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Assessment of the Safety and Efficacy of the COVID-19 Vaccines against Variants of Concerns: A Systematic Literature Review

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Abstract

Background: During the pandemic, researchers were successful in rapidly formulating a cure for the COVID- 19 disease. In this systematic review, we evaluated the safety and efficacy of three vaccines against three different variants of concern (VOCs).

Methods: This systematic review was carried out as per the Preferred Reporting Project for Systematic Evaluation and Meta-Analysis (PRISMA) standards. The primary objective of the study was to evaluate the efficacy of the COVID-19 vaccine against the selected VOCs. The secondary objective of the study included the assessment of the severity of adverse events induced by the selected COVID-19 VOCs after receiving the vaccination along with reinfection rate.

Discussion: A total of 22 studies were included in this systematic review with the mean age of participants ranging from 34.8 to 58.8 years. The participants affected with alpha, delta, and omicron VOCs vaccinated with either BNT162b2, mRNA1273, or ChAdOx1-S vaccine were included and assessed. The mean age of the participants from the included studies was 42 years (ranging from 34.8 to 58.8 years) while the median age of the participants was 54 years (ranging from 30 to 77 years). Among the three vaccines, mRNA1273 achieved highest efficacy of 73.1% ranging from 46.0% to 98.4% with approximately 24% adverse event reactions in participants.

Conclusion: This systematic review summarized the safety and efficacy of the various research studies conducted and represented by researchers worldwide. The review's findings showed that while the examined vaccinations are effective and safe for people, additional research is required to mitigate the adverse reactions and rates of reinfection in those who received the vaccinations.

Keywords: COVID-19, effective, vaccination, SARS-CoV-2, adverse events, reinfection.

Introduction

The coronavirus disease of 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has led the world to face one of the biggest and most challenging pandemics, even after all these technological advancements in the healthcare industry. Until now, the World Health Organization (WHO) has disclosed many COVID-19 variations and classified them according to their virulence rate and mode of transmission. As

per the WHO, like other viruses, SARS-CoV-2 mutates over time and will keep changing the more it spreads into different variants. 1 This virus has constantly evolved ever since its

emergence due to mutation, and at times these changes produce a new viral strain.Certain alterations and modifications enable the virus to proliferate more quickly, making it immune to drugs or vaccinations, producing different variants capable of immune escape.

Differentiating characteristics like enhanced transmissibility and antigenicity were observed in these variants, which were mostly caused by non-synonymous mutations in the spike protein.[2] These variants are also categorized into different categories, including Variants of Interests (VOI), Variants of Concerns (VOC), Variants of High Consequences (VOHC), and Variants Being Monitored (VBM).[3] As of now, the WHO (as well as national public health organizations) have designated five SARS-CoV-2 variations as variants of concern (VOCs), meaning that they should be closely monitored because of their significantly changed transmissibility or immune escape.[2] These variants include Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), and Omicron (B.1.1.529).[4]

Of these variants, Alpha, Beta, and Gamma were the first to spread in early 2021 and shared the N501Y substitution. These variations were replaced in summer 2021 by the Delta variant, which had unique changes like as the L452R substitution and was associated with increased virulence. It was rapidly superseded by the Omicron variant by the end of 2021, which has since become more prevalent due to its staggering number of mutations. The emergence of VOCs revealed a dynamic development of SARS-CoV-2 via selection and mutation accumulation. This has not only resulted in a gradual improvement in the transmissibility of SARS-CoV-2 but has also contributed to the virus's immunological escape.[5] These variants may spread faster and easier than others, increasing the number of COVID-19 cases. There were around 687 million COVID-19 instances worldwide as of May 2, 2023. Approximately 660 million individuals had recovered from the virus infection, while nearly 6.87 million had died. Among the nations most severely affected by the pandemic are Brazil, India, and the United States of America (USA).[6] With around 375,000 fatalities, COVID- 19 was the third largest cause of death in the USA in 2020, after heart disease and cancer. People of all ages are susceptible to this virus, especially people aged ≥60 years with comorbidities, who are most susceptible to the severe COVID-19 infection.[7-8]

To prevent the spread and virulence of these variants, healthcare organizations all around the world have developed plenty of vaccinations and guidelines. However, to date, there is no treatment available for the COVID-19 infection other than immunization. Pfizer,in collaboration with German biotech firm BioNTech, developed the first-ever nucleoside-modified mRNA vaccine encoding the nucleoside-modified mRNA named Comirnaty (BNT162b2) for emergency use.[9] Shortly after that, Moderna manufactured the second vaccine, the mRNA1273 vaccine for adults, which was also a nucleoside-modified mRNA vaccine.[10] Moreover, Oxford-AstraZeneca manufactured the ChAdOx1-S, a recombinant COVID-19 vaccine, which was also recommended by the WHO for use in people aged 18 and above.[11] These vaccines were listed by the WHO for emergency use during the pandemic.[12] Other than these vaccines, WHO has listed all the approved vaccines for immunization to prevent the spread and infection rate of the COVID-19 virus.[13] In this review, we will assess the safety and efficacy of these vaccines against different VOCs of the COVID-19 virus and their associated adverse events in the general population.

Method

***Objectives*:**

The primary outcomes of the study were to evaluate the efficacy of the COVID-19 vaccine

against the selected variants of concern (VOCs), including alpha (B.1.1.7), beta (B.1.351), and omicron (B.1.1.529) variants. The COVID-19 vaccines that were analyzed during this systematic review included BNT162b2 (Pfizer), mRNA-1273 (Moderna), and ChAdOx1-S (Oxford-AstraZeneca), since these vaccines were the most analyzed for their safety and efficacy rates.

The study's secondary objective included assessing the severity of adverse events induced by the selected COVID-19 VOCs after receiving the vaccination. In addition, this study also.evaluated the reinfection rate in the vaccinated participants

Eligibility criteria of the studies

This systematic review was carried out as per the Preferred Reporting Project for Systematic Evaluation and Meta-Analysis (PRISMA) standards. We included randomized-controlled trials (RCTs) or parallel individual clinical trials evaluating the safety, efficacy, and immunogenicity of the COVID-19 vaccines on different variants of concerns.

