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Affordability, availability and tolerability of anti-seizure medications are better predictors of adherence than beliefs: Changing paradigms from a low resource setting

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ABSTRACT

Objectives: Anti-seizure medication (ASM) non-adherence contributes to treatment gap and increases mortality and morbidity associated with epilepsy. Beliefs about medications are considered better predictors of ASM non-adherence than clinico-demographic factors. We aimed to look into ASM non-adherence rates among adults with epilepsy (AWE), identify the contributing barriers and determine whether medication beliefs were more powerful predictors than clinico-demographic factors.

Methods: This was a cross-sectional study of AWE receiving ASMs. Participants (n = 304) were assessed by validated questionnaires, for non-adherence (8-item Morisky Medication Adherence Scale) and perceptions of ASMs (Beliefs about Medicines Questionnaire) along with clinico-demographic details.

Results: Our group with high literacy and low-income had a high non-adherence rate (55 %) despite having positive beliefs (Mean necessity-concern differential [NCD] = 2.86). Among the beliefs, ASM non-adherence was significantly associated with ASM-concern ($t = 4.23$, $p < 0.001$) and NCD ($t = -4.11$, $p < 0.001$). Stepwise multiple linear regression analysis showed that non-adherence was significantly associated with per-capita income ($\beta -0.215$, $p < 0.001$), ASM side effects ($\beta 0.177$, $p = 0.001$), high seizure frequency ($\beta 0.167$, $p = 0.002$), ASM availability ($\beta -0.151$, $p = 0.004$), ASM costs ($\beta -0.134$, $p = 0.013$ and NCD ($\beta -0.184$, $p = 0.001$). NCD accounted for 2.9 % of the variance in non-adherence whereas the other clinico-demographic variables together accounted for 14.6 %.

Conclusion: We describe a paradigm shift in AWE with high non-adherence to ASMs, wherein clinico-demographic variables emerge as better predictors of non-adherence than beliefs. High literacy facilitates the perception of need for ASMs whereas costs and side effects hamper adherence.

1. Introduction

Epilepsy is one of the most common neurological disorders estimated to affect around 70 million people worldwide [1]. Anti-seizure medications (ASM) form the mainstay of treatment and help in achieving good seizure control in 70 % of patients with epilepsy (PWE). Medication non-adherence magnifies the morbidity and causes a threefold increase in mortality [2,3]. Medication adherence is defined as "the extent to which a person's behaviour including taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider" [4]. Adherence to long term treatment is around 50 % in developed countries whereas its is much less in the developing nations [4].

The prevalence of epilepsy in India is estimated to be 3.0–11.9 per 1000 populations, which is similar to the developed countries [5]. Treatment gap is a well known obstacle in developing countries, which ranges from 22 % among urban, middle-income people to 90 % in villages in India [6]. Medication non-adherence is one of the main causes of treatment gap which leads to poorer outcomes and increased utilisation and strain of the health care system of a resource poor nation like India.

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Hence, identification of barriers followed by implementation of targeted methods to improve adherence is essential to fix the treatment gap and improve outcomes and decrease mortality in our PWE.

Medication adherence is a dynamic process and not a stable patient characteristic [7]. In addition to the various clinical factors, specific and general medication beliefs are known to impact adherence to medications. This is operational as a theoretical necessity-concern framework (NCF) where the perception of need for ASMs is balanced by the concern about their adverse effects [8]. Negative beliefs wherein the patients perceive low necessity and high concern about ASM use are associated with non-adherence. Medication beliefs were found to be more powerful predictors of adherence compared to clinical factors in epilepsy as well as in other chronic illnesses [9,10]. In a metaanalysis of 94 articles, Horne et.al demonstrated the strong association of medication adherence with the NCF in many chronic disorders including epilepsy [11]. This association remained significant irrespective of the sample size, country of research and the type of adherence measure used. Very few studies show contradictory results. Shallcross et al. [12] and Kemp et al. [13] found no correlations between beliefs about medicines and ASM adherence. The sample sizes in these studies were very small and hence not sufficiently powered to draw conclusions. Nakhutina et al. [14] found nonsignificant association between beliefs and adherence with the Morisky scale but significant associations with participant self rating scale. The Morisky scale had low internal reliability in their sample.

