

Shared Care Guidelines for Prescribing Valproate in The Treatment of Bipolar Disorder

INDICATIONS

Within the traffic light system valproate has been classified as amber for the treatment of acute hypomania within bipolar disorder and for the long term treatment of bipolar disorder.

Bipolar disorder is a severe, chronic mental illness characterized by repeated episodes of mania or hypomania, depression or mixed affective states. Drug management depends on the phase of the disorder being treated. Many drugs used to treat acute episodes are also effective in prophylaxis. Therefore, recommendations for use of agents in acute episodes have implications for continuation therapy.

NICE CG185 recommends that valproate should be considered as an option for long-term treatment of bipolar disorder. Valproate should be initiated in Secondary Care but longer term management can be handed over to Primary Care. NICE does not recommend starting valproate in primary care. Valproate should be initiated for:

- Managing mania or hypomania in adults in secondary care
 - Where an antipsychotic has proved ineffective at maximum dose and lithium is either ineffective or not recommended
- Managing bipolar disorder in adults in the longer term in secondary care
 - Where lithium is not effective or not tolerated

There are two forms of valproate recommended for acute and longer term treatment in this guidance:

First Line:

Sodium valproate m/r (Episenta)

Alternative:

Valproate semisodium (Depakote)

All forms of valproate are metabolised to Valproic acid, the pharmacologically active component. New patients should not be prescribed Epilim.

Episenta is licensed for the treatment of mania and hypomania and the management of longer term bipolar disorder. Newly initiated patients should be prescribed Episenta. There is no evidence that semisodium valproate is better tolerated than modified release sodium valproate

Depakote is licensed for treatment of manic episodes associated with bipolar disorder.

Epilim (sodium valproate EC or MR) is not licensed for the management of bipolar disorder but there is a large body of evidence supporting its use. Existing patients on Depakote or Epilim should be maintained on current therapy.

AREAS OF RESPONSIBILITY FOR SHARED CARE

This shared care agreement outlines suggested ways in which the responsibilities for managing the prescribing of valproate can be shared between the specialist and general practitioner (GP). GPs are invited to participate. If the GP is not confident to undertake these roles, then he or she is under no obligation to do so. In such an event, the total clinical responsibility for the patient for the diagnosed condition remains with the specialist. If a specialist asks the GP to prescribe this drug, the GP should reply to this request as soon as practicable.

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Sharing of care assumes communication between the specialist, GP and patient. The intention to share care is usually explained to the patient by the doctor initiating treatment. It is important that patients are consulted about treatment and are in agreement with it.

The doctor who prescribes the medication legally assumes clinical responsibility for the drug and the consequences of its use.

SPECIALIST RESPONSIBILITIES

1.	To provide specialist assessment and determine a management strategy and ensure a care plan has been arranged.
2.	Where appropriate: To initiate and stabilise treatment of bipolar disorder with the locally approved valproate product obtain agreement from the patient's GP to continue prescribing once treatment has been stabilised. Monitor the patient and their therapy as clinically appropriate. Measurement of valproate plasma levels may be considered in addition to clinical monitoring when adequate therapeutic effect is not achieved or adverse effects are suspected
3.	To provide the GP with appropriate prescribing information and any additional information requested.
4.	To be available for advice if the patient's condition changes.
5.	Where appropriate, to ensure the patient has given informed consent to the 'off license' use for treatment.
6.	To provide the patient's therapy and prescriptions until their dose and mental state have been stabilised.
7.	To notify the GP of any changes in prescribed therapy or clinical status and ensure that the patient has sufficient medication until the GP has received this notification.
8.	To provide adequate advice in writing about the proposed duration and dose of any ongoing treatment in all cases where the patient is discharged from secondary care on maintenance treatment. Procedures should be in place for the rapid re-referral of the patient by the GP if required.
9.	If a woman of child-bearing potential is to be prescribed Valproate for a mental health condition and all other potential treatments are not appropriate, then she must be enrolled in the Pregnancy Prevention Programme. This requires: <ol style="list-style-type: none"> 1. Confirming the woman is not pregnant by means of a negative pregnancy test or assurance of highly effective contraception 2. Explaining to the patient and ensure she understands the associated risks using the information leaflets and give them the patient guide 3. Explaining to the patient the need to ensure highly effective contraception (e.g. progestogen only implant, copper intrauterine device or levonorgestrel intrauterine device) if not already on it and make appropriate referrals for this – in most cases to refer back to the GP 4. An annual review by a specialist prescriber for as long as she takes Valproate for treatment of a mental health condition.

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	5. The completion of a Risk Assessment Form annually which must be signed by the patient and specialist then shared with the woman, her GP and uploaded to the patient's electronic notes.
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GENERAL PRACTITIONER RESPONSIBILITIES

1.	Initially, to refer the patient for specialist advice.
2.	To review the patient as clinically appropriate
3.	To re-refer the patient or seek specialist advice from the Psychiatrist or CMHT in accordance with the patient's care plan or at such a time as is necessary.
4.	To prescribe maintenance psychotropic and general therapy when this has been agreed with the psychiatrist.
5.	To deal with general health issues of the patient and provide routine physical health checks where appropriate.
6.	To notify the specialist of any relevant changes in other medications or clinical status.
7.	Do not start valproate in primary care to treat bipolar disorder.
8.	To ensure any women of child-bearing potential who are prescribed Valproate are complying with the Pregnancy Prevention Programme, which includes having an annual review from a specialist prescriber and are prescribed highly effective contraception.

