Psychiatry/Mental Health Section

Self-reported Medication Adherence in Schizophrenia and Bipolar Disorder Patients during COVID-19 Pandemic in a COVID Care Hospital: A Cross-sectional Study

SAJAL SATHIADEVAN[1], NITHIN KONDAPURAM[2], NIMMY CHANDRAN[3], BIBIN V PHILIP[4], KS DEEPAK[5]

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ABSTRACT

Introduction: The Coronavirus Disease 2019 (COVID-19) pandemic has made it difficult for patients with Schizophrenia and Bipolar Affective Disorder (BPAD) to receive ongoing care, which has led to non adherence to medication and undesirable health outcomes. Lower treatment adherence in severe mental illness might lead to symptom exacerbation and relapses and might cause a strain on the health system during COVID-19 pandemic.

Aim: To assess the treatment adherence in Schizophrenia and BPAD patients during prevailing COVID-19 situation in India.

Materials and Methods: This cross-sectional study was conducted among 92 patients with Schizophrenia and BPAD through a questionnaire between January to September 2021 in a COVID-19 care hospital Government Medical College Palakkad/District hospital Palakkad, Kerala, India. Demographic and clinical data, adherence to treatment, along with Brief Psychiatric Rating Scale (BPRS), Young Mania Rating Scale (YMRS), Hamilton Rating Scale for Depression (HAM-D). Clinical Global impression (CGI S&I), Work and Social Adjustment Scale (WSAS), Modified COVID Threat Scale (CTS) and Medication Adherence Rating Scale (MARS) were collected. The outcomes included adherence to medication, deterioration of the psychopathology, improvement in severity, social functioning. Descriptive statistics was used to define the sample characteristics and presented as mean and standard deviation and frequency and percentages. Spearman's Correlation coefficient was used to find the correlation between MARS and other variables: CTS, BPRS, YMRS, HAM-D, CGI and WSAS.

Results: A total of 92 patients were interviewed which comprised of 43 patients with Schizophrenia and 49 patients with Bipolar disorder. As assessed by MARS rating scale 19 patients (20.65%) had a MARS score less than six suggesting poor adherence and 73 (79.35%) had MARS score 6 and greater suggesting better adherence to the treatment. This was supported by negative correlation with BPRS, YMRS, HAM-D and CGI-S and CGI-I scales which implies that the COVID-19 pandemic did not hinder the patients to take the medication. The mean MARS score was 7.31±2.11. A total of 37 (40.2%) patients had acute exacerbation of the illness during the COVID-19 related lockdown and 37 (40.2%) had exacerbation during the six months prior to COVID-19 lockdown. There was negative correlation between MARS scores and the CTS but was not statistically significant.

Conclusion: Despite the COVID-19 pandemic related restriction, patients with Schizophrenia and BPAD were adherent to the medication and the number of relapses during COVID-19 pandemic was similar to the period before the pandemic. COVID-19 related anxiety didn't have an impact on medication adherence and relapse in this study.

Keywords: Bipolar affective disorder, Coronavirus disease-2019, Medication non adherence

INTRODUCTION

The entire world is grappling with the COVID-19 outbreak, which is thought to have been caused by the virus Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which developed in Wuhan, China. Although COVID-19 primarily affects the respiratory system, it has also been shown to damage other organs, including the brain. Moreover, COVID-19 related neurological and psychiatric problems have recently been observed [1]. Apart from the physical consequences of the virus, the quarantine, limitations, and the millions of people who died throughout the world as a result of the outbreak produced major mental health issues. Furthermore, this pandemic has generated major complications for persons with mental illness [2]. Adherence to treatments involves attending outpatient clinics on a regular basis, taking prescribed medications on time and in sufficient quantities [3].

Non adherence to treatment is a major obstacle in successful treatment of Schizophrenia and BPAD [4]. Nearly 50% of Schizophrenia and BPAD patients are non adherent to treatment leading to symptom exacerbation and relapses [5-7]. Relapses in severe mental illness can lead to non compliance with COVID-19 norms like physical distancing, wearing masks etc., and can lead to increased risk of getting COVID-19 infection and higher risk of spreading [8]. Because of the COVID-19 pandemic related restrictions in movement to prevent spread of COVID-19, patients with severe mental illness had difficulty in maintaining regular psychiatry follow-up visits and which led to non adherence in medications leading to symptom exacerbation [9]. Psychological stress due to COVID-19 pandemic restrictions and health anxiety related to COVID-19 can also precipitate symptoms in patients with severe mental disorder [10-12].

