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DIAGNOSIS AND TREATMENT OF STATUS EPILEPTICUS : AN UPDATE SYSTEMATIC REVIEW

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ABSTRACT

Background: *Status epilepticus (SE) is a condition resulting from the failure of the mechanisms involved in seizure termination or the initiation of mechanisms responsible for seizure prolongation.*

The aim: *The aim of this study to show about diagnosis and treatment of status epilepticus.*

Methods: *By the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, this study was able to show that it met all of the requirements. This search approach, publications that came out between 2014 and 2024 were taken into account. Several different online reference sources, like Pubmed, SagePub, and Google Scholar were used to do this. It was decided not to take into account review pieces, works that had already been published, or works that were only half done.*

Result: *In the PubMed database, the results of our search get 110 articles, whereas the results of our search on SagePub get 163 articles, on Google Scholar 8200 articles. Records remove before screening are 7182, so we get 2761 articles fos screening. After we screened based on record exclude, we compiled a total of 10 papers. We included five research that met the criteria.*

Conclusion: *There are increasingly more drug options to treat SE, but rational polytherapy should consider the pharmacodynamics and kinetics of established and new antiepileptic drugs. When seizures cannot be controlled with conventional medical therapy, non-conventional treatments, including early surgical evaluation can be considered; however, high-quality evidence for these strategies are lacking. Neurointensivists are challenged to reduce secondary brain injury by managing common complications.*

Keyword: *Status epilepticus, refractory epilepticus, seizure, diagnosis, management.*

INTRODUCTION

Status epilepticus (SE) is one of the most common neurological emergencies and is associated with high morbidity and mortality, as high as 40% in refractory cases. In 2015 the International League Against Epilepsy Task Force provided a new definition, proposing that SE is a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms, which lead to abnormally, prolonged seizures (after time point T1). This condition can have long-term consequences (after time point T2), including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures.[1]

The classical definition of convulsive status epilepticus (CSE) is continuous seizure activity for at least 30 minutes, or two or more recurrent convulsive seizures with incomplete recovery of consciousness between seizures. Recently, the definition of CSE was revised in accordance with the various evidences of neuronal injury and changes in clinical settings. Currently, the most acceptable duration of continuous seizure activities is 5 minutes. In fulfilment of the revised definition and classification of status epilepticus (SE), the 2015 International League Against Epilepsy (ILAE) task force stressed that SE is either the failure of the mechanism responsible for seizure termination or the initiation of a mechanism leading to abnormally prolonged seizures, which can have long-term consequences.[2,3]

As seen in the definition, there are two operational dimensions. The first (T1) is how long a seizure has to persist to be regarded as "continuous seizure activity" and by so, with a low chance of spontaneous termination. The second time point (T2) is when an ongoing seizure activity will put the person at risk of long-term consequences[3]. This is an important conceptual definition, because there are different forms of SE, with different risk and treatment strategies.[1]

Before discussing the several factors responsible for the seizures gradually culminating into SE, it is imperative to briefly understand inhibitory and stimulatory neuronal pathways operating at the cellular levels. Primarily, failure of a seizure to stop is due to the imbalance between the inhibitory GABA (gamma-aminobutyric acid) pathway and the excitatory glutamate-mediated pathway. The inhibitory mechanisms are either temporarily diminished/sensitized or permanently damaged during SE, resulting in a prolonged period of epileptic bursting. Receptors exist in a highly dynamic state at the cellular level facilitating their movement along the axonal membrane. Receptor trafficking via internalization of the surface-positioned GABA receptors with a concomitant increase in the number of glutamatergic receptors at the cell surface results in persistent excitatory pathways with decreased or nonoperational limiting pathways.[4]

The treatment protocol for SE uses a staged approach depending on treatment response. Benzodiazepines (BZDs) are commonly used as the initial therapy for SE. Approximately 40% of convulsive SE does not show improvement after BZDs and is referred to as established SE. Intravenous (IV) antiseizure medication (ASM), such as fosphenytoin, valproate, or levetiracetam, then is used to manage established SE. However, 31% to 47% of patients with established SE are not controlled with ASMs, a state referred to as refractory SE.[5]

METHODS

Protocol

By following the rules provided by Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, the author of this study made certain that it was up to par with the requirements. This is done to ensure that the conclusions drawn from the inquiry are accurate.

