Epilepsy and epileptic disorder guidelines for diagnosis and treatment

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| --- | --- | --- |
| **Drugs available in Iraqi hospitals**  | **Drugs only available in private sectors**  | **Not available**  |
| sodium valproate  | levetiracetam  | clobazam  |
| Phenytoin | vigabatrin | zonisamide |
| phenobarbital, | pregabalin | tiagabine |
| carbamazepine | lacosamide, | eslicarbazepine acetate,  |
|  | oxcarbazepine, | **Stripentol**  |
|  | topiramate | ethosuximide |
|  | lamotrigine, | rufinamide |
|  | gabapentin |  |

**1-INTRODUCTION**

 In Iraq Accurate estimates of incidence and prevalence of epilepsy are difficult to achieve because people who may have epilepsy try to hide the disease as it is considered stigma especially in females. Good communication between treating physician and epileptic patient and their family is essential to decide the appropriate treatment choice in order to achieve the seizure free with no or minimal side effects

 The first priority in managing epileptic patient  is to ensure precise and early diagnosis and initiation of therapy as appropriate to their needs. .

* 1. **DEFINITIONS**

 **1-1-A First line treatment** – this refers to a drug that is tried first and usually used on its own. If more than one AED is listed in this row, one AED will be chosen and tried on its own first. If it does not work, the another may be tried, or a drug from the ‘alternative first line drug’ list might be used.

 **1-1-B Alternative first line treatment** – this is the ‘second round’ of AEDs that are tried. Like the ‘first line treatment’ they are usually tried on their own, although sometimes combinations might be used.

 **1-1-C Adjunctive treatment** (or ‘add-on treatment’) – these are AEDs that might be added to a first line treatment (so are used in combination). This happens if a first line treatment does not control the seizures or is not tolerated (for example, has side effects which means that the person cannot continue on that AED).

 **1-1-D Tertiary neurologic services** – these are specialist services in hospitals or units that have a team of neurologist , EEG neurophysiologist and neurosurgeon ; these facilities also have an intensive care units . the suggested hospitals in Iraq includes Baghdad teaching hospital ,neurosciences hospital , al emammamen al khademeen hospital , Alyermook teaching hospital , middile ephurttos neurosciences center in najaf erbil teaching hospital and Basra teaching hospital

1. **DIAGNOSIS**

 The clinical decision whether an epileptic seizure has occurred should be based on the combination of the description of the attack and different symptoms. Diagnosis should not be based on the presence or absence of single features but on collection of proper history ,detailed examination and electroencephalographic investigation . diagnosis of epilepsy can be done by well trained in epilepsy pediatrician , physician , neurosurgeon and psychiatrist as well as the neurologist .

 If the diagnosis cannot be clearly established, further investigations and/or referral to a [tertiary epilepsy specialist](http://www.nice.org.uk/guidance/cg137/chapter/appendix-g-abbreviations-and-glossary#tertiary-epilepsy-specialist) should be considered..

  psychological and psychiatric consultation is recommended in cases of suspected non epileptic attack disorder

 2-1- EEG ROLE :

 Repeated standard EEGs may be helpful when the diagnosis of the epilepsy or the syndrome is unclear

 In children and young people, a sleep EEG is best achieved through sleep deprivation or the use of melatonin The EEG should not be used in isolation to make a diagnosis of epilepsy as EEG in syncopal attacks and in childhood age group is associated with false positive results .

 When a standard EEG has not contributed to diagnosis or classification, a sleep EEG, Long-term video and ambulatory EEG are recommended

 2-2 NEUROIMIGING

  used to identify structural abnormalities that cause certain epilepsies; MRI should be the imaging investigation of choice in patient with epilepsy

**2-2- A MRI is particularly important in those:**

* who develop epilepsy before the age of 2 years or in adulthood
* who have any suggestion of a focal onset on history, examination or EEG
* in whom seizures continue in spite of first-line medication

 **2-2-B CT scanning is recommended in the following**

 brain CT scan is recommended only in acute phase of the illness , MRI contraindications and in childhood if the anesthesia is contraindicated

  other recommended investigations like ECG , plasma electrolytes, glucose, calcium to identify potential causes and/or to identify any significant co-morbidity should be considered

3 Classification

 Syndromic classification should be determined, because failure to classify the epilepsy syndrome correctly can lead to inappropriate treatment and persistence of seizures . Classification can be done only by highly trained neurologist and epilptologist

4--TREATMENT

* Treatment with AED therapy is generally recommended after a second epileptic seizure
* It is recommended that children, young people and adults should be treated with a single AED (monotherapy) wherever possible. If the initial treatment is unsuccessful, then monotherapy using another drug can be tried. Caution is needed during the changeover period.
* 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
* 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

4-1   first unprovoked seizure : TREAT IF

* the child, young person or adult has a [neurological deficit](http://www.nice.org.uk/guidance/cg137/chapter/appendix-g-abbreviations-and-glossary#neurological-deficit)
* the EEG shows unequivocal epileptic activity
* the child, young person or adult and/or their family and/or carers consider the risk of having a further seizure unacceptable
* brain imaging shows a structural abnormality.

#### 4-2- PHARMACOLOGICAL TREATMENT OF [FOCAL SEIZURES](http://www.nice.org.uk/guidance/cg137/chapter/appendix-g-abbreviations-and-glossary#focal-seizure)

* carbamazepine or lamotrigine as first-line treatment to children, young people and adults with newly diagnosed focal seizures.
* if carbamazepine and lamotrigine are unsuitable or not tolerated. If the first AED tried is ineffective, offer an alternative from these five AEDs[ levetiracetam, oxcarbazepine or sodium valproate]

##### **4-2-A  refractory focal seizures**

 Offer carbamazepine, clobazam , gabapentin , lamotrigine, levetiracetam, oxcarbazepine, sodium valproate or topiramate as adjunctive treatment; if the first line are not are ineffective or not tolerated. be aware of teratogenic risks of sodium valproate

 If adjunctive treatment is ineffective or not tolerated, refer the patient to a tertiary neurology center . Other AEDs that may be considered by the tertiary specialist are eslicarbazepine acetate, lacosamide, phenobarbital, phenytoin, pregabalintiagabine, vigabatrin and zonisamide Carefully consider the risk–benefit ratio when using vigabatrin because of the risk of an irreversible effect on visual fields.

