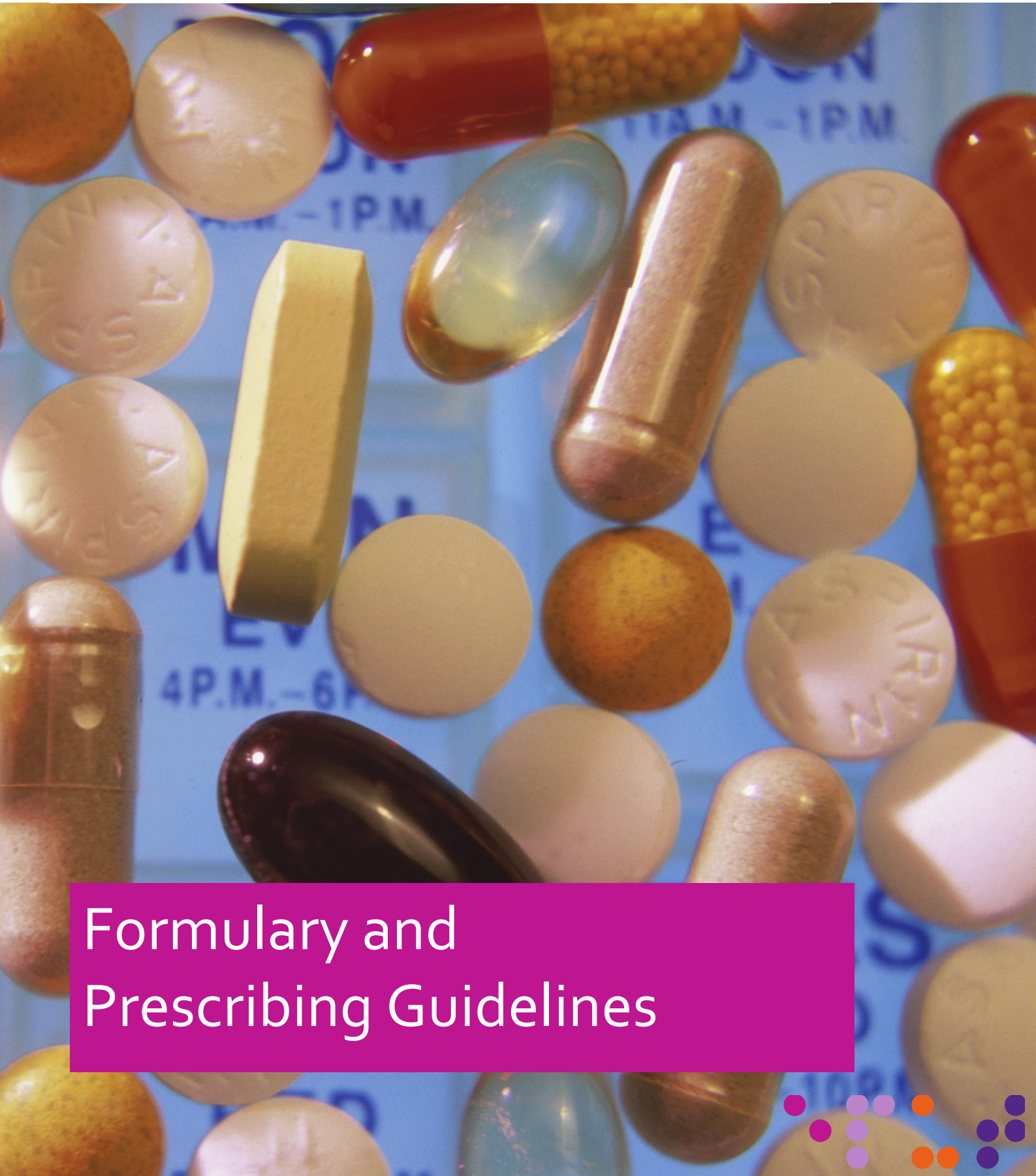
Essex Partnership University
NHS Foundation Trust

## SECTION 3: MANAGEMENT OF BIPOLAR AFFECTIVE DISORDER



# Formulary and Prescribing Guidelines

This section provides information regarding the pharmacological management of Bipolar affective disorder in secondary care. Readers should consult literature to gain a further understanding of the psychological strategies which may be employed or for further guidance relating to management in primary care (see NICE CG185).

