"COMPLIANCE TO ANTICONVULSANT THERAPY AMONG RURAL CHILDREN WITH EPILEPSY"

By

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Under the guidance of

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ABBREVATIONS

AEDs	–	Anti epileptic drugs
CNS	–	Central Nervous System
GABA	-	γ-aminobutyric acid
GTCS	-	Generalised tonic clonic seizures
AEDL	–	Anti epileptic drug levels

ABSTRACT

OBJECTIVE:

1. To study the compliance to anticonvulsant therapy among rural children with epilepsy.
2. To study the correlation of drug prescribed with compliance.
3. To study the correlation of cost and availability of drug with compliance.

METHOD:

All children between age group of 1-15 years who came to R.L.Jalappa Hospital & Research Centre with Epilepsy and who had come for follow up from march 2010 to february 2011 were prospectively analysed using self reporting structured interview schedule regarding various factors involved with compliance to anticonvulsant therapy.

RESULTS:

Among 231 children who were enrolled into the study over 1 year period, 145(62.77%) are found to be compliant to anticonvulsant therapy. Male to female ratio is 1.7:1. Generalized seizures were more common both in compliant group and non compliant group (71.03% vs 59.30%; p=0.051). 64% in compliant group have satisfactorily controlled seizures (having seizure after 1 month but within 3 years) vs 48.24% in non compliance group (p=0.048). Higher compliance was observed, even when access to medical store was beyond walking distance (78.62% vs 76.74%; p=0.70) . 15.86% in compliant group vs 30.23% in the non compliant group were having difficulty in getting the medicines (p=0.010). Majority of patients in compliant group were getting Sodium valproate (42.76%) vs Phenytoin in noncompliant (44.1%). "Poverty" remained as the common barrier to compliance followed by "local beliefs and "forgetfulness". Statistically significant barriers were non availability of medications (p=0.03), financial problems in purchasing the medications (p=0.045), duration of treatment (p=0.020), unawareness about importance of compliance to antiepileptic drugs (p=0.052).

CONCLUSIONS:

Our study showed a compliance of 62.77% among 231 patients. Epileptic patients are predominantly males (male to female ratio is 1.7:1). Though the results of different variables used in the study to determine compliance were in agreement with the literature, our study differed in the aspect that education of parent, age of onset, type of drug therapy (monotherapy/polytherapy) and side effects did not play any role in compliance. Modifying the parents perception about the disease and treatment effectiveness plays a key role in compliance. Non modifiable factors at individual level like poverty and non availability of drug require changes in govt policies for achieving better compliance.

KEYWORDS: Epilepsy, Anticonvulsants, Compliance.

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INTRODUCTION

HISTORICAL PERSPECTIVE

Among the diseases that have plagued humans over the centuries, few exhibit the brief, frightening manifestations of an epileptic attack and the relatively quick, seemingly miraculous recovery. Accounts of what may have been epileptic seizures can be found in several ancient scriptural literatures such as reference to the prophet Balaam falling down with the eyes open and to King Saul's fits of rage.

Naphal and Nôphêl were Old Testament and Talmudic terms for epilepsy. Israelites also used term nikpheh to refer to the disease. Similarly, the prohibition against entering the temple by those possessed by a malevolent power in the ancient Egyptian text of Esra has also been thought to be a reference to epilepsy. In contrast, the papyrus of Ebers, the oldest Egyptian medical book, has no mention of the condition. Initially, these ancient accounts of falling attacks attributed such "seizures" to an evil entity or punishment inflicted by a god or later, to some natural cause.

Not until Hippocrates was the origin of epilepsy placed in the brain. Temkin, in his book *The Falling Sickness,* describes a battle between rational, scientific thinking and magical beliefs that started with Hippocrates connection of epilepsy to the brain and continued at least until Jackson's time. Word seizure came from the Latin word sacire which mean *"to take possession of"*. John Hughlings Jackson (1835–1911), the neurologist, gives an accurate clinical-physiologic definition of epilepsy and classified seizures into generalized and focal (partial) that continue in use today.

By the end of the 19th century, there had been a marked quickening of the social conscience regarding care for the chronically ill and disabled. Indeed, for almost four decades, institutional care for people with refractory epilepsy had been gradually recognized as the duty of society.

By the beginning of the 20th century, the various bromide salts, particularly potassium bromide, had become the mainstay of the drug therapy of epilepsy. In 1912, Hauptmann, while using phenobarbitone to tranquilize patients, realized it had suppressed the seizures of those who also happened to suffer from epilepsy. Subsequently, two of its congeners, mephobarbital (N-methylphenobarbitone) and primidone (deoxybarbiturate) were found effective in treating epilepsy.

In the late 1930s, however, Putnam and Merritt began to systematically study in experimental animals molecules with structural resemblances to phenobarbital to find new antiepileptic agents. They tested several hydantoin derivatives (in which the central heterocyclic ring of the molecule lacked one of the carbon atoms of the barbiturate ring) and found that phenytoin (diphenylhydantoin) had an apparently promising balance between sedative and antiepileptic properties. It proved to be effective when tried in epileptic patients and thereafter came into widespread use. Other hydantoin derivatives, such as mephenytoin, were later developed and used in humans, but all proved unsatisfactory for reasons of lesser efficacy or toxicity.

The success of the Putnam-Merritt approach led to further experimental animal studies attempting to find other small heterocyclic molecules with potential antiepileptic properties. Beginning with trimethadione, various oxazolidinedione derivatives were shown effective in controlling absence seizures in which barbiturate and hydantoin derivatives were ineffective. Subsequently, succinimide derivatives were tested and proved more satisfactory than the oxazolidinediones. Carbamazepine was tested for antiepileptic activity by the pharmaceutical firm Geigy Ltd. in the 1950s and came into increasing use in humans during the following decade.

The next antiepileptic agent valproic acid was discovered by chance in 1961. Previously it was used as a solvent for possible antiepileptic agents in experimental animal studies. Subsequently, other agents (e.g. clonazepam, and other benzodiazepine derivatives) were discovered and came into use during the 1960s and 1970s.

Additional antiepileptic drugs have since been discovered as the outcome of strategies based on several approaches, random screening of numerous molecules with a wide range of chemical structures (e.g., felbamate), testing structural analogs of known antiepileptic agents (e.g., oxcarbazepine), and rational attempts to modify known factors believed to facilitate epileptic activity (e.g., vigabatrin, lamotrigine, tiagabine, gabapentin).

Though lot of AEDs has been developed for the treatment of epilepsy, still there is 20-30 % patients remained seizure free. This could be because of non-adherence or lack of compliance to the treatment prescribed to treat epilepsy.

Adherence was not usually defined in the published studies, but referred to generally as patients following medical recommendations. Authors generally considered adherence in behavioral terms, whereby the patient had an active and informed role to play in a therapeutic situation.[1,2] In this sense, adherence to prescribed medication was seen as a health-promoting behavior.[3]

Non-adherence to AED medication is not a modern phenomenon. Trostle (1988) cites the example of a Dr Gowers who, in 1881, reported on patients with epilepsy admitted to hospital with recurrence of seizures due to apparent non-adherence.[4]

The types of non-adherence were described as follows: reduced or increased amount of single dose; decreased or increased number of daily doses; extra dosing; incorrect dosing intervals; being unaware of the need for life-long regular medication; taking duplicate medication; taking discontinued medication; discontinuing prescribed medication; regularly forgetting to take medication, and incorrect use of medication.[2,5,6]

Medication use was assessed by review of medical records; patient self-report; family report; pill counts; prescription refill rates, and biological markers, including serum, urine and saliva assays to quantify medications or their metabolites.[7-12] The best indicator of adherence is believed to be serum levels of anticonvulsant drugs.[5,13]

In several studies, patients whose serum levels were outside the therapeutic range were classified as nonadherent.[11, 14, 15] However, serum levels are not a perfect measure.

Dowse et al. and Leppik et al. reported that indirect measures such as patient interview, tablet counts and prescription refill records gave no indication of the true amount of the drug present in the body and could be inaccurate or biased.[5,14]

A seizure is a paroxysmal event due to abnormal, excessive, hypersynchronous discharges from an aggregate of central nervous system (CNS) neurons. Depending on the distribution of discharges, this abnormal CNS activity can have various manifestations, ranging from dramatic convulsive activity to experimental phenomenon not readily discernible by an observer.

The meaning of the term seizure differs from that of epilepsy. *Epilepsy describes a condition in which a person has recurrent seizures due to a chronic, underlying process.* This definition implies that a person with a single seizure, or recurrent seizures due to correctable or avoidable circumstances, does not necessarily have epilepsy.

OBJECTIVES

1. To study the compliance to anticonvulsant therapy among rural children with epilepsy.
2. To study the correlation of drug prescribed with compliance.
3. To study the correlation of cost and availability of drug with compliance.

REVIEW OF LITERATURE

PREVALENCE AND INCIDENCE OF EPILEPSY

Prevalence

The lifetime prevalence of epilepsy varied among countries from 1·5 to 14·0 per 1000.[16] The median lifetime prevalence in Asia is estimated at 6 per 1000, which is lower than in developing countries i.e. 15 per 1000 in sub-Saharan Africa and 18 per 1000 in Latin America.

Incidence

The incidence of epilepsy is ~0.3-0.5% in different populations throughout the world, the epilepsy incidence rates reported from China are 28·8 to 35.0 per 1,00,000 person per year in the general population. Incidence in India is 60·0 per 1,00,000 person per year. Whereas, the incidence of epilepsy in developed countries are 24 to 53 per 1,00,000 person per year. In some developing countries, an incidence rate is as high as 190 per 1,00,000 person per year.

CLASSIFICATION OF SEIZURES

In 1981, the International League against Epilepsy (ILAE) published a modified version of the International Classification of Epileptic Seizures that has continued to be a useful classification system. This system is based on the clinical features of seizures and associated electroencephalographic findings.

A seizures may be either partial (synonymous with focal) or generalized. Partial seizures are those in which the seizure activity is restricted to discrete areas of the cerebral cortex and are usually associated with structural abnormalities of the brain. Generalized seizures involve diffuse regions of the brain simultaneously and may result from cellular, biochemical, or structural abnormalities that have a more widespread distribution.

Detail information is given in **table 1** below.

Table 1: Classification of Epileptic Seizures

SEIZURE TYPE*		FEATURES
Partial seizures: *(Seizure activity is restricted to discrete areas of the cerebral cortex)*	**Simple partial**	• P*reservation of consciousness.* • Clinical manifestations are relatively simple. • If motor cortex representing left thumb is involved, clonic jerking of left thumb results. • If somatosensory cortex representing left thumb is involved, paresthesia of left thumb results. • The seizure last for 20 to 60 seconds.
	Complex partial	• *Impairment of consciousness.* • Clinical manifestations are relatively complex; aura frequently present. • Often associated with purposeless movements such as lip smacking or hand wringing. • The seizure last for 30 seconds to 2 minutes.
	Partial with secondarily generalized tonic-clonic seizure	• Simple or complex partial seizure evolves into a tonic-clonic seizure. • Impairment of consciousness. • Sustained contractions (tonic) of muscles throughout the body followed by periods of muscle contraction alternating with periods of relaxation (clonic). • The seizure last for 1 to 2 minutes.
Generalized seizures: *(seizures activity involve diffuse regions of the brain simultaneously)*	**Absence seizure (Petit mal epilepsy)**	• Abrupt onset of impaired consciousness. • Associated with staring and cessation of ongoing activities without loss of postural control. • The seizure last for less than 30 seconds.
	Atonic seizure	• Consciousness is briefly impaired. • Sudden loss of postural tone. • The seizure last for 1-2 seconds.
	Myoclonic seizure	• Consciousness is preserved. • A brief (for a second), shock-like contraction of muscles which may be restricted to part of one extremity or may be generalized.
	Tonic-clonic seizure	• Impairment of consciousness. • Sustained contractions (tonic) of muscles throughout the body followed by periods of muscle contraction alternating with periods of relaxation (clonic). • The seizure last for 1 to 2 minutes.

