

## **A prospective observational study to assess compliance and factors influencing compliance with antiepileptic drugs among patients with epilepsy**

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### **ABSTRACT**

**Background:** The primary treatment for epilepsy is Antiepileptic drug (AED) therapy. Non-compliance to AEDs can result in break-through seizure, emergency department visits, hospitalizations, fractures, head injuries and increased mortality. Thus, compliance to AEDs is crucial to be studied. Objective is to study compliance and factors influencing compliance with AEDs among patients with epilepsy.

**Methods:** This observational study was conducted in 105 patients with epilepsy on AED therapy in community in Ludhiana (Punjab) after approval from Institutional Ethics Committee. Demographic data and drug history was collected. Monthly follow up for 6 months was done by paying home visits and data regarding type, dose, frequency of administration of AED was recorded on a semi-structured performa. Pill count was done by recording number of pills dispensed and number of pills remaining with patient. Response to Morisky's Medication Adherence Scale (MMAS) was also recorded. Results were correlated with patient demographics, type, frequency and number of AEDs.

**Results:** Out of 105 patients, 65 were males and 40 were females. Fifty-four patients were non-compliant with both pill-count and MMAS. Non-compliance was high in first month and decreased gradually. Poly-therapy, lower socio-economic status and multiple dosing regimens were most commonly associated with non-compliance.

**Conclusions:** Under-dosing was more common among non-compliers, which explains the high reporting of forgetfulness to take medicine in MMAS. Both pill count and MMAS are effective non-invasive tools to study compliance.

**Keywords:** Anti-epileptic drugs, Compliance, Epilepsy, MMAS, Pill-count, Seizures

### **INTRODUCTION**

Epilepsy is a condition in which a person has recurrent episodes of seizures due to a chronic, underlying process.<sup>1</sup> The primary treatment for epilepsy is Antiepileptic drug (AED) therapy which is often prescribed for a long duration. Treatment with AEDs substantially impact quality of life in Patients With Epilepsy (PWE) by controlling seizures. Although AEDs may not cure the condition but PWE may remain seizure-free and thus have

a better quality of life with an appropriate AED regimen. Approximately 80% of PWE are managed with single AED therapy and about 10-15% with combination of two AEDs.<sup>2</sup>

Non-compliance to medication is a prevalent and persistent healthcare problem, particularly for people with a chronic disorder like epilepsy. Approximately 21-42% of PWE show non-compliance to their prescribed treatment with AEDs.<sup>3</sup>

Compliance is defined as the extent to which behavior of patient matches with prescriber's advice.<sup>4</sup> Compliance to AEDs is crucial in preventing or minimizing seizure as non-compliance to AEDs can result in break through seizures, emergency department visits, hospitalizations, fractures, head injuries and increased mortality. Non-compliance can be intentional, with patients acting in a certain way according to their own expectations of treatment, adverse effects and lifestyle choice; or non-intentional, when patients do not adhere due to forgetfulness, misunderstanding or uncertainty about clinicians' recommendations.<sup>5</sup> Although poor compliance is considered to be one of the major causes of non-responsiveness to AED therapy, this has not been studied extensively in India. It is necessary to find whether the non-compliance is primary due to initiation of pharmacotherapy or secondary due to implementation of the prescribed regime, and to find factors which influence compliance to AED regimen so that proper intervention can then be tailored to improve the medication taking behavior of each patient.

## METHODS

### Study design

The information obtained in this study was collected prospectively with the approval of the Institutional ethics committee. All patients were enrolled after obtaining written informed consent.

