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# Evaluation of Antiepileptic Drug Use in A Tertiary Care Hospital

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## Abstract

**Background and Purpose:** The objective of this study was to evaluate the prescribing trends and the cost analysis (Fiscal impact analysis) of antiepileptic drugs (AEDs) at a tertiary care hospital.

**Material and Methods:** A retrospective data of 70 patients selected randomly, who were prescribed AEDs during July 2014 to Jan 2015 was gathered. It includes the AEDs prescribed to the patients in outpatient and inpatient. Patients were assessed for the prescribing indication, doses depending upon co-morbidities, duration of therapy, drug interactions, cost analysis, blood level monitoring and toxicity symptoms. Guidelines stated in the ACCP updates in therapeutics 2015 and NICE guidelines were followed as reference to conduct this study. Prescription evaluation for appropriateness of AED use was carried out by the staff clinical pharmacist and reviewed by senior clinical pharmacist.

**Results and Discussion:** Out of 70 patients 33(47.1%) were prescribed multiple AEDs; with 19(57.5%) patients prescribed unnecessarily. In these 19 patients, 6(18.1%) received triple regimen and 13(39.39) received double regimen. While out of 70 patients, 29(41.4%) were prescribed with irrational AED therapy on the basis of inappropriate dose, duration and indication and monitoring parameters. Total cost spent on irrational prescribing was PKR 393,162 approximately. Inappropriate use of AEDs leads to unnecessary drug exposure, risk of toxicities and wastage of cost.

**Keywords:** Antiepileptic drugs (AEDs); Central nervous system (CNS); Gamma amino butyric acid (GABA); Gabapentine (GBP); Carbamazepine (CBZ); Therapeutic drug monitoring (TDM)

## Introduction

Non-pharmacological options for management of epileptic or nonepileptic seizures are limited; hence AEDs are the mainstay of therapy. The goal of AED therapy is complete resolution of seizures, with minimal adverse effects and improvement in patient's quality of life [1]. AEDs are prescribed for the treatment of multiple types of seizures which may be due to reasons like tumors (gliomas), central nervous system (CNS) diseases (parkinsonism, epilepsy), psychiatric disorders (bipolar disorders, anxiety, social phobia, post-traumatic stress disorders, schizophrenia), alcohol abuse and withdrawal, infection (meningitis, encephalopathy, sepsis), electrolyte imbalance (hypo or hypercalcemia, hypo or hypernatremia), drug related (carbapenems, tramadol, vincristine, topiramate, drugs given through intrathecal route, floroquinolones). Drugs are chosen on the basis of efficacy, tolerability, interactions and adverse effect profile [2].

Most of the people respond very well to the mono-therapy but a small number of patients do require combination of AEDs. Addition of the second drug, rather than substitution may be a rational decision in some patients, particularly those who respond and tolerate the first drug quiet well. Accurate classification of seizure type, as well as the epilepsy syndrome with careful observation of seizure type and adverse effects is essential in effective and rationale AED therapy. The primary goal of therapy should be complete seizure freedom without any adverse effects with mono-therapy prescribed once or twice daily. If therapy is responding partially, the maximum tolerated dose of the drug should be explored on individual basis, while keeping strict eye to avoid any resulting adverse effect. In refractory patients the exact diagnosis of epilepsy and treatment compliance should be reviewed. Drugs used in combination should be selected carefully as poor adherence by patients; drug-drug interactions and toxicity are the major disadvantages of combination therapy [1].

Mono-therapy is the pharmacologic practice and strongly recommended while initiating AED therapy. However, it has been observed that despite good clinical response to single agents, 50% of the patients are prescribed with multiple drug therapy [3]. There are a number of classes of antiepileptic drugs (AEDs) with multiple mechanisms. The main classes include sodium channel blockers (phenytoin, carbamazepine (CBZ), oxcarbamazepine, zonisamide, lamotrigine), calcium channel inhibitors (Ethosuximide), gamma amino butyric acid (GABA) enhancers (benzodiazepines, barbiturates, tiagabine, vigabatrine, gabapentine (GBP), glutamate blockers (felbamate, topiramate), carbonic anhydrase inhibitors (acetazolamide), hormonal agents (progesterone), some newer agents with partially known mechanism of action (levetiracetam) [2].

