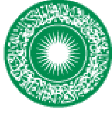
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EPILEPSY IN PAKISTAN: NATIONAL GUIDELINES FOR CLINICIANS

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ABSTRACT

Introduction

Epilepsy is one of the most common chronic neurological disorders requiring prolonged treatments and drugs. According to The World Health Organization (WHO), epilepsy is one of those serious brain disorders that affect not only the individual but has a deep impact on the family and society in general. Approximately 50 million people are affected with epilepsy around the world36, though proper epidemiological studies do not exist for Pakistan it is estimated that the prevalence of epilepsy is 9.99/1000. Highest prevalence is seen in people younger than 30 years of age, i.e. about 2 million people and 1/10th of the world burden of epilepsy is in Pakistan! The guidelines available in developed countries are gauged in a setting where epilepsy care is provided by epileptologists/neurologists. In Pakistan the scenario is different, there is only one neurologist for 1.4 million (14lac) population contrast to US where one neurologist for 26 thousand people 29. So there is a desperate need to adapt to alternate guidelines with strategies to provide epilepsy management at a primary care level and to standardize epilepsy care on a National level.

Methods

To form these guidelines we reviewed and adopted from many different available guidelines mainly

1. Local adaptations of the WHO recommendations[4]
2. Modification of the ILAE treatment guide lines: evidence based analysis of AEDs 2006[11]
3. Updated ILAE evidence review of AEDs special report 2013[12]
4. Existing guidelines in other low income countries[13-15]
5. NICE, AAN, AES recommendations.[17-21]

Results

These guidelines consist of

1. The universally ILAE accepted definition and classification of epilepsy and Epileptic syndromes with A step wise approach to a patient with seizures and epilepsy in Pakistan.
2. Tables Selecting the right drug with evidence based references keeping in mind the cost and availability in Pakistan.
3. AED selection in special populations e.g. women[20], children[17] and elderly

4. Status Epilepticus Protocol
5. Algorithms and tables for easy access

(Due to the limitation of space , points 3 and 4 will be published subsequently)

CONCLUSION

The primary scope of these guidelines is to provide a concise practical management plan which considers the role of AEDs especially their judicial useThese guidelines hope to provide the physicians treating epilepsy patients with a step wise cost effective approach to the patient with epilepsy. A separate guideline to classification and diagnosis is also available, and the guidelines in entirety are also available on line at the Pakistan Society of Neurology website.

Guidelines Introduction

Epilepsy is one of the most common chronic neurological disorders requiring prolonged treatments and drugs. It is a disorder that is widely misunderstood and carries a vicious stigma. Epilepsy comprises a vast group of disorders and syndromes with one common symptom, “The Seizure”. For the purpose of these guidelines we have integrated the International League Against Epilepsy (ILAE) definitions of seizures and epilepsy. There is a vast array of literature and guidelines that exist in developed countries for over a decade. These have been reviewed and compiled and modified to suit the Pakistani population and socioeconomic status. These guidelines hope to help improve medical decision making in Pakistan while treating the patient with epilepsy (PWE)

THE NEED FOR NATIONAL GUIDELINES FOR EPILEPSY IN PAKISTAN:

Epilepsy has varied etiologies and affects all age groups, but the vast majority of cases are treatable with Anti Epileptic Drugs (AEDs) most of which are easily available. However knowledge about epilepsy and its care is extremely low. The majority of people with epilepsy (PWE) are treated inadequately or inappropriately. According to The World Health Organization (WHO), epilepsy is one of those serious brain disorders that affect not only the individual but has a deep impact on the family and society in general. Approximately 50 million people are affected with epilepsy around the world,[4] and this number will increase with the new definition. Though proper epidemiological studies do not exist for Pakistan it is estimated that the prevalence of epilepsy is 9.99/1000. Highest prevalence is seen in people younger than 30 years of age5. That is: about 2 million people and 1/10th of the world burden of epilepsy is in Pakistan. The recent estimates of population of Pakistan exceed 180 million, whereas the total number of trained neurologists in Pakistan is estimated to be 135 (Pakistan Society of Neurology Directory 2013)[5]. Based on the available data, the estimated 2 million people suffering from epilepsy in Pakistan, makes it one neurologist available for every 15200 sufferers of epilepsy with only few trained in epilepsy. Despite efforts to create awareness there remains a wide treatment gap and misconception. The guidelines available in developed countries are gauged in a setting where epilepsy care is provided by epileptologists/ neurologists. In Pakistan it is a different scenario, there is only one neurologist for 1.4 million population contrast to US where one neurologist for 26 thousand people[4]. So there is a desperate need to adapt to alternate guidelines with strategies to provide epilepsy management at a primary care level and to standardize epilepsy care on a National level. The primary care physicians in civil hospitals and dispensaries, and general practioners (GPs), form the crux of health care in Pakistan and therefore see most of the PWE. Unfortunately neurology rotation is not a mandatory in undergraduate training thus most lack the information and skill needed for proper epilepsy diagnosis and management. In 2011, WHO mental health Gap Action Programme (mhGAP) released evidence based epilepsy care guidelines for use in low and middle income countries[4]. These guidelines provide a crudePerforma that requires local adaptation for use within individual countries. The guidelines state “For effective implementation and sustainability, the sense of ownership and empowerment must be transferred from the global health authorities to the local people. Socio-cultural and financial barriers that impede the implementation of the guidelines should be identified and ameliorated.[4]