#### 4-3 PHARMACOLOGICAL TREATMENT OF NEWLY DIAGNOSED [GENERALISED TONIC–CLONIC (GTC) SEIZURES](http://www.nice.org.uk/guidance/cg137/chapter/appendix-g-abbreviations-and-glossary#generalised-tonicclonic-gtc-seizure)

* sodium valproate is the first-line treatment
* Offer lamotrigine if sodium valproate is unsuitable.
* If the person has [myoclonic seizures](http://www.nice.org.uk/guidance/cg137/chapter/appendix-g-abbreviations-and-glossary#myoclonic-seizures) or is suspected of having[juvenile myoclonic epilepsy (JME)](http://www.nice.org.uk/guidance/cg137/chapter/appendix-g-abbreviations-and-glossary#juvenile-myoclonic-epilepsy-jme), be aware that lamotrigine may exacerbate myoclonic seizures
* Consider carbamazepine and oxcarbazepine but be aware of the risk of exacerbating myoclonic or [absence seizures](http://www.nice.org.uk/guidance/cg137/chapter/appendix-g-abbreviations-and-glossary#absence-seizure)
* If there are absence or myoclonic seizures, or if JME is suspected, do not offer carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin

##### **4-3-A- ADJUNCTIVE TREATMENT**

Offer clobazam, , lamotrigine, levetiracetam, sodium valproate or topiramate as adjunctive treatment

#### 4-4 -PHARMACOLOGICAL TREATMENT OF ABSENCE SEIZURES

* Offer ethosuximide or sodium valproate
* If there is a high risk of coexistent GTC seizures, offer sodium valproate
* Offer lamotrigine if ethosuximide and valproate are unsuitable, ineffective or not tolerated.
* carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin. Are contraindicated in patients with absence

##### **4-4-A ADJUNCTIVE TREATMENT IN ABSENCE SEIZURES**

If two first-line AEDs are ineffective in children, young people and adults with absence seizures, consider a combination of two of these three AEDs as adjunctive treatment: ethosuximide, lamotrigine[ or sodium valproate

 If adjunctive treatment is ineffective or not tolerated, refer to, a tertiary specialist and consider clobazam , clonazepam, levetiracetam topiramateor zonisamide

#### 4-5-PHARMACOLOGICAL TREATMENT OF MYOCLONIC SEIZURES

* sodium valproate is first-line treatment
* levetiracetam or topiramateare second line treatment ;  if sodium valproate is unsuitable or not tolerated
* carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin. Are contraindicated in patients with myoclonous

##### **4-5-A- ADJUNCTIVE TREATMENT IN PATIENTS WITH MYOCLONIC SEIZURES**

* levetiracetam, sodium valproate or topiramate
* if adjunctive treatment is failed consider clobazam, clonazepam, piracetam or zonisamide

#### 4-6 PHARMACOLOGICAL TREATMENT OF [TONIC](http://www.nice.org.uk/guidance/cg137/chapter/appendix-g-abbreviations-and-glossary#tonic-seizure) OR [ATONIC SEIZURES](http://www.nice.org.uk/guidance/cg137/chapter/appendix-g-abbreviations-and-glossary#atonic-seizure)

* sodium valproate is first-line treatment
* carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin. Are contraindicated in patients with tonic or atonic seizure

**4-6- A ADJUNCTIVE TREATMENT**

Offer rufinamide, or topiramate as adjunctive treatment

#### 5- EPILEPTIC SYNDROME

#### 5-1-Pharmacological treatment of [infantile spasms](http://www.nice.org.uk/guidance/cg137/chapter/appendix-g-abbreviations-and-glossary#infantile-spasms-2)

* prednisolone or tetracosactide or vigabatrin is the first-line treatment
* infants with infantile spasms due to tuberous sclerosis. vigabatrin is the first-line treatment
* Carefully consider the risk–benefit ratio when using vigabatrin or steroids

#### 5-2-PHARMACOLOGICAL TREATMENT OF [DRAVET SYNDROME](http://www.nice.org.uk/guidance/cg137/chapter/appendix-g-abbreviations-and-glossary#dravet-syndrome)

* Consider sodium valproate or topiramateas first-line treatment
* Second line treatment consider clobazamor stiripentol as adjunctive treatment
* carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin. Are contraindicated in Dravet

#### 5-3  PHARMACOLOGICAL TREATMENT OF [LENNOX–GASTAUT SYNDROME](http://www.nice.org.uk/guidance/cg137/chapter/appendix-g-abbreviations-and-glossary#lennoxgastaut-syndrome)

* sodium valproate is the first-line treatment
* Offer lamotrigine as adjunctive treatment
* Refer to tertiary specialist when adjunctive treatment is ineffective
* rufinamide and topiramate. Are considered for further treatment
* Only offer felbamate[ in centres providing tertiary specialist care and when treatment with all of the AEDs listed above has proved ineffective or not tolerated