Very little data is available from India about the prevalence and causes of non-adherence to ASMs. Hence we conducted this study in our centre located in the South Indian district of TamilNadu. We presumed that the changing socio-economic scenario of increasing literacy rate (>80 % vs the national literacy rate of 74 %) and unemployment rate (7.6 % vs the national rate of 6.1 %) [15] in our state would have a bearing on the predictors of ASM non-adherence. We aimed to (1) determine ASM non-adherence rates among adults with epilepsy (AWE) and identify the demographic and clinical barriers that contribute to ASM non-adherence (2)determine whether medication beliefs influenced non-adherence and if so whether they were more powerful predictors than the demographic and clinical factors.

2. Methodology

2.1. Study site and subjects

This prospective cross-sectional study was conducted at the PSG Comprehensive Epilepsy Care Centre located at Coimbatore, South India. The study was approved by the ethics committee of the hospital. Patients were recruited from the out-patient department of our epilepsy clinic from June 2019 to December 2019. **A**ll the patients are seen by the epilepsy specialist (RSI).The inclusion criteria was as follows (1) diagnosis of epilepsy according to the International League Against Epilepsy (ILAE) [16] and on ASMs (2) age ≥18 years (3) minimum 6 months of ASM therapy; (4) No major cognitive impairment; and (5) can read and write. The exclusion criteria consisted of (1) presence of psychogenic nonepileptic seizures and (2) any surgery for epilepsy. Our sample size was calculated using a single population proportion formula assuming 95 % confidence level, 5 % margin of error and 50 % medication adherence rate.

2.2. Questionnaire

After obtaining written informed consent, information was collected regarding the demographic details, epilepsy and ASM therapy using a questionnaire. The patients then completed few validated self-reported assessments with the assistance of a bilingual research assistant as required.

2.3. Demographic details

Age, sex, urban or rural residence, number of members in the house, marital status and family income details were collected from the participants. An age ≤30 years (median age) was considered young. Family percapita income (PCI) was calculated as total family income divided by the number of members in the house. Occupation was noted as currently employed or not. Educational status was considered as formal if they had completed tenth grade or more and informal if completed less than tenth grade.

2.4. Disease related details

Age at onset, duration and family history of epilepsy along with the presence of generalized tonic clonic seizures (GTCS) over the past six months were noted. Seizure frequency over the past six months was classified using the Engel seizure frequency scoring system [17]. They were divided into 2 groups of low seizure frequency or well-controlled epilepsy with score ≤4 (seizure free or those with auras only or non-disabling nocturnal seizures) and high seizure frequency or poorly controlled epilepsy with score >4. The epilepsy type according to the latest classification by ILAE was noted [16].

2.5. ASM related details

Details regarding ASM consumption were collected. ASMs were divided into old or conventional being marketed before 1980, and new. Thus, carbamazepine, clonazepam, diazepam, phenobarbital, phenytoin, primidone and valproate were defined as old, the remainder as new ASMs. Taking single ASM was considered monotherapy and more than one as polytherapy. Frequency of dosing was categorized into once or twice a day. Any drug intake other than ASMs was noted. Details of side effects and monthly costs of ASMs were collected. Participants were directly queried for adherence as to whether they ever missed ASMs and if so the reasons thereof. Whether they are dependent atleast on few occasions on reminders from family members was noted. The ease of availability of ASMs was obtained.

2.6. Measurement scales

We used the following scales: Morisky Medication Adherence Scale (MMAS) [18] and the Beliefs about Medicines Questionnaire (BMQ) [19]. The BMQ holds two sections: BMQ specific and BMQ general. BMQ specific contains questions regarding beliefs about medicines specific for a disease condition whereas BMQ general involves questions on general beliefs about pharmacotherapy. BMQ Epilepsy specific scale consisting of the ASM-Necessity and ASM-Concern scales and BMQ General scale consisting of the General-harm and General-overuse scales were used. These scales are well validated and used extensively in English language. However translated versions in Indian languages are not available. Two bilingual translators independently translated these scales from English to Tamil and another translator did the reverse translation. The forward and backward translated versions were compared and inconsistencies resolved by consensus. It was tested for content validity in a pilot study. Adequate internal reliability was indicated by post hoc Cronbach's alpha for MMAS (0.76), ASM-Necessity (0.74), ASM-Concern (0.71), General-harm(0.69) and General-overuse(0.72) scales.

2.7. Morisky – 8 item medication adherence questionnaire

An 8-item Morisky medication adherence questionnaire was used to assess patients' adherence to ASMs [18,20]. It consists of 8 questions, with the first seven items having a dichotomous answer(yes/no) indicating adherent or non-adherent behaviour. Scoring was reversed with the "no" answer getting a score of 0 and "yes" answer a score of 1, except for the fifth question which was scored as no = 1 and yes = 0 [21]. For

item 8, a patient can choose an answer on a 5-point Likert scale, expressing how often happens that he/she does not take the medications. The answer "never" was scored as 0 and the rest were taken as 1. MMAS-8 scores can range from 0 to 8 points. Adherence was considered high (score = 0), medium (score = 1) and low (≥2). Patients were dichotomized for further analysis as adherent (high adherence) and non-adherent (medium and low adherence).