Table 1: Factors to consider while developing National guidelines.

Factor	Developed country	Developing country like Pakistan
Gross National income	> USD 3036	< USD 565
Access to Health care	Primary care for all with established referral systems	Limited to very basic primary care
Health care funding	National programs and private insurance systems	Often ill funded rely on donors or volunteers. No set system of insurance
Cultural perception of seizures	Biomedical model	Traditional medicine, spiritual approach, contagion belief common
Common Epilepsy etiologies	Ideopathic, neoplastic cerebrovacular	Post infectious, antenatal, post traumatic
Socio-cultural attitudes towards epilepsy	At lease social presentation of neutrality	Overt negative public perception, stigmatization, and discrimination common
Treatment gap	<20%	70-94%

ARIABLES AFFECTING SELECTION OF AEDS IN PAKISTAN

Epidemiological studies of prevalence and incidence reviewedare problematic in Pakistan due to lack of proper data collection teams and resources. Data concerning seizure type, etiology, and severity of seizuresare contrasted with those from developed countries. Sociocultural aspects of epilepsy have been poorly studied, and yet are fundamental to effective medical management. Thus the principles and success of treatment in Pakistan may differ considerably from developed countries. The principles of drug therapy may not be understood by patients, and the supply of drugs is often erratic; and these are major reasons for poor compliance with treatment. Therapy need to be prioritized to cost effectiveness, requiring a cheaper drug eg.phenobarbital to be tried as first line contrary to international guidelines. Computations of treatment gap figures in three developing countries suggest that between 80-94% of patients with active epilepsy are not receiving anticonvulsant therapy, cost and cultural belief sare two of the main factors.

Table 2: Factors affecting AED selection

AED-specific variables	Patient-specific variables	Nation-specific variables
Seizure type or epilepsy syndrome specific efficacy or effectiveness Dose-dependent adverse effects Idiosyncratic reactions Chronic toxicities Teratogenicity Carcinogenicity Pharmacokinetics Interaction potential Formulations	Genetic background Age Gender Comedications Comorbidities Insurance coverage Ability to swallow pills/tablets	AED availability AED cost Insurance coverage Socio-cultural issues Compliance

To form these guidelines we reviewed and adopted from many different available guidelines mainly.

1) Local adaptations of the WHO recommendations [4]
2) Modification of the ILAE treatment guidelines: based analysis of AEDs 2006 [11]
3) Updated ILAE evidence review of AEDs special report 2013[12]
4) Existing guidelines in other low income countries [13'14'15'16]
5) NICE guidelines,[17]
6) AAN practice parameters, [18]
7) AES recommendations.[19]
8) A multitude of literature to support our selection and recommendations [20-43]

Management Guidelines:

QUESTIONS ADDRESSED

Q1-Q3: AEDs Initiation of therapy/Mono therapy; Adjuvant therapy; Cessation of therapy

Q4-Q7: Women (fertility, contraception, conception, pregnancy, lactation, teratogenicity), Children, elderly differences

Q8-Q9: Status Epilepticus in Adults and children (protocols)

Q10-Q13: Access to medications, direct and indirect costs, co-morbid conditions, preventable causes

Q14-Q15: Alternate Therapies, diet.

Q16: Epilepsy surgery.

Q17-Q19: Lifestyle, Career choices, Driving.

Q20-23: Epilepsy Diaries, lockets, keychain or bracelets, Help line.

Monotherapy Guideline questions:

Q1-Q3: Patients (adults/elderly/children) with partial-onset seizures

Q4-Q5: Patients (adults/children) with generalized-onset tonic-clonic seizures

Q6: Children with idiopathic localization-related epilepsies and syndromes (BECTS).

Q7-Q8: Children with idiopathic-generalized epilepsies (CAE, JME).

Q9: Special Issues related to Women.