Criteria for Eligibility

For the purpose of this literature review, we compare and contrast diagnosis and treatment of status epilepticus. It is possible to accomplish this by researching or investigating diagnosis and treatment of status epilepticus. As the primary purpose of this piece of writing, demonstrating the relevance of the difficulties that have been identified will take place throughout its entirety.

In order for researchers to take part in the study, it was necessary for them to fulfil the following requirements: 1) The paper needs to be written in English, and it needs to determine about diagnosis and treatment of status epilepticus. In order for the manuscript to be considered for publication, it needs to meet both of these requirements. 2) The studied papers include several that were published after 2014, but before the time period that this systematic review deems to be relevant. Examples of studies that are not permitted include editorials, submissions that do not have a DOI, review articles that have already been published, and entries that are essentially identical to journal papers that have already been published.

Search Strategy

We used " diagnosis and treatment of status epilepticus." as keywords. The search for studies to be included in the systematic review was carried out using the PubMed and SagePub databases by inputting the words: *(("*Status epilepticus*"[MeSH Subheading] OR "*Epilepticus*"[All Fields] OR "*Mechanism of status epilepticus*" [All Fields]) AND ("*Refractory epilepticus*"[All Fields] OR "* Diagnosis of status epilepticus *"[All Fields]) AND ("*Management of status epilepticus*"[All Fields]) OR ("*Treatment of status epilepticus" *[All Fields]))* used in searching the literature.

Data retrieval

After reading the abstract and the title of each study, the writers performed an examination to determine whether or not the study satisfied the inclusion criteria. The writers then decided which previous research they wanted to utilise as sources for their article and selected those studies. After looking at a number of different research, which all seemed to point to the same trend, this conclusion was drawn. All submissions need to be written in English and cannot have been seen anywhere else.

