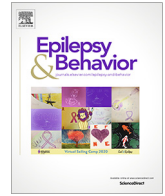




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Prevalence of depression and suicidal ideation in persons with epilepsy during the COVID-19 pandemic: A longitudinal study from India

Jatinder Katyal^{a,*}, Haroon Rashid^a, Manjari Tripathi^b, Mamta Sood^c

^aNeuropharmacology Laboratory, Department of Pharmacology, All India Institute of Medical Sciences, New Delhi 110029, India

^bDepartment of Neurology, All India Institute of Medical Sciences, New Delhi 110029, India

^cDepartment of Psychiatry, All India Institute of Medical Sciences, New Delhi 110029, India

ARTICLE INFO

Article history:

Received 19 July 2021

Revised 25 August 2021

Accepted 13 September 2021

Available online 20 September 2021

Keywords:

COVID-19

Seizures

Persons with epilepsy (PWE)

Depression

Suicidal ideation

Mini International Neuropsychiatric Interview (MINI)

Anti-seizure medication (ASM)

ABSTRACT

Objectives: COVID-19 pandemic has disrupted healthcare services for chronic disorders such as epilepsy. In this study, the impact of COVID-19 pandemic on persons with epilepsy (PWE) with regard to their seizure control, depression status, and medication adherence was assessed.

Methods: After ethical clearance, 449 PWE who had been previously evaluated for depression at All India Institute of Medical Sciences (AIIMS), New Delhi, India, were telephonically reevaluated using Mini International Neuropsychiatric Interview and surveyed for source of medication and medication adherence over past 6 months. The prevalence and the association of depression, suicidality, and seizures during pandemic with different PWE variables were determined.

Results: Out of 449 PWE, 70.6% responded. 19.9% were diagnosed positive for depression as per MINI while suicidal ideation was observed in 5.4%. Seventy six (23.9%) PWE reported seizures during pandemic. The incidence was greater in females, unemployed, previously uncontrolled epilepsy, polytherapy, altered use of medications, and depressed PWE. Seizure during pandemic, increased seizure frequency, previous history of depression, and altered use of medications were all significantly associated with depression during COVID-19 pandemic (2.6–95%CI, 1.45–4.73; 1.9–95%CI, 1.01–3.57; 8.8–95%CI, 4.54–17.21; 2.9–95%CI, 1.19–7.24), and polytherapy (2.9–95%CI, 0.92–9.04), seizures during pandemic (3.9–95%CI, 1.45–10.53) and previous history of depression and suicidality, were related with suicidal ideation. **Conclusion:** COVID-19 pandemic-induced disruptions can be detrimental for PWE, and restoring services to the pre-covid levels as well as putting appropriate continuity plans in place for care of PWE should be a priority.

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1. Introduction

The COVID-19 pandemic has resulted in a massive strain on healthcare facilities leading to major disruptions and collapses all over the world [1,2]. While wave after wave of infection spreads, the extremely high morbidity and mortality have necessitated imposition of stringent measures like curfews and lockdowns, diversion of available healthcare workers for COVID management, and changes in resource allocations. These changes in healthcare dynamics coupled with stress and financial hardships have invariably compromised the level of care for sick individuals particularly for chronic disorders like epilepsy [3]. It is conceivable that PWE are more likely to be affected during COVID19 pandemic because

of multiple stressors i.e., disease, mobility restrictions, financial hardships, lack of routine medical access, etc. In a survey conducted on 337 members of American epilepsy society, concerns were raised that PWE did not get adequate medical care. While 10% of respondents noted worsening in seizure frequency, 5% noted an improvement [4]. Epilepsy is one of the most common neurological disorders with an overall prevalence of 5–9 per 1000 population across the globe [5]. Whereas most PWE require anti-seizure medications (ASMs), the mainstay of treatment, for many years or even lifelong, nearly 25–30% do not respond i.e., patients with refractory seizures may require surgical intervention [6]. Epilepsy is also associated with multiple comorbidities and neuropsychiatric problems. Depression in particular has been reported in a sizable proportion of PWE [7–10] and a bidirectional relationship between epilepsy and depression is suggested [11]. While many studies over the past one year have reported an increase in seizure frequency in PWE [3,12–18], to the best of

* Corresponding author at: Department of Pharmacology, All India Institute of Medical Sciences, New Delhi 110029, India.