## 3.1 Approved Mood stabilisers

| Drug | Formulation | | Comment |
|---|---|---|---|
| Aripiprazole | Tabs 5mg, 10mg, 15mg, 30mg<br>Orodispersible tabs 15mg, 30mg<br>Liquid 1mg/ml | | Generic aripiprazole is only licensed in schizophrenia. |
| Asenapine<br>(for mod/severe manic episodes associated with bipolar if alternatives unsuccessful) | S/L tablets 5mg, 10mg<br>Consultant initiation & on-going prescribing only – consider switching once pt. stable. | | Acute phase bipolar 1. |
| Carbamazepine | Tablets 100mg, 200mg, 400mg<br>M/R tablets 200mg,400mg<br>Liquid 100mg/5ml | | For mood disorder use sustained release preparation. |
| Lamotrigine | Tablets 25mg, 50mg, 100mg 200mg<br>Dispersible tablets: 5mg, 25mg, 100mg | | |
| Lithium **Carbonate** (tablets) | Priadel: M/R tablets 200mg, 400mg (scored) | | Bioequivalence varies widely between brands and salts |
| | Camcolit:400mg (scored) Tabs Essential Pharma 250mg Tabs (Bioequivalent to Camcolit - rebranded) | | |
| Lithium **Citrate** (liquids) | Li-liquid | Yellow liq. 509mg/5ml (=200mg of Lithium tab)<br>orange liq. 1.018g/5ml (=400mg of Lithium tab) | Bioequivalence varies widely between brands and salts |
| | Priadel: Liquid 520mg/5ml (=204mg of Lithium tab)<br>NB. Exact conversion not required for Priadel. | | |
| Lurasidone | Tabs | | Off label use approved for bipolar disorder where aripiprazole has not been effective and patient has cardiometabolic risk factors.<br>*Formulary status may differ across ICBs and prescribing may need to remain within EPUT |
| Olanzapine | Tabs 2.5mg, 5mg, 10mg, 15mg, 20mg<br>Orodispersible tabs 5mg, 10mg, 15mg, 20mg | | |
| Quetiapine | Tabs 25mg, 100mg, 150mg, 200mg, 300mg<br>M/R tabs 50mg, 150mg, 200mg, 300mg, 400mg | | Liquid not approved, immediate release tablets to be crushed. |
| Risperidone | Tabs 0.5mg, 1mg, 2mg, 3mg, 4mg, 6mg<br>Orodispersible tabs 0.5mg,1mg, 2mg,3mg, 4mg<br>Liquid 1mg/ml | | |
| Sodium Valproate | Tablets 100mg, 200mg, 500mg<br>M/R tablets 200mg,300mg,500mg<br>M/R capsules 150mg, 300mg | | Must be prescribed in line with CG96- clinical guideline for the management and review of |

| Drug | Formulation | Comment |
|---|---|---|
| | Liquid 200mg/5ml<br>Other formulations e.g. Episenta granules, Epilim Chronosphere | valproate in all patients.<br><br>*Valproate must only be used where all alternatives have been considered and are either ineffective, not suitable or not tolerated.* |
| Semisodium Valproate (Depakote) | Tabs 250mg, 500mg | |
| **For EPUT use only, not to be initiated or continued by primary care prescribers:**<br>Omega-3 acid ethyl esters. Some evidence for improvement in bipolar disorder. Advise patient to purchase if possible. Review concordance. | | |

## Notes

- Due to variations in bioavailability between brands of lithium, products are not interchangeable. New prescriptions for tablets will be for Priadel unless clearly indicated otherwise. If a patient is already maintained on a different brand, this should be indicated on the prescription. Changing brands requires the same precautions as initiation. It is acceptable to convert someone who is taking 5ml Priadel liquid (204mg) to 200mg Priadel tablet or vice versa.

- If a patient is admitted on lithium no supply will be made (and the patient's own supply of lithium must be quarantined) until a lithium level is received. (This may mean taking an emergency blood lithium level). Baseline checks should be completed and confirmed to be satisfactory as soon as possible after admission, i.e. a 12 hour post dose lithium level has been received and is not above the therapeutic level, and kidney function tests demonstrate that prescribing lithium is still appropriate for the patient. This will prevent inadvertent administration to a patient for whom lithium is now contra-indicated and might cause harm. Any dose given without the full baseline checks being completed should not exceed 400mg.