CBZ, lamotrigine, levetiracetam, oxcarbazepine, topiramate and valproic acid are the drugs of first choice for focal and generalized tonic-clonic seizures. Phenytoin, phenobarbital and GBP are second choice. Ethosuximide and valproic acid are the drugs of first choice for absence seizures. Diazepam, lorazepam & phenytoin are the drugs of first choice for status-epilepticus with divalproate being the second choice. For infantile spasm adrenocorticotropic hormone (ACTH) and corticotropin, prednisolone and valproic acid are the drugs of first choice. For lennoxGastaut syndrome clobazam, clonazepam, lamotrigine and rufinamide are the drug of first choice [3].

Epilepsy is very common among patients with brain tumors. Multiple factors affect the mechanism of action of seizures in these patients; tumor size, location and genetic changes. There are no recommendations for the prophylactic use of AEDs [4]. However in symptomatic patients, lamotrigine, valproic acid and topiramate are the drugs of first choice; if insufficient then levetiracetam or GBP can be added. Evidence recommends starting with valproic acid and adding levetiracetam sequentially depending upon the need of the patient. Anti-epileptic drug therapy should be selected on the basis of side effect profile in particular patients [5,6].

AEDs should be used carefully due to potential for causing significant interactions (pharmacokinetic and pharmacodynamics) and side effects. This is particularly important for the patients taking medications like anti-retroviral, anti-coagulants, anti-tuberculosis, antifungals, and other AEDs. Hepatic metabolism is most common reason for pharmacokinetic interactions, and enzyme inducing drugs i-e phenytoin, phenobarbitone and carbamazepine will enhance the metabolism of all the substrates of these enzymes [7].

In patients receiving AEDs, therapeutic drug monitoring (TDM) is very useful tool in terms of therapeutic efficacy, toxicity and respective dose adjustments. Most commonly used AEDs i-e CBZ, phenytoin, and valproic acid exhibit very complex pharmacokinetics in terms of their serum drug concentrations depending upon serum albumin level and other pharmacokinetic alterations among various individuals.

Some other drugs like phenobarbitone also exhibit altered pharmacokinetics so therapeutic drug monitoring (TDM) of these drugs should be done periodically for optimal clinical outcome [8].

Among newer agents (felbamate, GBP, levetiracetam, oxcarbazepine, vigabatrin, tiagabine, topiramate, lamotrigine, and zonisamide) TDM is not usually recommended but further research is going on to evaluate the need.

Concomitant hepatic or renal impairment and other co-morbidities should be considered while deciding the dosage regimen of AEDs for a particular patient [9].

Over the past 20 years many new AEDs are registered for clinical use. As compared to the older agents newer ones exhibit simpler pharmacokinetics in terms of renal excretion and less potential for causing significant interactions. These newer agents are proved to be better tolerated among patients as compared to the older ones. Currently the main use of these newer agents is as an add-on therapy for those patients who are refractory to the older or other conventional agents i-e CBZ or valproate. Recommendation for use of these drugs is based on the risk vs. benefit ratio in terms of their potential advantage of tolerability, ease and drawback of their higher cost [10] .

Poly-therapy of AEDs is efficacious and studied well in appropriate conditions. Particularly combining a Na+ channel blockers with GABAergic (gamma amino butyric acid) antagonist is known to be therapeutically more beneficial. Combination of two GABA mimetic drugs or combination of an α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA) antagonist with an N-methyl-D-aspartate receptor (NMDA) antagonist may also improve therapeutic effect. Two Na+ channel blockers given in combination have no proven benefit. In patients with no known seizures, empirical AED use is to be studied [11].

A dramatic increase in antiepileptic (AED) therapy began in 1990s after the licensing of 9 new chemicals with the expectations of many more to come. It was becoming a challenge to determine the benefits and risks among multiple AEDs, based on daily clinical practice. Keeping this in view, the star systems have been developed as evidence based yet pragmatic and flexible models for comparing AEDs. Each drug has been assessed and allocated a score across a wide range of criteria which includes mechanism of action, pharmacokinetics, efficacy, tolerability, safety, drug interaction profile, compliance and a comfort factor. A complete treatment plan should be devised before starting treatment with the aim of preventing the development of refractory epilepsy. This may result in attaining maximal remission and may help many more people achieving a fulfilling life [12].