This was a prospective observational study conducted in PWE in community in the Ludhiana city of Punjab state in identified clusters. Patients diagnosed with epilepsy on AED therapy, aged  $\geq 18$  years and either gender with any co-morbid condition were enrolled. Patient demographics i.e. age, gender, height, weight, and socio-economic status (Kuppuswamy scale) was entered in a semi-structured performa. Monthly follow up of enrolled patients in each cluster was done for 6 months by paying home visits.<sup>6</sup>

Pill count and MMAS were two different tools used to assess compliance during home visits. Pill count was calculated using formula; (Pills Dispensed- Pills remaining)/ (Number of tablets to be consumed between 2 visits). Pill count value of 0.85 to  $\leq 1.15$  was recorded as appropriate compliance to prescribed regimen.<sup>7</sup> Value  $< 0.85$  was recorded as under-dose and  $> 1.15$  was recorded as overdose to prescribed AED regimen. Overdose or under-dose to prescribed regimen was labeled as non-compliance.

Morisky Medication Adherence Scale (MMAS) was administered to each patient during each home visit. Score of 1 was given to each positive answer and 0 for negative answer, thus giving a range of 0-4 score for each patient. Patients with score  $\geq 1$  were labeled as non-compliant. MMAS was used to differentiate between intentional and non-intentional behavior of non-compliance. Seizure

control and break-through seizures were assessed using seizure diary.

### Statistical analysis

The data obtained in study was subjected to statistical analysis with Microsoft Excel for Mac 2011 [version 14.0.0 (100825)] and SPSS (version 21.0, IBM). Relationship of demographic factors between compliant and non-compliant patients was analyzed using Chi-square test and rest of the data was analyzed using descriptive statistics.  $P < 0.05$  was considered as statistically significant.

## RESULTS

Out of 115 patients enrolled in the study, 7 patients withdrew their consent to participate and 3 patients shifted to another city. Complete analysis was performed in 105 patients.

The mean age of patients was  $33.6 \pm 13.6$  years and mean weight was  $58.6 \pm 14.7$  kg. Demographic distribution and comparison of demographic factors with non-compliance is given in Table 1. Mean age of onset of seizures was  $17.2 \pm 13.4$  years. Family history of epilepsy was present in 31 (29.5%) patients. Maximum number of patients ( $n=67$ , 63.8%) were diagnosed with Idiopathic Generalised Epilepsy (IGE) followed by Temporal Lobe Epilepsy ( $n=12$ , 11.4%) and IGE with Juvenile Myoclonic Epilepsy in 5 (4.8%). Generalised Tonic Clonic Seizures (GTCS) was maximum reported seizure semiology among patients ( $n=96$ , 91.4%) while only 2 (1.9%) patients reported with absence seizure.

During six months follow up, majority of the patients were on AED monotherapy (63-67%) compared to polytherapy (32-37%). Breakthrough seizure was reported in 39 (37.1%) of patients out of which 22 (56.4%) were non-compliant. Sodium valproate was prescribed in maximum number of patients ( $n=39$ , 37.1%) followed by Phenytoin in 37 (35.2%) patients. Lamotrigine and Clonazepam were least prescribed in only 1 (1.0%) patient. Pattern of non-compliance with pill-count and MMAS is shown in Figure 1 and 2 respectively. There is significant difference between non-compliant patients as per pill-count and MMAS ( $p=0.000$ ) (Table 2).

## DISCUSSION

Epilepsy is a chronic neurological disorder that requires long-term management with AEDs. Despite using effective combination of AEDs, approximately 25% of patients have epilepsy that is resistant to medical therapy.<sup>8</sup> Approximately 21-42% of patients prescribed AEDs for epilepsy do not adhere to their prescribed treatment.<sup>3</sup> The present study provides the insights of current trend of compliance to antiepileptic drugs and factors which affect compliance in community.

