesia in the treatment of status epilepticus: Clinical experience with 14 patients. *Neurology* **1988**, *38*, 395–400. [CrossRef] [PubMed]
38. Osorio, I.; Reed, R.C. Treatment of refractory generalized tonic-clonic status epilepticus with pentobarbital anesthesia after high-dose phenytoin. *Epilepsia* **1989**, *30*, 464–471. [CrossRef] [PubMed]
39. Yaffe, K.; Lowenstein, D.H. Prognostic factors of pentobarbital therapy for refractory generalized status epilepticus. *Neurology* **1993**, *43*, 895–900. [CrossRef] [PubMed]
40. Krishnamurthy, K.B.; Drislane, F.W. Relapse and survival after barbiturate anesthetic treatment of refractory status epilepticus. *Epilepsia* **1996**, *37*, 863–867. [CrossRef] [PubMed]
41. Krishnamurthy, K.B.; Drislane, F.W. Depth of eeg suppression and outcome in barbiturate anesthetic treatment for refractory status epilepticus. *Epilepsia* **1999**, *40*, 759–762. [CrossRef] [PubMed]
42. Pugin, D.; Foreman, B.; De Marchis, G.M.; Fernandez, A.; Schmidt, J.M.; Czeisler, B.M.; Mayer, S.A.; Agarwal, S.; Lesch, C.; Lantigua, H.; *et al.* Is pentobarbital safe and efficacious in the treatment of super-refractory status epilepticus: A cohort study. *Crit. Care (Lond. Engl.)* **2014**, *18*, R103. [CrossRef] [PubMed]
43. Serafini, R.; Bracamontes, J.; Steinbach, J.H. Structural domains of the human gabaa receptor 3 subunit involved in the actions of pentobarbital. *J. Physiol.* **2000**, *524*, 649–676. [CrossRef] [PubMed]
44. Steudel, H.; Steudel, A.; von Unruh, G.E. Assay for cyclo-, seco- and pentobarbital by multiple ion detection: Kinetics after a single dose. *J. Clin. Chem. Clin. Biochem.* **1982**, *20*, 267–269. [PubMed]
45. Stanski, M.D.; Donald, R.; Mihm, M.D.; Fred, G.; Rosenthal, M.D.; Myer, H.; Kalman, M.D.; Sumner, M. Pharmacokinetics of high-dose thiopental used in cerebral resuscitation. *Anesthesiology* **1980**, *53*, 169–171. [CrossRef] [PubMed]
46. Turcant, P.D.A.; Delhumeau, M.D.A.; Premel-Cabic, P.D.A.; Granry, M.D.J.-C.; Cottineau, M.D.C.; Six, P.D.P.; Allain, M.D.P. Thiopental pharmacokinetics under conditions of long-term infusion. *Anesthesiology* **1985**, *63*, 50–54. [CrossRef] [PubMed]
47. Russo, H.; Bressolle, F.; Brès, J.; Duboin, M.-P. Nonlinear pharmacokinetics of high-dose thiopental following long term treatment. *Clin. Drug Investig.* **2012**, *11*, 32–42. [CrossRef]
48. Ehrnebo, M.; Odar-Cederlof, I. Binding of amobarbital, pentobarbital and diphenylhydantoin to blood cells and plasma proteins in healthy volunteers and uraemic patients. *Eur. J. Clin. Pharmacol.* **1975**, *8*, 445–453. [CrossRef] [PubMed]
49. Morgan, D.J.; Blackman, J.L.; Paull, J.D.; Wolf, L.J. Pharmacokinetics and plasma binding of thiopental. I: studies in surgical patients. *Anesthesiology* **1981**, *54*, 468–473. [CrossRef] [PubMed]
50. Mion, G.; Villevieille, T. Ketamine pharmacology: An update (pharmacodynamics and molecular aspects, recent findings). *CNS Neurosci. Ther.* **2013**, *19*, 370–380. [CrossRef] [PubMed]
51. Gaspard, N.; Foreman, B.; Judd, L.M.; Brenton, J.N.; Nathan, B.R.; McCoy, B.M.; Al-Otaibi, A.; Kilbride, R.; Fernandez, I.S.; Mendoza, L.; *et al.* Intravenous ketamine for the treatment of refractory status epilepticus: A retrospective multicenter study. *Epilepsia* **2013**, *54*, 1498–1503. [CrossRef] [PubMed]