The inclusion criteria of the study included:

- Studies examining the virulence and transmission rate of the COVID-19 variants
- Randomized controlled trials on the efficacy of the COVID-19 vaccine
- Full-text articles
- English-language articles
- Articles published between 2012 and 2023
- Studies including the adverse effects linked to the COVID-19 vaccine

The exclusion criteria of the study included:

The following studies will be excluded:

- Systematic reviews and meta-analyses
- Editorial reviews and letters of communication
- Review articles
- News reports or commentaries
- Articles available only with abstracts
- Case reports/series
- Articles in other languages
- Conference papers

Literature search strategy

Studies falling under the inclusion criteria were searched in different electronic databases and journals like PubMed, Scopus, ResearchGate, Google Scholar, The Lancet, The New England Journal of Medicine (NEJM), Nature, BioMed Central (BMC), Frontiers, the Public Library of Science (PLOS), Journal of Biomedical Sciences, Cell, British Medical Journal (BMJ), MedComm, and the Journal of the American Medical Association (JAMA). Preprint repositories such as medRxiv and bioRxiv were also searched for related preprint articles. In addition, data related to vaccines and VOCs were also collected from the World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) websites. The publication year was restricted to 2012 to 2023.

Moreover, the search was conducted using the following keywords: “COVID-19” OR “SARS-CoV-2” AND “vaccine” OR “effective vaccination” OR “vaccine effectiveness” OR “efficacy of vaccines” OR “immunogenicity” AND “variants of concern” OR “VOC” OR “strains” AND “randomized-controlled trials” AND “side effects” OR “adverse events” AND “transmission” OR “spread” AND “virulence” AND “mechanism” AND “inflammation”. No additional filters were used during the research paper collection.

Data management and analysis

The data was stored in a Microsoft Excel sheet that included the required parts of the completed research. The data was extracted and evaluated systematically from these sheets and was analyzed with SAS software version 9.4.

Results

Study description and their baseline clinical characteristics

A total of 38 papers were collected and screened, of which 22 papers were included in the study as per the inclusion and exclusion criteria for the analysis. Out of the 22 included studies, 6 were peer-reviewed publications, 4 were retrospective cohort studies, 4 were research articles, and 1 study, each not peer-reviewed, was an open-label controlled interventional study, a cross-sectional study, a placebo-controlled trial, a randomized trial, a commentary research article, and a test- negative case-control study. Among these studies, 10 were included in the efficacy analysis, and three were included in the safety analysis. Besides these studies, 5 studies were analyzed for reinfection rate in patients treated with the COVID-19 vaccines.

The participants from the included studies were not restricted to any age group. The mean age of the participants from the included studies was 42 years (ranging from 34.8 to 58.8 years),[14-27, 29-30] while the median age of the participants from the included studies was 54 years (ranging from 30 to 77 years).[28, 31] Furthermore, only the participants affected with alpha, delta, and omicron VOCs were included in the study analysis. The studies included three vaccinations, including BNT162b2 by Pfizer, mRNA1273 by Moderna, and ChAdOx1-S by Oxford–AstraZeneca.

A few baseline clinical and demographic characteristics were not reported due to incomplete data from the included studies. The complete baseline clinical characteristics of the included studies are reported in **Table 1**.

Table 1 Clinical and Demographic Characteristics of the Studies

Article	Total patients(N)	Age (Mean)	Sex (n)			Race/Ethnicity				Variants			Vaccines
			Male	Female	Other[a]	Asian	White	Black	Other[b]	Alpha	Delta	Omicron	
Ward et al 2022[14]	10,35,149	41.1	4,78,268	5,56,881	NA	46,034	8,85,866	39,305	63,944	NR	2,21,146	8,14,003	NR
Nyberg et al 2022[15]	15,16,702	34.8	7, 09,107	8, 07,595	0	75,037	1,26,310 1	80,921	97,643	NR	4,48,843	1,067, 859	497,736[c]; 6,38,254[d,e]
Zali et al 2022[16]	2,70,624	48.2	1,35,931	1,34,693	NR	NR	NR	NR	NR	34,656	8,682	NR	NR
Strasser et al 2022[17]	1,02,315	44	38,833	6,34,82	NR	3,882	78,133	6,720	13,580	NR	20,770	81,545	NR
Webster et al 2022[18]	1,243,212	45.9	541,797	701,415	NR	112,272	978,894	40,756	63,544	NR	NR	1,243, 212	NR
Canetti et al 2022[19]	821	58.8	253	568	NR	NR	NR	NR	NR	NR	NR	NR	154[d], 120[e]

Gram et al 2022[20]	73,24,464	54.8	3,06,6307	42,58,157	NR	NR	NR	NR	NR	10,61,427	33,99,651	2,863,386	7,27,593[e]; 4,770,188[d]
Kirsebom et al 2022[21]	1,127,517	NR	426,669	698,771	2,077	20,519	104,522	4,979	997,497	NR	NR	511,889	NR
Lau et al 2023[22]	5,242	40.3	2,548	2,680	14	NR	NR	NR	NR	NR	NR	NR	3,759[d]
Bruxvoort et al 2021[23]	5,186	39.6	894	1,133	NR	75	634	309	1009	1,436	2,027	NR	NR
Alqahtani et al 2022[24]	958	NR	478	480	NR	NR	NR	NR	NR	NR	NR	NR	480[d]; 478[c]
Guo et al 2022[25]	7,17,577	NR	2,09,794	4,81,574	NR	NR	NR	NR	NR	NR	NR	NR	323,185[d]; 3,29,056[e]
Hammerman et al 2022 [26]	1,49,032	39.3	67,870	81,162	NR	NR	NR	NR	NR	NR	NR	NR	83,356[d]
Bernal et al 2021[27]	19,109	41.8	9,373	9,728	8	3563	11463	390	3,693	14,837	4,272	NR	758[d]; 3,444[c]
Skowronski et al 2022[28]	16,993	77*	8,336	8,657	NR	NR	NR	NR	NR	509	16	NR	10,569[d]; 1,882[e]
Andrews et al 2021[29]	1,87,887	41.3	75,088	112,541	258	NR	1,59,622	2,037	26,228	NR	56,439	581	98,022[d]; 65, 242[c];5,683[e]
Emary et al 2021[30]	8,534	36.5	3,469	5,065	NR	NR	7,863	NR	146	NR	NR	NR	4,244[c]
Madhi et al 2021[31]	2,021	30*	1,142	879	NR	NR	259	1,421	337	NR	NR	NR	1,011[c]
Neto et al 2022[32]	58,097	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	58,097[d]
Rahman et al 2022[33]	1,644	38.4	940	704	NR	NR	NR	NR	NR	NR	NR	NR	731[c]
Polack et al2020 [34]	36,523	53.2	19,075	18,631	NR	1,608	31,266	3,492	11,883	NR	NR	NR	18,860[d]
Yung et al 2023[35]	299,901	10.7	158,947	140,954	NR	NR	NR	NR	NR	NR	NR	3,644	135,197[d]

Abbreviation: NR, not reported.
Note: N, total number of patients; n, number of subjects with observation
*median age
[a]unknown, not determinable, and missing
[b]includes Hispanic and missing
[c]ChAdOx1-S vaccine
[d]BNT162b2/ booster vaccine
[e]mRNA1273 vaccine.

