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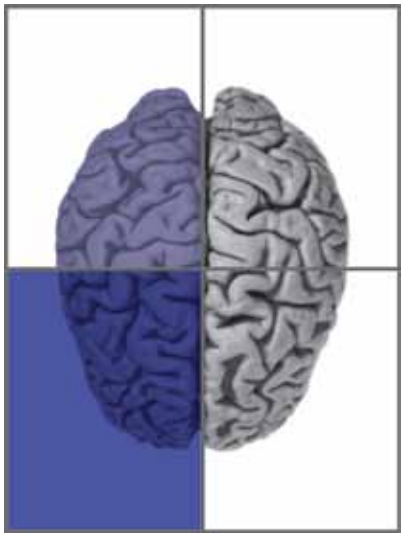

SPECIAL SUPPLEMENT ON

EPILEPSY IN PAKISTAN: NATIONAL GUIDELINES FOR CLINICIANS

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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 medication with AntiEpileptic Drugs (AEDs). 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[36], though recent epidemiological studies do not exist for Pakistan it is estimated that the prevalence of epilepsy is 9.99/1000. i.e. about 2 million people and 1/10th of the world burden of epilepsy is in Pakistan! The guidelines available are composed for a setting where epilepsy is managed by epileptologists/neurologists. In Pakistan it's a different scenario, there is only one neurologist for 1.4 million (14lac) population contrast to US where one neurologist for 26 thousand people[29]. So we felt a need to adapt to alternate guidelines with strategies to provide epilepsy management at a primary care/general practioner 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:

National guidelines consist of
1. The universally ILAE accepted definition and classification of epilepsy and Epileptic syndromes with a simplified 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 use. These 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, and Epilepsy Foundation Pakistan website.

Keyword: Seizures, epilepsy, Anti Epileptic Drugs AED, guidelines, fits, neurology, epilepsy surgery, convulsions

GUIDELINES INTRODUCTION:

Epilepsy is one of the most common chronic neurological disorders requiring prolonged medication with AEDs. It is a disorder that is widely misunderstood and carries a vicious stigma. Epilepsy is a constellation of several disorders, syndromes and conditions with "Seizure" being the common symptom . 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:

The causes of Epilepsy and numerous and symptomatology diverse, but most of cases are treatable with AEDs, most of which are easily available. However knowledge about epilepsy and its care is extremely low. The majority of PWEare 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 obviously this number will tend to increase with the new definition. Though recent 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[5]. That is: about 2 million people and 1/10th of the world burden of epilepsy is in Pakistan. The guidelines available in developed countries are composed for a setting where treatment of Epilepsy is provided by epileptologists/ neurologists.In Pakistan, the scenario is such, 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), are the mainstay 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 crude Performa 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 (modified from WHO guidelines)[4]

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 leasesocial presentation of neutrality	Overt negative public perception, stigmatization, and discrimination common
Treatment gap	<20%	70-94%

VARIABLES AFFECTING SELECTION OF AEDS IN PAKISTAN:

The Selection of AEDs depends on the proper diagnosis of the seizure type, etiology and severity of seizures. In Pakistan the cost, availability and socio-cultural issues also need to be considered. These factors affecting AED selection 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; Therapy needs to be prioritized to cost effectiveness, requiring a cheaper and widely available drug eg.Phenobarbital, carbamazepine or valproate 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 proper anticonvulsant therapy, cost and cultural beliefs aretwo of the main factors."[4]

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

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

Definition of Epilepsy:

In 2013 an international taskforce of the ILAE shaped out a communal definition of Epilepsy.[(2)] This definition is useful for all or most practical purposes, thus more helpful in management. Epilepsy was defined as recurrent unprovoked seizures i.e 2 or more at least 24 hours apart. The revised practical definition implies that Epilepsy can be considered even after a single seizure in individuals who have other factors predictive of a second unprovoked seizure, a risk set at 60%. The factors include the diagnosis of an epilepsy syndrome, structural lesions like stroke, CNS infections, intraparenchymal contusions after trauma, as well as reflex seizures such as photosensitive seizures.[(3)]

Table 3[(2)]

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 thegeneral 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 GUIDELINES:
Questions Addressed

Q1-Q3 AEDs Initiation of 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-Q23 Epilepsy Diaries, lockets, keychain or bracelets, Help line