Q10: Considerations in Elderly and Multiple handicapped

Questions 6-10 are discussed in the special population subset of these guidelines not published in this edition.

A person is considered to have epilepsy if they meet any of the following conditions:
At least two unprovoked (or reflex) seizures occurring greater than 24 hours apart. One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years. Diagnosis of an epilepsy syndrome

For Classification and Diagnosis guidelines see Appendix A

MANAGEMENT OF EPILEPSY

Non-pharmacological Management:

Once diagnosis is made patient and family members need to be counselled empathically. Since the disease still carries a strong stigma, confidentiality needs to be maintained at all steps, and the condition should be discussed with any family member with consent of the PWE.

- Establish the diagnosis
- Education/ counselling
- Address psychosocial issues
- Lifestyle modifications

Patients need counselling regarding the
- Disease
- Drognosis
- Need for medication
- Compliance
- Life style

Life style modification includes
- Adequate sleep - early to bed early to rise
- Change in job e.g. occupation, driving, swimmers, boxers, airplane pilots etc.
- Avoidance of alcohol, stimulants, energy drinks, gutka, JM, etc.
- Stress reduction — specific techniques, Yoga, meditation, early morning walks
- Adequate diet – high protein. Low carbohydrate, Vit. D, B rich diet
- Joining support groups
- Avoid social isolation

Pharmacological treatment of epilepsy

The mainstay of treatment for epilepsy is antiepileptic drugs (AEDs) taken daily to prevent the recurrence of epileptic seizures. It is important that the treatment strategy and suitability of the AED is determined by the prescriber keeping the individual with epilepsy and thecarer informed before drug therapy is started.

When to Start AEDs after first seizures

Whether to treat first seizure is controversial studies show 16-62% recur within 5 years, Relapse rate is reduced by antiepileptic drug treatment, and it is now recommended that since Neurological abnormalities, abnormal imaging, abnormal EEG or family history increase relapse risk these patients should be treated after first seizure.

(Table 4)

Definitely:	**Possibly:**
With structural lesion like Brain tumor, AVM, Infection, Without structural lesion: h/o Epilepsy in sibling EEG with definite pattern. Prior but remote sz prior neurological hist. Todds post ictal paresis statusepilepticus at onset.	Unprovoked seizure **Probably not:** alcohol withdrawal Drug abuse Sz with acute illness post impact seizure A benign epilepsy syndrome. Excessive sleep deprivation.

AED should be selected according to suitability of the patient, type of epilepsy etc.
Table 3 shows factors determining suitability.

Table 5

Factors determining AED suitability include:
seizure type and/or epilepsy syndrome; childbearing potential; the presence of comorbidity; individual and/or carer preferences; the presence of contraindications to the drug; potential interactions with other drugs; potential adverse effects the licensed indication of the drug. Cost of AED Patients socio-economic status Age Compliance AED availability Adult lifestyle

The diagnosis of epilepsy needs to be critically evaluated if events continue despite an optimal dose of a first line AED. Before combination therapy is considered, PWE should be given a trial of at least 2-3 appropriate monotherapy regimens, with caution during the transition.

General Recommendations:

1) It is recommended that PWE should be treated with a single AED (monotherapy). If the initial treatment is unsuccessful, then monotherapy using another drug can be tried.

