

Guidance on the use of mood stabilizers for the treatment of bipolar affective disorder

Version 2

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Introduction¹

Bipolar disorder is a cyclical mood disorder involving periods of profound disruption to mood and behaviour interspersed with periods of more or less full recovery. The key feature of bipolar disorder is the experience of hypomania or mania – grandiose and expansive affect associated with increased drive and decreased sleep, which ultimately can culminate in psychosis and exhaustion if left untreated.

There is increasing recognition of a spectrum of bipolar disorders that ranges from marked and severe mood disturbance into milder mood variations that become difficult to distinguish from normal mood fluctuation.

There is some heterogeneity between the major diagnostic classification systems in the criteria for bipolar disorder. In terms of classification, DSM-V requires a single episode of mania without any episode of depression (Bipolar I), or a single episode of hypomania with one major depressive episode, would warrant a diagnosis of bipolar disorder (Bipolar II). It must be noted that ICD-10 does not include bipolar II disorder. ICD-10 requires two discrete mood episodes, at least one of which must be hypomanic or manic.

Although mania or hypomania are the defining characteristics of bipolar disorder, throughout the course of the illness depressive symptoms are more common than manic symptoms. The risk of suicide is greatly elevated during depressive episodes. Approximately 17% of patients with bipolar I disorder and 24% of patients with bipolar II disorder attempt suicide during the course of their illness. Annually around 0.4% of patients with bipolar disorder will die by suicide, which is vastly greater than the international population average of 0.017%. The standardised mortality ratio (SMR) for suicide in bipolar disorder is estimated to be 15 for men and 22.4 for women.

Community-based epidemiological studies consistently report the lifetime prevalence of bipolar I disorder to be approximately 1% and bipolar II disorder at 0.2-5.0%. The prevalence of bipolar I disorder is similar in both men and women. Comorbid anxiety disorders and substance abuse are reported in 30-50% of patients with bipolar disorder.

Bipolar disorder has a fairly early age of onset, with the first episode usually occurring before the age of 30. The peak in onset rate occurs between the ages of 15 and 19 years.

Treatment and care should take into account people's individual needs and preferences. People with bipolar disorder should have the opportunity to make informed decisions about their care and treatment.

Good communication between healthcare professionals and patients is essential. When talking to people with bipolar disorder and their carers, healthcare professionals should use everyday, jargon-free language to give a full and clear explanation of bipolar disorder and its treatment. Written, evidence-based information about the condition and its treatment should also be provided. All information should be tailored to the needs of the individual patient. The treatment, care and information provided should be culturally appropriate and in a form that is

accessible to people who have additional needs, such as people with physical, cognitive or sensory disabilities, and people who do not speak or read English.

Unless specifically excluded by the patient, carers and relatives should have the opportunity to be involved in decisions about the patient's care and treatment. Carers and relatives should also be provided with the information and support they need.

Information leaflets on medication approved by the Trust can be found on the following link.
www.choiceandmedication.org.uk/sussex

Key points from the guidance

- Treatment selection should be guided where possible, by patient preference.
- Carers of adults with bipolar disorder should be involved in care planning, decision making and information sharing about the person as agreed in the care plan
- Psychological interventions should form the foundation of therapy for adolescents and children, as medicines used in bipolar disorder can have a damaging effect on children's growth and development. If pharmacological intervention is required then follow the recommendations for adults (below).
- Haloperidol, olanzapine, quetiapine and risperidone are the antipsychotics of choice for the treatment of mania.
- Fluoxetine is the only antidepressant that is effective in treating bipolar depression, and only in combination with the atypical antipsychotic olanzapine.
- Do not offer valproate to women of childbearing potential for long-term treatment or to treat an acute episode. If no effective alternative to valproate can be identified, adequate contraception should be used, and the risks of taking valproate during pregnancy should be explained.
- Lithium is the most effective long-term treatment for bipolar disorder and should be used first-line.
- Lithium prescribing and monitoring must follow Trust guidance due to a NPSA alert.⁴ The latest trust guidelines for [the prescribing and monitoring of lithium therapy](#) can be found on the Trust website.
- Lithium may not be appropriate if compliance is poor.
- Carbamazepine (CBZ) interacts with many other medications and this should be taken into consideration when prescribing (see appendix 4).

- Antidepressants should be tapered and discontinued in mania.
- Whenever a patient is transferred between settings and a review of medication is needed after transfer, the date of the review and what needs reviewing must be clearly communicated to the receiving GP, community team or ward. This information must also be shared with the patient and if appropriate the carer.