Efficacy of selected vaccines against variants of concerns

A total of 10 studies, in which participants were immunized with any one of three vaccines

(BNT162b2, mRNA1273, and ChAdOx1-S), were included for the efficacy analysis.[19-23, 27- 31] Pfizer's BNT162b2 vaccination had a mean effectiveness of 61.2% in 7 of 10 studies, with efficacy ranging from 33.0% to 90.0% across studies.[19-22, 27-29] Moderna's mRNA1273 vaccination had a mean effectiveness of 73.1% in 5 of 10 studies, with efficacy ranging from 46.0% to 98.4%,[19-21, 23, 28] whereas Oxford-AstraZeneca's ChAdOx1-S vaccination had a mean effectiveness of 68.7% in 5 of 10 studies, with efficacy ranging from 48.9% to 89.8%.[21, 27, 29-31]whereas Oxford-AstraZeneca's ChAdOx1-S vaccination had a mean effectiveness of 68.7% in 5 of 10 studies, with efficacy ranging from 48.9% to 89.8%.[21, 27, 29-31]

These vaccinations, when investigated against the alpha, delta, and omicron VOCs to identify which was the most effective, the BNT162b2 was found to have a mean effectiveness of 58.4%,[19, 27-28] 73.2%,[20, 27, 29] and 54.3%[19, 21-22, 29] against alpha, delta, and omicron variants, respectively.

Similarly, the mRNA1273 achieved a mean effectiveness of 73.3%,[19-20, 23, 28] 78.0%,[20, 23] and 67.9%[19, 21], whereas ChAdOx1-S achieved a mean effectiveness of 66.7%,[27, 30-31] 48.8%,[27] and 81.6%[21, 29] against alpha, delta, and omicron variants, respectively. The complete data representing the efficacy rates of these vaccines against different VOCs is presented in **Table 2**

Table 2 Efficacy Rates of the Vaccines against VOCs

Variants of Concerns (VOCs)	Article	Vaccines		
		BNT162b2 (%)	mRNA1273 (%)	ChAdOx1-S (%)
Alpha	Canetti et al 2022[19]	37.0	46.0	NR
	Gram et al 2022[20]	NR	81.9	NR
	Bruxvoort et al 2021[23]	NR	98.4	NR
	Bernal et al 2021[27]	71.2	NR	61.6
	Skowronski et al 2022[28]	67.0	67.0	NR
	Emary et al 2021[30]	NR	NR	64.0
Delta	Gram et al 2022[20]	83.7	74.5	NR
	Bruxvoort et al 2021[23]	NR	81.6	NR
	Bernal et al 2021[27]	59.4	NR	48.9
	Andrews et al 2021[29]	76.6	NR	NR
Omicron	Canetti et al 2022[19]	37.0	46	NR
	Kirsebom et al 2022[21]	89.8	89.8	89.8
	Lau et al 2023[22]	33.0	NR	NR
	Andrews et al 2021[29]	57.3	NR	73.4

Abbreviations: NR = not reported.
Note: Data is presented in percentage.

Safety results

The adverse event reactions for BNT162b2, mRNA1273, and ChAdOx1-S vaccines ranged from 8.1% to 41.0%, 3.8% to 16.9%, and 11.9% to 45.0%, respectively, across studies (Table S1). The total number of adverse events varied largely across these studies.

For the BNT162b2 vaccine, the most common adverse events (≥10% events) were systematic (41.0%), local (24.8%), myalgia (20.6%), fatigue (18.6%), fever (18.5%), headache (15.9%), and chills (10.9%). For the mRNA1273 vaccine, the most common adverse events (≥10% events) were headache (16.9%) and fatigue (14.5%). For the ChAdOx1-S vaccine, the most common adverse events (≥10% events) were systematic (45.0%), general system disorder NEC (31.4%), fever (27.2%), fatigue (25.1%), myalgia (20.3%), headache (15.7%), joint pain (11.9%), and infections (10.8%; Table S1). A complete description of the adverse events is reported in Supplementary Table 1.

Reinfection rate in patients after receiving vaccination

A few studies showed that even after receiving COVID-19 vaccination, some participants got reinfected with the virus. We included a total of 5 studies to evaluate the reinfection rate of participants infected with COVID-19 virus even after receiving the BNT162b2 and ChAdOx1-S vaccinations. No study was found or assessed for the reinfection rate related to the mRNA1273 vaccine. Four studies were analyzed for reinfection rate after receiving the BNT162b vaccine,[26, 32, 34-35] whereas only one study was found for the ChAdOx1-Sv vaccine. The reinfection rate reported in BNT162b-vaccinated participants ranged from 2.1% to 0.4%.[26, 32, 34-35] In case of the ChAdOx1-S vaccine, only 5.2% participants were found to be reinfected.[33] The complete description of the reinfection rate in vaccinated participants is represented in **Table 3.**

Table 3 Reinfection Rate in Vaccinated Participants

Article	Vaccine	Vaccinated, (n)	Reinfections, n(%)
Hammerman et al 2022[26]	BNT162b2	83,356	354 (0.42%)
Neto et al 2022[32]	BNT162b2	58,097	9 (0.02%)
Rahman et al 2022[33]	ChAdOx1-S	731	38 (5.19%)
Polack et al 2020[34]	BNT162b2	18,860	8 (0.04%)
Yung et al 2023[35]	BNT162b2	135,197	2,845 (2.10%)

Note: n, number of subjects with observation.

Discussion

This systematic review evaluated the safety, efficacy, and reinfection rates of the three COVID-19 vaccines, including BNT162b, mRNA1273, and ChAdOx1-S against alpha, delta, and omicron VOCs. The efficacy results showed that mRNA1273 vaccine by Moderna has the highest efficacy rate among the other vaccines with a mean effectiveness of 73.1% (ranging from 46.0% to 98.4%).[19-21, 23, 28] A similar efficacy was reported for the mRNA1273 and ChAdOx1-S vaccines concluding the fact that all of these three vaccines were effective, protecting thousands of people against COVID-19 VOCs (alpha, delta, and omicron).

