Journal of Psychiatry & Mental Disorders

Open Access

Austin Publishing Group

Review Article

Aggravation of Behavioural Side Effects of Antiseizure Medications during COVID-19

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Received: October 01, 2021; **Accepted:** October 29, 2021; **Published:** November 28, 2021

Abstract

Epilepsy affects more than 50 million people worldwide, 80% of whom reside in developing countries. The ongoing COVID-19 pandemic has impacted the physical, emotional and psychological well-being of people across the world including patients with epilepsy, who have a higher prevalence of psychological distress during public health emergencies. Long-term adherence to therapy is crucial for the successful management of epilepsy. Anti-Seizure Medications (ASMs) are however, known to be associated with Behavioural Adverse Events (BAEs) and psychiatric adverse events. Adverse events not only are a common cause of ASM discontinuation, they also negatively impact Quality of Life (QoL) in majority of Persons with Epilepsy (PWE). Many of the proposed COVID-19 treatments also have the potential for neuropsychiatric side effects as well as drug-drug interactions. Hence, it is important to carefully consider the risk-benefit of each agent before initiating therapy in a PWE.

Introduction

Epilepsy affects more than 50 million people world-wide and according to the World Health Organization (WHO), 80% of these people reside in developing countries [1]. India, a developing country, has a prevalence of epilepsy of about 1%. This translates to an estimated, more than 10 million Persons with Epilepsy (PWE) in India, the rate in rural communities being twice that of urban areas [2].

One of the biggest challenges that the world is facing currently, is the pandemic of Coronavirus Disease 2019 (COVID-19). This novel infectious disease, caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), brought along several complications which were previously unknown to society. Apart from the high mortality rates, this pandemic has also severely impacted the physical, emotional and psychological well-being of people around the world. [3,4].

Could Individuals with Epilepsy be at Higher Risk of COVID-19 than Others?

Until now, there has been no clear association between epilepsy and COVID-19, reported in literature. However, despite the lack of enough evidence, the Center for Disease Control and Prevention (CDC) suggests that neurological comorbidities, including epilepsy, may be a risk factor for COVID-19. [5]. A recently conducted cross-sectional observational study reported that the cumulative incidence, (defined as number of patients with active epilepsy and COVID-19 admitted to an emergency department divided by the total number of patients with epilepsy at risk) was higher in patients with active epilepsy compared to the population without epilepsy. Epilepsy was found to be associated with fatality during hospitalization. However, in Reverse Transcription-Polymerase Chain Reaction (RT PCR)-positive patients, there were no significant differences found in Case Fatality Rates (CFR) in patients with active epilepsy compared to patients without epilepsy. Further analysis showed that factors such as hypertension and age were associated with fatality during hospitalization [6].

The effect of COVID-19 on patients with epilepsy

Earlier studies have shown the presence two Angiotensin-converting enzyme receptors on the surface of glial cells and neurons of the Central Nervous System (CNS). Thus, making the CNS a potential target for SARS-CoV-2 [7].

The rate of neurological comorbidity is not thought to be greater for COVID-19 than any other respiratory viral infectious diseases. However, there is a likelihood of patients with epilepsy to get infected with COVID-19 or any other infectious diseases and have fever, which may later trigger seizures [5].

Symptoms pertaining to COVID-19 have been mainly associated with respiratory or gastrointestinal system and not commonly related to seizures [5]. A recent retrospective case series however, noted that seizures in patients with COVID-19 may be triggered by metabolic factors, systemic illness and possibly direct effects of the virus. In all these cases, patients presented to the emergency department with seizures, regardless of prior symptoms of COVID-19 [8]. Further supporting evidence will be required to determine conclusively, the possible effects of COVID-19 on patients with epilepsy and its role in development of new-onset epilepsy cases [5].

Some societies have suggested that COVID-19 could increase the risk of Sudden Unexpected Death in Epilepsy (SUDEP) based on previous evidence with pathogenic fungal agents. However, data is lacking to support such an association between COVID-19 and SUDEP [5].

The psychological impact of COVID-19 on patients with epilepsy

A World Health Organization assessment reported that any major public health emergency, can threaten the mental health of affected populations [9]. This includes patients with epilepsy, who

Citation: Brahma S, Bandagi RV and Kumar R. Aggravation of Behavioural Side Effects of Antiseizure Medications during COVID-19. J Psychiatry Mental Disord. 2021; 6(5): 1054.

have a higher prevalence of psychological distress during public health emergencies. Moreover, patients with drug-resistant epilepsy are at an even higher risk of developing severe psychological distress. This was shown by a recent Questionnaire based study that attempted to compare the severity of psychological distress between patients with epilepsy and healthy controls during the COVID-19 outbreak in southwest China. It also included a six-item Kessler Psychological Distress Scale [10].

Pharmacokinetic and Pharmacodynamic (PK PD) Changes in COVID-19 Patients

COVID-19 affects multiple organs, including the liver, kidneys, lungs, heart and the immune and hematological systems. Damage to these organs or systems may lead to pharmacokinetic changes that impact absorption, distribution, metabolism and/or excretion of medications as well as increase the propensity to develop certain psycho-tropic adverse effects [11].