#### 5-4 - PHARMACOLOGICAL TREATMENT OF [BENIGN EPILEPSY WITH CENTROTEMPORAL SPIKES](http://www.nice.org.uk/guidance/cg137/chapter/appendix-g-abbreviations-and-glossary#benign-epilepsy-with-centrotemporal-spikes-bects),  [PANAYIOTOPOULOS SYNDROME](http://www.nice.org.uk/guidance/cg137/chapter/appendix-g-abbreviations-and-glossary#panayiotopoulos-syndrome) OR [LATE-ONSET CHILDHOOD OCCIPITAL EPILEPSY (GASTAUT TYPE)](http://www.nice.org.uk/guidance/cg137/chapter/appendix-g-abbreviations-and-glossary#late-onset-childhood-occipital-epilepsy-gastaut-type)

* Offer carbamazepin or lamotrigine
* Levetiracetam,  oxcarbazepine or sodium valproate are the second line treatment
* carbamazepine and oxcarbazepine may exacerbate or unmask [continuous spike and wave during slow sleep](http://www.nice.org.uk/guidance/cg137/chapter/appendix-g-abbreviations-and-glossary#continuous-spike-and-wave-during-slow-sleep-csws), which may occur in some children with benign epilepsy with centrotemporal spikes
* adjunctive treatment

Offer carbamazepine clobazam gabapentin, lamotrigine levetiracetam, oxcarbazepine, sodium valproate or topiramate as adjunctive treatment

* eslicarbazepine acetat], lacosamide, phenobarbital, phenytoin, pregabalin], tiagabine], vigabatrin and zonisamide are recommended in tertiary facility when adjunctive treatment is failed

#### 5-5-  IDIOPATHIC GENERALISED EPILEPSY  & EPILEPSY WITH GENERALISED TONIC–CLONIC (GTC) SEIZURES ONLY

* sodium valproate is first-line treatment
* Offer lamotrigine or topiramate as a second line
* Offer lamotrigine[ levetiracetam[ sodium valproate or topiramate[ as adjunctive treatment
* If adjunctive treatment is ineffective or not tolerated refer to a tertiary specialist and consider clobazam[, clonazepam or zonisamide
* Do not give carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin

#### 5-6 -JUVENILE MYOCLONIC EPILEPSY (JME)

* sodium valproate is first-line treatment
* levetiracetam[ or topiramate is an alternative
* lamotrigine may exacerbate myoclonic seizures.
* Offer lamotrigine[ levetiracetam, sodium valproate or topiramate[ as adjunctive treatment
* Clobazam clonazepam or zonisamide are recommended if adjunctive treatment is failed
* Do not give carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin.

#### 5-7- [CHILDHOOD ABSENCE EPILEPSY](http://www.nice.org.uk/guidance/cg137/chapter/appendix-g-abbreviations-and-glossary#childhood-absence-epilepsy), [JUVENILE ABSENCE EPILEPSY](http://www.nice.org.uk/guidance/cg137/chapter/appendix-g-abbreviations-and-glossary#juvenile-absence-epilepsy)

* Offer ethosuximide or sodium valproate
* If there is a high risk of coexistent GTC seizures, offer sodium valproate
* Offer lamotrigine if ethosuximide and valproate are unsuitable, ineffective or not tolerated.
* carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin. Are contraindicated in patients with absence

##### **5-7- A Adjunctive treatment in absence seizures**

If two first-line AEDs are ineffective in children, young people and adults with absence seizures, consider a combination of two of these three AEDs as adjunctive treatment: ethosuximide, lamotrigine[ or sodium valproate

 If adjunctive treatment is ineffective or not tolerated, refer to, a tertiary specialist and consider clobazam , clonazepam, levetiracetam topiramateor zonisamide

#### 6- CONTINUATION OF PHARMACOLOGICAL TREATMENT

**6-1** [**ADHERENCE**](http://www.nice.org.uk/guidance/cg137/chapter/appendix-g-abbreviations-and-glossary#adherence)  to treatment can be optimized with the following:

1. educating children, young people and adults and their families and/or carers in the understanding of their condition and the rationale of treatment
2. reducing the stigma associated with the condition using simple medication regimens
3. positive relationships between healthcare professionals, the child, young person or adult with epilepsy and their family and/or carers

6-2 INDICATIONS FOR MONITORING OF AED BLOOD LEVELS ARE:

1. detection of non-adherence to the prescribed medication
2. suspected toxicity
3. adjustment of phenytoin dose
4. management of pharmacokinetic interactions (for example, changes in bioavailability, changes in elimination, and co-medication with interacting drugs)
5. specific clinical conditions, for example, status epilepticus, organ failure and certain situations in pregnancy

#### 7- WITHDRAWAL OF PHARMACOLOGICAL TREATMENT

* Withdrawal of AEDs must be managed by, or be under the guidance of, the specialist
* Patient who have been seizure free for at least 2 years should have the chance to withdraw treatment
* Withdrawal should be carried out slowly (at least 2–3 months) and one drug should be withdrawn at a time
* benzodiazepines and barbiturates may take up to 6 months or longer

**8-  REFERRAL TO TERTIARY CENTER** should be considered when one or more of the following criteria are present:

1. the epilepsy is not controlled with medication within 2 years
2. management is unsuccessful after two drugs
3. the child is aged under 2 years
4. a child, young person or adult experiences, or is at risk of, unacceptable side effects from medication
5. there is a unilateral structural lesion
6. there is psychological and/or psychiatric co-morbidity
7. there is diagnostic doubt as to the nature of the seizures and/or seizure syndrome

**9- KETOGENIC DIET**

 Refer children and young people with epilepsy whose seizures have not responded to appropriate AEDs to a tertiary specialist for consideration of the use of a ketogenic diet.