General principles in the treatment of acute mania. ^{1,2}

1. For patients not on long-term treatment for bipolar disorder

- If a person develops mania or hypomania and is not taking an antipsychotic or mood stabiliser, offer haloperidol, olanzapine, quetiapine or risperidone.
- If a person develops mania or hypomania and is taking an antidepressant (as defined by the British national formulary [BNF]) as monotherapy: consider stopping the antidepressant and offer an antipsychotic (as above), regardless of whether the antidepressant is stopped.
- Take into account any advance statements, the person's preference and clinical context (including physical comorbidity, previous response to treatment and side effects).
- If the first antipsychotic is poorly tolerated at any dose (including rapid weight gain) or ineffective at the maximum licensed dose, offer an alternative antipsychotic from the drugs listed above.
- If an alternative antipsychotic is not sufficiently effective at the maximum licensed dose, consider adding lithium. If adding 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.
- Where an agitated patient requires parenteral treatment to control behaviour without their full consent, the use of antipsychotics and benzodiazepines should follow established protocols. The lowest doses necessary should be employed.
- Do not escalate the dose of antipsychotic simply to obtain a sedative effect.
- For less ill manic patients, lithium or carbamazepine may also be considered as a short-term treatment. Lithium may not be appropriate if compliance is poor.
- Carbamazepine interacts with many other medications and this should be taken into consideration when prescribing (see appendix 4).
- To promote sleep for agitated overactive patients in the short term, consider adjunctive treatment with a benzodiazepine or a Z-drug.

1.1 For patients on long-term treatment

- In general, follow the same principles as for a first episode or an episode occurring off long-term treatment.
- If a person develops mania or hypomania and is taking an antidepressant (as defined by the BNF) in combination with a mood stabiliser, consider stopping the antidepressant.
- Long-term treatments will usually be lithium, CBZ or valproate, although long-term usage of second generation antipsychotics has grown substantially.

- d. If the person is already taking lithium, check plasma lithium levels to optimize treatment (see appendix 4). Consider adding haloperidol, olanzapine, quetiapine or risperidone, depending on the person's preference and previous response to treatment.
- e. If the person is already taking valproate or another mood stabiliser as prophylactic treatment, consider increasing the dose, up to the maximum level in the BNF if necessary, depending on clinical response. If there is no improvement, consider adding haloperidol, olanzapine, quetiapine or risperidone, depending on the person's preference and previous response to treatment.
- f. If the current episode is due to poor adherence, establish whether this is associated with actual or perceived side effects. If so, consider a more tolerable alternative regimen.
- g. If the episode is associated with lithium discontinuation because of poor adherence, and not related to tolerability, use of lithium long term may not be indicated.
- h. Do not offer lamotrigine to treat mania.
- k. Whenever a patient is transferred between settings and a review of medication is needed after transfer, the date of the review and what needs reviewing must be clearly communicated to the receiving GP, community team or ward. This information must also be shared with the patient and if appropriate the carer.

1.3 If symptoms are inadequately controlled with optimised doses of the first-line treatment and/or mania is very severe.

- a. Consider the combination of lithium or valproate with an antipsychotic.
- b. Consider clozapine in more refractory illness (unlicensed).
- c. Consider electro-convulsive therapy (ECT) for manic patients who are severely ill and/or whose mania is treatment resistant, those patients who express a preference for ECT and patients with severe mania during pregnancy.

1.4 For psychosis during a manic or mixed episode that is not congruent with severe affective symptoms.

- a. If the clinical presentation is of a mixed affective state, characterised by both manic and depressive symptoms, follow recommendations 2.1 -2.3 for the treatment of mania, and monitor closely for the emergence of depression.

1.5 Discontinuation of short-term treatments

- a. 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 (see section 1.7). Explain the potential benefits of long-term treatment and the risks, including side effects of medication used for long-term treatment.
- b. If the person decides to continue treatment for mania, offer it for a further 3-6 months, and then review.
- c. Medicines used solely for acute treatment may be reduced in dose and discontinued (tapering over 2 weeks or more) after full remission of symptoms. This will often occur within 3 months.

- d. Any medication used for symptomatic effect (hypnotics, sedatives) should be discontinued as soon as symptoms improve.
- e. Medicines shown to be effective or probably effective in relapse prevention are often used for short-term treatment of mania and may be appropriately continued when long-term treatment is planned.

1.6 Transferring patients

- a. Whenever a patient is transferred between settings and a review of medication is needed after transfer, the date of the review and what needs reviewing must be clearly communicated to the receiving GP, community team or ward. This information must also be shared with the patient and if appropriate the carer.

