Epilepsy

Establishing the correct diagnosis

Make sure you are certain of the diagnosis and rule out any of the other causes of impaired or loss of consciousness and / or Involuntary movement. If status epilepticus (**link 1**) is confirmed, act without delay.

- KHT has a First Fit epilepsy pathway, refer using proforma unless Immediate treatment is required http://home/khintranet/documents/201110210928_SGH_First_Fit_referral_form_final_2010.doc
- Treatment with anti-epileptic drugs (AEDs) is usually started when a patient has two or more *unprovoked* epileptic seizures of any type within a year and over a 24 h period.
- Before considering starting pharmacological treatment, it is important to obtain a complete history from the patient as well as eye-witness and assess risk factors (Table 1 – **link 2**).

Anti-epileptic drug (AED) therapy

General principles in adults (**link 3**)

The aim of drug therapy is to achieve adequate seizure control using the least number of drugs, at the lowest effective doses, causing a minimum of adverse effects.

- Choice of AED depends on; seizure type / epilepsy syndrome, patient and drug profile. In general **carbamazepine / lamotrigine is suitable for patients with localization related (partial) seizures** (in elderly lamotrigine may be better tolerated; see notes below [**link 4**]) and **sodium valproate for those with primary generalized seizures** (alternative may be levetiracetam in women of childbaring age [**link 5**]).

Address Guidance on Driving (**link 6**)

It is a legal requirement for any individual to inform the DVLA if they have had one or more epileptic events. Advice patient not to drive.

Counseling

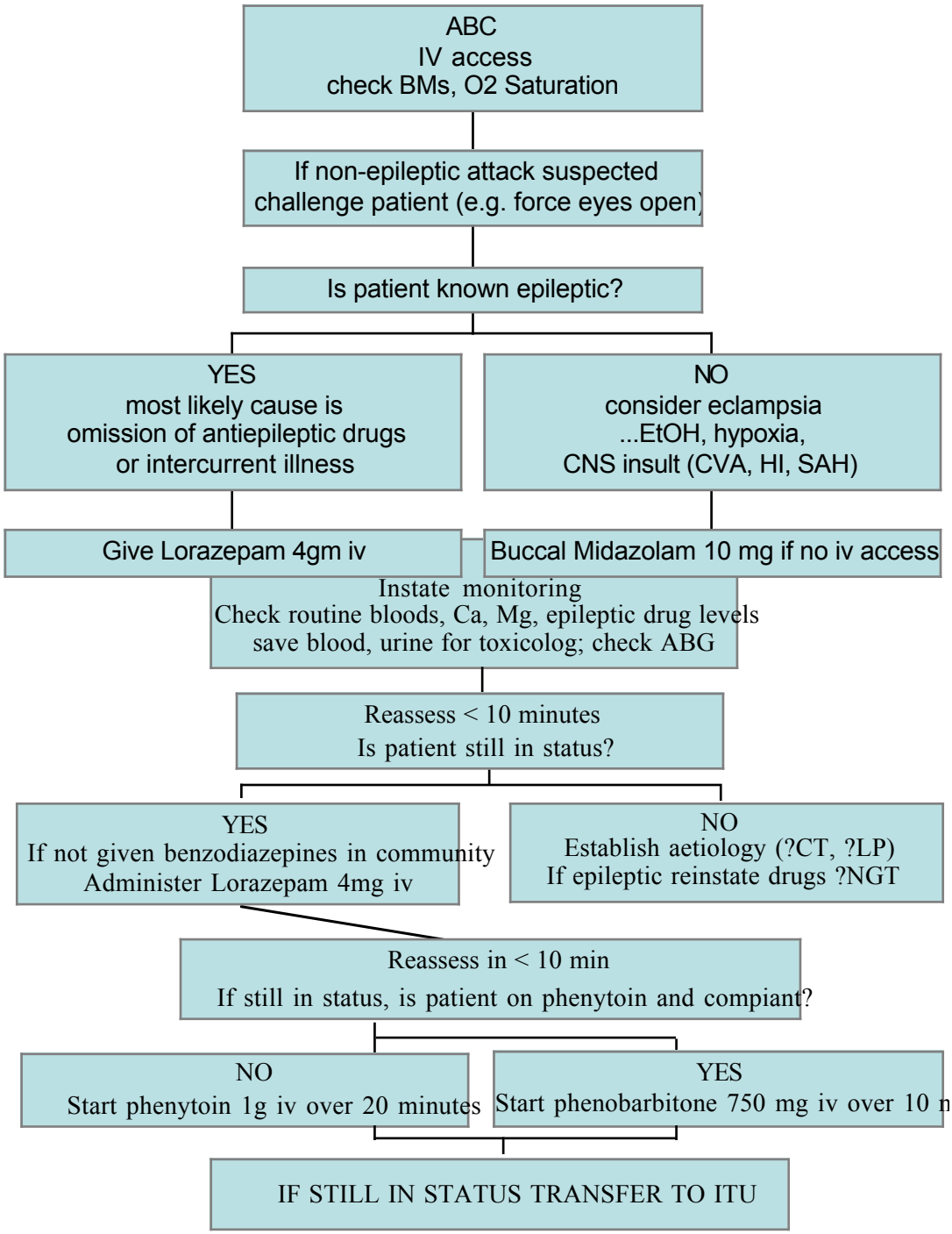
Patient, relatives and carers must receive counselling on the risks associated with epilepsy, safety in relation to seizures, and advice on avoiding seizure precipitants.

