Nottingham University Hospitals NHS
NHS Trust

Title	Guidelines for managing convulsive (tonic-clonic) status epilepticus in adults
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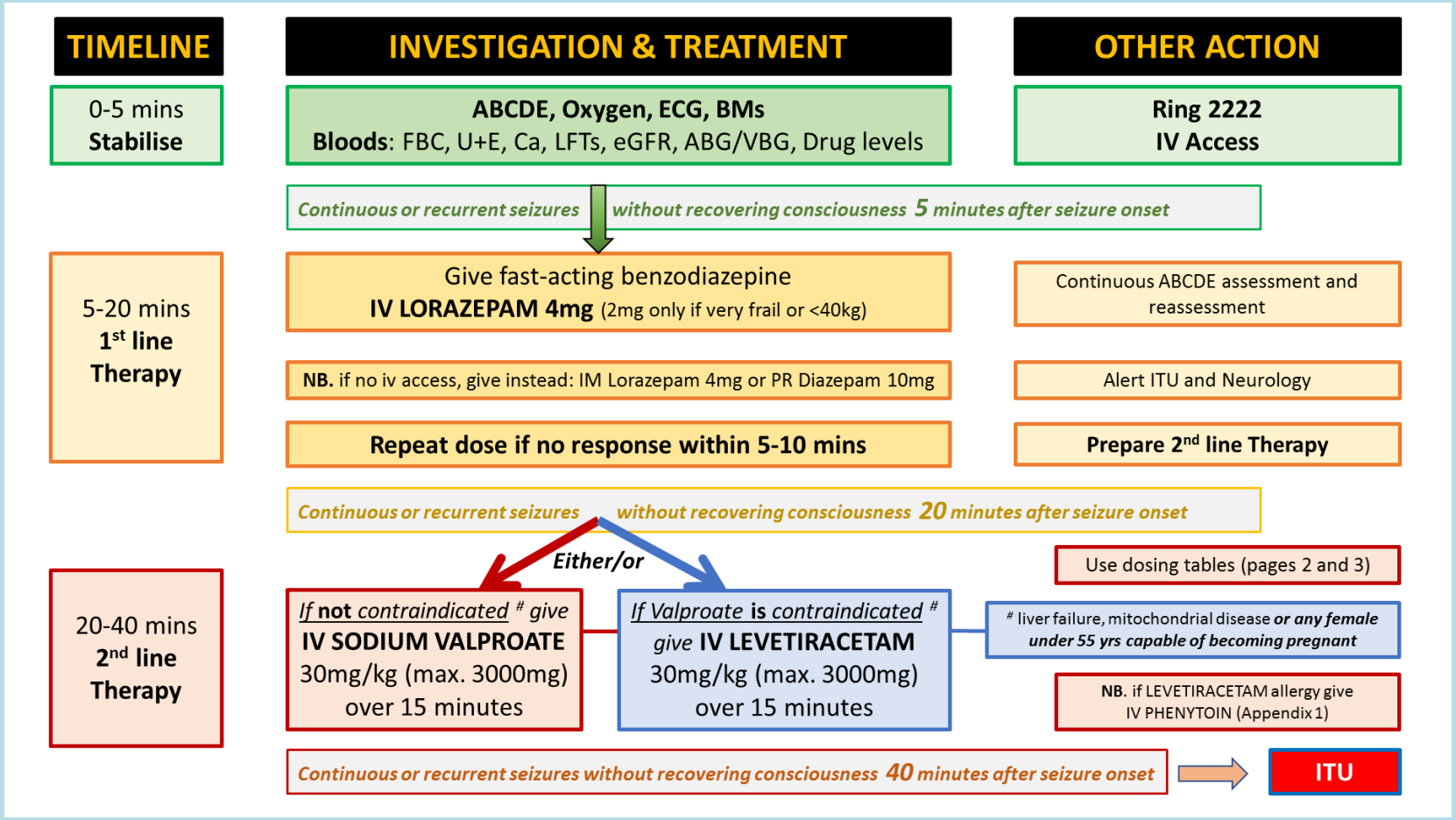
Directorate and Speciality	Musculoskeletal and Neurosciences Directorate (MSKN)
Date of submission	January 2018
Date on which guideline must be reviewed	January 2023
Explicit definition of patient group to which it applies (e.g. inclusion and exclusion criteria, diagnosis)	• Adult patients with convulsive (tonic-clonic) status epilepticus outside of the Critical Care setting • Excludes - All paediatric cases - Patients on the Adult Critical Care and other Critical Care units - Adults in whom a different approach or an alternative care plan has been put in place e.g. patients in the last days/weeks of life
Abstract	This protocol provides guidance for the in hospital pre-intensive care drug management of adult patients with status epilepticus. It is aimed at doctors working in the emergency department, admission wards and all other wards outside of the Critical Care Directorate.
Key words	Status epilepticus, sodium valproate, levetiracetam, Epilim, Keppra
Version	2 (October 2018)
Statement of the evidence base of the guideline	Protocol adapted from NICE guidance published in 2004 Evidence Base: 4 – Expert committee reports or opinions and/or clinical experiences of respected authorities
Consultation process	John Gell (Clinical Pharmacist) Emma Grace (Clinical Pharmacist) Elizabeth Jamieson (Clinical Pharmacist Adult Critical Care) Ela Akay (Neurology Registrar) Epilepsy Specialist Nurses (Catie Picton, Angela Jones, Sarah Pashley, Lisa Flinton) Emergency Department, NUH Dr Nick Woodier (Patient Safety Improvement Lead) Dr Patience Ehilawa and the SIM centre
Target audience	Medical and nursing staff in adult emergency department, medical assessment unit(s) and all other adult wards outside of Critical Care
This guideline has been registered with the trust. However, clinical guidelines are guidelines only. The interpretation and application of clinical guidelines will remain the responsibility of the individual clinician. If in doubt, contact a senior colleague or expert. Caution is advised when using guidelines after the review date.	