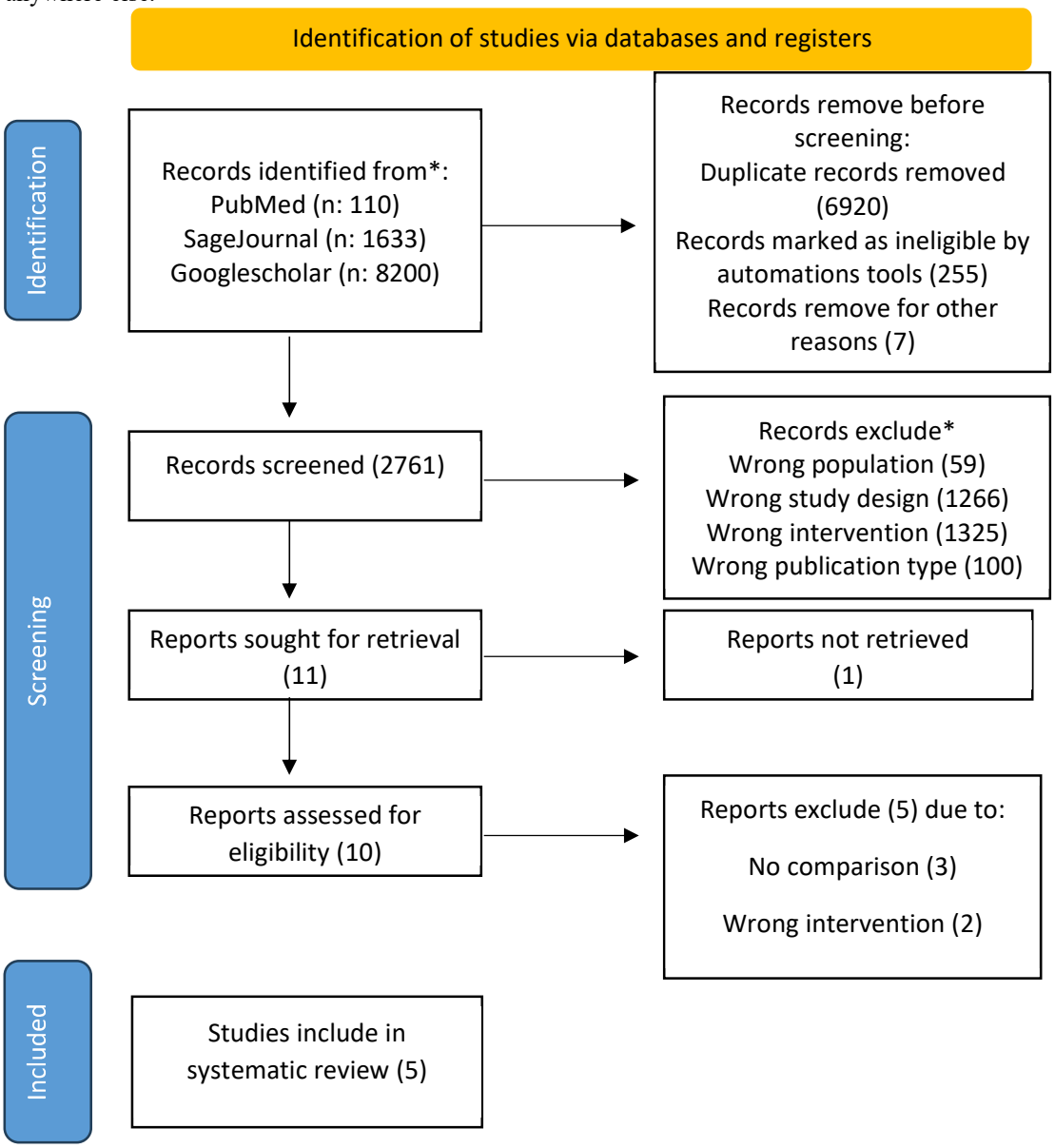

Figure 1. Article search flowchart

Only those papers that were able to satisfy all of the inclusion criteria were taken into consideration for the systematic review. This reduces the number of results to only those that are pertinent to the search. We do not take into consideration the conclusions of any study that does not satisfy our requirements. After this, the findings of the research will be analysed in great detail. The following pieces of information were uncovered as a result of the inquiry that was carried out for the purpose of this study: names, authors, publication dates, location, study activities, and parameters.

Quality Assessment and Data Synthesis

Each author did their own study on the research that was included in the publication's title and abstract before making a decision about which publications to explore further. The next step will be to evaluate all of the articles that are suitable for inclusion in the review because they match the criteria set forth for that purpose in the review. After that, we'll determine which articles to include in the review depending on the findings that we've uncovered. This criteria is utilised in the process of selecting papers for further assessment. in order to simplify the process as much as feasible when selecting

papers to evaluate. Which earlier investigations were carried out, and what elements of those studies made it appropriate to include them in the review, are being discussed here.

RESULT

From the PubMed database, the results of our search get 110 articles, whereas the results of our search on SagePub get 163 articles, on Google Scholar 8200 articles. Records remove before screening are 7182, so we get 2761 articles fos screening. After we screened based on record exclude, we compiled a total of 10 papers. We included five research that met the criteria.

Rollo, E et al (2023)[6] showed the effectiveness of PHT in terminating established SE, as well as refractory SE Anaesth+. Moreover, PHT was not associated with complications or increased mortality in our cohort. The superiority of PHT emerging from our results adds knowledge to the realworld management of SE, which may provide a clinical practice recommendation to guide the physician on the choice of the first drug for the treatment of benzodiazepine-refractory SE. Even with the limitations of a retrospective, not-blinded study, we believe that PHT is a good treatment option that may prevent the administration of anaesthetics, and furthermore manages to stop refractory SE under treatment with anaesthetics in more than half of employed cases. Taking into account that the ASM effectiveness and the prevention of anaesthetic treatment are the major predictors of a better outcome in a patient with SE, we advise considering treatment with phenytoin at least at the same rate as the other ASMs.

Chiarello, D et al (2020)[7] showed a significant role of non-antiepileptic treatments (chemotherapy-dialysis) and comorbidity (PRES) determining acute etiology and NCSE. Acute (mostly encephalitis), idiopathic-cryptogenic (mainly unknown-epilepsy) and NCSE were frequently detected in RSE. In the above mentioned conditions a high level of suspicion was recommended.