E-mail address: jatinderkatyal.aiims@gmail.com (J. Katyal).

our knowledge, studies assessing the impact on depression in PWE are scarce. A few studies have evaluated the mental health of PWE i.e., anxiety, depression, and psychological distress using online surveys [3,12,14–21], but in all these studies the baseline status of PWE was not available and therefore the impact of COVID-19 cannot be assessed.

In this study, in order to determine the effect of COVID19 pandemic on depression in PWE, we reevaluated PWE who had been previously evaluated for depression and suicidal ideation.

2. Material and methods

This longitudinal study was conducted from September to October 2020 which corresponds to unlock 3.0 in India.

2.1. Study participants

We had concluded an ongoing study on depression in PWE in March 2020 at All India Institute of Medical Sciences (AIIMS), New Delhi, a tertiary care center in India. Since a follow-up was planned, informed consent for the same was recorded which enabled us to carry out this study. Thus the demographic data, baseline data on depression and seizure frequency for comparison were available. After taking ethical clearance from the Institute Ethics Committee at AIIMS, New Delhi, the participants of the study i.e., the PWE who had previously attended neurology OPD at AIIMS, New Delhi, India, and had given informed consent, were telephonically informed about the study, evaluated for depression, and also a short survey pertaining to seizure frequency and compliance was carried out. The inclusion criteria followed for recruiting the patients were age ≥ 18 years, either gender, meet diagnostic criteria for epilepsy as per ILAE, and on ASMs. Those with any other comorbidity were excluded.

2.2. Assessment of depression in PWE

We had previously used Mini International Neuropsychiatric Interview (MINI: version 6.0.0) for evaluation of depression and suicidal ideation in these patients. The same version was reapplied. The permission for using MINI (version 6.0.0) was duly obtained. Both English and Hindi versions were used. The evaluator was naive to the previous status of PWE i.e., depressed or not depressed.

2.3. Survey questionnaire

The 6-item survey questionnaire was optional for the PWE. The respondents were asked closed-ended questions relating to the source of medication and the medication adherence over the past 6 months.

2.4. Statistical analysis

Statistical analysis was performed using STATA statistical software, version 14. The categorical variables between the group with depression and the group without depression were compared using the chi-square test, while continuous variables were compared using the Student t-test. A significance level of $p < 0.05$ (two-tailed) was adopted. Univariate and stepwise multivariate logistic regression were applied to find independent associative factor of depression, suicidality, and seizures during follow-up, and unadjusted and adjusted odds ratios were calculated. R (version 4.1.0) was used for paired plot analysis between PWE with and without depression, and PWE with and without seizures during pandemic period.

3. Results

Out of 449 PWE approached, 317 responded (response rate 70.6%) (Fig. 1). Of these, majority (52.05%) were assessed 13–24 months ago while 17.66% and 30.28% were assessed in the preceding 12 months and more than 24 months ago, respectively. There was a similar representation of both genders (162 male and 155 females), 35% PWE had a diagnosis of focal seizures, 65% had generalized seizures, 46% were on monotherapy, and rest were on polytherapy. A total of 17 PWE had undergone drug tapering. There was no significant difference when demographic features of these 317 PWE were compared with total study subjects i.e., 449.

3.1. Seizure frequency during COVID-19 pandemic

In all, 76 PWE reported seizures during the pandemic and the number of seizures ranged from 1 per year to >3 per month. Maximum seizures were seen in those followed up after 13–24 months (39.28%) and minimum (15.63%) in those evaluated after 24 months. Expectedly, 92.1% seizures were seen in PWE with uncontrolled seizures vs. 7.9% in PWE with previously controlled seizures. Only 1 seizure was seen from all PWE with previously controlled seizures. Among those PWE showing seizures during pandemic, the frequency of seizures declined in 25%, increased in 44.7%, and remained unchanged in the rest (Table 1).

Fifty percent of PWE who were not taking ASMs or had altered the dose of ASM showed seizures versus 24% in the whole follow-up group. Pair-wise analysis is given in Fig. 2(a).

3.2. Prevalence of depression

Out of 317 PWE, 19.9% met the criteria for depression as per MINI as opposed to 40.1% that were depressed in previous assessment (Table 2). Thus a highly significant reduction was observed. Of these, 13 PWE had new-onset depression i.e., had not screened positive previously. Among those who had undergone tapering, only 1 had depression and the subject had tested positive earlier also.