***Unclassified Seizures-** Not all seizure types can be classified as partial or generalized, e.g. infantile spasm and neonatal seizure.

Epilepsy syndrome- There are three important epilepsy syndromes. (Juvenile Myoclonic Epilepsy, Lennox-Gastaut Syndrome, Mesial Temporal Lobe Epilepsy Syndrome).

CAUSES OF SEIZURES AND EPILEPSY

Seizures are a result of a shift in the normal balance of excitation and inhibition within the CNS. There are many different ways to perturb this normal balance, and therefore many different causes of both seizures and epilepsy.

1. *The normal brain is capable of having a seizure under the appropriate circumstances, and there are differences between individuals in the susceptibility for seizures*. For example, seizures may be induced by high fevers in children who are otherwise normal and who never develop other neurologic problems, including epilepsy. This implies there are various underlying *endogenous factors* that influence the threshold for having a seizure.
2. *There are a variety of conditions that have an extremely high likelihood of resulting in a chronic seizure disorder. One of the best examples of this is severe, penetrating head* trauma, which is associated with up to a 50% risk of subsequent epilepsy. The high propensity for severe traumatic brain injury to lead to epilepsy suggests tha*t the injury results in a long-lasting pathologic change in the CNS that transforms a presumably normal neural netw*ork into one that is abnormally hyperexcitable. This process is known as *epileptogenesis*, and the specific changes that result in a lowered seizure threshold can be considered *epileptogenic factors*.
3. *Seizures are episodic.* Patients with epilepsy have seizures intermittently and, depending on the underlying cause, many patients are completely normal for months or even years between seizures. This implies there are important *precipitating factors* that induce seizures in patients with epilepsy. Precipitants can be intrinsic physiologic processes, such as psychological or physical stress, sleep deprivation, or hormonal changes associated with the menstrual cycle or can include exogenous factors such as exposure to toxic substances and certain medications.

MECHANISM OF SEIZURE INITIATION AND PROPAGATION

Partial seizure activity can begin in a very discrete region of cortex and then spread to neighbouring regions, i.e., there is a *seizure initiation* phase and a *seizure propagation phase.*

The initiation phase is characterized by two concurrent events in an aggregate of neurons: (1) high-frequency bursts of action potentials and (2) hypersynchronization. The bursting activity is caused by a relatively long-lasting depolarization of the neuronal membrane due to influx of extracellular calcium (Ca^{2+}), which leads to the opening of voltage-dependent sodium (Na^{+}) channels, influx of Na^{+}, and generation of repetitive action potentials. This is followed by a hyperpolarizing after potential mediated by γ-aminobutyric acid (GABA) receptors or potassium (K^{+}) channels, depending on the cell type.

Normally, the spread of bursting activity is prevented by intact hyperpolarization and a region of surrounding inhibition created by inhibitory neurons. With sufficient activation there is recruitment of surrounding neurons.

Repetitive discharges lead to the following:

(1) An increase in extracellular K^{+}, which blunts hyperpolarization and depolarizes neighbouring neurons;

(2) Accumulation of Ca^{2+} in presynaptic terminals, leading to enhanced neurotransmitter release; and

(3) Depolarization-induced activation of the *N*-methyl-D-aspartate (NMDA) subtype of the excitatory amino acid receptor, which causes Ca^{2+} influx and neuronal activation.

Mechanisms of Epileptogenesis

Epileptogenesis refers to the transformation of a normal neuronal network into one that is chronically hyperexcitable. There is often a delay of months to years between an initial CNS injury such as trauma, stroke, or infection and the first seizure. The injury appears to initiate a process that gradually lowers the seizure threshold in the affected region until a spontaneous seizure occurs.

In many genetic and idiopathic forms of epilepsy, epileptogenesis is presumably determined by developmentally regulated events. Pathologic studies of

the hippocampus from patients with temporal lobe epilepsy have led to the suggestion that some forms of epileptogenesis are related to *structural changes in neuronal networks*.

REFRACTORY EPILEPSY

Despite antiepileptic drug (AEDs) treatment, upto one-third of patients continue to have seizures and usually are resistant to all pharmacological treatment. These patients were considered to have refractory epilepsy and are usually treated with multiple AEDs.

Many terms have been used for refractory epilepsy that includes "treatment nonresponder," "refractory," "intractable," and "drug resistant." All these terms are used interchangeably. Criteria for defining 'refractory epilepsy' are elusive e.g. number of drugs tried, dose of drugs, duration of treatment etc. In several landmark studies evaluating incidence of refractory epilepsy from the time of diagnosis, treatment non-response is defined as the occurrence of even a single seizure breakthrough, within some period of follow-up. Using this definition, patients can fall into only two categories: remission or resistance.

Presumably, patients then may be identified as treatment resistant if they are rarely noncompliant or have an intercurrent illness. In contrast, other studies have defined treatment resistance as the occurrence of one seizure a month for some specified period of time or have included the number of drug failures into the definition. Some enlightened studies have recognized that two categories of outcome may not be sufficient and have added a third, such as one that subdivided epilepsy outcome into "good, bad, and in between".

Not surprisingly, the variability in definition leads to variability in results. A recent report investigated how many children from a cohort of newly diagnosed epilepsy patients would be considered refractory, if the definitions of treatment resistance from six different studies were applied. Even though the definitions were reasonably similar, each led to different determinations of the frequency of refractoriness in this population, ranging from 9% to 24%.

ANTIEPILEPTIC DRUG THERAPY

Antiepileptic drug therapy is the mainstay of treatment for most patients with epilepsy. The overall goal is to completely prevent seizures without causing any untoward side effects, preferably with a single medication and a dosing schedule that is easy for the patient to follow.

SELECTION OF ANTIEPILEPTIC DRUGS

Currently, conventional as well as newer antiepileptic drugs are available for treatment of epilepsy. Worldwide, conventional AEDs such as phenytoin, valproic acid, carbamazepine, and ethosuximide are generally used as first-line therapy for most seizure disorders. Most of the new drugs that have become available in the past decade are used as add-on or alternative therapy, although some are now being used as first-line monotherapy.

MECHANISMS OF ACTION OF ANTIEPILEPTIC DRUGS

Antiepileptic drugs appear to act primarily by blocking the initiation or spread of seizures. This occurs through a variety of mechanisms that modify the activity of ion channels or neurotransmitters, and in most cases the drugs have pleiotropic effects.

The mechanisms of antiepileptic drugs are summarised in **Table 2**:

Table 2: Mechanism of anti-epileptic drugs

SN	Mechanism	Name of antiepileptic drugs
1	Reducing the rate of recovery of Na^+ channels from inactivation	Phenytoin, carbamazepine, lamotrigine, topiramate, valproic acid, and zonisamide
2	Enhance $GABA_A$ receptor-mediated inhibition	Benzodiazepines and barbiturates
3	Inhibits the GABA reuptake (inhibit transporter GAT-1)	Tiagabine.
4	Inhibits the GABA transaminase enzyme	Vigabatrin and valproic acid
5	Releasing GABA from neuronal ending	Gabapentin
6	Act by decreasing low threshold calcium current (T current)	Ethosuximide, valproic acid, zonisamide.
7	Inhibits excitatory neurotransmitters	Lamotrigine, felbamate and topiramate.

Table 3: Information regarding conventional anti-epileptic drugs

Name	Indication	Mechanism of action	Properties & Adverse effects
Phenytoin, Fosphenytoin (Hydantoin)	Partial seizures (simple & complex), GTCS	Prolong Na^+ channels inactivation. Higher concentration: enhancement of responses to GABA	Non-linear elimination kinetics. Metabolized by as well as induces CYPs. Adverse event: CNS related, gingival hyperplasia, osteomalacia, and rash.
Carbamazepine (Iminostillbene)	Partial seizures (simple & complex), GTCS & neuralgia.	Prolong Na^+ channels inactivation.	Active metabolites 10, 11-epoxide. Metabolized by as well as induces CYPs, autoinduction. Adverse event: CNS related aplastic anemia, agranulocytosis, retention of water.
Phenobarbital (Barbiturate)	Partial seizures (simple & complex), GTCS	Enhance $GABA_A$ receptor-mediated inhibition (increases duration of opening of Cl^- channel).	Metabolized by as well as induces CYPs, induces UGT. Adverse event: sedation, behavioral disturbances.
Valproic acid (Alliphatic - carboxylic acid)	Absence, myoclonic, Partial seizures (simple & complex), GTCS	Similar to phenytoin and ethosuximide. Stimulate GAD enzyme & inhibit transaminase enzyme. K^+ channel agonists.	Metabolized by CYPs, as well as by UGT. Adverse event: Rash, alopecia, fulminant hepatitis, acute pancreatitis and teratogenic effects
Ethosuximide (Succinimide)	Absence seizures.	Reduces low threshold Ca^{2+} currents (T currents) in thalamic neurons.	Metabolism by CYPs-unknown. Adverse event: Parkinson like symptoms and photophobia, skin reaction, leucopenia, bone marrow depression.
Diazepam, Lorazepam, Clonazepam, Clobazam. (Benzodiaz-epines)	Absence Myoclonic Status epilepticus Partial seizures	Enhance $GABA_A$ receptor-mediated inhibition (increases frequency of opening of Cl^- channel).	Redistribution, variable plasma protein binding. Adverse event: drowsiness, Behavioral disturbances.

TREATMENT COMPLIANCE

INTRODUCTION

In assessing the effectiveness of prescribed medication there is a strong emphasis on the ability of the patient to adhere to the regime recommended by the clinician.[4,17] Various tools have been developed to measure adherence but have limitations. Most research has concentrated on quantifying levels of compliance/adherence.[18]

For individuals with epilepsy, adherence to medication is crucial in preventing or minimizing seizures and their cumulative impact on everyday life. Non-adherence to antiepileptic drugs (AEDs) can result in breakthrough seizures many months or years after a previous episode and can have serious effects on an individual's perceived quality of life.[19]

Reasons for non-adherence are complex and multiple.[17,20] Failure to adherence can happen due to forgetfulness, misunderstanding or uncertainty about clinician's recommendations or intentionally due to their own expectations of treatment, side-effects, and lifestyle choices. There are various strategies suggested for managing patient adherence but these are highly dependent on the reasons why a patient has not followed clinician advice initially.[21]

COMPLIANCE

The relationship between the clinician and patient is one of unequal power dynamics with the traditional definitions of compliance constructed within the medical model.[22]

While clinicians are the "gatekeepers" in providing medication, the patient is the one who ultimately decides whether they adhere to the recommended regime.[17]

The traditional medical model assumes that once the medication regime is recommended by the clinician it is then the responsibility of the patient to follow it; if patients do not comply then the various factors need to be examined. In other words the problem lies with the patient.[23]

A health belief model hypothesized by Becker and Maiman (Figure 1) includes the most frequently examined aspects of compliance (age, drug regime, peer effects, doctor relationship) interacting with an individual's motivations, and perceived benefits or costs of adherence to medication.[24]

