SYSTEMATIC REVIEW

Pharmacological management of seizures in patients with COVID-19: a systematic review [version 1; peer review: 1 approved, 1 approved with reservations]

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Abstract

Background: Some patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been reported to exhibit neurological symptoms such as seizures and impaired consciousness. Our study reviews reported cases to assess the pharmacological approach to managing seizures in SARS-CoV-2 patients and associated outcomes.

Methods: A systematic review of case reports on the incidence of seizures following coronavirus disease 2019 (COVID-19) among patients that reported use of antiepileptic drugs (AEDs) in management was performed by using the PRISMA (preferred reporting items for systematic reviews and meta-analysis) guidelines. Databases used included EMBASE, PubMed, SCOPUS, and Google Scholar. Data was presented as qualitative and descriptive data.

Results: In total, 67 articles were selected for full-text assessment, of which 19 were included in the final review. Patients had a median age of 54 years, most of whom were male. Remdisivir, dexamethasone, Laminavir, hydroxychloroquine, azithromycin, and Lopinavir-ritonavir were common agents used in the management of COVID-19. Most patients presented with either generalized tonic-clonic seizures or status epilepticus. Most patients received levetiracetam as drug choice or as part of their regimen. Other AEDs commonly prescribed included midazolam and sodium valproate. Some patients received no antiepileptic drug therapy. Most of the patients who died had more than one comorbidity. Also, most of the patients who died received COVID-19 treatment drugs. None of the patients who received midazolam as drug choice or as part of their regimen developed recurrent seizures in contrast to patients who received levetiracetam and sodium valproate as drug choice or as part of their regimen. Interestingly, none of the patients who received no AEDs suffered recurrent seizures or died.

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Any reports and responses or comments on the article can be found at the end of the article.

Conclusions: Standard guidelines for managing seizures in COVID-19 patients may be required. A limitation of this review is that it involved the use of case reports with no controls and a small number of patients.

Keywords

SARS-CoV-2, neurological symptoms, levetiracetam, status epilepticus, epilepsy

This article is included in the [Coronavirus \(COVID-19\)](#) collection.

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Introduction

Neurological manifestations have been reported in about one-third of patients with coronavirus disease 2019 (COVID-19). In addition to the primary respiratory symptoms, there have been neurological symptoms manifested at all levels of the nervous system (Mao *et al.*, 2020). Several case studies on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection have demonstrated neurological effects such as strokes, loss of consciousness, encephalopathy, generalized tonic-clonic convulsions and neuralgia (Beyls *et al.*, 2020). This is not entirely surprising as SARS-CoV-1 and Middle East respiratory syndrome coronavirus (MERS-CoV) have previously been associated with sporadic neuropathological changes (Desforges *et al.*, 2020; Lau *et al.*, 2004).

SARS-CoV-2 has been proposed to enter the central nervous system (CNS) either via systemic vascular dissemination or by crossing the cribriform plate of the ethmoid bone (Baig *et al.*, 2020). The latter mechanism is speculated to contribute to anosmia experienced by a quarter of patients (Baig *et al.*, 2020). Similar to SARS-CoV-1, the new SARS-CoV-2 is believed to make its way into biological cells via the angiotensin-converting enzyme 2 (ACE2) receptor (Lan *et al.*, 2020).

Although few cases have been reported, studies indicate that seizures may occur early in the disease process. Nevertheless, the presence of seizures bears heavily on the management and outcome of patients with SARS CoV-2. Recurrent or prolonged seizures, as occurs in status epilepticus, may contribute to or worsen hypoxic encephalopathy, cerebrovascular events, and cytokine storms that can further lead to acute seizures (Bartiromo *et al.*, 2020).

Further to this, COVID-19 may be more difficult to treat in patients exhibiting seizures than in other patients. Antiepileptic drugs (AEDs) tend to cause complex drug-drug interactions and adjustment of these drugs may be necessary to prevent heart, liver, or kidney complications that may occur in patients with severe COVID-19 (Asadi-Pooya *et al.*, 2020). No special guidelines currently exist for management of seizure symptoms in COVID-19. Hence, seizures in patients are controlled with currently available AEDs based on seizure types exhibited by patients. We provide a review of publications on cases of seizure disorders reported in patients with COVID-19, the pharmacological approach to management and outcomes on mortality exploring implications on management of patients.

Methods

Strategy for literature search

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used to perform a systematic review of the literature (Moher *et al.*, 2010; Uwizeye *et al.*, 2021). Comprehensive electronic literature searches were performed in EMBASE, PubMed, SCOPUS, and Google Scholar to identify articles that covered the neuropathological symptoms in COVID-19. This review primarily aimed to synthesize information on seizure-related complications in patients with COVID-19.