Additionally, we evaluated the safety of these vaccines with the same VOCs and analyzed the frequency of adverse event reactions in vaccinated participants. Moreover, the adverse event reactions for BNT162b2, mRNA1273, and ChAdOx1-S vaccines ranged from 8.1% to 41.0%, 3.8% to 16.9%, and 11.9% to 45.0%, respectively, across studies.[24-25, 31] It concluded the fact that even though the efficacy of these vaccination in their recipients is effective, the frequency of these adverse events were not less, which demands further research to improve the safety of these vaccines. Further analysis suggested that the reinfection rate of the BNT162b vaccine ranged from 2.1% to 0.4%, whereas the reinfection rate of the ChAdOx1-S vaccine was 5.2%,[26, 32-35] which suggested the waning efficacy of the vaccination doses in these participants.

These numbers urge the researchers to conduct further clinical trials to improve the safety and efficacy of these vaccinations for longer run in patients infected with different variants of COVID- 19.

Conclusion

This systematic review summarized the safety and efficacy of the various research studies conducted and represented by researchers worldwide. The review's findings showed that while the examined vaccinations are effective and safe for people, additional research is required to

mitigate the adverse reactions and rates of reinfection in those who received the vaccinations.

Conflict of interest

The authors whose names are listed in the paper have no confederations with or involvement in any organization or entity with any financial interest (similar to honoraria, educational grants, participation in speakers' divisions, membership, employment, consultancies, stock ownership, or other equity interest; and expert evidence or patent-licensing arrangements) or non-financial interest (such as personal or professional relationships, confederations, knowledge, or beliefs) in the subject matter or accouterments bandied in this paper.

Data availability statement

The data can be made available upon request from the author

Acknowledgement

Not applicable.

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Adverse Effects of Status Epilepticus and the Treatment Strategies - A Literature Review

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Abstract

Purpose: Status epilepticus (SE) is a neurological emergency characterized by a prolonged seizure lasting for more than 30 minutes or a person having multiple seizures with no recovery between them. The occurrence of more severe adverse events (AEs) may aggravate the condition and raise the mortality rate. This literature review is focused on reporting the AEs of SE and standard treatment approaches.

Methods: For this literature review, we have identified 78 articles via comprehensive searching using the PubMed database, of which 59 were selected.

Discussion: Neurological dysfunction was reported as the most common outcome among patients with SE. The high mortality rate was mainly due to co-morbidities associated with the disorder. Other AEs reported in the patients with SE were respiratory failure, hypotension, septic shock, renal failure, and rhabdomyolysis. Convulsive SE (CSE) is a life-threatening condition mostly present in pediatric patients, which is characterized by prolonged tonic-clonic seizures and always requires a medical emergency. In terms of seizures, elders are more prone than the younger ones. The refractory SE (RSE) and super-refractory SE (SRSE) conditions increase hospitalization and the risk of mortality.

Conclusion: In conclusion, SE conditions can cause serious AEs, which could lead to a high mortality rate. This review article highlights the need for regular patient follow-ups. Moreover, further research and randomized controlled studies are required to develop an effective treatment for SE.

Keywords: Status epilepticus, adverse effects, neurological, mortality, treatment.

Introduction

Status epilepticus (SE) is a life-threatening neurological disorder in which seizures last for more than 30 minutes, or a person may experience more seizures without recovery between them.[1-2] It is mainly caused by brain trauma, infections, cerebrovascular disorders, epilepsy syndromes, and treatment with low concentrations of the antiepileptic drug.[2]

The symptoms of the SE depend upon its types, i.e., convulsive SE and non-convulsive SE. In convulsive SE, patients mostly experience limb stiffness, jerking motions, drooling, rapid eye movements, and grunting sounds. In contrast, in non-convulsive SE, patients usually experience amnesia, confusion, clouding of consciousness, unusual behavior, daydreaming, and speaking problems.[3-5]

Globally, the incidence of SE is around 50 patients per 100,000 population per year. By age group, SE is more prevalent in neonates and infants than in the elderly adult population. The incidence of SE is around 150 patients per 100,000 population in the age group of below one year, <25 per 100,000 patients in the age group 1-5 years, and >50 patients per 100,000 in the age group of above 40 years. If SE is left unattended or delayed in its course of action, it may result in higher morbidity and mortality rates. Globally, the mortality rate of SE is around 2.5%.[6]

An intravenous lorazepam or an injectable midazolam is an effective early treatment for 64–73% of cases of SE.[7] Although high-class randomized studies are lacking, intravenous clobazam may be a helpful substitute.[8] When it is not possible to administer other benzodiazepines intravenously or intramuscularly to children, buccal midazolam can be used as a substitute.[7]

Around 30% of SE patients show resistance against the primary treatment,[9] and some patients delay the treatment after diagnosis, which increases the chance for the development of adverse. effects (AEs) such as metabolic disorder, thrombotic thrombocytopenic purpura, eclamptic seizures, multi-organ dysfunctions, cardiac issues, and respiratory and permanent neurological damage.[10] Moreover, the AEs associated with SE disorder can lead to morbidity and mortality. Therefore, this literature review summarizes the AEs of SE and known treatment strategies.

Methods

This literature review was performed to describe the AEs of SE and treatment strategies based on already published articles. We identified 78 articles via comprehensive searching using the PubMed database and selected 59 relevant published articles for this review. To create a search strategy, the following terms were used: “status epilepticus OR SE”, “causes AND status epilepticus”, “epidemiology AND status epilepticus”, prevalence AND status epilepticus”, “status epilepticus AND mortality”, “status epilepticus complication”, “adverse effects of status epilepticus”, “guidelines for prevention AND status epilepticus”, “current treatment for status epilepticus”, “future treatment against status epilepticus”, “development of drug for status epilepticus”, and “new treatment for status epilepticus”. The search was not limited by period.

All the prospective or retrospective studies were included, where the main focus was epidemiology, prevalence, mortality, AEs, and treatment options or strategies. The crucial data from selected studies were extracted into a separate bibliographic report.

