Management pathway:
Treatment of epilepsy in adults

Key messages
- Summary of treatment regimens supported by CUHFT/PSHFT consultants to support GP’s with prescribing responsibility of antiepileptic drugs.
- Dosage, titration and withdrawal guidance.

1 Scope

Trust-wide (CUH and PSHFT), CPFT and GPs in Cambridge and Peterborough Clinical Commissioning Group.

2 Purpose

Aim of the pathway is to ensure:
- Patients with seizures are assessed appropriately.
- Drug treatment for seizures is performed in a systematic manner based on current national guidance.
- Access to newer AEDs for patients who seizures persist despite accepted first line therapies.
- An acceptable line of responsibility for initiation, ongoing prescription and monitoring between primary care and hospital physicians.

3 Definitions

CUHFT        Cambridge University Hospitals Foundation Trust
PSHFT        Peterborough and Stamford Hospitals Foundation Trust
CPFT         Cambridgeshire and Peterborough Foundation Trust
AED          Antiepileptic drug
OD           Once daily
BD           Twice daily
TDS          Three times daily

4 Introduction

Patients with epilepsy have been cared for jointly between consultants and GPs for many years with GPs taking prescribing responsibility. The introduction in recent years of a number of new drugs with which GPs may be unfamiliar has led to concern about clinical responsibility. These drugs include zonisamide, eslicarbazepine, lacosamide, perampanel and rufinamide. Their
use is no different in principle from older drugs already prescribed by GPs.

There is a large range of novel antiepileptic drugs. These vary primarily in mechanism of action and adverse effect profile. The criterion for efficacy applied in pre-marketing trials is that there should be a significantly greater number of patients whose seizures are reduced by more than 50%, than in the placebo arm of the study. On this criterion, most new drugs are roughly equivalent to each other at the time of marketing, although differences do sometimes emerge with experience. For example gabapentin was shown to be significantly less efficacious than other antiepileptic drugs in the SANAD I study.

It is also important to note that newer drugs are generally only initiated after failure or intolerance to more established drug treatments or in particular patient populations (such as women at risk of potential teratogenic effects). The current NICE guidance (NICE CG: 137 Epilepsies: diagnosis and management, 2012) provides a framework for appropriate use of first, second and subsequent trials of antiepileptic medication. The newer drugs are most commonly used after failure of 2-3 antiepileptic drugs.

There is a common misconception about the cost of continued trials of newer antiepileptic drugs. However most of the newer drugs are comparable in price, and are commonly used in substitution with each other. It is also worthwhile to recognise the burden of epilepsy on the patient both from medical and psychosocial impact, and that the direct medical costs of patients who achieve seizure freedom are significantly less than those with ongoing seizures. The difference in non-medical costs (loss of earning potential, social care, welfare) between seizure free and non-seizure free patients is even greater.

Bearing this in mind, the drug and therapeutics committee of each hospital and clinical commissioning group should have in place procedures where access to new antiepileptic medications for drug refractory patients are not unduly delayed due to bureaucratic processes, if used within this accepted management pathway.

5 Responsibilities

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Drug Treatment – Indications, general principles and recommended treatment regimens

a) Indications, cautions, contraindications, side effects, doses and formulations are listed in the British National Formulary. These guidelines may differ slightly from the regimes stated in the British National Formulary, but represent acceptable practice in the UK. They are endorsed by the consultant neurologists at Peterborough City and Cambridge University Hospitals NHS Foundation Trust and are listed in the appendix to this protocol.

b) Drug information sheets for each drug are available on the CUHFT intranet.

Drug treatment - choice of antiepileptic drug

The choice of antiepileptic drug will depend on:

a) The type of epilepsy; in adults the distinction is usually between focal and generalised epilepsies, although occasional patients may have specific conditions such as Lennox Gastaut syndrome or Dravet’s Syndrome for which specific drugs are indicated;

b) Other antiepileptic drugs being taken; for example combining sodium channel blocking drugs tends to increase the risk of side-effects such as ataxia;

c) Adverse effect profile; for example some drugs may cause weight increase or weight loss, which may be particularly problematic given the profile of the patient.

d) Some drugs have a greater risk of particular neuropsychiatric side-effects which may need to be considered in individual patients.

