The Walton Centre
NHS Foundation Trust

Excellence in Neuroscience

STATUS EPILEPTICUS GUIDELINE

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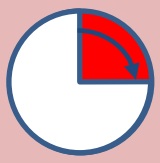
Treatment algorithm for tonic-clonic status epilepticus in adults

Timeline

t=0

t=5



t=15

Initial patient management 0-5 minutes

- Protect the patient. Do not restrain.
- Consider **airway** adjunct.
- Administer **oxygen**.
- Place patient in a semi-prone position, head down
- Gain **IV access**
- Obtain BM. **If hypoglycaemic** →

Give 150-200ml 10% glucose IV stat.

If seizures continue repeat this step AND commence 10% glucose infusion at 100ml/hr.

If suspicion of alcohol excess or malnutrition commence 1 pair Pabrinex IV BEFORE glucose replacement.

1st line treatment 5-15 minutes

If IV access

DOSE 1 – IV lorazepam 4mg bolus

Wait 5 minutes

DOSE 2 – IV lorazepam 4mg bolus

Wait 5 minutes

If no IV access

DOSE 1 – Buccal midazolam 10mg
(Alternative IM midazolam 10mg)

Wait 5 minutes

DOSE 2 – Buccal midazolam 10mg
(Alternative IM midazolam 10mg)

Wait 5 minutes

2nd line treatment 15 minutes onwards

IV or IO access
Escalate to Critical Care as per local policy

DOSE 3

IV Levetiracetam 60mg/kg, maximum 4500mg (in 100ml sodium chloride 0.9% over 10 minutes)

OR IV Phenytoin 20mg/kg, maximum 2g (rate 50mg/min, 25mg/min for elderly or patients with cardiac history, give undiluted)

OR IV Valproate 40mg/kg, maximum 3000mg (in 100ml sodium chloride 0.9% over 5 minutes)

Caution – phenytoin administration requires cardiac monitoring and wide bore IV access due to risk of extravasation and phlebitis.

	Preferred if	Avoid if
Levetiracetam (Keppra)	- Polypharmacy (fewest drug interactions)	- Mood or behavioural disorder (may worsen symptoms)
Phenytoin		- Cardiac monitoring not available - Known or suspected generalised epilepsy (genetic epilepsy) - Hypotension/bradycardia/heart block - Porphyria - Known or suspected overdose of recreational drugs / alcohol withdrawal.
Valproate	- Known or suspected idiopathic generalised epilepsy (genetic epilepsy) - Co-morbid mood disorder/migraines	- Women of childbearing potential (consider pregnancy test) - Liver disease - Pancreatitis - Known or suspected metabolic disorder/mitochondrial disease (risk of hepatotoxicity)

If ongoing seizures following the completion of the infusion **consider** 2nd IV antiepileptic drug infusion of a **different drug from the same list** (levetiracetam, phenytoin, valproate as above) **OR phenobarbital**.

Phenobarbital can be given 15mg/kg as a single dose, max. rate 100mg/min.
If at any point >30 minutes since seizure onset move to 3rd line treatment.

Ongoing management

Regular observations

12 lead ECG

Obtain FBC, U&Es, LFTs, Ca^{2+}, Mg^{2+}, clotting studies and if applicable antiepileptic drug levels and blood gas.

Treat acidosis if severe (discuss with critical care)

Determine if diagnosed epilepsy, medication history and acute seizure care plan

Consider neuroimaging and EEG

Consider possibility of non-epileptic seizures

Consider and treat potential causes:

- Medication related (poor compliance, poor absorption, recent antiepileptic drug changes, medication interactions or subtherapeutic levels)
- Infection
- Electrolyte disturbance
- Toxicity or drug withdrawal (including alcohol withdrawal)
- CNS pathology (tumour, stroke, encephalitis, PRES, neurodegenerative diseases etc.)

Seizure terminated

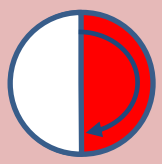
ABCDE assessment of patient at regular intervals.

Consider escalation to Critical Care setting if indicated

Start supportive medical care and look for underlying cause of status epilepticus

Caution when using multiple agents with similar mechanism of action in view of potential adverse effects. See Appendix 2.

Treatment algorithm for tonic-clonic status epilepticus in adults (cont.)



t=30

24hrs+

The following stages must occur with anesthetic input, airway support and early arrangements for transfer to ITU.

3rd line treatment 30 minutes onwards (Refractory Status)

General anesthesia – induction and maintenance.

The properties of each drug should be considered when selecting induction and maintenance agents (these may be different).

	Induction	Maintenance
Propofol	1-2mg/kg bolus	up to 4mg/kg/hour titrated to effect, continuous infusion for min. 24 hours
Thiopental sodium	3-5mg/kg bolus	3-5mg/kg/hour titrated to effect, continuous infusion for min. 24 hours
Ketamine	3mg/kg bolus	1mg/kg/hour titrated to effect maximum 10mg/kg/hour, continuous infusion for min. 24 hours
Midazolam	0.2mg/kg bolus	0.05-0.5mg/kg/hour titrated to effect, continuous infusion for min. 24 hours

- General anaesthesia maintenance is typically with propofol and/or midazolam in the first instance.
- If first maintenance agent is unsuccessful at terminating seizures a second anaesthetic agent should be used.
- As a minimum, intermittent **EEG** to be performed aiming for suppression of electrographic epileptic activity.
- Maintenance doses of **antiepileptic drugs** (commence 10-14 hours after loading dose to allow regular ongoing dosing).

4th line treatment 24+ hours (Super-Refractory Status)

Seizures that continue or recur 24 hours after third line treatment are considered Super Refractory Status Epilepticus. Treatment at this stage should be guided by specialists using an MDT approach. There is no high quality randomised controlled trial evidence to guide treatment decisions.

- Look for an **underlying cause and treat** (e.g. infectious/autoimmune encephalitis, systemic infection, electrolyte disturbance, toxicity)
- **Neurosurgical intervention** (e.g. lesional resection)
- If no underlying cause identified in a first presentation of seizures, **immunotherapy** can be considered: high dose steroids, IVIG and /or therapeutic plasmapheresis
- **Alternative treatments** at this stage include therapeutic hypothermia, ketogenic diet and magnesium infusion.

Treatments considered to be ineffective should be discontinued to minimise risk of adverse effects.

Ongoing management in Critical Care Unit

At point of admission to ITU all patients should have an up-to-date ECG.

Ensure regular antiepileptic drugs are prescribed alongside any additional treatment as part of this pathway.

It is important to document why treatment decisions have been made and ensure detailed communication with next of kin regarding treatment plan and prognosis.