## Material and Methods

A retrospective cross-sectional study was conducted at a tertiary care hospital. AED's use was assessed for accuracy of indication; duration of use, co-morbidities, drug interactions, cost analysis, adverse drug effects and toxicity data was collected from Jul 2014 to Jan 2015. 70 Patients were selected through randomization process. Guidelines stated in the ACCP updates in therapeutics 2015 and NICE guidelines were followed as reference guidelines to conduct this study. Prescription evaluation for appropriateness of AED use was carried out by the staff clinical pharmacist and reviewed by senior clinical pharmacist.

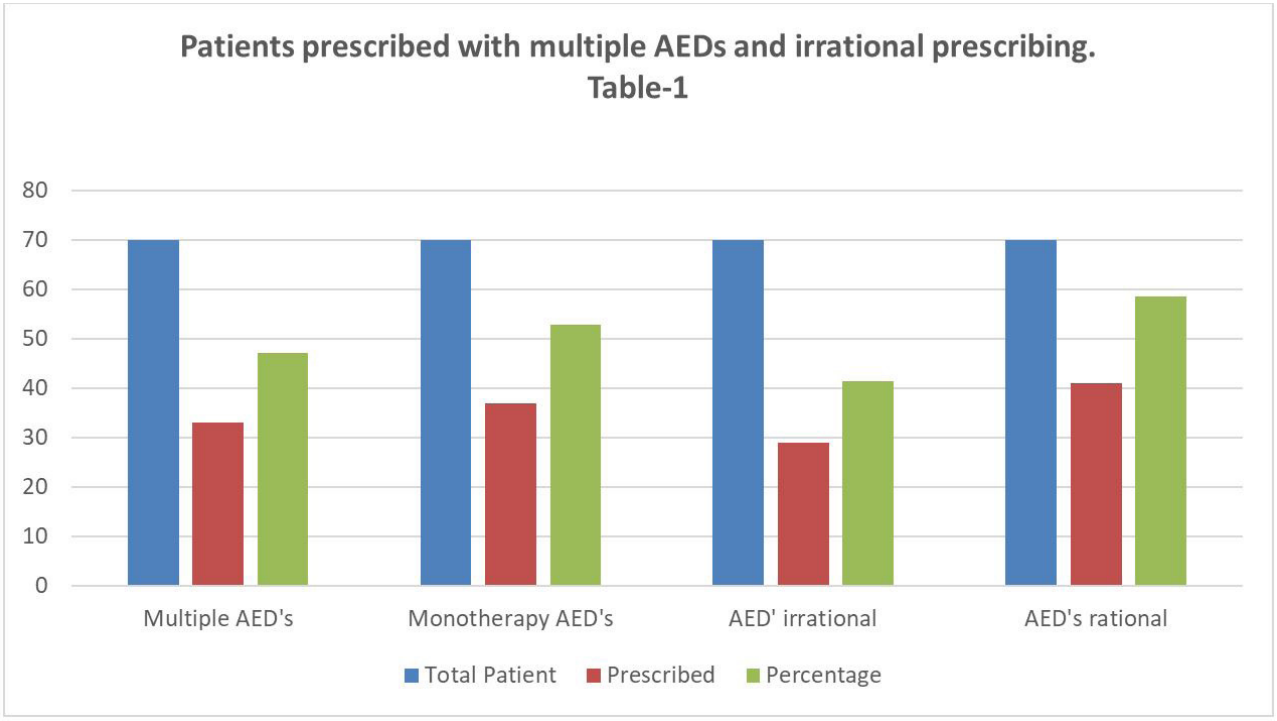
## Results & Discussion

Two major parameters to be determined in this study were prescribing multiple AEDs and irrational prescribing on the basis of prescribing indication, dose, duration, frequency, TDM and recommended labs for long term use. Among these two generalized parameters 33(47.1%) cases out of 70 were prescribed with multiple AEDs while 29(41.4%) out of 70 patients were prescribed AEDs irrationally on the basis of above indicators. (Table 1)