Discussion

Adverse Effects of Status Epilepticus

Status epilepticus has become a primary public health concern due to the significant morbidity and mortality rates and associated AEs such as cognitive impairment, permanent neurological deficits, and subsequent epilepsy. Various risk factors significantly affect the outcomes of SE or sometimes increase the mortality rate. The AEs are presented below in Figure1 and summarized in **Table** 1 and **Table 2**.

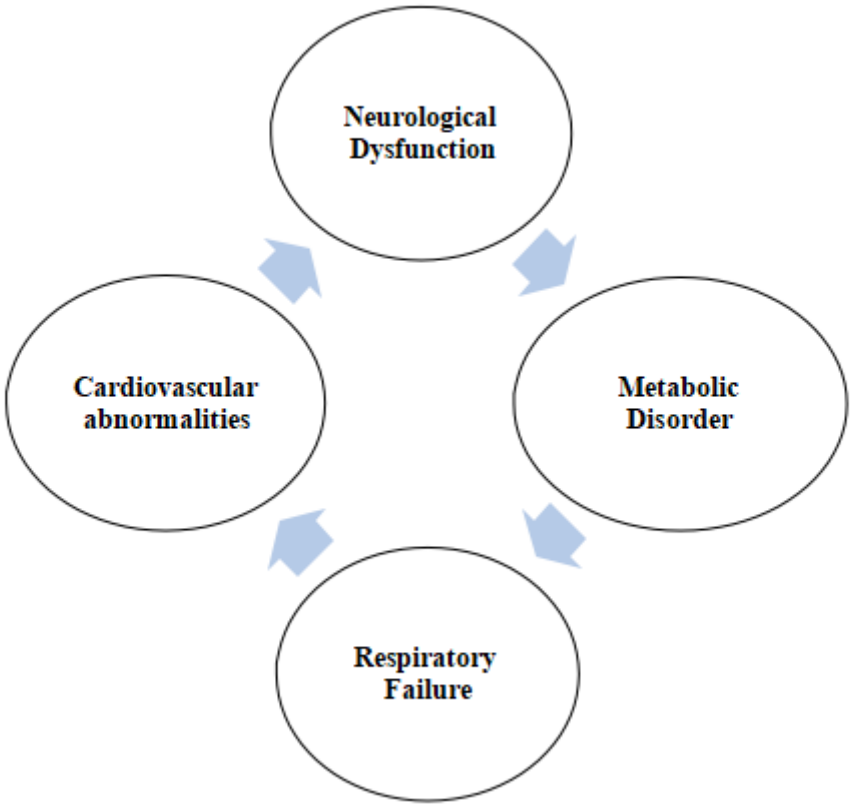

Figure 1 Adverse Effects Associated with Status Epilepticus

Neurological deficit is a persistent AE reported in children because seizures directly affect the brain system when they persist for a long time.[11] Cerebral edema occurs when water starts accumulating in the intra or extracellular spaces, which stops the oxygen circulation in the brain and results in brain damage.[12, 13] Therefore, cerebral edema increases fatality in SE patients.[14] This was reported in 5 children with SE; 4 children were reported to have brainstem dysfunction and cytotoxic edema with cerebral herniation, while 1 child had laminar necrosis. All children died due to severe brain swelling.[15]

Seizures activity for more than 30 minutes is the first sign of SE condition, which leads to neurological problems or sometimes damages the neurological system if seizures do not end immediately. The commonly reported neurological problems (>2%) were epilepsy (14.5%), speech impairment (10%), motor impairment (10%), and vision impairment (2.7%; Figure).[16]

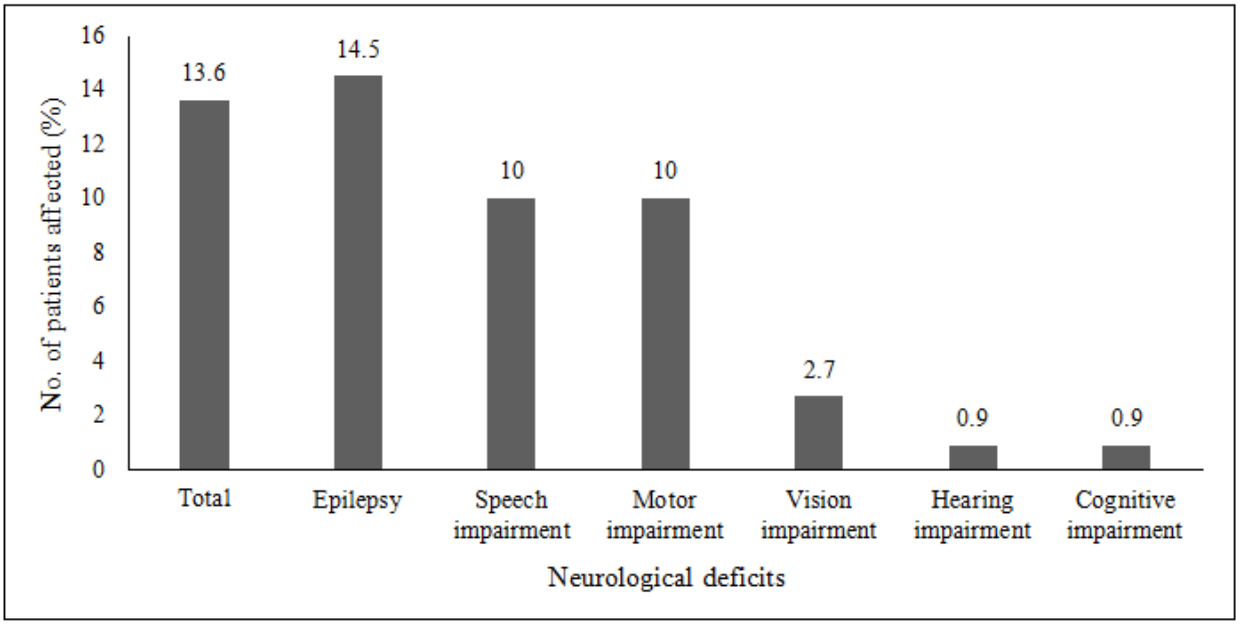

Figure 2 Common Neurological Problems in Children[16]

A study was conducted to ascertain an appropriate dosage of ganaxolone for patients with refractory SE (RSE) and to gather preliminary information regarding its safety and effectiveness. The study involved the enrolment of 17 patients in total. 15 (88%) reported 61 AEs, [23] (38%) of which were thought to be related to the treatment. Sedation was one of the two serious AEs of the treatment. There were 10 serious AEs reported by 6 (35%) patients. Two were considered to be related to the treatment (sedation). The eight serious AEs that were not related to treatment included single events in 2 (12%) patients (sepsis and perforated bowel), two events (respiratory depression and death from life support withdrawal) in 1 (6%) patient, and four events (multiple fractures, fall, loss of consciousness, and pneumothorax) in 1 (6%) patient.[17]