Caution

midazolam exhibits multiple drug interactions which should be considered: See appendix 2

Patients on **propofol** should be monitored for PRIS - propofol infusion syndrome (metabolic acidosis, rhabdomyolysis, renal failure, hypertriglyceridaemia, refractory bradycardia and cardiac failure)

Interpretation of processed EEG monitoring such as bispectral index (BIS) may become unreliable when using **ketamine** infusion.

Caution when using multiple agents with similar mechanism of action in view of potential adverse effects. See Appendix 2.

1. Introduction

Status epilepticus is a life-threatening neurological condition defined as five or more minutes of continuous seizure activity or repetitive seizures without regaining consciousness between episodes. On average, 20% of cases are fatal, although studies have reported mortality rates as high as 57% in adults [1]. Most patients have a background of epilepsy, however a number of secondary causes should be considered including stroke, infections, trauma, metabolic disorders, inflammatory conditions, CNS tumours and drug overdose.

Most convulsive seizures terminate spontaneously within three minutes and do not need emergency treatment. After five minutes of continuous seizure activity, the sooner treatment is initiated, the better the chances of seizure termination, and the lower the risk for adverse consequences.

1.1 Definitions and scope

Status epilepticus can be classified based on a number of clinical features [2]:

1) Tonic-clonic status epilepticus (generalised or focal evolving)

   Paroxysmal or continuous tonic-clonic motor activity that may be symmetrical or asymmetrical with impaired awareness. This variant of status epilepticus is the most common and has the highest associated morbidity and mortality. As a result most of the evidence for treatment interventions has focused on this patient group.

2) Focal aware motor status epilepticus

   Motor seizures localised to one side of the body with retained consciousness.

3) Status epilepticus without prominent motor symptoms

   These include a number of variants: impaired awareness cognitive status epilepticus (coma, obtundation, confusion, disorientation, confusion, disorientation, behavioural disturbance etc.), absence status epilepticus and focal impaired awareness status epilepticus.

This guideline will focus on the management of tonic-clonic status epilepticus.

The management of patients with focal aware motor status epilepticus OR status epilepticus without prominent motor symptoms (previously referred to as non-convulsive status epilepticus) have a lower risk of morbidity and mortality. The diagnosis and management of such cases can be complex and should be discussed with the on-call neurology registrar (contactable via the switchboard).

2 Treatment algorithm

2.1 Initial Management (t=0-5 minutes)

1. Protect the patient by using padded bed rails if in a bed or surrounding the patient with padding if on the ground. Do not restrain.
2. Insert an airway adjunct if safe to do so and administer oxygen.
3. Place patient in a semi-prone position with the head down to prevent aspiration.
4. Attempt to establish IV access.
5. Determine duration of seizure episode.
6. Obtain blood glucose. If the patient is hypoglycaemic give 150-200ml of 10% glucose rapidly, or equivalent dose of 20% glucose infusion. If there is any suspicion of alcohol excess or impaired nutrition commence intravenous infusion of Pabrinex 1 pair **before** glucose. If patient is hypoglycaemic and still fitting despite first glucose administration repeat IV glucose bolus then start a glucose infusion (10% glucose at 100ml/hr) [3].

Whilst continuing with the treatment pathway, the following should be considered **but should not delay drug administration**:

1. Commence regular monitoring of observations (respiratory rate, oxygen saturations, pulse rate, blood pressure and temperature).
2. Perform a 12 lead ECG for all patients.
3. Check blood glucose, full blood count, renal profile, liver function tests, corrected calcium, magnesium and clotting profile.
4. Consider treating acidosis if severe.
5. Determine epilepsy and medication history and acute seizure care plan
6. Check levels of anti-epileptic medication
7. Consider potential causes:
    a. Medication related (poor compliance, poor absorption, recent antiepileptic drug changes, medication interactions or subtherapeutic levels)
    b. Infection
    c. Electrolyte disturbance
    d. Toxicity or drug withdrawal (including alcohol withdrawal)
    e. CNS pathology (tumour, stroke, encephalitis, PRES, neurodegenerative diseases etc.)
8. Organise cross sectional neuroimaging and EEG where appropriate
9. Consider the possibility of non-epileptic seizures.

2.2 First Line Drug Treatment (t=5 minutes)

If seizures persist, at 5 minutes first line benzodiazepine drug therapy should be administered. If the patient has IV access, 4mg of IV lorazepam should be administered (DOSE 1). If after a further 5 minutes the seizure has not terminated a second 4mg of IV lorazepam can be administered (DOSE 2).

In a patient without IV access 10mg of buccal midazolam can be administered (DOSE 1) and repeated after 5 minutes if the seizure has not terminated (DOSE 2). IM midazolam can be used as an alternative if unable to give buccal midazolam due to trismus.

Dose-dependent depression of consciousness and respiratory drive may result from benzodiazepine administration. This should be considered when monitoring the patient, even once the seizure has terminated.

Up-to a third of cases are resistant to benzodiazepines and will require second line drug therapy [4,5]. This should commence 5 minutes after DOSE 2 has been administered.

2.3 Second Line Drug Treatment (t=15 minutes)

If seizures continue, IV or IO access must be obtained and the on-call anaesthetist alerted. There is no evidence based preferred second line drug treatment for status epilepticus, so the drug used should be chosen based on the underlying diagnosis, previous antiepileptic drug therapy, comorbidity and drug interactions. The results of the recently published Established Status Epilepticus Treatment Trial (ESETT) have demonstrated no significant difference in efficacy or adverse events between Fosphenytoin, Levetiracetam and Valproic Acid [6].

DOSE 3
IV Levetiracetam 60mg/kg, maximum 4500mg in 100ml of sodium chloride 0.9% over 10 minutes
OR
IV Phenytoin 20mg/kg, maximum 2000mg at 50mg/min, reduce rate to 25mg/min in elderly or patients with cardiac disease. Give undiluted with cardiac monitoring
OR
IV Valproate 40mg/kg, maximum 3000mg in 100ml of sodium chloride 0.9% over 5 minutes

The varied rate of loading should be noted. For example, in a 70kg patient phenytoin loading would take 28 minutes, levetiracetam 10 minutes and valproate 5 minutes at the above recommended rates.