2) Caution is needed during the changeover period, with the second drug titrated and the first drug decreased gradually.
3) It is recommended that combination therapy (adjunctive or ‘add-on’ therapy) should only be considered when attempts at monotherapy with AEDs have not resulted in seizure control.
4) If trials of combination therapy do not bring about worth while benefits, Diagnosis should be revisited and treatment should revert to the regimen with best control providing efficacy in reducing seizures and tolerability of side effects.
5) Refer to specialist for phase II evaluation and Epilepsy surgery, classify and diagnose cause of refractory epilepsy, epileptic or non-epileptic fits.
6) If an AED has failed because of adverse effects or continued seizures, a second drug should be started (which may be an alternative first-line or second-line drug) and built up to an adequate or maximum tolerated dose and then the first drug should be tapered off slowly.
7) If the second drug is unhelpful, either the first or second drug may be tapered, depending on relative efficacy, side effects and how well the drugs are tolerated before starting another drug.
8) It should be recognised that some PWEs (through their families in some instances) may choose not to take AED therapy following a full discussion of risks and benefits. Reason should be sought and addressed accordingly. Treatment should be insisted upon if risk of recurrence is high as described in table 3.
9) Treatment of a first unprovoked seizure reduces the risk of recurrence in the short-term. In children, treatment of a first unprovoked seizure does not alter the long-term prognosis for seizure remission.
10) AED therapy should only be started once the diagnosis of epilepsy is confirmed, except in exceptional circumstances that require discussion and agreement between the physician and the PWE and/or carers as appropriate.
11) Continuing AED therapy should be planned by the physician. It should be part of the PWE agreed treatment plan, which should include details of how specific drug choices were made, drug dosage, possible side effects, and action to take if seizures persist.
12) When possible, choose which AED to offer on the basis of the presenting epilepsy syndrome. If the epilepsy syndrome is not clear at presentation, base the decision on the presenting seizure type(s).
13) Consistent supply to the PWE of a particular manufacturer’s AED preparation is recommended. Different preparations of some AEDs may vary in bioavailability or pharmacokinetic profiles and care needs to be taken to avoid reduced effect orexcessive side effects.
14) Where partial seizures are suspected prefer sodium channel blockers as first line AEDs (see fig 1)
15) Where generalized seizure syndromes are suspected consider broader spectrum AEDs (see fig 1)
16) Phenobarbitone is a broad spectrum efficacious AED that is easily available in Pakistan at minimal price, therefore should still be considered as first line therapy where affordability is an issue as risk of seizures outweigh the long term side effects.
17) Phenobarbitone should be offered where compliance due to cost is suspectected.
18) If using carbamazepine, check LFTs.
19) When prescribing sodium valproate to women nd girls of present and future childbearing potential, discuss the possible risk of malformation and neurodevelopmental impairments in an unborn child, particularly with high doses of this AED or when using as part of polytherapy. Vit B, folate and calcium supplements should be added.
20) Lamotrigine should be administered with caution and slow titration when given as monotherapy and with even slower titration when combined with inducers like valproate to avoid the risk of idiosyncratic reactions like Steven Johnson’s syndrome and toxic epidermolysis. All patients should be counseled and warned to stop medication and contact the physician immediately if any rash appears.
21) Levitiracetam should be given with neuropsychiatric issues in mind and pyridoxine supplement.
22) Maintain a high level of vigilance for treatment emergent adverse effects (for example, bone health issues, blood dyscrasias, and neuropsychiatric issues)

23) If management is complicated, PWE should be referred to specialist.
24) The prescriber must ensure that the PWE and/or carers as appropriate are fully informed about treatment including action to be taken after a missed dose or after a gastrointestinal upset.
25) Regular blood test monitoring in PWE is not recommended as routine, and should be done only if clinically indicated or non-complance is suspected as below.
    Examples of blood tests include:
    Before surgery – clotting studies in those on sodium valproate. For Patients on enzyme inducing AEDs: CBC, Electrolytes, LFTs, Vit D levels, every 1-2 years. Test for serum amino acids, TSH and urine for organic acids in all children with neonatal non-infectious seizures and refractory seizures.
26) Asymptomatic minor abnormalities in test results are not necessarily an indication for changes in medication.
27) Every patient when stable should still have a 6 monthly follow-up to ensure compliance, and review treatment plan and side effects.
28) For uncontrolled patients treatment should be reviewed at regular intervals so PWE are not maintained for long periods on treatment that is ineffective or poorly tolerated, when in doubt early referral is more cost effective
29) **Compliance can be optimized with the following:**
- Educating PWE and their families and/or carers in the understanding of their condition and the rationale of treatment
- Reducing the stigma associated with the condition
- Using simple medication regimens
- Positive relationships between healthcare professionals PWE, and their family.
- SMS bulk reminder module
30) The risks and benefits of continuing or withdrawing AED therapy should be discussed with PWE and/or carers as appropriate, who have been seizure free for at least 2 years At the end of the discussion, they should understand their risk of seizure recurrence off treatment. This discussion should take into account details of the PWE's epilepy syndrome, prognosis and life style.
31) When AED treatment is being discontinued in PWE who has been seizure free, it should be carried out slowly (at least 2-3 months) and one drug should be withdrawn at a time.
32) Particular care should be taken when withdrawing benzodiazepines and barbiturates (may take up to 6 months or longer) because of the possibility of drug- related withdrawal symptoms and/or seizure recurrence.
33) PWE and carer should be counseled whereby if seizures recur the last dose reduction is reversed and medical advice is sought.

Table 6: List of available AED's worldwide vs those available in Pakistan with abbreviations, dosage, indication and common side effects.