A study was conducted to identify the risk factors determining outcomes in 92 children with SE aged 1 month to 12 years. Of 92 patients, 87 cases were analyzed, of which 74 (85%) recovered, 5 (6%) developed neurological sequelae, 13 (14%) died, and 5 (6%) were discharged with medical help. Of these patients, 25 (27%) had remote causes linked to SE, 18 (20%) had acute CNS infection, 17 (19%) had febrile seizure, and 15 (16%) had cryptogenic or idiopathic SD. The risk factors that significantly ($p<0.05$) affected the SE outcome were decompensated shock, hypoxia, acidosis, and respiratory failure.[18] Few other studies also reported risk factors associated with the poor functional outcome of SE, such as acute symptomatic etiology ($p<0.001$), old age ($p=0.036$), seizure ($p=0.043$), burst suppression ($p=0.016$), and periodic discharge during initial EEG ($p<0.0001$).[19, 20]

Convulsive SE (CSE) is a life-threatening condition mostly present in pediatric patients, which is characterized by prolonged tonic-clonic seizures and always requires a medical emergency. This was reported by a cohort study conducted on 70 children with SE in the children's hospital at Cairo University, Egypt. Twenty-six (37%) patients reported mortality, and 15 (21%) and 17 (24%) had a severe and moderate disability due to refractory CSE, respectively. Therefore, the refractory CSE was considered a significant predictor of morbidity and mortality in SE patients.[21] Another study reported recurred seizure (16%), mental retardation (16%), and mental retardation along with seizures (16%) in the children with CSE. The mortality rate was 22% due to acute symptomatic (11%), febrile (3%), progressive encephalopathy (7%), and idiopathic (1%).[19] It was also reported that acute bacterial meningitis can be a possible predictor of the first episode of CSE in children.[22] Neuropsychological impairments in the infants started early, within 6 weeks, and were present later for 1 year post CSE.[23]

In non-convulsive SE (NCSE), patients have an absence of prolonged seizures. De novo SE patients are more likely to develop NCSE and have poorer outcomes. This was observed in a retrospective study, which aimed to assess the AEs of 87 patients with SE admitted to intensive care units (ICU) of two hospitals in Hong Kong. Mortality was reported in 18% of patients, and 46% of patients reported poor outcomes on discharge. The most commonly reported effects (>11%) with various etiologies were breakthrough seizure (21%), encephalitis/meningitis (18%), idiopathic (15%), and cerebrovascular accident (12%).[24] The early diagnosis of PACNS and treatment with immunotherapy can improve the outcome of NORSE. The patient also reported neurophysiological effects such as a state of confusion and frequent non- convulsive seizures. Cerebrospinal fluid (CSF) analysis was proven helpful in diagnosing PACNS, and the findings showed an increased level of protein.[25]

The incidence of SE or prolonged seizures is higher in older than younger populations, which carry a high risk of mortality and morbidity. This was observed in a study that aimed to assess the outcome of SE in 121 patients and risk factors, including age, pre-existing epilepsy, and co- morbidities during the follow-up. The mortality rate was statistically significant among the older population (54%; $p<0.0001$), mainly due to co-morbidities such as stroke, tumor, and infection. Focal, generalized & combined types of epilepsy were reported in 67 (50%), 47 (35%), and 21 (16%) patients, respectively, and 9 (7%) patients had NCSE.[26]

In refractory status epilepticus (RSE) condition, seizures do not respond to treatment therapy and persist for longer than 60 minutes.[27] A retrospective cohort study was conducted on adult patients with NORSE. Eight (40%) of the 20 NORSE patients experienced potential AEs. Super-refractory SE (SRSE) occurred in 15 (75%) patients. Three patients died during SRSE; the median SE duration for the remaining 17 patients was 10 days (IQR 7–25 days). Two patients died within six months of being discharged from the hospital, and five patients died while they were in the hospital.[28]

In SRSE condition, SE continues for more than 24 hours after the onset of treatment. The SRSE condition increases mortality and morbidity rates and requires immediate treatment.[29-32] A retrospective analysis was conducted in 5 patients with SRSE to assess the clinical symptoms and associations between clinical characteristics of patients in India. Out of 5 patients, 4 had ventilator- associated pneumonia, 2 had metabolic disturbance, 2 died due to increased cerebrospinal fluid (CSF) protein, and another 1 died due to sepsis.[33] A few other cases of SRES revealed morbidities like pneumonia, sepsis, bilateral brain abnormalities, 5-8 seizures per day, and residual neurological deficits.[34, 35]

Rhabdomyolysis (severe muscle damage) was also observed in the patients with SE. This was confirmed by one case study of a 21-year-old man who was hospitalized for SE and had increased uric acid in his blood. He was diagnosed with rhabdomyolysis due to SE and developed acute kidney failure later.[36] .

Table 1 Adverse Effects Associated with Status Epilepticus

Study Author	No of patients	Adverse Effects					
		Neurological	Metabolic	Respiratory	Cardiovascular	Other	Fatality rate
Myers KA, et al15	388	Neurological deficit (4.1 %)	N/A	N/A	N/A	N/A	2.3%
Prins A, et al16	5	Cerebral edema (100%)	N/A	N/A	N/A	N/A	100%
Vaitkevicius H17	17	N/A	N/A	Respiratory depression, pneumothorax	N/A	Sedation, sepsis, perforated bowel, multiple fractures, fall,loss of consciousness	5.9%
Thandavarayan M,et al18	92	Neurological sequels (14 %)	N/A	Hypoxia, respiratory failure	Decompensated shock	N/A	14%
Uzair M, et al19	73	Mental retardation along with seizures(17%), seizure recurrent (16%)	N/A	N/A	N/A	N/A	22%
Kang BS, et al20	120	Simple partial and complex partial seizures, absence, myoclonic seizuretype (40%), generalized convulsive (40%), non-convulsive SE in coma (20%)	N/A	N/A	N/A	N/A	30.7%
Halawa EF, et al 21	70	Refractory CSE	N/A	N/A	N/A	N/A	37%
Martinos MM, et al23	54	Prolonged febrile seizures (50%), non-febrile CSE (50%)	N/A	N/A	N/A	N/A	N/A