Please see table below to assist with second line drug treatment decision:

	Preferred if	Avoid if
Levetiracetam (Keppra)	- Polypharmacy (fewest drug interactions)	- Mood or behavioural disorder (may worsen symptoms)
Phenytoin		- Cardiac monitoring not available - Known or suspected generalised epilepsy (genetic epilepsy) - Hypotension/bradycardia/heart block - Porphyria - Known or suspected overdose of recreational drugs / alcohol withdrawal
Valproate (Valproic Acid)	- Known or suspected idiopathic generalised epilepsy (genetic generalised epilepsy) - Co-morbid mood disorder/migraines	- Women of childbearing potential (consider pregnancy test) - Liver disease - Pancreatitis - Known or suspected metabolic disorder/mitochondrial disease (risk of hepatotoxicity)

Phenytoin administration requires cardiac monitoring and should only be given via wide bore intravenous access given the risk of tissue necrosis and extravasation.

If seizures continue despite completion of the first infusion and when it is also less than 30 minutes since seizure commenced, a second IV anticonvulsant should be considered before anaesthesia. Either a drug from the same list (levetiracetam, valproate, phenytoin as above) OR phenobarbital should be used. Phenobarbital can be given 15mg/kg as a single dose, max. rate 100mg/min. It should be avoided in acute porphyria and caution should be taken in the elderly or those at risk of respiratory depression.

If at any point more than 30 minutes have elapsed since seizure onset, general anaesthesia should not be delayed and third line drug treatments commenced.

It should be noted that there is no clear good quality evidence to guide therapy at this stage, and treatment decisions should be guided by senior clinicians with experience in managing refractory status epilepticus.

2.4 Third Line Drug Treatment (Refractory Status Epilepticus)

If seizures continue despite second line therapy, the patient is considered to have refractory status epilepticus. Mortality rates are high and as a result rapid initiation of IV anaesthetic agent should be commenced, titrated to suppress epileptic activity on EEG (urgent EEG should be arranged).

The properties of each drug should be considered when selecting induction and maintenance agents. Note that drugs selected for induction may be different to those

chosen for maintenance (general anaesthesia maintenance is typically with propofol and/or midazolam in the first instance)

Maintenance doses of antiepileptic drugs should be continued in addition to the anaesthetic agent. The general anaesthetic agent should be tapered after a minimum of 24 hours and if seizures recur either clinically or electrographically the infusion re-commenced for a further 12-24 hours.

Suggested agents:

Propofol

Induction: 1-2mg/kg bolus.
Maintenance: up to 4mg/kg/hour titrated to effect, continuous infusion for a minimum of 24 hours.

Propofol has a rapid onset of action. It commonly causes hypotension, and vasopressor support is required in 22-55% of patients undergoing infusion [7,10]. Prolonged infusions can lead to propofol infusion syndrome (PRIS), which is a rare but life threatening complication characterised by metabolic acidosis, rhabdomyolysis, renal failure, hypertriglyceridaemia, refractory bradycardia and cardiac failure. The main risk factors are high infusion rate and infusion duration above 48 hours. Management is supportive, including discontinuation of propofol along with appropriate organ support [11,12,16].

OR

Thiopental sodium

Induction: 3-5mg/kg bolus.
Maintenance: 3-5mg/kg/hour titrated to effect, continuous infusion for a minimum of 24 hours.

Thiopental is a barbiturate anaesthetic agent with good efficacy and a tendency to lower body temperature which may be beneficial in status epilepticus. Thiopental does, however, have major disadvantages. Firstly, as infusion it exhibits zero order kinetics and therefore tends to accumulate and have a long half-life. This can lead to an increased duration of ventilator dependency. Secondly, it has potent hypotensive and cardiorespiratory depressive effects, commonly requiring additional vasopressor support [14]. Continuous ECG monitoring should be performed in all patients and senior colleagues involved with treatment decision making.

OR

Ketamine

Induction: 3mg/kg bolus.
Maintenance: 1mg/kg/hr titrated to effect up to maximum 10mg/kg/hr, continuous infusion for a minimum of 24 hours.

There is an increasing body of literature supporting the use of ketamine as a third line agent in the management of refractory status epilepticus, with two randomised controlled trials assessing the efficacy and safety profile of ketamine to conventional anaesthetic agents for refractory status epilepticus currently in progress. Ketamine has a short half-life, reducing the likelihood of toxic accumulation. Compared with other drugs used for the treatment of refractory status epilepticus, respiratory depression and hypotension requiring vasopressor support are rarely observed [13].

Note, interpretation of processed EEG monitoring such as bispectral index (BIS) may become unreliable when using ketamine infusion.

OR

Midazolam

Induction: 0.2mg/kg bolus.
Maintenance: 0.05-0.5mg/kg/hour titrated to effect, continuous infusion for a minimum of 24 hours. Occasionally higher doses up to 50mg/hr may be used on consultant intensivist advice. The rationale for using the doses above 0.5mg/kg/hr need to be documented in case notes.

Midazolam is short acting, reducing the likelihood of toxic accumulation. Caution should be taken in obese patients due to accumulation in the fat tissues and those with renal insufficiency. It commonly causes hypotension, and vasopressor support is required in 30-50% of patients [7,8]. A number of studies suggest that breakthrough seizures occur more commonly with midazolam compared to other drugs used during this stage [7,9].

2.5 Fourth Line Drug Treatment

Super Refractory Status Epilepticus is defined as ongoing or recurring seizures for 24 hours after third line treatment. Treatment at this stage should be guided by specialists using an MDT approach. There is no high quality randomised controlled trial evidence to guide treatment decisions.

A detailed history should be obtained, and investigations guided by the clinical picture (usually MRI, CSF examination, metabolic screen, drug screen and autoimmune screen). Any underlying cause should be treated.

Administration and continuation of two antiepileptic drugs of differing mechanism of action should be considered alongside anaesthetic agents.

If neuroimaging demonstrates evidence of lesional epileptogenic focus, resective neurosurgery can be considered.

If no underlying cause identified and this is a first presentation of seizures a trial of high dose steroids can be considered. IVIG and therapeutic plasmapheresis can be used if no response despite 2 days of high dose steroids.

Other therapeutic options at this stage include [14,15]:

- IV Magnesium
- Therapeutic hypothermia
- Ketogenic Diet
- Paraldehyde infusion (particularly if porphyria a possibility)
- Electroconvulsive therapy

When treating outside of recommended dosage and licensing indications it is important to document treatment rationale. Detailed communication with next-of-kin should focus on causes of status epilepticus, treatment decisions and prognosis.

2.6 Indications for Intensive Care Admission (including but not limited to)

Consider admission:

- seizures continue despite 1st line (benzodiazepine) treatment at recommended dose
- unstable cardiorespiratory state
- unstable neurological state

Definite admission:

- seizures continue despite 2nd line treatments

2.7 Ongoing AED treatment

If a patient requires 2nd line treatment, antiepileptics that have been loaded should be continued at maintenance doses and discussed with neurology. The first maintenance dose of levetiracetam or valproate should be given as close to 12 hours (10-14 hours is acceptable) after the loading dose as is practical in order to allow regular maintenance dose administration, ideally during daytime hours. The first maintenance intravenous dose of phenytoin should be prescribed after 6-8 hours after the loading dose.