Qs1-3:
Initiation of Therapy:

To this day, Epilepsy remains a clinical diagnosis and making the correct diagnosis is essential for proper management. The treatment and AED selection depends on the type and frequency of seizures (Annex E for status epilepticus), the seizure and syndrome type, (see Annex A for classification guidelines) the patients gender,(see Annex C for Women) age group (Annex B for neonates and children and Annex D for elderly) and underlying physical and mental health. But for the purpose of General Management guidelines initiation of therapy will focus on Focal Epilepsies and Generalized 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,
- Prognosis,
- need for medication
- compliance
- life style

Life style modification includes

- Adequate sleep - early to bed early to rise
- Change in job e.g. professional drivers, 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, ketogenic diet
- Joining support groups, Avoid social isolation

Pharmacological treatment of epilepsy

The mainstay of pharmacologic treatment is AEDs, their proper selection and counselling of the patient and their care givers on the duration of therapy .It is important that Doctor discusses these clearly with patient but giving them hope of cessation of therapy if compliance is maintained.

When to Start AEDs after first seizures

Whether to treat first seizure is controversial studies show 16-62% recur within 5 years, depending on which review to consider. 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) When to Start AEDs after first seizures

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

- It should be kept in mind that there is no ideal AED. An AED is a drug which decreases the frequency and/or severity of seizures in people with epilepsy
- AED treats the symptom of seizures, not the underlying epileptic condition*
- Our goal should be to maximize quality of life by minimizing seizures and adverse drug effects.

Table 5: Shows factors determining AED suitability

Factorsdetermining AED suitability include:

a) seizure type and/or epilepsy syndrome;
b) childbearing potential;
c) the presence of comorbidity;
d) individual and/or carer preferences;
e) the presence of contraindications to the drug;
f) potential interactions with other drugs;
g) potential adverse effects
h) the licensed indication of the drug.
i) Cost of AED
j) Patients socio-economic status
k) Age
l) Compliance
m) AED availability
n) Adult lifestyle

Principals of Managements:

Focused Goals:

- Complete control of seizures
- No/minimum adverse events
- No/minimum drug-drug interactions
- Improve quality of life
- optimize growth and development in pediatric patients

Management Strategy:

It is recommended that PWE should be initiated on Monotherapy (single AED). If the initial treatment is unsuccessful, then monotherapy using another drug can be triedNever to start on two drugs unless a temporary build up period is required or patient has a progressive epilepsy syndrome with very frequent daily seizures.

For Example Follow below strategy:

- Monotherapy
- Monotherapy(2nd Agent) (titrate second first then taper first) Caution Pt may have seizure during transition!
- Monotherapy (additional trials) or Combination of 2AEDs
- Combination of 2 AEDs (additional trials), Reconsider diagnosis!
- Evaluation for surgery or three AEDs
- VNS
- Ketogenic diet

Points To Note:

1. The diagnosis of epilepsy needs to be critically evaluated if events continue despite an optimal dose of two firstline AEDs, before combination therapy is considered,
2. PWE should be given a trial of at least 2-3 appropriate monotherapy regimens, with caution during the transition.
3. If an AED has failed because of adverse effects it should be stopped immediately and a second effective firstline drug initiated.
4. If an AED has failed due to continued seizures, a second drug should be started and built to adequate dosetolerated dose and then the first drug should be tapered off slowly.
5. It should be noted that some PWEs like (un-affording families, teenagers, concerned parents, common belief that drugs are harmful) may choose not to takeAED therapy. In these cases reasons should be sought and addressed accordingly. It should be clarified if risk of recurrence is high as described in table 3.