e) Non-adherence to the licensed indications of new anti-epileptic drugs may be justified, for instance where the licence indications do not reflect current knowledge, the indications do not include well proven uses of the drug or the license indications are over restrictive. The Consultant or Epilepsy Nurses, who are independent non-medical prescribers, may recommend the use of drugs beyond the licensed indications and will detail this in the correspondence to the General Practitioner who is being asked to take over the prescription. Wherever the Consultant considers such a use to be indicated, they
will explain the drug’s unlicensed status to the patient or carer involved.

f) In general, the aim is to treat patients with the fewest antiepileptic drugs as possible to achieve seizure freedom, or if this is not possible, a reasonable compromise between seizure frequency and tolerability as determined by patient choice. Combinations of more than 3 AEDs rarely add additional efficacy.

8 Drug treatment – general principles of initiation of treatment

a) The consultant or epilepsy nurses (if independent prescribers) will initiate treatment with antiepileptic treatment after consultation with the patient, or patient’s family or carers (if appropriate) especially if delay in starting treatment is considered to be a clinical risk for the patient.

b) Generally the first four weeks of treatment will be provided by the hospital, with the GP taking on responsibility for prescription thereafter.

c) If there is a novel antiepileptic medication, especially in the first year of being licensed in the UK, the hospital will initiate treatment and provide the first three months’ supply or until dose escalation is completed, whichever is longer.

d) Thereafter, treatment of the novel AED should be continued from primary care.

9 Drug treatment – treatment regimens

a) Patients seen in the epilepsy clinic are provided with a personalised care plan and titration schedule outlined in the letter to the GP. Epilepsy nurse specialists (if not independent prescribers themselves) could assist in titration of antiepileptic medication within limits recommended by the Consultant Neurologist.

b) Changes in treatment advised by the nurse specialists will be notified in writing to the GP. If the nurse specialist is not an independent non-medical prescriber, the letter will explicitly record that a discussion has been had with a consultant regarding treatment changes.

c) Treatment plans will include:
   - Indication for new drug regime
   - Current seizure frequency
   - Potential side effects and need for specific monitoring
   - Contact details in case of difficulties
   - Time for review by Epilepsy Team
d) At an interval no later than six months after completion of dose escalation, the patient should be evaluated in secondary care and the decision made to continue or withdraw therapy. This should be made explicit in the patient record.

e) At review, the consultant will provide the GP with a further summary to include:
   - Ongoing drug regime, indication for continuation or change in regime.
   - Impact of drug regime on seizure frequency and/or quality of life.
   - Time for next review.

f) The consultant will endeavour to ensure that continuation of drug regimens will be supported by evidence of positive impact on seizure frequency and/or quality of life for the patient.

g) Where a decision is made to continue a therapy, if the patient is on polytherapy, then a decision should be made as to whether any other therapy can be withdrawn. Since new antiepileptic drugs are generally only licensed for polytherapy, it is likely that this will only be possible for patients taking three or more antiepileptic drugs.

10 Monitoring of treatment

a) Most drugs are titrated to tolerance and clinical effectiveness. Where intoxication is suspected, the Epilepsy Nurse Specialist (ENS) or Consultant involved should normally be consulted for advice. Routine blood tests for monitoring of liver function or white cell count are not indicated for any antiepileptic medication, but NICE guidance states that prescribers may wish to undertake baseline blood tests including blood count, electrolytes, vitamin D and calcium and repeat every 2-5 years.

b) Blood tests for monitoring of patients on antiepileptic drugs (AEDs) are very rarely required, and the practice of adjusting drug dose according to the results of antiepileptic drug levels is strongly discouraged unless there is a question of adherence (except in the case of phenytoin or lamotrigine in pregnancy).

c) Where specific monitoring is required, for example ophthalmological monitoring in patients taking vigabatrin, it will be the responsibility of the secondary care physician to ensure this is undertaken. Where there is more minor monitoring required, for example with blood tests or ECG, the primary care physician may agree to take responsibility but this should be made explicit in each case.
Assessment of the efficacy of an antiepileptic drug

a) Patients starting an antiepileptic drug, particularly a novel drug, in a non-emergency situation, should ideally complete a seizure diary for at least four weeks prior to initiating treatment and continue the diary during the assessment period.