Medication	Usual Starting Dose	Titrated Up or Down By	Usual Maximum Daily Dose	Common Side Effects	Summary Of Indications
Acetazolamie (AZM)	250 mgs bd	250mgs every 1/52	1000mgs daily In divided doses	GIT Dist. U&E Dist † urine output	Adjunctive for all sz types especially drop attacks
Carbamazepine (CBZ)	100-200 mgs 1-2 times daily 2-3mg/kg/day	100 mgs every 1/52	2000 mgs daily In divided doses 10-20mg/kg/day	GIT Dist. #Rash Hyponatremia agranulocytosis	Mono/adjunctive therapy. Worsens myoclonic and absence seizures
Clobazam (CBZ)	5-10 mgs daily	5-10 mgs every 1/52	Up to 60 mgs daily	Drowsiness	Adjunctive for all sz type
Clonazepam (CLB)	0.5 mgs bd	0.5 mgs	8 mgs daily	Drowsiness	Mono/adjunctive for all sz types

Diazepam (DZP)	5-10mgs daily	2.5-5mgs	30mgs per day	Drowsiness	Prolonged/cluster seizures
Ethosuximide* (ESM)	250 mgs bd	250 mgs every 1/52	2000 mgs daily	GIT Dist. Drowsiness	Mono/adjunctive for absence szs
**Felbamate	300 mgs tds	300 mgs every 1/52	3600 mgs daily In divided doses	Liver Failure and aplastic anemia rare risk 1:5000	Adjunctive for all Szs types which have failed all other AEDs. Used under strict specialist supervision
Gabapentin (GBT)	200-300 mgs tds	200-300 mgs every 1/52	3600 mgs daily In divided doses	GIT Dist. Weight Gain	Mono/adjunctive for partial onset szs +/- sec gen
Lacosamide (LCM)	Initially 50mgs bd 1-2mg/kg/day	Increase weekly by 50mg bid	200mgs bd or 6-9mg/kg/day	Nausea, dizziness, somnolence, headache	Adjunctive for partial onset szs +/- sec gen
Lamotrinine (LTG)	25 mgs od 25 mgs alternate days When on VPA To a target dose of 100mgs BD Children 0.5mg/kg/day	25 mgs every week In children with VPA 1-5 mg/kg/day Without VPA 2-10mg/kg/day	500 mgs daily Children 10mg/kg/day	#Rash Insomnia GIT Dist. Headache Tremor with VPA	Mono/adjunctive for all sz types
Levetiracetam (LEV)	250 mgs bd 250mgs od if Adjunctive therapy 10mg/kg/day	250-500 mgs every week	3000 mgs daily (1.5g bd) 20-60mg/kg/day	Psychosis Low Mood GIT	Mono/adjunctive for all sz types
Lorazepam (LZP)	1-2 mgs daily	1-2 mgs	4 mgs daily	Drowsiness Dependence	Adjunctive for all sz types Rescue use.
Midazalom	10 mgs daily	N/A	20 mgs	Drowsiness	For prolonged or clusters of all szs. Rescue use Status Epilepticus
Oxcarbazepine (OXC)	Initially 300mgs twice daily	Increased according to	2400 daily In divided doses	Encephalopathy Neutropenia	Mono/adjunctive for partial onset Szs +/- sec gen

	5-8mg/kg/day	response in steps of up to 600mgs daily at weekly intervals	5-15mg/kg/day	Hyponatremia *Rash	
Phenytoin (PHT)	150-300mgs daily 5mg/kg/day	Increased gradually as necessary (with plasma phenytoin concentration monitoring	Usual dose is 200-500mgs daily10-15mg/kg/day	GIT Dist. Gingival Hypertro-phy Hirsutism *Rash	Mono/adjunctive for all sz types Status Epilepticus
Phenobarbitone (PB)	30 mgs daily	15 mgs every month	180 mgs daily	Drowsiness	Mono/adjunctive for all sz types Status Epilepticus
Pregabilin	Initially 25mgs bd	50mgs every 1/52	600 mgs daily In divided doses	Weight gain	Adjunctive for partial onset szs +/- sec gen
Primidone* (PMD)	Initially 125mgs at bed time	Increased by 125mgs every 3 days to 500mgs daily in 2 divided doses (250mgs bd), then increased according to response by 250 mg s every 3 days	1500 mgs daily In 2 divided doses	Drowsiness	Mono/adjunctive for all sz types
Rufinamide*	200 mgs BD daily	200 mgs every 1/52	1600 mgs BD daily	GIT Dist. Dizziness, fatigue	Adjunctive for Lennox – Gastaut
Tiagabine* (TGB)	5mgs bd	5-10mgs every 1/52	30-45mgs daily (doses above 30 mgs given in 3 divided doses)	Diarrhoea Dizziness Nervousness	Adjunctive for partial onset szs +/- sec gen
Topiramate (TPM)	25 mgs daily 1mg/kg/day	25 mgs every 1/52	400mgs daily (mono) In 2 divided doses 800mgs (adjunctive) In 2 divided doses (6-9 mg/kg/day)	Weight Loss ↑ Renal Calculi Word Finding Difficulties Pins and needles	Mono/adjunctive for all sz types
Valproate (VPA)	300 mgs bd 5mg/kg/day	100-250 mgs every week	3000 mgs daily 15mg/kg/day	Weight Gain Tremor, hair loss Liver Toxicity	Mono/adjunctive for all sz types

