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Adverse Reactions Caused by Antiepileptic Medications in Real-World Medical Settings

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Epilepsy is a relatively common condition characterized by a tendency for recurrent seizures, which is due to the disturbance of spread of electrical discharge of the cortical neurons. Up to 80% of people with epilepsy are able to control their condition with anti epileptic drugs (AEDs). The growing number of newly approved drugs for various illnesses coupled with the complex treatment options have contributed to the increased risk of adverse drug reactions (ADRs). AEDs have a narrow therapeutic index with wide spectrum of ADRs. 10-30% of epileptic patients discontinue their initially prescribed AEDs due to ADRs. These ADRs can be the cause of non-adherence and subjective distress. The newer generation AEDs have reduced adverse events, fewer drug interactions if any and thus improved safety. Comparison of adverse effects in patients taking AEDs with adverse events in control groups is helpful; however, data from controlled studies are often lacking for most AEDs. Because of these limitations, the clinician must adopt a preventative and early detection approach based on some general principles. This review outlines various adverse reactions related to the use of Anti-epileptic drugs.

Keywords: adverse reactions, antiepileptic drugs, carbamazepine, phenytoin

Introduction

Epilepsy is a relatively common condition characterized by a tendency for recurrent seizures, which is due to the disturbance of spread of electrical discharge of the cortical neurons. UP to 80% of people with epilepsy are able to control their condition with antiepileptic drugs (AEDs). The type of drug therapy prescribed depends on the type of seizure, the underlying cause of the epilepsy, age of the patient and possible side effects. Treatment usually starts with one drug at a low dose. The dose is then increased slowly. In most patients, epilepsy remits over a period of years and drug therapy may be withdrawn slowly [1].

The mainstay of treatment of epilepsy is antiepileptic drugs often for a long duration. The primary goals of treatment of epilepsy include complete seizure remission, improvement in the quality of life (QoL), and do no harm, i.e., to avoid, minimize and amend any adverse effects that might occur as a result of treatment with AEDs. Adverse effects of remain a major cause of morbidity and sometimes mortality in the course of treatment of epilepsy and hence considerably impact the QoL of people with epilepsy, perhaps as much as the seizure burden [2]. The choice of most appropriate antiepileptic drug depends on classification of seizures and age of patient [3, 4]. Seizure control may be achieved by monothearpy in about 80% of the patients, with the other 20% requiring two to three AEDs [5]. Monotherapy is normally the first line of treatment, as it has less drug interactions and side effects; lower cost, better tolerability, medication adherence, and quality of life. When choosing an AED, factors such as mechanism of action, ease of dosing, efficacy, long term adverse

effects, neuropsychiatric profile, sedative burden, interaction with other medications, seizure types and other co-morbid conditions should be considered [6, 7]. The growing number of newly approved drugs for various illnesses, coupled with the complex treatment options, have contributed to the increased risk of adverse drug reactions (ADRs) [8] with antiepileptic drugs being no exception. Therefore, comprehensive ADR surveillance program is necessary to detect, evaluate and develop mechanisms to prevent ADRs and the associated morbidity, mortality and increased costs [9]. While effective pharmacological treatment of epilepsy is important, it is equally important to consider whether possible adverse events will outweigh benefits to patients [10].

A large number of drugs are currently available for the treatment of epilepsy. Older/conventional drugs like phenytoin, carbamazepine, valproic acid and ethosuximide are commonly used as first line drugs. They are relatively less expensive than the newer antiepileptics. Drugs like gabapentin, lamotrigine, vigabatrin, topiramate, tiagabine and zonisamide are the newer ones and currently used as add-on or alternative therapy. They have lesser adverse effects and have few, if any, drug interactions [11, 12]. Some side effects may be common with the above-mentioned drugs and include sedation and ataxia. They can be diverse as well, ranging from idiosyncratic reactions like bone marrow depression (carbamazepine) to acute myopia and glaucoma (topiramate). Monotherapy is the usual dictum, but polytherapy is needed for patients with multiple seizure types or refractory disease [13-15].