Suggested doses:

Levetiracetam – continue to prescribe levetiracetam maintenance 1000mg twice daily, unless eGFR<50 ml/min/1.73m^2 whereby drug monograph should be consulted. Higher doses as advised by neurology. Wait for 10-14 hours after loading dose to prescribe maintenance therapy.

Valproate – continue IV treatment up to maximum 2.5g daily (unless advised by specialist) in 2–4 divided doses by injection over 5 minutes or continuous infusion, usual dose 1000mg twice daily. When switching to oral therapy use the same total daily dose as IV treatment in 2 divided doses.

Phenytoin - initially continue to prescribe phenytoin maintenance 100 mg IV every 6–8 hours adjusted according to plasma-concentration monitoring. When converting to oral therapy use 3-4 mg/kg/day (usually 150 – 300mg given once daily at night)

Phenobarbital – then continue at 60–180 mg once daily, dose to be taken at night and discuss with neurology.

Caution: For underweight patients (less than 50kg), doses may need to be adjusted. Please discuss with local pharmacy.

For all patients on regular therapy, ensure their usual regular antiepileptic drugs are prescribed alongside any additional treatment as part of this pathway. It may be necessary to review treatment doses and discuss with the on-call neurologist or epilepsy team.

Note: some drug recommendations outlined in this guidance are 'off label' indications and based on more recent evidence.

3 Appendix 1. Drug monographs

LORAZEPAM

Mechanism of action
GABA agonist.

Dose and administration
4mg diluted 1:1 with sodium chloride 0.9% or water for injection given as a bolus. Dose can be repeated after 5 minutes.

Side effects
Respiratory depression, hypotension and sedation.

Notes
Contains propylene glycol.

MIDAZOLAM

Mechanism of action
GABA agonist.

Dose and administration
Buccal: 10mg, dose can be repeated after 5 minutes.
IM: 10mg, dose can be repeated after 5 minutes. Use 10mg/2ml ampoule which is stocked in the Intubation Kits.
IV in refractory status:
Bolus: 0.2mg/kg at an infusion rate of 2mg/min.
Continuous infusion: 0.05 – 0.5mg/kg/hr. Occasionally higher doses (up to 50mg/hr) may be required. The use of high doses above 0.5mg/kg/hr should only be done on consultant anesthetist instruction and the rationale must be documented in the case notes.

Side effects
Respiratory depression, hypotension, sedation.
When used as an infusion: withdrawal syndrome, delirium, tachyphylaxis after 72 hours, respiratory and cough reflex suppression, metabolites accumulation post prolonged infusion. Very high dose midazolam infusion over a long period can result in rapid development of non-anion gap hyperchloremic metabolic acidosis that resolves once the infusion of midazolam is discontinued.

Monitoring
Blood gases with continuous infusion.

Notes
See the Critical Care Sedation Guideline and Midazolam in Critical Care Monograph for further information on use as a continuous infusion in Critical Care.
Midazolam is metabolized by CYP3A4. Inhibitors and inducers of CYP3A4 can significantly raise or lower plasma concentrations.

LEVETIRACETAM

Mechanism of action

Synaptic vesicle protein 2A (SV2A) ligand.

Dose and administration

Loading dose in status epilepticus:
60 mg/kg (max 4500mg) in 100ml of sodium chloride 0.9% IV over 10 minutes (unlicensed).
Flush the giving set with about 25ml of sodium chloride 0.9% at the same rate (10ml/min) after the dose to ensure the full dose is administered.

Body weight (kg)	Loading dose
40-49	2500mg
50-59	3000mg
60-65	3500mg
66-74	4000mg
75+	4500mg

Maintenance dose (IV or enteral):
Commence maintenance dose 10-14 hours after the loading dose.

eGFR (ml/min/1.73m^2)	Maintenance dose (IV, PO or via a feeding tube)
≥50	1000mg BD (max 1500mg BD, higher doses up to 30mg/kg BD may be used on advice of neurologist)
30-49	750mg BD
<30	500mg BD
Intermittent dialysis patients	1000mg OD with 500mg supplemental dose post dialysis

Side effects

Neutropenia, agranulocytosis, leukopenia, thrombocytopenia and pancytopenia.
Acute kidney injury.
Aggressive behaviour, irritability and psychotic symptoms.
Somnolence, fatigue, nasopharyngitis and headache.
Suicide, suicide attempt, suicidal ideation.
Serious dermatologic reactions including Stevens-Johnson syndrome and toxic epidermal necrosis – discontinue therapy.

Monitoring

Monitoring plasma levels is not routinely recommended due to lack of consistent correlations between efficacy, tolerability and plasma concentrations. Therapeutic drug monitoring may however be useful to guide dosage adjustment in elderly, critical care patients, during pregnancy and throughout postpartum period, when co-prescribing with enzyme inducing antiepileptic drug, before considering increasing the dose above the maximum licensed dose or when assessing compliance or suspecting toxicity.

Notes

Levetiracetam has near 100% bioavailability when given enterally.
When switching between IV and enteral route keep the same dose and frequency of administration.

SODIUM VALPROATE

Mechanism of action

Sodium channel inhibitor, calcium channel inhibitor, GABA transaminase inhibitor, NMDA receptor antagonism.

Dose and administration

Loading dose in status epilepticus: 40mg/kg (max 3000mg) in 100ml of sodium chloride 0.9% over 5 minutes. Flush the giving set with about 25ml of sodium chloride 0.9% at the same rate (20ml/min) after the dose to ensure the full dose is administered.

Valproate vials containing powder need to be reconstituted with 3.8ml of the solvent provided (water for injection) prior to dilution. The concentration of the reconstituted sodium valproate is 100mg/ml.

Body weight (kg)	Loading dose
45-54	2000mg
55-64	2400mg
65-74	2800mg
>75	3000mg

Maintenance dose (IV or enteral):

Start maintenance dose 10-14 hours after the loading dose. Oral, NG and IV maintenance doses are typically 1000mg twice daily (maximum 2.5g daily for maintenance, unless advised by specialist).

Contraindications

- Pregnancy unless there is no suitable alternative treatment
- Woman of childbearing potential unless the conditions of the Pregnancy Prevention Programme are fulfilled and only if there is no suitable alternative treatment
- Active liver disease
- Personal or family history of severe hepatic dysfunction
- Acute porphyria
- Urea cycle disorders
- Known or suspected mitochondrial disorders.

