Policy title  Prescribing guidelines for the management of bipolar affective disorder

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Policy category Clinical

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Approved by (Group): Drugs and Therapeutic Committee

Approved by (Committee): Quality Committee

Document history

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<td>June 2015</td>
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Membership of the policy development/review team Dr Lucinda Donaldson, Consultant Psychiatrist, Dr Agnieszka Klimowicz, Consultant Psychiatrist, Christina Amin, Consultant Nurse for Physical Health

Consultation Members of the Drugs and Therapeutic Committee

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1 Introduction

These guidelines have been developed to provide clinical staff with clear guidance on prescribing for bipolar disorder to ensure safe effective care of patients in line with current NICE and national good practice guidance and trust formulary.

2.0 Aims and objectives

To ensure quality and cost-effective prescribing of medicines and provide optimal treatment for bipolar affective disorder.

3.0 Scope of the policy

This policy relates to prescribing in patients with a diagnosis of bipolar affective disorder.
4.0 Key points – medicine choice in the treatment of bipolar disorder (NICE).

Flow chart

**Mania and hypomania**
Consider stopping any antidepressant. Offer an antipsychotic – haloperidol, olanzapine, quetiapine or risperidone.

- If the first antipsychotic is poorly tolerated or ineffective at the maximum licensed dose, offer an alternative.
  - If the alternative antipsychotic is not sufficiently effective at max dose, consider adding lithium.

- If lithium is ineffective, or if lithium is not suitable (for example, because the person does not agree to routine blood monitoring), consider adding valproate instead.

- If the person is taking lithium, check levels and optimise treatment. If the person is taking valproate instead consider increasing the dose up to the maximum dose in the BNF. Consider adding an antipsychotic in either case if no improvement.

- Do not offer lamotrigine to treat mania.

**Moderate or severe depression**
Offer fluoxetine with olanzapine or quetiapine on its own. If the person prefers, consider either olanzapine (without fluoxetine) or lamotrigine on its own. If there is no response to fluoxetine combined with olanzapine, or quetiapine, consider lamotrigine on its own.

- If the person is already taking lithium, check their plasma lithium level. If it is inadequate, increase the dose of lithium; if it is at maximum level, add either fluoxetine combined with olanzapine or add quetiapine, depending on the person's preference and previous response to treatment.

- If the person prefers, consider adding olanzapine (without fluoxetine) or lamotrigine to lithium. If there is no response to adding fluoxetine combined with olanzapine, or adding quetiapine, stop the additional treatment and consider adding lamotrigine to lithium.

- If a person develops moderate or severe bipolar depression and is already taking valproate, 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 is a limited response to valproate add fluoxetine combined with olanzapine or add quetiapine, depending on the person's preference and previous response to treatment. If the person prefers, consider adding olanzapine (without fluoxetine) or lamotrigine to valproate. If there is no response to adding fluoxetine combined with olanzapine, or adding quetiapine, stop the additional treatment and consider adding lamotrigine to valproate.

When planning long-term pharmacological treatment to prevent relapse, take into account medicines that were 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. Lithium should be offered as a first-line long-term pharmacological treatment for BPAD. If lithium is ineffective consider adding valproate. If it is poorly tolerated or not suitable consider valproate or olanzapine or if it was effective during an episode of mania or bipolar depression, quetiapine. Valproate medicines are contraindicated in women or girls of childbearing potential unless a Pregnancy Prevention Programme is in place (PPP). A patient information booklet is available for women of childbearing age on the Medicines Healthcare Regulatory Authority website: https://www.gov.uk/government/publications/toolkit-on-the-risks-of-valproate-medicines-in-female-patients
4.1 When using any psychotropic medicine for bipolar disorder, the person should be given information suitable for their developmental level about the purpose and likely side effects of treatment including any monitoring that is required and he/she should be given the opportunity to ask questions regarding medicines. Patient information leaflets can be obtained from the Choice and Medication link on the intranet. The use of alcohol, prescription and non-prescription medication and illicit drugs should be discussed with the person and their carer if appropriate. The possible interference of these substances with the therapeutic effects of prescribed medication should be explained.

4.2 When offering psychotropic medicines to older people, the impact on cognitive functioning should be taken into account.

4.3 When prescribing medicines for older people, lower doses should be used. The risk of medicine interactions should be considered and the impact of medicines with anticholinergic activity on cognitive function and mobility should be considered. Medical co-morbidities should be recognised and treated.

4.4 The overall medication regimen is regularly reviewed so that the medicines that are not needed after an acute episode are stopped.

4.5 Treatment for bipolar disorder should be initiated by Trust clinicians and can be transferred to primary care when the patient is stable.

5.0 Management of mania, hypomania or mixed affective state

<table>
<thead>
<tr>
<th>Options</th>
<th>Medicine choice</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Management of mania or hypomania or mixed affective state and not taking an antipsychotic or mood stabiliser</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First line</td>
<td>An antipsychotic</td>
<td>Options listed in NICE – haloperidol, olanzapine, quetiapine, risperidone.</td>
</tr>
<tr>
<td>Second line</td>
<td>Another antipsychotic</td>
<td></td>
</tr>
<tr>
<td>Third line</td>
<td>Antipsychotic and lithium</td>
<td></td>
</tr>
<tr>
<td>Fourth line</td>
<td>Antipsychotic and valproate</td>
<td>Consider if lithium is ineffective or not suitable.</td>
</tr>
<tr>
<td>Management of mania or hypomania or mixed affective state and already prescribed lithium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First line</td>
<td>Check lithium levels. If inadequate, maximise levels.</td>
<td></td>
</tr>
<tr>
<td>Second line</td>
<td>Consider adding an antipsychotic to lithium</td>
<td>Options listed in NICE – haloperidol, olanzapine, quetiapine or risperidone depending on any advance directive, the patient’s preference and previous response to treatment, co-morbidity and side effects.</td>
</tr>
<tr>
<td>Management of mania or hypomania or mixed affective state and already prescribed valproate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First line</td>
<td>Maximise dose of valproate (off-label) within BNF limits.</td>
<td>Sodium valproate – off-label. This is the preparation of choice in the trust formulary.</td>
</tr>
<tr>
<td>Second line</td>
<td>Consider adding an antipsychotic to valproate</td>
<td>Options listed in NICE – haloperidol, olanzapine, quetiapine or risperidone depending on any advance directive, the patient’s preference and previous response to treatment, co-morbidity and side effects.</td>
</tr>
</tbody>
</table>
5.1 If a person develops mania or hypomania or mixed affective state and is taking an antidepressant as monotherapy:
- consider stopping the antidepressant and
- offer an antipsychotic (see table1).

5.2 In a patient with mixed affective state characterised by both manic and depressive symptoms, monitor closely for the emergence of depression.

5.3 Lamotrigine should not be offered to treat mania.

5.4 A short-term benzodiazepine (lorazepam up to 4mg per day or clonazepam up to 8mg per day) should be considered.

5.5.1 Reviewing treatment for mania

Within 4 weeks of resolution of symptoms, discuss with the person, and their carers if appropriate, whether to continue treatment for mania or start long-term treatment. The potential benefits of long-term treatment and the risks, including side effects of medication used for long-term treatment should be explained. If the person decides to continue treatment for mania, treatment should be offered for a further 3-6 months, and then reviewed.

6.0 Management of moderate to severe bipolar depression:

<table>
<thead>
<tr>
<th>Options</th>
<th>Medicine choice</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>First line 1a</td>
<td>Fluoxetine and olanzapine (off-label)</td>
<td>These are first line alternative options depending on the person’s preference and previous response to treatment.</td>
</tr>
<tr>
<td>First line 1b</td>
<td>Quetiapine</td>
<td></td>
</tr>
<tr>
<td>First line 1c</td>
<td>Olanzapine (off-label)</td>
<td></td>
</tr>
<tr>
<td>First line 1d</td>
<td>Lamotrigine (off-label)</td>
<td></td>
</tr>
<tr>
<td>Second line</td>
<td>Lamotrigine (off-label)</td>
<td>If treatment failure with (fluoxetine and olanzapine) or quetiapine.</td>
</tr>
</tbody>
</table>

Management of moderate to severe bipolar depression and already prescribed lithium

<table>
<thead>
<tr>
<th>First-line</th>
<th>Check lithium levels. If inadequate, maximise levels.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Second line</td>
<td>If lithium levels are maximum, undertake the addition of one of 1a - 1d above to lithium.</td>
</tr>
<tr>
<td>Third-line</td>
<td>Lamotrigine and lithium</td>
</tr>
</tbody>
</table>

Management of moderate to severe bipolar depression and already prescribed valproate

<table>
<thead>
<tr>
<th>First-line</th>
<th>Consider increasing the dose with the therapeutic range.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Second line</td>
<td>If at the maximum tolerated dose or at the top of the therapeutic range and there is a limited response, undertake the addition of 1a-1d above to valproate.</td>
</tr>
<tr>
<td>Third-line</td>
<td>Lamotrigine and valproate (off-label)</td>
</tr>
</tbody>
</table>
6.1 Toxicity in overdose should be taken into account when prescribing psychotropic medication during periods of high suicide risk. The need to limit the quantity of medication supplied to reduce the risk to life if the person overdoses should be assessed.

6.2 Reviewing treatment for bipolar depression

Within 4 weeks of resolution of symptoms, discuss with the person, and their carers if appropriate, whether to continue pharmacological treatment for bipolar depression or start long-term treatment. The potential benefits of long-term treatment and the risks, including side effects of medication used for long-term treatment should be explained. If the person decides to continue pharmacological treatment for bipolar depression, it should be offered for a further 3–6 months, and then reviewed.