Although adverse effects have been recorded since the dawn of antiepileptic drug treatment, only in recent years has substantial effort been made to define, quantify, and address their clinical relevance. In 1985, the Veterans Administration Cooperative I trial compared the effective ness of carbamazepine, phenobarbital, phenytoin, and primidone. ”The outcome of this project underscores the unsatisfactory status of AED therapy with medications currently available. Most patients whose epilepsy is reasonably controlled must tolerate some side effects. These observations emphasize the need for new AEDs and other approaches to treatment [16]”.

AEDs have a narrow therapeutic index with wide spectrum of ADRs. 10-30% of epileptic patients discontinue their initially prescribed AEDs due to ADRs [17]. These ADRs can be the cause of non-adherence and subjective distress. The newer generation AEDs have reduced adverse events, fewer drug interactions if any and thus improved safety [18]. Growing public concern over drug safety has stressed the importance of pharmacovigilance, especially in India where ADRs contribute to significant economic burden [19]. There is growing concern among the healthcare personnel to assess ADRs that has an impact on long term adherence so as to achieve better therapeutic outcome [20]. Pharmacovigilance, the science and activities related to the detection, assessment, understanding and prevention of adverse effects or any drug related problem, is highly essential in India, where there is lack of adequate safety related data for drugs [21].

Definitions and measurements of adverse effects have been inconsistent and, consequently, the methods by which adverse effects are defined and detected are changing. The growing list of new AEDs has also increased the need to compare AED risks. Although the dose-related adverse effects of new AEDs seem to be less, the new AEDs have introduced new adverse effects that require added vigilance during the chronic use. Adverse effects have also become major factors in the overall cost of epilepsy treatment. For all of these reasons, it has been difficult for the physician caring for patients with epilepsy to use adverse effects to help in the choice of an AED [22].

Class	Description	Drugs
Type I	Block sustained high frequency repetitive firing by enhancing sodium channel inactivation.	PhenytoinCarbamazepineOxcarbazepine LamotrigineFelbamate[a]
Type II	Multiple actions: enhance GABAergic inhibition, reduce T-calcium currents, and possibly block Sustained high frequency repetitive firing.	Valproic acidBenzodiazepinesPhenobarbitalPrimidone
Type III	Block T-calcium currents only.	EthosuximideTrimethadione
Type IV	Only enhances GABAergic inhibition.	Vigabatrin
Non-categorized	Has no known effect on Sustained high frequency repetitive firing, GABAergic inhibition, or T-calcium currents	Gabapentin[b]

Table 1. *Anticonvulsants and their mechanism of actions [23]* [a]Felbamate probably possesses other actions. [b]The mechanism of actions of gabapentin are unknown.

Pattern of adverse drug reactions to antiepileptic drugs

Adverse effects (AEs) of antiepileptic drugs are highly prevalent and can be potentially life threatening. UP to 61% of patients taking conventional AEDs, such as phenytoin, carbamazepine, valproate or phenobarbital, experience adverse reactions which are thought to contribute to initial treatment failure in up to 40% of patients. Deciding on which AED has the best side effect profile is not always straightforward [22]. In the past decade, 8 new AEDs have been approved for use in the United States, offering many new treatment options to patients with epilepsy. Each new medication provides a unique profile of pharmacokinetics, AEs, and mechanisms of action, making an appreciation of how these agents are best utilized even more difficult [24]. Studies have shown that 70% cases of seizures can be effectively controlled with the help of current AEDs. In the remaining 30%, recurrent seizures as well as intolerable ADRs can have a significant impact on the quality of life of patients [24].

