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NOTES ON ANTIEPILEPTIC DRUG THERAPY IN CHILDHOOD

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This is based in part on personal experience and preference and is not intended for use beyond the local paediatric epilepsy care programme. These have been revised in light of NICE and SIGN guidelines 2004

General Aspects

1. Drug treatment of epilepsy should be both as effective and as safe as possible. Certain drugs are deemed 'first line' in the various clinical seizure types or epilepsy syndromes because they most closely fulfil these criteria, viz table 1:-

Table 1 First line AEDs by seizure and epilepsy type

Neonatal Seizures	Phenobarbital Lignocaine Midazolam
Idiopathic or Cryptogenic Infantile Spasms	Vigabatrin 'Steroids' (prednisolone or depot tetracosactide)
Symptomatic Infantile Spasms with Tuberous Sclerosis	Vigabatrin
Generalised Tonic-Clonic Seizures	Sodium valproate Carbamazepine (not in idiopathic generalised epilepsy)
Focal Seizures (motor, sensory, autonomic, psychic, automatic, combinations)	Carbamazepine Sodium valproate
Idiopathic Focal Epilepsy esp. BRE (BECTS)	Clobazam Sodium Valproate Sulthiaime
Idiopathic Generalised Epilepsy with photosensitivity	Sodium valproate
Childhood Absence Epilepsy	Sodium valproate Ethosuximide
Juvenile Myoclonic Epilepsy	Sodium valproate Lamotrigine Levetiracetam
Myoclonic, atonic or tonic seizures	Sodium valproate Clobazam
Epilepsy with myoclonic absences	Lamotrigine Sodium valproate Ethosuximide
Atypical absence seizures	Sodium valproate Ethosuximide Lamotrigine
Lennox-Gastaut syndrome	Sodium valproate Lamotrigine
Dravet syndrome / SMEI / Borderline SMEI	Sodium valproate Clobazam Stiripentol (+ Clobazam)
Progressive Myoclonic Epilepsies	Sodium valproate Clonazepam Levetiracetam Piracetam
Convulsive Status Epilepticus **Prolonged epileptic convulsions (longer than 5-10 minutes)**	Buccal midazolam Rectal diazepam Rectal paraldehyde
Seizures in clusters	Clobazam Acetazolamide

However, the difficulty of categorising seizure types and epilepsy syndromes in childhood is well known and, for example, the child who is experiencing clinically 'small' attacks may be having typical or atypical absence seizures, or various types of focal seizures. This is just one of the reasons why the most effective antiepileptic drug (AED) for a child may sometimes have to be found by individual trial.

2. To begin with, the 'first line drug' is commenced in a dose at the lower end of the recommended dosage range. It is best to relate the dose of an AED to the child's weight rather than to his age. If the seizures do not respond, the dose is gradually increased until the full dose is reached or adverse-effects occur. An estimation of the plasma drug level may sometimes be helpful in deciding optimal dosage with phenytoin, carbamazepine, primidone, phenobarbital, ethosuximide and lamotrigine, valproate, levetiracitam, but levels should always be interpreted in close relationship with the clinical picture. The most common situations when an AED level is helpful, is the day after IV loading with phenytoin or phenobarbital; on admission with acute exacerbation of seizures; when a high dose has neither been effective nor toxic, to see if the level is high or if there is evidence of non-adherence or rapid elimination. It may be acceptable for the drug level to be below the so-called target range if seizures are well controlled or for the level to be above the target range if this is required to control the seizures and there are no adverse-effects. Do not drop the dose just because the level is 'high' unless there are symptoms of dose-related toxicity.

3. If the seizures do not respond to the 'first line drug' in full or maximum tolerated dose, another 'first line' or a 'second line' AED should be tried in a similar fashion until an effective one is found, see table 2.

4. There is a risk of precipitating seizures (even status epilepticus) if antiepileptic medication is suddenly withdrawn. To guard against this when antiepileptic therapy is to be changed, the new antiepileptic drug should generally be added to the old for a period before gradually withdrawing the old antiepileptic drug. For the same reason it is desirable that antiepileptic therapy should not generally be interrupted for reasons such as intercurrent illness operation or EEG examination. If necessary IV (sodium valproate, levetiracitam, diazepam, phenytoin or phenobarbital) or rectal (carbamazepine) antiepileptic medication can be given to a child who is nil by mouth or who is unable to take oral medication for a period.

