Ministry Of Health
General Directorate of Khoula Hospital
Neurology Department

Institution Name: Directorate general of khoula hospital

Document Title: Guidelines For Adult Patient with Epilepsy/Seizure Disorder

Approval Process

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Location of Original Copy: Document Owner

Distribution To: Quality Management & Patient Safety Directorate & Shared File

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Acronyms:

AED	Anti-Epileptic drug
ASE	Absence status epilepticus
CT	Computerized Tomography Scan
DRE	Drug-resistant epilepsy
EEG	Electroencephalography
ILAE	International League Against Epilepsy
MRI	Magnetic Resonance Imaging
DGMS	Directorate General of Medical Store

Guidelines for Adult Patient with Epilepsy/Seizure Disorder

1. Introduction:

Epilepsy is chronic non-communicable diseases of the brains that affects around 50 million people worldwide and close to 80% of them are found in developing regions. It is one of the world's oldest recognized conditions, with written records dating back to 4000 BC. Fear, misunderstanding, discrimination and social stigma have surrounded epilepsy for centuries. This stigma continues in many countries today and can impact on the quality of life for people with the disease and their families.

Epilepsy accounts for 0.5% of the global burden of disease, a time-based measure that combines years of life lost due to premature mortality and time lived in states of less than full health and it has significant economic implications in terms of health-care needs, premature death and lost work productivity.

In Oman, it is estimated that the same prevalence of the disease exist as in the other developing Arabic and Islamic countries (14 per 1000- WHO Statistics). To summarize the guidelines for management of an adult patient with first time seizure or a known epileptic patient presents with seizure, the following algorithm is recommended see **appendix 1.**

2. Scope

The scope of this guideline is to manage Epilepsy with the best healthcare services by Neurology, Emergency, Neurosurgery, Neurophysiology, Neuroradiology Pathology and Pharmacy departments in Koula Hospital, MOH-Oman.

3. Purpose:

3.1. This guideline is aiming to guide assessing and managing adults with epilepsy.

3.2. It aims to provide the best healthcare, from the time of diagnosis, and covers information and support, organisation of care, and managing symptoms, as well as complications of the disease.

3.3. To provide a standardized approach to the management of patients with Epilepsy in all involved departments at Khoula hospital

4. Definitions

4.1. Seizure: An abnormal excessive or synchronous neuronal activity/discharge in the brain.

4.2. Convulsion: A sudden, violent, irregular movement of a limb or the body caused by involuntary contraction of muscles and associated especially with brain disorders such as epilepsy, the presence of certain toxins, metabolic derangement or fever in children.

4.3. Epilepsy: Recurrent attacks of disturbance in brain function which can be manifested as motor, sensory, behavior, or cognitive, due to abnormal neuronal excitation in one or more than one region of the brain.

Epilepsy is a syndrome. it's a manifestation of a disease, It is a social stigma affecting the patient and his family, marriage, pregnancy, work, driving, sports in addition to serious idiosyncratic reaction from drugs even death .

5. Guideline:

5.1. Management of first Seizure:

5.1.1. Stabilize the Patient, maintain open airway, BP, saturation, temperature, if the patient is still seizing then abort the attack by IV 5mg diazepam, 2 mg of Midazolam or 2 mg Lorazepam.

5.1.2. Detailed history of patient should be taken include the following:

A. Make sure whether the seizure provoked or unprovoked

B. Make sure the attack is epilepsy not something Like pseudoseizure, Stockes-Adams attack, fainting attack…etc.

5.1.3. Check which type of epilepsy as there are many different seizures' types **(Figure 1)** and, therefore, classification of epilepsy is very important for the management **(Table 1).**

5.2 Diagnostic Approaches:

5.2.1. Brain imaging and investigation

A. Using computed tomography (CT) or preferably magnetic resonance imaging (Brain MRI) should be ordered.

B. Blood glucose, CBC, and electrolyte panels (particularly sodium) may be helpful in specific clinical circumstances and EEG.