2. General principles in the treatment of bipolar depression. ^{1, 2}

2.1 For patients not already on long-term treatment for bipolar disorder

- a. If a person develops moderate or severe bipolar depression and is not taking a drug to treat their bipolar disorder, offer fluoxetine combined with olanzapine, or quetiapine on its own, depending on the person's preference and previous response to treatment.
- b. If the person prefers, consider either olanzapine (without fluoxetine) or lamotrigine on its own.
- c. If there is no response to fluoxetine combined with olanzapine, or quetiapine, consider lamotrigine on its own.
- d. Where an early treatment effect is desirable, consider quetiapine.
- e. Consider initial treatment with lamotrigine, with the necessary dose titration.
- f. If not already on an antipsychotic, consider adding an antipsychotic when patients have psychotic symptoms.
- g. Consider ECT for patients with high suicidal risk, psychosis, severe depression during pregnancy or life-threatening inanition.
- h. Consider simplifying pre-existing polypharmacy, which may change seizure thresholds. When depressive symptoms are less severe; lithium or possibly valproate may be considered.
- i. Consider interpersonal therapy, cognitive behavior therapy or family-focused therapy (FFT) when available since these may shorten the acute episode.

2.2 For patients who suffer a depressive episode while on long-term treatment

- a. If a person develops moderate or severe bipolar depression and 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.
- b. If the person prefers, consider adding olanzapine (without fluoxetine) or lamotrigine to lithium.
- c. If there is no response to adding fluoxetine combined with olanzapine, or adding quetiapine, stop the additional treatment and consider adding lamotrigine to lithium.

- d. 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.
- e. If there is no response to adding fluoxetine combined with olanzapine, or adding quetiapine, stop the additional treatment and consider adding lamotrigine to valproate.
- f. If the person prefers, consider adding olanzapine (without fluoxetine) or lamotrigine to valproate.
- g. Address current stressors, if any.
- h. Ensure current choice of long-term treatments is likely to protect the patient from manic relapse (e.g. lithium, CBZ, valproate, antipsychotic).
- i. Take into account toxicity in overdose when prescribing psychotropic medication during periods of high suicide risk. Assess the need to limit the quantity of medication supplied to reduce the risk to life if the person overdoses.

2.3 Choice of antidepressant

- a. The limited evidence supports the modest efficacy of antidepressants such as the SSRIs (specifically fluoxetine) in bipolar disorder. However, antidepressants should not be uncritically employed as first-line medicines given continuing doubts about relative efficacy and their potential to destabilise mood.
- b. Antidepressants (imipramine, paroxetine and moclobemide) alone are ineffective compared with placebo.¹
- c. There is a risk of switch to mania or mood instability during treatment for depression. While this will often reflect the natural history of the disorder, it may be increased by active treatment with an antidepressant. Antidepressants appear less likely to induce mania when added to lithium, valproate or an antipsychotic.
- d. Tricyclic antidepressants and probably other dual action drugs like venlafaxine (and possibly duloxetine) carry a greater risk of precipitating a switch to mania than other antidepressants and are not recommended except for patients who fail to respond to an initial treatment.
- e. Consider quetiapine or lamotrigine for bipolar depression, especially when an antidepressant has previously appeared to provoke mood instability.

2.4 Discontinuation of treatment for bipolar depression, after full remission of symptoms

- a. Depressive episodes that remit in bipolar disorder tend to be shorter than in unipolar disorder, so discontinuation may occur after as little as 12 weeks of treatment. In the absence of convincing evidence in favour of long-term treatment with antidepressants, the usual policy should be discontinuation, although a small minority of patients appear to do well on combination treatment that includes an antidepressant.²
- b. Within 4 weeks of resolution of symptoms, discuss with the person, and their carers if appropriate, whether to continue psychological or pharmacological treatment for bipolar depression or start long-term treatment.

- c. Explain the potential benefits of long-term treatment and the risks, including side effects of medication used for long-term treatment.
- d. If the person decides to continue psychological or pharmacological treatment for bipolar depression, offer it for a further 3–6 months, and then review.

2.5 Next-step treatments following inadequate treatment response to an antidepressant

- a. Treatment resistance may occur in depressed bipolar patients.
- b. Since there is so little data from trials on the treatment of bipolar patients, practice derived primarily from experience in unipolar patients is recommended

2.6 Transferring patients

- a. Whenever a patient is transferred between settings and a review of medication is needed after transfer, the date of the review and what needs reviewing must be clearly communicated to the receiving GP, community team or ward. This information must also be shared with the patient and if appropriate the carer.