   In certain rare situations where antiepileptic drugs are thought not to be exerting any desired effect and may be exerting unwanted effects it is reasonable to withdraw antiepileptic therapy slowly (over weeks or months in an outpatient). Patients undergoing videotelemetry often need the reduction of (partially) effective antiepileptic drugs, including withdrawal in order to capture seizures. It is usually necessary to reinstate the usual dose as soon as videotelemetry is complete, before discharge from hospital. Sodium valproate is best tailed off completely before videotelemetry, with a valproate-free period of at least six weeks prior to admission.

5. Sometimes two antiepileptic drugs administered concurrently are required to control the seizures. The disadvantages of more than two antiepileptic drugs given concurrently often outweigh any advantages. The possibility of drug interactions should always be considered when two or more drugs are given together.

6. Lorazepam IV is the drug of choice for the hospital treatment of status epilepticus but there is a very slight risk of apnoea during administration so equipment for intubation and ventilation should be available when it is given. Rectal diazepam, buccal midazolam or paraldehyde are more suitable for home use. Diazepam IM does not produce rapid or reliable blood levels and should be avoided. After two doses of benzodiazepines, phenytoin (or fos-phenytoin) IV is usually given next. Phenytoin IM is unreliably absorbed and should not be used. Status responding to IV bolus lorazepam but then relapsing may be controlled with a continuous IV midazolam infusion. Status not responding to adequate IV lorazepam or diazepam may come under control with a continuous infusion of lignocaine, although high dose midazolam (2 to 36 microgrammes / kg / min) in PICU may be useful for refractory status epilepticus, in place of barbiturate anaesthesia, with continuous EEG monitoring (see status epilepticus guidelines). When Buccal Midazolam or Rectal Diazepam is prescribed for out of/pre-hospital use, apnoea is very unlikely if an emergency benzodiazepine did not cause apnoea in the past. If the child has not been exposed then consider a test dose in hospital with resus available (risk is probably less than 1/1000 children), or advise

parents to call ambulance/paramedic by 999 when they give it the 1st time. All parents of children with convulsive seizures should be offered or advised to get basic life support training.

Table 2 Second-line AEDs by seizure and epilepsy type

Neonatal seizures	Carbamazepine Sodium valproate Levetiracetam	
Idiopathic or Cryptogenic Infantile Spasms	Pyridoxine or Pyridoxal Phosphate Sodium valproate	Nitrazepam Zonisamide
Symptomatic Infantile Spasms	'Steroids' (prednisolone or depot tetracosactide) Pyridoxine or Pyridoxal Phosphate Sodium valproate	Nitrazepam Zonisamide
Generalised Tonic-Clonic Seizures	Levetiracetam Topiramate Clobazam Gabapentin Lamotrigine	Zonisamide Tiagabine (not in IGE) Phenytoin (not in IGE)
Focal Seizures (motor, sensory, autonomic, psychic, automatic, combinations)	Gabapentin Topiramate	Lamotrigine Levetiracetam
Idiopathic Generalised Epilepsy with photosensitivity	Lamotrigine Levetiracetam	
Childhood Absence Epilepsy	Lamotrigine	Clobazam Clonazepam
Juvenile myoclonic epilepsy	Clobazam Clonazepam	Zonisamide
Myoclonic, atonic or tonic seizures	Lamotrigine Ethosuximide	Acetazolamide
Epilepsy with myoclonic absences	Clobazam Clonazepam	
Atypical absence seizures	Clobazam Acetazolamide	Clobazam & Acetazolamide
Lennox-Gastaut syndrome	Clobazam Levetiracetam Topiramate Rufinamide	Phenytoin Zonisamide Clonazepam Felbamate
Progressive myoclonic epilepsies	Zonisamide Lamotrigine	Levetiracetam
Status epilepticus	IV lorazepam IV phenytoin IV phenobarbital	IV midazolam IV lignocaine IV thiopentone

7. The following regularly induce liver enzymes: carbamazepine, phenobarbital, lamotrigine, topiramate. The following have only renal elimination: gabapentin, levetiracetam, tiagabine, vigabatrin.

Individual drug notes

ACETAZOLAMIDE ('Diamox' : Storz)

Indications	
Typical or atypical absence seizures not responding to first line drugs. Sometimes used for other seizure types including Benign Rolandic Epilepsy, continuous spike wave in slow sleep, menstruation-related seizures, or other clusters of seizures. Not usually used as monotherapy	
Dose	**Dose form**
20 - 30 mg/Kg/day in two or three divided doses Max 1000mg/day	Tablets 250 mg (unscored) Capsules 250 mg (sustained release)
Adverse effects	
• Uncommon. • Nausea, vomiting, and loss of appetite • Renal crystalluria and stone formation, paraesthesiae, hypokalaemia and blood dyscrasia have been reported. • Routine blood counts and electrolytes recommended for prolonged use	