	infants 10mg/kg/day children			↑ Teratogenecity	
***Vigabatrin (VGB)	500 mgs bd 20-50mg/kg/day	Increased according to response in steps of 500mgs at weekly intervals	3000 mgs daily 50-150mg/kg/day	Hyperkinesia, insomnia,Visual field constriction in 30% of patients	Adjunctive for partial onset szs +/- sec gen Monotherapy for Wests syndrome
Zonisamide* (ZNG)	50 mgs daily or 25mg bd. 1-2mg/kg/day	Increased after 7 days to 100mgs daily in 2 divided doses then increased if necessary by 100mgs weekly	500 mgs daily 8-12mg/kg/day	Weight loss Ataxia ↑ Renal Calculi	Adjunctive for partial onset szs +/- sec gen

Not available in Pakistan or difficult to get
**Felbamate - Patients are usually electively admitted when initiating this AED due to the incidence of fatal liver failure and aplastic anaemia, for routine lab observation.
***Vigabatrinl - Its use is restricted to whom all other combinations are inadequate or not tolerated. It must only be initiated by a Neurologist. All patients must have visual field testing prior to commencement and every 6/12 thereafter.
Rash All AEDs carry the risk of rash, however the drugs highlighted as Rash carry a risk of Stevens - Johnsons Syndrome.
• Enzyme inducers and affect the metabolism of other drugs, for example Oral Contraceptives; women need to be alerted of this interaction.
weak enzyme inducers and may affect the metabolism of other drugs at high doses.
• Signs and Symptoms of Toxicity: vary from drug to drug however the following may indicate possible toxicity: Diplopia, blurred vision, unsteady gait, excessive tiredness, new onset of dizziness.
• GIT Dist may manifest as anorexia, nausea, vomiting dyspepsia, constipation, diarrhoea or any s/s of GI disturbance Interactions between antiepileptic drugs are complex and may enhance toxicity without a corresponding increase in antiepileptic effect. Interactions are usually caused by hepatic enzyme induction or hepatic enzyme inhibition. These interactions are highly variable and unpredictable.

AED INTERACTIONS

Some common interactons between antiepileptic drugs and non-antiepileptic drugs are listed below in table 7. For a full list consult the PDR Summary of Product Characteristics for each drug.

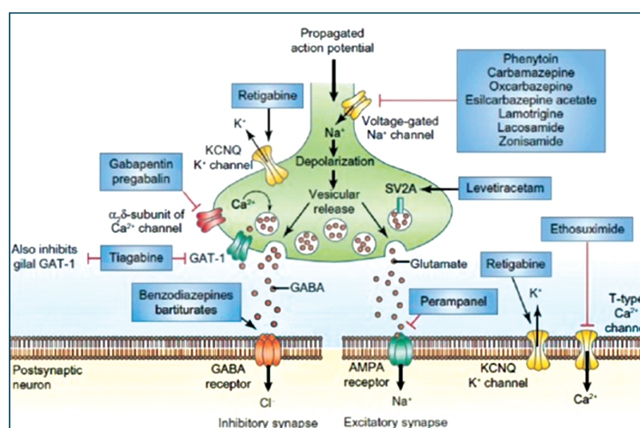
Note

- Enzyme inducing AED's increase the rate of metabolism of Warfarin and The INR should be monitored carefully when an enzyme AED is added or discontinued.
- Aspirin enhances valproate and phenytoin effects.
- Antibiotics, macrolides (clarithromycin/erythromycin) increase the plasma concentration of carbamazepine and inhibit the metabolism of phenytoin. Erythromycin possibly inhibits the metabolism of valproate.
- Meropenam, reduces plasma concentrations of valproate.
- Rifamycins accelerate phenytoin metaboism.
- Analgesics, NSAIDs enhance the effects of phenytoin.
- Estrogens, enzyme inducing drugs accelerate metabolism of Estrogens reducing contraceptive effects. Estrogens reduce lamotrigine levels.
- Plasma concentration of lamotrigine increased by valproate.