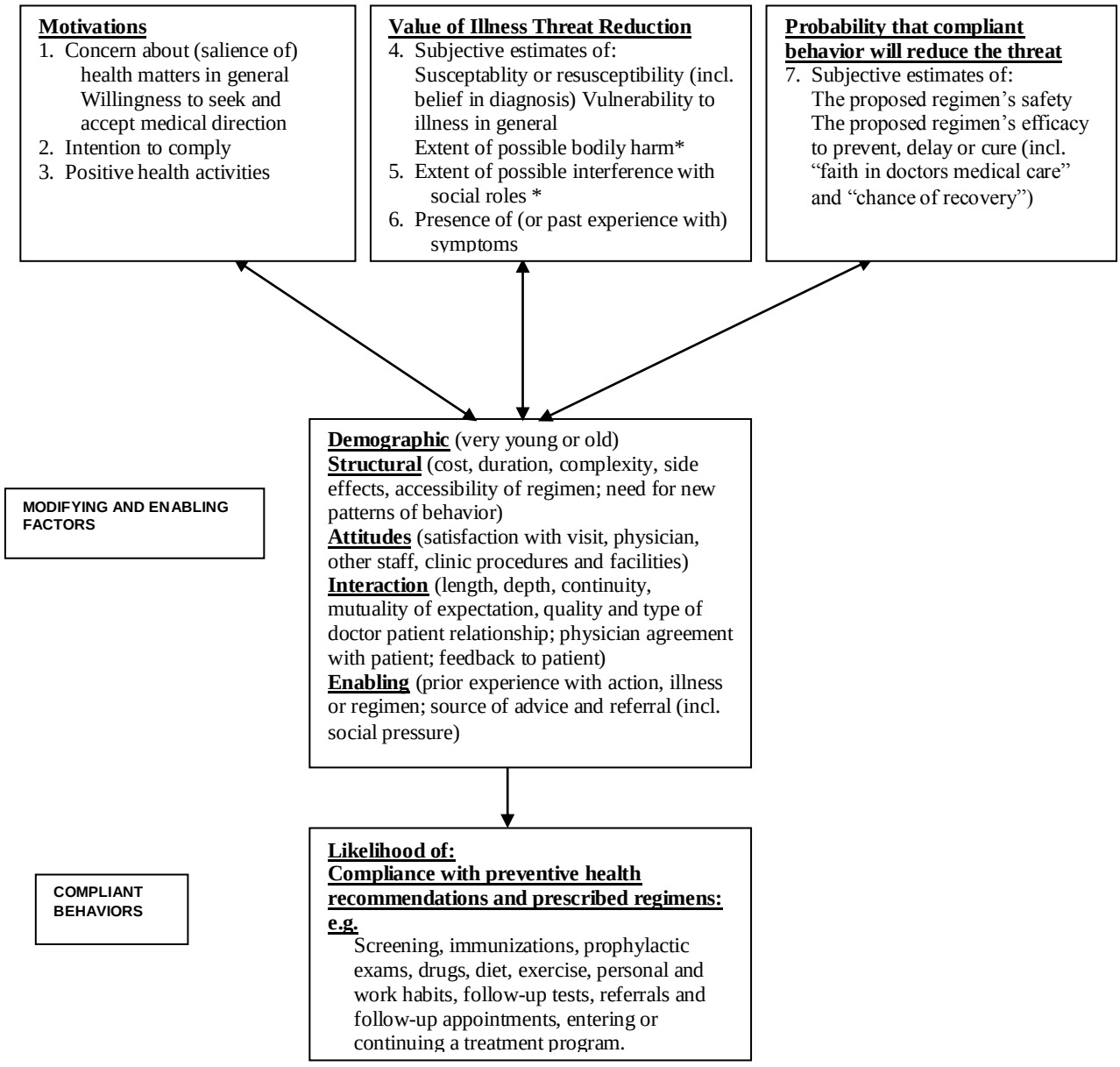

Figure 1: Model hypothesized by Becker and Maiman for predicting and explaining compliance behavior[24]

The level of patient compliance that is acceptable in medical practice varies from different reports and also according to the disease treated. Ideally it should be regarded as that degree of departure from the doctor's instructions known to be associated with a clinically important deterioration in the patient's condition. No universally acceptable level has been found for epileptic patients though it is believed that improved compliance leads to better seizure control.[25] A level of 85% intake of tablets prescribed has been chosen because at and above this level there was a definite relationship to improved control of seizures.

The compliance in epileptic children is as poor as in adult patients. Between 42% and 60% of adult epileptics have been found not to comply with treatment.[26,27] In a group of 'reliable' adult patients, 31% took less than 70% of their medication.[28] Compliance studies in children have been much fewer than in adults and those relating to epilepsy fewer still. In Shope's review of long term oral medication compliance in children between 1960 and 1980, sixteen publications were cited of which only five related to epilepsy.[29] In these, compliance ranged from 25% to 75%. Serum drug level was used to determine compliance in each case and inadequate prescribing was found to be an important factor in some studies.

GENERAL CONSIDERATION:

Wannamaker et al. noted that reducing clinic intervals from a mean of 3.4 months to 1.1 months results in improvement in seizure control. Of the 9 patients so improved only one also improved his AEDL. Indeed, 4 patients actually had a reduction in their AEDL. The improved control was thought to be due to better compliance but this was not reflected in drug levels. These authors concluded that it was difficult to utilize AEDL as sole analysis for compliance or non-compliance.[30]

The usefulness of AEDL in children must be taken in its full pharmacokinetic context. Single out-patient levels as were done in this study serve little, if any, useful purpose as a guide to therapy or compliance unless the latter is gross, as it was in one of our cases. Drug half lives in children are much shorter than adults and hourly

variations greater, particularly for carbamazepine and valproate, when it may be considerable.[31,32]

Lisk suggested that the finding of a therapeutic AEDL on a single out-patient estimation does not imply that the patient is fully compliant with treatment and, if such a patient is uncontrolled, the temptation to increase the dose or add another drug must be resisted until his degree of compliance is ascertained either by hospital admission or more frequent clinic visits.

It is noteworthy that all the controlled patients were on single medication thus confirming the views of ***Shorvon et al.*** that the majority of epileptic patients can be controlled on monotherapy. In addition, compliance may be further enhanced by a single dose regimen. Unfortunately because of the shorter half-lives of antiepileptic drugs in children this may not be possible with many preparations.[33] A possible exception to this rule is sodium valproate that has been shown by Covanis & Jeavons to be effective in single doses in children.[34]

ADHERENCE

The gradual shift away from using the term compliance has been encouraged due to the possibility of a patient somehow being labelled as "deviant" for not following a recommended drug regime.[21] In contrast, adherence, while not a perfect term (Barofsky describes it as what is expected of the patient as opposed to compliance being told what to do) at least implies a more mutual arrangement of co-operation and agreement but is still prone to the same difficulties in determining how it is measured.[22] The concept of both compliance and adherence is further complicated when it is broadened to include general lifestyle changes that have been recommended to promote optimum health alongside a drug regime.

Kobau and Dilorio in their study found that patients who were adherent to their medication schedule often failed to adapt general lifestyle (getting enough sleep, reducing alcohol intake, avoiding stress) which could be just as detrimental to seizure control and overall health.[35]

CONCORDANCE

Recently the concept of concordance has been promoted as a possible replacement to the notions of compliance or adherence, advocating a decision-making process where patients can feel more comfortable with their treatment.[36]

Adherence and concordance reflect a different process of decision making about treatment and health outcomes but ultimately, however, once treatment has been decided there will still be a need to measure whether the treatment regime has been effective both in terms of treating the condition and the relative cost.[4]

MEASURES OF ADHERENCE TO EPILEPSY TREATMENT

Adherence measures can be grouped into two categories: direct and indirect.

Direct measures of determining adherence to treatment for drug-managed epilepsy involve measurement of drug levels in hair or in body fluids such as blood or saliva.

Indirect measures involve non biological tools such as self-report measures, pill counts, appointment attendance, medication refills, and seizure frequency (Table 4).

Table 4: Direct and indirect measures of adherence to epilepsy medication treatment; their advantages and disadvantages

Adherence measure	Method	Advantages	Disadvantages
Direct Measures			
Plasma or serum antiepileptic drug levels	Plasma or serum levels are measured	• Commonly used • Effective in extreme low adherence	• Patient factors & drug types can result in variability • Less accurate in monotherapy
Detection in human hair	analyzed using chromatography	• Less invasive	Disagreement on effectiveness
Saliva concentration	Levels in saliva	• Painless • Good for pediatric and geriatric patients	Measurement must be calibrated to individual saliva production
Indirect Measures			
Self-report measures	By surveys, interviews	• Low cost • Adaptable to target population	• Not standardized & validated • Reporting bias
Pill counts	counting remaining pills	• regularity of dose measured	• No assurance of use of controlled environment
Appointment attendance	Regularity is documented	• Easy to collect • Can be related to other adherence behaviors	• Not ideal for life term treatment • Not a proof of drug use
Medication refills	Review of Medical/pharmacy records for refilling	• Easy to collect information • Can be correlated to serum levels	• Difficult to collect if prescription is not known • Not proof of drug use
Seizure frequency	Frequency of seizures is logged		

DIRECT MEASURES

There are three main direct measures of epilepsy medication adherence: the measurement of medication levels in **blood plasma** or **serum**, in **hair samples**, and in **saliva**. Direct measures lend themselves to evidence-based medical approaches and comparative analyses since they provide quantitative data on the physical presence of medication in a patient's body.

PLASMA OR SERUM ANTIEPILEPTIC DRUG LEVELS

The most commonly used measure of adherence among patients with epilepsy is the evaluation of medication levels in blood plasma or serum.[37-39] This method involves measuring plasma or serum levels for drugs such as phenobarbital at least twice, with intervals as long as several months.[39,46] A drop in medication level of a certain predetermined percentage, dependent on study and medication being studied, is indicative of noncompliance.

Several factors have been linked to variability in blood levels for a single patient, including age, food intake, and drug interaction.[8] Serum levels also vary according to drug taken. For example, Graves found phenytoin to differ from baseline in compliant patients by approximately 5 μg/ml or less, while carbamazepine varied only 2 μg/ml.[40] Inter patient variation of medication levels could be as high as 30% for phenytoin and 40% for carbamazepine.

Although plasma or serum measurement is effective in assessing drug intake even in extreme low adherence situations, some do not consider it to be sufficiently accurate for optimizing treatment, especially in newly diagnosed epilepsy and medication monotherapy cases.[50,51] This is presently the most common direct measurement of compliance among epilepsy patients, but researchers are increasingly associating the measurement of blood plasma or serum medication levels with psychological assessments or self-report measures in order to gather complete information about patient adherence to treatment.[52,53]

In a study of epileptic children in South Africa seizure control was poor (38%) in patients having therapeutic levels of phenobarbitone whilst it was good in those with subtherapeutic levels and even those showing no detectable drug in their serum.[54]

Lund found that by increasing phenytoin levels from 11.7 μg/ml to 15 μg/ml annual seizure frequency was reduced from 4.1 to 1.6.[55] This positive relationship between increasing AEDL and reduced seizure frequency is established.[56, 57]

DETECTION IN HUMAN HAIR

In addition to blood concentration levels, some researchers have analyzed medication levels in human hair in order to assess epilepsy therapeutic compliance. [46, 58-61] Human hair incorporates all medications taken by a patient, including recreational as well as therapeutic drugs. Typically, antiseizure medication levels are measured in hair by conducting gas chromatography, mass spectrometry or isocratic high-performance liquid chromatography assays.[58,60]

Drug detection in hair is not a very common form of adherence assessment, perhaps because researchers disagree on the effectiveness of this method. According to Kintz et al., the utilization of hair samples is not suitable for evaluating the quantity of a drug consumed.[59] By contrast, Williams et al. concluded that this method is easy to perform and has a similar sensitivity to blood plasma for detection and quantification of phenytoin and carbamazepine in hair samples from an epilepsy inpatient population.[46] Mei & Williams consider this method to be one of the most advanced in measuring adherence among epilepsy patients when used in conjunction with blood plasma monitoring of antiepileptic drug concentrations.[60]

SALIVA CONCENTRATION

Finally, adherence to treatment has also been directly measured by sampling saliva for anticonvulsant drug levels.[62-64] Researchers have repeatedly found this method of sampling to offer statistically similar results to blood plasma or serum

monitoring, though limitations of saliva sampling include the need to calibrate measurements to the saliva production of each individual as well as wide variability in the ratio of medication levels in serum to saliva.[65-73] Ryan et al. found saliva: serum ratios for lamotrigine ranging from 0.40 to 1.26 for a sample of 37 adult and paediatric patients; these ratios could vary still more depending on the medication used.[71] Therefore, this method of measuring adherence to treatment may be most effective when sampling is tailored to each individual. However, this method is not suitable in settings with large patient volume.