7.0 Long-term pharmacological management of bipolar disorder

<table>
<thead>
<tr>
<th>Table 3: Long-term pharmacological treatment of bipolar disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First line</strong></td>
</tr>
<tr>
<td><strong>Second-line</strong></td>
</tr>
<tr>
<td><strong>Third-line 3a</strong></td>
</tr>
<tr>
<td><strong>Third-line 3b</strong></td>
</tr>
</tbody>
</table>

7.1 When planning long-term pharmacological treatment to prevent relapse, medicines that have been effective during episodes of mania or bipolar depression should be taken into account. 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. The possible benefits and risks of each medicine for them should be discussed with the person. If stopping long-term pharmacological treatment: recognising early signs of relapse and what to do if symptoms recur should be discussed. Treatment should be stopped gradually and the person monitored for signs of relapse. Continue monitoring symptoms, mood and mental state for 2 years after medication has stopped entirely. This may be undertaken in primary care.

8.0 Treatment resistant bipolar disorder

8.1 Clozapine added to usual treatment principally lithium or anticonvulsants was superior to usual treatment alone over one year in treatment resistant bipolar patients including those with rapid cycling and mixed states. It however lacks formal proof of efficacy, but is mentioned in the Maudsley prescribing guidelines. Treatment with clozapine is monitored by the Clozapine Patient Monitoring Service, but is an unlicensed indication. The use of clozapine in the management of bipolar disorder would require a non-formulary approval (refer to the trust formulary policy).
9.0 Guidelines on the use of antipsychotic medicines:

See the Lester UK adaptation in appendix 1 for antipsychotic monitoring requirements.

<table>
<thead>
<tr>
<th>Table 4: Antipsychotic monitoring requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial baseline</strong></td>
</tr>
<tr>
<td>Weight or BMI, pulse, BP, fasting blood glucose, HbA1c, blood lipid profile. Before starting an antipsychotic, an ECG should be offered if:- it is specified in the specification of product characteristics or a physical examination has identified a cardiovascular risk factor, there a family history of cardiovascular disease, cardiovascular collapse or other risk factors such as a cardiac arrhythmia or an inpatient.</td>
</tr>
<tr>
<td><strong>Dose change</strong></td>
</tr>
<tr>
<td>Monitor BP and pulse.</td>
</tr>
<tr>
<td><strong>Ongoing</strong></td>
</tr>
<tr>
<td>Weight and BMI, weekly for six weeks, then at twelve weeks, one year and then annually. ECG – consider annually.</td>
</tr>
<tr>
<td><strong>Ongoing</strong></td>
</tr>
<tr>
<td>Blood glucose, HbA1c and blood lipid profile at twelve weeks, one year and then annually.</td>
</tr>
</tbody>
</table>

Treatment with antipsychotic medication should be considered an explicit individual therapeutic trial. The side effects should be discussed with the person and acceptable side effects should be recorded. The indications, benefits and risks should be recorded. The expected time of onset of benefit and side effects should be recorded¹. At the start of treatment, a dose that is appropriate for the phase and severity of the illness should be prescribed. Dose above the maximum recommended in the BNF or SPC should not be routinely prescribed. If high dose antipsychotic therapy (HDAT) is prescribed, the reasons should be recorded and justified. The person should be informed that HDAT is unlicensed. The rationale for continuing, changing or stopping medication, and the effects of such changes should be recorded¹. The Trust high dose antipsychotic therapy guidelines should be implemented.

9.1 Monitoring antipsychotic medication

The following should be monitored and recorded during dose titration and then regularly and systematically throughout treatment:
- response to treatment, including changes in symptoms and behaviour
- side effects and their impact on physical health and functioning
- the emergence of movement disorders
- adherence¹.

If out-of-range test results are reported at any stage of treatment, the person should be offered further investigations and treatment as needed¹.

9.2 'As required' (p.r.n.) prescriptions of antipsychotic medication

Clinical indications, frequency of administration, therapeutic benefits and side effects should be reviewed each week or more often if needed. ‘As required’ (prn) prescriptions should not unintentionally lead to a total antipsychotic dosage above the maximum specified in the BNF or SPC. Regular combined antipsychotic medication should not be started except for short periods (for example, when changing medication)¹.

9.3 Stopping antipsychotic medicines

When stopping an antipsychotic medicine, the dose should gradually be reduced over at least 4 weeks to minimise the risk of relapse¹.

9.4 Also see Trust antipsychotic prescribing guidelines.

9.5 GPs can be referred to the North Central London (NCL) antipsychotic factsheet:-
10.0 Guidelines on the use of lithium

When starting lithium the person should be advised that poor adherence or rapid discontinuation may increase the risk of relapse¹. A lithium booklet and a leaflet from the ‘Choice and Medication’ website on the trust intranet should be given to the patient.

10.1 Lithium monitoring

<table>
<thead>
<tr>
<th>Table 5: Lithium dosing and monitoring requirements¹</th>
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<td><strong>Initial baseline</strong></td>
</tr>
<tr>
<td><strong>Prescribing</strong></td>
</tr>
<tr>
<td><strong>After lithium initiation</strong></td>
</tr>
<tr>
<td><strong>Maintenance level for patients newly initiated.</strong></td>
</tr>
<tr>
<td><strong>Relapse while taking lithium in the past or taking lithium, but sub-threshold symptoms with functional impairment</strong></td>
</tr>
<tr>
<td><strong>Elderly patients</strong></td>
</tr>
<tr>
<td><strong>Frequency of plasma level monitoring for the first year</strong></td>
</tr>
<tr>
<td><strong>Frequency of plasma level monitoring after the first year</strong></td>
</tr>
<tr>
<td><strong>Frequency of monitoring BMI, Us &amp; Es, Ca, eGFR, TFTs.</strong></td>
</tr>
</tbody>
</table>
term treatment may result in impaired renal function, permanent changes in kidney histology, nephrogenic diabetes, diabetes insipidus and both reversible and irreversible kidney damage\(^2\).

If the patient's renal condition is a potential concern, a lithium dose can be withheld pending the results of the blood tests\(^7\). The following is a mental health resource to prevent, detect and know how to manage patients at risk of, or with, acute kidney injury: [https://www.thinkkidneys.nhs.uk/aki/resources/mental-health/](https://www.thinkkidneys.nhs.uk/aki/resources/mental-health/).

| Hepatic impairment | No dosage reduction required if renal function is normal. Use plasma levels to guide dosage if ascites status alters (volume of distribution will change)\(^2\). |

See the medication tab in the electronic patient records for the lithium monitoring form. The dose is guided by plasma levels.

### 10.2 Lithium toxicity

Toxic effects reliably occur at levels above 1.5mmol/l and usually consist of gastrointestinal effects (increasing anorexia, nausea and diarrhoea) and CNS effects (muscle weakness, drowsiness, ataxia, coarse tremor and muscle twitching). Above 2.0mmol/l, increased disorientation and seizures usually occur which can progress to coma and ultimately death.

In the presence of more severe symptoms, osmotic or forced alkaline diuresis should be used (NEVER thiazide or loop diuretics). Above 3mmol/l, peritoneal or haemodialysis is often used. These plasma levels are only a guide and individuals vary in their susceptibility to symptoms of toxicity. Most risk factors for toxicity involve changes in sodium levels or the way the body handles sodium e.g. low salt diets, dehydration, medicine interactions and some physical illnesses such as Addison's disease\(^2\).

### 10.3 Side effects of lithium

Most side effects are dose related\(^2\). These include mild gastrointestinal upset, fine tremor, polyuria and polydipsia\(^2,8\). Polyuria may occur more frequently with twice daily dosing. Propranolol may be useful for lithium-induced tremor. Some skin conditions such as psoriasis or acne can be aggravated by lithium therapy. Lithium can also cause a metallic taste in the mouth\(^8\), ankle oedema and weight gain\(^2\). Lithium can reduce urinary concentrating capacity – nephrogenic diabetes insipidus leading to the occurrence of thirst or polyuria (which may be reversible in the short-term, but irreversible in the longer –term (15 years). Lithium can also lead to a reduction the glomerular filtration rate. A very small number of people develop interstitial nephritis. Lithium levels of > 0.8mmol/l are associated with higher risk of renal toxicity\(^2\). Lithium toxicity causes acute kidney injury. A minority of patients develop progressive chronic kidney disease. Patients should be informed of these risks. There are specific requirements for regular monitoring of lithium levels, renal function and thyroid function for patients on lithium. Lithium is renally excreted and poor hydration whether due to physical problems (e.g. vomiting or diarrhoea – which can also be signs of lithium toxicity) or mental ill-health (e.g. depressive pyschomotor retardation) can cause a toxic rise in lithium levels that further increases the risk of AKI\(^7\). In the longer-term, lithium increases the risk of hypothyroidism. Hypothyroidism is easily treated with levothyroxine. TFTs usually return to normal when discontinued. Lithium also increases the risks of hyperparathyroidism and some recommend calcium levels should be monitored in the long-term. Clinical consequences of chronically of chronically increased serum calcium include renal stones, osteoporosis, dyspepsia, hypertension and renal impairment\(^2\).
**Lithium patient information**

When starting lithium the person should be advised that poor adherence or rapid discontinuation may increase the risk of relapse. A lithium booklet issued by the National Patient Safety Agency (http://www.nrls.npsa.nhs.uk/EasySiteWeb/getresource.axd?AssetID=65431, http://www.nrls.npsa.nhs.uk/EasySiteWeb/getresource.axd?AssetID=65430) and a leaflet from the ‘Choice and Medication’ link (http://www.choiceandmedication.org/candi/) on the trust intranet/internet should be given to the patient. People taking lithium should be advised to seek medical attention if they develop diarrhoea or vomiting or become acutely ill for any reason ensure they maintain their fluid intake, particularly after sweating (for example, after exercise, in hot climates or if they have a fever), if they are immobile for long periods or if they develop a chest infection or pneumonia talk to their doctor as soon as possible if they become pregnant or are planning a pregnancy. Warn people taking lithium not to take over-the-counter non-steroidal anti-inflammatory medicines and avoid prescribing these medicines for people with bipolar disorder if possible; if they are prescribed, this should be on a regular (not p.r.n.) basis and the person should be monitored monthly until a stable lithium level is reached and then every 3 months. Information relating to the symptoms of toxicity and common risk factors should always be given to patients when treatment with lithium is initiated. This information should be repeated at appropriate intervals to make sure it is clearly understood².