C. Lumbar puncture may be helpful in patient with fever and seizure; however, LP is not routinely indicated.

D. A toxicological screening may be helpful in specific clinical circumstance, as well as history of alcohol abuse.

5.2.2. Electroencephalography (EEG):

A. The presence of electrical activity clearly establishes the diagnosis, however a normal EEG does not exclude the diagnosis, as only 50% of routine scalp EEG in epileptic patient can be abnormal.

B. a normal ictal EEG excludes the diagnosis because Epileptiform activity consist of burst of spikes &/or sharp waves.

C. the EEG is helpful in classifying epilepsy disorder and help in selecting the proper anti-epileptic medications.

D. EEG is helpful in assessing the prognosis as normal EEG carry a better prognosis than one with poor background or profuse epileptiform discharges.

E. EEG should be used to confirm, but not to exclude, a diagnosis of epilepsy.

5.3. Treatment with Anti-Epileptic Drugs (AEDs)

5.3.1. Initiate Antiepileptic Drug Therapy

A. Antiepileptic drug therapy should be started in any patient with recurrent seizures of unknown etiology or a known cause that cannot be reversed.

B. Whether to initiate therapy in a patient with a single seizure is controversial. Patients with a single seizure due to an identified lesion such as a CNS tumor, infection, or trauma, in which there is strong evidence that the lesion is epileptogenic, should be treated. This

uncertainty arises from differences in the underlying seizure types and etiologies in various published epidemiologic studies.

D. Generally accepted risk factors associated with recurrent seizures include the following:

I. An abnormal neurologic examination,
II. Seizures presenting as status epilepticus,
III. Postictal Todd's paralysis,
IV. A strong family history of seizures,
V. An abnormal EEG, or
VI. Abnormal imaging of the brain.

E. Most patients with one or more of these risk factors should be treated even if it's the first seizure.

5.3.2. Selection of Antiepileptic Drugs:

A. The appropriate choice of anti-epileptic medication varies depending on seizure type. AEDs are associated with significant adverse effects, including subtle cognitive and behavioral effects occurring in up to 50% of treated patients; therefore, delaying their use until a second seizure is reasonable in some cases.

B. Older medications such as phenytoin, valproic acid, carbamazepine, phenobarbital, and ethosuximide are generally used as first-line therapy for most seizure disorders because, overall, they are as effective as recently marketed drugs and significantly less expensive overall. Most of the new drugs that have become available in the past decade are used as add-on or alternative therapy, although many are now being used as first-line monotherapy. The likelihood of seizure freedom does not differ substantially whether a single established (67%) or a new-generation AED (69%) is used.

C. Patients whose epilepsy is well controlled should tolerate side effects. Because the response to any antiepileptic drug is unpredictable, patients should be carefully educated about the approach to therapy. The goal is to prevent seizures and minimize the side effects of treatment; determination of the optimal dose is often a matter of

trial and error. This process may take months or longer if the baseline seizure frequency is low. Most antiepileptic drugs need to be introduced relatively slowly to minimize side effects. Patients should expect that minor side effects such as mild sedation, slight changes in cognition or imbalance will typically resolve within a few days.

D. Monotherapy with all indicated AEDs should be attempted before initiating combination therapy.

E. Starting doses are usually the lowest value and subsequent increases should be made only after achieving a steady state with the previous dose (i.e., after an interval of five or more half-lives).

F. Monitoring of serum antiepileptic drug levels can be very useful for establishing the initial dosing schedule. However, the published therapeutic ranges of serum drug concentrations are only an approximate guide for determining the proper dose for a given patient. The key determinants are the clinical measures of seizure frequency and presence of side effects, not the laboratory values.

5.3.3. Antiepileptic Drug Selection according to the Type of Seizure (ILAE /AES Guidelines) **appendix 2** shows the available AEDs selection and administration according to the type of seizure in adults.