The primary objective of this study was to assess treatment adherence in Schizophrenia and BPAD patients during prevailing COVID-19 pandemic in a COVID-19 care hospital in Kerala, India and secondary objective was to find the correlation between MARS and other variables: CTS, BPRS, YMRS, HAM-D, CGI and WSAS.

MATERIALS AND METHODS

The study was a cross-sectional hospital-based study and consisted of 92 patients with BPAD and Schizophrenia who were regularly followed-up in District Hospital Palakkad, Kerala, India. After obtaining approval from the Institutional Ethical Committee:

IEC/GMCPKD/31/20/85 dated 21/12/2020, patients with diagnosis of Schizophrenia and BPAD as per the ICD 10 criteria [13] were recruited for the study and convenience sampling method was used. The study was conducted at Department of Psychiatry at District Hospital Palakkad/Government Medical College, Palakkad at outpatient and inpatient department between January to September 2021 during the COVID-19 pandemic.

Sample size calculation: Based on the percentage of low medical adherence in bipolar patients of 54.7% observed in a study done in AIIMS Delhi in 2019 [7], using the below equation and with 95 % confidence and 20% precision, the minimum required sample size was 82.

$$n = \frac{4pq}{d^2}$$ where p=54.7%, q=100-p, d=precision=20% of 54.7.

In this study 92 patients with severe mental illness comprising of Schizophrenia and BPAD were recruited.

Inclusion criteria:

1. Patients over 18 years of age with Schizophrenia (F20 ICD criteria) and patients with BPAD (F31 ICD criteria) [13] registered in District Hospital Palakkad before October 2019 and on follow-up;

2. Patients and family relatives who may be contacted (direct or telephone);

3. Informed consent of relative and patient.

Exclusion criteria: Patients not willing to participate in study were excluded from the study.

Study procedure: Once patient satisfied the inclusion criteria as assessed by Psychiatrist, clinical examination was done to assess psychotic symptoms, mood symptoms, illness severity, perceived threat due to COVID-19 and medication adherence. Education and family income was assessed using Modified Kuppuswamy scale [14]. All the patients were assessed using BPRS, YMRS, HAM-D, CGI, Modified CTS, MARS and WSAS. The number of follow-up in the six months prior to COVID-19 related lockdown and the number of consultations during the first six months after the COVID-19 related lock-down was assessed to evaluate whether the patients had regular follow-up. Patients were considered as having regular follow-up if they used to come during the scheduled appointment week for consultation for the initial six months during the COVID-19 pandemic. Any exacerbation of symptoms during the initial six months of COVID-19 pandemic and six months prior to the COVID-19 pandemic was also assessed through the questionnaire evaluating the clinical characteristics of the sample. A written informed consent was obtained from all patients.

Assesment scales: The BPRS is a scale which assesses the severity of such as hostility, suspiciousness, hallucination, and grandiosity in patients. It is useful for assessing the effectiveness of treatment for individuals with mild to severe psychoses. It's a clinician assessed scale where the clinician's rates the patient behaviour based on his observations over the last 2-3 days. Inputs from the patient's family on their behaviour was also taken into account. For each of the 24 symptom construct, the rater enters a number that ranges from 1 (not present) to 7 (extremely severe). BPRS scale was administered on all patients of Schizophrenia and Bipolar disorder in this study to assess symptom severity of the patients [15].

The YMRS is one of the most frequently utilised rating scales to assess mania symptoms. The scale has 11 items and each item is rated 0 to 4 and is based on the patient's subjective report of his or her clinical condition over the previous 48 hours. Higher scores suggest worsening of Mania symptoms. Additional information is based upon clinical observations made during the course of the clinical interview. The items are selected based upon published descriptions of the core symptoms of mania [16].

The HDRS (also known as the HAM-D) is the most widely used clinician-administered depression assessment scale. The original version contains contains 21 items and scored 0 to 4 with higher scores suggesting to symptoms of depression over past one week [17].