### 10.4 Continuation of lithium

When discussing whether to continue lithium, the clinical efficacy, other risk factors for renal impairment and cardiovascular disease, and degree of renal impairment should be discussed. If needed seek advice from a renal specialist and a clinician with expertise in managing bipolar disorder. The person should be monitored at every appointment for symptoms of neurotoxicity, including paraesthesia, ataxia, tremor and cognitive impairment, which can occur at therapeutic levels of lithium¹. The discussion with the patients should include:

- risk of relapse after reducing or stopping medication for an acute episode.
- potential benefits and risks of long-term medication, and the need to monitor mood and medication.
- potential benefits and risks of stopping medication, including for women who may wish to become pregnant.
- person's history of bipolar disorder, including: previous response to treatment, possible duration of treatment, and when and how often this should be reviewed¹

### 10.5 GPs can be referred to the NCL lithium factsheet:


### 10.6 Stopping lithium

If stopping lithium, the dose should be reduced gradually over at least 4 weeks, and preferably up to 3 months, even if the person has started taking another mood stabiliser¹. Avoid incremental reductions in plasma levels of > 0.2mmol/l². During the dose reduction and for 3 months after lithium treatment is stopped, the person should be monitored closely for early signs of mania and depression¹. Intermittent treatment of lithium may worsen the natural outcome of bipolar illness. A much greater than expected incidence of manic relapse is seen in the first few months after discontinuing lithium, even if in patients who are symptom free for as long as five years.
11.0 Guidelines on the use of valproate

11.1 Starting valproate

Table 6: Valproate monitoring requirements

<table>
<thead>
<tr>
<th>Initial baseline</th>
<th>Weight/BMI, LFTs and FBC. Be aware of its interaction with lamotrigine.</th>
</tr>
</thead>
</table>
| Dosage instructions (as per standard dose in the SPCs) | Enteric coated or slow release preparations: Dosage should start at 600mg daily increasing by 200mg at three-day intervals until control is achieved. This is generally within the dosage range 1000mg to 2000mg per day, ie 20-30mg/kg/day body weight. Where adequate control is not achieved within this range the dose may be further increased to 2500mg per day.
| Plasma levels                        | Do not routinely measure plasma valproate levels unless there is evidence of ineffectiveness, poor adherence or toxicity.
| Frequency of monitoring              | Measure the person’s weight or BMI and carry out liver function tests and a full blood count again after 6 months of treatment with valproate and then annually.
| Older people                         | Monitor sedation, tremor and gait disturbance.
| Women of child-bearing potential     | Children exposed in utero to valproate are at high risk of serious developmental disorders (in up to 30-40% of cases) and/or congenital malformations (in approximately 10% of cases). Valproate should not be prescribed to women of child-bearing potential or pregnant women, unless other treatments are ineffective or not tolerated. Valproate must be started and supervised by a doctor experienced in managing bipolar disorder. The benefits versus the risks of valproate treatment should be considered when prescribed for the first time, at routine treatment reviews and when a woman plans a pregnancy or becomes pregnant. All female patients must be informed of and understand:
   1. Risks associated with valproate during pregnancy
   2. The need for effective contraception
   3. The need for regular review of treatment
   4. The need to rapidly consult if a pregnancy is planned or the woman becomes pregnant.

Valproate medicines are contraindicated in women or girls of childbearing potential unless a Pregnancy Prevention Programme is in place (PPP). The guide for healthcare professionals:

The trust requirements are listed below.

See appendix 4 (Pregnancy testing and patients who refuse information).

Women of child-bearing age prescribed valproate

If a woman of child-bearing age is currently prescribed valproate, a review with their respective mental health team should be arranged as soon as possible to fulfill the requirements of the Pregnancy Prevention Programme.

The potential risks of treatment and of untreated disease for the unborn child must be explained to the patient and carer. The patient must be informed of the need to use contraception (see below) and receive a patient guide. The patient should be advised to contact the prescriber immediately if she thinks she might be pregnant or is pregnant.

For patients who are assessed to lack capacity to consent to treatment:
- Valproate should only be initiated on a Psychiatric Intensive Care Unit (PICU).
- If a patient of PICU, refer to the guidance for this service (appendices 6
Women not taking effective contraception
If a woman reports she is not taking effective contraception, they should be advised to contact their GP and the prescriber for an urgent follow-up.

Woman of childbearing age who is planning pregnancy
The patient must be advised to contact the prescriber immediately if she is planning a pregnancy, thinks she might be pregnant or is pregnant. Valproate must be urgently reviewed and stopped. The potential risks of the disease on the unborn child should be explained independent from valproate’s own risks.

Woman with unplanned pregnancy
1. Urgent medical advice can be provided from a variety of sources depending on the woman’s current mental state and community support e.g:

- The North London Partners Specialist Perinatal Mental Health Team, which can be contacted during office hours by phone (020 3317 7114) or generic email (cim-tr.ncl.perinatal@nhs.net) with an expected response within the same working day
- Community mental health team
- Inpatient team
- GP
- Out of hours advice can be provided by the crisis team or following attendance at A&E/maternity triage.

2. Subsequent arrangements should then be made in arranging an urgent face-to-face medical review to discuss the associated risks of valproate exposure, to review mental state, to oversee discontinuation of valproate and to consider the need for alternative mood stabilising medication i.e. antipsychotics even before a suspected pregnancy is confirmed whilst bearing in mind the need to balance the preferential need for immediate cessation of valproate exposure to the foetus against the risk of relapse. Ideally, the consultation should be with the perinatal mental health team (but this is an outpatient service only and immediate clinical consultations can never be guaranteed).

   The patient should understand the risks of valproate and counselling considered. The patient should receive the patient guide.

3. Patients should be asked to continue with the valproate until the medical review.

4. Women and their clinicians may want to withdraw valproate as soon as possible. There is limited evidence to guide the duration of withdrawal, but a withdrawal period of at least 4 weeks is suggested. There is some relationship between valproate dosage and risk of its harmful effects, so risks for the foetus are declining during these 4 weeks. Should a woman experience a relapse in pregnancy and develop a manic episode, treatment with antimanic medicines (haloperidol, olanzapine or quetiapine) could be started, augmented by benzodiazepines if
necessary. If these treatments prove to be insufficient, electroconvulsive therapy could be considered.

5. Folic acid 5mg daily should be added.

6. Every woman should be referred to the perinatal team unless she does not wish so. The perinatal team then works with the community teams in the treatment plan. An urgent referral must be requested if the patient is psychiatically unwell. The perinatal service accept referrals up to six months after delivery in the event a woman who delivered and has been prescribed valproate which in fact was not detected while pregnant. The referral to the perinatal team must not delay stopping valproate and providing the patient with information to avoid a delay of necessary actions in a critical time period.

7. If there is a need for another mood stabiliser/antipsychotic, the perinatal consultant can be contacted via the NCL e-mail. Careful consideration and discussion of the relative risks of malformations and other intra-uterine and post-partum complications is needed before alternative medicines are introduced. The team would also undertake close monitoring of the mental state, further antenatal care planning, and formulate a relapse prevention plan.

8. In the longer term, the perinatal team should take on the patient for monitoring during pregnancy and the postnatal period (with or without additional support from multidisciplinary teams).

9. The woman should be referred to Foetal Medicine at the Maternity Hospital (by the hospital midwife) who provide scanning and counselling for women with a valproate-exposed pregnancy.

10. A datix should be completed and submitted. A Yellow card should also be completed and submitted (https://yellowcard.mhra.gov.uk/).


Trust requirements:-
1. Confirm if woman is of child bearing potential (e.g. pre-menopause).

2. Capacity of patient to consent to treatment with valproate assessed and documented.


4. Patient and specialist have signed the risk acknowledgement form (Valid
for 1 year) – Record kept on Carenotes, shared with GP, patient, carer -
https://www.gov.uk/drug-safety-update/valproate-medicines-and-serious-
harms-in-pregnancy-new-annual-risk-acknowledgement-form-and-
clinical-guidance-from-professional-bodies-to-support-compliance-with-
the-pregnancy-prevention-programme

5. Exclude pregnancy (pregnancy test) or intention to be become pregnant. Perform a serum pregnancy test at least 14 days after the last possible date on which the patient had or could have had unprotected sex.

6. Arrange for a highly effective method of contraception.

7. All women of childbearing potential who are prescribed sodium valproate should also be prescribed folic acid 5mg daily.

8. Arrangement in place for patient to be reviewed by specialist at least once a year.

9. Non-formulary form approval before prescribing. If valproate is already prescribed, a non-formulary form must be completed once the Trust requirements are undertaken.

Methods of contraception considered ‘highly effective’ in this context include the long-acting reversible contraceptives (LARC):

10. Copper intrauterine device (Cu-IUD)
11. Levonorgestrel intrauterine system (LNG-IUS)
12. Progestogen-only implant (IMP)
13. Male & female sterilisation

All of which have a failure rate of less that 1% with typical use (see guidance from FSRH for more about user-independent methods and failure rates). If a user-independent form is not used, two complementary forms of contraception including a barrier method should be used and regular pregnancy tests considered.


Hepatic impairment

Moderate hepatic impairment: dosage reduction with close monitoring of LFTs and plasma levels (if possible unbound valproate). Caution advised.

