South West Yorkshire Partnership NHS Foundation Trust

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Drug and Therapeutics Sub Committee
Communication
Focus on valproate (either as semisodium valproate or sodium valproate) in mental health

Introduction

Valproic Acid as semi-sodium valproate (**Depakote ®**) is licensed for treatment of manic episode in bipolar disorder when lithium is contraindicated or not tolerated. The continuation of treatment after a manic episode can be considered in patients who have responded to semi-sodium valproate for acute mania. Sodium valproate (**Epilim®**) is licensed for the treatment of all forms of epilepsy and has been used for the treatment of manic episodes but is unlicensed for this indication.
The treatment and prophylaxis of bipolar disorder using valproate is established clinical practice and is an acceptable use of a medicine outside its product licence. It is also used off licence/off label in mental health to treat aggressive behaviour of variable aetiology.
***V*alproate is known to be teratogenic and prescribing is not recommended in women of childbearing age, those planning a pregnancy, pregnant or considering breastfeeding.**

Dosage and Administration

Semi-sodium valproate (also known as valproate semisodium, divalproex sodium) is given orally.
Initial maximum daily dose is 750mg, in two or three divided doses.
Usual range 1-2g in divided doses.
Sodium valproate is given orally as tablets or liquid
Starting dose is 600mg in two divided doses preferably after food
Sodium Valproate (as Epilim Liquid) needs to be given in two or three divided doses.
Sodium valproate modified release tablets (Epilim Chrono ®) is given orally
Initially 500mg at night increasing to 1-2g in one or two doses
Sodium valproate modified release granules (Epilim Chronosphere® Episenta®) as one or two daily doses. These may be mixed with cold food or drink.

Therapeutic monitoring

Full blood count	Baseline, at 2 months then every 6 months
Hepatic function	Baseline then every 6 months
Weight and BMI	Baseline then at 3 months and 6 months

- In severe renal impairment (eGFR <10) it may be necessary to alter the dose.
- Valproate is contraindicated in severe or active hepatic impairment and caution is required in moderate hepatic impairment.
- Risk factors for hepatotoxicity include mitochondrial disease, learning disability, polypharmacy, metabolic disorders and underlying hepatic disease.
- Ensure service user and or carer are aware of the special precautions for use including the warning signs for hepatic dysfunction and pancreatitis (see below)

Plasma level monitoring

Valproate has a complex pharmacokinetic profile and **plasma level monitoring is of limited use** but may be used to detect non-compliance or to predict or confirm toxicity.
In acute mania there **may** be a linear association between valproate serum levels and response.

	Valproate level	
Acute mania	Less than 55mg/l	No more effective than placebo
	More than 94mg/l	Best response
Maintenance phase	More than 50mg/l	Level unknown but this would seem reasonable

Titrate by effect and tolerability. Use plasma levels to ensure adequate dosing and compliance only.

Contra-indications when prescribing valproate

- Active liver disease
- Family history of severe hepatic dysfunction
- Acute porphyria
- Hypersensitivity to valproate.

Special Precautions

Pregnancy

Valproate should not be prescribed to female children, female adolescents, women of childbearing potential or pregnant women unless other treatments are ineffective or not tolerated.

- Children exposed in utero to valproate are at a high risk of serious developmental disorders (*in up to 30-40% of cases*) and/or congenital malformations (*in approximately 10% of cases*).
- The risk of abnormal pregnancy outcomes is valproate dose dependent.
- Data suggests that valproate when taken with other anti-epileptic medication, increases the risk of abnormal pregnancy outcome.
- Valproate treatment must be started and supervised by a doctor experienced in managing epilepsy or bipolar disorder.

Where the use of valproate is clinically indicated and other treatments are ineffective or not tolerated, there must be clear documentation of the risks and of the capacity of the service user to accept these risks:

- Prior to initiation of valproate
- On a change of care setting (admission / discharge)
- Annually

See Appendix 1 for the required documentation.

Ensure female service users are aware of the TERATOGENIC effects to the foetus and of contraceptive measures required.

- **Provide written (***Appendix 2***) and verbal information to the service user regarding**
  - Need to use effective contraception.
  - Need for regular review of treatment.
  - The need to rapidly consult if she is planning a pregnancy or becomes pregnant.

If the service user is already pregnant and taking valproate, the valproate should be stopped unless no alternative can be found, and then a written care plan should be developed, with the woman and partner/family members/carers, covering:

- Pregnancy
- Delivery
- The postnatal period

These should be recorded in the woman's records in primary, maternity and secondary care.

If valproate treatment is continued during the pregnancy:

- **The lowest effective dose** should be used and the daily dose should be divided into several small doses to be taken throughout the day – the use of a prolonged release formulation may be preferable to other treatment forms.
- **Initiate specialised prenatal monitoring** in order to monitor the development of the unborn, including the possible occurrence of neural tube defects and other malformation.
- **Folic acid (5mg) supplementation before the pregnancy** may decrease the risk of neural tube defects common to all pregnancies; however the available evidence does not suggest it prevents the birth defects or malformations due to valproate exposure.

Liver dysfunction

Valproate has been associated with severe liver damage including hepatic failure and rarely fatalities, usually seen in the first 6 months of therapy.

Action: withdraw immediately if warning signs appear - asthenia, malaise, anorexia, lethargy, oedema and drowsiness or in patients with epilepsy, recurrence of seizures.

Monitor liver function, and other markers of hepatic function**-** albumin, prothrombin and clotting time.

If the patient is taking salicylates (aspirin) these should also be discontinued while investigations are carried out.