Table 7. Examples of important Drug interactions

Agents	General interactions	Agents that may increase plasma levels	Agents that may decrease plasma levels
Carbamazepine	The simultaneous administration of other liqu- id medicines with CBZ suspension can cause rubbery precipitate in stool. Co-administration with lithiumcan↑ neurotoxic SE. Other AEDs may alter thyroid functions. ↓es efficacy of hormonal contraceptives.	CYP 3A4 inhibitors Propoxiphene, Vigabatrin, VPA, protriptyline, loxopine, sertraline, ritonavir, nafimidone, isoniazid, verapamil, ketoconazole, cimetidine, flunerazine, viloxazine, macrolides, diltiazem	CYP 3A4 inducers, felbamate, PHT, mefloquin
Clonazepam	CNS depressants, MAOIs, TCAs and some anti convulsants may increase depressant effects of CNZ. With VPA in Absence seizures can induce absence status!	CYP 3A inhibitors Azole antifungals, cimetidine	CBZ
Divalproate Sodium, Valproaci acid	Drugs that elevate expression of hepatic enzymes increase the clearance of valproate. It increases free levels of warfarin	Asprin, felbamate, macrolides especially clarithromycin	Cholestyramine, meropenum, CBZ, PHT, PB, rifampin. Primidone, TPM
Phenytoin	Needs caution with other albumin binding drugs, PB, VPA, have un-predictable effect on levels.Antacids with calcium inhibitsabsorption. TCAs ↑risk for Sz.	CYP inhibitors, Azoles,, trimethoprim, chloramphenicol, isoniazid, disulfiram, phenylbutazone, cimetidine, SSRI, felbamate, TPM, CBZ, ranitidine, ibuprofen, amiodrone, diltiazem.	CYP inducers, Rifampin, doxorubicin, VPA, vigabatrin.

Fig 1: Mechanisms of action of antiepileptic drugs modified from j. physiology 2006



Modified from j. primary psych 2005

Initiation of AEDs Drug choice with seizure type:

Treatment (Monotherapy) of patients with newly diagnosed focal (partial, complex partial and secondarily generalized) seizures:

A) Adults with focal(partial) onset seizures (ILAE 2013)

RECOMMENDATIONS

1) Offer CBZ/ OXC or PB (where cost is an issue) as first line treatmentas firstline treatment to patients with newlydiagnosed focal seizures.
2) Offer LTG,PHT, OXC or VPA if CBZ and PB are unsuitable or not tolerated. If the first AED tried is ineffective, offer an alternative from these 5 AEDs. (Be aware of the teratogenic risks of sodium valproate and idiosyncratic rash of lamotrigine)
3) Consider adjunctive treatment if a second well tolerated AED is ineffective
4) If adjunctive treatment is ineffective or not tolerated, discuss with, or refer to, an epilepsy specialist or neurologist. Other AEDs that may be considered by the epilepsy specialist are eslicarbazepine acetate (ECA), clobazam, lacosamide, phenytoin, pregabalin, tiagabine, vigabatrin and zonisamide. Carefully consider the risk benefit ratio when using vigabatrin because of the risk of an irreversible effect on visual fields.

Table 8. Medication Selection In Patients with Focal onset seizures or symptomatic lesion related Epilepsies.

1st line AEDs	2nd Line AEDs	3rd Line AEDs
Carbamazepine CBZ	Levitiracetam LEV	Clonazepam CNZ
Phenytoin PHT	Valproate VPA	TiagabinTGN*
Oxcarbazepine OXC	Topiramate TPM	EsilCarbazepine Acetate ECA*
Lamotrigine LTG	Gabapentine GBP	ZonisamideZNS*
Phenobarbitone PB	Lacosamide LCM	Perampanel*
		Clobazam CLB
		Rufinamide*
		Vigabatrin
*Not available in Pakistan		

Table 9. Focal Seizures AED Selection guide by seizure type

Clinical Situation	Simple Partial Sz	Complex Partial Sz	Secondary generalized
Initial Monotherapy	CBZ	CBZ	CBZ
	OXC PHT LTG	OXC PHT LTG LEV ZNS	PHT OXC LTG VPA LEV ZNS

Pharmacological management(monotherapy) of Adults with newly diagnosed Generalized Epilepsy Syndromes (IGE).

The absence of class I and II RCTs(randomized controlled trials) for adults with GTC seizures implies a marked deficiency in published studies. No AED has reached the highest level of evidence (level A and B) for efficacy. VPA, LTG,TPM, OXC, PB, PHT, TPM, and CBZ are possibly level C, and GBP, LEV, and VGB are

potentially level D efficacious/effective as initial monotherapy for adults with newly diagnosed or untreated generalized onset tonic-clonic seizures. Class IV evidence suggests that CBZ and PHT and other sodium channel blockers may precipitate or aggravate generalized onset seizures. (ILAE updates 2013).