Severe and/or active hepatic impairment: contraindicated. Impairment of usual metabolic pathway can lead to generation of hepatotoxic metabolites via an alternative pathway. Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in patients. Mitochondrial disease, learning disability, polypharmacy, metabolic disorders and underlying hepatic disease may be risk factors. The greatest risk is in the first three months.

Renal impairment

May require a dose reduction. Dosage should be adjusted according to clinical monitoring (monitoring of plasma concentrations may be misleading). In renal impairment, free valproate levels may be increased. If GFR < 10mls/min, it may be necessary to alter doses according to free (unbound) valproate levels. Renal impairment, interstitial nephritis, Fanconi syndrome, renal tubular acidosis and renal failure have been reported.

Medicines interactions

When prescribing valproate, there may be interactions with other anticonvulsants
11.2 Side Effects of valproate

Valproate can cause gastric irritation and hyperammonaemia leading to nausea. Lethargy and confusion can occasionally occur with starting doses of above 750mg per day. Weight gain can be significant. Valproate causes dose-related tremor in up to a quarter of patients. In the majority of cases, intention/postural tremor occurs. A very small proportion develop parkinsonism associated with cognitive decline (reversible on discontinuation). Hair loss with curly regrowth and peripheral oedema can occur as can thrombocytopenia, leucopenia, red cell hypoplasia and pancreatitis. Valproate may cause hyperandrogenism in women and may be linked with the development of polycystic ovaries. It may rarely cause fulminant hepatic failure. Any patient with raised values in liver function tests (common in early treatment) should be evaluated clinically and other markers of hepatic function such as albumin and clotting time should be checked. Valproate and other anticonvulsant medicines may be associated with increased risk of suicidal behaviour. Patients with depression or who take another anticonvulsant medicine that increases the risk of developing depression may be a subgroup at greater risk. Many side effects of valproate are dose related and increase when the plasma level is >100mg/l. The slow release form of sodium valproate does not produce peak plasma levels as high as the conventional formulation, so may be better tolerated.

Valproate patient information:
A valproate leaflet from the ‘Choice and Medication’ link (http://www.choiceandmedication.org/candi/) on the trust intranet should be given to the patient. Advise people taking valproate, and their carers, how to recognise the signs and symptoms of blood and liver disorders and to seek immediate medical help if any of these develop. Stop valproate immediately if abnormal liver function or blood dyscrasia is detected. Symptoms are usually malaise, anorexia, lethargy, oedema and drowsiness, which are sometimes associated with repeated vomiting and abdominal pain. Patients and carers should also be advised told how to recognise signs and symptoms of pancreatitis and advised to seek immediate medical attention if symptoms such as abdominal pain, nausea or vomiting develop; discontinue if pancreatitis is diagnosed.

A patient information booklet is available for women of child-bearing age on the Medicines Healthcare Regulatory Authority website:

11.3 Stopping valproate
If stopping valproate, the dose should be reduced gradually over at least 4 weeks to minimise the risk of relapse.

12.0 Guidelines on the use of lamotrigine
12.1 Starting lamotrigine

<table>
<thead>
<tr>
<th>Table 7: Lamotrigine dosage and monitoring requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial baseline</strong></td>
</tr>
<tr>
<td><strong>Initiation dosage instructions to avoid the onset of a</strong></td>
</tr>
</tbody>
</table>

(particularly carbamazepine and lamotrigine) and with olanzapine and smoking.
<table>
<thead>
<tr>
<th>Rash.</th>
<th><strong>Lamotrigine and an enzyme inducer:</strong> 50mg per day for 1/52, 100mg per day for 1/52, 200mg per day for one week, then 300mg per day. In week 7, it can be increased to 400mg per day in divided doses if necessary.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Withdrawal of valproate</td>
<td>Double the stabilisation dose, not exceeding an increase of more than 100mg/week::- 100mg per day – increase to 200mg per day and maintain at the dose. 200mg per day – increase to 300mg per day for 1/52 then 400mg per day thereafter.</td>
</tr>
<tr>
<td>Withdrawal of inducers*</td>
<td>400mg per day – maintain at 400mg per day for one 1/52, then 300mg per day for one 1/52 then 200mg per day. 300mg per day - maintain at 300mg per day for 1/52, then 225mg per day for 1/52 then 150mg per day. 200mg per day - maintain at 200mg per day for 1/52, then 150mg per day for 1/52 then 100mg per day.</td>
</tr>
<tr>
<td>Addition of valproate</td>
<td>200mg per day – reduce to 100mg per day in the first week. 300mg per day – reduce to 150mg per day in the first week. 400mg per day – reduce to 200mg per day in the first week.</td>
</tr>
<tr>
<td>Addition of an inducer*</td>
<td>200mg per day – maintain at 200mg per day in the first week, then 300mg per day in the second week then 400mg per day from the third week onwards. 150mg per day – maintain at 150mg per day in the first week, then 225mg per day in the second week then 300mg per day from the third week onwards. 100mg per day – maintain at 100mg per day in the first week, the 150mg per day in the second week then 200mg per day from the third week onwards.</td>
</tr>
<tr>
<td>Medicines - unknown effect</td>
<td>The treatment regimen for lamotrigine with concurrent valproate is recommended.</td>
</tr>
<tr>
<td>Break in treatment</td>
<td>Dose titration should be repeated if restarting after an interval or more than five days.</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>For patients with end-stage renal failure, initial doses of lamotrigine should be based on patients' concomitant medicines. Reduced maintenance doses may be effective for patients with significant renal functional impairment. GFR &lt;10-50mls/min: use cautiously, start with a low dose, increase slowly and monitor closely. GFR&lt;10mls/min: use 100mg every other day.</td>
</tr>
<tr>
<td>Hepatic impairment</td>
<td>Initial, escalation and maintenance doses should generally be reduced by approximately 50% in patients with moderate (Child-Pugh grade B) and 75% in severe (Child-Pugh grade C) hepatic impairment. Escalation and maintenance doses should be adjusted according to clinical response. Discontinue if lamotrigine-induced rash (which can be serious). Extreme caution advised, particularly if co-prescribed with valproate. Elevated LFTs and hepatitis reported.</td>
</tr>
<tr>
<td>Plasma levels</td>
<td>Do not routinely measure plasma lamotrigine levels unless there is evidence of ineffectiveness, poor adherence or toxicity.</td>
</tr>
<tr>
<td>Women of child-bearing potential</td>
<td>Women should be advised to contact their doctor if they are pregnant or planning a pregnancy. There is growing evidence that lamotrigine is safer in pregnancy than carbamazepine or valproate across a range of outcomes, but should not routinely prescribed in pregnancy.</td>
</tr>
</tbody>
</table>

*Enzyme inducers are phenytoin, carbamazepine, phenobarbitone, primodone, rifampicin and lopinavir/ritonavir. There is some evidence of switching if lamotrigine is prescribed.

### 12.2 Side effects of lamotrigine

These include nausea, vomiting, diarrhoea, dry mouth, aggression, agitation, headache, drowsiness, dizziness, tremor and insomnia and blood disorders (including anaemia, leucopenia, thrombocytopenia and pancytopenia), hypersensitivity syndrome, lupus erythematosus reactions and reported suicidal ideation.

Serious skin reactions including Stevens Johnson syndrome and toxic epidermal necrolysis have developed. Most rashes occur in the first eight weeks. Rash is sometimes associated with hypersensitivity syndrome and is common in patients with a history of allergy or rash.
from other anti-epileptic medicines. Consider withdrawal if rash or signs of hypersensitivity syndrome develop. Factors associated with an increased risk of serious skin reactions include concomitant use of valproate, initial lamotrigine dosing higher than recommended and more rapid dose escalation than recommended$^{13}$.

<table>
<thead>
<tr>
<th>Lamotrigine patient information$^1$:</th>
</tr>
</thead>
<tbody>
<tr>
<td>A lamotrigine leaflet from the ‘Choice and Medication’ link (<a href="http://www.choiceandmedication.org/candi">http://www.choiceandmedication.org/candi</a>) on the trust intranet should be given to the patient.</td>
</tr>
</tbody>
</table>

Patients and carers should be alert for signs and symptoms suggestive of bone marrow failure such as anaemia, bruising or infection. Aplastic anaemia, bone-marrow depression and pancytopenia have been associated rarely with lamotrigine$^{13}$. Advise people taking lamotrigine to: contact their doctor immediately if they develop a rash while the dose of lamotrigine is being increased$^7$. Patient should be warned to see their doctor immediately if rash or signs and symptoms of hypersensitivity syndrome develop$^{13}$.  

### 12.3 Stopping lamotrigine

If stopping lamotrigine, the dose should be reduced gradually over at least 4 weeks to minimise the risk of relapse$^1$.

### 13.0 Guidelines on the use of carbamazepine.

Carbamazepine is not included in the current NICE guidance for the management of bipolar disorder$^1$. It is licensed for the prophylaxis of manic-depressive psychosis in patients unresponsive to lithium therapy$^{16}$ and therefore should only be considered if patients are unresponsive to mood stabilisers recommended in the NICE guidance as prophylactic treatment (on a non-formulary basis) or if patients are already prescribed it with good effect.