The search included articles published in the English Language from January to December, 2020. Keywords used included 'neurology' or 'neurological manifestations' or 'nervous system', 'neuropathy' or 'nerves' and 'COVID-19' or 'SARS-CoV-2' and 'antiepileptic drugs' or 'antiseizure drugs'. A combination of keywords and MeSH terms were applied to maximize the output from literature findings. The full search string for the database search was COVID-19* OR SARS-CoV-2* OR AND neurological manifestations* OR nervous system* AND antiepileptic drugs* OR antiseizure drugs*. The bibliography list of selected articles were screened by reading through the corresponding abstracts in order to identify additional appropriate studies. Screening was done by JPO and disagreements were resolved by all authors. As seizure complications were rare in COVID-19, all articles reporting seizures were included. We included all types of articles or preprints (from the bioRxiv) that met the following criteria: reported the incidence of seizures following COVID-19 among patients of all ages or reported the use of antiepileptic drugs (AEDs) in the management of COVID-19-related seizures. Studies that reported on patients with a history of seizure disorders were excluded from the study. Only reported cases of seizure complications for which explicit temporal or causal association with COVID-19 infection could be determined were included in the review. Animal studies were excluded. All studies selected were initially managed using Microsoft Word v16.45. This review has not been registered and a review protocol was not prepared.

Data extraction

Data was extracted with the aid of a pre-designed data extraction form. Data extraction from full text of eligible articles was done independently by two investigators (PKM and NOA). The following data were obtained: author, country of report, demographic details, the number of patients with COVID-19 having seizure complications, frequency and prevalence of seizures, electroencephalogram (EEG), neuroimaging and/or other laboratory investigations associated with other neuropathological symptoms, management strategies and outcomes. Accuracy of extracted data was rechecked by a third independent investigator. Investigators made every effort to prevent data duplication. Quality of the included cases was assessed based on Consensus-based Clinical Case Reporting (CARE) guidelines for case reports by ensuring the selected cases met the criteria as stated in the 2013 CARE checklist.

Data synthesis and statistical analyses

Studies were first tabulated as qualitative data as selected studies were case reports. Given the small number of cases, descriptive analysis was performed to generate frequencies and percentages. All analyses and data visualisation were conducted using STATA version 13 (StataCorp, College Station, TX, USA).

Results

Study characteristics

A search of literature yielded 249 citations. Following duplicates removal, and titles and screening of abstracts, 67 articles

were selected for full-text assessment. Subsequent to full-text evaluation, 19 articles were used for the final review (Figure 1). Characteristics of the included articles are provided in Table 1. All articles were case reports/series. One article was a multicenter study. Three case reports were of fair quality whereas all other studies were graded to be of good or excellent quality.

Patient characteristics

The 19 articles reported incidence of seizure complications among 29 patients with COVID-19 from nine countries (USA [n=12], Germany [n=2], Italy [n=2], Switzerland [n=2], Iran [n=5], Ireland [n=2], Spain [n=1], France [n=1], Japan [n=1], and Kuwait [n=1]). Of these, 13 (44.8%) had presented with seizures as their primary complaint and first symptom of COVID-19. One study described the incidence of reversible posterior leukoencephalopathy syndrome (PRES) presenting

as refractory status epilepticus. The age of the patients ranged from 2 days to 82 years, the median being 54 (interquartile range, 37–72) years. Of the patients, 41.4% (12/29) were females (Table 1). Moreover, 37.9% (11/29), 34.5% (10/29), and 25.8% (8/29) had 0, 1, and ≥ 2 comorbidities, respectively. COVID-19 treatment drugs were reported for 52% (15/29) of patients. The treatments for COVID-19 received included remdisivir (4 patients), dexamethasone (1 patient), Laminavir (1 patient), hydroxychloroquine (7 patients), azithromycin (1 patient), and Lopinavir-ritonavir (4 patients).

Seizure types and antiepileptic drugs administered

The distribution of the types of seizures presented by the patients are summarized in Figure 2a. Most patients presented with either generalized tonic-clonic Seizures (9/29; 31%) or status epilepticus (9/29; 31%). Two patients presented with non-convulsive status epilepticus while one patient suffered

Figure 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 flow diagram of the literature search and studies included in review (Page et al., 2021).

Table 1. Descriptive characteristics of included studies.