b) The time taken to judge the efficacy of a new antiepileptic drug depends in part on seizure frequency; those with a low seizure frequency will need longer to assess the impact of a new medication. We recommend that the efficacy of an antiepileptic drug is assessed no later than 6 months after reaching optimal dosage.

c) There is no single measure which can be used in all cases to measure the efficacy of antiepileptic drug. Several factors have to be taken into account:
   i. Seizure frequency.
   ii. Seizure severity; for example reduction in clustering of seizures especially that requires admission to hospital; reduction in tonic clonic or other more dangerous seizure types; reduction in incontinence, post ictal confusion or other socially disabling aspects of seizures.

d) Maintenance of seizure control with clinically useful reduction in adverse effects from medication, such as sedation, cognitive, psychiatric or behavioural symptoms.

Effects of liver induction/inhibition

a) Doctors should be aware that antiepileptic drugs, especially phenytoin, phenobarbital, primidone, carbamazepine, oxcarbazepine and topiramate, induce liver enzymes that this process is harmless but has a bearing when prescribed together with other drugs with similar liver enzyme inducing or inhibitory effects. Some drugs such as lacosamide or perampanel do not affect liver enzymes themselves, but affected by liver enzyme inducers or inhibitors and so dose adjustment may be required when adding or removing such medication.

b) Such induction of liver function means these AEDS interact with oral contraceptives. Dose adjustment of contraceptives or alternative contraception such as depot or IUD may need to be considered.

Hyponatraemia with some AEDs (particularly carbamazepine and oxcarbazepine)

a) Some AEDs cause hyponatraemia by Syndrome of Inappropriate antidiuretic hormone secretion (SIADH). In the majority of these cases, the hyponatraemia is not clinical significant, and in the order of 125
mmol/L - 135 mmol/L. Serum sodium levels below 125mmol/L may need adjustment in the dose of AED. The Hospital team should be contacted for advice if there is concern.

b) If serum sodium levels need to be monitored (especially with oxcarbazepine), the hospital will advise the GP by letter when the drug is initiated or doses adjusted at hospital review.

14 Co-administration of antiepileptic drug with sodium channel blocking properties

a) It is well recognised that coadministration of two sodium channel blocking AEDs (such as carbamazepine and lamotrigine) or the combination of certain AEDs with a sodium channel blocking antiepileptic (eg levetiracetam and carbamazepine/ phenytoin/ lamotrigine/ oxcarbazepine) can increase problems with tolerability.

b) This is particularly when a new AED is added to existing treatment with sodium channel blocking AED. This may require reduction in dose of the existing AED (or even its withdrawal) to allow titration of the new AED to a therapeutic dose. When this may be a possibility the Hospital team will warn the GP of potential interaction and provide advice on the dosage adjustments that are required.

15 MHRA Advice on switching between different manufacturers’ products for a particular AED

a) Different AEDs vary considerably in their characteristics, which influences the risk of whether switching between different manufacturers’ products of a particular drug may cause adverse effects or loss of seizure control. No switching between manufacturers should occur without the patient being informed and consented.

b) AEDs have been divided into three categories to help healthcare professionals decide whether it is necessary to maintain continuity of supply of a specific manufacturer’s product.

c) Antiepileptic drugs: New advice on switching between different manufacturers’ products for a particular drug

d) If it is felt desirable for a patient to be maintained on a specific manufacturer’s product, this should be prescribed either by specifying a brand name, or by using the generic drug name and name of the manufacturer (otherwise known as the marketing authorisation holder).
e) This advice relates only to AED use for treatment of epilepsy; it does not apply to their use in other indications (e.g., mood stabilisation, neuropathic pain).