**Table 1: Demographic distribution and comparison of non-compliant patients.**

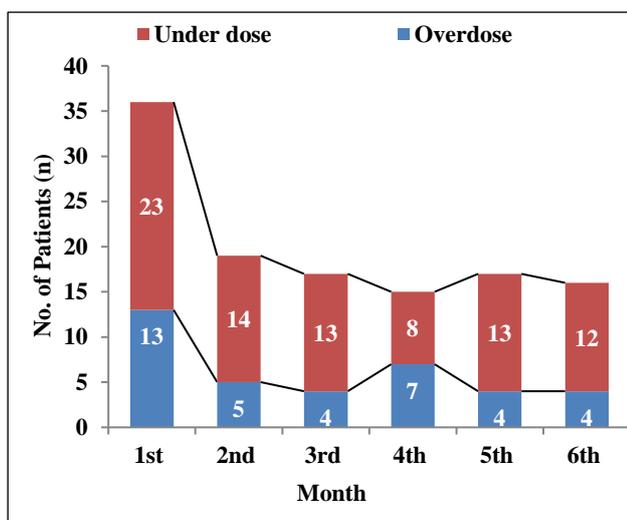
Characteristic	Total		Non-compliant				P value*	
			Pill-Count		MMAS		Pill count	MMAS
Age group	n	%	n	%	n	%		
18-40	77	73.3%	48	75.0%	50	78.1%	0.358	0.245
41-60	22	21.0%	14	21.9%	10	15.6%		
>60	6	5.7%	2	3.1%	4	6.3%		
Total	105	100.0%	64	100.0%	64	100.0%		
<b>Gender</b>								
F	41	39.0%	29	45.3%	30	46.9%	0.100	0.040
M	64	61.0%	35	54.7%	34	53.1%		
Total	105	100.0%	64	100.0%	64	100.0%		
<b>Residential area</b>								
Rural	12	11.4%	11	17.2%	10	15.6%	0.020	0.091
Urban	93	88.6%	53	82.8%	54	84.4%		
Total	105	100.0%	64	100.0%	64	100.0%		
<b>Socioeconomic status</b>								
Lower	8	7.6%	5	7.8%	6	9.4%	0.916	0.490
Lower middle	41	39.0%	21	32.8%	19	29.7%		
Upper	33	31.4%	1	1.6%	1	1.6%		
Upper lower	21	20.0%	26	40.6%	28	43.8%		
Upper middle	2	2.0%	11	17.2%	10	15.6%		
Total	105	100.0%	64	100.0%	64	100.0%		

\* Compliant versus non-compliant patients.

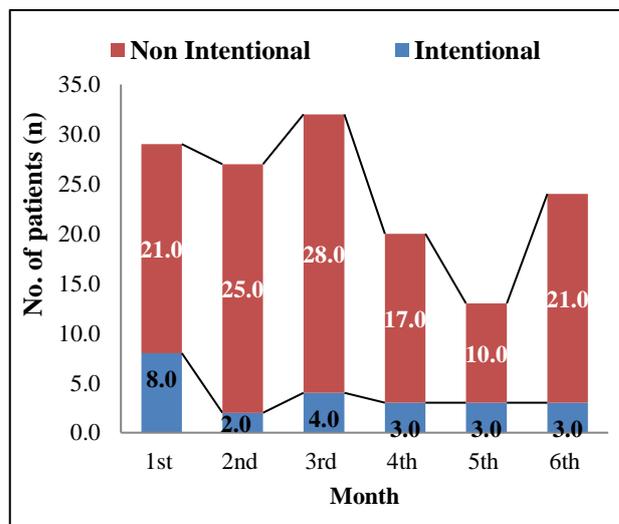
**Table 2: Pattern of non-compliance among PWE (Pill-Count and MMAS).**

Tool used	Patients	Pill-count			p-value (Chi-square)
		Compliant	Non-compliant	Total	
		n	%	n	
MMAS	Compliant	31	75.6%	10*	0.000
	Non-compliant	10#	24.4%	54	
Total		41	100.0%	64	

\* 4 patients lost their medicine, 5 patients took medicine from their own stock and 1 patient took extra medicine after a seizure episode.  
# All patients have pill-count value >0.85 but less than 1.15, hence classified as compliant but MMAS classified as non-compliant.