Among total of 33(47.1%) out of 70 cases who were prescribed with multiple AEDs, 19 (57.57%) were prescribed unnecessarily

| **Total no of patients** | **70** | | |
|---|---|---|---|
| Patients prescribed with multiple AEDs | 33 (47.1%) | Patients prescribed with monotherapy AEDs | 37 (52.85%) |
| Patients prescribed with AEDs irrationally | 29 (41.4%) | Patients prescribed with AEDs rationally | 41 (58.57%) |

**Table 1**: Patients prescribed with multiple AEDs and irrational prescribing

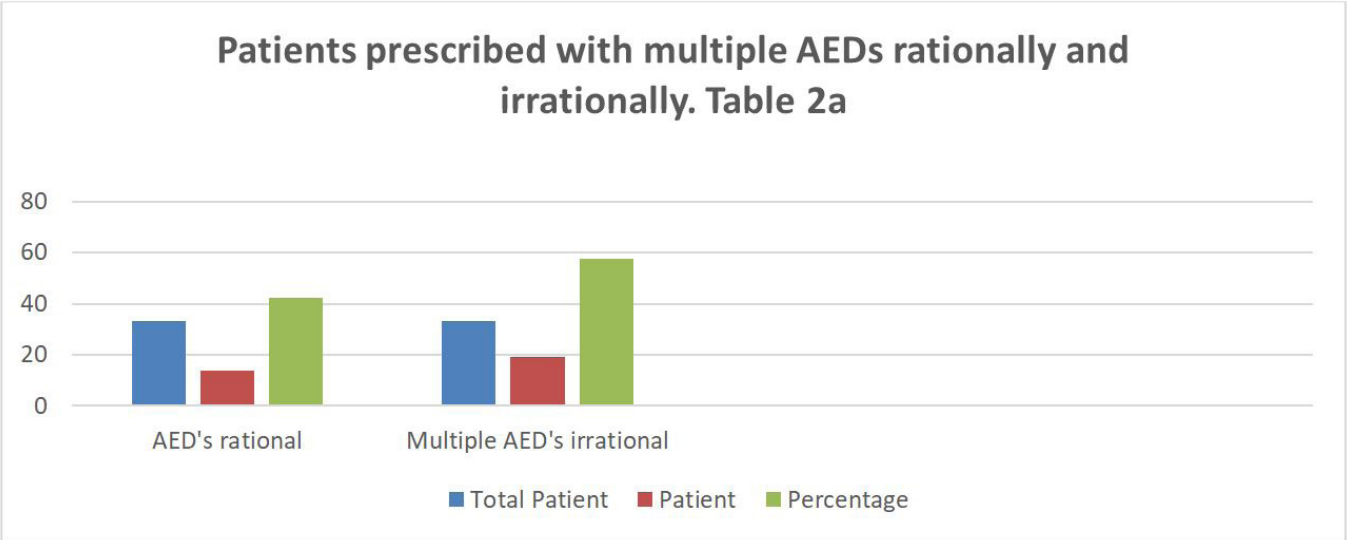



while 14 (42.42%) were prescribed rationally (Table 2a) Among the total of 19 (57.57%) patients out of 33, receiving irrational multiple AED therapy, 13(68.42%) received dual therapy (2 drugs) while 6 (31.57) patients received triple therapy (3 Drugs) and no patient was prescribed quadruple therapy (4 Drugs). Among 14 (42.42%) patients out of 33, who were prescribed with rational therapy 6 (42.85%) were prescribed with dual therapy (2 Drugs), 7 (50.00%) with triple therapy (3 drugs) and only 1(7.14%) was prescribed with quadruple therapy (4 Drugs). (Table-2b)

The details of quality indicators for second general parameter i-e irrational prescribing 29(41.4%) is here under: Among these 29 patients, 12(41.37%) patients were prescribed prophylactic