Side effects

Heptatotoxicity – discontinue treatment if persistent symptoms of hepatic dysfunction
Thrombocytopenia, agranulocytosis
Hyperammonaemic encephalopathy
Pancreatitis – discontinue treatment
Hyponatraemia
Severe cutaneous adverse reactions.

Monitoring

Plasma levels are not useful index of efficacy and are not routinely required but may be useful where there is poor control or side effects are suspected.
Target range: 50-100mg/l
Liver function tests including prothrombin time should be checked before therapy and during first 6 months of treatment.
Full blood count before starting treatment, before surgery or in case of spontaneous bruising or bleeding.

Pregnancy

Valproate is highly teratogenic and evidence supports that use in pregnancy leads to neurodevelopmental disorders (approx. 30–40% risk) and congenital malformations (approx. 10% risk). Consider pregnancy test before using in women of childbearing potential.

Notes

Can cause false-positive urine test for ketones.
Highly plasma bound.
Sodium valproate powder and solvent for solution for injection may have significant displacement value – this needs to be taken into account whenever part of a vial is being used.

PHENYTOIN

Mechanism of action
Sodium channel blocker

Dose and administration
Loading dose in status epilepticus:

- 20mg/kg (maximum 2g) given by intravenous infusion at 50mg/min. Give undiluted into large vein or via with continuous cardiac monitoring (ECG and blood pressure).
- A lower rate (25mg/min) should be considered for elderly patients and those with heart disease.

Loading dose for patients receiving regular phenytoin:

- If the patient is in status epilepticus and there is a concern regarding compliance give full loading dose.
- If the patient is in status epilepticus and a recent plasma phenytoin level is known a top up dose can be calculated:

Top-up phenytoin sodium (mg) = (20 – measured concentration (mg/l)) x 0.7 x body weight (kg).

- Expected increase in phenytoin concentration with a single top-up dose can be estimated from the table below:

	50 kg	60 kg	70 kg	80 kg
250 mg	7 mg/l	6 mg/l	5 mg/l	4.5 mg/l
500 mg	14 mg/l	12 mg/l	10 mg/l	9 mg/l
750 mg	21 mg/l	18 mg/l	15 mg/l	13.5 mg/l

Maintenance dose:
Initially prescribe IV, administer first dose 6-8 hours after the loading dose.

IV: 100mg given undiluted over 2 to 5 minutes (maximum rate 50mg/min) every 6 to 8 hours.
Oral: 3-4 mg/kg/day (usually 150 – 300mg given once daily at night)

Maintenance dose adjustments:
Phenytoin has non-linear pharmacokinetics and a long half-life; small dose increases can cause large increases in steady state plasma concentrations. The daily dose should not normally be increased by more than 25 to 50mg.

Corrected phenytoin should be calculated where serum albumin <32g/L:
Corrected phenytoin = measured phenytoin level (µg/ml) / ((0.1 x adjustment x albumin (g/L)) + 0.1)
Adjustment = 0.275; in patients with creatinine clearance <20 mL/min, adjustment = 0.2.

Contraindications
Sinus bradycardia, 2nd and 3rd degree heart block or Adam-Stokes syndrome.

Side effects

Cardiovascular side effects are usually associated with IV infusions especially at high rates: hypotension, cardiac arrhythmias including bradycardia, atrial and ventricular depression, ventricular fibrillation and cardiac arrest.
Anticonvulsant hypersensitivity syndrome, toxic epidermal necrolysis and Stevens-Johnson syndrome and purple glove syndrome.
Signs of toxicity: nausea, vomiting, nystagmus, blurred vision, ataxia, drowsiness, slurred speech, lethargy, confusion or coma.

Monitoring

- Target total phenytoin range: 10-20mg/l
- Check levels within 24 hours of loading dose
- Phenytoin is highly protein bound (90%). Serum levels need to be corrected (adjusted) if a patient has low albumin as total phenytoin is measured in the lab. Only the portion that is free and unbound is pharmacologically active. Seemingly normal levels in a hypoalbuminaemic patient may therefore actually be high.
- In some circumstances monitoring of free phenytoin levels may be necessary, for example when using drugs which may displace phenytoin (for example valproate).

Notes

- Refer to Guidelines for the safe use of Phenytoin.
- IV formulation contains propylene glycol
- Care must be taken when switching between different formulations of phenytoin. Preparations containing phenytoin sodium (capsules and injection) are not bioequivalent to phenytoin base (Epanutin Infatabs® and Epanutin® suspension)

  300mg of phenytoin sodium = 270mg of phenytoin base.

PHENOBARBITAL

Mechanism of action
GABA agonist

Dose and administration
15mg/kg IV at a maximum rate of 100mg/min. Dilute with water for injection 1:10 prior to administration. Maintenance dose typically 60-180mg once daily, dose to be taken at night and discussed with neurology.

Contraindications
Porphyria.
Sensitivity to phenobarbital or other barbiturates.

Side effects
Respiratory suppression that may require mechanical ventilation
Prolonged sedation
Hypotension that may require haemodynamic support.

Notes
Contains propylene glycol.

PROPOFOL

Mechanism of action
Propofol positively modulates the inhibitory function of the GABA through $GABA_A$ receptors. It is a NMDA antagonist and modulates calcium influx through calcium-ion channels.

Dose and administration
1-2mg/kg bolus then infusion at up to 4mg/kg/hr.

Side effects
Bradycardia, hypotension, apnoea, arrythmia, convulsions, thrombosis, phlebitis, deranged liver function tests (particularly transaminases), pancreatitis.
Propofol Infusion Syndrome (PRIS) is a rare but serious side effect of prolonged infusion of propofol. It is characterised by metabolic acidosis, hyperkalaemia, hyperlipidaemia, cardiac dysfunction, rhabdomyolysis and may proceed to renal failure (see Sedation Guideline for further information).

Monitoring
Creatine Kinase (CK) levels should be monitored daily in patients on Propofol. Rising CK levels in conjunction with acidosis and increasing lactate levels are a reliable indicator for the development of PRIS. Consideration should be given to stopping or reducing the dose of propofol.
Liver function.

Notes
See Sedation Guideline for further information.

THIOPENTAL

Mechanism of action
Thiopental enhances GABA transmission by binding to $GABA_A$ receptor.

Dose and administration
Dilute each 500mg vial with 20ml of water for injection.
Bolus: administer without further dilution. Can be given via a peripheral line.
Infusion: administer without further dilution via a syringe driver via a dedicated lumen of a central catheter.

