

Medication Adherence in Indian Epilepsy Patients

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Abstract

Purpose: While two-thirds of epilepsy patients can become seizure free on medical treatment, poor adherence to medication is a major problem to sustained remission and functional restoration. The aim of this study was to assess the prevalence and associated factors of antiepileptic drug (AED) non-adherence. **Methods:** We conducted a subgroup analysis based on results that emerged from a single center, cross-sectional study. Patients who were 18 years or older were included. The 4-item Morisky Medication Adherence Scale was used to measure adherence to AED (s). Multivariable logistic regression analysis was used to predict factors associated with AED non-adherence. **Results:** A total of 268 patients fulfilled inclusion criteria and were included in this subgroup analysis. Among the participants, 81 (30%) were non-adherent to medication. Three factors associated with non-adherence were AED polytherapy [OR: 4.5 (2.1-9.5) $P = 0.001$], drug related adverse events [OR: 3.9 (2.1-7.3) $P = 0.001$], and treatment duration exceeding 3 years [OR: 2.6 (1.3-5.0) $P = 0.003$]. **Conclusion:** About one-third patients were not compliant with their medication. If the treatment of patients is restricted to monotherapy as far as possible and patients are educated about duration of treatment and possible adverse effects of AEDs, non-adherence may be reduced.

Keywords: Drug resistant epilepsy, medication adherence, medication nonadherence

INTRODUCTION

There are seventy million epilepsy patients worldwide and 90% of them live in low and middle-income countries.^[1] Approximately two-thirds of epilepsy patients can be successfully controlled and made seizure-free with currently available antiepileptic drugs (AEDs). This would then leave one-third patients with uncontrolled epilepsy.^[2] However, uncontrolled epilepsy does not always imply drug-resistant epilepsy.^[3] There could be many causes for the epilepsy remaining uncontrolled. A person's attacks may be non-epileptic. Alternatively, uncontrolled epilepsy may be due to a patient being treated with wrong AEDs (misclassified epilepsy), or with suboptimal AED doses, or it may truly be drug resistant epilepsy. Finally, some patients may have been rightly diagnosed, may be on appropriate doses of correctly selected AEDs and yet be uncontrolled simply due to non-adherence.^[4] Reported non-adherence to AEDs ranges from 26 to 79% in different communities.^[5-10] The consequences of non-adherence are poor seizure control and an increased incidence of injuries, emergency department visits, hospital admissions, and mortality.^[11] Non-adherence also leads to increased resource utilization and health care cost to the patient, community, and nation.^[12,13] With an epilepsy burden of at least 12 million active epilepsy patients in India, the issue of non-adherence and all its implications assume a serious proportion.^[14] There is scarcity of information regarding the prevalence of AED non-adherence and even less is known regarding factors associated with it in the Indian epilepsy patient population. Information about the extent of non-adherence and what factors may lead to it may be important in designing appropriate interventions. In this paper, we look at the size of the problem of non-adherence in Indian epilepsy patients and discuss factors that may be implicated.

METHODS

Standard protocol approvals, patient consents and study design

A subgroup analysis to study adherence was prospectively planned. Adherence data were collected during the course of a single center, cross-sectional study conducted at a tertiary care teaching hospital that provides comprehensive epilepsy care in New Delhi, India.^[15] While consecutive epilepsy patients presenting to the Neurology outpatient clinic for the first time had been enrolled in the original study, only those patients who were 18 years or older were included to study adherence. We excluded younger patients as a self-reported scale was being used to assess adherence and reliability in younger patients was uncertain. Other exclusion criteria were: (a) treatment naïve patients, (b) patients taking only traditional medicines, and (c) cognitive impairment sufficient to impair memory and/or communication with investigators. All patients gave a written informed consent and the institutional ethics review board approved the study.