An advantage of this method is that it is the most painless of direct measures, an important consideration for paediatric patients.[74, 75] Also, it does not depend on venous access, a benefit for paediatric or geriatric patients who may have poor veins.[69] Still, very few physicians are familiar with saliva concentration measurement for evaluating treatment adherence.[75] Relatively few studies have assessed adherence to treatment using this method; most have focused on adherence only indirectly by studying the relationship between blood and saliva medication levels.

INDIRECT MEASURES

There are five major indirect measures of treatment adherence: **self-report measures, pill counts, appointment attendance, medication refills, and seizure frequency**. An evidence base is more difficult to document for indirect measures than for direct due to variations in methodology used, although these measures also yield quantitative data about patient adherence.

SELF-REPORT MEASURES

Self-report measures are the most commonly used measurement in most studies of medication adherence, and self-report methods such as surveys and interviews have been widely used to study adherence in epilepsy.[8, 20, 52, 76-79] Self-report measures have the advantage of being low cost, noninvasive, and easily adaptable to a target population. However, these measures vary greatly in terms of how they are developed, whether they have been validated, and to whom they are

administered. Researchers have developed several self-report measures specifically for adult and youth populations.[20, 80] Even within age groups, sampling methods, survey questions, and analytical methods vary. In terms of study populations, some researchers have studied outpatients, others have recruited from clinics, and still others have been drawn from ongoing studies.[52,77,78]

Despite the common use of self-report measures to determine treatment adherence, few measures have been validated specifically for the study of epilepsy. A notable exception is the QOLIE-AD-48, which measures health-related quality of life for adolescents with epilepsy and has been found to be reliable and valid. Instruments that specifically measure epilepsy treatment adherence are lacking, however, although more general self-report measures may include items relevant to treatment adherence. Gomes & Maia Filho used a questionnaire that included one adherence question ("Did you forget or miss any of your medicine last week?"). Although judgment of adherence was based on that single question, other questions on the survey also addressed patient medication use behaviors.[8]

While simple to implement (a reason for their common use), problems inherent to self-reported measures may further undermine results. Patient misperception or the tendency to give socially desirable responses might lead to over-reporting of adherence.[20, 81] Recent studies have combined self-report measures with direct measures of adherence in order to confirm self-report data.[53] However, a standardized, validated tool for measuring epilepsy patient adherence to treatment does not exist at this time.

PILL COUNTS

Osterberg & Blaschke indicate that pill counts, or counting the remaining pills in a patient's bottle or vial, are the second most common method (after self-report measures) used to judge adherence to treatment for many medication-dependent health conditions.[76] Pill counts are a noninvasive measure, but this method has rarely been used to determine adherence to epilepsy treatment.[81, 82] One reason is that pill

counts are most useful in research settings where control over medication dispensing can take place; the method might not be as useful in assessing adherence in clinical practice settings.[20] This method might be used more frequently in practice than is documented in the literature, although this seems unlikely since patients could easily alter pill counts outside of a controlled environment.

A related form of adherence measurement is the use of a Medication Event Monitor System, or event recorder. These are standard pill bottles with microprocessors in the caps that record bottle openings, each of which is considered a dose. This method was piloted on epilepsy patients and was found to be more accurate at determining daily compliance than either pill counts or blood serum concentrations, which do not measure the regularity of dosing.[6] However, event recording does not guarantee that medication is actually taken, and patients may not perceive their medication adherence accurately as determined by the event recorder.[83]

The information obtained from the **'pill' count method** is taken as an adequate assessment of drug intake. Previous studies have found a good correlation between pill count and more reliable methods such as tracer substances in the blood.[84] Questionnaires on this subject are known to overestimate patient compliance as it did in our study.

The accuracy of the 'pill' count can be further enhanced by not disclosing to the patients that a survey is undertaken until after the drugs are returned. An earlier disclosure may have prejudiced the outcome. The relationship between antiepileptic drug levels (AEDL), seizure control and patient compliance is inconsistent.[31]

APPOINTMENT ATTENDANCE

Documentation of appointment attendance is another method that has been used to measure adherence among epilepsy patients.[38, 85-87] For example, Mitchell et al. measured adherence to treatment among children aged 4–13 years of age over a 6-month period, using as their outcome measure whether families returned to the clinic

on scheduled dates. The study concluded that seizure frequency was unrelated to adherence, but that families with more stressors also adhered more closely to treatment in terms of clinical visits.[20] Other researchers have related appointment attendance to caregiver behavior or to pharmacological adherence.[43,88]

Studies that measured appointment attendance observed time spans ranging from 6 months to 18 months.[20,86] Appointment attendances is easily determined from medical records; thus this is a simple measure to implement. However, this method fails to capture some aspects of adherence since epilepsy treatment adherence may be a lifelong issue for patients. Sample sizes in such studies have ranged from as few as 35 to as many as 238.[41,89] Although appointment adherence may be a good indicator of a patient's general adherence to epilepsy treatment, it does not necessarily mean that patients are also taking their medications or consuming them properly.

MEDICATION REFILLS

Adherence to treatment may also be measured by determining whether patients fill and/or refill their prescriptions.[38,90] In a study on adherence among children with epilepsy, ***Mitchell et al***. reviewed medical records to assess whether patients requested medication refills.[20] ***Stanaway et al.*** also considered intervals between collections of drugs from pharmacies on their 95 subjects.[63] ***Ball & Taderera*** determined the number of antiepileptic drugs prescriptions that were written upon discharge of their patients, and determined how many prescriptions were refilled by their hospital.[80]

Similarly, ***Steiner et al***. measured adherence by examining prescription refill records of pharmacies and checking this data against patients' blood levels, finding significant correlation. They concluded that this method was feasible in managed care settings.[91] Consulting pharmacy prescription records for epilepsy patients works well in a closed pharmacy system or among centralized pharmacies.[76] However, with recent, growing use of Canadian pharmacists and on-line prescriptions, this method

may not be efficacious for most settings, and it is not proof that medications are properly taken.

SEIZURE FREQUENCY

One of the least common methods in assessing adherence to treatment is measuring seizure frequency over time, perhaps due to the fact that even nonadherent patients may experience seizures only rarely.[15] Only a few studies reported the use of this approach, and these did so in combination with other direct and indirect adherence measurements.[52] Still, seizure frequency is an essential manifestation of the degree to which epilepsy is managed, and clinicians are likely to consider frequency of epilepsy seizures in everyday practice as a valid measure of adherence.

METHODOLOGY

This chapter deals with the methods and techniques adopted to study the factors influencing compliance and non compliance to antiepileptic drugs in epilepsy patients. It includes research approach, research design, setting, population, sample and sampling technique, method of data collection and plan for data analysis.

Research Approach

Quantitative survey method

Research Design

Cross sectional study

Setting

The study was conducted in Pediatric dept, R.L.Jalappa Hospital and Research Centre, attached to Sri Devaraj Urs Medical College (SDUMC), Kolar. It is a tertiary care hospital which provides medical and nursing education and research. Both old and new cases were registered. Patients for the data collections were taken every day.

Population

Epileptic patients/parents of epileptic patients coming for follow up in Pediatric dept, R.L.Jalappa Hospital and Research Centre, Kolar.

Sample and Sampling technique

Convenience sampling technique were used to enroll epileptic patients/parents of epileptic patients coming for follow up in Pediatric dept, R.L.Jalappa Hospital and Research Centre, Kolar, from March 2010 to Feb 2011. The criteria used for sample selection:

Inclusion Criteria:

1. All children between age group of 1-15 years who comes to Pediatric dept, R.L.Jalappa Hospital and Research Centre with epilepsy and who are put on anticonvulsant therapy.
2. All types of Epilepsy (Both OPD and IPD cases).
3. Known cases of Epilepsy on Anticonvulsant therapy.

Exclusion Criteria:

1. Neuroinfection
2. Neurocysticercosis
3. Febrile seizures
4. Cerebral palsy
5. Neurodegenerative disorders

Sample size

Taking into account the availability of subjects and the time, a sample size of 231 was enrolled in the study.

Tool for data collection

The method used for data collection was self report method. The tool used for data collection was **structured interview schedule**.

Structured Interview schedule

Development of tool: An extensive review of literature was done based on the objectives of the study. A structured interview schedule including the demographic, epilepsy and antiepileptic medications related information, antiepileptic medications adherence barriers and antiepileptic medication's side effects assessment sheet was prepared to collect data in consultation with guide.

Description of tool:

The final Structured Interview schedule has 4 sections.

a) **Demographic profile:** It deals with socio economic background.

b) **Epilepsy and antiepileptic medications related characteristics:** It deals with the epilepsy and antiepileptic medications, including assessment of medication compliance which consists of items related to medication regimen and frequency.

c) **Antiepileptic drugs adherence barrier:** It deals with items which act as barriers for adhering to antiepileptic medications like local misbelieves, short of money, too many medications at a time etc. Each item is rated as yes or no.

d) **Antiepileptic drug's side effects assessment scale**: To assess the presence of the antiepileptic medication's side effects. The common side effects like poor scholastic performance, weight gain, loss of appetite, sedation etc., are included in the scale. Each item is rated on a 5 point scale ('does not have symptom' = 0 to 'have symptom and it bothers terribly' = 4). Higher the score, the more is the intensity of side effects.

Informed consent

A letter explaining the purpose of the study was readout and handed over to the patients and caregivers of epileptic patients and informed consent was signed before data collection.

Procedure for data collection

Epileptic patients/parents of epileptic patients, who met the inclusive criteria, were enrolled in the study. Informed consent form was signed before participation. Information about demographic characteristics, epilepsy and antiepileptic drugs related characteristics, compliance adherence barriers and antiepileptic medication’s side effects, was collected by structured interview method.

Duration of data collection

Data was collected for a period of 1 year i.e. from March 2010 to Feb 2011.

Data analysis

Data analysis was done using SPSS version 16. Descriptive statistics including mean, standard deviation, frequency and percentage and inferential statistics including t test, chi square test and fisher's exact test was used for data analysis, keeping the level of significance at $p \leq 0.05$.

This chapter dealt with the methodology adopted for the study. The next chapter deals with the analysis and interpretation of data.

ANALYSIS AND INTERPRETATION

The result of the study presented in this chapter are based on the data collected from a sample of 231 epileptic patients/parents of epileptic patients enrolled in the study, regarding the factors affecting compliance and noncompliance to antiepileptic medications.

Data was enrolled in Microsoft excel sheet and analyzed using SPSS version 16 with descriptive and inferential statistics such as mean, standard deviation, frequency, percentage, chi square test, Fisher's exact test and student's t test. All categorical variables were analyzed using chi square test and Fisher's exact test. **A P value of ≤0.05 was taken as significant**. Data analysis was done in accordance with the objectives of study.

The main objectives of study were:

1. To study the compliance to anticonvulsant therapy among rural children with epilepsy.
2. To study the correlation of drug prescribed with compliance.
3. To study the correlation of cost and availability of drug with compliance.

Presentation of Data

The analyzed data is organized according to the objectives of the study and presented under the following sections:

Section 1: Prevalence of compliance and noncompliance to antiepileptic medications

Section 2: Factors affecting the compliance and noncompliance to antiepileptic medications

- 2a) Demographic Characteristics
- 2b) Characteristics of epilepsy and antiepileptic medications

Section 3: Barriers to compliance with antiepileptic medications

Section 1: **Prevalence of compliance and noncompliance to antiepileptic medications**

Table 5: Comparison of compliant and noncompliant group

Total no.	Compliant	Noncompliant
231	145(62.77%)	86(37.23 %)

Table 5 shows that out of 231 epileptic patients only 145(62.77%) were compliant with the antiepileptic medication regimen with the self report criteria and 86(37.23 %) reported to be noncompliant with the medication regimen.