The percent depressed at all the three time intervals i.e., ≥ 1 year, 1–2 years, and ≥ 2 years was similar i.e., 16.07%, 20.6%, and 20.8% respectively. Similarly gender also did not have any effect, the prevalence of depression being nearly 20% in both genders. A higher percentage of those on polytherapy tended to be positive for depression as opposed to those on monotherapy (21.5% vs. 17.93%). This was not statistically significant. There

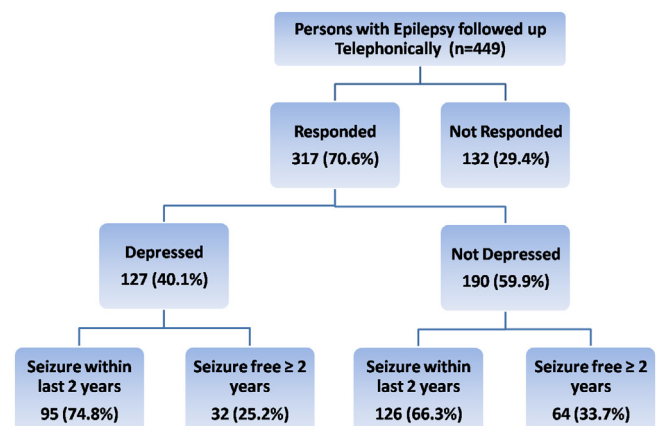


Fig. 1. Flow chart showing characteristics of persons with epilepsy enrolled in the study.

Table 1
Comparison of clinicodemographic variables in persons with epilepsy (PWE) showing or not showing seizure during COVID-19 pandemic.

Variable	Seizure during the COVID-19 pandemic				p value
	YES		NO		
	N	%	N	%	
Total	76	100.0	241	100.0	
Age					0.3997
18–30 years	55	72.4	162	67.2	
>30 years	21	27.6	79	32.8	
Gender					0.0391
Male	31	40.8	131	54.4	
Female	45	59.2	110	45.6	
Employment status					0.0282
Employed	20	26.3	97	40.2	
Unemployed	56	73.7	144	59.8	
Epilepsy type					0.2262
Focal	31	40.8	80	33.2	
Generalized	45	59.2	161	66.8	
Number of ASMs					<0.00001
Monotherapy	16	21.1	129	53.5	
Polytherapy	60	78.9	112	46.5	
Previous history of seizure control					<0.00001
Seizure free ≥2 yrs	6	7.9	90	37.3	
Seizures within 2 yrs	70	92.1	151	62.7	
Current Depression status					0.0011
Depressed	25	32.9	38	15.8	
Not Depressed	51	67.1	203	84.2	
Previous Depression status					0.0217
Depressed	39	51.3	88	36.5	
Not Depressed	37	48.7	153	63.5	
Current Suicidality status					0.0040
Present	9	11.8	8	3.3	
Absent	67	88.2	233	96.7	
Previous Suicidality status					0.4842
Present	5	6.6	11	4.6	
Absent	71	93.4	230	95.4	

was however no new-onset case of depression in PWE on monotherapy. The pairwise relationship between different variables is given in Fig. 2(b). Nearly 40% of PWE who had had a seizure in the past 6 months were depressed. When a comparison of previously controlled (no seizure in past 2 years) and uncontrolled (seizure episodes during past 2 years) was carried out, it was observed that of 221 PWE with uncontrolled seizures, 22.17% had depression and of this 16.33% was new onset. In case of PWE with controlled seizures, 14.58% had depression and of this 35.71% was new onset.

3.3. Suicidal ideation in PWE

Using MINI (B) module, 5.4% were screened positive for suicidal ideation. Out of these, 82% did not have suicidal ideation before. Fifty seven percent of fresh onset cases had seizures during the study period. Two PWE were not adhering to the ASMs due to financial difficulty. Most PWE with suicidal ideation were on polytherapy.

3.4. ASM compliance

A total of 12 PWE reported not taking the ASM at all while 9 had reduced the use of medication. The reasons cited were mostly financial difficulty or no access, although loss of interest was also cited as a reason. For nearly 96% of PWE, procuring ASMs was an out of pocket expense (Fig. 3). Noncompliance was more with monotherapy, in female PWE, and in those with previously uncontrolled seizures.