Table 6: shows different AEDs and their three letter abbrviations ,common side-effects

Medication	Usual Starting Dose	Titrated Up or Down By	Usual Maximum Daily Dose	Common Side Effects	Summary Of Indications
Acetazolamide (AZM)	250 mgs bd	250mgs every week	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 week	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 week	Up to 60 mgs daily	Drowsiness, addictive	Adjunctive for all sz type, espDravets syndrome
Clonazepam (CLB)	0.5 mgs bd	0.5 mgs	8 mgs daily	Drowsiness ↑Resp. secretions in children Addictive	Adjunctive for all refractory sz types as rescue use
Diazepam (DZP)	5-10mgs daily	2.5-5mgs	30mgs per day	Drowsiness Addictive	Prolonged/cluster seizuresi.v use or rectally for children
Eslicarbazepine acetate (ESL)	400mg/day		400mg/day	Contraindicated in heart block Encephalopathy, neutropenia, huponatremia *Rash	Mono/Adjuctive for partial sz.
Ethosuximide* (ESM)	250 mgs bd	250 mgs every week	2000 mgs daily	GIT Dist. Drowsiness	Mono/adjunctive for absence szs
Ezogabin[!!] (retigabin)	-	-	-	Blue discolation of skin and retinal changes	(held from market for now)
****Felbamate**	300 mgs tds	300 mgs every week	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 1-2 weeks	3600 mgs daily In divided doses	GIT Dist. Weight Gain Dizziness	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 Renal	Mono/adjunctive for all sz types
Lorazepam (LZP)	1-2 mgs daily	1-2 mgs	4 mgs daily	Drowsiness Dependence Respiratory depression	Adjunctive for all sz types Rescue use.
Midazalom	10 mgs daily	N/A	20 mgs	Drowsiness Respiratory depression	For prolonged or clusters of all szs. Rescue use **Status Epilepticus i.v, i.m, intranasal**
Oxcarbazepine (OXC)	Initially 300mgs twice daily 5-8mg/kg/day	Increased according to response in steps of up to 600mgs daily at weekly intervals	2400 daily In divided doses 5-15mg/kg/day	Encephalopathy Neutropenia Hyponatremia *Rash	Mono/adjunctive for partial onset Szs +/- sec gen
Perampanel *	4mg/day Can titrate to 8-12mg/day	Increased according to response and SE		Dizziness aggression GIT Boxed warning	Adjunctive partial seizures +/- sec gen.
Primidone* (PMD)	Initially 125mgs at bedtime	Increased by 125mgs every 3 days to 500mgs daily in 2 divided doses (250mgs bd), then increased according to response by 250mgs 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 week	1600mgs BD daily	GIT Dist. Dizziness, fatigue	Adjunctive for Lennox – Gastaut
Tiagabine* (TGB)	5mgs bd	5-10mgs every 1week	30-45mgs daily (doses above 30mgs 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 week	400mgs daily (mono) In 2 divideddoses 800mgs (adjunctive) In 2 divided doses (6-9mg/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 infants	100-250mgs every week	3000 mgs daily 15mg/kg/day	Weight Gain Tremor, hair loss	Mono/adjunctive for all sz types
	10mg/kg/day children			Liver Toxicity ↑ 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.
!! Withdrawn at present
Rash All AEDs carry the risk of rash, however the drugs highlighted as Rash carry a risk of Stevens-Johnsons Syndrome, toxic epidermolysis

 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 possibletoxicity: Diplopia, blurred vision, unsteady gait, excessive tiredness, new onset of dizziness, sometimes increase in seizures (as with PHT).
• 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 Selection some guiding principles:

1. When possible, choose AED 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), i.e Focal or generalised.
2. Selectingcommonly available manufacturer's AED preparation isrecommended. Changing preparations of some AEDs may vary in bioavailability or pharmacokinetic profiles therefore disrupting seizure control.
3. Where Focal seizures are suspected prefer sodium channel blockers as first line AEDs (see fig 1)
4. Where generalized seizure syndromes are suspected consider broader spectrum AEDs (see fig 1)
5. 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 However sub-optimal preparations need to be avoided.
6. Phenobarbitone (PB) should be offered where compliance due to cost is suspected.
7. Valproate is another broad spectrum AED, cost effective and easily available but should be avoided in women of child baring age, lamotrigine is an alternative for women with epilepsy but need to be aware of risk of skin rashes (see 11). Levitiracetam (LEV) should be considered as an emerging first line AED for generalized Epilepsies.
8. Carbamazepine(CBZ) and lacosamide are two commonly available sodium channel blockers and
9. If using carbamazepine and valproate, check LFTs, serum amylase.
10. When prescribing sodium valproate(VPA) to women and girls of present and future childbearing potential discuss the possible risk of malformation and neurodevelopmental impairments in 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.
11. Lamotrigine (LTG) 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.
12. Levitiracetam should be given with neuropsychiatric issues in mind and a pyridoxine supplement.
13. Renal clearance should be kept in mind when giving LEV, TPM, LCM especially in elderly.