10--VAGUS NERVE STIMULATION

 is indicated for use as an adjunctive therapy in reducing the frequency of seizures in children and young people who are refractory to antiepileptic medication but who are not suitable for resective surgery. This includes children and young people whose epileptic disorder is dominated by focal seizures (with or without secondary generalisation) or generalised seizures

VNS is currently indicated for patients older than 12 years with medically intractable partial seizures who are not candidates for potentially curative surgical resections,. Recent reports also indicate long-term efficacy and successful VNS use in pediatric epilepsy and other seizure types and syndromes.

Key recommendations of the updated guidelines include the following :

* VNS may be considered for (1) the adjunctive treatment of partial or generalized epilepsy in children, (2) seizures associated with Lennox-Gastaut syndrome, and (3) improving mood in adults with epilepsy
* VNS may have improved efficacy over time
* Children should be carefully monitored for site infection after VNS implantation

11- PROLONGED OR REPEATED SEIZURES AND CONVULSIVE STATUS EPILEPTICUS

* Give immediate emergency care and treatment to patient who have prolonged (lasting 5 minutes or more) or repeated (three or more in an hour) convulsive seizures
* assess his or her respiratory and cardiac function. By   monitoring the person's airway, breathing, circulation or other vital signs secure airway
1. give high-concentration oxygen
2. assess cardiac and respiratory function
3. check blood glucose levels **and**
4. secure intravenous access in a large vein.
* Administer buccal midazolam as first-line treatment
* if buccal midazolam is not available. If intravenous access is already established and resuscitation facilities are available, administer intravenous lorazepam

#### Administer intravenous diazepam if intravenous lorazepam is unavailable, or buccal midazolam if unable to secure immediate intravenous access

* Administer a maximum of two doses of the first-line treatment
* If seizures continue, administer intravenous phenobarbital or phenytoin as second-line treatment in hospital
* Administer intravenous midazolam[ propofol or thiopental sodium[ to treat adults with refractory convulsive status epilepticus. Adequate monitoring, including blood levels of AEDs, and critical life systems support are required.
* Administer intravenous midazolam or thiopental sodium[ to treat children and young people with refractory convulsive status epilepticus. Adequate monitoring, including blood levels of AEDs, and critical life systems support are require

12 - WOMEN AND GIRLS WITH EPILEPSY

* the risk of continued use of sodium valproate to the unborn child, being aware that higher doses of sodium valproate (more than 800 mg/day) and polytherapy, particularly with sodium valproate, are associated with greater risk of developmental malformation
* All women and girls on AEDs should be offered 5 mg per day of folic acid before any possibility of pregnancy
* If a woman or girl taking enzyme-inducing AEDs chooses to take the combined oral contraceptive pill
* The progestogen[ only pill The progestogen implant is not recommended as reliable contraception in women and girls taking enzyme-inducing AEDs
* significant reduction of lamotrigine levels leading to loss of seizure control can result from  simultaneous use of any oestrogen-based contraceptive

#### 12-1- PREGNANCY

* All pregnant women and girls with epilepsy should be encouraged to register their pregnancy in the primary health center
* Care of pregnant women and girls should be shared between the obstetrician and the specialist
* Epileptic women has low risk of increased attacks of epilepsy frequency during the pregnancy and labor
* The epileptic women has higher incidence of epilepsy complication
* Pregnant women and girls who are taking AEDs should be offered a high-resolution ultrasound scan to screen for structural anomalies. This scan should be performed at 18–20 weeks' gestation by an appropriately trained ultrasonographer, but earlier scanning may allow major malformations to be detected sooner
* delivery should take place in an obstetric unit with facilities for maternal and neonatal resuscitation and treating maternal seizures
* All children born to mothers taking enzyme-inducing AEDs should be given 1 mg of vitamin K parenterally at delivery
* Do not routinely monitor AED levels during pregnancy. If seizures increase or are likely to increase, monitoring AED levels (particularly levels of lamotrigine and phenytoin, which may be particularly affected in pregnancy) may be useful when making dose adjustments
* Breastfeeding for most women and girls taking AEDs is generally safe and should be encouraged

**13- PATIENTS WITH HEPATIC AND RENAL INSUFFICIENCY**

* Gabapentin, pregabalin, levetiracetam, and lacosamide are excreted mostly by means of renal clearance, and their doses can be adjusted for renal insufficiency. These agents are useful in patients with hepatic failure, especially when a drug-induced etiology is suspected. Lamotrigine, which is metabolized by means of glucuronidation, a phase II reaction, is also used in some patients with hepatic insufficiency.
* Considerable data are available on the use of phenytoin in the presence of hepatic and renal insufficiency. However, phenytoin is
* not a preferred medication because of its nonlinear kinetics, hepatic autoinduction, numerous drug interactions, and high degree of protein binding. Among all anticonvulsants, phenytoin, carbamazepine, valproic acid, and felbamate have been associated with acute hepatic injury.

**14- CONCLUSIONS**

**14-1- TREATMENT OF FOCAL SEIZURES**

Treatment of focal seizures in children, young people and adults.

* First line treatment: carbamazepine, lamotrigine
* Alternative first line treatment: levetiracetam, oxcarbazepine, sodium valproate
* Cautions: be aware of potential effect of sodium valproate in pregnancy
* Adjunctive treatment (if first line treatment is not effective or not tolerated): carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate, topiramate
* Cautions: be aware of potential effect of sodium valproate in pregnancy
* Action if adjunctive treatment is not effective or tolerated: consider referral to tertiary services (where other AEDs may be tried)

**14-2-TREATMENT OF GENERALISED TONIC CLONIC SEIZURES**

Treatment of generalised tonic clonic seizures in children, young people and adults.