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Definitions

We followed the practical clinical definition of epilepsy accepted by ILAE in 2014.^[16] Epilepsy was diagnosed if a patient had at least two unprovoked seizures occurring more than 24 hours apart or even one unprovoked seizure with a high probability of further seizures. Non-epileptic seizures were diagnosed if the patient's description of seizure semiology made non-epileptic seizures likely. The distinction of rural versus urban was made as per the NSSO.^[17] To determine per capita income, the income of the patient and his/her household was considered and categorized according to revised Kuppaswamy and B G Prasad socio-economic scales.^[18] For assessment of psychiatric comorbidity, M.I.N.I. (Mini International Neuropsychiatric Interview) English version 5.0.0 was used. Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 grading was used to record the severity of adverse drug events. For assessing cost of treatment, monthly cost of all prescribed medication including AEDs, multivitamins, and calcium supplements was added. We did not include the cost of diagnostic tests, travelling expenses, or any other expenditure related to patient care. Polytherapy was defined as two or more anti-epileptic drugs used at the same time. Seizures were defined as frequent if ≥ 1 seizure occurred per month and infrequent if there was < 1 seizure per month.

Assessment of medication adherence

Adherence to AED treatment was assessed using the four-item Morisky Medication Adherence Scale (MMAS-4), a standardized, validated questionnaire for measuring self-reported medication adherence.^[19] The four items of the MMAS-4 assess whether: (a) the patient has ever forgotten to take medication; (b) the patient has ever had problems remembering to take medication; (c) the patient has stopped medication due to alleviating symptoms; and (d) the patient has stopped medication due to worsening symptoms. Each item is scored as either 0 (Yes) or 1 (No). The score of each item is then summed to give a range of scores from 0 to 4. A score of 3–4 suggests that the patient is adherent, while a score of ≤ 2 suggests that the patient is nonadherent. We focused on adherence over the 4 weeks preceding the current outpatient clinic visit in order to minimize potential recall bias.

Data collection

Data were collected using a pre-structured proforma, which included demographic details, epilepsy type, psychiatric co-morbidities, number of AEDs, treatment duration, drug-related adverse events, monthly cost of treatment, and self-reported drug adherence.

Outcomes

We were interested in two outcomes: (a) determining the proportion of epilepsy patients who were non-adherent to medication based on MMAS-4 and (b) factors associated with AED non-adherence.

Statistical analysis

Data were entered into MS EXCEL® spreadsheets. Descriptive statistics were used to summarize baseline characteristics. Continuous data following normal distribution were presented as means (with standard deviation). Categorical data were presented as numbers and percentages. Continuous variables were compared using independent *t*-test; categorical variables were analyzed using Chi-square test. The potential predictors for non-adherence were analyzed using univariable logistic regression analysis. With an aim to find most potential independent predictors, we used Hosmer and Lemeshow purposeful multivariable analysis to build the multivariable model. In the multivariable analysis, all the predictors that showed a potential influence in the bivariate analyses (i.e., predictors for which *P* value less than 0.25 or clinically relevant) and were considered to build the best model. Significance in the final model was considered at *P* value lower than 0.05. All the statistical analysis was conducted using software version STATA version 13.

RESULTS

From January 2017 to July 2017, a total of 422 patients were assessed. Two hundred sixty-eight patients fulfilled inclusion criteria and were included in this subgroup analysis. Among the participants ($n = 268$), 81 (30%) were non-adherent and 187 (70%) were adherent to medication over the 4 weeks preceding the current outpatient clinic visit. The characteristics of the study participants are presented in Table 1.

On univariate regression analysis, there was a statistically significant difference in epilepsy type, AED polytherapy, monthly cost of medication, frequent seizures, drug related adverse events, and treatment duration between adherent and non-adherent groups [Table 1]. However, on multivariable stepwise logistic regression analysis, only three factors were found to be associated with non-adherence [Table 2]. Patients on AED polytherapy [OR: 4.5 (2.1-9.5) $P = 0.001$], with drug related adverse effects [OR: 3.9 (2.1-7.3) $P = 0.001$] and epilepsy treatment duration exceeding 3 years [OR: 2.6 (1.3-5.0) $P = 0.003$] were most likely to be associated with AED non-adherence [Table 2]. The multivariable analysis revealed an area under ROC curve of 0.81 [Table 2].