3.5. Regression analysis

Table 3 gives the odds ratio for different variables. Univariate analysis revealed that the incidence of seizures during pandemic was greater in females, unemployed, those on polytherapy, depressed PWE, and altered use of ASMs. In case of depression, seizures during pandemic, increased seizure frequency, positive for depression previously, and altered use of ASMs were all significantly

associated with depression during Covid-19 pandemic. After multiple regression analysis, seizures during pandemic (2.2 (95% CI 1.14–4.17), *p* value = 0.019) and precovid depression (7.8 (95% CI 3.99–15.38), *p* value <0.001) were significantly associated with depression during pandemic. Univariate analysis also revealed association between seizures during pandemic, precovid depression as well as suicidal ideation and polytherapy with suicidal ideation during pandemic.

4. Discussion

Although many studies are now focused on understanding seizure control in PWE in relation to various COVID19 pandemic-associated factors like suspension of routine outpatient department services, non-availability of EEG facilities, inaccessible medication due to shortages and mobility restrictions, uncertainty over finances and change in societal and family dynamics, very few are focusing on impact on comorbidities like depression. Some workers carried out online surveys across countries, but mostly through social media to determine the effect on depression and anxiety and psychological stress as a measure of depression and anxiety [12,20,22]. These studies have some inherent limitations like small sample size, limited and very specific reach due to use of online media, and importantly lack of baseline data. Here it is worthwhile to mention that prevalence of depression in PWE up to even 88% has been reported though the range is 20–55% in most studies [23,8,24]. Since we had evaluated 449 PWE for depression using four different scales over the past few years before the start of pandemic in India [7], these same patients were re-evaluated telephonically for depression. The response rate was 70%, and MINI was used.

Mini International Neuropsychiatric Interview is a semi-structured diagnostic interview recognized as gold standard for validation of diagnosis of depression [25]. It uses Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) and International Classification of Diseases, Tenth Revision (ICD-10) criteria to diagnose depression and has been validated previ-