* First line treatment: sodium valproate, lamotrigine (if sodium valproate is not suitable)
* Cautions: be aware of potential effect of sodium valproate in pregnancy. If the person has myoclonic seizures or may have juvenile myoclonic epilepsy lamotrigine may worsen myoclonic seizures
* Alternative first line: treatment carbamazepine, oxcarbazepine
* Cautions: be aware that these drugs may worsen myoclonic or absence seizures
* Adjunctive treatment (if first line treatment is not effective or not tolerated): clobazam, lamotrigine, levetiracetam, sodium valproate, topiramate
* Cautions: be aware of potential effect of sodium valproate in pregnancy. If the person also has absences or myoclonic seizures, or may have juvenile myoclonic epilepsy do not offer carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin

**14-3- TREATMENT OF ABSENCE SEIZURES**

Treatment of absence seizures in children, young people and adults.

* First line treatment: ethosuximide, sodium valproate (offer first if additional tonic clonic seizures are likely)
* Cautions: be aware of potential effect of sodium valproate in pregnancy
* Alternative first line treatment: lamotrigine
* Adjunctive treatment (if first line treatment is not effective or not tolerated): consider a combination of ethosuximide, lamotrigine or sodium valproate.
* Cautions: be aware of potential effect of sodium valproate in pregnancy
* Action if adjunctive treatment is not effective or tolerated: consider referral to tertiary epilepsy services (where other AEDs may be tried)
* Cautions: do not offer carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin

**14-4-TREATMENT OF MYOCLONIC SEIZURES**

Treatment of myoclonic seizures in children, young people and adults.

* First line treatment: sodium valproate
* Cautions: be aware of potential effect of sodium valproate in pregnancy
* Alternative first line treatment: levetiracetam, topiramate
* Cautions: be aware that topiramate has poorer side effects than sodium valproate or levetiracetam
* Adjunctive treatment (if first line treatment is not effective or not tolerated): levetiracetam, sodium valproate, topiramate
* Cautions: be aware of potential effect of sodium valproate in pregnancy
* Action if adjunctive treatment is not effective or tolerated: consider referral to tertiary epilepsy services (where other AEDs may be tried)
* Cautions: do not offer carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin

**14-5-TREATMENT OF TONIC AND ATONIC SEIZURES**

Treatment of tonic and atonic seizures in children, young people and adults.

* First line treatment: sodium valproate
* Cautions: be aware of potential effect of sodium valproate in pregnancy
* Adjunctive treatment (if first line treatment is not effective or tolerated): lamotrigine
* Action if adjunctive treatment is not effective or not tolerated: consider referral to tertiary epilepsy services (where other AEDs may be tried)
* Cautions: do not offer carbamazepine, gabapentin, oxcarbazepine, pregabalin, tiagabine or vigabatrin

 **Multiple Sclerosis**

Guidelines of diagnosis and treatment

1-- Definition

 is a [chronic](http://en.wikipedia.org/wiki/Chronic_%28medical%29) [inflammatory](http://en.wikipedia.org/wiki/Inflammation) [demyelinating disease](http://en.wikipedia.org/wiki/Demyelinating_disease) that affects the [central nervous system](http://en.wikipedia.org/wiki/Central_Nervous_System) (CNS). MS is considered to be an immune-mediated disease in which the body’s immune system mistakenly attacks myelin in the central nervous system. It is unpredictable disabling disease of the CNS affecting young age group and characterized by dissemination in time and space .

##  1—1 epidemiological estimates

 Most people are diagnosed between the ages of 20 and 50 , It affect female two to three times more common than male , MS is more common in areas farthest from the equator

 the prevalence of MS in Saudis to be 40/100,000 in 2008 , The total prevalence rate in Kuwait was [14.77/100,000 in 2000. in Dubai the prevalence rate was 54.77/100,000 in 2007 in Iraq the prevalence rate was estimated to be 4/100000 and this is very low percentage in comparison to the neighboring countries ; this low figures may be related to poor awareness of the disease , low numbers of neurologist in Iraq and the lack of diagnostic facilities like 3 T MRI and laboratories CSF immunological studies

1—2 pathogenesis

* In MS, immune system T cells pass from the bloodstream into the central nervous system to attack the myelin coating around nerve fibers
* Within the CNS, the immune system attacks [myelin](http://www.nationalmssociety.org/What-is-MS/Definition-of-MS/Myelin) — the fatty substance that surrounds and insulates the nerve fibers — as well as the nerve fibers themselves.
* The damaged myelin forms scar tissue (sclerosis), which gives the disease its name.
* When any part of the myelin sheath or nerve fiber is damaged or destroyed, nerve impulses traveling to and from the brain and spinal cord are distorted or interrupted, producing a wide variety of symptoms.
* The disease is thought to be [triggered](http://www.nationalmssociety.org/What-is-MS/What-Causes-MS)in a genetically susceptible individual by a combination of one or more environmental factors.

1—3 Disease types

 People with MS typically experience one of [four disease courses](http://www.nationalmssociety.org/What-is-MS/Types-of-MS), which can be mild, moderate or severe

1. Relapsing remitting MS [RRMS] —

 the most common disease course — Approximately 85 percent of people with MS are initially diagnosed with relapsing-remitting MS is characterized by clearly defined attacks of worsening neurologic function.

 These attacks — also called relapses, flare-ups or exacerbations — are followed by partial or complete recovery periods (remissions), during which symptoms improve partially or completely and there is no apparent progression of disease.

1. Secondary progressive MS [SPMS] it follows the relapsing-remitting course. Most people who are initially diagnosed with RRMS will eventually transition to SPMS, which means that the disease will begin to progress more steadily (although not necessarily more quickly), with or without relapses..
2. Primary progressive MS [ PPMS] is characterized by steadily worsening neurologic function from the beginning. there are no distinct relapses or remissions. About 10 percent of people with MS are diagnosed with PPMS.
3. Progressive relapsing MS very rare start as progressive form and transition to relapsing remitting

Relapse definition : it is neurological deficit lasting more than 24 hours and the gap between the 2 relapse should be more than 1 month

**1—4 Clinically isolated syndrome :** it is the a first episode of neurologic symptoms  that lasts at least 24 hours and is caused by inflammation and demyelination , When CIS is accompanied by MRI-detected brain lesions that are similar to those seen in MS, the person has a high likelihood of a second neurologic event and [diagnosis of MS](http://www.nationalmssociety.org/Symptoms-Diagnosis/Diagnosing-MS) within several years . approximately 50% of patients who develop a CIS will experience a second event within 2 years (CDMS).