Special Precautions (continued)

Pancreatitis -This may be severe and associated with fatalities. Warning signs include nausea, vomiting or acute abdominal pain.
Action- withdraw immediately if pancreatitis diagnosed. Prompt medical assessment is essential including measurement of serum amylase.

Haematological - Valproate has been associated with thrombocytopenia, leucopenia, red cell hypoplasia and pancytopenia. (Note: there is an increased risk with co-administration of olanzapine)
Action –withdraw immediately in case of spontaneous bruising or bleeding while investigations are carried out.

Adverse effects

Frequency of side effects	**Side -effects are dose related**	**Actions to take**
Common *(many people affected)*	Gastric irritation, nausea and abdominal pain	Change to sustained release preparation or take with or after food
Common	Increase in appetite and weight gain	Especially if given in combination with some antipsychotics or lithium. Encourage healthy eating /physical activity.
Common	Drowsiness	Change timing of dose
Uncommon *(some people affected)*	Confusion, ataxia and tremor	To avoid start at low dose and increase slowly.
Uncommon	Hair loss with curly re-growth	
Rare *(few people affected)*	peripheral oedema	Exclude heart disease
Very rare	rash	Stop valproate

Valproate is now a black triangle medicine and is subject to additional monitoring. Therefore please report any suspected side effects to valproate via the Yellow Card scheme www.gov.uk/yellowcard

Summary table of the drug interactions involving valproate

Valproate increases the plasma level of the drugs listed below	**Valproate decreases the plasma level of the drugs listed below**	***Valproate's level is increased by***	**Valproate's level is decreased by**
Ethosuximide	**Topiramate**	***Risperidone***	**Carbamazepine**
Free Phenytoin	**Total Phenytoin**	***Erythromycin***	**Phenobarbital**
Lamotrigine		***Felbamate***	**Phenytoin**
Oxcarbazepine		***Aspirin***	**Primidone**
Phenobarbital		***Cimetidine***	**Topiramate**
Primidone			**Mefloquine**
Benzodiazepines			**Chloroquine**
Bupropion			***Carbapenems***
Tricyclic Antidepressants			
Zidovudine			
Vitamin K dependent analogues eg Warfarin			

Clinically relevant interactions with valproate

Antibacterials	Erythromycin may increase the level of valproate *Carbapenems reduce valproate plasma concentrations*	Use an alternative antibiotic if possible or monitor closely if essential . *Potential for inadequate seizure control , use an alternative antibacterial, as monitoring of valproate levels or dosage adjustment are unlikely to manage this interaction.*
Antidepressants	Fluoxetine may increase or decrease levels of valproate. *Caution: seizure threshold reduced with antidepressants*	Use an alternative SSRI if possible or monitor closely if essential.
Anticonvulsants	Complex interactions with anticonvulsants e.g. Increased toxicity with Carbamazepine Increased risk of rash with Lamotrigine *Caution: seizure threshold reduced with antipsychotics*	Monitoring of both medications would be required and dose adjustments considered . See summary table consult BNF, pharmacist or neurologist.
Antipsychotics	Increased risk of neutropenia with Olanzapine	Monitor closely.
Anxiolytics	Increased risk of side effects when given with clonazepam and possibly clobazam.	Use an alternative to valproate or another anxiolytic.
Ulcer healing drugs	Cimetidine increases valproate level	Use an alternative to cimetidine

References

- British National Formulary. Number 68. London: British Medical Association & Royal Pharmaceutical Society of Great Britain, 2014 www.bnf.org.uk .
- Taylor D et al. the South London & Maudsley NHS Trust Prescribing Guidelines in Psychiatry 12th Edition. 2015
- Summary of Product Characteristics. (Depakote, Sanofi-Synthelabo, www.medicines.org.uk
- Summary of Product Characteristics. (Epilim, Sanofi-Synthelabo, www.medicines.org.uk
- National Institute of Health and Clinical Excellence (September 2014). The management of bipolar disorder in adults, children and young people in primary and secondary care (Clinical guideline 185).
- National Institute of Health and Clinical Excellence (2014). Antenatal and postnatal mental health: clinical management and service guideline (clinical guideline 192).
- Information from the European Medicines Agency Nov 2014
- Drug Safety Update volume 8 issue 6 January 2015

Appendix 1 (NB: This is an embedded document, please open it prior to printing)

Treatment with valproate for female patients: Checklist for patients and prescribers

A. Checklist for Prescribers

Name of Patient /carer
I confirm that the above named patient does not respond adequately or tolerate other treatments or medical treatments and requires valproate ☐

I have discussed with the above named Patient/carer:

The overall risks of an approximately 10% chance of birth defects and up to 30-40% chance of a wide range of early developmental problems that can lead to significant learning difficulties in children exposed to treatment with valproate during pregnancy. ☐
Individual risk can be minimised by use of the lowest possible effective dose ☐
The need for contraception (if child bearing age) ☐
The need for regular review of the need for treatment ☐
The need for urgent review if the patient is planning a pregnancy ☐
I have given the patient/carer a copy of the patient information booklet ☐

Name of Prescriber **Date**

B. Patient /Carer Checklist

I understand
Why treatment with valproate rather than another medicine is considered necessary for me ☐
The risks of an approximately 10% chance of birth defects and up to 30-40% chance of a wide range of early developmental problems that can lead to significant learning difficulties in children exposed to treatment with valproate during pregnancy. ☐
That I am advised to use contraception if not planning a pregnancy ☐
That my treatment should be reviewed regularly ☐
That I should request an urgent review if planning a pregnancy PRIOR to attempting to conceive ☐

Name of Patient/ Carer **Date**

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Appendix 2 (*NB: This is an embedded document, please open it prior to printing)*