Table 1. The litelature include in this study

Author	Origin	Method	Sample Size	Result
Rollo, E et al., 2023[6]	Italy	A retrospective cohort study	244	A total of 244 episodes in 219 patients were included in the study. The mean age of the final study cohort was 63.6 ± 19.2, with 108 (49%) men. In the total cohort, phenytoin (PHT) showed the highest response rate (57.6%), followed by lacosamide (LCM) (40.7%) and valproate (VPA) (39.8%). The comparative efficacy among the different drugs was significantly different ($p < 0.001$). In the pairwise comparisons, VPA was superior to levetiracetam (LEV) (response rate: 39.75% vs 24.71%; $p = 0.004$), but not to LCM. Phenytoin had a significantly higher resolution rate compared to VPA (response rate: 57.63% vs 39.75%; $p = 0.02$) and LEV (response rate: 57.63% vs 24.71; $p < 0.001$). The clinical predictors of anaesthetics administration were a disorder of consciousness upon clinical presentation, previous diagnosis of epilepsy, and younger age.
Chiarello, D et al., 2020[7]	Italy	Retrospective study	124	We enrolled 124 patients. Mean and median age was 4.6 ± 4.2 years and 3.3 [1.2-7.5] years respectively. SE had a "de novo" onset in 66.9%. Focal convulsive-SE was the

				most common semiology (50.8%) whilst generalised (32.3%) and nonconvulsive-SE (NCSE) (16.9%) were less represented. Some etiologies showed a different age distribution: febrile in youngest age (p = 0.002, phi 0.3) and idiopathic-cryptogenic in older children (p = 0.016, phi 0.2). A statistical significance correlation was detected between semiology and etiology (p < 0.001, Cramer's V 0.4), chemotherapy and NCSE (n = 6/21 vs 3/103, p < 0.001) as well as PRES and NCSE (n = 7/21 vs 5/103, p < 0.001). Only 17.7% had a RSE. No correlation was found in demographic and clinical data, but NCSE, acute and idiopathic-cryptogenic etiologies were more frequently associated to RSE. Encephalitis was the most common diagnosis in acute etiologies whereas unknown epilepsy in idiopathic-cryptogenic group.
Sairanen, JJ et al., 2019[8]	Finland	A prospectively recruited study cohort	151	We recorded 151 cases of SE during the study period. First-line treatment was initiated outside of hospital in 79 cases (52.3%), with a significantly shorter median delay compared to intrahospital initiation (28 min vs. 2 h 5 min, $p < 0.001$). Forty-six episodes of SE (30.5%) were not recognized during the prehospital phase. The median delay in recognition of tonic-clonic SE (23 min) was significantly shorter than in focal aware (2 h 0 min, $p = 0.045$) or focal impaired awareness SE (2 h 25 min, $p < 0.001$). Second-line treatment was used in 91 cases (60.3%), with a median delay of 2 h 42 min. Anesthesia was used in seven cases (4.6%) with refractory SE, with a median delay of 6 h 40 min.
Cruz, MH et al., 2019[9]	Spain	Retrospective study	65	Thirty patients (46.2%) had history of epilepsy. The most frequent causes of SE were cerebrovascular disease (27.7%) and systemic infection (16.9%). The following deviations were observed in the administration of the

				antiepileptic drugs: benzodiazepines were used as first option in only 33 (50.8%) patients; the combination of 2 benzodiazepines was recorded in 7 cases (10.8%); and lacosamide was used as an off-label drug in 5 patients (7.7%). Electroencephalography studies were performed in only 26 patients (40%); and only 5 studies (7.7% of patients) were performed within 12 hours of seizure onset. The mortality rate was 21.5%. Acute stroke and cerebrovascular complications were associated with higher mortality rates, while previous history of epilepsy and admission to intensive care were related to better prognosis (P < .05).
Abbasi, H & Leach, JP., 2016[10]	UK	Retrospective study	466	Of the total assessed, 289 (62%) had SE without prior diagnosis of epilepsy ('De Novo Status Epilepticus – DNSE). Of these, 146 (51%) were precipitated by alcohol and/or non-prescription drugs. Other causes included infections (9%), metabolic (7%), idiopathic (6%) and Pseudo seizure (1.7%). Outcome studies showed 50% patients recovered with no deficit, 27% recovered with neurological deficit. In 16% patients outcome data was not available. Mortality during admission occurred in 7.7%. At one year after admission, mortality rate was 19%. 172 patients had a previous diagnosis of epilepsy (37%). The most commonly identified cause was alcohol and drug abuse n=53 (30%). Other causes included sepsis 11%, change in medication or non-compliance 10% and Pseudo seizures 3%. Immediate mortality was 5%. 1 year mortality was 10.2%. 66% patients recovered with no deficit, 21% with deficit, no outcome data was available for 8% patients. No information on prior epilepsy n=5 (1%).