16 Women on sodium valproate

a) The MHRA has issued guidance on the use of sodium valproate in to female children, female adolescents, and women of childbearing potential or pregnant women unless other treatments are ineffective or not tolerated. [Valproate and risk of abnormal pregnancy outcomes: New communication materials](#)

b) There is a dose dependent effect with a:
   - 10% risk of congenital malformations at doses above 1000mg daily.
   - 30-40% risk of serious developmental disorders (delays in early development with talking, low intellectual abilities, poor language skills and memory problems) in preschool children exposed to valproate in utero.
   - Possibility of risk throughout pregnancy cannot be excluded.
   - Risk with high dose valproate monotherapy could be reduced with combination AED therapy, if this allows reduction in dose of valproate.

c) Valproate treatment must be started and supervised by a specialist experienced in managing epilepsy.

d) The benefits of valproate must be balanced against the risks, when prescribing valproate for the first time, at routine treatment reviews, when a female child reaches puberty and when a women plans a pregnancy or becomes pregnant.

e) If a woman is already on valproate, the decision to withdraw treatment must be made in consultation with a specialist in epilepsy.

f) All female patients on valproate must be informed of and understand:
   - Risks associated with valproate during pregnancy
   - Need to use effective contraception if not planning to conceive
   - Need for regular review of treatment
   - The need to rapidly consult if she is planning a pregnancy or becomes pregnant
   - Be provided with the MHRA Patient Guide on valproate
   - Use the MHRA checklist on valproate to guide discussion and document the discussion has taken place.
17 Patients with drug resistance/ drug refractory epilepsy

a) Standard practice in the UK is to consider patients who continue to have seizures despite achieving and tolerating therapeutic doses of two AEDs to be ‘drug refractory’. This is based on epidemiological data that suggests that 60-70% of patients will become seizure free after trials of the first or second tolerated AED. These patients are unlikely to require newer AEDs unless published research suggests one is particularly successful above older AEDs for certain patient populations.

b) In contrast, chances of seizure freedom diminish with increasing trials of medication, plateauing at less than 10% after the fourth AED and subsequent AEDs. However, due to the medical and psychosocial impact of ongoing epileptic seizures (termed ‘active’ epilepsy) which includes increased mortality as well as morbidity, further trials of medication are indicated if the patient wishes.

c) Patients with drug refractory active epilepsy will also be considered for reassessment of diagnosis, treatment plan and potential other therapies (including epilepsy surgery or vagal nerve stimulator) may need to be considered.

18 Management and referral guidelines for Primary Care

First unprovoked seizure (i.e. not caused by alcohol, anoxia due to syncope, etc)

a) Do not initiate antiepileptic drugs.

b) Refer all patients for assessment and investigation. An eye witness of the attack should be asked to accompany the patient to hospital if possible.

c) Perform an ECG, particularly checking QT interval and refer to cardiologist if abnormal

d) Give advice about driving regulations referring to current DVLA regulations

e) Provide patient with first seizure leaflet: First Seizure

Second seizure before outpatient appointment

a) Normal practice would be to discuss therapeutic options by letter, telephone or Choose and Book Advice and Guidance (preferred route) with consultants or Epilepsy Nurse Consultant (see below).

b) Immediate drug initiation may be appropriate and would involve first line treatment as per NICE guidance (NICE CG: 137 Epilepsies: diagnosis and management, 2012), taking account of patient preference, characteristics and lifestyle (valproate NOT for women of childbearing age).

c) Advise about current DVLA guidance on Epilepsy Regulations.
d) Advise about teratogenic risk of drugs in women (doubling of risk of major congenital abnormalities (from 1 - 2 in 100 background risk to 2-3 in 100 on exposure to single AED, except for valproate where the risk is much higher). The risk of minor abnormalities, including learning difficulties are unknown, except for valproate which has an increased risk of particularly verbal learning deficits.

e) Consider impact of AED on contraceptive choices in women
   i. Note the interaction of carbamazepine, phenytoin, phenobarbital, primidone and topiramate with oral contraceptive pill (double dose of oestrogen combined pill equivalent to a minimum of ethinylestradiol 50mcg required).
   ii. Lamotrigine also interacts with the oral contraceptive pill to a limited degree, and we recommend warning the patient that the contraceptive efficacy might be affected.
   iii. Depo contraceptives such as Depo Provera injections and intrauterine coils are acceptable however contraceptive implants should be avoided. Depo injections should be given every 12 weeks even to patients taking antiepileptic drugs.

f) Warn about risk of allergic reactions, which can be serious (Stevens Johnson syndrome) with phenytoin, carbamazepine, phenobarbital and lamotrigine (can be delayed up to 6-8 weeks after initiation or dose increase).

g) Warn about an increased risk of suicidal ideation (1-2%) with antiepileptic drugs and more commonly behavioural and mood change.

h) Inform patients that medication should be taken continuously and changes or withdrawal made only after recommendation at the time of medical review (by GP or Epilepsy specialist).