CONVULSIVE STATUS EPILEPTICUS

- **i.e for Tonic-clonic activity ≥ 5 minutes**
  = EITHER continuous convulsing OR recurrent seizures without any recovery of consciousness in between
- NB. Timings are approximate and for guidance only
- NB. The drug recommendations apply **even if** the patient is already prescribed the drug



LOADING DOSE OF SODIUM VALPROATE

Sodium Valproate is contra-indicated in:

- women of childbearing potential† unless the conditions of "Prevent"– the valproate pregnancy prevention programme - are fulfilled
- severe liver failure or mitochondrial disorder.

In these clinical situations Levetiracetam should be used instead (see page 3).

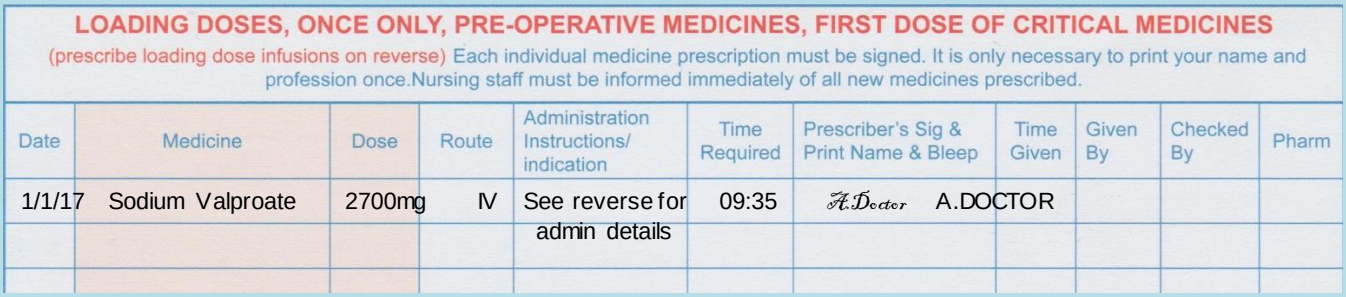
†any biological female upto the age of 55 years who is capable of becoming pregnant