**Figure 1: Pattern of Non-compliance (Pill counts) among PWE.**



**Figure 2: Behaviour pattern of non-compliance (MMAS) among PWE.**

Most of the patients in this study belonged to 18-40 year age group (n=77, 73.3%). In a cross-sectional study conducted by Gurumurthy et al, 318 (70.5%) patients were between 18-30 year of age group.<sup>9</sup>

Among 105 patients studied; males patients (n=64, 61%) were predominant as compared to females in this study, which is in concordance with another study by Kalyani et al, where 65% patients were males and 35% were female.<sup>10</sup> The higher prevalence in males could be because in some population, the symptoms and diagnosis of epilepsy in women is concealed from public because the exposure of epilepsy may become a hurdle in their marriage.

Out of 105 enrolled patients in this study, we found that family history of epilepsy was present in 31 (29.5%) of patients. Saad et al, conducted a prospective observational study and found that family history of epilepsy was present in 19 (18.3%) out of 104 enrolled patients.<sup>11</sup> As there is a social stigma about the disease among PWE, due to which patients may hide their family history.

GTCS was the most common seizure semiology noticed by patients and relatives of patients. GTCS was reported in 91.4% of this study population as presenting symptom. Results are in concordance with the maximum reported etiology of epilepsy in this study, which was IGE.

Most common prescribed AED in this study was sodium valproate (37.1%). This is in view of Sodium Valproate being drug of choice in IGE, which was the most common etiology of epilepsy reported in this study. Also, sodium valproate being a broad spectrum AED is useful in almost every type of seizure semiology. Similarly, 34 % of patients were prescribed with sodium valproate in another study by Kalyani et al.<sup>10</sup>

During 6-month follow up in this study, 64 (61%) patients were found to be non-compliant according to pill count. Prevalence of poor compliance to AED therapy in a study by Tan et al, was 64.1% of the study subjects (n=93).<sup>12</sup> Non-compliance according to pill-count was high during initiation of therapy and in patients belonging to 18-40 years of age group (56%). Age group of 18-40 years being productive years of life and patients from this age group are mostly out of their home due to job related work. Thus, younger patients at times do not take their medication due to busy schedule. Also, patients of elder age group realize the importance and benefits of compliance more than younger patients and therefore tend to be more compliant. Also at initiation of therapy, patients are not familiar with dosing regimen, but with time, they become habitual and thus become more compliant. Under-dosing was more in patients (8-23 subjects) compared to over-dosing (4-13 subjects) throughout the study. Similarly 6 out of 16 (38 %) patients were under-dose in a study by Lisk et al, but nothing was mentioned about those who took more than advised number of tablets.<sup>7</sup> As we reported both under-dose and over-dose, this might be the reason that 64 (61%) were found to be non-compliant in this study.

Non-compliance was more in males (n=35, 54.7%) and patients living in urban area (n=53, 82.8%) in this study. In a study conducted by Jabbar et al, on 104 PWE, compliance was high among females (n=40, 72.5%)<sup>13</sup> As in this study population, most of the male patients were daily-wage workers and they didn't carry their medicine along with them, which could be the reason of high non-compliance among males. Fifty-three (82.8%) non-compliant patients in this study were from urban area. In a prospective cross-sectional study by Hasiso et al, which has shown that 78 (73.2 %) non-compliant patients were from urban background and 54 (62.8%) from rural.<sup>14</sup>

In this study, non-compliance was highest among upper lower socio-economic group (44.1%). In a cross-sectional study conducted by Gurumurthy et al, it was shown that out of 125 non-compliant patients 33 were from lower middle and 68 were from upper lower/ lower socio-economic class.<sup>9</sup> The findings of this study suggest that PWE who are of a lower socioeconomic class may be at a higher risk of non-compliance. As people of lower socioeconomic status are less educated and they do not understand the need of compliance to AEDs.