Patients may be discharged to Primary Care (GP) if:
   I. They become seizure free
   II. No active epilepsy management is required (either on clinical grounds or patient/carers preference) despite ongoing seizures
   III. At patient or carers request

Criteria for Referral of patients to Specialist epilepsy service at CUH, Peterborough Hospital or Learning Disability services [CPFT] any of the following:
   i. When patient or general practitioner is not comfortable to continue with the existing regime due to either continuing seizures, seizure recurrence after period of seizure freedom or drug side effects (including behavioural effects).
   ii. Ongoing seizures despite trials of >2 AEDs at optimum doses and not had a specialist epilepsy review in last 2-3 years.

i) Advice in respect of concordance.
   i. Special situations, e.g.
   ii. Pregnancy, preconception counselling
   iii. Occupational advice
   iv. Driving
   v. Discontinuing medication.
19 Education, information, advice and support

The epilepsy nurse specialist (ENS) or epilepsy nurse consultant may be contacted for advice to GPs and for information, advice and support for patients. For medical advice and drug changes the consultant neurologists should be contacted. They may refer enquirers to the ENS if appropriate.

Telephone advice from:
Epilepsy nurse consultant: 01223 217992

Consultant neurologists:
Addenbrooke’s Hospital
Dr Mitchell and Dr Manford 01223 216759
Or
On call neurology specialist registrar at Addenbrooke’s Hospital

Peterborough City Hospital
Dr Mitchell, Dr Thorpe, Dr Baumer, Dr Stacpoole 01733 673549

Peterborough Epilepsy Specialist Nurses
Lynda Morris and Karen Wilkins 01733 776140

20 Budget implications

Prescribing costs should not form part of discussions on clinical responsibilities between clinicians. Where there are major financial implications of the prescribing of certain drugs by hospital doctors the CCG pharmacy advisor should be consulted.

21 Monitoring compliance with and the effectiveness of this document

22 References

Provide an up-to-date evidence base for procedural documents.

23 Associated documents

Equality and diversity statement
This document complies with the Cambridge University Hospitals NHS Foundation Trust service equality and diversity statement.

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# Neurology

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Appendix 1: Antiepileptic Drug Regimes

This documents outline information about drugs where local recommendations vary from those in British National Formulary, including significant adverse effects, withdrawal recommendations, precautions and any requirement for blood testing. The BNF remains the authoritative resource.

1. **Acetazolamide**: Begin at a dose of 250mg daily, increasing in 250mg steps every one to four weeks until seizures are controlled, intoxication becomes unacceptable or a dose of 1g is reached in three divided doses. Withdraw at a rate of 250mg every week or so.

2. **Brivaracetam**: Add on for partial seizures, especially those responding to levetiracetam but with behavioural side effects, start prescribing at 50mg BD in most patients. This can be reduced to 25mg BD in the elderly or in those with hepatic impairment or otherwise vulnerable to sedative side effects. Maximum dose is 100mg BD, 75mg BD in those with hepatic impairment. Main adverse effects are sedation or dizziness. Withdrawal by 25mg per week.

3. **Carbamazepine modified release**: Begin at 100mg once or twice daily, increasing in 100-200mg steps every two weeks until a dose of 200mg BD is reached. Thereafter increase only if further seizures occur at a rate of 200mg every two to four weeks until seizures are controlled or symptoms of intoxication become unacceptable. In case of rash (unless severe) withdraw at a rate of 200mg per week. Severe rash may require admission and immediate withdrawal of carbamazepine. In non-urgent withdrawal, withdraw at a rate of 200mg every two to four weeks.

4. **Clobazam**: Can be used as adjunct on a daily basis, or short courses for clusters of seizures including catamenial seizures. Start at 10mg OD, can increase one week later to 10mg BD.