- The loading dose of IV sodium valproate* should be **30 mg/kg**
- Administer via a syringe pump in 50ml of 0.9% Sodium chloride (can use the DERS programme) over **15 minutes** to a **maximum of 3g (3000mg)**.
- Use the table below to calculate the loading dose

Example: 92 kg patient
Find correct range in Weight (kg) column (highlighted in Table below)
→ read across row to **Loading dose of Sodium Valproate**
→ gives a loading dose of 2700 mg (highlighted in Table below)

Weight (kg)	Loading dose of Sodium Valproate (400mg/4ml)
45-54	1500 mg (15ml)
55-64	1800 mg (18 ml)
65-74	2100 mg (21 ml)
75-84	2400 mg (24 ml)
85-94	2700 mg (27 ml)
>95	3000 mg (30 ml) max dose

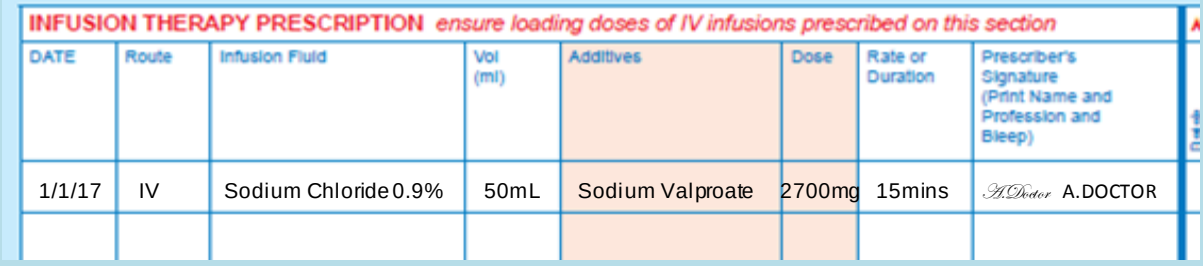
The written prescription on the Drug Card for this example is shown below:



LOADING DOSES, ONCE ONLY, PRE-OPERATIVE MEDICINES, FIRST DOSE OF CRITICAL MEDICINES

(prescribe loading dose infusions on reverse) Each individual medicine prescription must be signed. It is only necessary to print your name and profession once.Nursing staff must be informed immediately of all new medicines prescribed.

Date	Medicine	Dose	Route	Administration Instructions/ indication	Time Required	Prescriber's Sig & Print Name & Bleep	Time Given	Given By	Checked By	Pharm
1/1/17	Sodium Valproate	2700mg	IV	See reverse for admin details	09:35	A.Doctor A.DOCTOR				



INFUSION THERAPY PRESCRIPTION *ensure loading doses of IV infusions prescribed on this section*

DATE	Route	Infusion Fluid	Vol (ml)	Additives	Dose	Rate or Duration	Prescriber's Signature (Print Name and Profession and Bleep)
1/1/17	IV	Sodium Chloride 0.9%	50mL	Sodium Valproate	2700mg	15mins	A.Doctor A.DOCTOR

LOADING DOSE OF LEVETIRACETAM

No contraindications except for previous allergic reaction, in which case reconsider Valproate* or use Phenytoin (Appendix 1, page 6).

- The loading dose of IV Levetiracetam should be **30 mg/kg** irrespective of eGFR
- Administer as an infusion (can use the DERS programme) in 100ml of 0.9% Sodium chloride or 5% Dextrose over **15 minutes** to a **maximum of 3g (3000mg)**
- Use the table below to calculate the loading dose

Example
92 kg patient
Find correct range in Weight (kg) column (highlighted in Table below)
→ read across row to **Loading dose of Levetiracetam (mg)**
→ gives a loading dose of 2700mg (highlighted in Table below)

Weight (kg)	Loading dose of Levetiracetam (500mg/5ml)
45-54	1500 mg (15ml)
55-64	1800 mg (18 ml)
65-74	2100 mg (21 ml)
75-84	2400 mg (24 ml)
85-94	2700 mg (27 ml)
>95	3000 mg (30 ml) max dose

The written prescription on the Drug Card for this example is shown below:

LOADING DOSES, ONCE ONLY, PRE-OPERATIVE MEDICINES, FIRST DOSE OF CRITICAL MEDICINES
(prescribe loading dose infusions on reverse) Each individual medicine prescription must be signed. It is only necessary to print your name and profession once.Nursing staff must be informed immediately of all new medicines prescribed.