2--Diagnosis of MS

 delaying treatment in MS: what is lost is not regained’’ is always true ]. Therefore, early intervention requires early diagnosis, and the 2010 McDonald criteria promote early diagnosis. And use the McDonald 2010 criteria for diagnosing MS is recommended tool for diagnosis

 Diagnosis of MS should be done by neurologist and Need the following

* Dissemination in space : Find evidence of damage in at least two separate areas of the central nervous system (CNS), which includes the brain, spinal cord and optic nerves AND
* Dissemination in time : Find evidence that the damage occurred at least one month apart
* Rule out all other possible mimicker diagnoses

 The Revised McDonald Criteria, published In 2010 by the International Panel on the Diagnosis of Multiple Sclerosis, include specific guidelines for using MRI, visual evoked potentials (VEP) and cerebrospinal fluid analysis to speed the diagnostic process. These tests can be used to look for a second area of damage in a person who has experienced only one [attack](http://www.nationalmssociety.org/For-Professionals/Physicians/Managing-MS/Relapse-Management) (also called a relapse or an exacerbation) of MS-like symptoms — referred to as [clinically-isolated syndrome (CIS)](http://www.nationalmssociety.org/Symptoms-Diagnosis/Clinically-Isolated-Syndrome-%28CIS%29). A person with CIS may or may not go on to develop MS.

1. RR-MS

a) Dissemination in space:

 -clinically: 2 different locations or

-clinically and with MRI: one clinical location + positive MRI

 -clinically and with MRI and CSF: one clinical location + abnormal MRI showing lesions (at least two) in the same strategic locations + positive CSF

b) Dissemination in time: clinically (2 relapses) or clinically and with MRI (lesions of different ages, or active lesions)

c) Other possible etiologies should be ruled out. Some tests are systematic.

 In Iraq , it is important to consider infectious diseases (HIV,Brucella, Syphillis, immunologic diseases (clinical examination, ANA,etc.).

. 2- PP-MS These patients do not experience clear attacks like patients with relapsing-remitting onset, and MRI activity is usually lacking. Separate criteria have been developed to diagnose MS in patients with progressive onset. CSF analysis is recommended for this category of patients. Dissemination in time relies on clinical evolution over at least one year (retro or prospectively). Dissemination in space is proved clinically or with CSF, brain MRI, spinal cord MRI and VEPs.

2—1 Tool used for diagnosis :

 Magnetic resonance imaging (MRI) is the [diagnostic tool](http://www.nationalmssociety.org/Symptoms-Diagnosis/Diagnosing-Tools) that currently offers the most sensitive non-invasive way of imaging the brain, spinal cord, or other areas of the body. It is the preferred imaging method to help establish a [diagnosis of MS](http://www.nationalmssociety.org/Symptoms-Diagnosis/Diagnosing-MS) and to monitor the course of the disease

* Most conventional MRI machines are 1.5T or 2.0T. [ most widely available in Iraqi hospital ].
* Open MRIs are usually less than 1.5T and do not provide the best images for detecting MS
* the recommended MRI technique include the following:
* High field; 1 tesla and more
* Identical sequences
* Axial planes (bicallosal)
* Thin (3mm); interleaved

 1-Sagittal FLAIR

 2-Axial spT2 with double ET

 3-Axial T1 before gadolinium

 4-Gadolinium infusion –After 5 min. –0.2ml/Kg –Distant from MPIV (> 4weeks)

 5- Axial FLAIR may be acquired in the mean time

 6-Axial T1 post-gadolinium \*A T13D sequence is optional

2-2--The CSF of people with MS usually contains:

* Elevated levels of IgG antibodies, ; The % of CSF IgG is normally 3-5% of total CSF protein. In MS IgG levels > 13% of total CSF protein is considered diagnostic. An IgG index > 0.77 is considered abnormal.
* A specific group of proteins called oligoclonal bands. Two or more bands only present in CSF are necessary for the diagnosis.

Unfortunately not available in Iraq ; there private labs which collect the samples and send them outside the country

2—3 Evoked potential like VEP SEP used to detect hidden sites of involvement

III. Therapy

3—1—acute phase treatment

1. Relapses Relapses are treated with high doses of methylprednisolone (MPIV). A total of 3-5 gr is usually given for 3 to 7 days. Sometimes, no treatment is required. The use of oral corticosteroids in the treatment of relapses is not recommended.
2. If not sufficient efficacy try it again with MPIV (2g per day for 3-7 days .
3. Six sessions every other day of plasmapheresis may be given in disabling relapses not responding to corticosteroid pulse therapies within 4 weeks.

**3—2--DISEASE-MODIFYING TREATMENTS**

The following twelve are U.S. Food and Drug Administration (FDA)-approved disease-modifying agents reduce disease activity and disease progression for many people with relapsing forms of MS, including relapsing-remitting MS, as well as secondary-progressive and progressive-relapsing MS in those people who continue to have relapses.