3-5mg/kg bolus then 3-5mg/kg/hr titrated to effect; after 2-3 days infusion rate needs reduction as fat stores are saturated.

Contraindications
Porphyria.

Side effects
Hypotension, respiratory and cardiac depression, arrythmias, hypothermia, shivering, accumulation after repeated IV boluses or infusion, laryngo-and bronchospasm, gastroparesis, immunosuppression, rhabdomyolysis, tissue necrosis on extravasation. Maintenance infusion causes hypokalaemia, rebound hyperkalaemia is observed on cessation of therapy. Potassium replacement must be done with extreme caution while on infusion. Potassium levels need to be monitored regularly during weaning and for 72 hours post cessation of drug therapy.

Monitoring
EEG or BIS, plasma levels (when doses above 4mg/kg/hr are being used), potassium levels, continuous cardiac monitoring, LFTs, CK, FBC, CRP, body temperature.

Notes
Above serum concentrations of 35mg/l thiopental metabolism is saturated and the elimination follows zero order kinetics. Infusions at doses above 4mg/kg/hr for over 3 days lead to high-plasma concentrations associated with profound coma, dilated pupils, with no reaction to light.

KETAMINE

Mechanism of action
NMDA receptor antagonist.

Dose and administration
3mg/kg bolus then infusion starting at 1mg/kg/hr and titrated as required (doses up to maximum 10mg/kg/hr are currently in use in ongoing clinical trials) [13].

Contraindications
Patients with severe coronary or myocardial disease or cerebrovascular accident.

Cautions
- Hepatic impairment – metabolised in the liver, action may be prolonged in patients with impaired liver function
- Acute intermittent porphyria
- Psychiatric illness
- Conditions where an elevated ICP may be detrimental
- Cardiac disease – increases myocardial oxygen consumption
- Concomitant neuromuscular blockers – ketamine may potentiate effects of atracurium
- Interpretations of EEG monitoring (e.g. BIS) may be unreliable during ketamine administration.

Side effects
- Psychiatric – confusion, agitation, hallucinations
- Nervous system - Nystagmus, hypertonia, tonic-clonic movements, prolonged sedation when used in high doses
- Cardiac – hypotension or hypertension, tachycardia, tachyarrhythmia
- Respiratory depression
- Raised intra-ocular pressure
- Hypersalivation
- Deranged liver function tests (when used for >3days)
- Rash

Monitoring
Continuous cardiac monitoring and respiratory function.

Interpretation of processed EEG monitoring such as bispectral index (BIS) may become unreliable when using ketamine infusion.

Notes
See Ketamine in Critical Care.

4 Appendix 2. Mechanism of action and interaction table

Please note the table below is NOT an exhaustive list of interactions. It has been compiled to aid clinical judgment; a full list of interactions should be taken from the BNF and product summary of characteristics (SPC). See also list of common sodium channel antagonists. Avoid co-administration of multiple sodium channel antagonists where possible.

Drug	Mechanism of action	Interactions affecting other drugs	Interactions affecting principal drug	Comments
Diazepam	GABA agonist	➢ Diazepam may affect **phenytoin** concentration (toxicity has been reported). In addition, phenytoin may reduce diazepam concentration. Monitor for reduced diazepam efficacy and phenytoin toxicity and additive CNS adverse effects. ➢ Diazepam competitively inhibits **ketamine** metabolism – ketamine effect can be prolonged with concurrent use.	➢ **Cannabidiol** may increase the concentration of diazepam. Monitor for adverse effects and reduce diazepam dose accordingly if required. ➢ **Carbamazepine** causes a three fold increase in diazepam clearance. May require increased dose of diazepam. ➢ **Fluconazole** moderately increases diazepam exposure, which would be expected to increase sedative effects. ➢ **Rifampicin** moderately decreases diazepam exposure. Monitor for loss of benzodiazepine efficacy. May require increase in dose of diazepam. ➢ **Sodium valproate** may displace diazepam from protein binding sites causing an increased diazepam concentration.	

Ketamine	NMDA receptor antagonist	➢ Ketamine may potentiate the neuromuscular blocking effects of **atracurium**. Be alert for increased and prolonged neuromuscular blockade. ➢ Ketamine can cause profound hypotension in patients taking **alfuzosin**, avoid concurrent use. ➢ Ketamine may antagonise the hypnotic effect of **thiopental**.	➢ **Diazepam** competitively inhibits ketamine metabolism – ketamine effect can be prolonged with concurrent use. ➢ **Halogenated anaesthetics** may prolong the half-life of ketamine. Patients may also develop bradycardia, hypotension or decreased cardiac output. Dose adjustment of both agents may be required.	
Midazolam	GABA agonist	➢ Benzodiazepines may affect **phenytoin** concentrations (toxicity has been reported). Monitor for signs of phenytoin toxicity. In addition, phenytoin dramatically reduces midazolam exposure, reducing its effects.	➢ **Carbamazepine** reduces oral midazolam exposure and reduces its effects. A higher dose of oral midazolam is likely to be required. ➢ **Clarithromycin** markedly increases the exposure to oral midazolam and moderately increases the exposure to intravenous midazolam. Oral midazolam: reduce dose by 50 to 75%. IV midazolam bolus: doses might not need adjusting. High doses given long-term will need to be carefully titrated. ➢ **Diltiazem** moderately increases oral midazolam exposure. IV midazolam is affected to a lesser extent. Consider reducing initial midazolam dose by 50%.	

Midazolam continued			➢ **Erythromycin** moderately increases the exposure to oral and IV midazolam. Oral midazolam: reduce dose by 50 to 75%. IV midazolam: bolus doses might not need adjusting. ➢ **Fluconazole** moderately increases oral midazolam exposure, increasing its sedative effects. IV midazolam is affected to a lesser extent. Oral midazolam: reduce dose by up to 50%. ➢ **Itraconazole** markedly increases midazolam exposure resulting in heavy sedation and prolonged amnesia. IV midazolam might interact to a lesser extent. If using oral midazolam reduce dose by 75% or more, however, most manufacturers contraindicate concurrent use. ➢ **Phenobarbital** is predicted to increase midazolam clearance. Midazolam dose adjustment may be required. ➢ **Primidone** may increase midazolam clearance. Midazolam dose adjustment may be required. ➢ **Rifampicin** very markedly decreases oral midazolam exposure and effects, and	