Date	Medicine	Dose	Route	Administration Instructions/ indication	Time Required	Prescriber's Sig & Print Name & Bleep	Time Given	Given By	Checked By	Pharm
1/1/17	Levetiracetam	2700mg	IV	See reverse for admin details	09:35	A.Doctor A.DOCTOR				

INFUSION THERAPY PRESCRIPTION *ensure loading doses of IV infusions prescribed on this section*

DATE	Route	Infusion Fluid	Vol (ml)	Additives	Dose	Rate or Duration	Prescriber's Signature (Print Name and Profession and Bleep)
1/1/17	IV	Sodium Chloride 0.9%	100mL	Levetiracetam	2700mg	15mins	A.Doctor A.DOCTOR

POST STATUS ALGORITHM

IDENTIFY AND TREAT CAUSE OF STATUS EPILEPTICUS

Potential Causes are listed on Page 5

Investigations

- Brain imaging (CT quicker)
- CSF examination (if there is no history of seizures or obvious cause)

Also consider:

- Anti-epileptic drug levels
- MRI brain / MR venogram
- EEG
- Septic screen
- CXR if suspected aspiration
- Pregnancy test in women of childbearing age
- Toxicology screen, alcohol levels
- Serum ammonia
- Serum lactate
- Other more specialist tests e.g. VGKC antibodies (seek Neurology advice first)

PLAN REGULAR ANTI-EPILEPTIC DRUGS

Start maintenance anti-epileptic drugs within 4-8 hours of loading:

- Sodium Valproate* - Oral, NG and IV doses are 1000mg twice a day
- See Appendix 2, pg.8 for details
- Levetiracetam - Oral, NG and IV doses are 1000 mg twice a day; reduce doses in renal failure
- See Appendix 2 pg.8 for details

Always continue the patient's existing anti-epileptic drugs

- Many of these have liquid or dispersible formulations if there is no oral route (see Appendix 3).

Please Refer all patients with Status Epilepticus to the on-call Neurology Registrar

Referrals are made

via Switchboard 9am - 5pm or via Medway/Notis out of hours using the order term 'SEIZURE'

MHRA SODIUM VALPROATE WARNING FOR WOMEN

Valproate is contra-indicated in women of childbearing potential† unless the conditions of ***Prevent*** – the valproate pregnancy prevention programme – are fulfilled.

†any biological female upto the age of 55 years who is capable of becoming pregnant

POTENTIAL CAUSES OF STATUS EPILEPTICUS

Infection:	Infection/sepsis, encephalitis (most commonly herpes virus), meningitis and cerebral abscess
Vascular:	Ischaemic stroke, intracerebral or subarachnoid haemorrhage, cerebral venous sinus thrombosis, hypertensive encephalopathy, posterior reversible encephalopathy syndrome (PRES)
Inflammatory:	Limbic encephalitis, demyelinating diseases or immune-mediated disorders
Metabolic:	Acute metabolic disturbances (most commonly sodium, calcium, magnesium and glucose), hypoxia/cardiac arrest
Trauma:	Head injury
Neoplasia:	Cerebral tumour (primary or secondary)
Paraneoplastic:	Some types of encephalitis
Degenerative:	All dementia syndromes
Congenital:	Idiopathic epilepsy, developmental anomalies of cerebral structure (e.g. focal cortical dysplasias)
Iatrogenic:	Non-concordance (forgetting or omitting medication)
Lifestyle:	Alcohol, illicit drugs, 'legal highs'

NB *Upto 50% of status admissions are non-epileptic attacks (NEA)* **not** *epilepsy. Always consider this possibility.*

Please ask a Neurologist for help where there is any doubt.