* [Aubagio](http://www.nationalmssociety.org/Treating-MS/Medications/Aubagio) (teriflunomide)
* [Avonex](http://www.nationalmssociety.org/Treating-MS/Medications/Avonex) (interferon beta-1a) available in Iraq
* [Betaseron](http://www.nationalmssociety.org/Treating-MS/Medications/Betaseron) (interferon beta-1b) available in Iraq
* [Copaxone](http://www.nationalmssociety.org/Treating-MS/Medications/Copaxone) (glatiramer acetate)
* [Extavia](http://www.nationalmssociety.org/Treating-MS/Medications/Extavia) (interferon beta-1b)
* [Gilenya](http://www.nationalmssociety.org/Treating-MS/Medications/Gilenya) (fingolimod) available in Iraq
* [Lemtrada](http://www.nationalmssociety.org/Treating-MS/Medications/Lemtrada) (alemtuzumab)
* [Novantrone](http://www.nationalmssociety.org/Treating-MS/Medications/Novantrone) (mitoxantrone)
* [Plegridy](http://www.nationalmssociety.org/Treating-MS/Medications/Plegridy) (peginterferon beta-1a)
* [Rebif](http://www.nationalmssociety.org/Treating-MS/Medications/Rebif) (interferon beta-1a) available in Iraq
* [Tecfidera](http://www.nationalmssociety.org/Treating-MS/Medications/Tecfidera%E2%84%A2) (dimethyl fumarate)
* [Tysabri](http://www.nationalmssociety.org/Treating-MS/Medications/Tysabri-%C2%AE) (natalizumab) available in Iraq

3—3 CIS

 early treatment of CIS after the initial presentation can delay the development of clinically definite multiple sclerosis (CDMS). These results support the use of interferon after a first clinical demyelinating event and indicate that there may be beneficial effects of immediate treatment compared with delayed initiation of treatment

 CIS patients who do not wish to start treatment should be followed up by MRI at 3 month intervals. It should be stated that many cases of CIS are reclassified as definite MS, according to final amendment of McDonald Criteria 2010, and should be treated accordingly

 in CIS patients with normal or few lesions on brain MRI and especially those with monofocal symptoms and complete recovery, a brief watchful phase with a follow up brain MRI at 3–6 months is appropriate

 recommendation :

1. more than nine lesion recommended for treatment
2. zero lesion no treatment is recommended
3. 1-8 lesion on brain MRI ; recommended fo search of abnormalities in CSF oligoclonal band or abnormal VEP ; if there is abnormality ,recommend treatment
4. CIS patients who do not wish to start treatment should be followed up by MRI at 3 month intervals. Any new lesions or any other relapse recommend to treat

3—4 Interferon beta

 IFNβ are immunomodulators that switch Th1 lymphocytes to Th2 lymphocytes. In various clinical trials, IFNβ have been shown to have efficacy in MS

* + 1. They diminish the frequency of relapses between 30-45%.
		2. They diminish the accumulation of MRI lesion.
		3. They extend the survival rate, supporting a long-term benefit of initiating early treatment

 Three different IFNβ formulations are available in IRAQ

1. β Subcutaneous IFN -1b, Betaferon/Betaseron, 250 µg QODβ
2. 1a, Avonex, 30 µg weekly βIntramuscular IFN
3. 1a, Rebif, 22 or 44 µg TIW βSubcutaneous IFN

 IFNβ therapy is generally safe and well-tolerated. It often causes side effects, such as flulike symptoms, and laboratory abnormalities, such as elevation in liver function tests or lymphopenia. However, these side effects are generally mild, tend to disappear within the first months of treatment, and thus do not necessitate discontinuation of therapy. Subcutaneous IFNβ might also cause injection site reactions, and higher doses of IFNβ are more likely to cause side effects. CBC, AST and ALT should be checked every month for the first 3 months, then every 3 months for the next 6 months, then every 6 month .

* there is no evidence for superiority of one drug over the other

3—5 - Immunosuppressive agents

 Natalizumab Natalizumab (Tysabri; Biogen Idec), a selective immunosuppressor, is a humanized• monoclonal antibody to the α 4 subunit of α4β1 integrin (VLA-4), a protein found on the surface of lymphocytes. α4β1 integrin allows adhesion and subsequent migration of inflammatory cells into the brain and spinal cord. Natalizumab selectively blocks this interaction, thus preventing the transmigration of inflammatory lymphocytes across the blood brain barrier into the CNS. This agent increases the blood lymphocyte count.

* Natalizumab is given as an intravenous infusion at the dosage of 300mg monthly.
* PML diagnosis is suspected if the patient has epileptic seizures or behavioral changes. A brain MRI should be performed in less than 24 hours. CSF analysis with an ultrasensitive polymerase chain reaction assay for JC viral DNA confirms the diagnosis. Five to seven plasma exchanges are performed every other day. The proportion of survivors is near 70%.
* After plasma exchange, nearly all of the patients (91%) develop immune• reconstitution inflammatory syndrome (IRIS). IRIS presents as new or worsening neurologic symptoms, tends to be severe, and usually occurs within days or weeks after rapid removal of natalizumab. By 6 months post diagnosis, most of these patients either recover from IRIS or start to recover. IRIS is suspected if brain MRI shows gadolinium+ lesions. IRIS is treated by cortisone
* It is recommended to determine anti-JVC antibodies before starting treatment to stratify the risk of developing PML. In case of positivity the benefits and risks should be assessed to guide the practice. Another treatment may be considered for high risk patients.
* Natalizumab is contra-indicated in pregnancy. Thereafter, information should be reviewed with the patient and informed consent• should be signed by him annually
* Natalizumab is recommended for patients with more active, rapidly evolving relapsing disease and in those who have failed to respond to first-line DMTs (IFNβ or glatiramer acetate).