Midazolam continued			moderately decreases intravenous midazolam exposure. Avoid midazolam use if patient prescribed rifampicin. ➢ **Rufinamide** may decrease the exposure to midazolam. Monitor for a reduction in midazolam efficacy and adjust the dose if necessary. ➢ **Verapamil** moderately increases midazolam exposure. Consider reducing initial dose of midazolam up to a 50%.	
Levetiracetam	SV2A ligand	➢ Levetiracetam may decrease **methotrexate** clearance resulting in increased/prolonged blood methotrexate concentration and potentially toxic levels. Blood methotrexate levels should be carefully monitored.	➢ **Carbamazepine** may increase levetiracetam clearance, dose adjustment not usually required. ➢ **Phenytoin** may reduce levetiracetam concentration, dose adjustment not usually required.	There is decreased levetiracetam efficacy when macrogols (Movicol®, Laxido®) are given with enteral preparations. Not to be given one hour before or one hour after levetiracetam dose.
Lorazepam	GABA agonist	➢ Benzodiazepines might affect **phenytoin** concentrations (toxicity has been seen). In addition, phenytoin may reduce lorazepam concentration. Monitor for reduced lorazepam	➢ **Cannabidiol** may increase lorazepam concentration. Lorazepam dose adjustment may be needed. ➢ **Clozapine** and lorazepam concomitant use can cause	

		efficacy, phenytoin toxicity and additive CNS adverse effects.	severe hypotension, respiratory depression, and potentially fatal respiratory arrest. <u>Very close monitoring for CNS depression is essential.</u> ➢ **Rifampicin** moderately increases the clearance of IV lorazepam. An increased dose of lorazepam may be needed. ➢ **Valproate** increases lorazepam exposure and may increase sedative effects. Lorazepam dose may need to be reduced.	
Phenobarbital		➢ Phenobarbital increases the clearance of **aminophylline**. Monitor **theophylline** levels and adjust dose as required. ➢ Phenobarbital may decrease the exposure to **apixaban.** <u>Avoid</u> concurrent use. ➢ Phenobarbital may reduce **aripiprazole** exposure. Oral and IM aripiprazole doses may need to be doubled with concurrent use. ➢ Phenobarbital may decrease **cannabidiol** concentration. ➢ Phenobarbital greatly reduces **ciclosporin** concentration. Monitor ciclosporin levels and adjust dose accordingly. ➢ Phenobarbital can reduce **combined and progesterone only hormonal contraceptive** concentration. See literature for further dosing advice.	➢ **Phenytoin** may increase phenobarbital serum concentration. Although this can be advantageous, monitoring is required as toxicity has been reported. ➢ **Rifampicin** may increase clearance of phenobarbital. In addition, phenobarbital may modestly increase rifampicin clearance. Doses of one or both may need to be increased. ➢ **Stiripentol** causes large increases in the serum concentrations of phenobarbital. Dose adjustment may be needed. ➢ **Valproate** may increase serum phenobarbital concentrations. Phenobarbital dose may need to be reduced by up to 50%.	

Phenobarbital continued		➢ Phenobarbital reduces serum **clobazam** concentration. Clobazam dose adjustment may be needed. ➢ Phenobarbital may reduce **doxycycline** serum concentration. Doxycycline dose may need to be doubled. ➢ Phenobarbital may reduce **dronedarone** exposure. Avoid concurrent use as dronedarone likely to be ineffective. ➢ Phenobarbital may decrease the exposure to **edoxaban.** Avoid concurrent use. ➢ Phenobarbital decreases **lamotrigine** concentration. Lamotrigine dose may need to be doubled. Monitor for blood dyscrasias. ➢ Phenobarbital may reduce serum **methadone** concentration. Monitor for signs of opioid withdrawal. Anticipate the need to increase the methadone dose and note that twice daily dosing might be required. ➢ Phenobarbital may increase the clearance of **methotrexate,** resulting in lower efficacy. Monitor methotrexate levels. ➢ Phenobarbital markedly increases the metabolism of **metronidazole.** Metronidazole dose may need to be increased 2-3 fold.		

Phenobarbital continued		➢ Phenobarbital may increase **midazolam** clearance. Midazolam dose adjustment may be required. ➢ Phenobarbital can reduce **nimodipine** exposure. Concurrent use is contraindicated. ➢ Phenobarbital may decrease the exposure to **rivaroxaban**. Avoid concurrent use. ➢ Phenobarbital decreases **tacrolimus** serum concentration. Increase monitoring frequency of tacrolimus levels. ➢ Phenobarbital may decrease **ticagrelor** exposure. Avoid concurrent use. ➢ Phenobarbital may reduce serum **tiagabine** concentration. Dose adjustment may be needed ➢ Phenobarbital markedly increases **verapamil** clearance. Consider using alternative agent. ➢ Phenobarbital substantially reduces the anticoagulant effect of **warfarin**. Monitor INR. Warfarin dose may need to be increased by 30-60%.		
Phenytoin	Sodium channel blocker	➢ Phenytoin decreases the exposure to **apixaban**, and therefore also decreases its anticoagulant effects. Avoid concurrent use. ➢ Phenytoin may decrease **cannabidiol** concentration. ➢ Phenytoin can reduce **combined hormonal contraceptive**	➢ **Amiodarone** may increase serum phenytoin concentration. Monitor for signs of toxicity. Phenytoin dose may need to be reduced by 25-30%. ➢ **Benzodiazepines** may affect phenytoin concentration (toxicity has been reported).	Phenytoin has zero order kinetics. About 90% of phenytoin in plasma is bound to albumin. Dose

Phenytoin continued		concentration. See literature for further dosing advice. ➢ Phenytoin reduces the plasma concentration of **caspofungin**. Consider using 70mg for all patients. ➢ Phenytoin can greatly reduce **ciclosporin** concentrations. Monitor ciclosporin levels and adjust accordingly. ➢ Phenytoin moderately decreases the exposure to **dabigatran**. Avoid concurrent use. ➢ Phenytoin may reduce **diazepam** concentrations. Monitor for reduced diazepam efficacy, phenytoin toxicity and additive CNS adverse effects. ➢ IV Phenytoin administered with **dopamine** can cause severe rapid hypotension. ➢ Phenytoin reduces the serum concentration of **doxycycline**. Consider doubling the dose of doxycycline. ➢ Phenytoin greatly reduces **dronedarone** exposure. Avoid concurrent use as dronedarone likely to be ineffective. ➢ Phenytoin may decrease exposure to **edoxaban**, decreasing its anticoagulant effects. Avoid concurrent use. ➢ Phenytoin decreases **lamotrigine** concentration, lamotrigine dose should be increased.	Monitor for signs of phenytoin toxicity. ➢ **Carbamazepine** may increase or decrease phenytoin serum concentration. Close monitoring is required. ➢ **Co-trimoxazole** may increase serum phenytoin concentration. Dose adjustment may be required after monitoring levels. ➢ **Diltiazem** may increase phenytoin concentration leading to toxicity. ➢ **Eslicarbazepine** can increase phenytoin exposure and phenytoin may reduce eslicarbazepine exposure. ➢ **Fluconazole** may increase serum phenytoin concentrations.Monitor closely as toxicity has been reported. Phenytoin dose reduction may be required. ➢ **Fluoxetine** may increase phenytoin serum concentration. Monitor for signs of toxicity. ➢ **Methotrexate** may reduce phenytoin serum concentration. Monitor methotrexate levels. ➢ **Rifampicin** markedly reduces phenytoin serum concentration. Monitor levels, and dose adjustment may be required.	adjustment may be required if hypoalbuminaemia. Enteral phenytoin may interact with enteral feeds. Ensure phenytoin is not given with 2 hours of enteral feed.