A definite diagnosis of status can usually only be made by a Neurologist **seeing** *the seizures. Videoing seizures is potentially justified as part of a 'Best Interests' decision, because treatment of presumed status has been known to kill in NEA.*

The Trust is currently looking into the best way to allow safe and secure videoing of seizures in the emergency setting. These guidelines will be updated as soon as possible, regarding the specific data protection issue of videoing seizures on personal devices.

Until then, please follow the current Trust Guidance GG/CM/013.

APPENDIX 1

Loading and maintenance dosing for IV Phenytoin

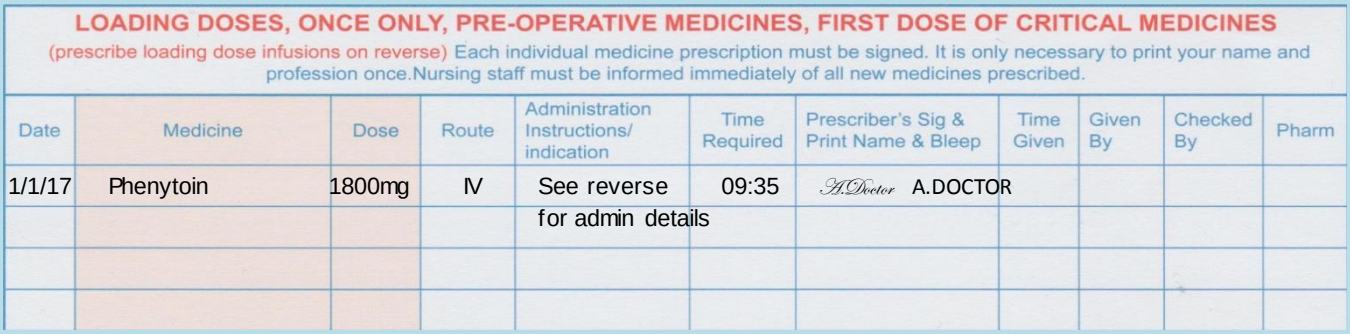
LOADING DOSE OF PHENYTOIN

- To be used in those instances where both Sodium Valproate and Levetiracetam are contra-indicated (e.g. previous allergic reaction)
- DO NOT load a patient without a level if the patient is already on phenytoin prior to admission (Discuss with Neurology)
- The loading dose of IV Phenytoin should be **20 mg/kg**
- Administer as an undiluted infusion via a syringe pump using the DERS programme to a **maximum of 2g (or 2000mg)**
- The maximum infusion rate is **50mg per minute**. No filter is required on the giving set.
- **During the loading dose infusion, continuous cardiac monitoring (ECG) should be used, *unless* it is likely to lead to significant delay**. If bradycardia or hypotension occur, halve the infusion rate to 25mg/min
- **An appropriately skilled physician should be in attendance during administration of IV phenytoin**
- Cardiac resuscitation equipment should be available in the clinical area
- Use the table below to calculate the loading dose

Example
92 kg patient
Find correct range in Weight (kg) column (highlighted in Table below)
→ read across row to **Loading dose of Phenytoin (mg)** → gives a loading dose of 1800mg (highlighted in Table below)

Weight (kg)	Loading dose of Phenytoin (250mg/5ml)
45-54	1000mg (20ml)
55-64	1200mg (24ml)
65-74	1400mg (28ml)
75-84	1600mg (32ml)
85-94	1800mg (36ml)
>95	2000mg (40ml) max dose