Treatment of patients with AEDs, as with many other medications, is complicated by increased sensitivity to drug effects, narrow therapeutic ranges and complex pharmacokinetics. Anticonvulsants related AEs are very difficult to detect due to a number of reasons. [19]Firstly because epilepsy is a chronic disease so treatment with AEDs is given for a long period of time. Secondly, as the drugs act at selected Central Nervous System (CNS) receptors so AEs involving the CNS is not uncommon. Thirdly drug toxicity with AEDs occurs in therapeutic ranges. Fourthly the chances of drug interaction (DI) increase highly in patients in whom combination therapy is used to control difficult-to treat-seizures. Lastly AEDs related ADRs are difficult to distinguish from the manifestations of seizure or of other independent diseases. Thus much care is needed in its correct identification and management.Treatment with AEDs should be tailored in individual patients. Specific consideration should include AEs profiles of drugs, DIs and pharmacokinetics [24] and also individual patient profile. Worldwide, older medications such as phenytoin, valproic acid, carbamazepine, and ethosuximide are generally used as first-line therapy for most seizure disorders because they are effective as recently marketed drugs and significantly less expensive. Although the long established AEDs are very much effective in controlling seizures, AEs with these drugs are very common. Usually these drugs are meant to be taken for many years continuously in epileptic patients so avoidance of unwanted effects is particularly important [25]. Few studies which compared the older drugs with the newer one found similar efficacy but improved tolerability of the newer agents. There remain no well established guidelines for selecting a particular drug or choosing a newer agent over an older one. Careful consideration of seizure type, patient co-morbidities and specific drug toxicities help in determining the most appropriate drug therapy [24].

Antiepileptic drugs	Protein binding, %	Metabolism	Advantages	Disadvantages
Traditional agents				
Carbamazepine	80	Hepatic	Extensive patient exposure	Drug interactions, hyponatremia
Phenobarbital	50	Hepatic	Inexpensive, once daily dosing	Sedation, cognitive effects
Phenytoin	90	Hepatic	Inexpensive, once daily dosing	Nonlinear kinetics, drug interactions
Valproate	95	Hepatic	Broad spectrum	Weight gain, tremor, hair loss
Newer agents				
Felbamate	25	Hepatic	Broad spectrum	Risk of aplastic anemia, hepatotoxicity
Gabapentin	<10	Renal	No drug interactions, rapid titration	Sedation, weight gain
Lamotrigine	55	Hepatic	Broad spectrum, favorable adverse effect profile	Slow titration, rash
Topiramate	15	Hepatic/Renal	Broad spectrum	Slow titration, cognitive effects, kidney stones
Tiagabine	95	Hepatic	Novel mechanism of action	Multiple doses per day, tremor
Levetiracetam	<10	Renal	No drug interactions, rapid titration	Rare behavioral changes
Oxcarbazepine	50	Hepatic	Less neurotoxic adverse effects than carbamazepine	Hyponatremia risk
Zonisamide	40	Hepatic	Broad spectrum, once daily dosing	Slow titration,Anorexia

Table 2. *Comparison of traditional and newer antiepileptic drugs [24]*

Classification of adverse effects of antiepileptic drugs

In order to understand better the impact of ADRs, so frequently reported in many scientific journals, it is pertinent to review various classifications of ADRs. The original Rawlins and Thompson's classification (1977) of ADRs into type A (augmented) and type B (bizarre) has been expanded to types A to F [26, 27] (Figure 1).