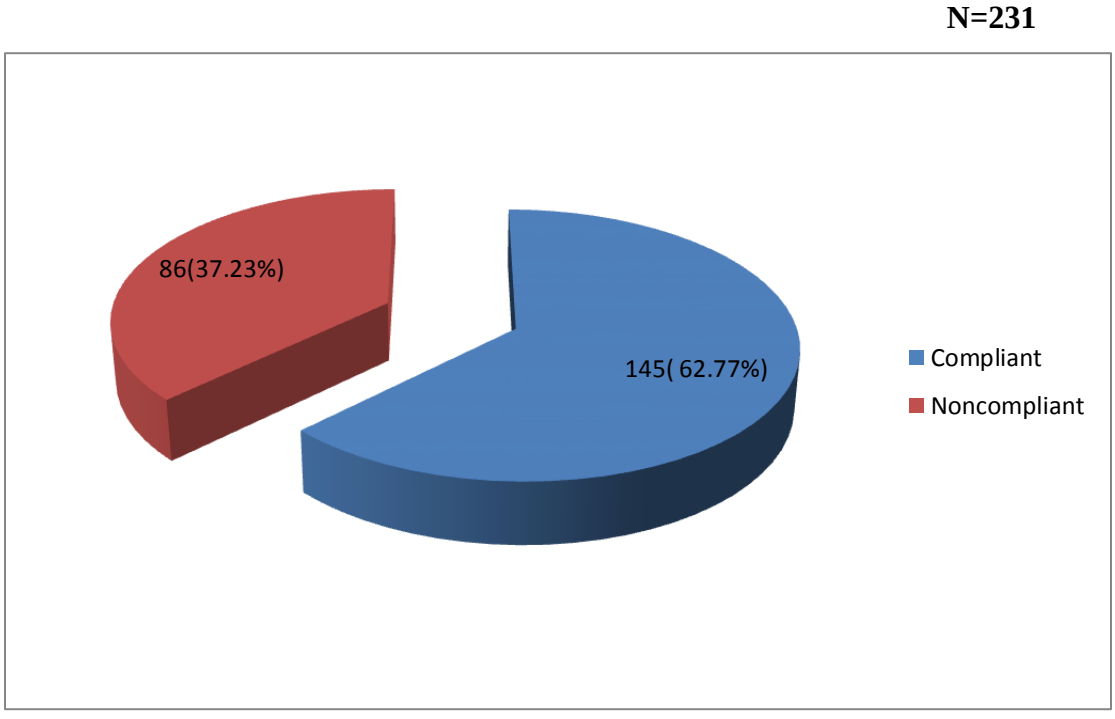

Fig 2: Pie diagram showing distribution of patients according to compliance with antiepileptic medications

Section 2(a): Demographic characteristics

Table 6: Comparison of demographic variables in compliant & noncompliant group

VARIABLE		Compliant(145)	Noncompliant(86)	p value
Age	≤7YRS	51(35.17)	26(30.23)	χ^2=0.59 p=0.441
	>7YRS	94(64.83)	60(69.77)	
Gender	Female	56(38.62)	29(33.72)	χ^2=0.45 p=0.455
	Male	89(61.38)	57(66.28)	
Education of parent	Illiterate	5(3.45)	6(6.98)	χ^2=1.92 p=0.383
	Pri/Sec/PUC	101(69.66)	61(70.93)	
	Higher Education	39(26.9)	19(22.09)	

As shown in table 6, 64.83% in compliant group and 69.77% in noncompliant group were above the age of 7 years. χ^2 test done to compare the groups reveals no statistically significant association between age of the patient and compliance to the medications (p= 0.441). The noncompliant patients were equally distributed in both the age groups.

More than half of the patients were male, both in compliant group (61.38%) and noncompliant group (66.28%). Females were only 38.62% in compliant group and 33.72% in the noncompliant group. χ^2 test shows no statistically significant association between gender of the patient and compliance to the medications (p=0.455). The noncompliant patients were equally distributed in both the genders.

More than half of the parents i.e. 69.66% in compliant group and 70.93% in the noncompliant group had completed their education up to PUC. Only 3.45%in compliant group and 6.98% in the noncompliant group were illiterate. χ^2 test shows no statistically significant association between parent's education and compliance/non compliance to the medications (p=0.383). Hence, compliance to the medications was found to be independent of parent's education.

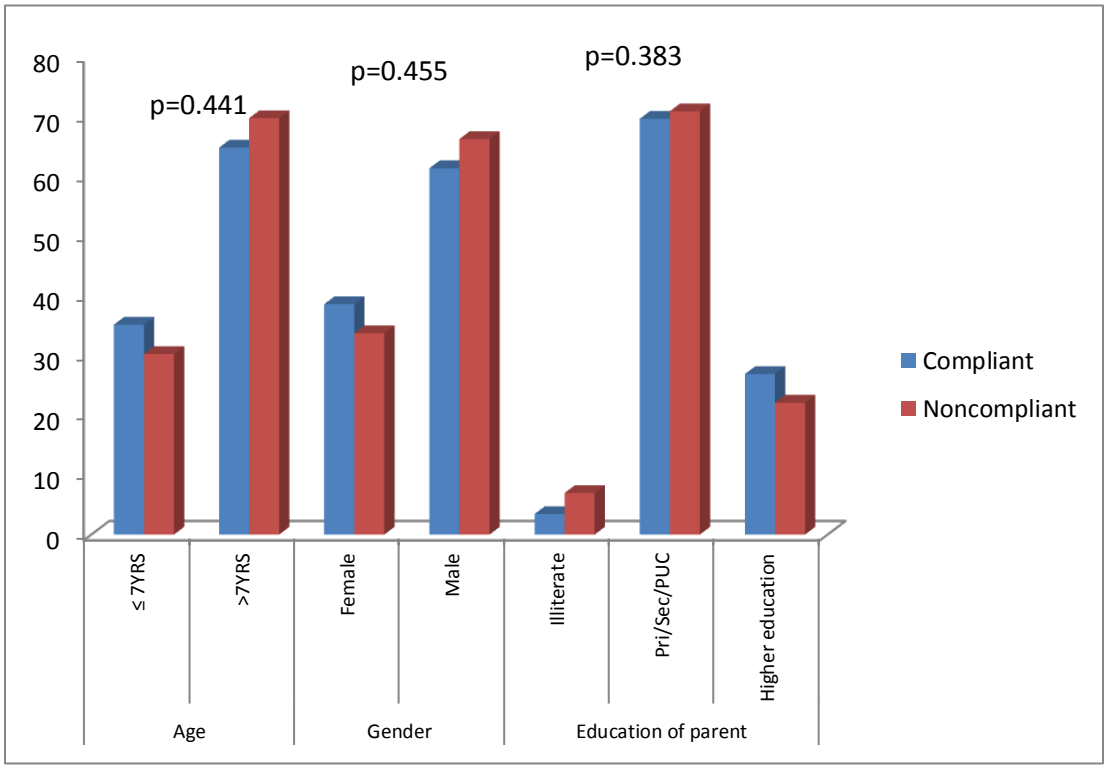

Fig 3: **Bar diagram showing distribution of patients according to age, gender and education of parent**

Table 7: Comparison of family characteristics in compliant and noncompliant group

Variable		Compliant(145)	Noncompliant(86)	p value
Type of family	Joint	42(28.97)	33(38.37)	χ^2=2.17
	Nuclear	103(71.03)	53(61.63)	p=0.140
Per capita income	<2000	42(28.97)	27(31.40)	χ^2=0.15
	2001-6500	85(58.62)	49(56.98)	p=0.923
	>6500	18(12.41)	10(11.63)	
Family history	Epilepsy	28(19.31)	17(19.77)	p=0.932

Table 7 shows that more than half of the patients both in compliant groups (71.03%) and noncompliant group (61.63%) had nuclear family. Comparing the groups using χ^2 test reveals no statistically significant association between type of family and compliance/noncompliance to the medications (p=0.140). Hence, patient's compliance with the medications was found to be independent of type of family, they belong.

Almost half of the patients both in compliant group (58.62%) and noncompliant group (56.98%) were in middle income group (i.e. 2001-6500). Only 12.41% in compliant group and 11.63% in noncompliant group were in high income group (i.e. >6500). χ^2 test reveals no statistically significant association between family's monthly income and medication compliance/noncompliance (p=0.923). It means that regardless of family monthly income, patients were noncompliant with the medications.

Some patients, both in compliant group (19.31%) and noncompliant group (19.77%) had positive family history of epilepsy. On comparing the groups using χ^2 test reveals no statistically significant association between family history of epilepsy and compliance/noncompliance with antiepileptic medications (p=-0.932).

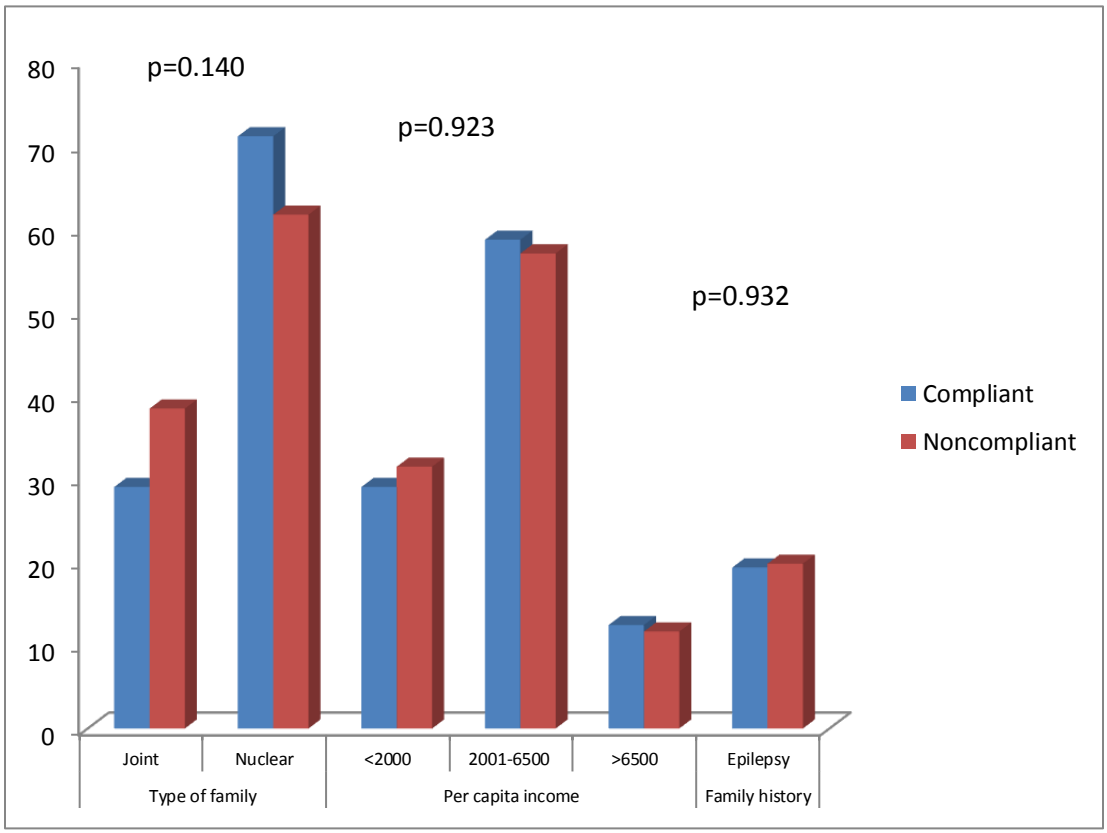

Fig 4: **Bar diagram showing distribution of patients according to family characteristics**

Section 2 (b): Characteristics of Epilepsy and antiepileptic medications

Table 8: Comparison of epilepsy profile in compliant and noncompliant group

Epilepsy profile		Compliant(145)	Noncompliant(86)	p value
Age at onset of epilepsy	0-5 years	16(11.03)	13(15.12)	
	5-10 years	80(55.17)	46(53.49)	χ^2=0.83
	10-15 years	49(33.79)	27(31.40)	p=0.657
Type of seizure	Generalized	103 (71.03)	51 (59.30)	
	Complex partial	23 (15.86)	25 (29.07)	χ^2=5.74
	Simple partial	19 (13.10)	10(11.63)	**p=0.051**
Frequency of seizures	≥1/ month	32(22.38)	31(36.47)	
	1month - 3yrs	91(63.64)	41(48.24)	χ^2=6.07
	After 3yrs	20(13.99)	13(15.29)	**p=0.048**

As shown in the table 8, more than half of the patients both in compliant (55.17 % + 33.79%) and noncompliant group (53.49 % + 31.40%) had effect of epilepsy at the age of 5-15 years followed by the age of less than 5 years both in compliant (11.03%) & noncompliant group (15.12%). χ^2 test reveals no statistically significant association between the age of onset of epilepsy and medications compliance/noncompliance (p=0.657). Hence, it can be interpreted that compliance with medications is not dependent on age of onset of illness.