Reference	Patient No.	Country	COVID -19 Drugs	AEDs	Sex	Age (yrs.)	Seizure Disorder Reported	Comorbidities	Seizure History	Outcome
(Karambelkar <i>et al.</i> , 2020)	1	USA	Hydroxychloroquine.	Not stated	male	32	Generalized Tonic-Clonic Seizure	Sleep apnea	Negative	Patient ultimately discharged from intensive care unit after being deemed hemodynamically stable.
	2	USA	None	Lorazepam, Levetiracetam	male	82	Generalized Tonic-Clonic Seizure	Chronic systolic heart failure, atrial fibrillation, hypertension	Negative	The patient succumbed to septic shock despite optimal medical therapy.
(Abdulsalam <i>et al.</i> , 2020)	3	Kuwait	Lopinavir-Ritonavir, Hydroxychloroquine	Diazepam, Midazolam, Levetiracetam	male	32	Generalized Tonic-Clonic Status Epilepticus	Nil of note	Negative	Convulsions aborted on Midazolam. He was discharged after 14 days in stable condition, remaining afebrile after two negative swabs for SARS-CoV-2.
(Balloy <i>et al.</i> , 2020)	4	France	None	Clobazam, Levetiracetam	male	59	Non-convulsive status epilepticus	Atrial fibrillation, obstructive sleep apnea	Negative	Patient was clinically stable and discharged from ICU.
(Chen <i>et al.</i> , 2020)	5	USA	Remdisivir	Levetiracetam, Phenytoin	female	37	Status epilepticus	Multiple; end stage renal disease	Negative	Seizures resolved, discharges slowed, mental status improved.
	6	USA	Remdisivir	Levetiracetam	female	60	Non-convulsive status epilepticus	Hypertension	Negative	Improvement.
	7	USA	Remdisivir	Levetiracetam	male	50	Seizure-like	Nil of note	Negative	Rapid-EEG showed moderate to severe seizure activity.
	8	USA	Remdisivir	Levetiracetam	female	38	Seizure-like	Orthotopic heart transplant, heterotopic kidney transplant, diabetes, chronic congestive hepatopathy, pulmonary hypertension	Negative	No epileptiform discharges or seizures observed. Rapid-EEG converted to conventional EEG, showed moderate-severe.

Reference	Patient No.	Country	COVID -19 Drugs	AEDs	Sex	Age (yrs.)	Seizure Disorder Reported	Comorbidities	Seizure History	Outcome
(Gómez-Enjuto <i>et al.</i> , 2020)	9	Spain	Hydroxychloroquine, Lopinavir-ritonavir, dexamethasone, ceftriaxone, enoxaparin	Diazepam, lacosamide, sodium valproate	male	74	Refractory Status Epilepticus	IgG kappa multiple myeloma		Patient stabilized.
	10	Iran	None	Levetiracetam, midazolam	female	54	Status Epilepticus	HIV		Expired in ICU.
(Emami <i>et al.</i> , 2020)	11	Iran	Hydroxychloroquine	Midazolam	male	42	Status Epilepticus	No	Negative	Expired in ICU.
	12	Iran	Lopinavir-Ritonavir	Midazolam, levetiracetam	male	35	Seizure-like events	HIV	Negative	Expired in ICU.
	13	Iran	Dexamethasone	Phenobarbital, levetiracetam, valproate, phenytoin, midazolam, thiopental, fentanyl	male	2.9	Seizure-like events	Nil of note	Negative	Discharged.
	14	Iran	None	Phenobarbital	female	2 days	Seizure-like events	Low birth weight	Negative	Expired in ICU.
(Bhatta <i>et al.</i> , 2020)	15	USA	None	Lorazepam, Levetiracetam	male	11	Generalized tonic-clonic seizure	Nil of note	Negative	Seizures aborted.
(Moriguchi <i>et al.</i> , 2020)	16	Japan	Laminavir*	Levetiracetam	male	24	Generalized tonic-clonic seizure	Nil of note	Negative	Patient was still undergoing treatment.
(Duong <i>et al.</i> , 2020)	17	USA	Hydroxychloroquine	Levetiracetam	female	41	Generalized tonic-clonic seizure	Obesity, Diabetes	Negative	Improvement in mentation.
(Haddad <i>et al.</i> , 2020)	18	USA	Hydroxychloroquine, azithromycin	None	male	41	Generalized tonic-clonic seizure	Well controlled HIV	Negative	On day 6 of hospitalization, the patient's level of consciousness improved off sedation and was successfully extubated.
(Sohal & Mansur, 2020)	19	USA	Hydroxychloroquine, azithromycin	Levetiracetam, Valproate	male	72	Tonic seizures	Coronary artery disease with stent, DM type 2, Hypertension, end stage kidney disease	Negative	A code blue was called on admission day 5 after patient became pulseless. ROSC was not be achieved.