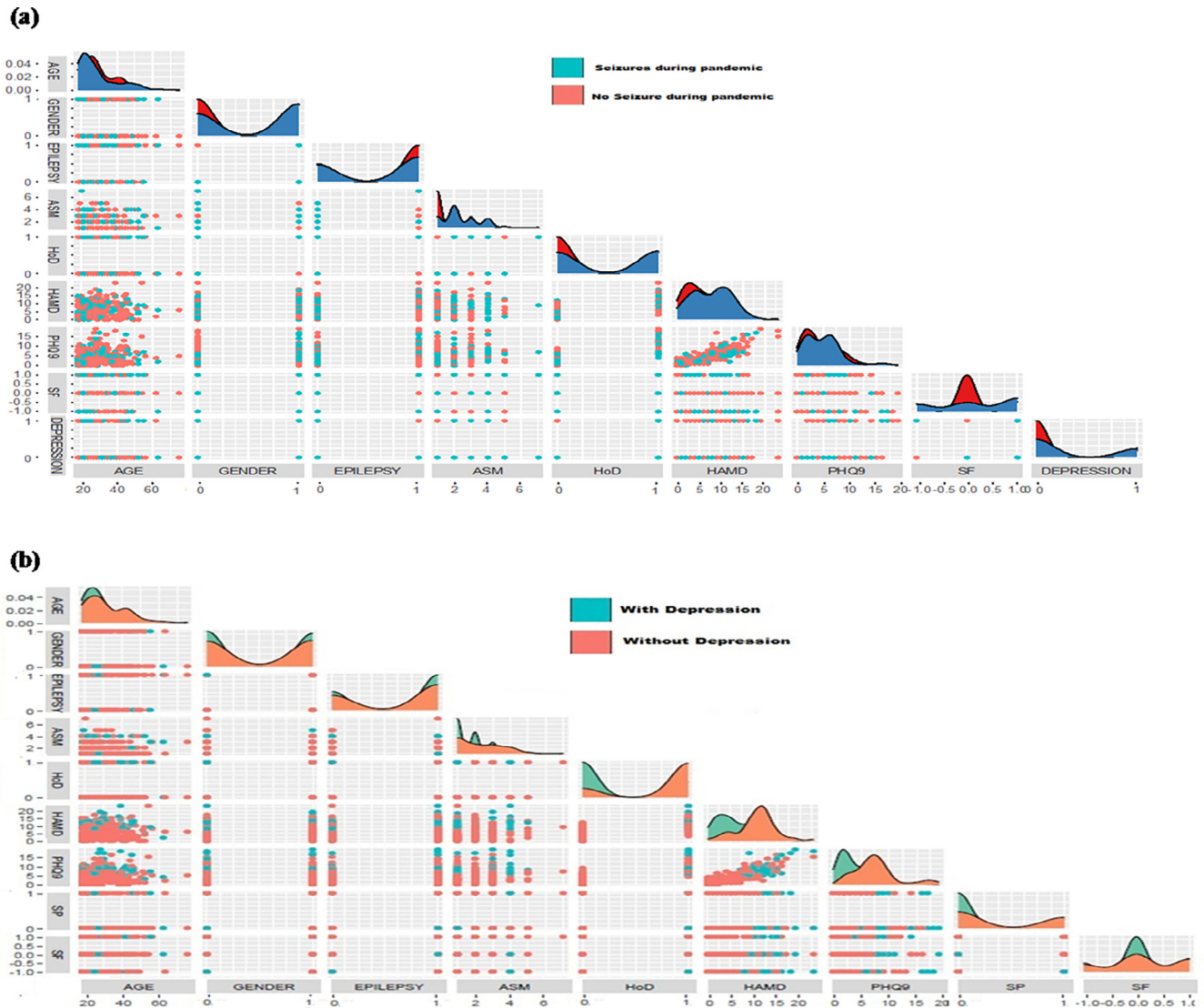


Fig. 2. Clinical variables in persons with epilepsy according to incidence of seizure and depression status during the COVID-19 pandemic. The figure displays paired plot that highlights differences between (a) PWE who had seizures (Blue) and those who did not (Red); (b) PWE who had depression (Blue) and those who did not (Red). ASM, Anti-Seizure Medications; Gender (0 = Male, 1 = Female); Epilepsy (0 = Focal, 1 = Generalized tonic-clonic seizures); HoD = History of depression (0 = No, 1 = Yes), SP = Seizure during pandemic period (0 = No, 1 = Yes), SF = Seizure frequency (1 = Increased, 0 = same & -1 = decreased). Depression (0 = No, 1 = Yes).

ously against structured clinical interview for diagnosis (SCID) in PWE [25]. Previously a number of studies have used telephonic mode for MINI to assess depression [26–29] and it has been reported that telephone versus in-person mode do not influence findings [26,30–33].

We observed a highly significant decrease in prevalence of depression in PWE during the follow-up during COVID 19 pandemic. Although we did not come across any comparable, i.e. both pre-COVID and post-COVID studies, in PWE, in studies comparing PWE with healthy subjects, mostly an increased depression and anxiety in PWE has been reported [3,21]. Van Hees et al. also reported a prevalence of 39.8% and 46.9% using HADS and PHQ-9, respectively in PWE [20]. These values fall in the reported range of 20–55% [8]. However, Abokalawa et al. reported prevalence of depression as high as 66.2% [22], whereas it was 12.2% in a Spanish study [14].

The reasons for decrease in depression prevalence are not clear. While it can be contended that the patients identified as depressed previously would have received treatment for it and therefore

decreased incidence. However, of the previously depressed PWE, in this follow-up among the respondents, only 03 PWE were on antidepressants, and of these three, 02 were still screened positive for depression. A case-to-case analysis of previously depressed and now not-depressed PWE reveals that 17 were PWE with controlled seizures who were no longer on ASMs. Among these only one was assessed as depressed as opposed to 03 previously. A good percentage screening positive with MINI, 65% were previously assessed as mild cases using PHQ-9 and HAM-D, respectively, and almost 96% were strictly adhering to their ASM schedules. Since the survey was carried out during lockdown, a probable better support structure and care with regard to ASM schedule could have contributed. The role of social capital in enhancing quality of life in PWE and mitigating neuropsychiatric problems has been proposed [34–36]. A large longitudinal study during the COVID-19-related lockdown in the UK has reported that those with higher levels of perceived social support had markedly lower depressive symptoms and depression risk [37]. Many other studies have suggested that having positive and enjoyable social experiences is linked to lower

Table 2
Comparison of clinicodemographic variables in persons with epilepsy (PWE) with or without depression during COVID-19 pandemic.

