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

There are two valproate products covered by this guidance, namely:-

- Valproate semisodium (Depakote®)
- Sodium valproate m/r (Epilim Chrono®)

Valproate is one of the options for long term treatment of bipolar disorder listed in NICE Clinical Guidelines CG38 and the evidence based British Association of Psychopharmacology (BAP) Guidelines.

It is also used in the acute treatment of mania/hypomania

There is inadequate evidence to recommend valproate in an acute depressive episode

Maintenance treatment with sodium valproate (usually Chrono) should be used. Depakote® should only be used as a second line option for those patients who have had a partial response to sodium valproate but developed intolerable GI side effects

This Guidance should not be used in isolation. Further information and evidence-based guidance for treating bipolar disorder, is available from the following sources:

- Evidence-based guidelines for treating bipolar disorder: revised second edition—recommendations from the British Association for Psychopharmacology BAP 2009

The NICE CG38 recommends that valproate should be considered as an option for long-term treatment of bipolar disorder. The choice should depend on:

- response to previous treatments
- the relative risk, and known precipitants, of manic versus depressive relapse
- physical risk factors, particularly renal disease, obesity and diabetes
- the patient’s preference and history of adherence
- gender (valproate should not be routinely used to treat bipolar illness for women of child-bearing potential)
- a brief assessment of cognitive state if appropriate, for example, for older people.

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.

Valproate semisodium (Depakote®) is licensed for the acute treatment of a manic episode associated with bipolar disorder. It is not licensed for other phases of bipolar
disorder. Sodium Valproate m/r (Epilim Chrono®) is not licensed for either phase but has sufficient body of evidence to support its use (BAP Guidelines 2009).

NICE CG38 states that. If the patient has frequent relapses, or symptoms continue to cause functional impairment, switching to an alternative monotherapy or adding a second prophylactic agent (lithium, olanzapine, valproate) should be considered. Clinical state, side effects and, where relevant, blood levels should be monitored closely. Possible combinations are lithium with valproate, lithium with olanzapine, and valproate with olanzapine. The reasons for the choice and the discussion with the patient of the potential benefits and risks should be documented.

**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.

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.
GENERAL PRACTITIONER RESPONSIBILITIES

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<tbody>
<tr>
<td>1.</td>
<td>Initially, to refer the patient for specialist advice.</td>
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<td>2.</td>
<td>To review the patient as clinically appropriate</td>
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<td>3.</td>
<td>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.</td>
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<td>4.</td>
<td>To prescribe maintenance psychotropic and general therapy when this has been agreed with the psychiatrist.</td>
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<td>5.</td>
<td>To deal with general health issues of the patient and provide routine physical health checks.</td>
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<td>6.</td>
<td>To notify the specialist of any relevant changes in other medications or clinical status.</td>
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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

SUPPORTING INFORMATION

Women of child bearing age must be informed of the increased risk of teratogenicity in pregnancy.
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.
Product Information Leaflets are available at the point of dispensing from the Pharmacy.

Initial workup
General medical history with special attention to hepatic, haematological and bleeding abnormalities, physical examination and weight.
Liver function tests.
Pregnancy test in women of childbearing age.

**Dosing**
Valproate semisodium contains a higher fraction (about 30%) of the valproate moiety than sodium valproate and dosing should reflect this when switching between agents. Doses will be given for valproate semisodium because almost all the controlled data was obtained with this formulation. For hospitalised patients with mania, divalproate semisodium can be administered at an initial dosage of 20–30 mg/kg/day in inpatients. A valproate level between 50 and 125 μg/mL has been associated with acute response.

For outpatients, elderly patients or patients with hypomania or euthymia, start at 500 mg valproate semisodium at night. Titrate the dose upward by 250–500 mg/day every few days, depending on side effects. The data sheet suggests divided doses but in practice a single dose can often be given at night. The maximum adult daily dosage is 60 mg/kg/day, but all patients receiving daily doses higher than 45 mg/kg should be carefully monitored. However, a total dose of 1250 mg/day is the highest usually well tolerated by outpatients.

For sodium valproate, Maudsley recommends for mania 500mg/day increasing according to tolerability and plasma levels.

**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 thrombocytopenia 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.

**Discontinuation**
Valproate should be discontinued slowly over at least one month.

**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.

**Quick Reference Monitoring Guide**

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<tr>
<td>Liver Function Tests</td>
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## REFERENCES

Evidence-based guidelines for treating bipolar disorder: revised second edition—recommendations from the British Association for Psychopharmacology BAP 2009
The Maudsley Prescribing Guidelines in Psychiatry 2011

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<tr>
<th>Reviewed and updated by</th>
<th>Richard Bradshaw</th>
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<td>Content Approved By</td>
<td>Medicines Management mental health group</td>
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