Reference	Patient No.	Country	COVID -19 Drugs	AEDs	Sex	Age (yrs.)	Seizure Disorder Reported	Comorbidities	Seizure History	Outcome
(Bernard-Valnet <i>et al.</i> , 2020)	20	Switzerland	None	Clonazepam, Valproate	female	64	Focal status epilepticus	None stated	Negative	The patient markedly improved 96h after admission with resolution of her symptoms.
	21	Switzerland	None	None	female	67	Unclassified	None stated	Negative	Neurological symptoms resolved within 24h.
(Zanin <i>et al.</i> , 2020)	22	Italy	None	lacosamide, levetiracetam, phenytoin	female	54	Generalized tonic Clonic seizures	AcomA aneurysm	Negative	The patient was transferred to rehabilitation without sensorimotor deficits after 12 days.
(Hepburn <i>et al.</i> , 2021)	23	USA	Not stated	Levetiracetam	male	76	Myoclonic and Focal Seizures	Asthma, , chronic kidney disease, diastolic dysfunction, hypertension hyperlipidemia, left bundle branch block, cervical fusion	Negative	Clinical and electrographic seizure activity subsided.
	24	USA	Not stated	Levetiracetam	male	82	Focal Status Epilepticus	COPD, complete heart block, chronic kidney disease, venous thromboembolic disease,	Negative	Seizure frequency improved after receiving levetiracetam. Patient remained on the ventilator, family opted for withdrawal of life-sustaining support after 20 days of ICU stay
(Logmin <i>et al.</i> , 2020)	25	Germany	Not stated	Not stated	female	70	Non-epileptic seizures/ Convulsive syncope	Syncope, neuropathic pain, atrial fibrillation	Negative	She recovered well without requiring intensive care.
	26	Italy	Lopinavir-Ritonavir	None	male	54	Focal Seizure	Nil of note	Negative	Patient's EEG recorded the following day after first incident indicated no abnormalities. Patient recovered after 2 weeks of antiviral therapy

Reference	Patient No.	Country	COVID -19 Drugs	AEDs	Sex	Age (yrs.)	Seizure Disorder Reported	Comorbidities	Seizure History	Outcome
(Gaughan <i>et al.</i> , 2020)	27	Ireland	None	None	male	87	Generalized tonic-clonic seizure	Nil of note	Negative	Patient remained clinically well, no respiratory symptoms during admission. EEG was performed following discharge demonstrated intermittent fronto-temporal dysfunction maximal on the right side, compatible with the known imaging abnormalities.
	28	Ireland	None	Lorazepam	female	77	Generalized tonic-clonic seizure	Nil of note	Negative	Seizure aborted, Montreal Cognitive Assessment (MOCA) performed four months post hospitalization was 24/30, suggesting persistent cognitive deficit.
(Elgamasy <i>et al.</i> , 2020)	29	Germany	None	Levetiracetam, Clobazam, Lacosamide Magnesium	female	73	Focal seizure	Hypertension	Negative	The patient was discharged home for self-isolation

Figure 2. Seizure types (A) and of anti-epilepsy drugs administered (B) in 29 coronavirus disease 2019 (COVID-19) patients with seizure disorders.

refractory status epilepticus. The majority (19/29; 65.5%) of patients received levetiracetam as drug choice or as part of their regimen (Figure 2b). Moreover, 17.2% (5/29) and 13.8% (4/29) received midazolam and sodium valproate as drug choice or as part of their regimen, respectively, whereas 17.2% (5/29) received no drug therapy (Figure 2).

Seizures and patient outcomes

In all, 24.1% (7/29) of patients died, including 9.1% (1/11) of patients with no comorbidities and 33.3% (6/18) of those with ≥ 1 comorbidity. Moreover, 28.6% (4/14) of patients who received no COVID-19 treatment drugs died whereas 20% (3/15) of those who received COVID-19 treatment drugs died. Overall, 31.0% (9/29) of patients had recurrent seizures of whom 22.22% (2/9) died. None of the patients who received midazolam as drug choice or as part of their

regimen developed recurrent seizures whereas 52.6% (10/19) and 25% (1/5) of patients who received levetiracetam and sodium valproate as drug choice or as part of their regimen developed recurrent seizures, respectively (Table 2). The proportion of patients who received midazolam, levetiracetam, or sodium valproate as drug choice or as part of their regimen who died were 60% (3/5), 26.3% (5/19), and 50% (2/4), respectively. Moreover, none of patients who received no AEDs suffered recurrent seizures or died.