- Consider the childbearing potential of all patients prior to initiating any medicine – see section 20, prescribing in pregnancy, for further information.

- There is emerging evidence for the mood stabilising effects of atypical antipsychotic drugs. Olanzapine, Aripiprazole, Risperidone, Quetiapine, within their licensed indications, are recommended as options for control of the acute symptoms associated with the manic phase of bipolar disorder. Of the drugs available for the treatment of acute mania, the choice of which to prescribe should be made jointly between the individual patient and the clinician. In all situations where informed discussion is not possible advance directives should be taken fully into account and the individual's advocate and/or carer should be consulted.

- Valproate Semisodium ("Depakote") is licensed for the treatment of mania in bipolar disorders. Sodium Valproate may be used in bipolar mania, but these formulations are unlicensed. Valproate m/r tablets can be administered once daily to aid patient adherence.

- The use of sodium valproate must be in line with CG96- clinical guideline for the management and review of valproate in all patients which covers both the requirements of initiation and continuation of sodium valproate.

- If the patient becomes pregnant on valproate they must be referred for an urgent consultant review and be advised not to stop valproate until that review. Consideration should be given to tapering the valproate down carefully, while introducing suitable alternative drug treatment. Treatment of BPAD in children & adolescents and antenatal & postnatal services users is discussed in section 12 and section 20 respectively. Additional information regarding prescribing in older adults can also be found in section 11.

- The management of lithium in secondary care is described below and in Appendix 1. The shared management of lithium between primary and secondary care is described in the document Shared Care Protocol for the Prescribing and Monitoring of Lithium. It includes useful information on prescriber, patient and carer responsibilities, dosing and monitoring of lithium, cautions, contraindications, interactions, and advice on lithium toxicity.

- The use of Lurasidone in bipolar disorder is off-label. It can be initiated in EPUT for patients who have had an adequate trial of aripiprazole which has not been effective and have one or more cardiometabolic risk factors (diabetes, high cholesterol, obesity, QTc prolongation). The formulary status varies across ICBs therefore not all areas will accept ongoing prescribing and prescribing may have to remain within EPUT. If requesting for a GP to continue prescribing the rationale for prescribing including the cardiometabolic risk and off-label prescribing must be included in the request.

## 3.2 Management of Mania/Hypomania

Of the drugs available for the treatment of mania, the choice of which to prescribe should be made jointly between the individual patient and the clinician. In all situations where informed discussion is not possible advance directives should be taken into account and the individual's advocate and/or carer should be consulted when appropriate.

Pre-monitoring and on-going monitoring should be undertaken in line with section 2 of the F&PG, NICE CG185 and specific SPC requirements for a named drug. Clinical judgement should also be used to determine if additional monitoring is required for the individual service user.

- If a person is taking an antidepressant as monotherapy, consider stopping the antidepressant and offering an antipsychotic – regardless of whether the antidepressant is stopped

- If the person develops mania or hypomania and is not taking an antipsychotic or mood stabiliser offer haloperidol, olanzapine, quetiapine, risperidone (or aripiprazole), taking into account advanced statements, the person preference and clinical context (including physical comorbidity, previous response to treatment and side effects)

- If the first antipsychotic is poorly tolerated or ineffective at the maximum licensed dose offer an alternative

- If the alternative is not effective at the maximum dose consider adding lithium. If lithium is ineffective or unsuitable consider valproate instead (not for women of child bearing age).

- If the person is taking an antidepressant in combination with a mood stabiliser already, consider stopping the antidepressant.

- If the person is already taking lithium, check plasma levels to optimise treatment. Consider adding an antipsychotic depending on previous response.

- If the patient is already taking another mood stabiliser as prophylactic treatment consider increasing the dose (up to maximum level in BNF). If there is no response consider adding an antipsychotic. If the patient is already taking valproate consider a review of the ongoing use of valproate and alternatives, if switching is not possible consider increasing the dose (up to maximum level in BNF).

- Within 4 weeks of symptom resolution, discuss with the person/carers whether to continue treatment or start long term treatment. Explain potential benefits and risks of long term, including side effects. If the person decides to continue treatment offer it for a further 3 to 6 months then review.