How to continue AEDs and Follow-up visits guideline:

1. It is imperative for the physician to have a treatment plan and schedule follow-up visits. This should include the patient and/or caregiver and they should be mentally prepared for a long-term AED use.
2. Monthly visits till stable, then 3 visits every 3 months and then when completely stable 6monthly to ensure compliance, review side-effects and treatment plan.
3. PWE should be counselled to follow-up immediately if adverse effects (for example, bone health issues, blood dyscrasias, and neuropsychiatric issues,excessive drowsiness,) or if there is increase in seizure frequency.
4. If management is complicated, PWE should be referred to specialist.
5. All PWE should be counselled about action to be taken after a missed dose or after a gastrointestinal upset like diarrhea and vomitting.
6. The risks and benefits of continuing or withdrawing AED therapy should be discussed with PWEwho have been seizure free for at least 2 years and patient lifestyle modifications and risk of recurrence should be understood by PWE.
7. 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 to specialist is more cost effective.

Examples of blood tests include:

1. 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
2. Before surgery – clotting studies in those on sodium valproate should be checked.
3. For Patients on enzyme inducing AEDs (CBZ,

PHT, PB, PMD): CBC, Electrolytes, LFTs, Vit D levels, every 1-2 years.

4. Serum creatinine levels for those on drugs cleared through the kidney (LCM, LEV, TPM, GBT,)
5. Test for serum amino acids, TSH, B12, and urine for organic acids in all children with neonatal non-infectious seizures and refractory seizures and for all those with consanguineous parents.
6. Asymptomatic minor abnormalities in test need not change AED but keep vigilance on.
7. Serum Blood levels of AEDs should be done if non-compliance or toxicity is suspected, or when there is breakthrough seizure after a period of seizure freedom.

Compliance can be optimized with the following:

- Educating the PWE and their caregivers in a positive and hopeful way.
- Reducing the stigma associated with the condition
- Using simple and cost effective medication regimens
- Minimising side effects.
- Being available to counsel the patient as needed.
- SMS bulk reminder module

Discontinuation of AEDs :

1. Ideally A sleep deprived EEG should be done prior to considering medicine taper.
2. Patient should be seizure free for at least 2 years on AEDs.
3. 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.
4. 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.
5. PWE and caregiver should be counseled if seizures recurs the last dose reduction is reversed and schedule visit immediatly.

AED-AED and AED-Drug Interactions

The list below is to help guide the physician to select the most appropriate AED when the patient is on other classes of drugs and multiple medications. Some common interactions between antiepileptic drugs and non!antiepileptic drugs are listed below in table 7. Table 8 is a list of AEDs and interactions to help guide the physician to select the most appropriate AED when a patient is on other classes of drugs. The tables list only the common drugs used and interactions noted and are in no way exhaustive.

Table 7.Few 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 otherliqu- id medicines with CBZ suspension can cause rubbery precipitate in stool. Co-administration with lithiumcan↑ neurotoxic SE. Other AEDs may alter thyroid functions. ↓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, cimitidine	CBZ
Divalproate Sodium, Valproic 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.