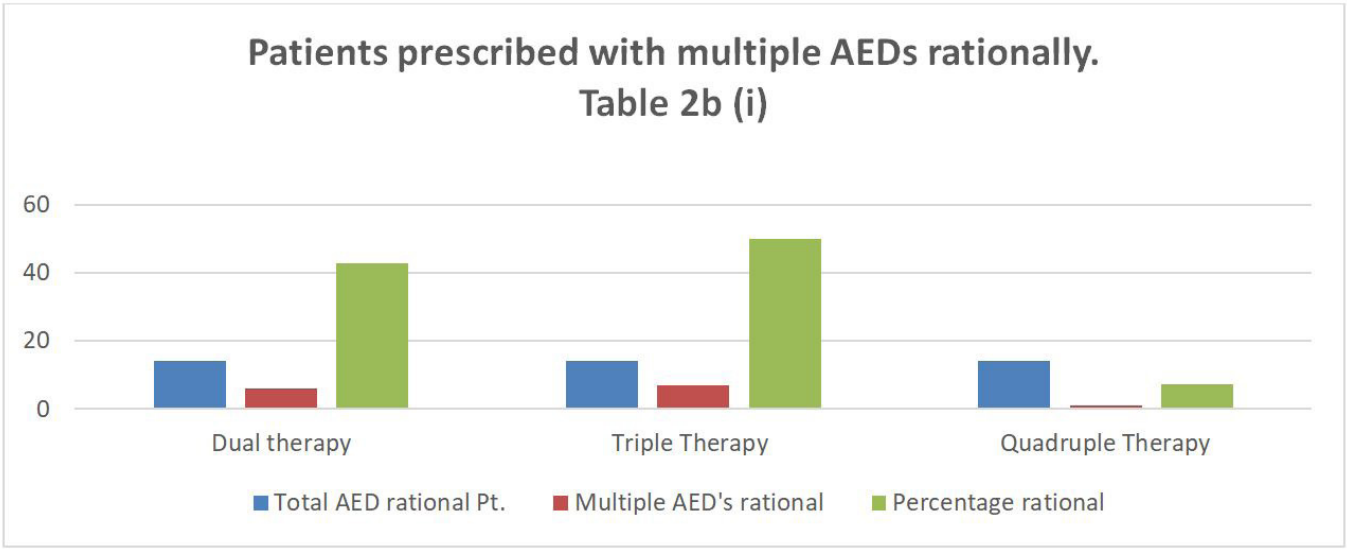
| **Patients prescribed with multiple AEDs** | **33** |
|---|---|
| Patients prescribed with multiple AEDs rationally | 14 (42.42%) |
| Patients prescribed with multiple AEDs irrationally | 19 (57.57%) |

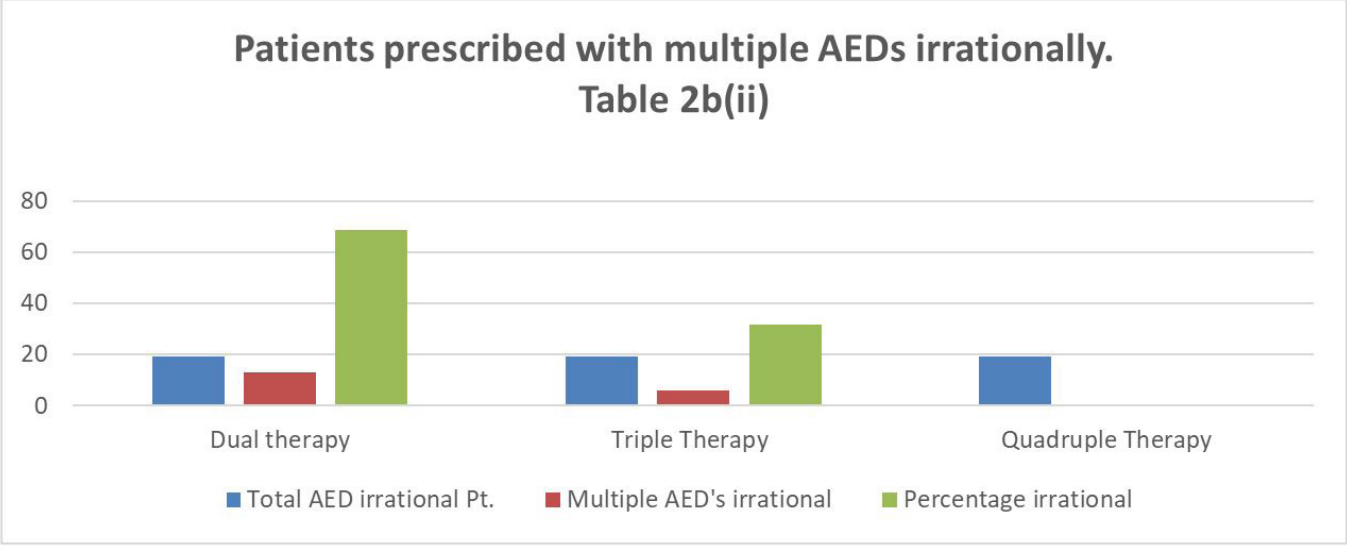
**Table 2a:** Patients prescribed with multiple AEDs rationally and irrationally