Discussion

This systematic review synthesized evidence on the pharmacological management and outcomes in patients with COVID-19 who experienced seizure disorders. Our findings revealed significant heterogeneity in the pharmacological management of seizures in COVID-19 patients. This may be

Table 2. Outcomes of AED-treated COVID-19 patients experiencing seizures.

AED(s)	Recurrent seizures		Survived	
	Yes (n = 9)	No (n = 20)	Yes (n = 22)	No (n = 7)
Levetiracetam (n = 19)	9 (47.37)	10 (52.63)	14 (73.68)	5 (26.31)
Midazolam (n = 5)	0 (0)	5 (100)	2 (40)	3 (60)
Sodium Valproate (n = 4)	3 (75)	1 (25)	2 (50)	2 (50)
Other drugs (n=2)	0 (0)	2 (100)	1 (50)	1 (50)
No drug (n=6)	0 (0)	6 (100)	6 (100)	0 (0)

AED = antiepileptic drug; COVID-19= coronavirus disease 2019

ascribed to the limited knowledge of the pathophysiology of seizures in COVID-19 patients and the lack of evidence-based guidelines. In all, nearly 1 in 4 patients died which may reflect the poor prognosis and clinical challenge in managing these patients. The study also identified status epilepticus and generalized tonic-clonic seizures as the seizure types with highest incidence in COVID-19 patients. Moreover, development of recurrent seizures and mortality appeared to vary according to the AED used.

Researchers have related the incidence of seizures in COVID-19 patients to factors such as multiple organ failure, hypoxia and severe metabolic and electrolyte changes that may be experienced by these patients (Asadi-Pooya *et al.*, 2020). A suggested mechanism by (Nikbakht *et al.*, 2020) associates the incidence of seizures in patients with COVID-19 to increased proinflammatory cytokine (IL-1B, IL-6, TNF-a) levels by microglia/astrocytes in the brain after viral entry through nerve pathways (directly) or ACE2 receptors (indirectly). This results in the elevation glutamate and aspartate levels, and reduction in levels of Gamma-amino butyric acid (GABA) and disruption of the blood brain barrier (BBB), in the CNS. These effects are notably involved in the pathophysiology of seizures in patients (Nikbakht *et al.*, 2020).

Evidence from literature suggests poorly-controlled brain inflammation in the pathophysiology of status epilepticus (SE). Elevated levels of proinflammatory cytokines have been identified in the CSF of patients with refractory SE (Wang & Chen, 2018). Generalized seizure pathogenesis has also been associated with cytokines - TNF-a, IL-1B and IL-6 (Dede *et al.*, 2017). The increased cytokine levels suggested in COVID-19 may explain the high incidence of status epilepticus and generalized seizures in COVID-19 patients.

Levetiracetam is one of three drugs identified to have high efficacy and comparable side effect profiles in the management of refractory SE (Chamberlain *et al.*, 2020; Kapur *et al.*, 2019). Regardless, the benzodiazepines remain first line in SE

according to the NICE Guidelines (Nunes *et al.*, 2012). Levetiracetam is an AED initially approved for partial onset seizure as an adjunct and subsequently as an adjunct in juvenile myoclonic seizures and generalized tonic-clonic seizures in the US. In the European Union, it is used as initial monotherapy in these conditions. With low protein binding and predominant kidney excretion, pharmacokinetic interactions are not a major concern. However, enzyme-inducing AEDs have been shown to cause a reduction in levetiracetam serum levels and promote higher clearance (Abou-Khalil, 2008). Its good pharmacokinetic interaction profile may warrant its use in COVID-19 cases. The mechanism of action of levetiracetam is via binding to SV2A, a synaptic vesicle protein, which results in the reduction of vesicle release rate of neurotransmitters (Lynch *et al.*, 2004).

Levetiracetam has been identified to decrease levels of the cytokines, IL-1B, IL-2 and TNF-a (Himmerich *et al.*, 2013) and may therefore be beneficial in seizure management in COVID-19 patients. However, a study conducted by Li *et al.* (2013) revealed the role of levetiracetam in inhibiting CD8+ T-Lymphocyte function, which is key in protection against viral infections. The study related this effect to the elevated incidence of upper respiratory tract infections in patients receiving levetiracetam. Administration of levetiracetam in COVID-19 patients may therefore be associated detrimental respiratory effects and may explain the association between increased mortality and levetiracetam administration in COVID-19 patients with seizures as seen in our study. However, further research will be needed in drawing definite conclusions on this association.