A. Antiepileptic Drug Selection for Focal Seizures

According ILAE treatment guidelines, first-generation AEDs Carbamazepine, Phenytoin, and probably Valproic acid have demonstrated effectiveness as monotherapy for partia/focal-onset seizures. According to AAN/AES subcommittees, of the second generation AEDS, Lamotrigine, Oxcarbazepine, and Topiramate may be effective for monotherapy, although the ILAE has added Gabapentin, Vigabatrin also as efficacious or effective monotherapy and Eslicarbazepine is another option.

Alternative choice in partial/focal seizures: If Carbamazepine is effective against seizures but poorly tolerated, try Oxcarbazepine or Lamotrigine next. If Carbamazepine fails to control seizures, Levetiracetam or Topiramate are likely to be more powerful than Gabapentin or Lamotrigine. Valproate also remains an option.

The choice of antiepileptic medications in focal seizure disorders is summarized in **Table 2**

B. Antiepileptic Drug Selection for Generalized Seizures

Valproate is recommended for patients who are first diagnosed with generalized seizure. If valproate fails as the first AED, Lamotrigine monotherapy is unlikely to be successful. Therefore, Topiramate or Levetiracetam are preferred. For non-motor (absence) seizure, the first single drug is Ethosuximide or Valproate. Lamotrigine can be considered if Ethosuximide or valproate were inappropriate, ineffective, or not tolerated by the patient. For myoclonic seizure, Valproate is recommended as the primary treatment. Levetiracetam, Zonisamide, and Topiramate can be considered as first-line antiepileptic drugs if Valproate is inappropriate. Clonazepam can also be used in myoclonic seizures and in absence seizues patients who failed succinimides.

The choice of antiepileptic medications in focal seizure disorders is summarized in **Table 3.**

5.3.4. Monitoring of AED Therapy

A. Routine monitoring of drug levels is not correlated with any reduction in adverse effects or improvement in effectiveness and is not recommended.

B. Routine monitoring of AED levels is not recommended unless clinically indicated.

C. Conventional assays of serum drug levels measure the total drug (i.e., both free and protein bound). However, it is the concentration of free drug that reflects extracellular levels in the brain and correlates best with efficacy. Thus, patients with decreased levels of serum proteins (e.g., decreased serum albumin due to impaired liver or renal function) may have an increased ratio of free to bound drug, yet the concentration of free drug may be adequate for seizure control. These patients may have a “sub-therapeutic” drug level, but the dose should be changed only if seizures remain uncontrolled, not just to achieve a “therapeutic” level. It is also useful to monitor free drug levels in such patients.

D. In practice, other than during the initiation or modification of therapy, monitoring of antiepileptic drug levels is most useful for documenting adherence.

5.3.5. Adding a Second AED Therapy

If seizures continue despite gradual increases to the maximum tolerated dose and documented compliance, then it becomes necessary to switch to another antiepileptic drug. This is usually done by maintaining the patient on the first drug while a second drug is added. The dose of the second drug should be adjusted to decrease seizure frequency without causing toxicity. Once this is achieved, the first drug can be gradually withdrawn (usually over weeks unless there is significant toxicity). The dose of the second drug is then further optimized based on seizure response and side effects. Monotherapy should be the goal whenever possible. Abrupt stoppage of AEDs should not be done except in few critical conditions like Steven Johnsons syndrome, fulminate hepatitis, severe bone marrow depression etc.

5.3.6. When to Discontinue Therapy

Overall, about 70% of children and 60% of adults who have their seizures completely controlled with antiepileptic drugs can eventually discontinue therapy. The following patient profile yields the greatest chance of remaining seizure free after drug withdrawal:

(1) Complete medical control of seizures for 1–5 years

(2) Single seizure type, either focal or generalized

(3) Normal neurologic examination, including intelligence

(4) Normal EEG

(5) Normal brain imaging.