<table>
<thead>
<tr>
<th>Table 8: Carbamazepine monitoring requirements$^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial baseline</strong></td>
</tr>
<tr>
<td>Us &amp; Es, LFTs and full blood count, baseline weight desirable$^2$.</td>
</tr>
<tr>
<td><strong>Dosage instructions</strong></td>
</tr>
<tr>
<td>Start with 100-200mg twice a day and aim for 400mg twice a day (some patients will require higher doses). The modified release formulation can be given once or twice a day and is associated with less severe fluctuations in serum levels and generally better tolerated$^2$.</td>
</tr>
<tr>
<td><strong>Plasma levels</strong></td>
</tr>
<tr>
<td>Plasma levels can be used to ensure adequate dosing and treatment adherence. Blood samples should be taken immediately before the next dose. Carbamazepine induces its own metabolism. Serum levels if used should be rechecked a month after an increase in dose$^2$.</td>
</tr>
<tr>
<td><strong>Frequency of monitoring</strong></td>
</tr>
<tr>
<td>As a minimum, Us &amp; Es, FBC and LFTs after six months. Weight or BMI$^2$.</td>
</tr>
<tr>
<td><strong>Women of child-bearing potential</strong></td>
</tr>
</tbody>
</table>
| Do not offer carbamazepine to treat a mental health problem in women who are planning a pregnancy, pregnant or considering breastfeeding$^{17}$. If deemed essential, the dose is best limited to 1000mg per day$^2$. Ideally all patients should take folic acid (5mg per day) for at least one month before conception (this may reduce the risk of neonatal neural tube defects). Some authorities recommend a lower dose (possibly because of the risk of twin births$^2$. Note that there is no evidence that folate protects against anticonvulsant-induced neural tube defects if given during pregnancy. It may do so if given prior to conception (the neural tube is essentially formed by the eighth week of pregnancy before many women realise they are pregnant). However folate supplementation may be beneficial with regards to early neurodevelopment and so should always be offered$^2$. The use of carbamazepine in the third trimester may necessitate
maternal vitamin K. Prophylactic vitamin K should be administered to the mother and neonate after delivery\(^2\). Also see pregnancy and breastfeeding section.

| Hepatic impairment | Extensively hepatically metabolised and potent inducer of CYP450 enzymes. Contraindicated in severe and/or acute liver disease. In chronic stable disease, caution is advised. Reduce the starting dose by 50% and titrate slowly using plasma levels to guide dosage. Stop if the LFTs deteriorate. Adverse hepatic effects are most common in the first month of treatment\(^2\). |
| Renal impairment | Dose reduction is not necessary in renal disease, although cases of renal failure, tubular necrosis and tubulointerstitial nephritis have been reported rarely and metabolites may accumulate. Carbamazepine can cause Stevens-Johnson syndrome and toxic epidermal necrolysis which may result in acute renal failure\(^2\). |

### 13.1 Side effects of carbamazepine

The main side-effects associated with carbamazepine are dizziness, diplopia, drowsiness, ataxia, nausea and headaches. These can sometimes be avoided by starting with a low dose and increasing slowly. Avoiding high peak blood levels by splitting the dose throughout the day or using the controlled-release formulation may also help. Dry mouth, oedema and hyponatraemia are also common. Sexual dysfunction can occur. 3% of patients treated with carbamazepine develop a generalised erythematous rash. Serious exfoliative dermatological reactions occur rarely and are genetically determined (particularly in people of Han Chinese or Thai origin)\(^2\).

Carbamazepine can commonly cause a chronic low white blood cell count. One patient in 20, 000 develops agranulocytosis and/or aplastic anaemia. Raised alkaline phosphatase and gamma-glutamyl transferase (GGT) are common. A GGT of 2-3 times normal is rarely a cause for concern. A delayed multi-organ hypersensitivity reaction occurs rarely, mainly manifesting itself as various skin reactions, a low white blood cell count and abnormal LFTs. Fatalities have been reported\(^6\).

Carbamazepine patient information:-

A carbamazepine leaflet from the ‘Choice and Medication’ link (http://www.choiceandmedication.org/candi/) on the trust intranet should be given to the patient. Advise people taking carbamazepine, and their carers, how to recognise the signs and symptoms of blood, liver or skin disorders and to seek immediate medical help if any of these develop such as fever, rash, mouth ulcers, bruising or bleeding develop. Stop carbamazepine immediately in cases of aggravated liver dysfunction or acute liver disease. Leucopenia that is severe, progressive or associated with clinical symptoms requires withdrawal (if necessary under cover of a suitable alternative)\(^13\).

### 14.0 Antiepileptic hypersensitivity syndrome

Anti-epileptic hypersensitivity syndrome is a rare but potentially fatal syndrome associated with some anti-epileptic medicines (including carbamazepine and lamotrigine; also see BNF). Rarely cross-sensitivity occurs between some of these antiepileptic medicines. The symptoms usually start between 1-8 weeks of exposure, fever, rash and lymphadenopathy are most commonly seen. Other systemic signs include liver dysfunction, haematological, renal and pulmonary abnormalities, vasculitis and multi-organ failure. If signs or symptoms of hypersensitivity syndrome occur, the medicines should be withdrawn immediately, the patient must not be re-exposed and expert advice should be sought\(^13\).
15.0 Monitoring physical health

15.1 An annual physical health check should be carried out to include the following:

- weight or BMI, diet, nutritional status and level of physical activity
- cardiovascular status, including pulse and blood pressure
- metabolic status, including fasting blood glucose, glycosylated haemoglobin (HbA1c)
- and blood lipid profile
- liver function
- renal and thyroid function, and calcium levels, for people taking long-term lithium.

15.2 People with bipolar disorder especially those taking antipsychotics and long-term medication who have hypertension, have abnormal lipid levels, are obese or at risk of obesity, experienced rapid or excessive weight gain, have diabetes or are at risk of diabetes (as indicated by abnormal blood glucose levels), or are physically inactive should be identified at the earliest opportunity. The NICE guidelines for these conditions should be followed. Patients should be offered a combined healthy eating and physical activity programme.

15.3 Routinely monitor weight and cardiovascular and metabolic indicators of morbidity in people with bipolar disorder.

16.0 Cardiovascular disease

Many psychotropic medicines are associated with ECG changes and some are casually linked to serious ventricular arrhythmia and sudden cardiac death. Specifically some antipsychotics block cardiac potassium channels and are linked to prolongation of the cardiac QT interval, a risk factor for the ventricular arrhythmia torsade de pointes, which is often fatal. ECG monitoring is essential for all patients prescribed antipsychotics. An estimate of the QTc interval should be made on admission to inpatient units and considered annually thereafter. Overall risk is probably dose-related. Medicine interactions are important, especially when metabolic inhibition results in increased plasma levels of the medicine affecting QTc. Commonly used metabolic inhibitors include fluvoxamine, fluoxetine, paroxetine and valproate. Guidance on risk factors and the effect of antipsychotics on the QT interval is outlined in the Maudsley prescribing guidelines. Also refer to the specifications of product characteristics for further information and contact the pharmacy department if further advice is required.

<table>
<thead>
<tr>
<th>QTc</th>
<th>Action</th>
<th>Refer to cardiologist</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;440msec (men) or &lt;470msec (women)</td>
<td>None unless abnormal T-wave morphology</td>
<td>Consider if in doubt</td>
</tr>
<tr>
<td>&gt;440msec (men) or &gt;470msec (women), but &lt;500msec</td>
<td>Consider reducing dose or switching to a medicine of lower effect; repeat ECG</td>
<td>Consider</td>
</tr>
<tr>
<td>&gt;500msec</td>
<td>Repeat ECG. Stop suspected causative medicine(s) and switch to a medicine of lower effect</td>
<td>Immediately</td>
</tr>
<tr>
<td>Abnormal T-wave morphology</td>
<td>Review treatment. Consider reducing dose or switching to a medicine of lower effect.</td>
<td>Immediately</td>
</tr>
</tbody>
</table>
Depression confers an increased risk of cardiovascular disease and sudden death, perhaps because of platelet activation, decreased heart rate variability, reduced physical activity, an association with an increased risk of diabetes and/or factors\(^2\). Refer to the specifications of product characteristics for antidepressants and mood stabilisers for further information and contact the pharmacy department if further advice is required.

### 17.0 Co-morbid diabetes

Olanzapine and clozapine has a high risk of causing impaired glucose tolerance and diabetes, quetiapine, risperidone and phenothiazines a moderate risk, and haloperidol low risk. Antipsychotics with minimal effects are aripiprazole, amisulpride, asenapine (non-formulary) and lurasidone\(^2\).

### 18.0 Weight gain

Olanzapine has the greater propensity to cause weight gain and to a more significant extent. Quetiapine and risperidone have a moderate risk of causing weight gain and to a more moderate extent\(^2\). Aripiprazole or lurasidone may reverse weight gain. Haloperidol has a low risk of causing weight gain and to a low extent. In relation to valproate, weight gain can be significant. Lithium can also cause weight gain\(^2\).

### 19.0 Dyslipidaemia

19.1 Olanzapine, clozapine appears to have the greatest propensity to increase lipids, quetiapine and risperidone moderate propensity\(^2\). Aripiprazole may be treatment of choice for antipsychotic induced dyslipidaemia\(^2\).

### 20.0 Extrapyramidal side effects

20.1 Haloperidol appears to have the greatest propensity to cause extrapyramidal side effects, risperidone a mild propensity, olanzapine mild to no propensity and quetiapine, none and aripiprazole. Clozapine is an alternative\(^2\).

### 21.0 Hyperprolactinaemia

21.1 Risperidone appears to have the greatest propensity to cause hyperprolactinaemia, haloperidol, moderate propensity, olanzapine, mild propensity and quetiapine, aripiprazole, asenapine (non-formulary) and clozapine none\(^2\).

### 22.0 Pregnancy and breastfeeding

Any woman with a diagnosis of bipolar affective disorder who is planning a pregnancy should be referred for preconception counselling from the Perinatal Mental Health Services

22.1 Principles of prescribing and breastfeeding include choosing a medication with the best safety profile, using the minimum effective dose and avoidance of polypharmacy.