The finding of increased mortality in patients with SE is consistent with the general high mortality associated with SE. Status epilepticus has evidently remained a clinical emergency with poor short- and long-term outcomes as well as high morbidity and mortality in the affected population (Marawar *et al.*, 2018; Stelzer *et al.*, 2015). An acute symptomatic cause such as a CNS infection, as occurs in COVID-19, has been identified

as a critical factor related to morbidity. Treatment challenges such as delayed initiation of therapy and lack of effective medication have been identified to be possibly related to higher mortality (Stelzer *et al.*, 2015).

Conclusion

The adequacy of antiseizure medication administered may be of concern and there is a need for the establishment of proper seizure management guidelines in COVID-19.

Study limitation

Our study involved the use of case reports with no controls and a significantly small number of patients.

Data availability

All data underlying the results are available as part of the article and no additional source data are required.

Reporting guidelines

DRYAD: PRISMA checklist for ‘Pharmacological management of seizures in patients with COVID-19: a systematic review’. <https://doi.org/10.5061/dryad.2jm63xspf> (Uwizeye *et al.*, 2021).

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Current Peer Review Status: ? ✓

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Thomas A. Tagoe

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The authors present here a systemic review of case reports on the incidence of seizures among patients who were hospitalised due to COVID-19 infections. The reports include those published between January to December 2020. The databases that were searched as well as the search string used is provided to allow reproduction of their work. The authors identify 67 articles which was narrowed down to 19. Based on these reports, the frequency of specific anti epileptic drugs used in case management is clearly reported as well as the type of seizures and patient outcomes. Studies that reported on patients with a history of seizures were excluded. Only cases of seizure complication for which a temporal or causal relationship with COVID-19 infection could be determined were included. This contributed towards focusing the scope of the review. The authors do a good job of pulling out key pieces of information from each report and discuss the potential pathways by which AEDs could overlap with COVID-19. Based on the reports presented as part of the review, the authors conclude that AEDs could potentially be worsening patient outcomes. Although the review is scientifically sound, there are a few outstanding points which could further strengthen the review if addressed.

1. Figure 1 shows that 48 out of 67 retrieved records were excluded. Details on the common reasons for exclusion among the 48 cases that were cut will be useful.
2. According to the methodology, data extracted included "...frequency and prevalence of seizures, electroencephalogram (EEG), neuroimaging and/or other laboratory investigations associated with other neuropathological symptoms,...". However this information is not included in any of the tables or results presented.
3. Under the study characteristics, there is no basis given for judging case reports as "fair", "good" or "excellent".
4. The labelling of the flow diagram in figure 1 could be done vertically rather than horizontally, purely for aesthetic reasons and better reading.

5. Information on seizure history is absent for some of the reported cases (9 and 10). Considering that this was a critical point in selection of cases, it will be great to know if this information was absent from the primary reports or erroneously left out of the review.
6. The data in this review clearly shows that all the patients who did not receive AEDs ($n = 6$), did not suffer recurrent seizures and also survived. This is a curious finding which could have been further explored in the discussion.
7. Based on the mechanism of action of levetiracetam, the authors propose that "Administration of levetiracetam in COVID-19 patients may therefore be associated detrimental respiratory effects and may explain the association between increased mortality and levetiracetam administration in COVID-19 patients with seizures as seen in our study". Although this is sound, patients that received levetiracetam also showed the highest survival rates among all the patients who received AEDs. A discussion around another AED with a different mechanism of action from levetiracetam and worse survival rates would have enriched the review.

Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?

Yes

Is the statistical analysis and its interpretation appropriate?

Not applicable

Are the conclusions drawn adequately supported by the results presented in the review?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Epilepsy, Plasticity, Learning and Memory

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 05 Nov 2021

Priscilla Mante, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana

1. Figure 1 shows that 48 out of 67 retrieved records were excluded. Details on the common reasons for exclusion among the 48 cases that were cut will be useful.

Answer: The authors have provided information on the inclusion/exclusion criteria in the methods section. The 48 records excluded did not meet the strict inclusion criteria.

2. According to the methodology, data extracted included "...frequency and prevalence of

seizures, electroencephalogram (EEG), neuroimaging and/or other laboratory investigations associated with other neuropathological symptoms,...". However this information is not included in any of the tables or results presented.

Answer: This information, where available and relevant to the study and findings, were added to the outcome section of Table 1.

3. Under the study characteristics, there is no basis given for judging case reports as "fair", "good" or "excellent".

Answer: The Murad tool was used to evaluate the studies for methodological quality and risk of bias. Studies were considered as "poor," "moderate/fair," or "good/excellent" quality when 3 or fewer, 4, or 5 of the criteria were fulfilled, respectively. This criterion has been updated in the manuscript.