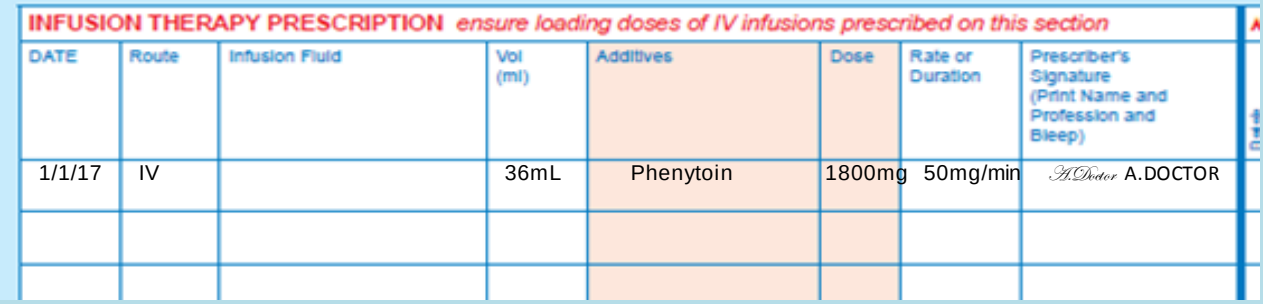
Example prescription



LOADING DOSES, ONCE ONLY, PRE-OPERATIVE MEDICINES, FIRST DOSE OF CRITICAL MEDICINES

(prescribe loading dose infusions on reverse) Each individual medicine prescription must be signed. It is only necessary to print your name and profession once.Nursing staff must be informed immediately of all new medicines prescribed.

Date	Medicine	Dose	Route	Administration Instructions/ indication	Time Required	Prescriber's Sig & Print Name & Bleep	Time Given	Given By	Checked By	Pharm
1/1/17	Phenytoin	1800mg	IV	See reverse for admin details	09:35	A.Doctor A.DOCTOR				



INFUSION THERAPY PRESCRIPTION *ensure loading doses of IV infusions prescribed on this section*

DATE	Route	Infusion Fluid	Vol (ml)	Additives	Dose	Rate or Duration	Prescriber's Signature (Print Name and Profession and Bleep)
1/1/17	IV		36mL	Phenytoin	1800mg	50mg/min	A.DOCTOR

When used in the management of status epilepticus check phenytoin levels 12-24 hours after the loading dose to ensure the drug level is in the therapeutic range of 10-20mg/L. If subtherapeutic a top up dose may be required (discuss with Neurology).

MAINTENANCE DOSE OF PHENYTOIN

- To be used in those patients who are:
  - To be started on maintenance dose 4-8hours after receiving the phenytoin load (as above)
  - Already established on phenytoin
- Usual starting maintenance dose is 300mg once daily (PO) or 270 mg once daily (liquid, via NG tube)
- If enteral access is not available, give 100mg IV three times daily, to be administered undiluted via a hand held syringe at a rate not exceeding 50mg per minute. For patients already established on a dose of phenytoin their usual dose should be split into three to four divided IV doses.
- Cardiac monitoring (ECG) is not essential for these low doses, but observe patient for signs of bradycardia and hypotension during administration.
- Flush line well with Sodium Chloride 0.9% before and after administration of Phenytoin. This helps reduce venous irritation and the likelihood of contact with other drugs
- Convert to a once daily oral /enteral dose as soon as possible.

APPENDIX 2

Maintenance dosing for Sodium Valproate* and Levetiracetam

MAINTENANCE DOSING OF SODIUM VALPROATE*

- Start maintenance doses 4-8 hours after receiving the Valproate* load
- Oral, NG and IV maintenance doses are 1000mg twice daily
- Avoid in women of childbearing potential†
- **NOTE:** Sodium Valproate* inhibits the metabolism of Lamotrigine.
    - For patients on pre-existing Lamotrigine, Lamotrigine dose will need to be reduced by up to 50% when starting regular Valproate* doses
    - Seek advice from Neurology on dosing these cases
- Convert to a twice daily oral /enteral dose as soon as feasible

***Valproate is contra-indicated in women of childbearing potential† unless the conditions of *Prevent* – the valproate pregnancy prevention programme – are fulfilled.**

†any biological female upto the age of 55 years who is capable of becoming pregnant.