More than half of the patients both in compliant group (71.03%) and noncompliant group (59.30%) were having generalized seizures, followed by complex partial seizures i.e. 15.86% in compliant group and 29.07% in non compliant group. χ^2 test reveals a statistically significant association between the types of seizures and compliance to medications (p=0.051). Patients with generalized seizures were more compliant than those with partial seizures. This shows lesser the severity of the seizures, lower is the compliance with medications.

More than half of the patients had adequately controlled seizures (having seizure after 1 month but within 3 years) i.e. 63.64 % in compliant group and 48.24% in non compliance group. Only 22.38% in compliant group and 36.47% in non compliant group were having poorly controlled seizures (having seizure once or more in a month). χ^2 tests reveals statistically significant association between frequency of seizure and compliance/noncompliance with antiepileptic medications (p=0.048). That means, patients with poorly controlled and very well controlled seizures are less compliant than the patients with adequately controlled seizures.

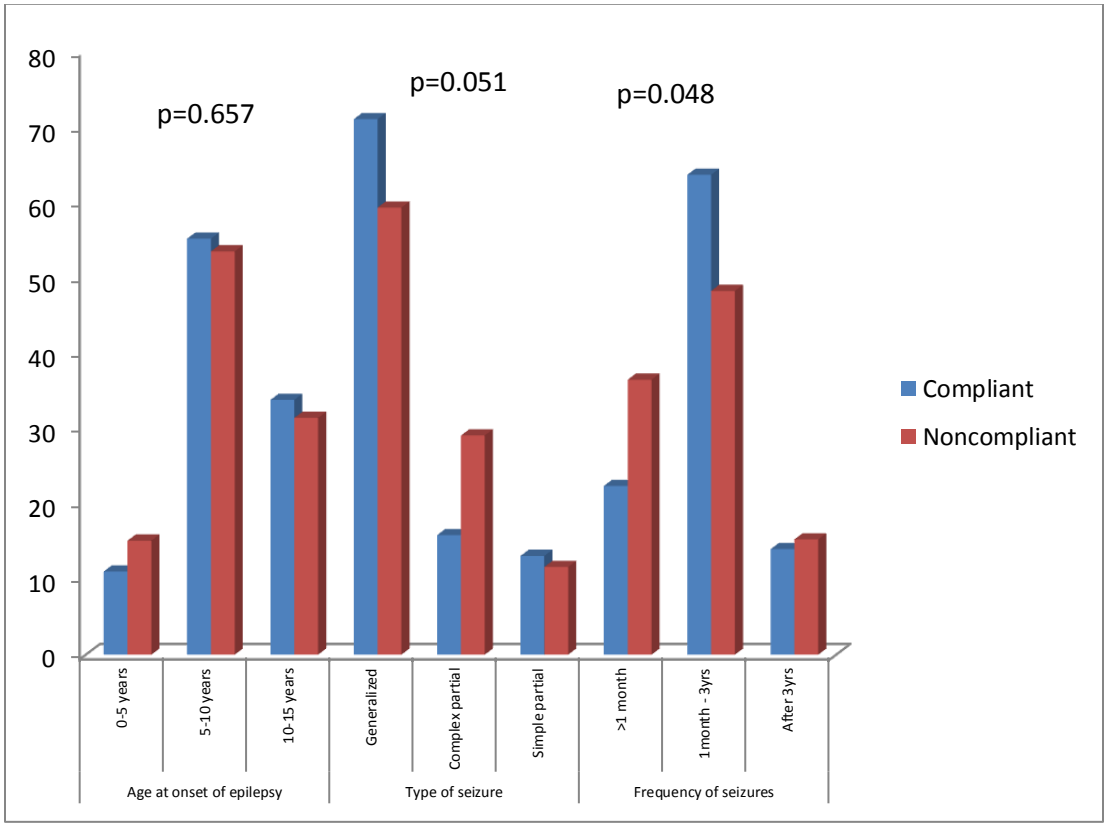

Fig 5: **Bar diagram showing comparison of epilepsy profile**

Table 9: Comparison of drug regimen and side effects in compliant and noncompliant group

Variables		Compliant (145)	Noncompliant (86)	p value
Type of drug therapy	Monotherapy	89(61.38)	58(67.44)	χ^2=1.33 p=0.512
	Polytherapy	56(38.62)	28(32.56)	
Drug frequency	OD	22(15.17)	18(20.93)	χ^2=1.28 p=0.264
	BD/TID	123 (84.83)	68(79.07)	
Side effects of drugs	Troublesome	120(82.76)	74 (86.05)	χ^2=0.43 p=0.510
	Not troublesome	25(17.24)	12(13.95)	

Table 9 shows that more than half of the patients in compliant group (61.38%) and noncompliant group (67.44%) were getting monotherapy. χ^2 test reveals no statistically significant association between type of drug therapy and compliance/noncompliance to the medications (p=0.512). This shows that non compliant patients were equally distributed in both types of drug therapy.

Majority of the patients both in compliant group (84.83%) and noncompliant group (79.07%) were having BD/TID schedule for drug administration. However, χ^2 test reveals no statistically significant relationship between frequency of drug administration and compliance/noncompliance with medications (p=0.264).

Majority of the patients in compliant group (82.76%) and noncompliant group (86.05%) were having troublesome side effects of drugs. χ^2 test reveals that presence of troublesome side effects is not significantly associated with compliance/noncompliance to the medications (p=0.510).

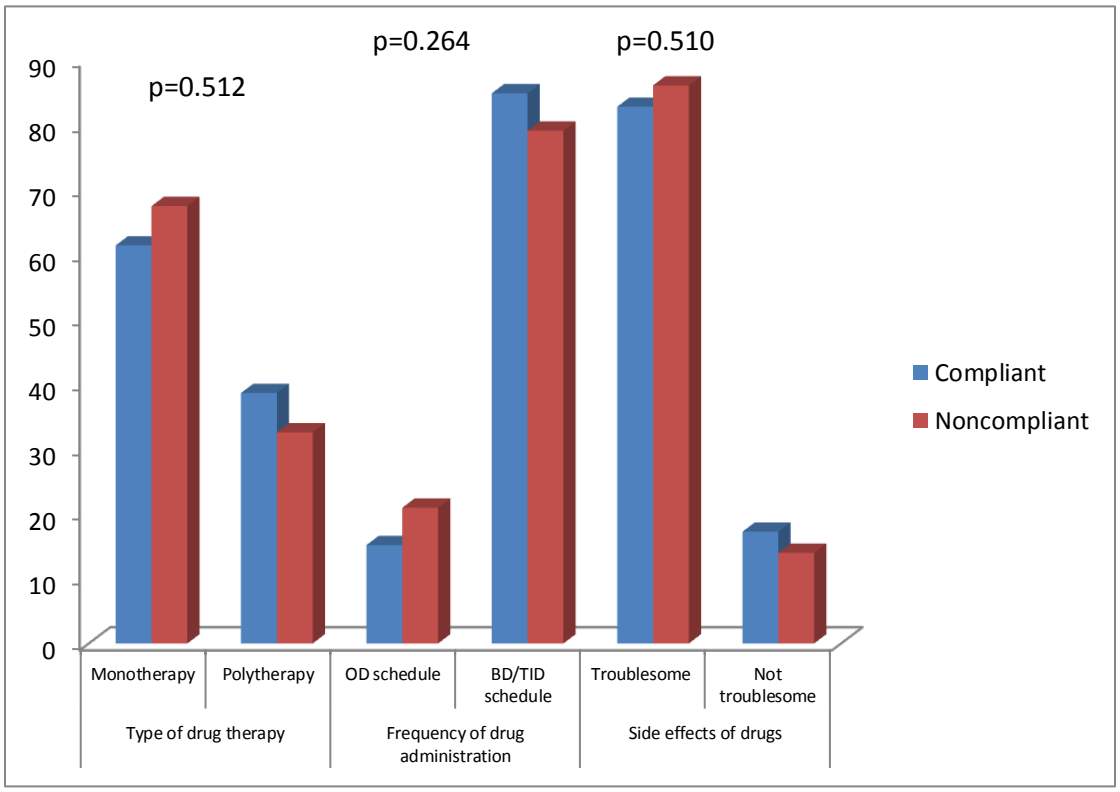

Fig 6: **Bar diagram showing comparison of drug regimen and side effects**

Table 10: Comparison of accessibility, availability and cost of medications in compliant and noncompliant groups

Variables		Compliant (145)	Noncompliant (86)	p value
Access to medical store	Near	31(21.38)	20(23.26)	χ^2=0.11 p=0.74
	Far	114(78.62)	66(76.74)	
Availability of medications	Easily	122(84.14)	60(69.77)	χ^2=6.67 **p=0.010**
	Difficulty	23(15.86)	26(30.23)	
Monthly expenditure on medications	≤200 rupees	79(67.52)	53(74.65)	χ^2=1.07 p=0.584
	200-500 rupees	23 (19.65)	11(15.49))	
	>500 rupees	15(12.82)	7(9.86)	

Table 10 shows that most of the patients i.e. 78.62% in compliant group and 76.74% in the noncompliant group had access to medical store beyond walking distance. χ^2 test reveals no statistically significant association between accessibility to medical store and compliance/noncompliance to the medications (p=0.74). This shows that compliance with the medications in independent of access to the medical store.

Medicines were easily available to the most of patients both in compliant group (84.14%) and noncompliant group (69.77%). Only 15.86% in compliant group and 30.23% in the noncompliant group were having difficulty in getting the medicines. χ^2 test reveals statistically significant association between availability of medicines and compliance/noncompliance with medications (p=0.010). Hence, it can be interpreted that the patients with easy availability of medicines were more compliant (84.14%) than the patients who were having difficulty in getting the medicines (15.86%).

Monthly expenditure on medicines was up to rupees 200 per month in majority of patients i.e. 67.52% in compliant group and 74.65% in noncompliant group. χ^2 test reveals no statistically significant association between monthly expenditure on medicines and compliance/noncompliance to the medications (p=0.584). Hence, irrespective of the expenditure on the medications, patients were compliant with the antiepileptic medications.