CARBAMAZEPINE ('Tegretol' : Ciba-Geigy)

Indications	
Drug of first choice for focal / partial seizures and for secondarily generalised tonic-clonic seizures Avoid in idiopathic generalised epilepsies	
Dose	**Dose form**
10 - 20 mg/Kg/day in two or three divided doses Max 40mg/Kg/day Introduce gradually Target plasma levels are 6-12mg/L Plasma half-life 8-24 hours (or 48 hours initially)	Tablets 100mg, 200mg, 400mg (all scored) Chewtabs 100mg and 200mg Retard tablets 200mg and 400mg (both scored) Liquid 100mg/5ml. Suppositories 125mg and 250mg (equivalent to 100mg and 200mg oral)
Adverse effects	
• Dizziness, drowsiness, dry mouth, nausea, rashes, diplopia, chorea, cerebellar ataxia, jaundice, rickets, megaloblastic anaemia, hyponatraemia and blood dyscrasias have been reported. • Gradual introduction reduces the risk of adverse effects. • Enzyme inducer so will need a higher dose oral contraceptive pill. • Regularly worsens absence, myoclonic, atonic seizures, e.g. in idiopathic generalised epilepsies. • Occasionally worsens Benign Rolandic Epilepsy. • Toxicity can be precipitated by erythromycin. • Oxcarbazepine may be better tolerated in some patients.	

CLOBAZAM ('Frisium' : Hoechst)

Indications	
Drug of first choice for myoclonic, atonic or tonic seizures. Also effective for focal seizures. Valuable for short-term treatment of 'bad patches' in children with difficult epilepsy. Also used for short-term intermittent therapy to cover times of increased seizure risk (e.g. menstruation in some teenage girls) or times when seizures would be particularly inconvenient (e.g. social functions) May be used regularly	
Dose	**Dose form**
200-1000mcg/Kg/day in two or three divided doses Max 40mg/day Plasma half-life 10-30 hours	Tablets 5mg, 10mg (scored). Suspension can be made by pharmacy in various strengths.
Adverse effects	
• Early tolerance less than with other benzodiazepines • Drowsiness, ataxia, dysarthria, behaviour problems, sleep disturbance, and increased secretions have been described • Should be discontinued slowly to avoid withdrawal symptoms, unless used for a couple of days to treat a cluster.	

CLONAZEPAM ('Rivotril' : Roche)

Indications	
Similar to clobazam for myoclonic, atonic and tonic seizures. Second choice drug for many other seizure types May be helpful in PMEs	
Dose	**Dose form**
50-200mcg/Kg/day in two or three divided doses Max 6mg/day Plasma half life 20-30hours	Tablets 500mcg and 2mg (both quarter-scored). Suspension can be made by pharmacy in various strengths.
Adverse effects	
• Early tolerance, drowsiness, ataxia, dysarthria, behaviour problems, sleep disturbance, and increased secretions have been described. • Should be discontinued slowly to avoid withdrawal symptoms.	

DIAZEPAM ('Valium' : Roche)

Indications	
Drug of first choice for status epilepticus PR though increasingly replaced by buccal midazolam. May also be given IV for status epilepticus	
Dose	**Dose form**
250mcg/Kg/dose slow IV bolus 500mcg/Kg/dose rectally (round dose down to the nearest tube) Either may be repeated after 10 minutes if necessary	Ampoules 10mg in 2ml (solution or 'Diazemuls' emulsion) Rectal tubes 2.5mg in 1.25ml, 5mg in 2.5ml, 10mg in 2.5ml and 20mg in 5ml
Adverse effects	
• Rarely apnoea may follow IV bolus injection. Equipment for intubation and ventilation should be available whenever diazepam is given IV • Rectal diazepam is considered safer in this respect	

ETHOSUXIMIDE ('Zarontin' : Parke-Davis)

Indications	
Drug of first choice for typical childhood absence epilepsy Sometimes of value for atypical absence, myoclonic, atonic and tonic seizures	
Dose	**Dose form**
20-40mg/Kg/day in two divided doses Max 2000mg/day Target plasma levels are 40-100mg/L Plasma half -life 20-40 hours	Capsules 250mg Syrup 250mg/5ml (often spat out)
Adverse effects	
• Nausea, loss of appetite, weight loss, psychological changes, rashes, hiccup, ataxia, photophobia, headaches and blood dyscrasias have been reported	

FELBAMATE ('Taloxa': Schering-Plough)