Anti-epileptic drug-interactions (**link 7**)

Withdrawing anti-epileptic drug therapy (**link 8**)

Link 1 Status epilepticus / Convulsive seizures

STATUS EPILEPTICUS (call for help if not confident)



Status epilepticus is a common medical emergency that requires urgent treatment. Status due to non-epileptic seizures (pseudostatus) is frequently misdiagnosed.

It is defined as a continuous seizure lasting longer than 30 minutes or repeated seizures with failure to regain consciousness. Treatment must begin if a seizure lasts longer than 5 minutes.

- After 30 minutes homeostatic mechanisms start to fail and there is a significant risk of cardiorespiratory and metabolic decompensation. The death rate is about 10%, and higher in the elderly. New neurological deficits can occur after status epilepticus.
- In patients with a previous diagnosis of epilepsy, status is more common in those with learning disability or frontal seizures.

Possible causes of status

Eclampsia, stroke, intracranial haemorrhage, head injury, hypoxia, meningitis, encephalitis, alcohol or sedative withdrawal, hypoglycaemia, other metabolic disturbance

Parenteral phenytoin administration:

- Phenytoin **must NOT be**: Given im. or subcutaneously
  Given by central line
  Added to a glucose infusion
  Given with any other drug
- Phenytoin must only be administered iv. with cardiac monitoring
- Dilute phenytoin in normal saline to a concentration of 10mg/mL
- Use an infusion pump if available

Common problems in the treatment of status epilepticus

- Failure to give drugs in quick enough succession
- Failure to recognize and treat pre-status in people with epilepsy
- Delay in obtaining venous access
- Delay in seeking anesthetic help and advice

- Sudden cardio-respiratory decompensation after large doses of barbiturates and/or benzodiazepines
- Delay in inducing anesthesia to finally stop the seizures
- Using only diazepam or lorazepam with no other subsequent drug to stop relapse
- Failure to diagnose non-epileptic seizures

Preventing seizures recurring following status

If status is due to antiepileptic drug failure, fully restore usual medication using loading doses if appropriate. Otherwise, give phenytoin parenterally. Phenobarbitone, valproate or levetiracetam may also be used.