Clinical Global Impression- Severity (CGI-S) and Improvement (CGI-I) scales: The CGI-S [18] is a 7-point scale that requires the clinician to rate the severity of the patient's illness at the time of assessment, relative to the clinician's past experience with patients who have the same diagnosis. The CGI-I [19] is a seven-point scale that requires the clinician to assess how much the patient's illness has improved or worsened relative to a baseline state at the beginning of the intervention. CGI severity is scored as 0=Not assessed, 1=normal, not at all ill, 2=borderline mentally ill, 3=mildly ill, 4=moderately ill, 5=markedly ill, 6=severely ill, 7=among most extremely ill patients. CGI improvement is scored as 0=not assessed, 1=very much improved, 2=much improved, 3=minimally improved, 4=no change, 5=minimally worse, 6=much worse, 7=very much worse.

Higher scores CGI severity indicates worsening of symptoms and lower scores suggesting lesser severity of illness. Higher scores on global improvement suggest worsening of symptoms and lower scores suggests improvement in symptoms. The CGI severity and improvement scales offer a readily understood, practical measurement tool that can easily be administered by a clinician in a busy clinical practice setting.

The CTS is used to measure the degree of anxiety related to contracting or spreading COVID-19 [20]. The scale was translated into five Indian languages (Kannada, Tamil, Telugu, Malayalam, and Hindi), following norms laid out by the World Health Organisation (WHO) [21]. The scale has 10 item and is scored on a likert scale from 1 to 5 with higher scores indicating higher anxiety. The Malayalam translation of the scale was used for this study.

The WSAS [22] is an outcome measure assessing degree of functional impairment. Subjects would be provided instructions to rate how various aspects of their lives in five domains (work, home management, social leisure, and private leisure, and close relationships) were affected due to the pandemic. It is rated from 0 to 8 with higher scores indicating higher impairment. It was translated to Malayalam following norms laid by WHO [21]. Its psychometric properties, validity and sensitivity to change have been supported in several studies.

The MARS [23] is a self-rated scale which determines an individual's medication adherence. It determines adherence in three dimensions of medication adherence behaviour, attitude and negative side-effects along with attitudes to psychotropic medication. It is a self-report measure of medication adherence and patients give yes/no response to 10 questions and it is rated from 0 to 10. 10 is best adherence to medication and 0 is non adherence to medication. A MARS score of less than six was considered as poor adherence to medications in this study and a score of six and more considered as good adherence.

A specially designed socio-demographic and clinical data sheet was used to record the demographic and clinical variables.

STATISTICAL ANALYSIS

The statistical data analysis was done using Statistical Package for Social Sciences (IBM SPSS, version 20. Chicago, SPSS Inc.) Descriptive statistics was used to define the sample characteristics and presented as mean and SD and frequency and percentages. One sample Kolmogorov-Smirnov (KS) test was done for checking the normality. As the distribution was not normally distributed, non parametric, Spearman rank correlation was used for finding correlation between MARS and other variables (CTS, BPRS, YMRS, HAM-D, CGI- S&I, WSAS) p-value <05 was considered significant.

RESULTS

The sample comprised of 92 patients with severe mental illness comprising of 43 patients (46.74%) with diagnosis of Schizophrenia and 49 patients (53.26%) with diagnosis of BPAD and the total sample was analysed. However, subgroup analysis according to the diagnosis was not attempted. [Table/Fig-1] depicts the mean age (standard deviation) of participants was 38.4±13.3 years. The