- Do not offer lamotrigine to treat mania.

For all patients consider adding short-term benzodiazepine (lorazepam or clonazepam).[1]

## 3.3 Treatment of Bipolar Depression

**Not currently receiving treatment**

- If a person develops moderate to severe bipolar depression and is not taking a drug to treat their bipolar depression, offer fluoxetine combined with olanzapine **or** quetiapine monotherapy, depending on the person's preference and previous response to treatment.

- If the person prefers, consider either olanzapine monotherapy or lamotrigine monotherapy

- If there is no response to fluoxetine with olanzapine or quetiapine monotherapy consider lamotrigine monotherapy.

**Currently taking lithium**

- If a person develops moderate to severe bipolar depression and is taking lithium check lithium plasma levels and if necessary increase dose.

- If at maximum lithium dose, add either fluoxetine with olanzapine **or** quetiapine depending on the person preference or previous response to treatment.

- If the person prefers, consider adding olanzapine (without fluoxetine) or lamotrigine to lithium therapy.

- If there is no response to adding fluoxetine combined with olanzapine or quetiapine, or adding quetiapine, stop the additional treatment and consider adding lamotrigine to lithium.

**Currently taking valproate**

- If a person develops moderate to severe bipolar depression and is taking valproate consider switching to an alternative but if that is not possible consider increasing the dose within the therapeutic range.

- If the maximum tolerated dose, or the top of the therapeutic range has been reached and there has been limited response with valproate add fluoxetine combined with olanzapine **or** add quetiapine alone.

- If the person prefers, consider adding olanzapine (without fluoxetine) or lamotrigine to valproate.

- If there is no response to adding fluoxetine with olanzapine or quetiapine alone, stop the additional treatment and consider adding lamotrigine.

- Within 4 weeks of resolution of symptoms, discuss with the person whether to continue treatment for bipolar depression or start long term treatment. Explain the benefits and risks associated with long term treatment and potential side effects. If the person decides to continue with treatment for bipolar depression offer medication for 3 to 6 months and then review.

## 3.4 Prophylactic Treatment of Bipolar Affective Disorder

After each episode of mania or bipolar depression, discuss with the person, and their carers if appropriate, managing their bipolar disorder in the longer term. Discussion should aim to help people understand that bipolar disorder is commonly a long-term relapsing and remitting condition that needs self-management and engagement with primary and secondary care professionals and involvement of carers.

When planning long-term pharmacological treatment to prevent relapse, take into account drugs that have been effective during episodes of mania or bipolar depression. Discuss with the person whether they prefer to continue this treatment or switch to lithium, and explain that lithium is the most effective long-term treatment for bipolar disorder.

- Offer lithium as a first line, long term treatment for bipolar disorder.
- If lithium is poorly tolerated or is not suitable (e.g. person does not agree to blood monitoring) consider an antipsychotic in line with NICE guidance.
- Valproate should only be used where all alternatives have been considered and are either ineffective, not suitable or not tolerated.
- If stopping long-term treatment discuss with the person early signs of relapse and what to do if symptoms recur. Treatment should be stopped gradually (at least 4 weeks, see BNF).
- Carbamazepine may be used under specialist supervision for the prophylaxis of bipolar disorder in patients unresponsive to a combination of other prophylactic drugs; it is used in rapid cycling manic depressive illness (4 or more episodes/year). The dose should not normally be increased if an acute episode of mania occurs[5]

## 3.5 Rapid Cycling disorder management

Rapid cycling disorder is usually defined as bipolar disorder where there have been 4 or more episode of mania/hypomania or depression within a 12 month period. There is relatively little evidence supporting strategies and response to treatment tends to be less pronounced compared to ‘typical’ bipolar disorder.

- Consider withdrawal of antidepressants in all patients[1]
- Consider a combination of lithium and valproate
- For patients already taking lithium consider keeping towards top end of therapeutic level.
- For the management of depressive symptoms, avoid the use of an antidepressant. Instead, consider increasing the dose of the antimanic agent or the addition of a second mood stabiliser (including lamotrigine). On occasions, and on advice from a specialist in bipolar disorder, antidepressants can be considered. When a patient is in remission from depressive symptoms (or symptoms have been significantly less severe for 8 weeks), stopping the antidepressant medication should be considered, to minimise the risks of switching to mania and increased rapid cycling
- Consider combinations of lithium or valproate with lamotrigine, especially in bipolar II disorder

## 3.6 Monitoring Physical Health

*See Appendix 1 for monitoring required for Lithium, Carbamazepine and Valproate. See Section 2 appendices for physical health monitoring relating to antipsychotics*

There is growing concern about the physical health of service users with bipolar disorder.