52. Zeiler, F.A.; Teitelbaum, J.; West, M.; Gillman, L.M. The ketamine effect on intracranial pressure in nontraumatic neurological illness. *J. Crit. Care* **2014**, *29*, 1096–1106. [CrossRef] [PubMed]
53. Sheth, R.D.; Gidal, B.E. Refractory status epilepticus: Response to ketamine. *Neurology* **1998**, *51*, 1765–1766. [CrossRef] [PubMed]
54. Pruss, H.; Holtkamp, M. Ketamine successfully terminates malignant status epilepticus. *Epilepsy Res.* **2008**, *82*, 219–222. [CrossRef] [PubMed]
55. Hsieh, C.Y.; Sung, P.S.; Tsai, J.J.; Huang, C.W. Terminating prolonged refractory status epilepticus using ketamine. *Clin. Neuropharmacol.* **2010**, *33*, 165–167. [CrossRef] [PubMed]
56. Kramer, A.H. Early ketamine to treat refractory status epilepticus. *Neurocrit. Care* **2012**, *16*, 299–305. [CrossRef] [PubMed]

57. Rosati, A.; L'Erario, M.; Ilvento, L.; Cecchi, C.; Pisano, T.; Mirabile, L.; Guerrini, R. Efficacy and safety of ketamine in refractory status epilepticus in children. *Neurology* **2012**, *79*, 2355–2358. [CrossRef] [PubMed]
58. Synowiec, A.S.; Singh, D.S.; Yenugadhati, V.; Valeriano, J.P.; Schramke, C.J.; Kelly, K.M. Ketamine use in the treatment of refractory status epilepticus. *Epilepsy Res.* **2013**, *105*, 183–188. [CrossRef] [PubMed]
59. Zeiler, F.A.; Kaufmann, A.M.; Gillman, L.M.; West, M.; Silvaggio, J. Ketamine for medically refractory status epilepticus after elective aneurysm clipping. *Neurocrit. Care* **2013**, *19*, 119–124. [CrossRef] [PubMed]
60. Esaian, D.; Joset, D.; Lazarovits, C.; Dugan, P.C.; Fridman, D. Ketamine continuous infusion for refractory status epilepticus in a patient with anticonvulsant hypersensitivity syndrome. *Ann. Pharmacother.* **2013**, *47*, 1569–1576. [CrossRef] [PubMed]
61. Basha, M.M.; Alqallaf, A.; Shah, A.K. Drug-induced eeg pattern predicts effectiveness of ketamine in treating refractory status epilepticus. *Epilepsia* **2015**, *56*, e44–e48. [CrossRef] [PubMed]
62. McGinn, K.A.; Bishop, L.; Sarwal, A. Use of ketamine in barbiturate coma for status epilepticus. *Clin. Neuropharmacol.* **2016**, *39*, 62–65. [CrossRef] [PubMed]
63. Zeiler, F.A.; Teitelbaum, J.; Gillman, L.M.; West, M. Nmda antagonists for refractory seizures. *Neurocrit. Care* **2014**, *20*, 502–513. [CrossRef] [PubMed]
64. Kowalski, R.G.; Ziai, W.C.; Rees, R.N.; Werner, J.K., Jr.; Kim, G.; Goodwin, H.; Geocadin, R.G. Third-line antiepileptic therapy and outcome in status epilepticus: The impact of vasopressor use and prolonged mechanical ventilation. *Crit. Care Med.* **2012**, *40*, 2677–2684. [CrossRef] [PubMed]
65. Sutter, R.; Marsch, S.; Fuhr, P.; Kaplan, P.W.; Ruegg, S. Anesthetic drugs in status epilepticus: Risk or rescue? A 6-year cohort study. *Neurology* **2014**, *82*, 656–664. [CrossRef] [PubMed]
66. Marchi, N.A.; Novy, J.; Faouzi, M.; Stahli, C.; Burnand, B.; Rossetti, A.O. Status epilepticus: Impact of therapeutic coma on outcome. *Crit. Care Med.* **2015**, *43*, 1003–1009. [CrossRef] [PubMed]
67. Porhomayon, J.; Joude, P.; Adlparvar, G.; El-Solh, A.A.; Nader, N.D. The impact of high *versus* low sedation dosing strategy on cognitive dysfunction in survivors of intensive care units: A systematic review and meta-analysis. *J. Cardiovasc. Thorac. Res.* **2015**, *7*, 43–48. [CrossRef] [PubMed]