Is patient already taking phenytion?			**Recommended action to prevent seizures**
Yes			▪ Check serum phenytoin levels ▪ Give 0.7 x (blood level required – actual blood level) in mg/ml of phenytoin to ensure that the level of phenytoin is therapeutic
No			▪ Give 15mg/kg at a maximum of 50mg/min with cardiac monitoring

Link 2 Establishing the correct diagnosis

Source of information	**Details**	
From the patient	▪ Frequency, timing and pattern of seizures ▪ Symptoms before, during and after seizures ▪ Were any injuries sustained? Incontinence?	▪ Any trigger factors? ▪ Duration of symptoms
From a witness	▪ Frequency of seizures ▪ Description of seizures	▪ Behaviour after seizures

		▪ Witness contact details
Other	▪ Age and sex ▪ Any previous insult such as: head injury, meningitis, encephalitis or other CNS injury? ▪ History of febrile convulsions (simple/complicated)? ▪ Alcohol use/withdrawal? ▪ Family history of neurological disorder ▪ Any potential epileptogenic drugs (illicit or prescribed)?	

Table 1. Information sought from history in a patient with epilepsy

Link 3

Anti-epileptic drug (AED) therapy

General principles in adults

- **Treat with ONE drug whenever possible**; approximately 70% of patients can be successfully managed with a single AED.
- Do not assume that low doses or levels of AEDs are not effective. In some patients so-called “sub-therapeutic” doses or levels are sufficient to control seizures.
- Increasing the dose of an AED should only be done if unprovoked seizures remain uncontrolled (consider compliance, alcohol etc).
- Continue increments until seizures are controlled, intolerable side effects occur or maximal recommended dose is reached.
- If on maximal tolerated dose of antiepileptic drug seizures continue, consider introducing second agent (exclude non-compliance).
- Slowly reduce / withdraw first agent if seizures resolve; review second agent if seizures continue on high therapeutic dose.
- To improve tolerability avoid rapid changes in drug dose.
- Serum phenytoin levels are essential before increasing dose - small dose changes (25-50mg) are recommended due to non-linear kinetics and severe neurological toxicity.

A sub-group of patients have been described who continue to have seizures despite several pharmacological interventions. This may be as

a result of inappropriate AED selection, misdiagnosis, progressive neurological disease or intractability of their epilepsy. Referral / reinvestigation may be needed.

Link 4

Treating epilepsy: Elderly

The choice of anti-epileptic drug depends on patient and drug profile, and concomitant disease states.

- Starting and maintenance doses are usually lower in the elderly than in younger adults - seek advice if epilepsy is severe.
- Sodium valproate is usually well tolerated in low doses in this patient group, although it may exacerbate tremor or extrapyramidal features.
- There are published studies on the use of lamotrigine and gabapentin in the elderly.
- Heart block must be excluded before prescribing carbamazepine, therefore an ECG must be performed.
- Phenytoin is difficult to use in the elderly because of its interaction with other medications and pharmacokinetics. “Therapeutic” levels may not be tolerated. If chosen, use a low starting dose, look for side effects and monitor levels and response to therapy carefully.
- Cerebrovascular disease, intracranial haemorrhage, dementia, tumour or trauma can be precipitating factors.
- Elderly patients are likely to have an epilepsy syndrome that is partial in nature.
- Post seizure confusion may be prolonged, and may contribute to any injury sustained.
- EEGs are helpful in prolonged confusional states that may have an epileptic basis (non-convulsive status).

Link 5

Treating epilepsy in Women of childbearing age and in pregnancy

- Anti-epileptic drugs (AEDs) are known to increase the risk of congenital abnormalities. However, women when pregnant **should not** be advised to discontinue drugs, but started on folic acid 5mg od and referred for urgent neurology / epilepsy review. Sudden drug withdrawal may lead to status!

- Therapy with AEDs carries an increased risk of neural tube defects, cleft lip/ palate and other malformations as well as increased educational need in offspring. The risks are greater in women taking more than one AED (baseline risk of 2 to 3% for major malformations, one AED 4 to 6% and polytherapy may increase risk to 15%).

- Pregnant women with epilepsy should be advised of the availability and range for screening fetal abnormalities.