Indications for re-referral or need for specialist advice include:-

any spontaneous deterioration in mental state that cannot be managed by the GP; patient intolerance and/or adverse effects; when considering concomitant psychotropic therapy or the initiation of therapy that may interact with the patient's psychotropic therapy or mental state; non-concordance, lack of efficacy or need for alteration of dose of psychotropic therapy.

PATIENTS ROLE (OR THAT OF CARER)

To take their medication regularly and enter a concordant relationship with those involved in the delivery of their care.

Report any adverse effects to their GP/Specialist service nurse whilst taking the medication

To ensure that they have a clear understanding of their treatment

Attend appropriate GP and other follow up appointments

Share any concerns in relation to treatment with their GP or Consultant

Use written or other information on the medication

Seek help urgently if they suspect side effects or are otherwise unwell

If of child-bearing potential, ensure they are taking highly effective contraception and complying with Pregnancy Prevention Programme, including attending annual reviews and signing the risk acknowledgement form.

SUPPORTING INFORMATION

Women and Girls of Child Bearing Age:

The MHRA has issued guidance on avoiding valproate in women of child bearing potential due to the significant risk of birth defects (1 in 10) and developmental disorders (4 in 10) in children born to women who take Valproate during pregnancy Valproate must no longer be used in any woman or girl able to have children unless she has a pregnancy prevention programme in place. This is designed to make sure patients are fully aware of the risks and the need to avoid becoming pregnant.

Further guidance and resource materials are available from the MHRA at <https://www.gov.uk/guidance/valproate-use-by-women-and-girls>

Cost of treatment

Drug	Regimen	Annual Cost per Patient (Jan 2020)
Episenta® (sodium valproate) 150 mg and 300 mg capsules	1000–2000 mg once daily	£142.35 (900 mg per day) – £332.15 (2,100 mg per day)
Episenta® (sodium valproate) 500mg and 1,000mg granules	1000–2000 mg once daily	£149.65 – £299.30
Depakote® (valproate semisodium) 250 mg and 500 mg tablets	1000–2000 mg per day	£276.67 – £553.34
Epilim Chrono 200mg, 300mg and 500mg tablets	1000 – 2000 mg per day	£212.43 - £424.86

Dosing

Mania, ADULT over 18 years, initially 750 mg daily, adjusted according to response, usual dose 1–2 g daily; doses greater than 45 mg/kg daily require careful monitoring; total daily dose given in 1–2 divided doses

Episenta capsules contain granules that can be opened and sprinkled on food. The sachets contain the granules. The granules should not be crushed or chewed. Episenta is not suitable in a blister pack/ medication aid. Depakote and Epilim are only suitable for a maximum of one week's supply where benefit outweighs risk of hygroscopic effects that can affect release profile.

Long-Term Monitoring of Laboratory Values

Repeat liver function tests may be indicated in the first 6 months of treatment, although clinical vigilance is more important. Severe reported complications have occurred early in treatment and usually in children in treatment for epilepsy.

Side Effects

Common dose-related side effects of valproate include gastrointestinal pain, benign hepatic transaminase elevations, tremor and sedation. Patients with past or current hepatic disease may be at increased risk for hepatotoxicity. Mild, asymptomatic leukopaenia and thrombocytopaenia occur less frequently and are reversible on drug discontinuation.

Other side effects include hair loss, increased appetite and weight gain.

Rare, idiosyncratic, but potentially fatal adverse events include irreversible hepatic failure, hemorrhagic pancreatitis and agranulocytosis; patients should contact their physician immediately if severe symptoms develop.

Patients or their carers should be told how to recognize signs of blood and liver toxicity or pancreatitis and they should be advised to seek immediate medical attention if symptoms develop.

Patients should be informed of the signs of bleeding and of the increased risk of taking salicylates. See the individual product characteristics for a complete list.

Discontinuation

Valproate should be discontinued slowly over at least one month

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Drug Interactions

Valproate displaces highly protein-bound drugs from their protein-binding sites. Dosage adjustments will be needed.

Valproate inhibits the metabolism of lamotrigine which must be initiated at half the usual dose when added to valproate. Accordingly, lamotrigine dosage should be reduced when valproate is added to it. See the individual products for a full list

Quick Reference Monitoring Guide

Baseline (Specialist)	At 3 - 6 months (GP)	Annually (GP)
Weight and BMI Full blood count Liver Function Tests	FBC LFT with albumin and clotting if enzyme levels are abnormal BMI	FBC LFT with albumin and clotting if enzyme levels are abnormal BMI

REFERENCES

Evidence-based guidelines for treating bipolar disorder: revised third edition—recommendations from the British Association for Psychopharmacology Goodwin GM et al, BAP 2016 https://www.bap.org.uk/pdfs/BAP_Guidelines-Bipolar.pdf

NICE Clinical Guideline 185. Bipolar Disorder. September 2014
<https://www.nice.org.uk/guidance/cg185>

MHRA guidance on Valproate use by women and girls
<https://www.gov.uk/guidance/valproate-use-by-women-and-girls>

Specialist Pharmacy Service, <https://www.sps.nhs.uk> accessed June 17

BNF, <https://www.medicinescomplete.com/mc/bnf/current/> accessed June 17

Summary of Product Characteristics of individual drugs,
<https://www.medicines.org.uk/emc/> accessed June 17

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