| | Number of patients prescribed with multiple AEDs rationally | Total no of patients prescribed with multiple AEDs irrationally |
|---|---|---|
| Dual therapy (2 Drugs) | 6 (42.85%) | 13(68.42%) |
| Triple therapy (3 Drugs) | 7 (50.00%) | 6 (31.57) |
| Quadruple therapy (4 Drugs) | 1(7.14%) | 0 |

**Table 2b:** Extent of therapeutic duplication prescribed rationally and irrationally




AEDs, 8(27.58%) were prescribed with dual / triple regimen (therapeutic duplication) without performing TDM, 3(10.34%) received inappropriate dose of AEDs including 2 sub-therapeutic and 1 toxic blood levels, 1(3.44%) received AEDs with inappropriate duration.

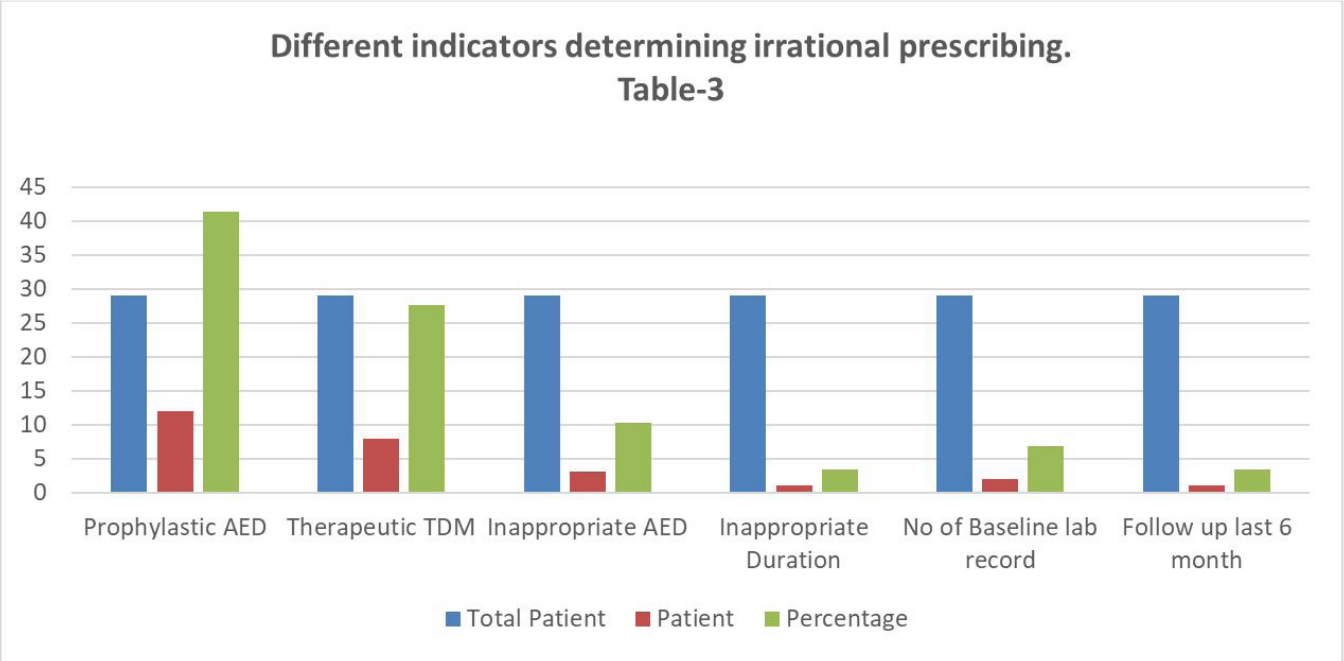
21(72.41%) patients among 29 were prescribed AEDs including divalproic acid, CBZ and phenytoin without base line liver function tests (LFTs) done, while 1 (3.44%) patient had missing LFTs for the last 6 months. (Table-3)