2.8. BMQ

The BMQ has been validated in the general population as well as across different patient groups [22,23]. It has high internal consistency, allows assessment of self efficacy and has good test-retest reliability [24–26]. BMQ-epilepsy specific scale comprises of two 5-item factors assessing perceptions about the necessity of ASMs (ASM-Necessity) and concerns about prescribed medication based on beliefs about the danger of dependence and long-term toxicity of ASMs (ASM-Concerns). The BMQ general has two 4-item sections, one looking into the perceptions of patients towards the adverse effects caused by medications in general (General-Harm) and the other focussing on the patient perceptions of physician's approach including overuse of medicines and adequacy of time spent with them(General-Overuse).The response for each question was scored on a five-point Likert type scale (1=strongly agree, 2=agree, 3=uncertain, 4=disagree, and 5=strongly disagree). Scores were reverse coded (score 1 becomes 5 and vice versa) so that higher scores indicate higher and lower scores indicate lower necessity, concern, harm and overuse. Each individual item score was added and the total score calculated for each of the four sections.

2.9. Necessity-Concerns Differential (NCD)

This was calculated by subtracting ASM-Concerns scores from ASM-Necessity scores. The NCD score is an indicator of the personal need for ASMs felt by the patients in relation to their concerns about their side effects. It ranges from -20 to +20, where positive scores indicate that patient perceived benefits outweigh their perception of risk and hence considered as positive belief about ASMs.

2.10. Attitudinal groups

Based on the scoring of necessity and concern, patients were divided into four groups of attitudes towards medications. Patients were dichotomized depending on their score below and above the midpoint of 15. Patients with higher score (≥15) were considered to have high necessity and high concern and those scoring <15, low necessity and low concern. Patients were then categorized into 4 groups with regard to their perception of ASM treatment; Accepting (high necessity & low concern), Indifferent (low necessity and low concern), skeptical (low necessity and high concern) and ambivalent (high necessity and high concern) [27]. For statistical comparison, accepting group was considered to have positive attitude and the remaining three together to have negative attitude.

2.11. Statistical analysis

Statistical package of social sciences (SPSS) version 24 was used to analyze the data. For descriptive statistics, mean and standard deviation were calculated for continuous variables whereas frequency distribution and percentage were used for categorical or ordinal variables. Independent samples t-tests were used to test for differences between adherence and non-adherence groups on perceptions of ASM (ASM Necessity, ASM Concerns, NCD, General Overuse and General Harm). To compare the size of these differences, standardized effect sizes (Cohen's d) were calculated. Stepwise linear regression analysis was used to identify factors associated with treatment non-adherence (dependent variable) by including all demographic and clinical variables and NCD

Table 1
Clinico-demographic details of adults with epilepsy (n = 304).