The appropriate seizure free interval is unknown and undoubtedly varies for different forms of epilepsy. However, it seems reasonable to attempt withdrawal of therapy after 2 years in a patient who meets all of the above criteria, is motivated to discontinue the medication, and clearly understands the potential risks and benefits. In most cases, it is preferable to reduce the dose of the drug gradually over 2–3 months. Most recurrences occur in the first 3 months after discontinuing therapy, and patients should be advised to avoid potentially dangerous situations such as driving or swimming during this period.

5.4. Non-Pharmacological Treatments for Epilepsy

5.4.1. Surgical Intervention in Epilepsy

A. About 10% of patients need epilepsy surgery; it is the next treatment option after AEDs. Patients with disabling complex partial seizures, with or without secondary generalized seizures, who have failed appropriate trials of first-line antiepileptic drugs, should be considered for referral to an epilepsy surgery center.

Patients who meet the established criteria for antero-mesial temporal lobe resection and accept the risks and benefits of this procedure, as opposed to continuing pharmacotherapy, should be offered surgical treatment. Seizure freedom is achieved in up to 76% of patients after resection.

B. Factors associated with seizure freedom after surgery includes seizures without loss of consciousness, complete or extensive resection of the lesion, and prolonged febrile seizures.

C. Factors associated with postoperative recurrence includes non-lesioned (non-structural) epilepsy, normal magnetic resonance imaging, preoperative generalized tonic-clonic seizures, and infantile spasms or tonic seizures. Also, the need for invasive intracranial EEG monitoring to determine seizure focus predicts a worse outcome.

D. Cognitive deficits are common following surgery and depend on the site of the resection. Left temporal lobe resection is associated with verbal memory deficits (44%) and naming deficits (34%). After a right temporal lobe resection, verbal memory deficits are also common (20%).

E. Operative mortality in most centers is below 0.5%. Lower mortality is associated with procedures limited to the temporal lobe.

F. Other adverse effects include neurologic deficits (5%).

6. Responsibilities

6.1.Head of Neurology shall:

6.1.1. Ensure all doctors are aware about these guidelines.

6.1.2. Ensure all staff are adhering to these guidelines.

6.2.Neurology Doctors shall:

6.2.1. Aware and adhere about this guideline
6.2.2. liaise with pharmacist about the medication availability
6.2.3. monitor the side effect of the medications

6.3.Head of Pharmacy:

6.3.1. Ensure all staff are adhering to these guidelines.

6.3.2. Ensure all staff are Checking prescription before dispensing.

6.3.3. Ensure the availability of medication and approval from DGMS

7. Document History and Version Control

Document History and Version Control			
Version	**Description of Amendment**	**Author**	**Review Date**
01	Initial Release		
02			
03			
04			
05			