DISCUSSION

Results of this subgroup analysis showed that 30% epilepsy patients who were 18 years or older reported non-adherence to prescribed AED treatment in the 4 weeks preceding the current outpatient clinic visit. Non-adherence reported in literature varies from 26 to 79% [Table 3].^[5-10] This difference may be a consequence of variability in the characteristics of the study population, operational definitions, and different adherence measurement scales. The three factors we found to be associated with non-adherence were AED polytherapy, drug related adverse events and treatment duration exceeding 3 years.

Table 1: Demographic and clinical characteristics of study participants*

Characteristics	Non-adherent	Adherent	P	Univariate analysis
	n=81 (100%)	n=187 (100%)		OR† (95% CI‡)
Age (Yr) Mean (SD) [§]	31.2 (±13.7)	30.5 (±12.3)	0.7	1.0 (0.9-1.0)
Male gender	45 (55.6)	112 (59.9)	0.5	0.8 (0.5-1.4)
Rural resident	35 (43.2)	77 (41.1)	0.7	1.1 (0.6-1.8)
Education below matriculation	35 (43.2)	64 (34.2)	0.1	1.5 (0.8-2.4)
Unemployed	23 (28.4)	59 (31.5)	0.6	0.5 (0.5-1.5)
Lower Socioeconomic class	38 (46.9)	77 (41.2)	0.4	1.2 (0.7-2.1)
Marital status (single)	43 (53.1)	96 (51.3)	0.8	1.1 (0.6-1.8)
Epilepsy duration (yr) Mean (SD)	6.4 (±7.4)	6.3 (±5.3)	0.9	1.0 (0.9-1.04)
Focal epilepsy	62 (76.5)	119 (63.6)	0.04	1.8 (1.02-3.3)
Generalized epilepsy	13 (16.56)	49 (26.2)	0.07	0.5 (0.3-1.05)
Uncertain epilepsy	6 (7.4)	19 (10.1)	0.5	0.7 (0.3-1.8)
Frequent seizures	31 (38.2)	50 (26.7)	0.06	1.7 (0.9-2.9)
AED [¶] Polytherapy	69 (85.1)	80 (42.8)	0.001	7.6 (3.9-15.1)
Medication cost (INR)**	1386.5	1039.1	0.002	1.0 (1.01-1.07)
CTCAE ^{††} grade I or more	55 (67.9)	53 (28.3)	0.001	5.3 (3.0-9.4)
Treatment duration (>3 years)	60 (74.1)	83 (44.1)	0.001	3.5 (2.0-6.3)
Psychiatric comorbidity	16 (19.7)	27 (14.4)	0.27	1.4 (0.7-2.8)

*Total 268 patients included in this study, among them 81 were non-adherent to medication. †OR: Odd ratio. ‡CI: Confidence Interval. §SD: Standard deviation. ||Included single, separated and widows. ¶AED: Anti-epileptic drugs. **Direct monthly cost of all drugs (Mean, Indian rupees). ††CTCAE: Common terminology criteria for adverse events

Table 2: Multivariable logistic regression analysis to predict factors associated with AED non-adherence

Characteristics	Non-adherence	P
	OR* (95% CI†)	
Focal epilepsy	1.3 (0.6-2.7)	0.40
AED [‡] polytherapy	4.5 (2.1-9.5)	0.001
Medication cost	1.0 (0.9-1.0)	0.10
Drug related adverse events	3.9 (2.1-7.3)	0.001
Treatment duration (>3 years)	2.6 (1.3-5.0)	0.003
Frequent seizure	1.1 (0.6-2.2)	0.60

Area under ROC curve=0.81. *OR: Odd ratio. †CI: Confidence Interval. ‡AED: Anti-epileptic drugs