Age(years)	33.36 ± 15.59 (18–82)[a]	ASMs	
≤30 years	173 (56.9)[b]	New	245 (80.6)[b]
>30 years	131 (43.1)[b]	Old	21 (6.9)[b]
		New & old	38 (12.5)[b]
Gender			
Male	185 (60.9)[b]	**Use of individual ASMs**	
Female	119 (39.1)[b]	Oxcarbazepine	136 (44.7)[b]
		Levetiracetam	95 (31.3)[b]
Education		Clobazam	91(30)[b]
Informal	109 (35.9)[b]	Divalproex	63(20.7)[b]
Formal	195 (64.1)[b]	Lamotrigine	29 (9.5)[b]
		Lacosamide	17 (5.6)[b]
Occupation		Carbamazepine	29 (9.5)[b]
Unemployed	166 (54.6)[b]	Phenytoin	21(7)[b]
Employed	138 (45.4)[b]	Phenobarbitone	6 (2)[b]
Place of residence		**Number of ASMs**	
Urban	195 (64.1)[b]	Mono therapy	151 (49.7)[b]
Non-urban	109 (35.9)[b]	Poly therapy	153 (50.3)[b]
Marital Status		**Frequency of administration**	
Married	143 (47)[b]	Once daily	86(28.3)[b]
Unmarried / Separated / Divorced	161 (53)[b]	Twice daily	218 (71.7)[b]
Per capita income (INR)	7757.99 ± 13928.62[a]	**Cost of ASMS (INR)**	1042.84 ± 1000.67[a]
Age of onset (years)	20.1 ± 16.11[a]		
Duration of Epilepsy (years)	13.97 ± 13.06[a]	**Side effects**	
		Present	91 (29.9)[b]
Family History of Epilepsy		Absent	213 (70.1)[b]
Present	60 (19.7)[b]		
Absent	244 (80.3)[b]	**Patient perceived side effects**	
		Drowsiness	37 (12.2)[b]
Epilepsy type		Weight gain	31 (10.2)[b]
Focal Epilepsy	247 (81.3)[b]	Forgetfulness	10 (3.3)[b]
Generalized Epilepsy	49 (16.1)[b]	Fatigue	9 (3)[b]
Combined Focal & Generalized Epilepsy	8 (2.6)[b]	Mood changes	1 (0.3)[b]
Seizure frequency		**Adherence**	
Low	179 (58.9)[b]	Low	112 (36.8)[b]
High	125 (41.1)[b]	Medium	57 (18.8)[b]
		High	135 (44.4)[b]
GTCS			
Present	112 (36.8)[b]	**Perceived reasons for non-adherence**	132 (43.4)[b]
Absent	192 (63.2)[b]	Forgetfulness	62 (20.4)[b]
		Non-availability of ASMs	24 (7.9)[b]
Family reminds medicine		Belief	21 (7)[b]
Yes	71 (23.4)[b]	Fear about side effects	9 (3)[b]
No	233 (76.6)[b]	Cost	9 (3)[b]
		Lack of benefit	1 (0.3)[b]
Drugs other than ASMs			
Yes	85 (28)[b]	**Availability of ASMs**	
No	219 (72)[b]	Good	211 (69.4)[b]
		Poor	93 (30.6)[b]

a = Mean ± SD b = n(%).
ASM: Anti-seizure medications, GTCS = Generalized tonic clonic seizure.

(independent variables). This linear regression model was used to assess the relative strength of medication beliefs (NCD scores) vis-à-vis clinical and demographic factors in predicting non-adherence by stepwise entry and removal method. Stepwise linear regression analysis was again used to compare the attitudinal groups wherein negative attitude was used as dependent variable and all clinical and demographic factors and adherence were used as independent variable. Statistical significance was set at $P < 0.05$.

3. Results

Our study included 304 patients. The demographic, disease and ASM related variables are depicted in Table 1.

3.1. Demographic variables

The mean age of the study population was 33.3 years and consisted of 185(60.9 %) males and 119(39.1 %) females. Majority were young (56.9 %) and unemployed (54.6 %). Around 195(64.1 %) of them were staying in urban areas and had formal education whereas 143(47 %) were married. The mean per-capita income of the study group was 7758 INR. The PCI was significantly more in the adherent group than the nonadherent group (7228.77 INR vs 5525.88 INR p = 0.004).

3.2. Disease related variables

The mean age of onset of epilepsy was 20.1 years and the mean duration 13.97 years. Seizure frequency was high in 125(41.1 %) and low in 179(58.9 %) patients. Around 247(81.3 %) had focal epilepsy and 49(16.1 %) generalized epilepsy syndromes whereas 112 (36.8 %) had atleast one GTCS over the past six months.

3.3. ASM related variables

Around half of our population was on monotherapy. Eighty six of them (28.3 %) were on once daily dosing and the remaining on twice daily dosing. The average cost of ASMs was around 1042.84 INR per month. The average ASM costs were the same in the adherent and non-adherent groups. (1105.53INR vs 992.75INR p = 0.33). Only 132 AWE (43.4 %) perceived non-adherence. Forgetfulness and non-availability were the most common reasons of nonadherence. For 211(69.4 %) patients, ASMs were freely available whereas the remaining 93(30.6 %) had difficulty in the local availability of ASMs. Overall 91(29.9 %) patients reported side effects which were predominantly drowsiness and weight gain. Newer ASMs were used exclusively in 245(80.6 %) patients. Oxcarbazepine, clobazam and levetiracetam were the most frequently used newer ASMs.

3.4. Belief variables

Descriptive statistics about the belief variables is given in Table 2. The overall belief about medications is positive with 70 % showing high necessity beliefs and positive NCD scores and 55 % showing low concern beliefs. Similarly 47 % showed low overuse beliefs and 76.7 % had low harm beliefs.