Indications	
Lennox-Gastaut syndrome and intractable partial seizures shown to be unresponsive to 2 or more AEDs at a maximum tolerated dose. Available only on a named-patient basis.	
Dose	**Dose form**
15mg/Kg/day for a week, then 30mg/Kg/day in two or three divided doses. Max 45mg/Kg/day or 3600mg/day whichever is the smallest.	Tablets 400mg, 600mg Suspension 600mg/5ml
Adverse effects	
• Nausea, anorexia, headache, dizziness, diplopia, drowsiness, insomnia have been reported and may be dose-related. • Aplastic anaemia occurs in 1/5000 and acute liver failure in 1/30000 patients. FBCs and LFTs recommended fortnightly initially and then monthly. • Affects metabolism of carbamazepine, sodium valproate, phenytoin and barbiturates and the dose of any of these drugs must be reduced by about 30% on starting felbamate. • May need a higher dose of the oral contraceptive pill.	

GABAPENTIN ('Neurontin' : Parke-Davis)

Indications	
Drug of second choice for focal seizures including secondarily generalized seizures	
Dose	**Dose form**
20-40mg/Kg/day Maximum 70mg/Kg/day in three divided doses Start at about 15mg/Kg/day and build up fairly rapidly, over a few weeks. Plasma half -life 5-7 hours.	Capsules 100mg, 300mg and 400mg
Adverse effects	
• Unusual • Dizziness, sedation, ataxia, nystagmus, headache, tremor, diplopia, and nausea have been reported. • Relatively safe in overdose.	

INTRAVENOUS IMMUNOGLOBULIN

Indications	
Severe intractable epilepsy unresponsive to other antiepileptic drugs, however no convincing evidence to encourage its use in epilepsies, and has to be requested specially, in discussion with pharmacy and immunology departments.	
Dose	**Dose form**
200mg/Kg IV over 6 hours on alternate days for three doses. Repeat after 3 weeks, or use other published protocol, for 6 month trial	Many different commercial preparations available
Adverse effects	
• Malaise, chills, fever, flushing, wheezing and anaphylaxis, have been reported • Transmission of hepatitis C or other viruses is unlikely now with routine donor testing	

LACOSAMIDE ('Vimpat' : UCB Pharma)

Indications	
Marketing is authorised in adults for adjunctive treatment of focal seizures with or without secondary generalisation. No efficacy or safety data available for children under 16 years of age.	
Dose	**Dose form**
Child 16-18 years: 50mg bd increasing in steps of 50mg twice daily every week Max dose 200mg bd	Tablets 50mg, 100mg, 150mg, 200mg Syrup 15mg/ml IV 10mg/ml
Adverse effects	
• Nausea, vomiting, flatulence, constipation, dizziness, headache, depression, diplopia, nystagmus, impaired coordination, impaired memory, cognitive disorder, drowsiness, tremor, asthenia, fatigue, pruritus have been reported	

LAMOTRIGINE ('Lamictal' : Glaxo-Wellcome)

Indications	
Drug of first choice for Lennox-Gastaut syndrome, juvenile myoclonic epilepsy and epilepsy with myoclonic absences. Second choice drug for many other seizures. Avoid in Dravet syndrome (Severe Myoclonic Epilepsy of Infancy).	
Dose	**Dose form**
Adjunctive therapy with valproate Single daily dose: 0.15mg/Kg/day for two weeks, then; 0.3mg/Kg/day for two weeks then; increase by 0.3mg/Kg/day every 1-2 weeks and maintain Max 10mg/Kg/day or 300mg/day, whichever is smaller Sodium valproate increases plasma half life so that toxicity occurs at a lower dose. Levels of up to 20 mg/l may be needed if tolerated *Monotherapy or adjunctive therapy with other drugs apart from valproate* Two divided doses: 0.5mg/Kg/day for two weeks, then; 1mg/Kg/day for two weeks then; 2mg/Kg/day. Max 15mg/Kg/day or 500mg/day, whichever is smaller Plasma levels 5-20mg/L Plasma half life 8-70 hours	Tablets 25mg, 50mg, 100mg and 200mg (all unscored). Dispersible tablets 2mg, 5mg (scored) 25mg (unscored) and 100mg (unscored).
Adverse effects	
• Rash, headache, drowsiness, difficulty going off to sleep, dizziness, seizure exacerbation, diplopia, nausea, blurred vision, itchy eyes, ataxia, irritability and aggression have been reported. • May increase levels of carbamazepine epoxide when given concurrently with carbamazepine. • Toxic levels can occur on withdrawal of any concurrent enzyme inducing drug. • Dose should be halved if sodium valproate is added (e.g. change to once a day), or when a concurrent enzyme inducer has been withdrawn. • Need dose increase if starting the oral contraceptive pill. • May need higher dose of oral contraceptive pill.	