BAEs Caused by ASMs

ASMs are known to be associated with BAEs and psychiatric adverse events. It is important to carefully consider these potential adverse events before initiating therapy in a PWE. Long term adherence to therapy is crucial for the successful management of epilepsy, especially in those who may be at a higher risk of these events, including those with a history of psychiatric conditions and intractable seizures [12]. Even though this is a well understood fact, the differentiation between psychiatric adverse events and BAEs is not yet standardized. The terms are often used interchangeably or may overlap, making the clinical decision-making process, difficult [12].

Chen et al. described BAEs as behavioural problems which included irritability, aggression, tantrum, emotional/mood changes, and hyperactivity and psychiatric adverse events as psychiatric conditions which included depression, psychosis, anxiety, and suicidal thoughts. Yet, the demarcation is not quite clear as certain characteristics like aggression can considerably overlap between the two [12].

The ASMs, Levetiracetam (LEV), Brivaracetam (BRIV), Perampanel (PER) and Topiramate (TPM) have been known to have the strongest risk of association with BAEs of aggressive behaviour (i.e., irritability, anger, aggression) [13]. 3% to 4% of patients who received LEV in the clinical development program experienced hostility [14]. Phase 3, Randomized Controlled Trials (RCTs) of PER reported BAEs associated with hostility/aggressive behaviour in 11.8% of patients with focal epilepsy and 18.5% of patients with primary generalized tonic-clonic seizures in idiopathic generalized epilepsy [15]. A pooled analysis of phase 2 and 3 RCTs of BRV in PWE showed the incidence of BAEs to be 4.0% [16].

An open label phase 3b study of adults with epilepsy, which studied the switching from LEV to BRV, found a clinically meaningful reduction in BAEs in 93.1% of patients. At the end of the treatment period, complete abatement (events which ended during the treatment period) from primary BAEs was reported in 62.1% patients. Of these, 10.3% were free from BAEs throughout the treatment period [17]. Other ASMs, such as Oxcarbazepine (OXC), Eslicarbazepine Acetate (ESL), and Lamotrigine (LTG), are associated with a lower risk of BAEs [18,12]. Insufficient or inconclusive data is available for ASMs such as Felbamate (FBM) and Zonisamide (ZNS) [13].

However, in actual clinical practice the results may not be consistent with those seen in these controlled trials. As, the controlled environment and criteria for these types of trials may not include the variabilities that exist in the real-world. For example, these studies tend to exclude PWE who may be at maximum risk for BAEs such as patients with a history of comorbid psychiatric conditions. Observational post-marketing studies can help fill this gap since they include all the variabilities associated with real-world epilepsy management and ASM use. A recent systematic review, analysed both retrospective and prospective observational studies which reported the incidence of irritability, anger, or aggression with BRV, LEV, PER, and TPM in PWE. Since, a wide range of results were reported by these observational studies, the weighted mean was calculated for all the parameters. The observed trend following this analysis of the weighted means, suggested that irritability may be seen more often in clinical practice with PER and LEV than with BRV and TPM, aggression may occur most frequently with PER followed by LEV and BRV, and anger, more frequently with BRV, LEV, and PER than with TPM. This systematic review also provided a robust real-world evidence that switching from LEV to BRV may improve BAEs. All these data can prove invaluable in treatment decision-making in PWE [19].

Possible Mechanisms Behind ASMs Causing BAE

BAEs observed with ASM treatment is linked to a-amino-3-hydroxy-5-methyl-4- Isoxazolepropionic Acid (AMPA) receptor. The differences seen in BAEs of different ASMs depends on how each ASM exerts its antagonistic action at these receptors. Perampanel is a non-competitive AMPA receptor antagonist. Levetiracetam, is a Synaptic Vesicle Glycoprotein 2A (SV2A) ligand that has some activity toward AMPA-gated currents, resulting in its association with BAEs. Topiramate (TPM) acts on multiple molecules, including voltage-gated sodium channels, Gamma Aminobutyric Acid (GABA) receptors, AMPA/kainate receptors, and carbonic anhydrase resulting in its anti-seizure actions but TPM appeared to have a lower incidence of BAEs than the other ASMs in the systematic review. BRV is a selective high- affinity ligand for SV2A but has no known activity on AMPA, which may contribute to improvement of BAEs making a switch from LEV to BRV. The mechanism(s) underlying BAEs by BRV are still unknown, as BRV does not act on any other neurotransmitter systems that have been implicated in modulating BAEs, including serotonin (5-HT) and GABA [20].

Factors Influencing BAEs

Certain co-existing conditions may make patients more vulnerable to BAEs than others. These include patients who have a prior history of psychiatric problems, absence seizures, intractable epilepsy, or frontal lobe epilepsy. It has also been noted that Psychiatric and Behavioral Side Effects (PBSEs) tend to occur more frequently in adolescents and children treated with LEV when compared to other AEDs. PBSEs due to LEV-usually leads to intolerability and subsequent reduction in dose. Zonisamide use is associated with higher cessation

rate secondary to PBSE. Absence seizures and frontal lobe epilepsy are associated with higher PBSE rates [21]. Men and women are equally affected by psychiatric side effects when treated with AEDs but aggression is more commonly seen in men [22]. Compared to polytherapy, monotherapy tends to reduce the potential for adverse drug interactions [23]. The propensity of developing behavioral adverse effects is higher in patients with uncontrolled seizures [13].