Written by	**Reviewed by**	**Approved by**

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Title of book/ journal/ articles/ Website	Author	Year of publication	Page
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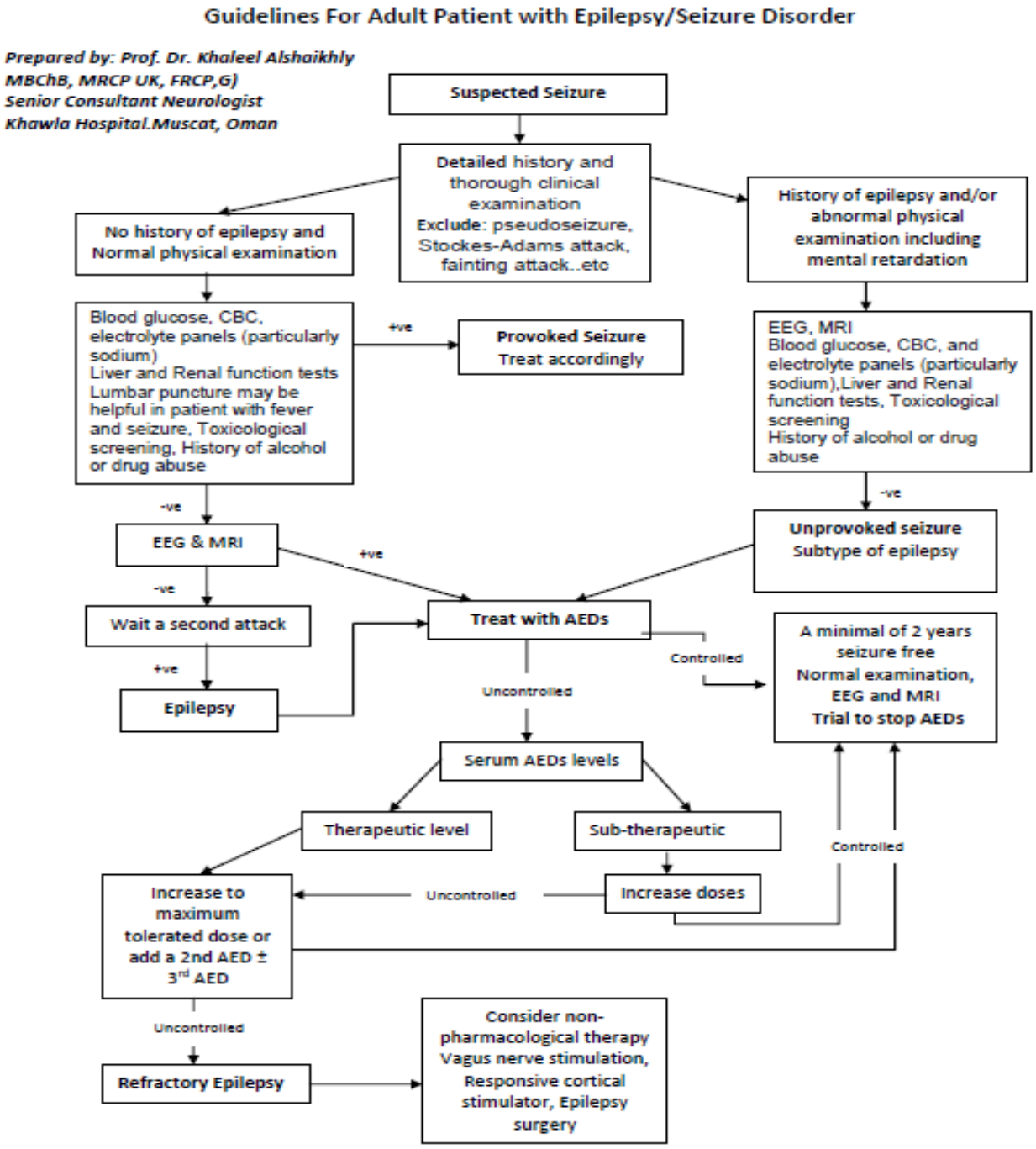
Appendix 1.