5. **Clonazepam**: Begin at a dose of 0.5-1mg nocte, increasing in 0.5-1mg steps every two to four weeks until seizures are controlled, symptoms of intoxication become unacceptable or a dose of 2mg TDS is reached. Some patients may require even smaller increments because of sedative effects. Withdraw at a rate of 2mg per month.

6. **Diazepam (rectal)**: Used as a rescue medication with an individualised care plan. BNF guidelines recommend 0.5mg /kg body weight, maximum 30mg daily.

7. **Ethosuximide**: Begin at a dose of 250mg BD (only for absence seizures in idiopathic generalised epilepsy). Maximum dose 1g BD. Withdraw at a rate of 500mg every two to four weeks.

8. **Eslicarbazepine**: Begin at 400mg nocte, increasing by 400mg every 2-4 weeks to 800mg nocte if continuing seizures. Can be increased in 400mg steps to 1600mg until seizures are controlled or symptoms of intoxication become unacceptable.
9. **Felbamate – special monitoring required:** Commence at a dose of 400mg TDS. Maximum dose usually 3600mg daily.

10. **Gabapentin:** Introduce at 300-400mg OD, increasing in 300-400mg steps every one to four weeks until seizures are controlled, symptoms of toxicity become unacceptable or a dose of 1.2g TDS is reached. A small number of patients may benefit from (and tolerate) higher doses even up to 4.8g daily. Withdraw gabapentin at a rate of 400mg every one to four weeks.

11. **Lacosamide:** Introduce at a dose of 50mg once or twice daily and increase in 50-100mg daily every one to two weeks to a maximum of 200mg BD. Some patients may benefit from doses up to 400mg BD. Withdraw at a rate of 50-100mg every 1 to 2 weeks.

12. **Lamotrigine:**

   **For patients not taking other anti-epileptic drugs:**
   Introduce at 25mg daily for two weeks before increasing further as follows.
   Increase to 50mg daily for two weeks.
   Then increase in steps of 25mg- 50mg per fortnight can be until seizures are controlled, symptoms of toxicity become unacceptable or a dose of 200mg BD is reached.

   **For patients taking Sodium Valproate:**
   Introduce at 25mg on alternate days for two weeks, then 25mg once daily for two weeks, then increase by 25mg every two weeks until symptoms of toxicity become unacceptable or a dose of 100mg BD is reached. (Doses up to 300mg/day may also be given in a single undivided daily dose). Patients who are also taking Sodium Valproate sometimes tolerate higher doses, but monitor closely for intoxication above 200mg daily.

   **For those patients taking an enzyme inducing anti-epileptic drug (Carbamazepine, Phenytoin, Phenobarbital, and Primidone):**
   Introduce at 50mg of Lamotrigine daily and increase in 50mg steps every two to four weeks until seizures are controlled, symptoms of intoxication become unacceptable or a dose of 200mg BD is reached. Some patients on enzyme inducing drugs will tolerate higher doses.

   **Withdraw Lamotrigine at a rate of 25mg-50mg every one to four weeks:** NOTE Lamotrigine theoretically increases the metabolism of hormones in the OCP and thus may have the potential to reduce its efficiency.

   **Oral contraceptives:** In patients established on lamotrigine treatment addition of oral contraceptives to their drug regime may lower the effectiveness of the anti-epileptic medication. In these circumstances an increase of lamotrigine dose of about 30% should be considered.

13. **Levetiracetam:** Introduce at 250mg a day and increase in 250mg steps every fortnight to 500mg BD, unless further seizures when can be increased to a maximum of 2000mg BD.
14. **Buccal Midazolam**: Rescue medication for prolonged (≥5 minutes) seizures / clusters of seizures with an individualised care plan and training of carers by Epilepsy Nurse Consultant/Epilepsy Nurse Specialists or Learning Disability Community Nurses.

15. **Paraldehyde**: Available as a rectal solution (50:50) in olive oil from Stockport Pharmaceuticals (details under Special-order Manufacturers in BNF). Adult dose 5-10ml (i.e. 10-20ml of solution). Patients will be provided with an individualised care plan.

16. **Perampanel**: Introduce at 2 mg at bedtime and increase by 2 mg every fortnight until seizures are controlled or as tolerated up to a maximum dose of 8 mg nocte in mild hepatic impairment and 12 mg nocte in other patients. Withdraw at 2mg per month.