22.2 An antipsychotic should be offered as prophylactic medication if a woman with bipolar disorder becomes pregnant and is stopping lithium, or plans to breastfeed\(^15\).
22.3 When assessing the risks and benefits of antipsychotic medication for a pregnant woman, the risk of gestational diabetes and excessive weight gain and the limited data of safety for antipsychotics in pregnancy and postnatal period should be taken into account. Pregnant women taking antipsychotic medication should be advised about diet and weight gain should be monitored, in line with the guideline on weight management before, during and after pregnancy. Monitor for gestational diabetes in pregnant women taking antipsychotic medication in line with the guideline on diabetes in pregnancy and offer an oral glucose tolerance test. Prolactin levels should be monitored in women who are taking prolactin-raising antipsychotic medication and planning a pregnancy, because raised prolactin levels reduce the chances of conception. A prolactin-sparing antipsychotic should be considered if prolactin levels are raised.17

22.4 If a pregnant woman is stable on an antipsychotic and likely to relapse without medication, she should be advised to continue the antipsychotic. Depot antipsychotics should not be offered to a woman who is planning a pregnancy, pregnant or considering breastfeeding, unless she is responding well to a depot and has a previous history of non-adherence with oral medication.17

22.5 Both carbamazepine and valproate have a clear causal link with an increased variety of foetal abnormalities, particularly spina bifida. Both medicines should be avoided if possible and an antipsychotic prescribed instead. Valproate confers a higher risk than carbamazepine.2

22.6 Sodium valproate is an established teratogen. Valproate should not be offered for acute or long-term treatment of a mental health problem in women who are planning a pregnancy, pregnant or considering breastfeeding because of the risk of foetal malformations and adverse neurodevelopment outcomes after any exposure in pregnancy. If a woman is already prescribed valproate, the patient must be advised to contact the prescriber immediately if she is planning a pregnancy, thinks she might be pregnant or is pregnant. Valproate must be urgently reviewed and stopped. The potential risks of the disease on the unborn child should be explained independent from valproate’s own risks.12 Also see section 11.

22.7 Valproate medicines must not be used in women or girls of childbearing potential unless a Pregnancy Prevention Programme (PPP) is in place.21

<table>
<thead>
<tr>
<th>Highly effective methods of contraception:</th>
</tr>
</thead>
<tbody>
<tr>
<td>The long-acting reversible contraceptives:</td>
</tr>
<tr>
<td>• Copper intrauterine device</td>
</tr>
<tr>
<td>• Levonorgestrel intrauterine system</td>
</tr>
<tr>
<td>• Progestogen only implant</td>
</tr>
<tr>
<td>• Male and female sterilisation</td>
</tr>
<tr>
<td>User dependent: two complementary forms of contraception including a barrier method and regular pregnancy testing</td>
</tr>
</tbody>
</table>

22.8 Carbamazepine is an established teratogen. Carbamazepine should not be offered to treat a mental health problem in women who are planning a pregnancy, pregnant or considering breastfeeding. If a woman is already taking carbamazepine and is planning a pregnancy or becomes pregnant, the possibility of stopping the medicine (because of the risk of adverse medicine interactions and foetal malformations) should be discussed. If a woman is already taking carbamazepine and is planning a pregnancy or becomes pregnant, the possibility of stopping the medicine (because of
the risk of adverse medicine interactions and foetal malformations) should be discussed with the woman\(^\text{17}\).

22.9 If carbamazepine cannot be avoided, adequate contraception should be ensured and prophylactic folate prescribed. Preparations containing not less than 50 micrograms oestrogen or a non-hormonal method should be used\(^2\).

22.10 Lamotrigine should not routinely prescribed in pregnancy. There is growing evidence that lamotrigine is safer in pregnancy than carbamazepine or valproate across a range of outcomes\(^2\). If a woman is taking lamotrigine during pregnancy, lamotrigine levels should be checked frequently during pregnancy and into the postnatal period because they vary substantially at these times\(^1\). Clearance increases radically during pregnancy and then reduces post-partum\(^2\).

22.12 Lithium should not be offered to women who are planning a pregnancy or pregnant, unless antipsychotic medication has not been effective. If antipsychotic medication has not been effective and lithium is offered to a woman who is planning a pregnancy or pregnant, the woman should be advised:

- that there is a risk of foetal heart malformations (Ebstein’s anomaly, atrial and ventricular septal defects\(^5\)) when lithium is taken in the first trimester, but the size of the risk is uncertain\(^1\).
- Women of child-bearing age should be advised to use a reliable form of contraception\(^2\).
- The woman knows that lithium levels may be high in breast milk with a risk of toxicity for the baby. Lithium levels should be monitored more frequently throughout pregnancy and the postnatal period\(^1\).

22.13 The period of maximum risk to the foetus is 2-6 weeks after conception before many women know they are pregnant\(^6\).

22.14 If a woman taking lithium becomes pregnant, consider stopping the medicine gradually over 4 weeks if she is well. It should be explained that stopping medication may not remove the risk of foetal heart malformations, that there is a risk of relapse, particularly in the postnatal period, if she has bipolar disorder\(^1\).

22.15 If a woman taking lithium becomes pregnant and is not well or is at high risk of relapse, consider:

- switching gradually to an antipsychotic or
- stopping lithium and restarting it in the second trimester (if the woman is not planning to breastfeed and her symptoms have responded better to lithium than to other medicines in the past) or
- continuing with lithium if she is at high risk of relapse and an antipsychotic is unlikely to be effective\(^1\).

22.16 If a woman continues taking lithium during pregnancy:

- inform the obstetrician of any first trimester exposure and request particular attention towards foetal screening for cardiovascular anomalies\(^2\).
- an increasing dose of lithium is required to maintain the lithium level during pregnancy as total body water increases, but requirements return to pre-pregnancy levels immediately after delivery\(^2\).
- high resolution ultrasound and echocardiography should be performed at 6 and 18 weeks of gestation to screen for Ebstein’s anomaly\(^2\).
• Lithium levels should be monitored every three weeks until 34 weeks of pregnancy and then at least weekly until delivery.²³
• Before 17 weeks of pregnancy, lithium levels are likely to progressively decrease. Levels will start increasing afterwards²³.
• Lithium levels should be maintained within therapeutic levels which are as low as possible. Appropriate levels can be obtained from the patient history. If possible obtain preconception lithium levels, creatinine levels and corresponding lithium doses²³.
• Twice a day dosing of lithium should be considered to minimise peak levels.
• Consider monitoring creatinine levels. Decreasing levels in the first and second trimester suggests pregnancy related increase in renal function²³.
• If the woman exhibits preterm birth, pre-aclampsia, dehydration and other illnesses affecting renal function, the monitoring of lithium and creatinine levels should be increased²³.
• ensure the woman maintains an adequate fluid balance.¹⁷
• ensure the woman gives birth in hospital.¹⁷
• ensure monitoring by the obstetric team when labour starts, including checking plasma lithium levels and fluid balance because of the risk of dehydration and lithium toxicity.¹⁷
• stop lithium during labour and check plasma lithium levels 12 hours after her last dose or.¹⁷
• suspend lithium 24 -48 hours before a planned Caesarean section or induction. The lithium level should be measured 12 hours after the last dose.²²
• If the levels are not above the therapeutic range, restart lithium on day 1 postnatal and check the lithium level after 1 week.²² Consider lithium levels twice a week during the first two postpartum weeks.
• Stopping medication other than lithium before delivery is not known to have any benefits for the neonate, but may place the mother at greatly increased risk of bipolar relapse.²²

22.17 Neonatal goitre, hypotonia, lethargy and cardiac arrhythmia can occur in association with lithium.²²

22.18 Combinations of mood stabilisers should be avoided.⁶

22.19 When considering fluoxetine take into account:
• the woman’s previous response to SSRIs.
• the stage of pregnancy.
• what is known about the reproductive safety of SSRIs (for example, the risk of foetal cardiac abnormalities and persistent pulmonary hypertension in the new born baby).
• the uncertainty about whether any increased risk to the foetus and other problems for the woman or baby can be attributed directly to these medicines or may be caused by other factors.
• the risk of discontinuation symptoms in the woman and neonatal adaptation syndrome in the baby.¹⁷

22.20 In bipolar depression during pregnancy, CBT should be considered for moderate depression and an SSRI for more severe depression. Olanzapine plus fluoxetine may also be used.

22.21 In acute mania in pregnancy, consider an antipsychotic and if ineffective consider ECT.²² Obtain advice regarding pre-medication used in ECT.

25 PRESCRIBING GUIDELINES FOR THE MANAGEMENT OF BIPOLAR DISORDER – PHA54: AUGUST 2019
22.22 Benzodiazepines should not be offered to women in pregnancy and the postnatal period except for the short-term treatment of severe agitation.\textsuperscript{17}

22.23 Consider gradually stopping benzodiazepines in women who are planning a pregnancy, pregnant or considering breastfeeding.\textsuperscript{17}

See the ‘Choice and Medication’ link for pregnancy leaflets

22.24 Premature infants and infants with renal, hepatic, cardiac and neurological impairment are at greater risk of exposure to psychotropics via breastfeeding.

22.25 Breastfeeding is not recommended if carbamazepine, clozapine, lithium or valproate (valproate is not recommended to treat a mental health problem in women of childbearing potential) is prescribed.\textsuperscript{17}

22.26 Significant amounts of lithium pass into breast milk\textsuperscript{22} with risk of toxicity for the baby.\textsuperscript{17}

22.27 When assessing the risks and benefits of antipsychotic medication for women who are breastfeeding, take into account:
- the limited data on the safety of these medicines and the level of antipsychotic.
- medication in breast milk depends on the medicine.\textsuperscript{17}

22.28 If a woman is taking psychotropic medication while breastfeeding, monitor the baby for adverse effects.\textsuperscript{7}

22.29 When assessing the risks and benefits of fluoxetine for women who are breastfeeding, take into account:
- the limited data about the safety of SSRIs and
- the risks associated with switching from a previously effective medication.\textsuperscript{17}

Seek advice from a specialist (preferably from a specialist perinatal mental health service) if needed for specific medicines. Also liaise with the wider multidisciplinary team including the obstetric and midwifery services.