LEVETIRACETAM ('Keppra' : UCB Pharma)

Indications	
First/Second line treatment of focal seizures with or without secondary generalisation Also effective for generalised seizures. First line treatment of Juvenile Myoclonic Epilepsy in teenage girls.	
Dose	**Dose form**
Titrated up over 6 weeks from 10-20mg/kg/day to 60mg/kg/day in divided doses	250mg, 500mg, 1000mg Liquid 1ml=100mg (sugar free) IV 100 mg/ml, but dilute dose e.g. in 100 ml
Adverse effects	
• Headache, anorexia, nausea, diarrhoea, dyspepsia, nausea, drowsiness, amnesia, ataxia, dizziness, emotional liability, tremor, vertigo, skin rash and diplopia have been reported.	

LIGNOCAINE (' Lignocaine 0.2% in glucose' : Baxter)

Indications	
Status epilepticus not responding to drugs of first choice on PICU	
Dose	**Dose form**
4mg/Kg/hour (2ml/Kg/hour) for the first hour and then 1-4mg/Kg/hour (0.5-2ml/Kg/hour) for 24 hours	500ml containers of 0.2% lignocaine in 5% glucose (2mg lignocaine/ml solution)
Adverse effects	
• Dizziness, paraesthesia, hypotension, bradycardia, respiratory depression and hypersensitivity have been reported • Blood pressure, ECG, and respiration should be continuously monitored during infusion and respiratory support should be available if necessary.	

LORAZEPAM ('Ativan' : Wyeth)

Indications	
Intravenous drug of first choice in the treatment of status epilepticus	
Dose	**Dose form**
0.1mg/kg slow IV bolus Max 4mg, Can be repeated after 10 minutes	Ampoules 4mg in 1 ml
Adverse effects	
• Rarely apnoea may follow IV bolus injection. Equipment for intubation and ventilation should be available.	

MIDAZOLAM ('Hypnovel' : Roche (IV); 'Epistatus' : Special Products (buccal); 'Suptamid': Penn (buccal))

Indications	
Drug of first choice for status epilepticus, or prolonged convulsions, buccally or IV. Particularly useful when status settles transiently but then recurs (see PICU protocol)	
Dose	**Dose form**
Buccal midazolam for home or hospital use for convulsive status or acute seizures: 6m-1yr 2.5mg, 1-4 yrs 5mg, 5-9 yrs 7.5 mg, Over 10 years 10 mg. Initial loading dose of 100-500mcg/Kg IV. Then 1-5mcg/Kg/min (60-300mcg/Kg/hour) IV infusion. In PICU the infusion can be increased if necessary to a maximum of 36mcg/Kg/min (2160mcg/Kg/hour).	Buccal liquid bottle 10mg = 1 ml Ampoules 10mg in 5ml and 10mg in 2ml.
Adverse effects	
• Respiratory depression less common than with diazepam but has been described. • Interaction with erythromycin can raise blood levels and cause greater sedation. • Withdrawal following prolonged administration may be associated with agitation and involuntary movements.	

PARALDEHYDE (Proprietary pre-diluted with olive oil)

Indications	
Drug of second choice for status epilepticus PR	
Dose	**Dose form**
0.8ml/kg PR (will contain 0.4ml/kg paraldehyde with equal volume of oil). Higher doses may be indicated in some.	Bottle premixed paraldehyde with olive oil
Adverse effects	
• A very safe drug which does not cause respiratory depression. • Rectal irritation may occur following repeated rectal administration.	

PHENOBARBITAL (=Phenobarbitone) ('Gardinal Sodium' : Rhone-Poulenc Rorer)

Indications	
Drug of first choice for neonates Alternative to phenytoin in convulsive status epilepticus Also effective for generalised tonic clonic, focal seizures in childhood but little used now in ambulant patients because of adverse-effects.	
Dose	**Dose form**
3-10mg/Kg/day orally in one, two, three or four divided doses Loading dose in neonatal seizures or convulsive status epilepticus is 20mg/Kg IM or IV followed by maintenance dose of 5-10 mg/Kg/day IM, IV or oral Target plasma levels are 15-50mg/L Plasma half life 37-73 hrs (less in neonates)	Tablets 15mg, 30mg, 60mg and 100mg (all unscored). Elixir 15mg/5ml Ampoules 200mg in 1ml
Adverse effects	
• Drowsiness, irritability, rickets, megaloblastic anaemia, rashes and paradoxical hyperactivity and cognitive adverse effects have been reported	

PHENYTOIN ('Epanutin' : Parke Davis)