Type	Description	Examples
Type A	Predictable, dose-related ADRs	With most AEDs (with some interindividual variations between AEDs and patients): sedation, somnolence, fatigue, tiredness, dizziness, unsteadiness, depression, agitation, nervousness, blurred vision, diplopia, ataxia, headache With specific AEDs: leukopenia (carbamazepine), thrombocytopenia and deranged coagulation profile (valproate), hyponatremia (carbamazepine, oxcarbazepine), tremors (valproate), hypohiderosis (topiramate, zonimsamide), anxiety (levetericetam), paresthesiae (topiramate)
Type B	Unpredictable, idiosynchratic ADRs	Skin rash both-, benign and anticonvulsant hypersensitivity syndrome (phenytoin, carbamazepine, phenobarbital, lamotrigine, zonisamide) Aplastic anemia (phenytoin, carbamazepine, felbamate), angle closure glaucoma (topiramate), liver failure (valproate, felbamate, carbamazepine, phenytoin)
Type C	Chronic, cumulative ADRs	Osteomalacia and osteoporosis (phenytoin, carbamazepine, phenobarbital, valproate), gingivial hyperplasia (phenytoin), hirsutism (phenytoin), weight gain (valproate, pregabalin, gabapentin), visual field loss (vigabatrin)
Type D	Delayed ADRs	Carcinogenesis (unproven in most cases, e.g., phenytoin-induced myeloma and lymphoma), teratogenesis
Type E	ADRs evident only after withdrawal of drug	NA
Type F	Therapeutic failure of drug	NA

Figure 1. *Rawlins and Thompson's classification (1977) of ADRs into type A (augmented) and type B (bizarre)*

Adverse reactions due to AEDs can also be classified as dose related toxicities and idiosyncratic reactions [28].

Dose related toxicity

These are common and related to the dose of the drugs. Factors that influence dose related toxicity are pharmaceutical (different fillers, preparations), pharmacokinetic (differences in absorption, metabolism and elimination) and pharmacodynamic (different susceptibilities to toxicity due to age and/or organ dysfunction). Examples of dose related toxicity are gastrointestinal (GI) symptoms like nausea, vomiting associated with sodium valproate or sedation typically associated with the use of phenobarbital. Dose related toxicity with carbamazepine are very common and is seen in about one-third of patients treated with monotherapy and in about half when treated with other AEDs. Carbamazepine induced diplopia, blurred vision, fatigue, vertigo are mild and usually reversible with reduction in doses. Adverse behavioral reactions associated with carbamazepine include difficulty in sleeping, agitation, irritability, and emotional liability-possibly occurring more frequently in patients with preexisting CNS problems [29]. Again in case of phenytoin the incidence of toxicities increases with higher drug levels. At higher phenytoin levels the degrading enzyme system is saturated and thus there is a shift from linear to non-linear pharmacokinetics which leads to accumulation of the drug in the body and hence the toxicity. Gingival hyperplasia, hirutism and coarsening of facial features are the well-known dose related toxicities associated with long term use of phenytoin [30]. Dose related toxicity is mostly restricted to CNS in case of newer AEDs. Eg somnolence, ataxia, nystagmus are the frequent complains of gabapentin, lamotrigine and topiramate [31].

Idiosyncratic toxicity [28]

They are also known as drug induced diseases. They are rare and not dose dependent. Such toxicities should be recognized early and managed promptly otherwise may lead to severe morbidity or even death. The major idiosyncratic reactions involve multiple organ system, but can also cause skin reactions or systemic serum like illness, hepatitis, agranulocytosis and aplastic anemia. Adverse skin reactions are the most common idiosyncratic toxicity with AEDs. These include exanthema, exfoliative dermatitis, Steven Johnson Syndrome (SJS) and Lyell’s syndrome. Aplastic anemia and agranulocytosis are reported with both phenytoin and carbamazepine. Mortality of AED related aplastic anemia may be as high as 77%. Thus carbamazepine therapy should always be avoided in patients with an active or passive history of hematopoietic suppression [32]. Carbamazepine is well known to cause hyponatremia. Carbamazepine is thus inappropriate for patients who are consuming a salt restricted diet or who are on drugs that predispose hyponatremia like lithium, Diuretics or chlorpropamide [32]. Phenytoin and combination of phenobarbital/ mephenytoin and primidone/ethosuximide have been found to be associated with malignant lymphoma [28].