3—6 Fingolimod Fingolimod (Gylenia ; Novartis, Basel, Switzerland)

 is a sphingosine-1- phosphate receptor (S1P1) agonist, which binds to S1P1 receptors on T-cells, affecting the receptor's signaling pathways. The result is inhibition of T-cell migration from lymphoid tissue into the peripheral circulation and target organs, including the CNS, thus attenuating inflammation without affecting their function. Lymphopenia is dose dependent and can be observed as early as 2 hours after a• single dose, reaching nadir at 6–8 hours. With chronic treatment, nadir is reached at 2–4 weeks

Fingolimod is the first oral treatment approved for RR-MS in patients with high disease activity despite treatment with IFNβ and those with rapidly evolving RRMS. Dosage: 1 tablet 0.5 mg/d.•

 Discontinuation rates due to side effects were low. Frequently reported minor side• effects were nasopharyngitis, headache, diarrhea and nausea. Clinically asymptomatic lymphopenia was common. Serious Adverse Events were bradycardia (mostly asymptomatic, appearing 4-5• hours after therapy initiation, and transient) and rarely atrioventricular block. Oral fingolimod may also increase the risk of some infections. In addition, fingolimod may be associated with an increased risk of macular edema, hepatic effects and fetal toxicity.

 *Work-up before starting treatment:*

1. o CBC, liver function tests, EKG, pregnancy test if indicated o Varicella-zoster IgG antibodies; if negative,
2. Pox vaccination is given before starting treatment
3. Ophthalmologic exam including optic coherence tomography in patients with diabetes or uveitis
4. Dermatologic exam and check for a history of melanoma (risk of melanoma)

 *First visit:*

1. It is recommended to have close EKG and blood pressure monitoring for• at least six hours after intake of the tablet
2. . If the patient stops the treatment for more than 3 weeks, the same procedure of observation is repeated when the drug is reintroduced.

 Follow-up:•

1. CBC, liver function tests monthly for 3 months If blood lymphocytes count falls below 200/mm3, treatment should be stopped.
2. Ophthalmologic exam including optic coherence tomography: 3-4 months after the first visit
* . Wash-out period of 3 months if fingolimod is replaced by another DMD.
* Since most MS patients are of childbearing age, it may be advisable to avoid• pregnancy while taking fingolimod until more information is available and a registry is opened.
* A monitoring program for assessing the long-term safety of fingolimod and a• registry of patients should be created
* . F ingolimod is recommended for RR-MS in patients with high disease activity despite• treatment with IFNβ and those with rapid evolution.

3—8 Clinically Isolated Syndrome treatment choice

1. DMT should be initiated at the onset of the first clinically demyelinating event
2. the decision as to when to commence diseasemodifying therapy should be jointly made by the neurologist and patient after considering all the available evidence.
3. more than nine lesion recommended for treatment
4. zero lesion no treatment is recommended
5. 1-8 lesion on brain MRI ; recommended fo search of abnormalities in CSF oligoclonal band or abnormal VEP ; if there is abnormality ,recommend treatment
6. CIS patients who do not wish to start treatment should be followed up by MRI at 3 month intervals. Any new lesions or any other relapse recommend to treat

3—9 secondary progressive MS

1. It is appropriate to consider IFNβ as treatment for patients with SPMS still experiencing relapses or showing MRI activity (gad + lesions) (Type A)
2. There is no utility of IFNβ in patients with SPMS that do not suffer superimposed relapses.
3. IFNβ-1b and subcutaneous IFNβ-1a can be used for SPMS with superimposed relapses.
4. Only one trial showed a slowing of disease progression with IFNβ-1b.

 Non Responders:

1. A minimum of two clinical relapses, and progression towards disability, i.e., increase in EDSS of one point, within one year of treatment.

 2. More than two clinical relapses, more than 2 Gado + lesions and 3 new lesions on T2 on treatment.

3. One clinical relapse per year

 4. Variation of 0.5 on EDSS per year.

When patients are considered as non-responders to immunomodulators as first line therapy, second line therapies (immunosuppressors) may be used

Figure [1] showing the step of treatment

Acute relapse treatment

Methylprednisolon pulse therapy 1 gm infusion daily /5 days

 if no response

Give 2 gm methylprednisolon day for 5-7 days

 if no response

Plasma exchange 6 sessions every other day

* [Avonex](http://www.nationalmssociety.org/Treating-MS/Medications/Avonex) (interferon beta-1a) available in Iraq Basic
* first

 Line therapy

* [Betaseron](http://www.nationalmssociety.org/Treating-MS/Medications/Betaseron) (interferon beta-1b) available in Iraq
* [Rebif](http://www.nationalmssociety.org/Treating-MS/Medications/Rebif) (interferon beta-1a) available in Iraq

 Suboptimal responder escalation

* [Gilenya](http://www.nationalmssociety.org/Treating-MS/Medications/Gilenya) (fingolimod) available in Iraq
* [Tysabri](http://www.nationalmssociety.org/Treating-MS/Medications/Tysabri-%C2%AE) (natalizumab) available in Iraq

Figure [2] showing how to treat suboptimal first line non responder by second line therapy



 Figure [3] Non Responders [suboptimal responder ]

1. A minimum of two clinical relapses, and progression towards disability, i.e., increase in EDSS of one point, within one year of treatment.

 2. More than two clinical relapses, more than 2 Gado + lesions and 3 new lesions on T2 on treatment.

3. One clinical relapse per year

 4. Variation of 0.5 on EDSS per year.

Figure [4] the risk of getting PML is higher if :

* TYSABRI for a long time, especially longer than 2 years
* Use of Cytotoxic drugs before you start receiving TYSABRI
* have been exposed to John Cunningham Virus (JCV). JCV is a common virus that is harmless in most people but can cause PML in people who have weakened immune systems, such as people taking TYSABRI. Most people who are exposed to JCV do not know it or do not have any symptoms. This exposure usually happens in childhood. Before receiving TYSABRI or during treatment
* Your risk of getting PML is greatest if you have all 3 risk factors listed above.