Sodium valproate should not generally be a first line agent in women of childbearing age. On current evidence sodium valproate appears less safe than other drugs with a higher dose-related risk of spina bifida and other malformations. Women of child bearing age should be also warned of the concerns regarding the increased educational needs in children born to mothers on valproate and on polytherapy. Where it is still considered indicated, make sure the patient is well informed, keep daily dose below 1000mg if possible, use the Epilim Chrono® preparation (modified release) and split doses to avoid high peak levels.

Birth defects

Screening for major malformations does not prevent the birth of children with more minor physical anomalies or children who will later experience learning difficulty or developmental delay.

Patient group		Regimen for preventing birth defects
Women expecting to conceive		Folic acid 5mg three months before conception and during the first four months of pregnancy
Women on anti-epileptic enzyme inducing drugs		Vitamin K1 (Konakion®) 10mg orally during the last month of pregnancy to protect the baby from haemorrhagic disease of the newborn.
Neonates		Vitamin K 1mg as a single intramuscular injection immediately after birth.

Women taking oral contraception

- Carbamazepine, oxcarbazepine, phenytoin, phenobarbitone,

topiramate and possibly ethosuximide may reduce the effectiveness of combined and progestogen only oral contraceptives, potentially increasing the risk of pregnancy. Gabapentin, levetiracetam and sodium valproate do not.

- The Family Planning Association advises that women with epilepsy who are unable to use alternative methods of contraception, should take a combination of oral contraceptivess to provide a daily intake of 50 micrograms or more of ethinyloestradiol. "Tricycling" where 3 or 4 packets of monophasic tablets are taken without a break followed by a tablet-free interval of 4 days is recommended. Women should be warned of the uncertainty about the effectiveness of this regimen.

- Inform the patient that contraceptive protection may still be reduced even with high doses of ethinyloestradiol (failure rates increase form 0.3 to 3/100 women-years).

- Additional precautions must be used until the dose is effective and there is no mid-cycle bleeding. Consider screening 3 consecutive cycles to ensure they are anovulatory.

- Medroxyprogesterone acetate (Depo-Provera®) is a long acting progestogen. There are no known interactions with enzyme inducing AEDs and it is thought to be an effective contraceptive in women with epilepsy.

Emergency contraception: no change in dose recommended.

Link 6

Address Guidance on Driving

It is a legal requirement for any individual to inform the DVLA if they have had one or more epileptic events.
https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/232964/At_a_glance.pdf

Patients with epilepsy may drive a motor vehicle (not HGV or PSV) provided that they have had a seizure-free period of one year or a three-year period of attacks arising from sleep without awake attacks.

The Driver and Vehicle Licensing Authority (DVLA) recommends that patients are advised not to drive during withdrawal of antiepileptic medication, or for six months afterwards.

Link 7

Anti-epileptic drug-interactions

- Some clinically significant interactions involving anti-epileptic drugs (AEDs) occur as a result of hepatic enzyme induction, inhibition or drug displacement from protein binding sites.
- Major interactions occur with AEDs and oral contraceptives, corticosteroids and other immunosuppressants, some antibiotics and analgesics - refer to BNF for more information.
- Combining anti-epileptic agents may result in altered plasma concentrations of either drug.

Action on hepatic enzyme systems		**Anti-epileptic drugs**
Induction		Carbamazepine, oxcarbazepine, phenytoin, phenobarbitone, primidone
Inhibition		Sodium valproate
No action		Lamotrigine, levetiracetam, gabapentin, tiagabine, lacosamide

Table I: Expected changes in plasma concentrations when an antiepileptic drug (AED) is added to an existing AED regimen: long-established AEDs