Characteristics	Total, n (%)	Poorly adherence to treatment (n=19) MARS score 5 and lesser, n (%)	Good adherence to treatment (n=73) MARS score 6 and greater, n (%)
Age (years) (mean±SD)	38.46±13.35	34.15±14.20	39.41±13.00
Gender			
Male	40 (43.5)	7 (7.6)	33 (35.9)
Female	52 (56.5)	12 (13.0)	40 (43.5)
Education			
Profession or Honours	2 (2.2)	0	2 (2.2)
Graduate,	13 (14.1)	2 (2.2)	11 (12.0)
Intermediate or Diploma,	18 (19.6)	6 (6.5)	12 (13.0)
High school	41 (44.6)	9 (9.8)	32 (34.8)
Middle school	12 (13.0)	1 (1.1)	11 (12)
Primary school	4 (4.3)	1 (1.1)	3 (3.3)
Illiterate	2 (2.2)	0	2 (2.2)
Income (INR)			
>126360,	0	0	0
63182 to 126356,	0	0	0
47266 to 63178	3 (3.3)	1 (1.1)	2 (2.2)
31591 to 47262,	1 (1.1)	1 (1.1)	0
18953 to 31589	11 (12.0)	2 (2.2)	9 (9.8)
6327 to 18949	45 (48.9)	10 (10.9)	35 (38)
<6323	32 (34.8)	5 (5.4)	27 (29.3)
Marital status			
Unmarried	33 (35.9)	9 (9.8)	24 (26.1)
Married	49 (53.3)	10 (10.9)	39 (42.4)
Divorced	9 (9.8)	0	9 (9.8)
Widowed	1 (1.1)	0	1 (1.1)
Location			
Rural	87 (94.6)	19 (20.7)	68 (73.9)
Urban	5 (5.4)	0	5 (5.4)
Diagnosis			
Schizophrenia	43 (46.7)	6 (6.5)	37 (40.2)
BPAD	49 (53.3)	13 (14.1)	36 (39)
Did patient have regular follow-up			
No	57 (62.0)	17 (18.5)	40 (43.5)
Yes	35 (38.0)	2 (2.2)	33 (35.9)
Did patient have regular medicine intake			
No	20 (21.7)	12 (13.0)	8 (8.7)
Yes	72 (78.3)	7 (7.6)	65 (70.1)
Any symptom exacerbations in the six months prior to first lockdown			
No	55 (59.8)	7 (7.6)	48 (52.2)
Yes	37 (40.2)	12 (13.0)	25 (27.1)
Any symptom exacerbation during the first 6 months of lockdown			
No	55 (59.8)	7 (7.6)	48 (52.2)
Yes	37 (40.2)	12 (13.0)	25 (27.1)
Medication monitoring by caregiver			
No	26 (28.3)	5 (5.4)	21 (22.8)
Yes	66 (71.7)	14 (15.2)	52 (56.5)

[Table/Fig-1]: Clinical characteristics of the patients.

majority were female (n=52; 56.52%), with most having high school of formal education (n=41; 44.57%). Over half of the participants were married (n=49; 53.26%) and unemployed (n=61; 66.3%).

The mean age of getting illness was 25.34±8.81. The mean duration of illness was 156.63±100.4 months and mean duration of treatment was 134.63±100.9 months. Only 35 (38%) patients had regular follow-up during the COVID-19 lockdown but majority, 72 patients (78.3%) reported taking medicines regularly. In 66 (71.7%) patients medication intake was monitored by a caregiver. A total of 37 (40.2%) patients had acute exacerbation of the illness during the COVID-19 related lockdown. Eight patients (8.70%) had COVID-19 and 20 (21.74%) underwent COVID-19 related quarantine.

The mean MARS score was 7.32±2.11. The scores ranged between 0 and 10; the median score was 8, while the interquartile range was between 2 and 6. There were no differences in mean MARS scores across gender (p=0.146) or whether patient had Schizophrenia or BPAD (p=0.43). More details regarding the correlation with MARS score are shown in [Table/Fig-2,3]. In this study's sample, 19 patients (20.65%) had MARS score less than six implying poor adherence to medications, 24 patients (26.09%) had MARS score of six and seven suggesting medium adherence, and 49 patients (53.26%) had MARS score of eight and higher indicating high adherence to medications. For the purpose of analysis medium and high adherence were considered as good adherence group and compared with poor adherence group as risk of relapse are higher in poor adherence group.

MARS score	1	2	3	4	5	6	7	8	9	10
n	1	1	5	2	10	8	16	17	19	13
%	1.09	1.09	5.43	2.17	10.87	8.7	17.39	18.48	20.65	14.13

[Table/Fig-2]: MARS scoring.
Frequency and percentages of patients with each score are depicted

One-Sample Kolmogorov-Smirnov Test		MARS
Normal Parameters	Mean	7.32
	Std. Deviation	2.117
Most extreme differences	Absolute	0.159
	Positive	0.102
	Negative	-0.159
Test statistic		0.159
p-value		<0.001

[Table/Fig-3]: One-sample Kolmogorov-Smirnov test.
Here, p-value <0.001 that is MARS did not follow normal distribution

There was no correlation between The MARS scores and The CTS as shown in the [Table/Fig-4].