Acute idiosyncratic hepatitis is commonly associated with phenytoin and carbamazepine and less commonly with phenobarbital. The hepatotoxicity with valproate differs from other AEDs. Dose related hepatotoxicity though increase liver enzymes, do not cause abnormality with synthetic liver function and usually resolves with dosage reduction or discontinuation of medications. A very rare idiosyncratic toxicity of valproate therapy is irreversible liver failure affecting I in 10,000-49,000 patients but the relative risk is different in certain subpopulations. The risk is lowest in patients below 20 years of age and taking valproate as monotherapy. The risk was found to be most vulnerable in the age group of below 2 years receiving valproate in polytherapy with an incidence of 1 in 500-800 [33]. This is due to the 4-ene metabolite of valproate which has been found to be directly toxic to the hepatocytes in vitro. Drugs like phenytoin, phenobarbital and carbamazepine which stimulate cytochrome P450 enzyme may increase 4-ene metabolite increase the risk of fatal

hepatitis. A profile of susceptibility has been established for valproate associated hepatic failure. Infants, and patients on anticonvulsant polytherapy, with mental retardation and progressive or congenital neurological illnesses, poor nutritional status and metabolic disorders are at highest risk [32].

Among the newer AEDs, lamotrigine causes the most well recognized idiosyncratic reactions like rash as the older drugs, which affects almost 10% of the patients. The rash can be serious and can lead to life threatening SJS or toxic epidermolysis necrosis (TEN) in 0.3% of the adults. This AE may also precipitate in 1% of the pediatric patients co-administered with sodium valproate or with a faster titration [34].

The use of felbamate has been restricted to most severe cases of intractable partial seizure and Lennox-Gastaut syndrome that prove unresponsive to all other treatments and only where therapeutic benefits clearly outweigh the risks due to felbamate associated aplastic anemia and hepatic failure [32, 33].

Drugs	Typical dose; dosing interval	Half life	Therapeutic range	Adverse effects	
				Dose related (Predictable)	Non-dose related (Unpredictable)
Carbama-zepine	600-1800 mg/d (15-35 mg/kg, child); Bid-qid	10-17 h	6-12 µg/mL	Diplopia, drowsiness, headache, nausea, Orofacial dyskinesia, arrhythmias, ataxia	Photosensitivity, Steven-Johnson syndrome, agranulocytosis, aplastic anemia, hepatotoxicity, hyponatremia
Phenytoin	300-400 mg/d (3-6 mg/kgadult; 4-8 mg/kg, child); qid-bid	24-h wide variation dose- depende-nt	10-20 µg/mL	Ataxia, nystagmus, drowsiness, gingival hyperplasia, hirsutism, diplopia, asterixis, orofacial dyskinesia, folate deficiency, lymphadenopathy	Blood dyscrasias, rash, Dupuytren's contracture, hepatotoxicity, aplastic anemia, lymphadenopathy Neuropathy, nystagmus pancreatitis, steven-johnson syndrome
Sodium valproate	750-2000 mg/d (20-60 mg/kg); bid-qid	15 h	50-125 µg/mL	Dyspepsia, nausea, vomiting, hair loss, anorexia, drowsiness, tremor, ataxia	Acute pancreatitis, aplastic anemia, thr ombocytopenia,hep atotoxicity, rash,Steven Johnson syndrome, blood dyscrasias.
Phenobarbital	60-180 mg/d (1-4 mg/kg, adult); (3-6 mg/kg, child); qid	90 h (70 h in children)	10-40 µg/mL	Fatigue, listlessness, depression, poor memory, impotence, hypocalcemia, osteomalacia, folate deficiency,	Macropapular rashes, exfoliation, hepatotoxicity, seizure exacerbation, sedation
Etho-suximide	750-1250 mg/d(20-40 mg/kg); qid-bid	60 h, adult 30 h, child	40-100 µg/mL	Nausea, vomiting, drowsiness, headache, lethargy	Rash, erythema multiforme, Steven-Johnson syndrome
Clona-zepam	1-12 mg/d (0.1-0.2 mg/kg); qid-tid	24-48 h	10-70 ng/mL	Fatigue, drowsiness, ataxia	Rash, thrombocytopenia
Lamo-trigine	150-500 mg/d; bid	25 h 1 h with enz-ind, 5 h with val acid	Not estd	Headaches, drowsiness, diplopia, ataxia, rash, tremor, nausea	Liver failure, disseminated intravascular coagulation, rash, SJS, blood dyscrasias