17. **Phenobarbital**: Introduce at 30mg nocte and increase in 30mg steps every four weeks until seizures are controlled or symptoms of intoxication become unacceptable. Maximum dose usually around 240mg daily. Withdraw at a rate of 30-60mg per month.

18. **Phenytoin**: Introduce at 250mg daily, increasing in 25mg steps every four to eight weeks until seizures are controlled or symptoms of intoxication become unacceptable. Withdraw at a rate of 50-100mg per month.

19. **Pregabalin**: Initially 25mg TDS, increase every few weeks until seizures are controlled to maximum 600mg daily. Pregabalin has a similar therapeutic profile to gabapentin which is cheaper, but is easier to take at therapeutic doses.

20. **Primidone**: Begin with 125mg lying flat in bed at night first dose. Increase in 125mg steps every fortnight until seizures are controlled, symptoms of intoxication become unacceptable or a dose of 750mg BD is reached. Withdraw at a rate of 250mg per month.

21. **Retigabine – Needs to be initiated by specialist only, but no longer used**: Can prolong QT interval therefore needs requires monitoring of ECG pre-treatment and during titration, particularly in high risk groups. Also reported to cause ocular pigmentation, and skin and nail discolouration. Need pre-treatment ophthalmological assessment and 6 monthly thereafter. Introduce 50mg TDS, increasing by 50mg every 2 weeks, aiming for a maintenance dose of 0.6g-1.2g daily in divided doses.

22. **Rufinamide**: Introduce at 100mg once or twice daily and increase in 100-200mg increments every 1-2 weeks. Target dose 900mg BD but can be increased further depending on body weight.

23. **Stiripentol**: Dose is calculated on an mg/kg body weight to a maximum of 50mg/kg/day. Usually initiated as an adjunct to sodium valproate or clobazam (0.5mg/kg/day) in Dravet’s Syndrome. A dose reduction in clobazam may be required if tolerability becomes problematic on introduction of stiripentol.
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24. **Topiramate**: Introduce at 25mg OD. Increase in steps of 25-50mg every one to two weeks to an initial dose of 50mg BD. Consider further dose increases in steps of 25-50mg every one to two weeks until seizures are controlled or maximum dose of 400mg BD is reached. Withdraw topiramate at a rate of 50mg every two to four weeks. Adverse effects include weight loss, ataxia, slowed thought and speech and mood disturbances.

25. **Sodium valproate**: Use standard or slow release preparation. Begin at a dose of 300-500mg once or twice daily, increasing after two to four weeks to 500mg BD. Thereafter increase only if further seizures occur and at a rate of 500mg each month until seizures are controlled, symptoms of toxicity become unacceptable or a dose of 1.5g BD is reached. Withdraw at a rate of 500mg per month unless serious adverse event demands more rapid withdrawal. Note this drug interacts with lamotrigine.

26. **Vigabatrin**: Test visual fields arranged by hospital prior to introduction and check 3 monthly for first year and six monthly thereafter. Introduce at a dose of 500mg OD, increasing in 500mg steps every one to four weeks until seizures are controlled, symptoms of intoxication become unacceptable or a dose of 1.5g BD is reached. Withdraw at a rate of 500mg per month.

27. **Zonisamide**: Begin with 25mg OD, increasing in 25-50mg increments every two to four weeks until seizures are controlled to maximum 400mg OD. Withdraw at the same rate.
Appendix 2: Treatment Pathway

First seizure
→ Refer for assessment and investigations
→ Treatment not usually commenced (considered on an individual basis)

Second or further seizures
→ Further investigations if required
→ Start first line treatment (NICE CG137)
→ Seizure free

Consider withdrawal of AED after 2 years, depending on epilepsy syndrome and patient preference

Trial of first/second line treatment (NICE CG137)
→ Seizure free

Reconsider diagnosis, and consider further investigations
→ Consider combination therapy
→ Seizure free

"DRUG REFRACTORY ACTIVE EPILEPSY"
Consider further trials of combination therapy with second/third and subsequent choices of AEDs, depending on patient preference (consider epilepsy surgery, Vagal nerve Stimulator if appropriate)

Seizure free