Modified from j. primary psych 2005

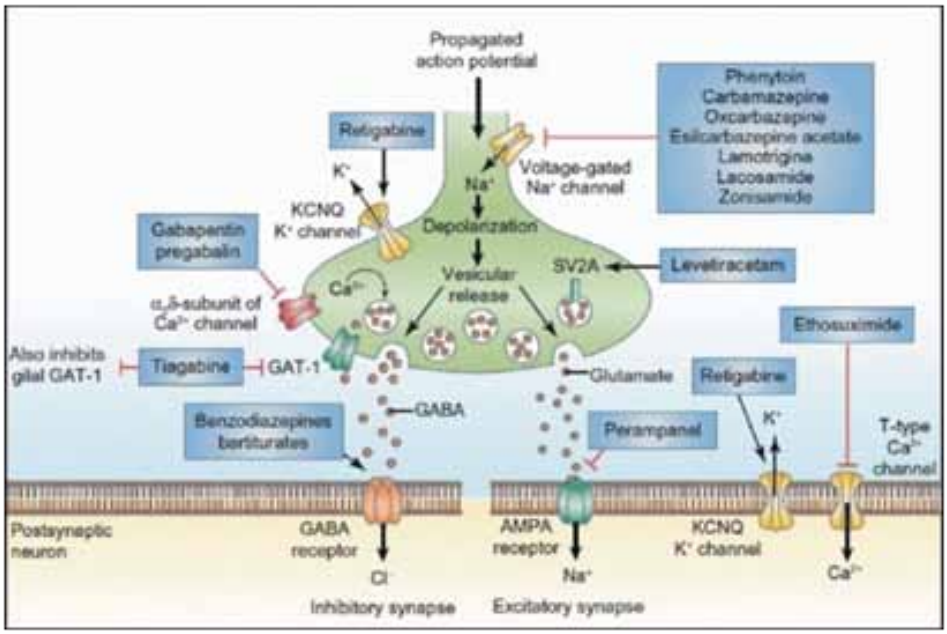
Table 5 AED interactions with other drug classes

	Enzyme inducers			VPA	LTG	ZNG	ETX	CLZ	CLB	OXZ	TPM	FLB	TIG	LEV	LAC
	PHT	CBZ	PHB												
Anticoagulants															
Apixaban	⊗↓	⊗↓	–	–	–	–	–	–	–	–	–	–	–	–	–
Dabigatran	↓	↓	↓	–	–	–	–	–	–	–	–	–	–	–	–
Edoxaban	↓	↓	↓	–	–	–	–	–	–	–	–	–	–	–	–
Rivaroxaban	↓	↓	–	–	–	–	–	–	–	–	–	–	–	–	–
Warfarin	↓*↑	↓	↓	↑	–	–	–	–	–	↓/↑	↓	↑	–	–	–
Typical antipsychotics															
Droperidol	–	–	S	–	–	–	–	S	S	S	–	–	–	–	–
Haloperidol	–	↓	S	–	–	–	–	S	↑	–	S	–	–	–	–
Trifluoperazine	–	–	S	–	–	–	–	S	–	–	S	–	–	–	–
Atypical antipsychotics															
Aripiprazole	↓	↓	↓S	–	–	–	–	S	↑S	↓	↓S	–	–	–	–
Asenapine	–	↓	↓	–	–	–	–	–	S	–	–	–	–	–	–
Clozapine	↓	⊗↓	↓S	↓	–	–	–	S	S	↓	↓S	–	–	–	–
Lurasidone	⊗↓S	⊗↓S	⊗↓S	–	S	S	S	S	–	⊗↓	S	S	S	S	–
Olanzapine	–	↓	↓S	–	–	–	–	S	S	–	S	–	–	–	–
Paliperidone	↓	↓	↓S	–	–	–	–	S	S	–	S	–	–	–	–
Quetiapine	↓	↓*↑	↓S	–	–	–	–	S	S	↓	↓S	–	–	–	–
SSRIs															
Citalopram	–	↓	–	–	S	–	–	–	–	–	–	–	–	–	–
Paroxetine	–	–	–	–	S	–	–	–	↑	–	–	–	–	–	–
Fluoxetine	*↑	*↑	–	–	S	–	–	–	↑	–	–	–	–	–	–
Sertraline	↑	*↑	–	–	S	–	–	–	↑	–	–	–	–	–	–
SNRIs															
Duloxetine	–	↓	↓	–	–	–	–	–	↑	–	–	–	–	–	–
Venlafaxine	–	–	–	–	–	–	–	–	↑	–	–	–	–	–	–
TCAs															
Amitriptyline	↓*↑	↓	↓S	–	–	–	–	S	↑S	↑	↓S	↑	–	–	–
Nortriptyline	↓	↓	↓S	–	–	–	–	S	↑S	–	S	–	–	–	–
MAOIs															
Phenelzine	–	⊗	*↑	–	–	–	–	–	–	–	–	–	–	–	–
Other antidepressants															
Bupropion	–	↓	↓	–	–	–	–	–	–	–	–	–	–	–	–
Mirtazapine	–	–	S	–	–	–	–	S	↑S	–	S	–	–	–	–

Notes: ↓, AED causes decrease in medication level/efficacy; ↑, AED causes increase in medication level/efficacy; *↓/*↑, medication causes decrease or increase in AED level/efficacy; ⊗, combination contraindicated; S, increased CNS depression; ↓/↑, OXZ decreases warfarin by CYP34A but increases it by CYP2C19.