Gaba-pentine	900-2400 mg/d;tid-qid	5-9 h	Not estd	Drowsiness, diplopia,ataxia, headache, somnolence, peripheral edema	Neutropenia
Topira-mate	200-400 mg/d; bid	20-30 h	Not estd	Dizziness, drowsiness, nervousness, fatigue, weight loss, cognitive impairment, paresthesias	Nephrolithiasis, narrow angle glaucoma
Zonisa-mide	200-400 mg/d; qid-bid	50-68 h	Not estd	Ataxia, dizziness, somnolence, anorexia, agitation	Hypersensitivity, weight decrease, GI problems, nephrolithiasis, SJS, cross allergy to sulphonamides, aplastic anemia
Felbamate	2400-3600 mg/d, (45 mg/kg, child); tid-qid	16-22 h	Not estd	Anorexia, nausea, weight loss, insomnia	Rash, aplastic anemia, SJS, hepatic failure, anorexia, insomnia
Levetira-cetam	1000-3000 mg/d; bid	6-8 h	Not estd	Sedation, Fatigue, In-coordination, Psychosis	Anemia, Leukopenia
Oxcarba-zepine	900-2400 mg/d (30-45 mg/kg, child); bid	10-17 h (for active metabolite)	Not estd	Fatigue, Ataxia, Dizziness, Diplopia, Vertigo, Headache	Hyponatremia

Table 3. *Dosage and adverse effects of commonly used antiepileptic drugs [35-38]*

Phenobarbital, phenytoin, primidone and carbamazepine decreases the plasma level of several drugs including Oral Contraceptives which may lead to unwanted pregnancy and thus needs special attention in women of child bearing age. AEDs which do not induce hepatic enzyme activity like gabapentin, lamotrigine and valproate would not be expected to affect the efficacy of Oral Contraceptives [39-41].

The newer AEDs cause less interactions compared to the older ones particularly in patients taking other medications.eg gabapentin, and lamotrigine [32].

Drug	Behavioral effects	Cognitive effects
Phenobarbital (luminal)	Hyperactivity, fussiness, lethargy, disturbed sleep, irritability, disobedience, stubbornness, depressive symptoms	Deficits on the neuropsychologic tests, impaired short-term memory and memory concentration tasks.
Phenytoin(Dilantin)	Unsteadiness, involuntary movements, tiredness, alteration of emotional state	Deficits on neuropsychologic tests, impaired attention, problem solving and vasomotor tasks
Carbamazepine (Tegretol)	Difficulty sleeping, agitation, irritability, emotional lability	Impaired task performance
Clonazepam(Clonopin)	Irritability, aggression, hyperactivity, disobedience, antisocial activities	
Valproic acid (Depakene)	Drowsiness (especially when used in combination with barbiturates)	Minimal adverse effects on psychosocial tests [56-80]

Table 4. *Potential adverse and cognitive effects of anticonvulsant agents [29, 41-56]*

Conclusion

A regular follow-up of patients on AEDs is required for the early detection and prevention of ADRs to increase patient's compliance to drug therapy and to provide a better drug therapy by prevention of related morbidity and mortality. Minimization of the adverse effects of antiepileptic drugs is a multistage process that requires implementation of preventive measures, careful monitoring, and prompt interventions, as needed. For this approach to succeed, a "therapeutic alliance" between the patient and the clinician is essential. The drug interactions capable of producing, potentially life-threatening results in patients requiring AEDs should be clinically anticipated, based on the pharmacology of the AEDs used. Minimizing polytherapy and selecting AEDs with favorable pharmacokinetic profiles may help minimize drug interactions and AEs.

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