Guidelines For Adult Patient with Epilepsy/Seizure Disorder
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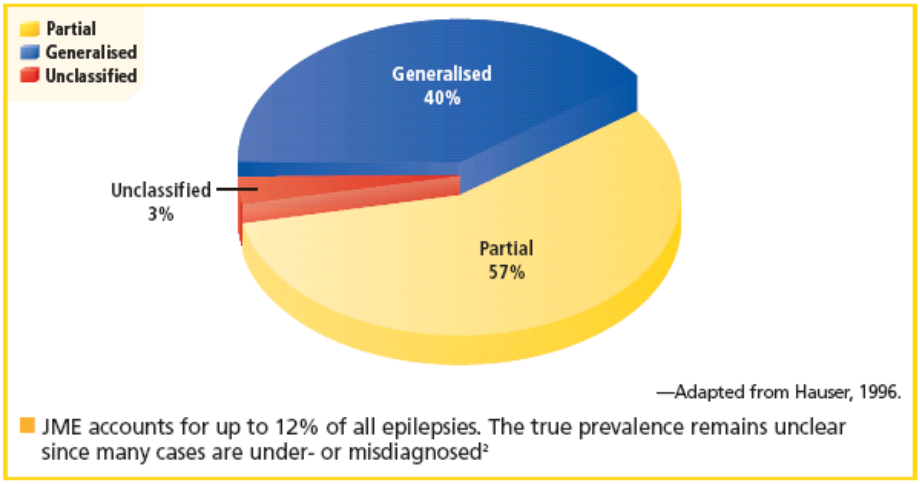
Suspected Seizure
Detailed history and thorough clinical examination
Exclude: pseudoseizure, Stockes-Adams attack, fainting attack..etc
No history of epilepsy and Normal physical examination
History of epilepsy and/or abnormal physical examination including mental retardation
Blood glucose, CBC, electrolyte panels (particularly sodium)
Liver and Renal function tests
Lumbar puncture may be helpful in patient with fever and seizure, Toxicological screening, History of alcohol or drug abuse
+ve
Provoked Seizure
Treat accordingly
EEG, MRI
Blood glucose, CBC, and electrolyte panels (particularly sodium),Liver and Renal function tests, Toxicological screening
History of alcohol or drug abuse
-ve
-ve
EEG & MRI
+ve
Unprovoked seizure
Subtype of epilepsy
-ve
Wait a second attack
Treat with AEDs
+ve
Epilepsy
Controlled
A minimal of 2 years seizure free
Normal examination, EEG and MRI
Trial to stop AEDs
Uncontrolled
Serum AEDs levels
Therapeutic level
Sub-therapeutic
Controlled
Increase to maximum tolerated dose or add a 2nd AED ± 3rd AED
Uncontrolled
Increase doses
Uncontrolled
Refractory Epilepsy
Consider non-pharmacological therapy
Vagus nerve stimulation, Responsive cortical stimulator, Epilepsy surgery

Figure 1



Percentages of types of Seizures

Table 1: ILAE 2017 Classification of Seizure Types

Focal Onset	Generalized Onset	Unknown Onset
Aware | Impaired Awareness		
Motor Onset automatisms atonic [2] clonic epileptic spasms [2] hyperkinetic myoclonic tonic **Non-Motor Onset** autonomic behavior arrest cognitive emotional sensory	**Motor** tonic-clonic clonic tonic myoclonic myoclonic-tonic-clonic myoclonic-atonic atonic epileptic spasms **Non-Motor (absence)** typical atypical myoclonic eyelid myoclonia	**Motor** tonic-clonic epileptic spasms **Non-Motor** behavior arrest
focal to bilateral tonic-clonic		Unclassified [3]

[1] Definitions, other seizure types and descriptors are listed in the accompanying paper and glossary of terms

[2] Degree of awareness usually is not specified

[3] Due to inadequate information or inability to place in other categories

Table 2: Antiepileptic Drug Selection for Focal Seizures

Treatment of Epilepsy
The Expert Consensus

First-line Medications by Dominant Seizure Type

Simple partial	Complex partial	Secondary generalized
Carbamazepine	**Carbamazepine**	**Carbamazepine**
Oxcarbazepine	**Lamotrigine**	**Oxcarbazepine**
Lamotrigine	**Oxcarbazepine**	Lamotrigine
Levetiracetam	Levetiracetam	Levetiracetam

Table 3: Antiepileptic Drug Selection for Generalized Seizures

Treatment of IGE
The Expert Consensus

First-line Medications by Dominant Seizure Type

Generalized Tonic Clonic	Absence	Myoclonic
Valproate	**Valproate**	**Valproate**
Lamotrigine	**Ethosuximide**	
Topiramate	Lamotrigine	Clonazepam

Appendix 2: Available Antiepileptic Medication Selection According to the Type of Seizure in Adults