Indications	
Effective drug for generalised tonic-clonic seizures and focal seizures and convulsive status epilepticus. Not often used in childhood now because of long term cosmetic and cognitive adverse-effects. Short term use also for acute symptomatic epileptic seizures e.g. for 4-8 weeks, and for patients needing emergency neurosurgery	
Dose	**Dose form**
4-10mg/Kg/day orally in two, three or four divided doses (may have short half -life in some children). In status epilepticus give initial loading dose of 20mg/Kg IV, then maintenance of 6mg/Kg/day IV given 12hourly. Phenytoin IV injections must be given slowly, diluted in sodium chloride under blood pressure and ECG control and at a rate of less than 50mg/min, or 2mg/Kg/min. Target plasma levels are 10-25mg/L	Capsules 25mg, 50mg, 100mg and 300mg. Tablets 50mg and 100mg (unscored) Chewable tablets (Infatabs) 50mg(scored). Suspension 30mg/5ml. Ampoules 250mg in 5ml
Adverse effects	
• Ataxia, dysarthria and nystagmus are acute dose-related adverse-effects. • Chronic adverse-effects include hirsutism, rickets, megaloblastic anaemia, gum hypertrophy and coarsening of features. • Skin rashes, lymphadenopathy and 'pseudolymphoma', phlebitis and extravasation causing full thickness necrosis have been reported. • Hypotension and cardiac arrhythmias are possible risks when given IV. • Enzyme inducer, so higher dose of the oral contraceptive pill required. • Fos-phenytoin is easier to give IV as it is less alkaline	

PIRACETAM ('Nootropil' : UCB Pharma)

Indications	
Cortical and subcortical myoclonus, especially in the progressive myoclonus epilepsy syndromes	
Dose	**Dose form**
Adult dose is 5-24grams/day in two or three divided doses	Tablets 800mg and 1200mg (scored) Oral solution 333mg/ml
Adverse effects	
• Unusual: Diarrhoea, weight gain, somnulence, hyperkinesia, nervousness, sleep disturbance and rashes have been reported	

PREDNISOLONE (Various proprietary and non-proprietary)

Indications	
Idiopathic or cryptogenic infantile spasms (vigabatrin probably better choice for children with Tuberous Sclerosis) Sometimes given to children with severe intractable epilepsy temporarily unresponsive to other antiepileptic drugs	
Dose	**Dose form**
4mg/Kg/day in two or three divided doses for 2 weeks Usual max dose is 60 mg/day. Then tail off over a two to four week period, or see ICISS study protocol. Example of tail off dosing 10 mg QDS for 2 weeks, 10mg BD for 1 week, 10mg OD for 1 week, 5 mg OD for 1 week, 5mg alternate days for a week then stop	Tablets 1mg, 2.5mg, 5mg and 25mg. Soluble tablets ('Prednesol' Glaxo) 5mg (scored)
Adverse effects	
• Peptic ulceration, growth retardation, Cushingoid features, hypertension, adrenal suppression, muscle wasting, immunosuppression with risk of severe measles or chicken pox and osteoporosis have been described • Varicella antibody status check advised prior to commencing treatment.	

PRIMIDONE ('Mysoline' : Zeneca)

Indications	
Partial and generalised tonic clonic seizures not responding to drugs of first and second choice. A pro-drug for phenobarbitone, rarely if ever used in Nottingham.	
Dose	**Dose form**
10-30mg/Kg/day in two divided doses Primidone is partially metabolised to phenobarbital in the body - target plasma levels of phenobarbital (15-50mg/L) may be used to guide primidone dosage	Tablets 250mg (scored) Suspension 250mg/5ml
Adverse effects	
• Drowsiness, ataxia, nausea, rashes, rickets, megaloblastic anaemia and psychological changes have been reported	

PYRIDOXAL PHOSPHATE ('P-5-P' : Solgar Vitamins)

Indications	
Test and treatment for pyridoxine dependent epilepsy and pyridoxine responsive seizures, and PNPO-mutation related seizures	
Dose	**Dose form**
10mg/Kg 2 hours apart as a test Then 50mg/Kg/day in four divided doses Seizures should settle within a day or two and recur when the drug is withdrawn after a few weeks. Can precipitate respiratory and or cardiac arrest in children with pyridoxine dependent epilepsy so resus needs to be available. In either event the drug is commenced orally at 50mg/Kg/day and continued long term.	Tablets 50mg Liquid 300mg/5ml
Adverse effects	
• Hypotonia and apnoea and bradycardia may occur following very large doses (especially in infants with pyridoxine dependent seizures). See Pyridoxine (below).	