Sairanen, JJ et al (2019)[8] showed status epilepticus is often not recognized during the prehospital phase of treatment, which delays the initiation of first-line treatment. Intrahospital delay could be reduced by streamlining patient transition between the three lines of treatment.

Cruz, MH et al (2019)[9] showed that to improve the management and prognosis of SE, periodic training activities targeting emergency department staff should be implemented in order to update their knowledge regarding the management of AEDs (especially newer drugs) and to raise awareness of the need to perform emergency EEG studies. We also recommend implementing elective ICU admission for patients presenting characteristics associated with higher mortality rates (patients without history of epilepsy, SE duration longer than 10 minutes, acute stroke as the aetiology of SE, and/or associated cardiovascular complications).

Abbasi, H & Leach, JP (2016)[10] showed preliminary data suggest that DNSE leading to ITU admission is more common (62% cases) than SE as a complication of epilepsy. Among our sample, 43% of SE cases were caused by chronic alcohol and drugs intake. Patients with known epilepsy have better outcome and less mortality than those with DNSE.

DISCUSSION

Status epilepticus presents in several forms: 1) convulsive status epilepticus consisting of repeated generalized tonic–clonic (GTC) seizures with persistent postictal depression of neurologic function between seizures; 2) nonconvulsive status epilepticus where seizures produce a continuous or fluctuating "epileptic twilight" state; and 3) repeated partial seizures manifested as focal motor signs, focal sensory symptoms, or focal impairment of function (e.g., aphasia) not associated with altered awareness (epilepsia partialis continua).[11]

Refractory status epilepticus has lacked a consensus definition; most today regard it as status epilepticus that continues despite treatment with benzodiazepine and one antiepileptic medication (AED), e.g., Lorazepam + phenytoin. Others regard refractory status epilepticus as failure of benzodiazepine and 2 antiepileptic medications, e.g., Lorazepam + phenytoin + phenobarb. The first definition is often referred to as 2 AED failure and the second one is termed the 3 AED failure.[12]

As longer duration of SE is associated with higher morbidity the treatment maxim "time is brain" applies not only for stroke but also for SE. Although it is the second most frequent neurological emergency, there is a surprising lack of high level evidence regarding treatment strategies after the application of benzodiazepines as first line treatment that fails in approximately 40% or more of the case. Irrespective of a convulsive or nonconvulsive SE, the commonly used antiepileptic drugs (fos)phenytoin, valproate (VPA), levetiracetam (LEV), phenobarbital and lacosamide are recommended for the treatment of BRSE.[13,14]

In 2019, first data of the multicentre trial "Established Status Epilepticus Treatment Trial-ESETT" were published about the efficacy and tolerability of the three most commonly used drugs LEV, VPA and fosphenytoin (FPHT) in generalized convulsive BRSE. Each of the three drugs led to seizure cessation and improvement of consciousness in approximately half of the patients with similar incidences of adverse events. As only 50 (13%) patients were older than 65 years and only convulsive SE has been considered in this study, the question about an effective and safe therapy in the elderly remains unanswered. Also, there is no precisely defined pathway for the SE-treatment after the first stage concerning drugs, their dosages or time intervals for application.[13,15]

CONCLUSION

There are increasingly more drug options to treat SE, but rational polytherapy should consider the pharmacodynamics and kinetics of established and new antiepileptic drugs. When seizures cannot be controlled with conventional medical therapy, non-conventional treatments, including early surgical evaluation can be considered; however, high-quality evidence for these strategies are lacking. Neurointensivists are challenged to reduce secondary brain injury by managing common complications.

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