According to a study conducted on Psychotropic Medication Patterns among Youth in Foster Care at a south western state of US in 2008, 41.3% of patients were prescribed with ≥ 3 different classes of these drugs, 15.9% were prescribed with ≥ 4 different classes of drugs. The most frequent class of drugs was antidepressants 56.8%, attention deficit hyperactivity disorder (ADHD) drugs 55.9% and antipsychotic agents 53.2%. The use of ≥ 2 drugs from the same class of psychotropic drugs were 22.2% [13].

| Patients prescribed with AEDs irrationally | 29 |
|---|---|
| a- Prophylactic AEDs | 12(41.37%) |
| b- Therapeutic duplication without performing TDM | 8(27.58%) |
| c- Inappropriate dose of AEDs | 3(10.34%) |
| d- Inappropriate duration | 1(3.44%) |
| e- No Baseline lab record | 21(72.41%) |
| f- Follow up labs missing for last 6 months | 1 (3.44%) |

**Table 3:** Different indicators determining irrational prescribing

Total expense spent on irrational prescribing of AEDs in this study was, Rs. 393,162




Use of inappropriate AEDs is increasingly identified as a major cause in the aggravation of idiopathic generalized epilepsy (IGE). In this study all patients with idiopathic generalized epilepsy (IGE) taking at least one aggravating AED were evaluated over 8 years retrospectively for the development of video electroencephalogram (EEG) documented status epilepticus (SE) and their long-term clinical outcome was favorable after appropriate adjustment of the patients' medications. All patients were treated with CBZ and had experienced aggravation of seizures or development of new seizures before referral. 7 patients had poly-therapy with phenytoin, vigabatrin or gabapentin (GBP). Important precipitating factors were dose increment of CBZ or phenytoin, initiation of CBZ, GBP, vigabatrin and decrease of phenobarbital. Discontinuation of the aggravating factor and dosage adjustment accordingly resulted in complete seizure control. This study showed that aggravation of seizures in IGE pharmacodynamically may result in atypical myoclonic status epilepticus (MSE) or typical absence status epilepticus (ASE) [14].

According to a study conducted to evaluate the potential of prescribing inappropriate AEDs for elderly patients with epilepsy, newly diagnosed patients were less likely to be given phenobarbital monotherapy and combination therapy and more likely to be given GBP or lamotrigine monotherapy. Statistics of this study showed that patients with more severe disease were less likely to be given phenobarbital monotherapy than other monotherapy and phenobarbital combinations than other combinations. The patients who were given AED after specialty consultation were less likely to be given phenytoin monotherapy than AED monotherapy which is consistent with the standard recommendations [15].

There is a lack of evidence for the benefit of using prophylactic AEDs in Glioma patients. Prophylactic uses of AEDs result in discomfort, increased cost of therapy and unnecessary side effects on the part of patients. Most commonly occurring side effects due to typical anticonvulsants are cognitive impairment, myelosuppresion, liver dysfunction and dermatologic reactions.

Particular side effects in glioma patients include induction of cytochrome P 450 (CYP450) enzyme system resulting in accelerated metabolism of various chemotherapeutic drugs i-e paclitaxel, cyclophosphamide, irinotecan, methotrexate etc. which has resulted in one of the major problems in clinical outcome. The immunosuppressive effect of anticonvulsants is again a major risk factor in already immune-compromised glioma patients [16].

AEDs cause overall changes in the excitation level and leads to cognitive and behavioral defects. Side effect profile depends upon the drug used, dosages, frequency, age of patients and comorbidities. Some general side effects are insomnia, depression, dizziness [17].

Inappropriate use of AEDs leads to unnecessary drug exposure, risk of toxicities and loss of monetary resource. It is recommended to adopt guideline based anti-epileptic therapy to ensure optimal therapeutic outcome with minimal harm and fiscal loss.

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