Variable		Number of PWE	PWE (with Depression)		PWE (Without depression)		p value
			N	%	N	%	
Total		317	63	100.0	254	100.0	
Age	18–30 years	217	39	61.9	178	70.1	0.2114
	>30 years	100	24	38.1	76	29.9	
Gender	Male	162	31	49.2	131	51.6	0.7364
	Female	155	32	50.8	123	48.4	
Employment status	Employed	117	21	33.3	96	37.8	0.5112
	Unemployed	200	42	66.7	158	62.2	
Time to follow-up	≤12 months	56	9	14.3	47	18.5	0.7336
	13–24 months	165	34	54.0	131	51.6	
	≥25 months	96	20	31.7	76	29.9	
Epilepsy type	Focal	111	23	36.5	88	34.6	0.7815
	Generalized	206	40	63.5	166	65.4	
Number of ASMs	Monotherapy	145	26	41.3	119	46.9	0.4261
	Polytherapy	172	37	58.7	135	53.1	
Seizure Control	Seizure free ≥2 yrs	119	18	28.6	101	39.8	0.1005
	Seizures within 2 yrs	198	45	71.4	153	60.2	
Seizure during Pandemic period	YES	76	25	39.7	51	20.1	0.0011
	NO	241	38	60.3	203	79.9	
Previous Depression status	Depressed	127	50	79.4	77	30.3	<0.00001
	Not Depressed	190	13	20.6	177	69.7	
Previous Suicidality status	Present	16	8	12.7	8	3.1	0.0019
	Absent	301	55	87.3	246	96.9	
Current Suicidality status	Present	17	16	25.4	1	0.4	<0.00001
	Absent	300	47	74.6	253	99.6	

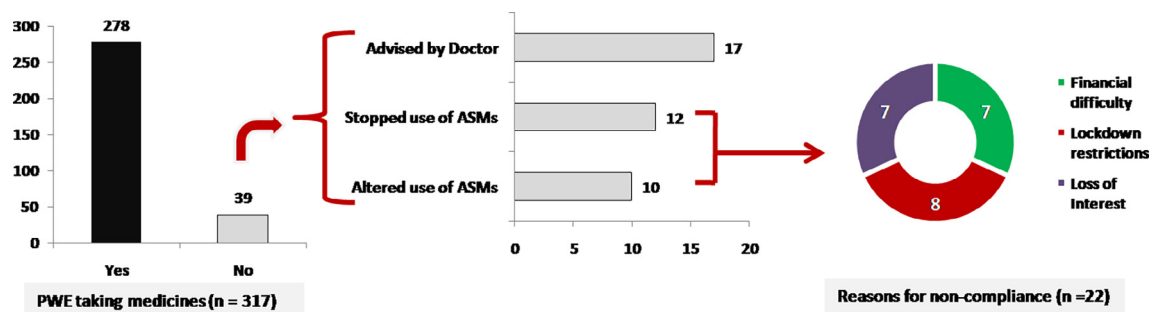


Fig. 3. Anti-seizure medication (ASM) compliance and the reasons for non-compliance.

depressive symptoms [38]. The risk of underestimating however on account of telephonic interview cannot be ruled out, it has been reported that in population with low or intermediate risk of psychiatric disorder, the sensitivity of telephonic interview is low, implying that many of the cases might be missed by the telephone interview in comparison with the face-to-face interview [39–41].

In contrast to the precovid results for factors affecting depression in PWE, no association between female gender and depression was observed. Polytherapy was however significantly associated along with seizure incidence and frequency. A similar trend was seen for suicidal ideation as well.

Polytherapy, seizure frequency, and seizure incidence are well-recognized risk factors for depression in PWE. Polytherapy itself would imply a more severe disorder, and use of multiple ASMs further compounds the risk due to their inherent adverse effect profiles [7,42,43]. Occurrence of seizures on the other hand is a major stressor [11,44].

Another notable finding in this study was an altered seizure control in 70% PWE. The seizure frequency tended to increase in 44.7% PWE who experienced seizures. Seizure worsening during COVID-19 pandemic has been reported by other workers also

[3,12,13,16,17], but report of worsening as well as improvement are also available [4]. Fonseca et al. and Tedrus et al. reported an increase in seizure frequency in almost 10% of PWE during the pandemic period [14,15]. As for factors associated with seizure worsening, sleep disorder, polytherapy, and compliance issues were found to be related. We did not delve into sleep disorders, but in our study also polytherapy and altered use of medicine were associated. Apart from these, depression was also identified as a significant contributing factor. It is conceivable that previously proposed bidirectional relationship between seizure and depression is not restricted to neuropathological changes but has some component of ASM as well [8,11,42].