COVID-19 Medications and Anti-Seizure Medications (ASMs): Drug-Drug Interactions

Adverse events not only are a common cause of ASM discontinuation, they also negatively impact Quality Of Life (QoL) in the majority of PWE. This was supported by a study by Luoni et al. which used a validated Adverse Event Profile (AEP) questionnaire in patients of drug- resistant epilepsy. It reported that the QoL was most likely determined by adverse events associated with ASMs rather than seizure frequency [24].

Carbamazepine has a potential for causing drug-induced liver injury and may cause leukopenia and rarely aplastic anemia in patients with COVID-19. Valproic acid also has a potential for causing drug-induced liver injury and is associated with thrombocytopenia in patients with COVID-19. Gabapentin has the potential for acute kidney injury [11]. Many of the proposed COVID-19 treatments have the potential for neuropsychiatric side effects as well as drug-drug interactions [11].

Recently, Remdesivir, an antiviral drug was approved by US FDA, for use in adults and pediatric patients above the age of 12 years for the treatment of COVID-19 requiring hospitalization. [11,25]. Apart from this medication, several pre-existing medications have been tested for their potential as treatment of COVID-19. The Italian League against Epilepsy provides a list of possible interactions of these medications and ASMs. Combinations may either not be recommended or may require greater caution. Drug interactions should thus be taken into consideration in such PWE affected by COVID-19, as interactions can either diminish or enhance the effectiveness of drugs, or cause side effects [26,27].

Remdesivir is known to increase serum transaminase levels, for example, alanine aminotransferase can reach up to 20 times the upper limit of normal. This may influence the metabolism of drugs such as valproic acid that are mainly metabolised by the liver. Carbamazepine, phenytoin, and phenobarbital also have been recommended to be used with caution when given concomitantly with remdesivir. Chloroquine and hydroxychloroquine which are proposed COVID-19 treatment options may by themselves cause psychiatric side effects including psychosis, delirium, suicidality, personality changes, depression, nervousness, irritability, compulsive impulses, preoccupations, and aggressiveness. It is metabolized by CYP3A4 in the liver. Hence, potential drug interactions with CYP3A4 inducers such as carbamazepine, oxcarbazepine may occur decreasing the levels of chloroquine or hydroxychloroquine and rendering them less effective. However, a higher risk of neuropsychiatric side effects may be seen when combined with CYP3A4 inhibitors like ritonavir. Psychiatric side effects have also been reported with other proposed COVID-19 treatment options like Azithromycin, colchicine, corticosteroids, interferon and Lopinavir/Ritonavir [11].

Literature also shows that certain combinations of Anti-Epileptic drugs (AEDs) such as the combination of eslicarbazepine/lacosamide and COVID-19 therapies such as atazanavir/lopinavir/ritonavir can cause potentially fatal arrhythmias. Some other drugs like levetiracetam however, has not been reported to have any drug-drug interactions by COVID-19 drugs [28].

Management and Precautions for BAEs

Selection of an agent which has minimal potential for interaction may be a wise decision. This may include consideration of switching to an AED with less potential for interactions in patients who may need treatment for COVID-19. On the other hand, it is well documented that changing the AED may result in increased frequency of seizures. Hence, risk-to-benefit considerations must be made to determine whether the potential risks of causing seizures when switching AEDs are outweighed by the potential benefits of reducing drug interactions between AEDs and COVID-19 treatments [28]. In some cases, supportive treatment with an antihistamine drug suffices to reduce seizure threshold [5].

Besides this, each patient must be carefully evaluated to determine the involvement of drug- related, epilepsy-related or patient-related cause. Non-AED-related causes should be excluded at the start. Appropriate diagnosis of the epilepsy type, its possible etiology plays a crucial role. Special attention should also be given to previous personal or familial psychiatric history. Psychiatric and Behavioural Adverse Reactions (PBAR) may not present itself at the onset, it may first be recognized clinically several weeks or months after starting a drug. The patient, relatives, or caregivers must be informed about any potential PBAR, and the possibility of their delayed onset [20].

Conclusion

Anti-Seizure Medications (ASMs) are effective against seizures, but their use is often limited by adverse effects. This includes psychiatric and behavioural adverse effects. LEV, PER, and TPM are associated with a higher risk of Aggressive Behaviour (AB) than other AEDs. They have several mechanisms of action and they are thought to cause these side effects through an inhibitory effect on glutamatergic transmission via the AMPA receptor. Those patients treated, particularly with LEV, PER, and TPM, need long-term and comprehensive clinical monitoring along with awareness of emergent adverse behaviour. Caution must be exercised in PWE with COVID-19 as many of the proposed COVID-19 treatments have the potential for neuropsychiatric side effects as well as drug-drug interactions. A low total drug burden and a slow dose titration ensures the achievement of the best possible outcomes.

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