If a person gains weight during treatment their medication should be reviewed, and the following considered:

- Dietary advice and support from primary care and mental health services
- Advising regular aerobic exercise
- Referral to relevant health services for specific programmes to manage weight gain
- Refer to a dietician if the person has complex co-morbidities (e.g. coeliac disease).
- Drug treatments such as sibutramine are not recommended to promote weight loss.

A physical health review is needed to ensure that the following are assessed at least each year

- Fasting lipid levels, including cholesterol in all patients over 40 even if there is no other indication of risk.
- Fasting plasma glucose levels
- Blood pressure
- Weight
- Smoking status and alcohol use

**References**


1. South London & Maudsley NHS Foundation Trust Prescribing Guidelines 12th edition, Wiley Blackwell, 2015
2. Psychotropic Drug Directory 2016, Bazire S., Page Bros Ltd
3. Summary of Product Characteristics for Individual Drugs [accessed May 2017], sodium valproate (Epilim) accessed 23/5/2018.
4. BNF on-line, Current edition, Accessed 23/5/2018.
5. NICE Clinical guideline [CG185]. Bipolar disorder: assessment and management. Published date: September 2014 Last updated: April 2018. Accessed 23/5/2018.
6. Guidance for Mental Health Professionals on the management of Acute Kidney Injury

**Appendix 1**

# Physical Health monitoring for mood stabilisers

Clear (unshaded boxes) indicate monitoring required - See section 2 for physical health monitoring relating to antipsychotics.

## Lithium

| Parameter | Baseline | 1 month | 3 months | 6 months | 9 months | 12 months | Then… |
|---|---|---|---|---|---|---|---|
| Weight/BMI | | | | | | | 6 monthly |
| TFTs | | | | | | | 6 monthly |
| U&Es | | | | | | | 6 monthly |
| eGFR | | | | | | | 6 monthly |
| Calcium | | | | | | | Annually |
| FBC | | | | | | | Annually |
| BP and pulse | | | | | | | Annually |

Perform **full physical examination** and **ECG (risk factors)** before starting lithium and issue NPSA lithium therapy booklet. Check **plasma lithium 12(±2) hours post-dose** every 5-7 days until level is 0.4 –1.0 mmol/l, then 3 monthly or more frequently whenever toxicity, reduced renal function is suspected, other medication is changed and 1 week after dose changes. Target range will be dependent on indication and individual. Annual physical check should also be performed. See 3.5 for more details. There is an increased risk of Acute Kidney Injury (AKI) [6]This can be investigated by measuring Serum Creatinine.

## Carbamazepine

| Parameter | Baseline | 1 month | 3 months | 6 months | 9 months | 12 months | Then… |
|---|---|---|---|---|---|---|---|
| Weight/BMI | | | | | | | 6 monthly |
| LFTs | | | | | | | 6 monthly |
| U&Es | | | | | | | 6 monthly |
| FBC | | | | | | | 6 monthly |

Perform **full physical examination** before starting carbamazepine. Perform **ECG** in elderly/risk factors. **Plasma levels** are not useful when carbamazepine is used for mood stabilisation, and only needed if toxicity suspected. Therapeutic and toxic levels are close. Annual physical check should also be performed. See 3.5 for more details

## Valproate (sodium, e.g. “Epilim” and semisodium “Depakote”) – Lamotrigine (baseline parameters)

| Parameter | Baseline | 1 month | 3 months | 6 months | 9 months | 12 months | Then… |
|---|---|---|---|---|---|---|---|
| Weight/BMI | | | | | | | 6 monthly |
| LFTs | | | | | | | 6 monthly |
| U&Es | | | | | | | 6 monthly |
| FBC | | | | | | | 6 monthly |

Perform **full physical examination** before starting valproate. **Plasma levels** are not useful when valproate is used for mood stabilisation, & only needed if toxicity suspected. ? Pregnancy test. Annual physical check should also be performed. See 3.5 for more details