3.5. ASM economics

This is displayed in Table 3. The average PCI of our study group was 73.6 % of the national PCI (10,534 INR). Corresponding values for the adherent and non-adherent groups were 90 % and 60.5 % respectively. Average monthly cost of ASMs for the group was equivalent to 4 days of their PCI or 5.8 days of wages of the lowest paid labour in India in 2019 (178 INR). Corresponding values for the adherent and non-adherent groups were 3.5 days PCI / 6.2 days of daily wages and 4.7 days PCI / 5.6 days of daily wages respectively. An additional cost of 1–4 days of PCI or daily wages is incurred for the monthly purchase of originator brands of newer ASMs when compared to the commonly available generic brands. For the older ASMs, the difference in costs between the originator and generic brands is very negligible.

Table 3
ASM economics of our study group.

	Income (%)[a]	Expenditure[b]
Overall (n = 304)	73.6	(4, 5.8)
Adherent group (n = 135)	90	(3.5, 6.2)
Non-adherent group (n = 169)	60.5	(4.7, 5.6)
Cost of ASMs		
Antiseizure medication (DDD)	**Generic[b]**	**Brand[b]**
Oxcarbazepine (1200 mg)	(1.8, 2.6)	(4.6, 6.7)
Clobazam (20 mg)	(0.6, 0.87)	(1.5, 2.2)
Levetiracetam (1500 mg)	(1.9, 2.8)	(4.6, 6.7)
Divalproate (1000 mg)	(1.2, 1.8)	(1.4, 2)
Phenytoin (300 mg)	(0.15, 0.22)	(0.46, 0.67)
Carbamazepine (1000 mg)	(0.7, 1)	(0.83, 1.26)
Phenobarbitone (100 mg)	(0.12, 0.16)	(0.51, 0.75)

DDD = Defined daily dose.
[a] Per capita income (PCI) as a proportion of the national PCI.
[b] Mean number of day's income required for one month of ASM treatment as a proportion of (PCI of the study group, minimum daily wages in India [2019]).

Table 2
Beliefs about medications in the study group and in both adherence groups.

Variable	Mean(SD)	Median (range)	People above the midpoint[d]	Adherent (n = 135) Mean(SD))	Non-adherent (n = 169) Mean(SD))	Cohen's d (95 %CI)	t (304)	p-value
ASM necessity[a]	17.26 (4.69)	18 (5–25)	213 (70)	17.77 (4.94)	16.86 (4.46)	0.19 (-0.03, 0.42)	1.68	NS
ASM concern[a]	14.41 (4.76)	14 (5–25)	137 (45)	13.15 (4.85)	15.41 (4.45)	−0.48 (-0.71, -0.25)	−4.23	<0.001
ASM NCD[b]	2.86 (6.86)	3 (-17 to 19)	211 (69.4)	4.62 (6.76)	1.44 (6.62)	0.47 (0.24, 0.7)	4.11	<0.001
General overuse[c]	18.74 (3.02)	19(4–18)	161 (53)	12.72 (3.19)	12.75 (2.89)	−0.01 (-0.23, 0.21)	−0.09	NS
General harm[c]	16.22 (3.22)	16(4–20)	71 (23.3)	10.12 (3.6)	10.3 (2.89)	−0.05 (-0.28, 0.17)	−0.49	NS

[d]N(%) Midpoint is 15 in case of necessity and concern, 0 in case of NCD and 12 for overuse and harm. NS = non significant, M (SD) = Mean (standard deviation).
[a] Scale from 5 to 25 where high scores indicate high necessity and high concern towards anti-seizure medication use.
[b] Scale from –20 to 20 where positive scores indicate that patient perceived benefits outweigh risks.
[c] Scale from 4 to 20 where low scores indicate positive attitude towards medicines.

Table 4
Stepwise multiple linear regression model for reported non-adherence to ASMs.

Predictors	β	p	Adjusted R^2 (%variance)
Per capita income	−0.215	<0.001	0.046 (4.6)
ASM side effects	0.177	0.001	0.084 (3.8)
Seizure frequency	0.167	0.002	0.108 (2.4)
ASM availability	−0.151	0.004	0.131 (2.3)
Cost of ASMs	−0.134	0.013	0.146 (1.5)
NCD	−0.184	0.001	0.175 (2.9)

3.6. Adherence to ASMs

MMAS scores were dichotomized into an adherent group (n = 135, 44.4 %) and a nonadherent group (n = 169, 55.6 %).