Phenytoin continued		➢ Phenytoin may reduce serum **methadone** concentrations. Monitor for signs of opioid withdrawal. Methadone dose may need to be increased and/or administered twice daily. ➢ Phenytoin may increase the clearance of **methotrexate** resulting in lower efficacy. Monitor methotrexate levels. ➢ Phenytoin may decrease **perampanel** exposure. Monitor perampanel efficacy, dose adjustment in 2mg increments may be required. ➢ Phenytoin may increase **phenobarbital** serum concentration. Although this can be advantageous, monitoring is required as toxicity has been reported. ➢ Phenytoin decreases the exposure to **rivaroxaban**. Avoid concurrent use. ➢ Phenytoin decreases **tacrolimus** serum concentration. Increase monitoring of tacrolimus levels. ➢ Phenytoin increases the clearance of **theophylline**. Theophylline may also reduce phenytoin levels. Monitor serum levels of both drugs, adjusting the doses if necessary. Aminophylline dose may need to be increased up to 50% or more. This interaction may be reduced by administering the drugs 2 hours apart.	➢ **Stiripentol** causes large increases in serum phenytoin concentrations. Phenytoin dose adjustment may be required. ➢ **Topiramate** may slightly increase phenytoin serum concentration. Phenytoin may decrease topriamate serum concentrations. Both drugs may require dose adjustment. ➢ **Verapamil** may increase phenytoin concentration. Verapamil may decrease phenytoin concentrations. Monitor phenytoin levels, blood pressure and heart rate.	

Phenytoin continued		➢ Phenytoin is predicted to decrease **ticagrelor** exposure. Avoid concurrent use. ➢ Phenytoin may decrease **valproate** concentration. In addition, total serum phenytoin concentration may decrease, but this is offset by an increase in free phenytoin concentrations. Monitoring of both total and free serum phenytoin levels in addition to valproate level may be required. ➢ Phenytoin decreases **voriconazole** exposure. In addition, voriconazole increases phenytoin exposure. If concurrent use is unavoidable, monitor phenytoin concentration and adverse effects. Oral voriconazole dose may need to be doubled. IV voriconazole may also need to be increased. ➢ Phenytoin can increase the anticoagulant effect of **warfarin.** Monitor INR and adjust warfarin dose.		
Propofol	Allosteric GABA agonist		➢ **Valproate** may increase propofol concentration. Propofol dose may need to be reduced. ➢ **Cannabidiol** may increase propofol concentration.	
Sodium Valproate	Sodium channel blocker, calcium	➢ Valproate-induced encephalopathy might be increased in patients taking **acetazolamide.** Close monitoring for valproate toxicity is advised, with	➢ **Carbapenems (ertapenem, imipenem**, **meropenem)** all dramatically reduce valproate	Caution: in women of childbearing potential consider

Sodium valproate continued	channel blocker, GABA modulator	monitoring of serum ammonia concentration. ➢ Valproate may potentiate the toxic effects of **carbamazepine**, increasing the concentration of active metabolite. In addition, concurrent use may slightly reduce concentrations of both drugs. Monitor efficacy of both drugs especially at the start of combined therapy. ➢ Valproate increases **lamotrigine** concentrations. The lamotrigine dose should be reduced. ➢ Valproate increases **lorazepam** exposure and may increase its sedative effects. Lorazepam dose may need to be reduced. ➢ Valproate may increase serum **phenobarbital** concentration. Phenobarbital dose may need to be reduced by a third to a half. ➢ Valproate affects the concentration of primidone. Manufacturer advises monitor and adjust dose. ➢ Valproate may increase **propofol** concentration. ➢ Valproate appears to increase the concentration of **rufinamide**, particularly in younger children. Patients weighing < 30 kg, should be treated with maximum 600mg daily dose. ➢ The risk of valproate induced encephalopathy may be increased in	concentration. Avoid concurrent use. ➢ **Felbamate** can increase valproate serum concentration causing toxicity. In addition, valproate might slightly decrease the clearance of felbamate. Monitor for adverse effects and consider dose reduction. ➢ **Methotrexate** can cause subtherapeutic serum valproate concentration. Avoid concurrent use if possible. Otherwise, monitor levels of valproate. ➢ Phenytoin may decrease **valproate** concentration. In addition, total serum phenytoin concentration may decrease, but this is offset by an increase in free phenytoin concentrations. Monitoring of both total and free serum phenytoin levels in addition to valproate level may be required. ➢ **Rifampicin** causes a small increase in the clearance of oral valproate. An increase in valproate dose may be needed.	pregnancy test and refer to the MHRA Valproate pregnancy prevention programme.

		patients taking **topiramate**. Close monitoring for valproate toxicity is advised, with monitoring of serum ammonia concentration. It might be necessary to stop one or both drugs. ➢ Exposure to **nimodipine** might be increased by valproate.		
Thiopental	GABA agonist	➢ Thiopental can cause profound hypotension in patients taking **alfuzosin**. Avoid concurrent use. ➢ Thiopental can cause marked hypotension in patients taking **ACE inhibitors and angiotensin II receptor antagonists.** Consider temporary suspension of antihypertensive agents.	**Ketamine** may antagonise the hypnotic effect of thiopental.	

Please note the table above is NOT an exhaustive list. It has been compiled to aid clinical judgment; a full list of interactions should be taken from the BNF and product summary of characteristics (SPC).

List of non-AED sodium channel antagonists

Vaughan Williams Class 1A antiarrhythmics (quinidine and procainamide)
Vaughan Williams Class 1A antiarrhythmics (lidocaine, mexiletine and phenytoin)
Vaughan Williams Class 1A antiarrhythmics (flecainide and propafenone)
Local anaesthetics
Tricyclic antidepressants (amitriptyline, nortriptyline, imipramine)
Propranolol
Quinine, chloroquine, hydroxychloroquine
Cocaine

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