Out of 64 (61%) patients who showed non-compliance according to MMAS in this study, 50 (78.1%) were of 18-40 year age group with males showing more non-compliance 34 (53.1%). Most Non-compliant patients were from upper lower socioeconomic status 28 (43.8%). In an analytical, cross-sectional study conducted by Pasha et al, 38 out of 71 (53.5%) non-compliant patients were males.<sup>15</sup> Gurumurthy et al, have showed similar results in a cross-sectional study They have reported that out of 125 non-compliant patients, 87 (69.6%) were from 18-30 years age group. 63 (50.4%) out of 125 were males and 68 (54.4%) from upper lower/lower socio-economic groups.<sup>9</sup>

Non-intentional non-compliance (MMAS) was found to be main reason of non-compliance (10-28 patients) throughout this study with a mixed trend over a period of 6 months. Forgetfulness to take medicine was found to be main reason of non-compliance (5-16 patients) followed by patients who were careless (3-11 patients) to take their medicine. Very few (1-5 patients) were non-compliant because of both reasons. Those found intentionally non-compliant throughout this study were mainly because of the feeling of not getting any better with AEDs (2-3 patients) followed by few patients missing their pills when they think they have been cured (1 patient). In a study by Liu et al, it was seen that out of the patients who did not adhere to drugs (69.6%), the primary reason was forgetfulness (65.8%).<sup>16</sup> Similarly in a cross-sectional study including 45 patients by Gomes et al. it was shown that out of 45, (13.3 %) of patients reported to be non-compliant when they felt better with medicine and 13.3% were non-compliant when they thought they were not getting any better with AEDs.<sup>17</sup>

In this study, distribution of break-through seizures was found to be more (n=22) (56.4%) among patients with non-

compliance. In a study by Ferrari et al. patients in the moderate-to-low compliance group reported a higher seizure frequency in the previous 30 days (64.7% vs. 50.0%).<sup>18</sup> Breakthrough seizure can be due to many reasons like use of intoxicants can lower seizure threshold or drug-drug interactions can lead to microsomal enzyme induction and thus fall in plasma concentration of AED. For adequate seizure control, steady state plasma concentration of AEDs needs to be maintained by being compliant to treatment. Inability to do so can lead to fall in steady state plasma concentration and hence breakthrough seizure. To conclude that break-through seizures were because of non-compliance, plasma trough levels of AED should be assessed in patients.

In this study, total number of non-compliant patients assessed with pill-count and MMAS were 64 (61%). Out of these, 54 (51.4%) patients were non-compliant with both pill-count and MMAS. Ten patients didn't report non-compliance in MMAS as they used medicine from their own stock or they lost some tablets. Out of those found non-compliant in MMAS, 10 patients were compliant in pill-count as they were lying between range of 85-115%, the range of compliance as per pill-count. In a study by Lisk et al, it was found that out of 3 patients who admitted missing therapy, one was good complier on pill-count.<sup>7</sup> Similarly four out of 13 patients who said they took all their medication were poor compliers on Pill-count.<sup>7</sup>

The gold standard method to check compliance still remains Therapeutic Drug Monitoring (TDM) in which plasma trough levels of AED are assessed in patients. These can be correlated with Pill-count and MMAS.

Limitations of the present study include it being conducted for a shorter duration of 6 months. Thus, pattern and prevalence of long-term compliance with AEDs cannot be evaluated. Also, factors, which influence long-term compliance, cannot be ascertained. Incidence of ADRs with AEDs was not explored in this study, as ADRs can be one of the reasons of non-compliance to AEDs. More number of patients can help to generate more robust data. As small sample size in this study could have affected the possibility to establish a statistical difference among various factors that influence compliance. Study population in this study is mainly from urban background with socioeconomic spectrum being more of lower than upper status. Thus, comparison of patients from different socioeconomic strata could not be done.

## CONCLUSION

To conclude, non-compliance among patients with epilepsy is high and emphasis should be given during initiation of therapy as non-compliance is high during start of therapy. Though under dosing is frequently seen among non-compliant patients, overdosing is also present among PWE which can result in dose related adverse effects with AEDs. Both MMAS and pill-count are effective tools to identify patients with compliance. Though MMAS is easy

to administer, it can unduly report over or under compliance. Patients can cause pill dumping in order to become compliant as per pill counting. Pill-count and MMAS used along with TDM can increase sensitivity to assess compliance in patients with epilepsy. Repeated counseling about compliance is important for patients on AEDs to reinforce the idea for effective seizure control.

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