The altered use of medicine was implicated not just in seizure occurrence but also in depression and suicidal ideation. In the latter, it may be an outcome rather than a cause as 02 PWE described loss of interest as a reason for not taking ASMs. Nearly 50% of those not adhering to ASMs were found to be depressed. In other cases financial difficulty and inability to obtain medicine were cited as reasons for non-compliance. Surveys conducted worldwide have reported that PWE experienced difficulties during the pandemic in obtaining medications [19]. Asadi-Pooya et al. also reported that

Table 3
Univariate and multivariate analysis of variables associated with seizures, depression and suicidality in persons with epilepsy (PWE) during COVID-19 pandemic.

Seizures during pandemic				
Variable	Unadjusted Odds Ratio	p value	Adjusted Odds Ratio	p value
Female	1.7 (95% CI 1.02–2.92)	0.040	–	
Unemployed	1.9 (95% CI 1.06–3.34)	0.030	–	
Seizure within 2 years (at enrolment)	6.9 (95% CI 2.90–16.66)	<0.001	10.3 (95% CI 3.86–27.74)	<0.001
Polytherapy	4.3 (95% CI 2.35–7.92)	<0.001	–	
Depression (at enrolment)	1.8 (95% CI 1.09–3.08)	0.023	–	
Altered use of ASMs	3.3 (95% CI 1.36–7.91)	0.008	2.8 (95% CI 0.96–8.26)	0.060
Depression (during follow-up)	2.6 (95% CI 1.45–4.73)	0.001	1.9 (95% CI 0.95–3.77)	0.069
Depression in PWE during follow-up				
Variable	Unadjusted Odds Ratio	p value	Adjusted Odds Ratio	p value
Depression (at enrolment)	8.8 (95% CI 4.54–17.21)	<0.001	7.8 (95% CI 3.99–15.38)	<0.001
Seizure during pandemic	2.6 (95% CI 1.45–4.73)	0.001	2.2 (95% CI 1.14–4.17)	0.019
Increased seizure frequency	1.9 (95% CI 1.01–3.57)	0.048	–	
Altered use of ASMs	2.9 (95% CI 1.19–7.24)	0.019	–	
Suicidality in PWE during follow-up				
Variable	Unadjusted Odds Ratio	p value	Adjusted Odds Ratio	p value
Polytherapy	2.9 (95% CI 0.92–9.04)	0.070	–	
Depression (at enrolment)	5.3 (95% CI 1.69–16.66)	0.004	–	
Suicidality (at enrolment)	4.7 (95% CI 1.21–18.53)	0.026	4.5 (95% CI 1.09–18.34)	0.037
Seizure during pandemic	3.9 (95% CI 1.45–10.53)	0.007	3.8 (95% CI 1.4–10.41)	0.009

about one-third of PWE faced difficulties in obtaining their medicines [18]. Van Hees et al. have reported the unavailability of ASMs to be majorly on account of non-availability (69.4%), mobility restrictions (12.5%), and financial problems (12.5%) [20]. However, few studies reported that no significant problem was experienced by PWE in accessing drugs [16], and most of the patients were compliant with their ASMs. A 93% compliance rate was reported in an Italian study [3], 93.5% in the Saudi study [12], and 96% in Kuwaiti study [22] which is similar to this study.

Limitations of study: One of the major limitations is that the COVID status for self and any impact on family were not determined. Besides, owing to different times to follow-up, the role of progression of disease in depression cannot be accounted for.

5. Conclusions

The pandemic appears to have had a mixed effect on PWE depending on the individual profile. In view of the risks involved i.e., seizure exacerbation and precipitation of depression, it is imperative that efforts be made to restore medical care mechanisms for this highly vulnerable population and suitable continuity plans put in place to overcome any disruption in future.

Acknowledgements

We would like to acknowledge Dr David V. Sheehan for permission to use MINI. This work was supported in part by a research grant from All India Institute of Medical Sciences, New Delhi to JK & MT.

We would also like to thank Ms Aishani Katyal for her assistance with R software.

Disclosure of conflicts of interest

None of the authors have any conflict of interest to declare.

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