Abbreviations: AED, antiepileptic drug; PHT, phenytoin; CBZ, carbamazepine; PHB, phenobarbital; VPA, valproic acid; LTG, lamotrigine; ZNG, zonisamide; ETX, ethosuximide; CLZ, clonazepam; CLB, clobazam; OXZ, oxcarbazepine; TPM, topiramate; FLB, felbamate; TIG, tiagabine; LEV, levetiracetam; LAC, lacosamide; SSRIs, selective serotonin-reuptake inhibitors; SNRIs, selective serotonin–norepinephrine reuptake inhibitors; TCAs, tricyclic antidepressants; MAOIs, monoamine oxidase inhibitors; CNS, central nervous system.

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



Initiation of AEDs Drug choice with seizure type:

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

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
Lacosamide LCM	Valproate VPA	TiagabinTGN*
Oxcarbazepine OXC	Topiramate TPM	EsilCarbazepine Acetate ECA*
Lamotrigine LTG	Gabapentine GBP	ZonisamideZNS*
Phenobarbitone PB	Phenytoin PHT	Perampanel*
		Clobazam CLB
		Rufinamide*
		Vigabatrin
*Not available in Pakistan		

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

Recommendations:

1. Offer CBZ/ OXC/LTG/LCM or PB (where cost is an issue) as first line treatmentto 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 welltolerated AED is ineffective
4. If adjunctive treatment is ineffective or not tolerated, discuss with, or refer to, an epilepsy specialist.Other AEDs that may be considered by the epilepsy specialist are eslicarbazepine acetate(ECA), clobazam, phenytoin, pregabalin, tiagabine, vigabatrin and zonisamide.

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	OXC	PHT
	PHT	PHT	OXC
	LTG	LTG	LTG
	LCM	LEV	VPA
		ZNS	LEV

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

According to the ILAE studies, "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)

AED Selection General Recommendations:

1. VPA as first-line treatment to adults with newly diagnosed GTCs, avoiding women of childbaring age if possible. (teratogenic risks of sodium valproate in women of child bearingage)
2. LTG if VPA is unsuitable. LEV,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. LEVand TPM in patients where VPA and LTG are not suitable.
4. CBZ, OXC, PHT 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, PHT.) (Be aware of word finding difficulties and renal stones with TPM)
5. If there are absence or myoclonic seizures, or if JME is suspected, do not use CBZ, GBT, OXC, PHT, pregablin , tiagabine or vigabatrin

Table 10. Generalized Tonic Clonic Epilepsy – AEDs of choice

1st line	2nd line	3rd line
VPA LTG # TPM LEV	TPM ZNS* LEV PB PHT #	CNZ CBM GBP CBZ # 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 mono-therapy	VPA LTG	VPA ESM	VPA LEV
2nd Mono-therapy if VPA failed	LTG LEV	ESM LTG	LEV TPM
2nd Mono-therapy if LTG/LEV failed	TPM LEV LTG ZNS	LEV VPA ESM ZNS LTG	TPM LEV VPA ZNS

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 carbohydrate (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
- Very effective in children with gluten related genetic defects
- Recommended in refractory epilepsies in children where multiple regimens of AEDs proven ineffective
- Local ketogenic recipies are available and cost effective.

Epilepsy Surgery

- Upto 85% seizure-free rates if proper selection of patients.

Types of surgical options:

- **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 undergo and MRI seizure protocol (Appendix) and 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 assist the primary care physician to identify the PWE and select an appropriate AED, and be involved in the care and management in a systemic and organized manner. The guidelines are aimed to minimize inappropriate or inadequate treatment methods, identify preventable etiologies, make individualized selections for women and children with epilepsy, advice about pregnancy and contraception. Guidelines for selecting AEDs in elderly are also provided with common drug interactions. A protocol for Status Epilepticus in adults and children is also included, with the hope of achieving a standardized level of care. These guideline will be revisited and modified on applicability every three years.

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