Lui HK, et al[24]	87	Breakthrough seizure (21.0%), encephalitis/meningitis (18.3%), cerebrovascular accident (11.5%),hypoxic brain damage (6.9%), traumatic, subdural hemorrhage / subarachnoid hemorrhage	Metaboliccause (10.3%)	Idiopathic(17.8%)		Sepsis (4.6 %)	18%
Horváth L , et al[26]	121	Focal (49.6%), generalized (34.8%) &combined types of epilepsy (34.8 %)	N/A	N/A	N/A	N/A	53.7%

CSE = convulsive status epilepticus; N/A = not applicable: SE = status epilepticus

Table 2 Adverse Effects Associated with Status Epilepticus – Case Studies

Study Author	Patient's Age (Year)	Adverse Effects					
		Neurological	Metabolic	Respiratory	Cardiovascular	Other	Fatality rate
Matar RK, et al[25]	46	State of confusion, frequent non-convulsive seizures	N/A	N/A	N/A	N/A	N/A
Valappil AMN, et$_{al}$[34]	13	Five to eight seizure, bilateral brainabnormalities, visual hallucinations,progressive cerebellar atrophy	N/A	N/A	N/A	Nausea and abdominal pain,small tumor on adrenal gland	N/A
Aroor S, et al[35]	7	Persisting seizures, CSE, residual neurological deficits	N/A	N/A	N/A	N/A	N/A
	7	Spastic quadriparesis, dystonia andchoreo-athetoid movements, generalized tonic-clonic, focalseizures	N/A	N/A	N/A	N/A	N/A
	6	Generalized tonic-clonic seizures, cognitive dysfunction, mutism andorokinetic dyskinesia, autoimmuneencephalitis	N/A	N/A	N/A	N/A	N/A
Wang L, et al[36]	21	N/A	Rhabdomyolysis, acute kidneyfailure	N/A	N/A	N/A	N/A

CSE = convulsive status epilepticus; N/A = not applicable

Treatment Options for Status Epilepticus

SE requires rapid treatment to prevent systemic and neurologic pathology.[6] For this, anti-seizure drugs are effective against SE conditions. Including treatment options, initial management of the SE condition is also necessary, which includes checking airway status, blood pressure, cardiac rhythm, circulatory support, maintaining adequate ventilation, and securing IV access in large veins during seizure activity to prevent future medical

complications.[37] As various studies identified anti-seizure drugs for the management of SE, discussed below:

Treatment for SE:

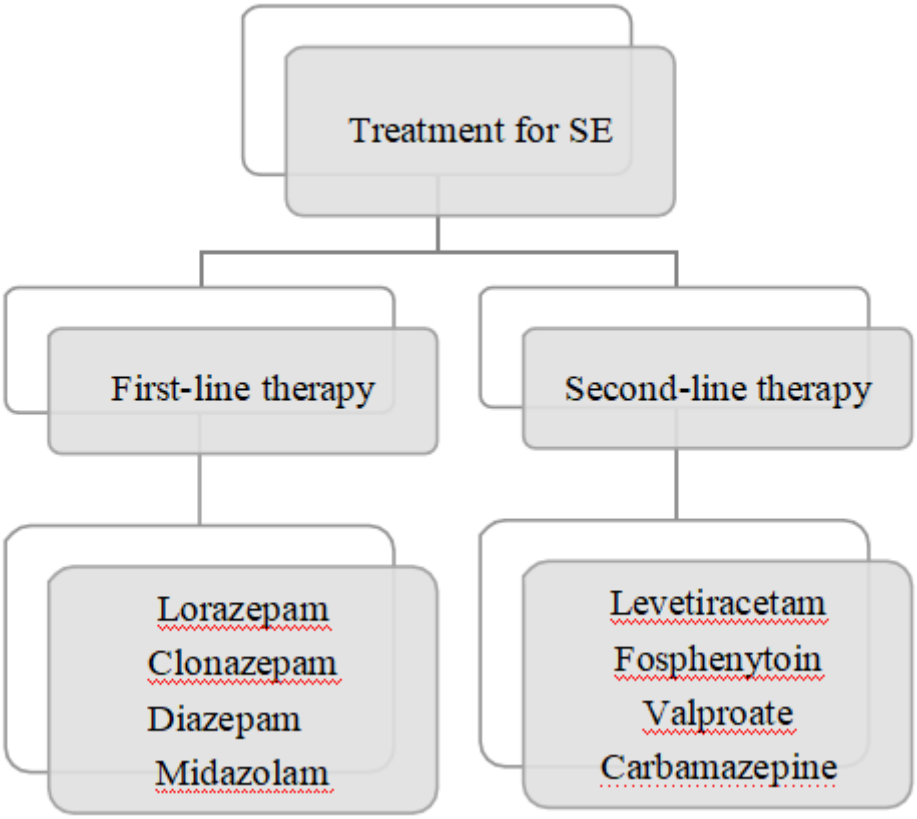

Figure 3 Treatment Option for Status Epilepticus Patients

First-Line Treatment: Benzodiazepines (BZD) such as lorazepam, clonazepam, diazepam, and midazolam are effective drugs used as first-line treatment for prolonged seizures in patients with SE.[38, 39] However, inadequate doses of BZD can lead to the progression of RSE or may increase the tendency of coma in NCSE patients (**Table 3**).[40]

Table 3 FDA-approved Medications among Benzodiazepines for Status Epilepticus

Benzodiazepine	FDA approved forSE	FDA approved fortreatment of seizures	Formulation (route)	Recommended Dose
Clonazepam	No (off-label use)	Yes	Disintegrating tablet (oral)	0.125 mg, 0.25 mg, 0.5 mg, 1 mg, 2 mg
Diazepam	Yes (rectalgel)	Yes	Gel (rectal)	Children <2 years: Safety and efficacy have n ot beenstudied Children 2-5 years: 0.5mg/kg Children 6-11 years: 0.3mg/kg Children 12 years or above: 0.2 mg/kg
Lorazepam	Ye; (paren teral only)	No – off-label use(focal sei zures)	Parenteral	N/A
Midazolam	No (off-labeluse)	No – only forseda tion	Solution (IV, IM, buccal), Syrup, and Buccal	13-40 kg: 5 mg once >40 kg: 10 mg once

IV = intravenous; IM = intramuscular; N/A = not applicable; FDA = Food and Drug Administration; SE = status epilepticus

Second-Line Treatment: After first-line treatment with BZD drugs, SE patients are treated with second-line therapies, i.e., levetiracetam (LEV), fosphenytoin (FPHT), valproate (VPA), and carbamazepine (CBZ).[41-43] The LEV drug is reported to be more effective and safe for the prevention of recurrent seizures in SE patients than FPHT after following the BZD treatment.[41] It has been demonstrated that intramuscular midazolam, intravenous lorazepam,

intravenous diazepam, and intravenous phenobarbital are effective as initial therapies (Level A) in adults with convulsive SE.[44] Including this, IV midazolam is also used as a second-line treatment for pediatric SE. But, when midazolam is compared with FPHT, both drugs have similar efficacy.