AEDs	Focal Seizure			Generalized Seizure			Loading Dose	Maintenance Dose
	Focal Aware or Simple partial	***Focal Impaired Awareness or Complex partial***	***Secondary generalized***	***Tonic clonic***	***Absence***	***Myoclonic***		
Phenytoin Na 100 mg Cap 6mg/ml suspension		✓		✓			• 1 g PO divided into three doses (400 mg, 300 mg, 300 mg) and administered at two-hour intervals (in adults requiring rapid steady-state serum levels & IV not recommended. • This regimen should be applied at a health facility setting where phenytoin serum levels can be measured. • Patients with history of renal or liver disease should not receive the oral loading regimen; normal maintenance dosage is then initiated 24 hours after the loading dose, with frequent serum level monitoring.	• 100-mg capsules TID daily or single dose of 300 mg capsules OD or 150-300 mg divided into 2 doses. • Usual maintenance dose 200-500 mg/day after food. • Dose to be increased gradually. • Measure serum total concentrations between 10 and 20 mcg/mL (unbound phenytoin concentrations between 1 and 2 mcg/mL) to avoid toxicity.
Sodium Valproate 200 mg tab 500 mg tab 57.64mg/ml syrup		✓	✓	✓	✓	✓	• Initiate therapy at 10 to 15 mg/kg/day or 600 mg daily in 1-2 divided doses. • Increase dose by 5 to 10 mg/kg/week or increased in steps of 150-300 mg every 3 days to achieve optimal clinical response.	• 1-2 g daily or 20-30 mg/kg daily (2.5g/day). • Total daily dose to be divided into 1-2 doses. • If satisfactory clinical response not achieved; plasma levels should be

								measured to determine whether or not, they are in the usually accepted therapeutic range (50 to 100 mcg/ml).
Carbamazepine 200 mg tab 200 mg Controlled release tab	✓	✓	✓	✓			• Either 200 mg twice a day for tablets and CR tablets. Increase at weekly intervals by adding up to 200 mg/day using a twice a day regimen of Carbamazepine –CR or a three times a day or four times a day regimen of the other formulations until the optimal response is obtained.	• Usual dose 800-1200 mg in divided doses; increased if necessary up to 1.6-2 g daily in divided doses. • Adjust dosage to the minimum effective level, usually 800 to 1200 mg daily. • Generally, dose should not exceed 1200 mg daily in patients above 15 years of age. • Doses up to 1600 mg daily have been used in adults rarely.
Oxcarbazepine 600 mg tab	✓	✓	✓				• 300 mg BD, then increase in steps of up to 600 mg daily, adjusted according to response, dose to be adjusted at weekly intervals. • The maximum daily dose is 1200 mg/day. • As monotherapy, the dose should be increased by 300 mg/day every third day to a dose of 1200 mg/day	• 600-1200 mg/day in divided doses. • Larger doses showed somewhat greater effectiveness in controlled trials, but most patients were not able to tolerate 2400 mg/day dose because of CNS effects.
Phenobarbital 30 mg tab		✓	✓	✓			—	• Adults oral sedative dose, 30 - 120 mg daily in 2 or 3 divided doses.