PYRIDOXINE (Non-proprietary)

Indications	
Test and treatment for pyridoxine dependent epilepsy and pyridoxine responsive seizures. We will probably move to using Pyridoxal Phosphate when possible, although oral formulation only is currently available.	
Dose	**Dose form**
As a test, 30mg/Kg/day is given orally in two or three divided doses. Seizures should settle within a day or two and recur when the drug is withdrawn after a few weeks. Alternatively 50mg IV should improve the EEG considerably within 8 min and stop the seizures within 30 min. Can precipitate respiratory and or cardiac arrest in children with pyridoxine dependent epilepsy so resus needs to be available. In either event the drug is commenced orally at 30mg/Kg/day and continued long term. Measure pipecolic acid in plasma.	Ampoules 50mg in 2ml. Tablets 10mg, 20mg, 50mg and 100mg
Adverse effects	
• Hypotonia and apnoea and bradycardia have been described following very large doses IV (especially in infants with pyridoxine dependent seizures)	

RUFINAMIDE ('Inovelon' : Eisai)

Indications	
Lennox-Gastaut syndrome shown to be unresponsive to 2 or more AEDs at a maximum tolerated dose	
Dose	**Dose form**
Weight <30kg: Initially 100mg twice daily increasing according to response in 100mg twice daily steps every 2 days. Max dose 500mg bd (300mg bd if cotherapy with valproate). *Weight >30kg:* Initially 200mg twice daily increasing according to response in steps of 200mg twice daily up to every 2 days Max dose 900mg bd (weight 30-50kg); 1200mg bd (weight 50-70kg); 1600mg bd (weight >70kg)	Tablets 100mg, 200mg, 400mg
Adverse effects	
• Nausea, vomiting, constipation, diarrhoea, dyspepsia, abdominal pain, rhinitis, epistaxis, weight loss, anorexia, dizziness, headache, drowsiness, insomnia, anxiety, fatigue, worsening of seizures, impaired coordination, hyperactivity, tremor, gait disturbance, influenza-like symptoms, oligomenorrhoea, back pain, nystagmus, diplopia, blurred vision, rash, acne, hypersensitivity syndrome have been reported.	

SODIUM VALPROATE ('Epilim' : Sanofi Winthrop)

Indications	
Drug of first choice for most generalised and focal seizures Particularly valuable for seizures associated with photosensitivity and in juvenile myoclonic epilepsy	
Dose	**Dose form**
Usually 20-40mg/Kg/day in two divided doses Occasionally higher doses, but LFTs need to be checked if doses above 50mg/kg/day are used Target plasma level of 40-120mg/L not very useful Plasma half life 7-15 hours	Crushable tablets 100mg (scored) Enteric coated tablets 200mg and 500mg (unscored) Sugar free liquid 200mg/5ml. Syrup 200mg/5ml Chrono tablets 200mg, 300mg and 500mg (unscored) Ampoules containing 400mg powder for making up IV infusion
Adverse effects	
• Nausea, dyspepsia, weight gain, amenorrhoea, drowsiness, hair loss, tremor, liver failure, pancreatitis, thombocytopenia and blood dyscrasias have been described • Liver failure may be fatal. Highest risk in children <5 years old with abnormal development and focal or multifocal refractory epilepsy with episodes of convulsive status epilepticus (like Alpers' syndrome). In children under 5 years, check blood ammonia, lactate, LFTs and platelets, urine organic and amino acids before and after 3 months of treatment. • Controversy surrounds the endocrine effects in young women: amenorrhoea reported in 20-80%, risk of polycystic ovary disease may be increased. Teratogenic with major malfomations in about 10% (twice the risk of other AEDs in monotherapy), and possibly increases the risk of learning difficulties.	

STIRIPENTOL ('Diacomit' : Alan)

Indications	
Adjunctive therapy of severe myoclonic epilepsy of infancy (Dravet syndrome) in combination with sodium valproate and clobazam	
Dose	**Dose form**
Initially 10mg/kg/day in 2-3 divided doses Increase slowly to max 50mg/kg/day	Capsules 250mg, 500mg Powder 250mg, 500mg sachets
Adverse effects	
• Monitor full blood count and liver function tests prior to and during therapy • Nausea, vomiting, aggression, anorexia, ataxia, drowsiness, dystonia, hyperexcitability, hyperkinesia, hypotonia, irritability, sleep disorders, weight loss, neutropenia	

SULTHIAME ('Opsolot')

Indications	
Focal seizures not fully controlled by other antiepileptic drugs Useful for Benign Rolandic Epilepsy and related syndromes	
Dose	**Dose form**
5-10mg/Kg/day in two or three divided doses	Tablets 50mg and 200mg (scored)
Adverse effects	
• Do not use in cases of porphyria, hyperthyroidism, hypertonia, or poor renal function • Renal stones have been reported • Dose dependent paraesthesia, tachypnoea, tachycardia, diplopia, hiccups, weight gain and weight loss have been reported • Regular FBC has been recommended. Currently not licensed in UK, available and popular in Germany.	