RECOMMENDATIONS

1) Offer sodium valproate as firstline treatment to adults with newly diagnosed GTCs. (Be aware of teratogenic risks of sodium valproate in women of child bearing age)
2) Offer lamotrigine if sodium valproate is unsuitable. If the person has myoclonic seizures or is suspected of having juvenile myoclonic epilepsy (JME), (be aware that lamotrigine may exacerbate myoclonic seizures. Be aware of idiosyncratic reaction of lamotrigine by slow escalation)
3) Consider levitiracetamand Phenobarbital in patients where VPA and LTG are not suitable.
4) Offer clobazam, CBZ, OXC and TPM as adjunctive treatment to adults with GTC seizures if first line treatments as above are ineffective or not tolerated. (Be aware of the risk of exacerbating myoclonic or absence seizures with CBZ and OXC)
5) If there are absence or myoclonic seizures, or if JME is suspected, do not offer carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin.

Table 10: Generalized Tonic Clonic Epilepsy – AEDs of choice

1st line	2nd line	3rd line
VPA	TPM	CNZ
LTG#	ZNS*	CBM
TPM	LEV	GBP
LEV	PB	CBZ#
	PHT#	OXC# VIGABATRIN ETHOSUXIMIDE
#Avoid in myoclonus *not available in Pakistan		

Table 11. Idiopathic Generalized Epilepsy: Medication Selection

AED selection	Clinical situation		
	GTC	Absence	Myoclonic
Initial monotherapy	LPA LTG	VPA ESM	VPA LEV
2nd Monotherapy if VPA failed	LTG LEV	ESM LTG	LEV TPM
2nd Monotherapy if LTG/LEV failed	TPM LEV LTG	LEV VPA ESM	TPM LEV VPA
	ZNS	ZNS	ZNS
		LTG	

KETOGENIC DIET

INTRODUCTION

The ketogenic diet (KD) is a high fat, low carbohydrate and protein diet designed to mimic the biochemical response of the body to starvation when ketone bodies become the main fuel for the brain's energy demands (Hartman 2008)It has long been used in the treatment of refractory epilepsy in children, although the exact mechanism of action is unclear. The KD diet was initially reported for use in epilepsy in 1921 (Wilder 1921). The initial diet used was the classical ketogenic diet, based on the ratio of fat to carbo-hydrate (with protein), of 3 or 4:1. Later an alternative was suggested using triglyceride oil as a supplement, the Medium chain Triglyceride (MCT) Diet (Huttenlocher et al 1971). These diets have to be carefully administered with the aid of a dietician.

- There is no evidence of efficacy of ketogenic diet in adults.
- 50% efficacy range is achieved in children.
- Recommended in refractory epilepsies in children where multiple regimens of AEDs proven ineffective.
- Local ketogenicrecipies are available and cost effective.

Epilepsy Surgery

FDA approved surgical procedures:

- Vagus nerve stimulation
- Surgical treatment

Investigational:

- Deep brain stimulation
- Gene therapy

- Laser Ablation

Surgical Treatment

- Upto 85% seizure-free rates
- ***Resections:***
- lesionectomy, lobectomy, hemispherectomy
- ***Disconnections:***
- Callosotomy, subpial transection, steriotactic ablations
- ***Augmentations:***
- Vagal, cerebellar, thalamic, deep brain stimulation

All patients with focal onset seizures that are refractory to an adequate trial of two or more AEDs of choice and are refractory to treatment should be referred for phase 1 surgical evaluation to an epilepsy specialist. All lesion-related Epilepsy syndromes should be considered for surgical management

SUMMARY:

These guidelines hope to highlight the problems that exist in the care and management of epilepsy patients like Patient and physician awareness , social and cultural beliefs, easy access to treatment,misdiagnosis, inappropriate or Inadequatetreatment, sudden unexpected death that might have been prevented, preventable etiologies, Women with epilepsy, epilepsy in children, epilepsy in the elderly, advice about pregnancy and contraception and management of status epilepticus in children and adults. These guideline will be revisited and modified on applicability every four years and it is vital that a spotlight is kept on the need to further develop variable services for people with epilepsy. The place of newly licensed drugs, stigmas, and cost for epilepsy also needs careful consideration. The primary scope of these guidelines ofcourse is to provide a concise practical management plan which considers the role of AEDs especially their judicial use. The role of established and newly licensed drugs is considered with comparison of cost effectiveness. People with epilepsy remain at the centre of this guideline, and the need for services to consider the needs of each individual and their care givers have been focused. Attention has been paid to ensure that the recommendations are written in clear language and be accessible, and, I hope, useful to all. We remain committed to the care ofpeople with epilepsy and commend these guidelines to you in that light.

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