		EXISTING AED								
		PB	**PHT**	**PRM**	**ETS**	**CBZ**	**DZP**	**CZP**	**VPA**	**CLB**
AED	**PB**	AI	PHT↑↓	NCCP	ETS⇓	CBZ⇓	DZP↓	CZP↓	VPA⇓	CLB⇓ NDMC⇑
	PHT	PB↑	AI	PRM↓ PB↑	ETS⇓	CBZ⇓	DZP↓	CZP↓	VPA⇓	CLB⇓ NDMC⇑
	PRM	NCCP	PHT↑↓	AI	ETS⇓	CBZ⇓	DZP↓	CZP↓	VPA⇓	CLB⇓ NDMC⇑
ADDED	**ESM**	*	*	NA	-----	*	NA	NA	VPA↓	NA
	CBZ	*	PHT↑↓	PRM↓ PB↑	ETS⇓	AI	DZP↓	CZP↓	VPA⇓	CLB⇓ NDMC⇑
	DZP	NA	PHT↑↓	NA	NA	NA	-----	NA	NA	NA
	CZP	NA	PHT↑↓	NA	NA	CBZ↓	NA	-----	NA	NA
	VPA	PB⇑	PHT↑↓	PB⇑	ETS↑↓	CBZ-E⇑	DZP⇑*	NA	-----	NA
	CLB	PB↑	PHT↑↓	PB↑	NA	CBZ↓	NA	NA	VPA↑	-----

CBZ = carbamazepine; CBZ-E = carbamazepine epoxide; CLB = clobazam; CZP = clonazepam; DZP = diazepam; ETS = ethosuximide; NDMC = N-desmethylclobazam; PB = phenobarbitone; PHT = phenytoin; PRM = primidone; VPA = valproic acid; NA = none anticipated; * = free pharmacologically active concentration; AI = autoinduction; NCCP = not commonly co-prescribed, * = No change.

↓= an infrequently observed decrease in plasma concentration ⇓= a frequently observed decrease in plasma concentration

↑= an infrequently observed increase in plasma concentration ⇑= a frequently observed increase in plasma concentration

Table II: Effect of newly licensed AEDs on plasma concentrations of the long-established AEDs

		EXISTING AED					
		PB	PHT	PRM	ETS	CBZ	VPA
ADDED	VGB	•	PHT↓	•	NA	•	•
	LTG	•	•	•	•	•	•
	GBP	•	•	NA	NA	•	•
	TPM	•	PHT↑	•	NA	•	VPA↓
	PGB	•	•	NA	NA	•	•
ADED	FBM	PB⇑	PHT⇑	?	?	CBZ↓ CBZ-E↑	VPA⇑
	TGB	•	•	•	NA	•	•
	OXC	PB↑	PHT↑	?	?	CBZ↓	•
	LEV	•	•	•	NA	•	•
	ZNS	•	PHT↑	•	NA	CBZ⇅	•

CBZ = carbamazepine; CBZ-E = carbamazepine epoxide; ETS = ethosuximide; FBM = felbamate; GBP, = gabapentin; LEV = levetiracetam; LTG = lamotrigine; OXC = oxcarbazepine; 10-OH-OXC = 10, 11-dihydroxycarbazepine; PB = phenobarbitone; PHT = phenytoin; PRM = primidone; PGB = pregabalin; TGB = tiagabine; TPM = topiramate; VPA = valproic acid; VGB = vigabatrin; ZNS = zonisamide; NA = none anticipated, ? = indicates an unknown effect; • = No change.

Link 8

Withdrawing anti-epileptic drug (AED) therapy

- Withdrawal can be considered in patients who have been seizure-free for 2 or more years.
- The decision is one that the informed patient should make.
- There is a reduced risk of relapse the longer the period of seizure freedom, however some syndromes often need life-long treatment (e.g. juvenile myoclonic epilepsy).
- Even in patients seizure-free for several years there is a risk of relapse. Consider referral to Neurologist.
- Avoid abrupt withdrawal of AEDs as severe rebound seizures maybe precipitated.
- Patients on several AEDs should have only one withdrawn at a time. Withdraw first drug only when new regimen established.
- Be aware of the effect of interactions – the dose of the remaining

drug(s) may need to be adjusted.

- Patients must be given an estimated risk of relapse before they embark on drug withdrawal. They may find the 20-40% risk of relapse depending on the case unacceptable.
- Be aware of DVLA regulations.

Selecting the right AED / Adult doses of AEDs

formulary