a) Differences in the adherence groups on perception of ASMs:
This is displayed in Table 2. The necessity, overuse and harm scores were distributed equally between the two groups of adherence. ASM-concern scores and NCD were significantly high in the non-adherent and adherent groups respectively ($p < 0.0001$). Both the factors accounted equally for the largest differences between the adherence groups when effect sizes were compared using Cohen's d.
b) Multivariate analysis for non-adherence:
Stepwise entry and removal of the clinical, demographic, and belief variables resulted in a linear regression model explaining 17.5 % of the variance in reported non-adherence to medication (Table 4). Higher non-adherence rates were associated with PCI (β -0.215, $p < 0.001$), ASM side effects (β 0.177, $p = 0.001$), high seizure frequency (β 0.167, $p = 0.002$), ASM availability (β -0.151, $p = 0.004$), ASM costs (β -0.134, $p = 0.013$ and patients' beliefs represented by NCD (β -0.184, $p = 0.001$). NCD accounted for 2.9 % of the variance in non-adherence whereas the other clinico-demographic variables together accounted for 14.6 % of the variance.

3.7. Attitudinal outcome

This is depicted in Fig. 1. Majority of our patients were either "Accepting" of their ASMs and having positive attitude (n = 114; 37.5 %) or were "Ambivalent" (n = 108; 35.5 %). Very few were "Skeptical" (n = 43; 14.1 %) or "Indifferent" (n = 39; 12.8 %). The non-adherence rate in the various groups was as follows: Accepting (57/114; 50 %), Ambivalent (63/108; 58.3 %), Skeptical (31/43; 72 %) and Indifferent (18/39; 46.1 %). The respective contributions to the overall non-adherence (n = 169) of the four attitudinal groups were 33.7 %, 37.2 %, 18.3 % and 10.6 % respectively. Multiple linear regression analysis with negative attitude as the dependent variable and the various clinico-demographic factors and adherence as independent variables showed 3 predictors of negative attitude; education (β 0.173, $p < 0.001$), positive family history(β 0.156, $p = 0.002$), and ASM side effects(β 0.134, $p = 0.005$).

4. Discussion

Our centre receives more refractory cases and this explains why more than 80 % of our patients were suffering from symptomatic focal epilepsy. Our study group is predominantly urban and educated. Majority is unemployed and the average PCI is 73.6 % of the average national PCI. We involve our patients in all decisions including choice of ASMs and counsel them at every visit regarding side effects and drug compliance. Our patients generally express more concern about potential adverse effects than the cost of ASMs and hence newer ASMs were used in more than 80 % of them. The commonly used ones were oxcarbazepine, clobazam and levetiracetam. We use ASMs either once daily or twice daily to facilitate adherence. Since conventional sodium valproate is administered thrice daily, we use only the divalproex or chrono preparations.

We found that non adherence to ASMs is still very common and seen in 55 % of our population of AWE. Our study demonstrated one demographic (PCI) and four clinical (high seizure frequency, presence of side effects, low costs and poor availability of ASMs) predictors of non adherence. The PCI was significantly high in the adherent group than the non-adherent group whereas the ASM costs in both the groups were similar. This would mean that lower ASM costs would improve affordability and hence improve adherence. However regression analysis showed a reversal in the expected relationship between ASM costs and non-adherence. This is explained by a possible correlation between the predictor variables, low R-squared value and a small sample size. The sixth predictor was related to patient perception wherein those with low