### 23.0 Medicine interactions

#### 23.1 Lithium

<table>
<thead>
<tr>
<th>Medicine group</th>
<th>ACE inhibitors</th>
<th>Thiazide diuretics</th>
<th>NSAIDs</th>
<th>Carbamazepine</th>
<th>Serotonin reuptake inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effect on plasma concentration</td>
<td>Unpredictable up to four fold increase</td>
<td>Unpredictable up to four fold increase</td>
<td>Unpredictable from 10% to &gt; 4 fold increase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Timescale of effect</td>
<td>Develops over several weeks</td>
<td>Usually apparent in the first ten days</td>
<td>Variable; few days to several months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Additional information</td>
<td>Sevenfold increased risk of</td>
<td>Can trigger AKI. Loop diuretics are safer. Any NSAIDs are widely used on an ‘as</td>
<td>Rare reports of neurotoxicity and in the</td>
<td>SSRIs can cause hyponatraemia</td>
<td></td>
</tr>
</tbody>
</table>
hospitalisation for lithium toxicity in the elderly. Angiotension II receptor antagonists may be associated with a similar risk of interaction. Can trigger AKI.

effect will be apparent in the first month.

required basis. Can be bought without a prescription. Can trigger AKI.

context of involving high plasma lithium levels. Carbamazepine can cause hyponatraemia which may lead to lithium retention and toxicity.

and there are rare reports of CNS toxicity.

Valproate

23.2 Be aware of potential interactions between valproate and fluoxetine, lamotrigine and olanzapine\(^1\).

23.3 Valproate may interact with other anticonvulsants (particularly carbamazepine and lamotrigine) and with olanzapine and smoking\(^1\).

23.4 Valproate is highly protein-bound and can be displaced by other protein-bound medicines such as aspirin leading to toxicity. Aspirin also inhibits the metabolism of valproate\(^2\). Salicylates should not be used concomitantly with sodium valproate since they employ the same metabolic pathway\(^3,4\). A dose of at least 300mg aspirin is required. Other less strongly protein-bound medicines such as warfarin can be displaced by valproate leading to higher free levels and toxicity. Valproate is heptatically metabolised; medicines that inhibit CYP enzymes can increase valproate levels (e.g. erythromycin, fluoxetine and cimetidine). Valproate can increase plasma levels of tricyclic antidepressants (particularly clomipramine), lamotrigine, quetiapine, warfarin and phenobarbital. Valproate may significantly lower plasma olanzapine concentrations\(^2\).

23.5 The anticonvulsant effect of valproate is antagonised by medicines that lower the seizure threshold e.g. antipsychotics. Weight gain can be exacerbated by other medicines such as clozapine and olanzapine\(^2\).

Lamotrigine

23.6 The use of an ethinyloestradiol/levonorgestrel (30 μg/150 μg) combination increases the clearance of lamotrigine by approximately two-fold, resulting in decreased lamotrigine levels. Following titration, higher maintenance doses of lamotrigine (by as much as two-fold) may be needed to attain a maximal therapeutic response. During the pill-free week, a two-fold increase in lamotrigine levels has been observed. Dose-related adverse events cannot be excluded. Therefore, consideration should be given to using contraception without a pill-free week, as first-line therapy (for example, continuous hormonal contraceptives or non-hormonal methods)\(^4\).

23.7 If the person is already prescribed a maintenance dose of lamotrigine and not taking enzyme inducers, the maintenance dose of lamotrigine will in most cases need to be increased by as much as two-fold. It is recommended that from the time that the...
hormonal contraceptive is started, the lamotrigine dose is increased by 50 to 100 mg/day every week, according to the individual clinical response. Dose increases should not exceed this rate, unless the clinical response supports larger increases. Measurement of serum lamotrigine concentrations before and after starting hormonal contraceptives may be considered, as confirmation that the baseline concentration of lamotrigine is being maintained. If necessary, the dose should be adapted. In women taking a hormonal contraceptive that includes one week of inactive treatment ("pill-free week"), serum lamotrigine level monitoring should be conducted during week 3 of active treatment, i.e. on days 15 to 21 of the pill cycle. Therefore, consideration should be given to using contraception without a pill-free week, as first-line therapy (for example, continuous hormonal contraceptives or non-hormonal methods).

23.8 If the person is stopping hormonal contraceptives, the maintenance dose of lamotrigine will in most cases need to be decreased by as much as 50%. It is recommended to gradually decrease the daily dose of lamotrigine by 50-100 mg each week (at a rate not exceeding 25% of the total daily dose per week) over a period of 3 weeks, unless the clinical response indicates otherwise. Measurement of serum lamotrigine concentrations before and after stopping hormonal contraceptives may be considered, as confirmation that the baseline concentration of lamotrigine is being maintained. In women who wish to stop taking a hormonal contraceptive that includes one week of inactive treatment ("pill-free week"), serum lamotrigine level monitoring should be conducted during week 3 of active treatment, i.e. on days 15 to 21 of the pill cycle. Samples for assessment of lamotrigine levels after permanently stopping the contraceptive pill should not be collected during the first week after stopping the pill.

23.9 When starting lamotrigine in patients already taking hormonal contraceptives, dose escalation should follow the normal dose recommendation. When starting and stopping hormonal contraceptives in patients already taking maintenance doses of lamotrigine and TAKING inducers of lamotrigine glucuronidation, an adjustment to the recommended maintenance dose of lamotrigine may not be required.

23.10 No adjustments to the recommended dose escalation of lamotrigine should be necessary when lamotrigine is added to atazanavir/ritonavir therapy. In patients already taking maintenance doses of lamotrigine and not taking glucuronidation inducers, the lamotrigine dose may need to be increased if atazanavir/ritonavir is added, or decreased if atazanavir/ritonavir is discontinued. Plasma lamotrigine monitoring should be conducted before and during 2 weeks after starting or stopping atazanavir/ritonavir, in order to see if lamotrigine dose adjustment is needed.

23.11 No adjustments to the recommended dose escalation of lamotrigine should be necessary when lamotrigine is added to the existing lopinavir/ritonavir therapy. In patients already taking maintenance doses of lamotrigine and not taking glucuronidation inducers, the lamotrigine dose may need to be increased if lopinavir/ritonavir is added, or decreased if lopinavir/ritonavir is discontinued. Plasma lamotrigine monitoring should be conducted before and during 2 weeks after starting or stopping lopinavir/ritonavir, in order to see if lamotrigine dose adjustment is needed.

Carbamazepine

23.12 Carbamazepine is a potent inducer of hepatic cytochrome enzymes and is metabolised by CYP3A4. Plasma levels of most antidepressants, most antipsychotics, benzodiazepines, some cholinesterase inhibitors, methadone, thyroxine, theophylline, oestrogens and other steroids may be reduced by carbamazepine resulting in treatment failure. Patients requiring contraception should either receive a preparation
containing not less than 50 micrograms oestrogen or a non-hormonal method. Medicines that inhibit CYP3A4 will increase carbamazepine plasma levels and may precipitate toxicity e.g. cimetidine, diltiazem, verapamil, erythromycin and some SSRIs².

23.13 Pharmacodynamic interactions also occur. The anticonvulsant activity of carbamazepine is reduced by medicines that lower seizure threshold (e.g. antipsychotics and antidepressants). The potential for carbamazepine to cause neutropenia may be increased by other medicines that have the potential to depress the bone marrow e.g. clozapine. The risk of hyponatraemia may be increased by other medicines that have the potential to deplete sodium e.g. diuretics. Rarely neurotoxicity has been reported when carbamazepine is combined with lithium. As carbamazepine is structurally similar to tricyclic antidepressants. In theory it should not be given within fourteen days of discontinuing a monoamine oxidase inhibitor².

The above is not an exhaustive list of interactions. If further information is required contact your ward pharmacist.

24.0 References

24. Personal Communication from Dr Klimoovicz, 9th of April 2019.
26. Royal College of Psychiatrists. Withdrawal of, and alternatives to, valproate-containing medicines in girls and women of childbearing potential who have a psychiatric illness. PS 04/18. December 2018.

25.0 Associated documents

- Antipsychotic prescribing guidelines
- Clozapine treatment guidelines.
- Depot antipsychotic medication. Guidelines for prescribing and administering.
- Guidance for the use of zuclopenthixol acetate (clopixol acuphase) in adults.
- Rapid tranquillisation guidance.
26.0 Dissemination and implementation arrangements

This document will be circulated to all managers who will be required to cascade the information to members of their teams. It will be available to all staff via the Foundation Trust intranet.

27.0 Training requirements

Staff will be provided training in how to use this policy in line with the Trust’s Mandatory Training Policy and the Learning and Development Guide. For training requirements please refer to the Trust’s Mandatory Training Policy and Learning and Development Guide.

28.0 Monitoring and audit arrangements

See table above.

29.0 Review of the policy

3 years – September 2021
<table>
<thead>
<tr>
<th>Element to be monitored</th>
<th>Lead</th>
<th>How Trust will monitor compliance</th>
<th>Frequency</th>
<th>Reporting arrangements</th>
<th>Acting on recommendations and Lead(s)</th>
<th>Change in practice and lessons to be shared</th>
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</thead>
<tbody>
<tr>
<td>See list of NHSLA minimum requirements if relevant</td>
<td>Chief Pharmacist</td>
<td>ePACT data Clinical pharmacy checks</td>
<td>ongoing</td>
<td>Bitcoin</td>
<td>How will changes be implemented and lessons learnt/ shared?</td>
<td></td>
</tr>
</tbody>
</table>

Formulary adherence

<table>
<thead>
<tr>
<th>Lead</th>
<th>How Trust will monitor compliance</th>
<th>Frequency</th>
<th>Reporting arrangements</th>
<th>Acting on recommendations and Lead(s)</th>
<th>Change in practice and lessons to be shared</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chief Pharmacist</td>
<td>ePACT data Clinical pharmacy checks</td>
<td>ongoing</td>
<td>Bitcoin</td>
<td>How will changes be implemented and lessons learnt/ shared?</td>
<td></td>
</tr>
</tbody>
</table>
Appendix 1: Positive cardiometabolic health resource. Lester UK adaptation. 2014.