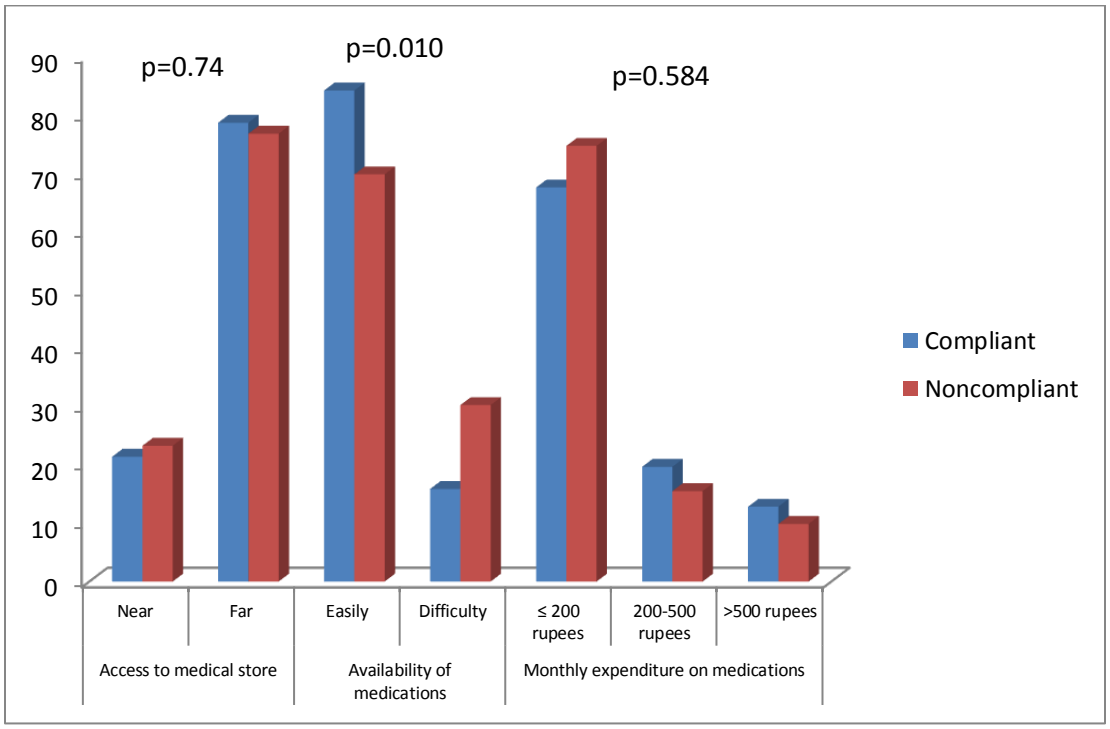

Fig 7: **Bar diagram showing comparison of accessibility, availability and cost of medications**

Table 11: Comparison of type of antiepileptic drugs in compliant and noncompliant group

Drugs	Compliant(145)	Noncompliant(86)	p value
Sodium valproate	62(42.76)	28(32.56)	χ^2=2.36 p=0.364
Phenytoin	52(35.86)	38(44.19)	χ^2=1.57 p=0.210
Carbamazepine	48(33.1)	28(32.56)	χ^2=0.01 p=0.932
Phenobarbitone	13(8.97)	8(9.3)	χ^2=0.01 p=0.931
Clonazepam	5(3.45)	1(1.16)	Fisher's exact=1.11 p=0.416
Clobazam	2(1.38)	3(3.49)	Fisher's exact=1.13 p=0.364

Table 11 shows that majority of patients in compliant group (42.76%) were getting Sodium valproate, followed by Phenytoin (35.86%) and Carbamazepine (33.10%). While in noncompliant group, majority were getting Phenytoin (44.19%), followed by Sodium valproate (32.56%) and Carbamazepine (32.56%). Least commonly used drug in compliant group was Clobazam (1.38%) while in noncompliant group clonazepam (1.16%) was least commonly used drugs.

χ^2 test and Fisher's exact test reveals no statistically significant association between type of antiepileptic drug and compliance (p=>0.05).This shows that irrespective of type of antiepileptic drugs, patients were compliant/noncompliant with the medications.

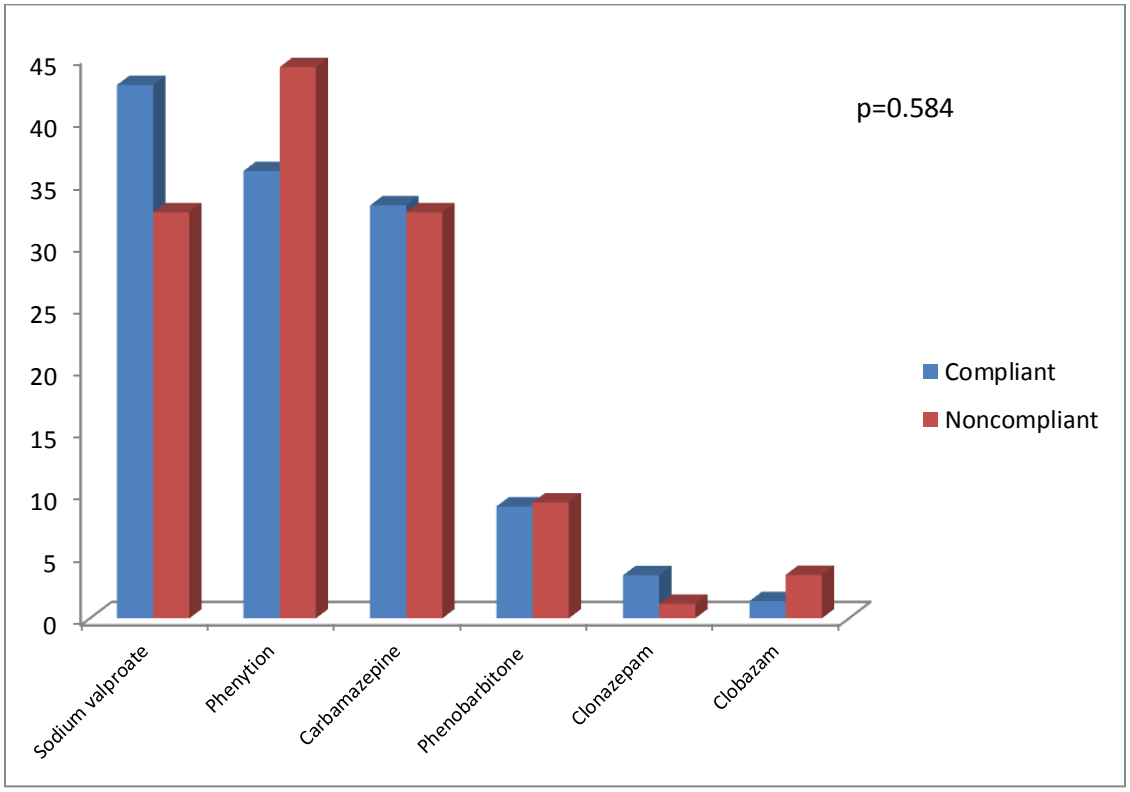

Fig 8: **Bar diagram showing comparison of type of antiepileptic drugs**

Section 3: Barriers to compliance with antiepileptic medications

Table 12: Barriers to compliance with antiepileptic medications

Barriers	Compliant(145)	Noncompliant(86)	p value
Poverty	89(61.38)	60(69.77)	χ^2=1.65 p=0.198
Local misbelieves	78(53.79)	53(61.63)	χ^2=1.34 p=0.245
Forgetfulness	51(35.17)	38(44.19)	χ^2=1.85 p=0.174
Unavailability of medications	27(18.62)	32(37.21)	χ^2=11.83 **p=0.003**
Social stigma	26(17.93)	20(23.26)	χ^2=0.95 P=0.327
When child is better they skip the doses	24(16.55)	18(20.93)	χ^2=0.69 p=0.404
Financial problems in purchasing medications	15(10.34)	17(19.77)	χ^2=4.01 **p=0.045**
Due to/fear of side effects	12(8.28)	14(16.28)	χ^2=3.46 p=0.063
Antiepileptic drugs are not effective	12(8.28)	16(18.6)	χ^2=5.40 **p=0.020**
It is a hereditary disease and can't be treated	12(8.28)	6(6.98)	χ^2=0.12 p=0.722
Inadequate knowledge regarding the importance of compliance to medication	8(5.52)	11(12.79)	χ^2=3.78 **p=0.052**
Miscellaneous	8(5.52)	12(13.95)	χ^2=4.85 **p=0.028**

Table 12 depicts that the many patients in both the compliant group (61.38%) and noncompliant group (69.77%) expressed "poverty " as the commonest barrier to compliance with medications, followed by "local misbelieves"(53.79% in compliant and 61.63% in noncompliant group) and "forgetfulness" (35.17% in compliant group and 44.19% in noncompliant group).

Barriers which were found to be significantly influencing the compliance in both the groups as revealed by χ^2 include unavailability of medications (p=0.03), financial problems in purchasing the medications (p=0.045), antiepileptic drugs are not effective (p=0.020), inadequate knowledge regarding the importance of compliance to medication (p=0.052), and miscellaneous (p=0.028).

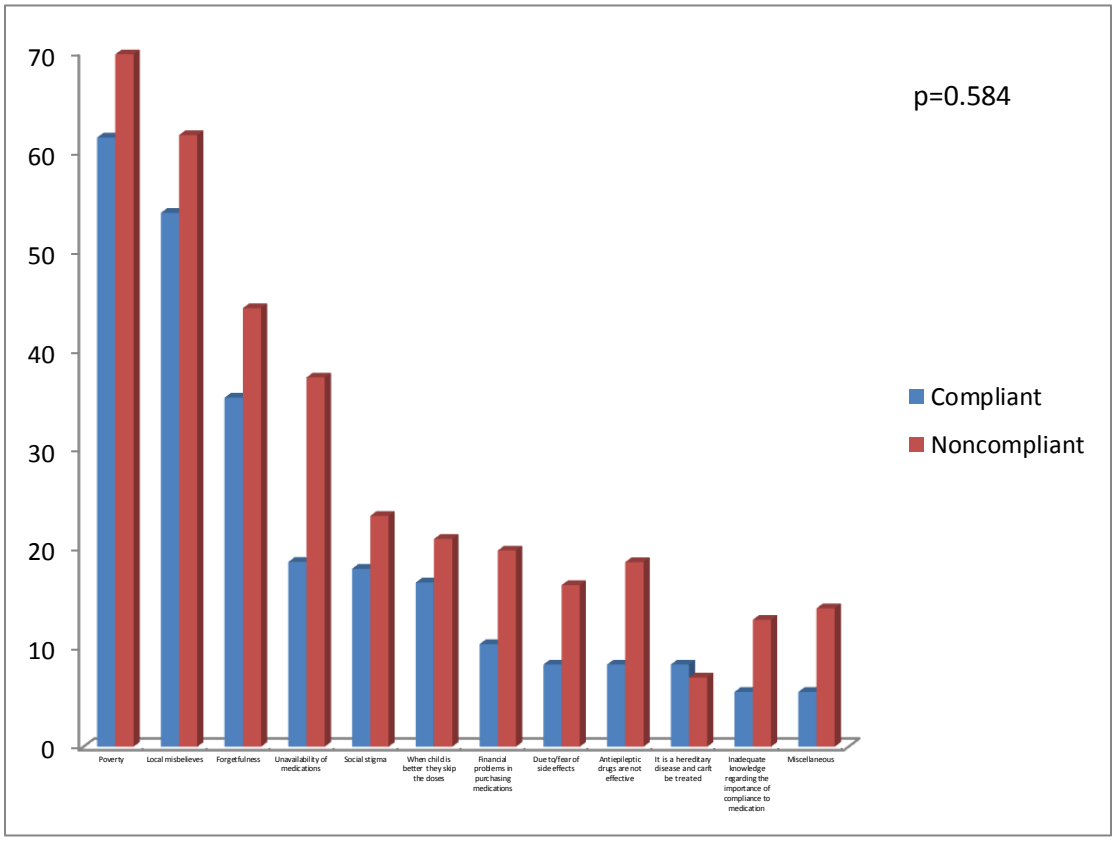

Fig 9: **Bar diagram showing barriers to compliance with antiepileptic medications**

DISCUSSION

Epilepsy is an episodic illness, which requires continuous treatment for good outcome. In Indian context, different surveys have shown that more than 70% of patients with epilepsy are not getting any forms of treatment or they have not consulted with doctors for their epilepsy problem.