However, midazolam therapy treats SE in the pediatric population without barbiturate coma therapy (BCT), while FPHT requires BCT. Mechanical ventilation is more frequently reported in midazolam treatment than in FPHT therapy (32.0% vs. 4.7%, $p = 0.01$).[45]

A 21-year-old male diagnosed with SE associated with Wilson disease was admitted to the ICU and treated with lorazepam (0.1 mg/kg IV) and phenytoin (20 mg/kg bolus IV followed by 6 mg/kg IV as maintenance dosages). The condition improved, and at the 3 month follow-up, the patient showed signs of recovery.[46]

Treatment for RSE:

Benign epilepsy with centrotemporal spikes (BECTS) is a common form of childhood epilepsy, and usually, it can be cured before 16 years. A case study of a 16-year-old girl reported propofol medication-induced RSE in patients with BECTS. Her prolonged seizure, which lasted for about 14 hours, was controlled with diazepam (4 mg/h), propofol (6 mg/kg/h), and VPA (2400 mg/d IV injection). Then, she received VPA (800 mg/d po), oxcarbazepine (600 mg/d po), and LEV (1000 mg/d po). On Day 17, she was discharged without any seizure recurrence during 3 months of follow-up.[47]

Seizure activity in RSE patients can be improved with parenteral phenobarbital (dose 5 to 19.8 mg/kg) without causing any significant complications.[48] In addition, treatment with phenobarbital improved the short-term outcome and decreased the hospital stay of neonates with SE.[49] Phenobarbital terminated the seizure activity faster than parenteral phenytoin ($p<0.0001$). Therefore, phenobarbital can be safely & effectively given to infants for the management of refractory CSE[50]

Treatment for SRSE:

The SRSE patients who did not respond to IV VPA, LEV, lacosamide, thiopental, and midazolam can be improved with 4 mg or 8 mg dose of perampanel.[51] A case study of a 28-year-old female diagnosed with SRSE recovered with 3 cycles of midazolam (3 mg/kg/hr), 2 cycles of thiopentone (6 mg/kg/hr), methylprednisolone, IV immunoglobulin, and acyclovir.[52]

A female with generalized tonic status epilepticus (TSE) initially failed to respond to the anti-seizure drug therapy (LEV and VPA), and later, her seizure was controlled with lacosamide.[53]

Potential Treatment Options for Future Recommendation

The future-recommended treatment options for the treatment of SE condition are discussed below and presented in **Table 4**.

Brexanolone (SAGE-547) is a formulation of allopregnanolone (neuroactive steroid) which was under development (Phase 3) as adjunctive therapy for the treatment of SRSE condition. It effectively controls seizures in SRSE patients without causing any serious side effects.[54, 55]

Ketamine is a strong N-methyl-d-aspartate glutamate receptor antagonist, which was in Phase 3 for the treatment of refractory CSE. The study was completed on 31 March 2020.[56, 57]

Few pre-clinical studies also suggested drugs against SE conditions. Moreover, patients are already treated with LEV as a second-line treatment. However, in a pre-clinical study, when LEV was given via rectal mode to the dogs, this drug showed reasonable control on seizure activity than standard treatments (IV/rectal diazepam and IV phenobarbital).[58] Another pre-clinical study

evaluated novel anticonvulsant/neuroprotectant drugs such as scopolamine, memantine, and phenobarbital in the BZD refractory nerve agents-induced SE. This study found that scopolamine terminated the seizure activity more effectively than memantine, while phenobarbital delayed the seizure termination.[59]

Table 4 Future-Recommended Treatment Options for Status Epilepticus

Study Author	Stage of drugdevelopment	SE ConditionType	Treatment	Dose	Frequency
Rosenthal ES, et al[55]	Phase 1/2	Super-RSE	Brexanolone	N/A	N/A
Rosati A, et al[56]	Phase 3	Refractory CSE	Ketamine	Initial bolus of2–3 mg/kg Continuous infusion of 10 µg/kg/min Preceded by a bolus of 1–2 mg/kg	N/A N/A
			MDZ	2–4 µg/kg	Per minute
			BZD	Reduced from6 to 2 µg/kg Reduced from6 to 3–4 µg/kg/min	Per minute
Cagnotti G, et al[58]	Pre-clinical	SE	LEV	40 mg/kg rectally	N/A
			IV/rectal diazepam and IV phenobarbital	N/A	Every 8 hours
Jackson C, et al[59]	Pre-clinical	RSE	Scopolamine, memantine, and phenobarbital.	N/A	20 min afterSE onset
			Atropine, 2-Pralidoxime, and midazolam	N/A	5, 20, or 40 min afterSE onset

BZD = benzodiazepine; CSE = convulsive status epilepticus; LEV = levetiracetam IV = intravenous; MDZ = midazolam; N/A = not applicable; RSE = refractory status epilepticus; SE = status Epilepticus

Conclusion

Status epilepticus can cause severe AEs, which could lead to a high mortality rate. Neurological complications were considered the most common AEs in patients with SE. Other AEs reported were respiratory failure, hypotension, septic shock, renal failure, and rhabdomyolysis. All these complications occur when there is a delay in the treatment after diagnosis or patients cannot respond to the primary treatment. The worst outcomes of SE are linked to old age, etiology, NCSE, and focal status epilepsy. This review article highlights the need for regular patient follow-ups. Additionally, further research and randomized controlled studies are required to develop an effective treatment of SE.

Conflict of interest

The authors whose names are listed in the paper have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria, educational grants, participation in speakers' bureaus, membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements) or non-financial interest (such as personal or professional relationships, affiliations, knowledge, or beliefs) in the subject matter or materials discussed in this paper.

Data availability statement

The data can be made available upon request from the author.

Acknowledgement

Not applicable.

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