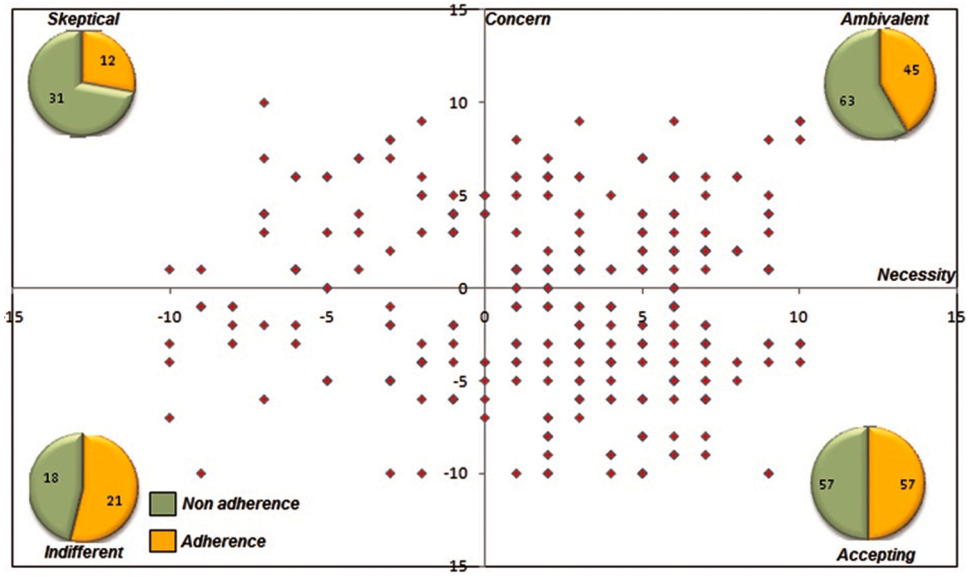

Fig. 1. Scatter diagram showing the four attitudinal groups and their adherence to ASMs. The midpoint (0,0) indicates (15,15) of the necessity and concern scores. Every point score more or less than 15 will have a similar point added or subtracted from 0 so that +10 on the graph represents a score of 25 and -10 represents a score of 5.

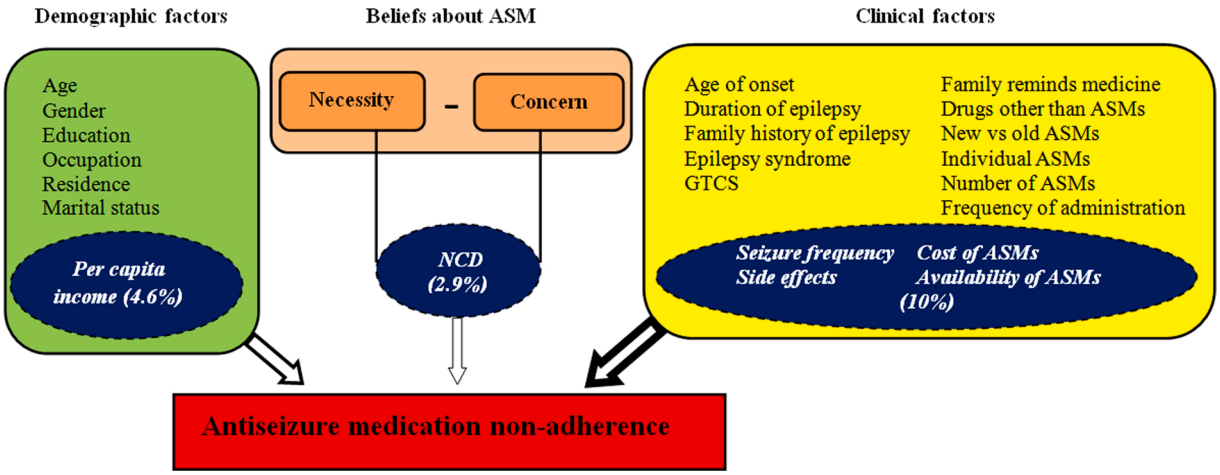

Fig. 2. Schematic diagram showing the various clinico-demographic variables and beliefs. The predictors and their contribution (%) to the variance of non-adherence are shown in dotted oval circles.

NCDs had higher non-adherence.

The two key factors deciding adherence, availability and affordability of ASMs are poor in low- and middle-income countries. Newer ASMs are better available in the private sector compared to the public sector. Data for five conventional ASMs from multiple low- and middle-income countries including India has shown that the average availability of generic ASMs in the public sector was <50 % and 40–70 % in the private sector [28]. Our hospital is in the private sector and patients pay for medicines. Initially they buy ASMs for 2–4 weeks from our pharmacy and subsequently depend on the local pharmacies. Thirty six percent of the study group was from the non-urban or rural setup where there are problems with the availability of ASMs. Many a time, the originator brand ASMs prescribed by us are not available in the rural pharmacies. Some of them use lower-priced generics which may not be quality-assured resulting in breakthrough seizures. Similar problems exist with regard to the ASM costs. The average PCI of our non-adherent group was 30 % less than the adherent group whereas they were spending 1.2 days of PCI more for the monthly purchase of ASMs. For the more commonly used newer ASMs, oxcarbazepine and levetiracetam, an additional 3 days of PCI was needed when compared to their respective generics to meet the monthly requirements. The above data suggest that use of generic medicines in our setup would improve affordability. However we are generally reluctant to switch from brand to generic ASMs for fear of loss of seizure control. Ensuring the supply of quality generic ASMs with good average bioequivalence should improve ASM prescribability for those being treated for the first time.

Around 30 % of our population of AWE reported side effects to ASMs which contributed to non adherence. Drowsiness and weight gain were the most common side effects. The presence of polytherapy in about half of the population has probably contributed towards adverse effects. Studies have shown the negative association of adverse effects of ASMs with adherence [29]. The non-adherence rate in our study goes against the common belief that newer ASMs result in better adherence due to low potential for adverse effects. Recent studies show that despite the increasing use of newer ASMs as the initial therapy, the overall tolerability has not changed [30].