4. The labelling of the flow diagram in figure 1 could be done vertically rather than horizontally, purely for aesthetic reasons and better reading.

Answer: The authors would appreciate further clarification on this comment.

5. Information on seizure history is absent for some of the reported cases (9 and 10). Considering that this was a critical point in selection of cases, it will be great to know if this information was absent from the primary reports or erroneously left out of the review.

Answer: The seizure histories of patients 9 and 10 were not reported and negative respectively; the table has been updated accordingly.

6. The data in this review clearly shows that all the patients who did not receive AEDs (n = 6), did not suffer recurrent seizures and also survived. This is a curious finding which could have been further explored in the discussion.

Answer: The discussion has been updated accordingly.

7. Based on the mechanism of action of levetiracetam, the authors propose that "Administration of levetiracetam in COVID-19 patients may therefore be associated detrimental respiratory effects and may explain the association between increased mortality and levetiracetam administration in COVID-19 patients with seizures as seen in our study". Although this is sound, patients that received levetiracetam also showed the highest survival rates among all the patients who received AEDs. A discussion around another AED with a different mechanism of action from levetiracetam and worse survival rates would have enriched the review.

Answer: The discussion has been updated accordingly.

Competing Interests: None to declare

Reviewer Report 06 July 2021

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Ella A. Kasanga

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Anthony Oppong-Gyebi

Biogen Inc., Cambridge, MA, USA

This is an interesting review on reported cases of seizure disorders in COVID-19 cases in 2020, the diverse pharmacological agents used and outcomes on mortality. The authors shed light on the limitations of this review as there are not a lot of reported cases within the timeline of the investigation. In our opinion, the authors should consider the following highlighted points to expound on the findings from their review.

Major Comments

1. In reading the introduction, the authors state the information provided by this review. However, it is still unclear what unmet need this review is aiming to answer. Providing more clarification (at least a sentence or two) on the purpose of this review, in our opinion, will underscore the relevance of the review.
2. What were the criteria for selecting the 4 electronic literature search platforms used for this review? Could more information be garnered from these additional search platforms - the Cochrane Library, Web of Science Core Collection, CENTRAL, and clinicaltrials.gov?
3. What was the rubric for the grading system for the reports (fair quality vs good/excellent quality)?
4. There are a number of inconsistencies in the patient and publication counts. Specifically,
 1. It is stated that there are 19 studies/references but Table 1 only shows 18 references.
 2. Under patient characteristics, it is stated that the patients were from 9 countries, however, there are 10 countries listed.
 3. The patient count from the patient characteristics section adds up to 29, however, the table only shows data for 28 patients.
5. In table 1, for patients 9 and 10, are the seizure histories not reported or negative? Please clarify.
6. The authors stated that there is significant heterogeneity in the pharmacological management of seizures in COVID-19. Was that conclusion based on any inferential statistics run or it was based on the observation from the descriptive statistics?

7. In patient 16, Moriguchi *et al.* ¹ indicated that the patient received Laninamivir. Is this the same as Laminavir indicated in Table 1? Why is there an asterisk on Laminavir (no information is provided on the use of the asterisk in the table legend)?
8. The conclusion of the review article could be expounded a little bit further. The authors stated that 'The adequacy of anti-seizure medication administered may be of concern'. How did they come up with this conclusion?
9. In the title of this review, the authors refer to the pharmacological management of seizures. However, the term, 'pharmacological management' does not just entail the choice of pharmacological agent (which is the highlight of this review), but also the duration of therapy, dose, possible side effects, and other aspects. Thus, in our opinion, the title does not fully represent the content of the review.

Minor Comments

1. In the co-morbidities column for table 1, different terms have been used to signify no comorbidities – no, nil of note, and none stated. The authors can consider using one term for consistency.
2. In table 1, the seizure description for patients 7 & 8 are incomplete (as compared to patients 12, 13 and 14).
3. Please define ROSC (as used for patient 19 in table 1).
4. There are words omitted in the discussion section, for instance:
 1. This results in the elevation **of** glutamate and aspartate levels.....
 2. Administration of levetiracetam in COVID-19 patients may therefore be associated **with** detrimental.....

References

1. Moriguchi T, Harii N, Goto J, Harada D, et al.: A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. *Int J Infect Dis.* 2020; **94**: 55-58 [PubMed Abstract](#) | [Publisher Full Text](#)

Are the rationale for, and objectives of, the Systematic Review clearly stated?