MAINTENANCE DOSING OF LEVETIRACETAM

- Start maintenance dose 4-8 hours after receiving the Levetiracetam load
- Oral, NG and IV maintenance doses are 1000mg twice daily
- Convert to a twice daily oral /enteral dose as soon as feasible
- **NOTE:** Reduce maintenance doses in renal failure
    - For eGFR 50-80, give 1000mg bd
    - For eGFR 30-50, give 750mg bd
    - For eGFR <30, give 500mg bd
    - For dialysis patients, give 500mg once daily and consider giving an extra 250mg or 500mg dose post dialysis
    - See BNF for further advice in renal disease

APPENDIX 3

Alternative formulations in patients unable to take tablets

The following AEDs have liquid or dispersible formulations which could be considered for patients unable to take standard tablets / capsules by the oral route:

- Carbamazepine (can also be given rectally – see BNF for guidance)
- Clobazam
- Lacosamide
- Lamotrigine
- Levetiracetam
- Phenobarbitone
- Phenytoin
- Primidone
- Topiramate (sprinkle capsules – the internal powder can be dissolved in water)
- Valproate*
- Zonisamide (capsules – the internal powder can be dissolved in water)

The following AEDs can be given intravenously if there is no oral route:

- Phenytoin
- Valproate*
- Levetiracetam
- Lacosamide
- Phenobarbitone (ITU or HDU only as requires respiratory support facilities to be immediately available)

For full details see the Trust's Guideline on Conversion between Different Formulations of Antiepileptic Drugs (or discuss urgently with your Pharmacist)

http://nuhnet/nuh_documents/Guidelines/Diagnostics%20and%20Clinical%20Support/Pharmacy/2286.pdf

APPENDIX 4

How we decided on the 2nd line agent

After reviewing all the available literature, the authors all felt that an alternative to iv Phenytoin was required, due to safety concerns specific to this Trust. We decided to advocate iv Sodium Valproate* as 2nd line after benzodiazepine failure in status epilepticus, because:

- It showed non-inferiority to Phenytoin
- It was generally safer than Phenytoin
- It would not require cardiac monitoring that is unavailable on many wards

We advocated iv Levetiracetam as the second choice after iv Valproate* because although it met the same criteria, there was much less robust evidence for efficacy compared with iv Valproate*.

There are however 3 situations where Levetiracetam must be used over Valproate:

1) **All women of childbearing potential†**
2) Mitochondrial disorders (proven or suspected)
3) Acute or chronic liver failure

****MHRA SODIUM VALPROATE WARNING FOR WOMEN****

- Sodium Valproate is associated with a high rate of developmental malformations and reduced intelligence in children born to mothers who conceived on this drug
- In all women of childbearing potential† we recommend the use of iv Levetiracetam over Valproate in status epilepticus, to avoid the risk of these women subsequently conceiving on regular Valproate
- Please refer to the MHRA Booklet for Healthcare Professionals 2018 (ref. 14)
- **NOTE:** As status epilepticus is a life-threatening condition, the immediate and over-riding concern is to control seizures. Thus, Valproate can still be used in these women if no safe or suitable alternative exists

We will continue to review our recommendations as more evidence emerges.

NOTE: For the rare cases where both iv Sodium Valproate ***and*** iv Levetiracetam are contraindicated, iv Phenytoin may still be used if safe. Please refer to the detailed guidance in Appendix 1. Remember to contact Neurology if in doubt what to use.

***Valproate is contra-indicated in women of childbearing potential† unless the conditions of *Prevent* – the valproate pregnancy prevention programme – are fulfilled.**

†any biological female upto the age of 55 years who is capable of becoming pregnant.

GLOSSARY

ABC	Airway Breathing Circulation
AED	Antiepileptic Drug
BD	Twice a day
BM	Blood metabolites (glucose)
BNF	British National Formulary
Ca	Calcium
CRP	C-reactive protein
CT	Computed tomography
ECG	Electrocardiogram
EEG	Electroencephalogram
FBC	Full blood count
IV	Intravenous
LFT	Liver function test
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	Magnetic resonance imaging
NG	Nasogastric
PO	Oral
PR	Rectal
QTc	Corrected QT interval (on an ECG)
TDS	Three times a day
U+E	Urea and electrolytes
VBG	Venous blood gas
VGKC	Voltage gated potassium channel antibodies

References:

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