Antiepileptic medications are the mainstay of treatment for majority of the patients with epilepsy. Failure to follow prescribed drug regimen (i.e. noncompliance) is known to be wide spread among patients with epilepsy and is associated with poor epilepsy control.

Therefore, present study was done to identify the factors affecting compliance and non compliance to antiepileptic medications among epileptic patients based on the objectives.

Data for the present study was collected from 231 epileptic patients/parents using a structured interview schedule.

Adherence to antiepileptic drugs in patients with epilepsy generally ranges from 20 %to 80% as reported by French J et al, Hargrave R et al, Leppik IE et al, Buck D et al and Lannon SL et al.[2,3,9,14]

In the present study, prevalence of noncompliance as reported by epileptic patients/parents was 37.23%, which is consistent with other researcher's findings. Hovinga CA et al (2008) found, 29% of the epileptic patients being noncompliant with antiepileptic medications.[98] Enrique Caceres et al (2006) reported prevalence of noncompliance among epileptic patients to be comparatively high i.e. 67.2%.[99] Non-adherence was found in 59 % of the epileptic patients as reported by Jones RM et al (2006).[52] Thus, it is imperative to place a high priority on the development of techniques, which minimize this problem.

More than half of the patients were males both in compliant group (61.38%) and non compliant group (66.28%). Females were only 38.62% in compliant group and 33.72% in the non compliant group. This is different from the existing literature which shows male to female ratio of 1-1.5:1.[2,52,103]

Education of parents was not significantly associated with compliance in present study. On contrary to present study, Burger S et al (2005) found that higher the educational qualification, better is the compliance with drugs.[100] As most of the people believe in alternative treatment modalities, that may be the reason, educational background did not affect compliance.

Family history of epilepsy can be influential factor for compliance. Asadi Pooya et al (2005) discovered that patients with positive family history of epilepsy were more noncompliant with medications.[110] Though in present study, there was no significant relationship between compliance and positive family history of epilepsy, they were more likely to comply; this reflects the possibility that patients with family history of epilepsy are aware of importance of compliance.

Fenton in Kendell and Zealley (1993: 345) maintain that the onset of epilepsy occurs before the age of five years in approximately a quarter and before school-leaving age in more than half of the cases.[92] Thiele (1999: 672) quotes Lennox et al who maintain that 30% of the seizures have their onset between birth and 4 years of age.[93] In our study more than half of the patients both in compliant (55.17 % + 33.79%) and non compliant group (53.49 % + 31.40%) had effect of epilepsy at the age of 5-15 years followed by the age of less than 5 years both in compliant (11.03%) & noncompliant group (15.12%).

In the present study, gender and age of onset of illness are the factors which are found to be not influencing compliance, which is consistent with the findings of Das K et al (2007) and Wendy G et al (2000).[103,104]

Generalized seizures accounted for the majority of our cases (66.6%). In a study by Shankar PS et al (65.6%), Sureka RK et al (84%) and Dhanaraj M et al (66.5%) generalized seizures were the most common type of seizures, which is consistent with our study.[94-96] As generalized seizures are socially embarrassing they are well motivated to be compliant to their antiepileptic drug regimen.

In contrary to expectations as per the findings of Wendy G et al (2000), who found that seizure frequency does not contribute to treatment adherence, in present study, patient with poorly controlled (having seizure atleast once or more in a month) and well controlled epilepsy (having seizure after 3 yrs) are less compliant with medication than those with satisfactorily controlled epilepsy (having seizures after one month but with in 3 yrs). This could be because, patients with poorly controlled epilepsy think their disease is incurable and taking medication is of no use. This is consistent with the findings of Jones RM et al (2006), who found negative correlation between adherence and frequency of seizures.[52] While patients with well controlled epilepsy are more casual about the disease and less compliant which is consistent with findings of Lusic I et al (2005), who found that more thoroughly controlled epileptic condition had a tendency towards low compliance. [105]

Type of drug therapy (monotherapy / polytherapy) had no impact on compliance in the present study. This is inconsistent with findings of Buck D et al (2005), who reported polytherapy is associated with poor compliance. Findings in the present study could be because patients with intractable epilepsy are called more frequently and are usually treated with polytherapy. Inspite of this, most of them have poor response to treatment. Hence, type of drug therapy may not have influenced their compliance with medication.[106]

In the present study, drug frequency, type of drug therapy and their side effects were not significantly associated with compliance, which is not consistent with Buck D et al (1997), who concluded that poor compliance is associated with more complex drug regimen.[2] Buck D et al and Liu WJ (2004) et al, who reported

more the side effects of drugs, poorer is the compliance.[106,107] This could be because majority of patients in present study were getting monotherapy that is usually associated with mild side effects, which do not interfere with psychosocial functioning of individual.

Accessibility to medical store was not found to be significantly different between two groups (p=0.74) and this is inconsistent with findings of Meinardi H et al (2001), who found that long distance to health care facilities associated with treatment discontinuation.[101]

Majority of patients in both the compliant group and non compliant group reported: non availability / difficulty in getting medications as the most common barrier to compliance with antiepileptic drugs. This finding is consistent with findings of Das K et al (2007), who found epileptic patients miss the doses due to non availability of medications locally.[103]

Financial problem in purchasing the medication was reported as a significant barrier to compliance by 19.77% of noncompliant patients. This may be due to the fact that majority (67.52%) of those who had financial constraints as major barrier to compliance, were in low expenditure group (≤200 rupees/month). Hence, despite of low cost of medications they could not afford. These findings of the study are inconsistent with other researchers findings, i.e. Asawavichienjinda et al (2003) and Das K et al (2007).[102,103]

With reference to the effect of antiepileptic drugs, patients in both the groups i.e 8.28% in compliant group and 18.6% in noncompliant group are of opinion that antiepileptic drugs are not effective in control of seizures and this is significant (p=0.02). This is consistent with the findings of Buelow JM et al (2004).[108] So it can be argued that compliance with medications depends not only on understanding and following doctor's orders but also on how they fit into patient's life (perception of disease and treatment effectiveness), as found by Buck D et al (1997), that

satisfaction with the amount of information given by general physician or clinic doctor had no effect on the likelihood of missing antiepileptic drugs.[2]

Barriers to compliance in most of the patients are **poverty**, **local misbelieves** and **forgetfulness**. **Unavailability of medications**, **financial problems in purchasing the medications**, **antiepileptic drugs are not effective**, **inadequate knowledge regarding the importance of compliance to medication** are the barriers to compliance with significance. These findings are consistent with the findings of study done by Buelow JM et al (2004) in which they have indentified that financial issues and forgetfulness as reasons for noncompliance.[108] Das k et al (2007), Caroline K. Mbuba et al (2008) also reported the most frequently cited reasons for noncompliance were simply forgetting, followed by financial constraints, being busy with other things.[103,109]

CONCLUSION

- About two third of the patients with epilepsy are compliant with the medications.
- Epileptic patients are predominantly males (male to female ratio is 1.7:1).
- Education of parent, age of onset, type of drug therapy (monotherapy/ polytherapy) and side effects did not play any role in compliance which is in contrast to other studies.
- Patients with generalized seizures are more compliant with the medications than those with simple and complex partial seizures.
- Patients with adequately controlled seizures are more compliant with the medications.
- Patients are more compliant with the antiepileptic medications if they have good availability of medications.

Main reasons for noncompliance are:

- Poverty and local misbelieves.
- Forgetfulness to purchase the medications in time.
- Unavailability of medications.
- Financial problems in purchasing the medications.
- Antiepileptic drugs are not effective.
- Inadequate knowledge regarding the importance of compliance to medication.

Modifying the parents perception about the disease and treatment effectiveness plays a key role in determining compliance to the drug. Non modifiable factors at individual level like poverty and non availability of drug require changes in govt policies for achieving better compliance.

LIMITATIONS

- Main drawback of this study is the methodology being cross sectional study where further randomized controlled study is required for conclusion.
- Self-report method is used in the study, so there is more of subjectivity, which is not supported by any objective measure of compliance.

RECOMMENDATIONS

- Interventional studies such as monitoring the drug levels can be conducted.

SUMMARY

This study is conducted in the Pediatric dept, R.L.Jalappa Hospital and Research Centre, attached to Sri Devaraj Urs Medical College (SDUMC), Kolar, to study the compliance to anticonvulsant therapy among rural children with epilepsy:

1. Compliance with medication is higher (63%) in comparison to the noncompliance (37%).
2. Prevalence of epilepsy is higher in male (77%) as compared to female (23%). Male to female ratio is 1.7:1.
3. Parental characteristics like level of education, type of family, financial status, and family history of epilepsy have lesser role on compliance.
4. Type of seizure ($p=0.051$) and frequency of seizures (0.048) is statistically significant, while age of onset of epilepsy do not have any statistical significance.
5. Type of therapy (monotherapy or polytherapy), frequency of drug administration (OD/BD/TID), and side effects of drugs did not have statistical significance.
6. The study shows availability of the drug in medical store has statistical significance ($p=0.010$), while accessibility to the medical store and monthly expenditure on drugs did not have statistical significance.
7. Commonest drug prescribed in compliant group was sodium valproate, while in noncompliant group was phenytoin.
8. Poverty, local misbelieves & forgetfulness was the barriers in most of the patients.
9. Unavailability of medications, financial problems, antiepileptic drugs are not effective and inadequate knowledge regarding the importance of compliance to medication regularly are the barriers with significant statistical correlation ($p<0.05$).

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Questionnaire

Hospital number ----------

1. Name ----------

2. Age ----------

3. Sex ----------

4. Informant:
   - ❑ A parent
   - ❑ A caregiver

5. Occupation of the father ----------

6. Fathers education level:
   - ❑ Have no education
   - ❑ Not completed high school
   - ❑ High School
   - ❑ PUC
   - ❑ Graduate
   - ❑ Post Graduate
   - ❑ Other---------- (specify)

7. Number of family members ----------

8. Number of children in the family ----------

9. Per capita income ----------

10. Please mention the age when your child started to suffer from epilepsy ----------

11. What are the types of seizures?
    - ❑ Generalized tonic-clonic seizures
    - ❑ Simple partial seizures
    - ❑ Complex partial seizures
    - ❑ Atonic seizures
    - ❑ Absence seizures

12. To whom/where did you go first for help and advice after the first episode of epilepsy (seizure) in your child?
    - ❑ A general practitioner
    - ❑ A pediatrician
    - ❑ A neurologist
    - ❑ A psychiatrist
    - ❑ A quack
    - ❑ Other---------- (specify)

13. Is the EEG suggestive of epilepsy?
    - ❑ Yes
    - ❑ No

14. Please mention the name of the anticonvulsant drugs that your child is prescribed?

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15. Does your child receive the prescribed treatment for his/her epilepsy regularly?
    - ❑ Yes
    - ❑ No

16. If not, what are the reasons of not receiving the prescribed treatment regularly?
    - ❑**Socioeconomic-related factors**
        - □ Poverty
        - □ Illiteracy
        - □ High cost of medication
        - □ Local beliefs
    - ❑**Health care team/health system-related factors**
        - □ Lack of availability of drug
        - □ Lack of education about AEDs
    - ❑**Condition-related factors**
        - □ Forgetfulness
        - □ Duration
        - □ Previous treatment failures
    - ❑**Therapy-related factors**
        - □ Complex treatment regimens
        - □ Adverse effects of treatment
    - ❑**Other** ---------- (specify)

17. Does your child receive the prescribed dosage for his/her epilepsy regularly?
    - ❑ Yes
    - ❑ No

18. Are there any side-effects due to anticonvulsant therapy?
    - ❑ Yes
    - ❑ No

19. If yes, what are they?

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20. Is there any role of primary health workers in compliance?
    - ❑ Yes
    - ❑ No