The relationship between seizure outcome and ASM non-adherence is not linear [31]. That non adherence leads to poor seizure control is well known. Early educational and behaviour interventions to improve adherence improve seizure frequency and seizure outcome [32,33]. The paradoxical effect of uncontrolled seizures contributing to non adherence is also well documented in the literature [34–36]. The time since the last seizure has been shown to determine adherence. The presence of seizures within 30 days or 6 months result in more non adherence while absence of seizures for more than a year result in better adherence [36, 37]. The high non-adherence rate would have contributed to high seizure frequency observed in 41 % of our patients. Since our centre deals with more refractory cases, the paradoxical response to uncontrolled seizures of non adherence, arising out of increasing concern is also a possibility. While the relationship between non adherence and poor seizure control could be established by drug level monitoring, the relationship between illness perception and non adherence needs more exploration and understanding.

That the clinico-demographic factors emerged as better predictors accounting for 14.6 % of the explained variation in adherence in contrast to beliefs which accounted for 2.9 % of the variation was not necessarily expected as it was contradictory to the existing observations about medication adherence in epilepsy [10]. Neither was this surprising considering the socioeconomic situation of the state which is reflected in our study group. The overall belief about medications of our group has been positive. A good proportion of those with negative attitude were still adherent, demonstrating that negative attitude doesn't necessarily result in non-adherence. The ASM-related side effects seem to make them develop a negative attitude but being better educated has helped them feel the need for the medications. The human adherence behaviour depends more on the cognitive representation of the beneficial effects of a drug than on the concern regarding its adverse effects [38]. It is possible therefore that high literacy of our group acted as a protective factor against non-adherence by contributing to increased perception of necessity, whereas unemployment with its resultant poverty made the ASM economics more significant contributor to non-adherence.

We acknowledge the following limitations of our study. First, is the use of self-reported adherence scale which is subjected to retrospective and recall bias and usually underestimates non-adherence by 20 % [39]. Direct measures of adherence are impractical in our population. We preferred an ordinal rather than an interval scale of assessment of adherence and gained confidence from our patients by a non-confrontational consultation and ensured the confidentiality of their responses. We also considered both medium and low adherence as non adherent to minimize underestimation of non adherence. Second, is the problem of low adjusted R-squared value. This could be due to the non-inclusion of other potentially important predictors like depression and anxiety, health care related factors and support systems. Any study trying to predict human behaviour is also expected to have low R-squared value. Regardless of the R-squared, the presence of significant

coefficients will help us draw important conclusions about how changes in the predictor value will affect the response value. Third, we recognize that adherence is dynamic and hence best understood by prospectively looking at trajectories rather than by cross-sectional point estimates. Fourth, we did not try to differentiate between unintentional and intentional non-adherence. Intentional non-adherence is more likely to be associated with perceptions of need and concern. Fifth, our findings are not generalizable and could be different in scenarios of low literacy, high dependence on traditional healers and medicines etc.

Despite its limitations, this study demonstrates a high degree of non-adherence and identifies the factors linked to non-adherence to ASMs in our relatively well literate, low income group of adults with chronic epilepsy. The clinico-demographic variables of PCI, ASM related side effects, ASM costs, availability and seizure frequency along with medication beliefs were the predictors identified. Improving the affordability, availability and tolerability of ASMs would facilitate adherence more than interventions to improve beliefs. Making available good quality generic ASMs will be an important step in this direction. Older ASMs may be initiated as monotherapy. Newer ASMs could be limited to those who could afford them, those who develop side effects to older ASMs and also in special situations and to prevent drug interactions. It is imperative to look for side effects during each visit and take corrective steps including proper counselling of patients. We describe a paradigm shift in the relative roles of medication beliefs and clinical factors wherein the latter emerges as better predictor of adherence than beliefs. The closing knowledge gaps due to improving literacy rates and various accesses to epilepsy specific education would mean that our study could herald a changing trend rather than remain an isolated finding. Further studies on adherence to ASMs focussing on various demographic and geographic groups are required to support our observation.

5. Conclusion

The findings of our study are summarized in Fig. 2. We found a high degree of non-adherence to ASMs of 55 % in our study group. We provide novel insights into the predictors of medication adherence from a robust sample of low-income and high literacy. Though medication beliefs predicted non-adherence, the clinico-demographic factors of ASM cost, availability and tolerability proved to be better predictors.

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Declaration of Competing Interest

The authors report no declarations of interest.

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