As shown in [Table/Fig-5], MARS was negatively correlated with BPRS, YMRS, HAM-D, which means that patients did not have any significant symptoms either in symptoms of Schizophrenia or BPAD (Mania and Depression). The CGI Severity and Improvement had

Spearman Rank Correlation (r value)	p-value
-0.077	0.464

[Table/Fig-4]: Spearman's Correlation between MARS and CTS.
Negative low non significant correlation

	Correlation between MARS And				
	BPRS	YMRS	HAM-D	CGI severity	Work and social
Spearman rank correlation (r-value)	-0.211	-0.398	-0.238	-0.372	-0.032
p-value	0.043	<0.001	0.022	<0.001	0.762

[Table/Fig-5]: Spearman's Correlation between MARS and BPRS, MARS and YMRS, MARS and HAM-D, MARS and CGI-S, MARS and WSAS.
Here, r-value shows low negative correlation between MARS and other parameters

negative correlation with MARS score implying that patients were doing well and improving in terms of the symptomology as MARS scores are higher. All these, BPRS, YMRS, HAM-D and CGI-S&I were statistically significant. The WSAS which measure outcome of functional impairment, was also negatively correlated but it was not statistically significant.

DISCUSSION

The present study was done to evaluate medication adherence in patients with severe mental illness during the COVID-19 pandemic in India and had direct interview with patients as compared to other studies which relied on telephonic interview during the pandemic. The purpose of this study was to find out how the COVID-19 pandemic and its restrictions impacted the treatment adherence of patients who had Schizophrenia or BPAD who had been taking their medications as prescribed and had come for a follow-up. The treatment adherence was assessed using the self-reported MARS. The study had adequate representation from male and female gender, comprised of patients mostly coming from rural background 94.6% and lower income group.

Present study observed that only 38% of the patients had regular follow-ups but 78.3% said that they took the medicines regularly. In this study's, sample as per MARS score of six and greater 73 patients (79.35%) had good adherence to treatment during the COVID-19 pandemic. Only 19 patients (20.65%) of them had their adherence affected. Patient adherence to medicines and follow-ups is a major issue in clinical practise across all medical specialities. In a study assessing medication adherence in a Lithium maintained cohort of 76 patients with Bipolar disorder conducted in AIIMS Delhi in 2019, medication non adherence was reported as 54.7% when MARS score for lower adherence was considered as seven and lesser [7]. In the present study, MARS score of less than six was considered as poor adherence. On comparison present study observed that 43 patients (46.74%) in the present study had MARS score of seven and lesser which suggest that medication adherence during pre pandemic time and that during the COVID-19 pandemic time was similar. In a study done in JIPMER, Puduchery between 2015 and 2016 in 160 patients with Bipolar disorder, 97 patients (60.6%) had lower than 6 score on Morisky MARS suggesting poor adherence [6]. In the present study during the COVID-19 pandemic the poor adherence to medication was found only in 19 patients (20.65%) of sample (MARS score less than 6), medium adherence was found in 24 patients (26.09%) of sample (MARS score of 6 and 7) might be due to the measures taken by the Government and patient's caregivers to ensure medication adherence to prevent risk of relapse and subsequent hospital admission. In a study conducted in DY Patil Medical College, Maharashtra in 2016 in 50 Schizophrenia patients, 26 patients (52%) were found to have poor adherence to medications [5] which was comparable to this study having 43 patient (46.74%) having poor adherence and medium adherence to medication. In a study done in Turkey in 2020 during the COVID-19 pandemic, it was found that 59% of the 396 patients with Schizophrenia interviewed through telephone reported that they were able to continue their medications [24]. These findings suggest that medication adherence was not significantly affected during the COVID-19 pandemic. In a study done in China in 800 Schizophrenia patients in 2021 during the COVID-19 pandemic it was found that only 332 patients (41.5%) had regular medication [25] intake during the pandemic which was significantly lower compared to this study's sample's medication adherence of 79.35% during the COVID-19 pandemic.

In a study, it was reported that 28.4% of the patients dropped out after first visit with a psychiatrist. A 61.5% patients had 1-3 follow-up and 10% had more than 4 follow-ups in a 2-year period [26]. This issue was amplified by COVID-19 pandemic. It impacted both patients' compliance with clinical follow-up and adherence to treatment. A prior study revealed that 40% of readmissions to hospitals within a year after being discharged from a psychiatry clinic were caused by non adherence with treatment [27]. Another study reported that the rate of missed follow-up was reported as high as 48% [28]. The present study shows that despite COVID-19 pandemic and associated lockdown, the adherence to the treatment was good as the mean MARS score of the sample was 7.32±2.11.