Positive Cardiometabolic Health Resource
An intervention framework for people experiencing psychosis and schizophrenia

http://www.rcpsych.ac.uk/pdf/Lester%20update%20June%202014%20FINAL.pdf
It can be accessed via the Royal College of Psychiatrists:
https://www.rcpsych.ac.uk/quality/nationalclinicalaudits/schizophrenia/nationalschizophreniaaudit/nasresources.aspx#CMH
31.0 Appendix 2

Medicines not recommended in the management of bipolar affective disorder

19.1 Gabapentin or topiramate should not be offered to treat bipolar disorder\(^1\).

19.2 Valproate refers to 3 formulations of valproate available in the UK: sodium valproate, valproic acid and semi-sodium valproate. Sodium valproate and valproic acid had UK marketing authorisation for the treatment of epilepsy. Semi-sodium valproate had a UK marketing authorisation for the treatment of acute mania and for continuation treatment in people who have had mania that has responded to treatment with semi-sodium valproate. Both semi-sodium and sodium valproate are metabolised to valproic acid (also known as valproate), which is the pharmacologically active component\(^1\). The Trust formulary included sodium valproate the management of bipolar disorder. Sodium valproate is contraindicated in women of child-bearing age unless a pregnancy prevention programme is in place. Valproic acid and semi-sodium valproate are not included in the trust formulary for the management of bipolar disorder.

19.3 Aripiprazole or risperidone should not be offered to treat bipolar depression\(^1\).

19.4 Tricyclic antidepressants and monoamine oxidase inhibitors should not be offered to treat bipolar depression\(^1\).

19.5 Serotonin reuptake inhibitors performs poorly compared to first line treatment (olanzapine + fluoxetine, olanzapine, quetiapine) in the management of bipolar depression\(^1\).

19.6 Aripiprazole is licensed for the treatment of bipolar disorder type-I, both as a monotherapy as well as an add-on therapy in acute mania and in long-term maintenance therapy\(^1\). It is not referred to in the NICE guidance for this indication in adults\(^1\). A systematic review concluded Compared with haloperidol, aripiprazole shows fewer extrapyramidal symptoms (EPS), but has a slightly lower efficacy in mania. It has a better metabolic parameter profile and fewer cardiovascular adverse events than other atypical antipsychotics although the add-on treatment shows a higher risk of EPS. Presently, data doesn't support its use as a first choice maintenance monotherapy. Studies in bipolar depression were disappointing\(^1\).
### 32.0 Appendix 3: Summary of monitoring requirements for medicines\(^1\)\(^2\)

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Pre- and Post-</th>
<th>Weight/BMI</th>
<th>BP</th>
<th>Pulse</th>
<th>ECG</th>
<th>HbA1c</th>
<th>Blood lipid profile</th>
<th>Us &amp; Es</th>
<th>Calcium</th>
<th>eGFR</th>
<th>LFTs</th>
<th>TFTs</th>
<th>FBC</th>
<th>Serum level</th>
<th>Frequency</th>
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<td>Valproate</td>
<td>Pre-</td>
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</tbody>
</table>
33.0: Appendix 4: Pregnancy testing

Pregnancy should be excluded before initiation on valproate medicines by a negative plasma pregnancy test, confirmed by a healthcare professional.

The aim of pregnancy testing is to provide as much certainty as possible that the service user is not pregnant, before prescribing valproate. In the early stages after implantation, an hCG serum assay more sensitively detects pregnancy than an hCG urine dip test.

If there is any possibility that the patient has recently been sexually active, valproate should not be prescribed until:

- 14 days have elapsed since the last possible day on which the patient could have had unprotected sex (for example, this could be 14 days from the point of admission, or 14 days from the last day on which the patient was given unescorted leave from the ward), AND
- A negative hCG serum assay has been obtained after this 14 day period has elapsed.

For patients who have been admitted and who are already prescribed valproate for mood stabilisation in the community, if there is any possibility that the patient has recently had unprotected sex, valproate should be stopped. If clinically appropriate, the drug can be restarted provided that a negative serum hCG test has been obtained a minimum of 14 days after the last possible day on which the patient could have had unprotected sex.

For patients who have been admitted and who are already prescribed valproate in the community for the treatment of epilepsy, if there is any possibility that the patient has recently had unprotected sex, the patient’s neurology team must be consulted before stopping the valproate. This consultation should be considered extremely urgent and should occur at the earliest possible opportunity after the patient is admitted. The consultation should involve a thorough discussion about the risks posed by either continuing the valproate or stopping it.

34: Appendix 5: Patients who refuse information

Occasionally patients may not wish to receive information when valproate is prescribed, or they may not currently be receptive to such information.

- In these circumstances, serious consideration should be given to delaying valproate treatment until the patient is willing and able to accept information about the risks posed by the medicine.
- However, if the initiation of valproate is considered to be absolutely necessary, then the prescriber must complete the following actions:
  - Complete as much of the Risk Acknowledgement Form as possible at the current time, and add this to the patient’s notes.
  - Ensure that another attempt to provide the information to the patient is made at the earliest possible opportunity.
• Make an entry in the patient’s medical notes stating why it was not possible to complete the full checklist, and why it was considered necessary to prescribe the medication despite this.
• Put a clear risk-minimisation plan in place. This may involve putting the patient on an increased observation level and restricting their leave from the ward until the valproate prescription has been stopped, or until the patient has received the necessary risk information about the medicine. The plan must be clearly documented in the patient’s notes.
Flowchart 1

Safely prescribing and administering Valproate for women in inpatient settings if they were already receiving Sodium Valproate at the point of admission

How do I know if it’s safe to prescribe and administer Valproate to my patient?

Use of Valproate in pregnancy is associated with a 40% risk of persistent neurodevelopmental disorders and a 10% risk of physical birth defects to the unborn baby.

The Trust guidelines must be followed to minimise the:
- risk of woman becoming pregnant whilst on Valproate
- risk of pregnant women receiving Valproate

Non-adherence to trust guidelines of staff that prescribe or administer Valproate may result in professional liability.

Any woman ≤ 55yrs on Valproate at the point of admission*

*Women > 55yrs can be safely assumed to be post-menopausal and not of child-bearing potential

Blood or urine pregnancy test

Positive

Negative or unable to complete

Assume patient is of childbearing potential unless clear evidence of exception**

Is there a clearly documented Pregnancy Prevention Plan?***

No

Yes

Is the Valproate prescribed for epilepsy?

Yes or Not Sure

Add Folate Smg OD.
Discuss case with the Responsible Clinician or SpR or Consultant on call as soon as possible.
Agree and document plan to stop Valproate safely (in acutely unwell patients gradual reduction advised over up to 7 days).
Individual plans must consider current dosage, risk of seizure, risk of relapse in mental state and alternative medication available.

Add Folate Smg OD.
Sudden withdrawal of antiepileptic medication can cause life-threatening seizures.
Case must be discussed with Medical Registrar on call – via switchboard at Whittington (02072723070) or UCLH (02034567890). Any plan and rationale must be clearly documented, discussed with a responsible clinician or consultant on-call.

ANY doctor, nurse or pharmacist should feel able to question the safety of a Valproate prescription or administration!
36.0 Appendix 7:

**Flowchart 2**

Starting or re-starting Valproate on Women's Psychiatric Intensive Care Unit (WPICU)

**Is the woman of childbearing potential?**

- No
  - Valproate can be prescribed depending on clinical need

- Yes
  - Has current pregnancy been excluded?
    - No
      - Has prevention of future pregnancy whilst on Valproate been ensured?
        - No
          - Do NOT prescribe Valproate
        - Yes
          - Valproate can be started as per Trust policy
    - Yes
      - Are there other measures in place to effectively eliminate risk of pregnancy such as no leave?
        - No
          - Do NOT prescribe Valproate
        - Yes
          - Valproate can be prescribed if there is a clearly documented clinical indication and other treatments have been ineffective or are not available and a senior pharmacist (band 8a and above) and Responsible Clinician agree.

**Women > 55yrs are can be safely assumed to be post-menopausal and therefore not of child-bearing potential. Pregnancy test is not required.**

For Women ≤ 55yrs we assume patient is of childbearing potential unless clear evidence of exception:

- post hysterectomy or tubal ligation
- transgender woman who does not have a uterus
- post-menopause i.e. <50 yr old a reliable history of no periods for ≥2 years
- and a negative pregnancy test (urine or blood)

Women's fertility at 50 years old approaches 0%. Therefore for patients 50 to 55yrs old a single negative pregnancy test (urine or blood) will suffice to confirm an acceptably low risk of pregnancy equivalent to non-childbearing potential.

FSH/LH levels are not a reliable method of confirming post-menopausal status and are not advised.

**Has prevention of future pregnancy whilst on Valproate been ensured?**

- Yes
  - 4 consecutive weeks of negative urine pregnancy tests or 2 consecutive weeks of negative blood pregnancy tests or 1 negative blood pregnancy test min. 14 days after WPICU admission

**This is equivalent to a clearly documented Pregnancy Prevention Plan which must include:**

- highly effective contraception in situ AND
- completed PREVENT risk form AND
- negative pregnancy tests (urine or blood)
- completed and approved non-formulary request form (Medication tab on Care Notes)

**Prior to stepping down/any leave/being discharged:**

- a plan for reduction and/or stopping Valproate must be in place OR
- a shared agreement between PICU consultant and Responsible Clinician on receiving ward to continue Valproate after step-down must be ensured

ANY doctor, nurse or pharmacist should feel able to question the safety of a Valproate prescription or administration!