TETRACOSACTIDE (Synacthen Depot : Alliance)

Indications	
Idiopathic and cryptogenic infantile spasms (see also vigabatrin) Sometimes a course is given to children with severe intractable epilepsy temporarily unresponsive to other antiepileptic drugs	
Dose	**Dose form**
For Infantile Spasms (West syndrome) see ICISS study protocol Give 0.5mg on alternate days increasing to 0.75mg alternate days if necessary	1 ml ampoules 1mg/1ml
Adverse effects	
• All corticosteroid side-effects have been reported. (See prednisolone)	

THIOPENTAL (Thiopentone) ('Intraval' : Rhone-Poulenc Rorer)

Indications	
Status epilepticus not responding to drugs of first and second choice in ventilated child receiving intensive care (see PICU protocol)	
Dose	**Dose form**
2-8mg/Kg/hour by continuous IV infusion Monitor with CFAM or sub-continuous EEG to produce a suppression burst pattern (burst 1-10 seconds every 5 seconds to 5 minutes)	Ampoules containing 500mg powder for making up IV infusion
Adverse effects	
• Cardio-respiratory depression has been reported. • Irritant if extravasates from vein. • Recovery after status has been controlled may be prolonged if thiopentone has been given for more than a couple of days as it has a 2 phase elimination, and fat stores become saturated • Cardiotoxicity may contribute to mortality so if inotropic support is needed, stop thiopentone and use an alternative	

TIAGABINE ('Gabitril' : Sanofi-Winthrop)

Indications	
Focal seizures not responding to drugs of first and second choice Avoid in IGE	
Dose	**Dose form**
150mcg/Kg/day for first week, then 300mcg/Kg/day for second week, then 450mcg/Kg/day for third week then 600mcg/Kg/day and continue Give as two or three divided doses per day. Increase doses by 30% if patient is receiving inducing antiepileptic drugs Plasma half -life 8hrs	Tablets 5mg, 10mg and 15mg (unscored)
Adverse effects	
• Dizziness, poor concentration, diarrhoea, nervousness, tiredness, slow speech, behaviour problems, and tremor have been reported • Can precipitate absence status in idiopathic generalised epilepsy.	

TOPIRAMATE ('Topamax' : Janssen-Cilag)

Indications	
Focal and secondarily generalised seizures not fully controlled by other antiepileptic drugs	
Dose	**Dose form**
Commence with 0.5-1mg/Kg/day in two divided doses Increase to 3mg/Kg/day for the second week and then to 6mg/Kg/day and continue Depending on response, further increases may be made up to a maximum of 12mg/Kg/day or 800mg/day whichever is the smaller (Higher doses have been used in North America in children. i.e. up to 20mg/kg/day)	Tablets 25mg, 50mg, 100mg and 200mg (unscored) Sprinkle 15mg
Adverse effects	
• Ataxia, poor concentration, tremor, nausea, diarrhoea, weight loss, somnolence, apathy, paranoid psychosis and renal stones have been reported • Enzyme inducer, so a higher dose oral contraceptive pill is required.	

VIGABATRIN ('Sabril' : Merrell)

Indications	
Focal and secondarily generalised seizures not responding to drugs of first choice A drug of first choice for idiopathic and symptomatic infantile spasms	
Dose	**Dose form**
40-100mg/Kg/day in two divided doses Max 5000mg/day total Up to 150mg/Kg/day for infantile spasms (West syndrome) – see ICISS trial protocol	Tablets 500mg (scored). Sachets containing 500mg powder to be dissolved prior to administration. (Check how much the family dissolve each sachet in)
Adverse effects	
• Sedation, dizziness, irritability, excitation, weight gain, diarrhoea, anorexia and abdominal pain have been reported. • May aggravate myoclonic seizures. • Irreversible nasal or circumferential visual or field defects (difficult or impossible to detect in young children) have been described in 1/3 of patients - discuss the potential adverse effects with child and family.	

ZONISAMIDE ('Zonegran' : Eisai)

Indications	
Second line treatment for infantile spasms Second line treatment for Progressive Myoclonus Epilepsies, and any other epilepsies Can use in refractory IGE	
Dose	**Dose form**
Start at 2-4mg/kg per day increasing at 2 weekly intervals. Max 12mg/Kg/day.	Capsules 100mg
Adverse effects	
• Sedation, ataxia, renal calculi.	