To prevent the COVID-19 spread and related deaths, countries had implemented a variety of measures, including quarantine, social distance, and transportation restrictions. In India, these measures were also done in response to the pandemic [29]. Due to the lack of evidence and uncertainty surrounding SARS-CoV-2 worldwide, these limitations became more stringent when the first case was discovered in India. Many felt that this will lead to a mental health pandemic and would create a chaos among those who are already on treatment especially those with Schizophrenia and BPAD [30]. But the present study, suggested that high treatment adherence was negatively correlated with CTS but it was not statistically significant. In a study done in NIMHANS in OCD patients in 2020 during the early phase of COVID-19 pandemic in India it was found that relapse rate in Obsessive-Compulsive Disorder (OCD) during COVID-19 pandemic was 21% was almost similar to the pre pandemic relapse rate of 20% [21]. In the present study sample of 92 patients, 37 patients (40.2%) had exacerbation of illness in the six months prior to COVID-19 related lockdown and 37 patients (40.2%) had exacerbation during the first six months of COVID-19 related lockdown. In a cross-sectional telephonic interview survey in patients with severe mental illness conducted during the initial phase of COVID-19 pandemic in Puducherry, South India in 132 patients it was found that 103 patients (78%) were able to continue their medications during the pandemic and 39 patients (29.5%) had symptoms of relapse [31]. The present study had comparable medication adherence of 79.35% patients with medium and high adherence to medication but had slightly higher relapse of symptoms 40.2% but had comparable relapse to the pre pandemic relapse rate. In a retrospective chart review done during the initial months of COVID-19 pandemic in a community mental health centre in Ankara, it was found that 11% of patients had relapse out of the total sample of 155 patients comprising of Schizophrenia and Bipolar disorder and it was comparable to the pre pandemic relapse rate of 6.5% in the same sample [32]. Relapse rate might have been lower than expected during the pandemic as caregivers might have been able to ensure medication adherence in patients despite not coming for regular follow-up visits during the time of pandemic. In a longitudinal cohort study done in UK in 356 patients with Bipolar disorder and mood symptoms assessed by an online monitoring tool it was found that mood symptoms during the COVID-19 pandemic in 2020 didn't significantly differ from the pre pandemic period in 2019 even though higher rates of anxiety related to the pandemic was observed [33]. The present study suggests that COVID-19 related pandemic control measures and COVID-19 related anxiety didn't play a role to cause exacerbation in Schizophrenia and Bipolar patients and didn't affect their medication adherence.

In this present study, MARS score was negatively correlated with the Scales of BPRS, YMRS and HAM-D which suggests that as medication adherence improves the psychopathology assessed using these scales had lower scores in Schizophrenia and Bipolar patients. In this study's sample the mean MARS score was 7.32±2.11 implying better adherence to medication and hence lower scores on BPRS, YMRS, HAM-D. This suggests that there was reduction in psychopathology which may have occurred due to good adherence of the medications even though COVID-19 pandemic related restrictions were imposed.

Limitation(s)

1. Self-reported question of medication adherence has lower sensitivity, recall bias might be present.

2. Present study considered MARS score of 5 and lesser as poor adherence as this is the group with higher chance of relapse rather than medium adherence group. This might have impacted the study interpretation of lesser patients with poor adherence.

3. Patients who are non adherent might not be coming to COVID-19 hospital for follow-up due to fear of COVID-19.

4. Patients who are having good adherence might be continuing medications through prescription refills, teleconsultation, using e sanjeevani, obtaining medicines from District Mental health programme clinics or consulting non COVID-19 hospitals and might be missed in the study.

CONCLUSION(S)

Non-adherence to treatment in persons with Schizophrenia and BPAD was less among patients who followed-up in a COVID-19 care hospital during the COVID-19 pandemic. Though the patients did not follow-up regularly, they had good adherence to the medications and the symptom exacerbation during COVID-19 pandemic was similar to the pre pandemic period. COVID-19 related anxiety didn't have any significant association with medication adherence and relapse.

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PARTICULARS OF CONTRIBUTORS:
1. Assistant Professor, Department of Psychiatry, Government Medical College, Palakkad, Kerala, India.
2. Consultant Psychiatrist, Department of Psychiatry, Aster Prime Hospital, Hyderabad, Telangana, India.
3. Assistant Professor, Department of Psychiatry, Government Medical College, Palakkad, Kerala, India.
4. Psychiatry Social Worker, Department of Psychiatry, Government Medical College, Palakkad, Kerala, India.
5. Statistician, Department of Community Medicine, Government Medical College, Palakkad, Kerala, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Sajal Sathiadevan,
Assistant Professor, Department of Psychiatry, Government Medical College,
Palakkad-678013, Kerala, India.
E-mail: sajalsathiadevan@gmail.com