Partly

Are sufficient details of the methods and analysis provided to allow replication by others?

Yes

Is the statistical analysis and its interpretation appropriate?

Yes

Are the conclusions drawn adequately supported by the results presented in the review?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Parkinson's disease, stroke, neurological disorders, neuropharmacology

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however we have significant reservations, as outlined above.

Author Response 05 Nov 2021

Priscilla Mante, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana

Major Comments:

1. In reading the introduction, the authors state the information provided by this review. However, it is still unclear what unmet need this review is aiming to answer. Providing more clarification (at least a sentence or two) on the purpose of this review, in our opinion, will underscore the relevance of the review. Answer:

Answer: The introduction has been updated accordingly.

2. What were the criteria for selecting the 4 electronic literature search platforms used for this review? Could more information be garnered from these additional search platforms - the Cochrane Library, Web of Science Core Collection, CENTRAL, and clinicaltrials.gov?

Answer: The four search platforms were made the focus of the search after preliminary search for such cases. Given that the review was focused on case reports due to the scarcity of such cases, majority of the databases stated by reviewers were not useful.

3. What was the rubric for the grading system for the reports (fair quality vs good/excellent quality)? Answer: The Murad tool was used to evaluate the studies for **methodological quality** and risk of bias. Studies were considered as "poor," "moderate," or "good/excellent" quality when 3 or fewer, 4, or 5 of the criteria were fulfilled, respectively.

Answer: This criterion has been updated in the manuscript.

4. There are a number of inconsistencies in the patient and publication counts. Specifically, It is stated that there are 19 studies/references but Table 1 only shows 18 references.

Answer: This has been corrected.

Under patient characteristics, it is stated that the patients were from 9 countries, however, there are 10 countries listed.

Answer: This has been corrected.

The patient count from the patient characteristics section adds up to 29, however, the table only shows data for 28 patients.

Answer: Table 1 does show data for 29 patients and not 28, in accordance with the patient count from the patient characteristics.

5. In table 1, for patients 9 and 10, are the seizure histories not reported or negative? Please clarify.

Answer: The seizure histories of patients 9 and 10 were not reported and negative respectively; the table has been updated accordingly.

6. The authors stated that there is significant heterogeneity in the pharmacological management of seizures in COVID-19. Was that conclusion based on any inferential statistics run or it was based on the observation from the descriptive statistics?

Answer: This conclusion was based on the observation from the descriptive characteristics.

7. In patient 16, Moriguchi *et al.* ¹ indicated that the patient received Laninamivir. Is this the same as Laminavir indicated in Table 1? Why is there an asterisk on Laminavir (no information is provided on the use of the asterisk in the table legend)?

Answer: The study reported the use of Laninamivir. This has been made consistent throughout the manuscript. The asterisk was used to indicate the ongoing nature of the case. It has however been removed from the table.

8. The conclusion of the review article could be expounded a little bit further. The authors stated that 'The adequacy of anti-seizure medication administered may be of concern'. How did they come up with this conclusion?

Answer: Based on the information available, adequacy of antiseizure medications used may still be in question as the results of the study. Provide no concrete conclusions on the advantage of specific anti-seizure drugs.

9. In the title of this review, the authors refer to the pharmacological management of seizures. However, the term, 'pharmacological management' does not just entail the choice of pharmacological agent (which is the highlight of this review), but also the duration of therapy, dose, possible side effects, and other aspects. Thus, in our opinion, the title does not fully represent the content of the review.

Answer: The term 'pharmacological management' may also simply describe the use of drug therapy for management of conditions and as such, may have emphasis laid on medication choice

Minor Comments

1. In the co-morbidities column for table 1, different terms have been used to signify no

comorbidities – no, nil of note, and none stated. The authors can consider using one term for consistency.

Answer: Authors agree that the use of 'nil of note' and 'no' connote the same thing and has all been changed to 'nil of note' for consistency. However, the use of 'none stated' is to suggest that the reference provided no such information and as such, does not suggest the absolute absence of any comorbidity.

2. In table 1, the seizure description for patients 7 & 8 are incomplete (as compared to patients 12, 13 and 14).

Answer: This has been corrected.

3. Please define ROSC (as used for patient 19 in table 1).

Answer: ROSC has been defined in table 1.

4. There are words omitted in the discussion section, for instance:

This results in the elevation **of** glutamate and aspartate levels.....

Answer: This has been corrected.

Administration of levetiracetam in COVID-19 patients may therefore be associated **with** detrimental.....

Answer: This has been corrected.

Competing Interests: None to declare