Lamotrigine 25 mg tab 50 mg tab	✓	✓	✓	✓	✓	✓	**<u>Immediate-Release (IR) Formulations</u>:** For Patients Taking VALPROATE: -Initial dose: 25 mg orally every other day (week 1 and 2), then 25 mg orally once a day (week 3 and 4) -Maintenance dose (week 5 and onward): Increase by 25 to 50 mg/day every 1 to 2 weeks --Usual maintenance dose with valproate alone: 100 to 200 mg/day in 1 or 2 divided doses --Usual maintenance dose with valproate and other drugs that induce lamotrigine glucuronidation: 100 to 400 mg/day in 1 or 2 divided doses For Patients NOT Taking CARBAMAZEPINE, PHENYTOIN, PHENOBARBITAL, PRIMIDONE, OR VALPROATE: -Initial dose: 25 mg orally once a day (week 1 and 2), then 50 mg orally once a day (week 3 and 4) -Maintenance dose (week 5 and onward): Increase by 50 mg/day every 1 to 2 weeks --Usual maintenance dose: 225 to 375 mg/day in 2 divided doses For Patients Taking CARBAMAZEPINE, PHENYTOIN, PHENOBARBITAL, PRIMIDONE, RIFAMPIN, or LOPINAVIR/RITONAVIR, and NOT taking VALPROATE: -Initial dose: 50 mg orally once a day (week 1 and 2), then 100 mg orally once a day (week 3 and 4) -Maintenance dose (week 5 and onward): Increase by 100 mg/day every 1 to 2 weeks --Usual maintenance dose: 300 to 500 mg/day in 2 divided doses valproate	
Levetiracetam 500 mg tab 100mg/ml syrup	✓	✓	✓	✓		✓	• Initially 250 mg OD daily for 1-2 weeks, then increase in steps to 250 mg BD (max. pre dose 1.5 g BD daily) adjusted according to response, dose to be increased every 2-4 weeks.	• Daily dose may be depending on the patient response to treatment. Additional dosing increments may be given (1000 mg/day

								additional every 2 weeks) to a maximum recommended daily dose of 3000 mg. There is no evidence that doses greater than 3000 mg/day confer additional benefit.
Topiramate 25 mg tab 50 mg tab 100 mg tab	✓	✓		✓			**MONOTHERAPY:** <u>Immediate-Release: 400 mg orally daily in 2 divided doses</u> -The dose should be achieved by titration according to the following schedule: Week 1: 25 mg orally in AM and 25 mg orally in PM Week 2: 50 mg orally in AM and 50 mg orally in PM Week 3: 75 mg orally in AM and 75 mg orally in PM Week 4: 100 mg orally in AM and 100 mg orally in PM Week 5: 150 mg orally in AM and 150 mg orally in PM Week 6: 200 mg orally in AM and 200 mg orally in PM **ADJUNCTIVE THERAPY**: <u>Immediate-Release:</u> -Partial onset seizures: 200 to 400 mg orally daily in 2 divided doses -Primary generalized tonic-clonic seizures: 400 mg orally daily in 2 divided doses The dose should be achieved by titration: Initiate with 25 to 50 mg orally once a day; increase in increments of 25 to 50 mg orally daily every week to an effective dose.	
Clonazepam 0.5 mg tab 2 mg tab					✓	✓	• Adult: Initially 1 mg OD daily for 4 nights, increase dose over 2-4 weeks (initial dose for seizure disorders should not exceed 1.5 mg/day divided into three doses). • Elderly: Initially 0.5 mg OD daily for 4 nights, increase dose over 2-4	• 4-8 mg daily, adjust according to response. • Dosage may be increased in increments of 0.5 to 1 mg every 3 days until seizures are adequately controlled

							weeks.	or until side effects preclude any further increase. Maximum recommended daily dose is 20 mg. • Usually doses are administered at night & may be given in 3-4 divided doses
Lacosamide 100mg tab. (form A)	✓	✓					• **Monotherapy:** 100 mg twice daily (200 mg per day) • **Adjunctive Therapy:** 50 mg twice daily (100 mg per day) • **Alternate Initial Dosage:** 200 mg single loading dose, followed 12 hours later by 100 mg twice daily • **Titration** Increase by 50 mg twice daily (100 mg per day) every week	• **Monotherapy:** 150 mg to 200 mg twice daily (300 mg to 400 mg per day) • **Adjunctive Therapy:** 100 mg to 200 mg twice daily (200 mg to 400 mg per day)
Gabapentin 300mg cap	✓	✓	✓				• The starting dose is 300 mg three times a day.	• The recommended maintenance dose of Gabapentin capsules is 300 mg to 600 mg three times a day. • Dosages up to 2,400 mg/day have been well tolerated in long-term clinical studies. • Administer Gabapentin capsules three times a

								day using 300 mg capsules. The maximum time between doses should not exceed 12 hours.