When a large treatment gap is reported from a community, one reflexively thinks of patients who have never been diagnosed or started on AEDs. While such patients do constitute an important component of the treatment gap, the problem has several more layers. Secondary treatment gap alludes to patients who were at some point diagnosed and started on AEDs but prematurely discontinued medication.^[20] Frequent non-adherence too may lead to a secondary treatment gap. Non-adherence feeds into a vicious cycle where missed medication leads to breakthrough seizures, which further reinforces the patients' skepticism about efficacy of AEDs. This problem especially manifests in communities where epilepsy patients are poor and struggle to buy AEDs, are often not well informed about epilepsy, not entirely convinced about modern medicines and ridden with superstition and culturally steeped dogma. Awareness about epilepsy improves adherence.^[21]

Patients, who were subjects of this study, were presenting for the first time to our hospital, which is a tertiary care providing

referral center. As discussed in a previous paper, at least 40% of these patients did not actually need tertiary care.^[15] Yet, we found that a significant proportion of patients were already on polytherapy—85% in the non-adherent group and 43% in the adherent group. Excessive, often irrational use of polytherapy reflects a lack of standardization of prescribing practices for epilepsy in the country. Overuse of polypharmacy provides no benefit in seizure control while unnecessarily adding AED-related side effects and increasing cost of treatment. While our analysis did not directly implicate treatment cost as a factor leading to non-adherence, the non-adherence related to polytherapy may in part be due to the treatment expenses. A longer duration of treatment also translates into increased cost. Non-adherence in patients who are on AED treatment for longer may also be a manifestation of patients not being informed about the need for prolonged treatment. Patients, who are better informed about epilepsy including the likely duration of treatment and the potential of AED-related adverse effects and how those can be mitigated, may be more likely to adhere to treatment.

Our study is limited by the fact that patients self-reported AED non-adherence and some instances of missing the drug may have been forgotten or even deliberately concealed. We tried to limit this recall bias by evaluating non-adherence in a narrow 4-week window prior to the current visit. Occasionally, patients may withhold information about non-adherence due to embarrassment or a fear of offending the treating doctor. Self-reporting the MMAS-4 consists of checking appropriate boxes on the form in relative privacy and anonymity. We hope this allayed some fears and hesitation that patients may have felt in revealing non-adherence. We have taken the

Table 3: Studies assessing prevalence of medication adherence in epilepsy

Study authors (year)	No. of patients	Type of study	Method used to assess adherence	Prevalence of non-adherence	Factors associated with non-adherence
Das <i>et al.</i> (2020)	100	Cross-sectional study	Morisky scale	71	Polytherapy increased drug frequency
Niriayo <i>et al.</i> (2019)	292	Cross-sectional study	Self-reported questionnaires	65	Forgetfulness unavailability of drug safety concern
Gurumurth <i>et al.</i> (2017)	451	Cross-sectional study	Morisky scale	28	Forgetfulness
Getne <i>et al.</i> (2016)	450	Cross-sectional study	Morisky scale	38	Treat duration >6 yr AED cost Drug adverse effects Lack of health information Poor social support, etc.
Molugulu <i>et al.</i> (2016)	272	Cross-sectional study	Structured questionnaire	49	Seizure frequency Patient satisfaction Illness understanding
Malek <i>et al.</i> (2016)	44-388564	Systematic review (1946-2015) 17 studies	Morisky scale, Medication possession ration, Therapeutic drug Concentration Monitoring and others	26-79	Longer use of AED Side effects of AED Lack of treat benefit Epilepsy stigma Forgetfulness Sz free for a time period Generalized epilepsy Depression Multiple comorbidities Lower social status Lower educational status

MMA-4 as a screening tool to assess the prevalence of AED non-adherence and individual components of the scale were not analyzed which can be more informative to decide the level of non-adherence. While our study included psychiatric comorbidities and AED pharmacy details, other comorbidities and coexistent non-AED pharmacy were not included.

A prospective study with a larger sample size may yield more reliable data but we think our observations are important for two reasons: (1) not much is reliably known about non-adherence in Indian epilepsy patients and (2) the factors associated with non-adherence are in large measure, correctable. If the treatment of patients is restricted to monotherapy as far as possible and patients are given enough information especially about duration of treatment and possible adverse effects of AEDs, non-adherence may be reduced.

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Conflicts of interest

There are no conflicts of interest.

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