3. General principles in long-term treatment. ^{1, 2}

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. The discussion should cover:

- a. The nature and variable course of bipolar disorder
- b. The role of psychological and pharmacological interventions to prevent relapse and reduce symptoms
- c. The risk of relapse after reducing or stopping medication for an acute episode
- d. The potential benefits and risks of long-term medication and psychological interventions, and the need to monitor mood and medication
- e. The potential benefits and risks of stopping medication, including for women who may wish to become pregnant
- f. The person's history of bipolar disorder, including: the severity and frequency of episodes of mania or bipolar depression, with a focus on associated risks and adverse consequences previous response to treatment symptoms between episodes
- g. Potential triggers for relapse, early warning signs, and self-management strategies
- h. Possible duration of treatment, and when and how often this should be reviewed.
- i. Provide clear written information about bipolar disorder, including NICE's information for the public, and ensure there is enough time to discuss options and concerns.
- j. Discuss the use of alcohol, tobacco, prescription and non-prescription medication and illicit drugs with the person, and their carer if appropriate. Explain the possible interference of these substances with the therapeutic effects of prescribed medication and psychological interventions.

3.1 Prevention of new episodes

- a. Consider long-term treatment following a single severe manic episode (i.e. diagnosis of bipolar-I disorder) because, although there is no controlled evidence, the natural history of the illness implies that preventing early relapse may lead to a more benign illness course.
- b. However, without active acceptance of the need for long-term treatment, adherence may be poor. Consider a wider package of treatment offering enhanced psychological and social support. When a patient has accepted treatment for several years and remains very well, they should be strongly advised to continue indefinitely unless there are signs of adverse effects. This is because the risk of relapse remains high.
- c. Consider extrapolating the advice concerning bipolar-I to bipolar-II disorder given increasing evidence from clinical trials for common effects.

3.2 Options for long-term treatment

- a. Long-term agents are often called mood stabilisers. An ideal mood stabiliser would prevent relapse to either pole of the illness.
- b. The available medicines are probably more often effective against one pole than the other.
- c. At present the preferred strategy is for continuous rather than intermittent treatment with oral medicines to prevent new mood episodes. However, the use of additional short-term medication (e.g. benzodiazepines or antipsychotics) is necessary when an acute stressor is imminent or present, early symptoms of relapse (especially insomnia) occur or anxiety becomes prominent. Consider supplying short-term medicines prospectively to patients to use with clear advice (e.g. suggest taking for 4 days, but if not settling or getting worse to seek medical attention). Higher doses of the long-term treatments may also be effective, thus avoiding the need for additional medications.

3.3 Choice of long-term medicines

- a. 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.
- b. Offer lithium as a first-line, long-term pharmacological treatment for bipolar disorder and monotherapy. Lithium monotherapy is probably effective against both manic and depressive relapse, although it is more effective in preventing mania.
- c. If lithium is ineffective, consider adding valproate if lithium is poorly tolerated, or is not suitable (for example, because the person does not agree to routine blood monitoring), consider valproate or olanzapine instead or, if it has been effective during an episode of mania or bipolar depression, quetiapine.
- d. The latest trust guidelines for [the prescribing and monitoring of lithium therapy](#) can be found on the Trust's website.
- e. Discuss with the person the possible benefits and risks of each drug for them.

- f. Long-term treatment in general and lithium specifically, is associated with a reduced risk of suicide in bipolar patients.
- g. The BALANCE trial showed combination therapy with lithium plus valproate and lithium monotherapy are more likely to prevent relapse than is valproate monotherapy. There were more side effects with combination therapy compared to monotherapy. This benefit seems to be irrespective of baseline severity of illness and is maintained for up to 2 years.³
- h. Consider other options, not necessarily in this alphabetical order, if lithium is ineffective or poorly tolerated:
 - Aripiprazole may prevent manic relapse.
 - Carbamazepine is less effective than lithium but may sometimes be employed as monotherapy if lithium is ineffective and especially in patients who do not show the classical pattern of episodic euphoric mania. Be aware of the pharmacokinetic interactions that are a particular problem for CBZ.
 - Oxcarbazepine may be considered by extrapolation because of its lower potential for such interactions.
 - Lamotrigine prevents depressive more than manic relapse.
 - Olanzapine prevents manic more than depressive relapse.
 - Quetiapine prevents manic and depressive relapse.
 - Valproate probably prevents manic and depressive relapse.
 - Do not offer gabapentin or topiramate to treat bipolar disorder
- i. In individual cases, if one of the above medicines led to prompt remission from the most recent depressive or manic episode, this may be considered evidence in favour of its long-term use as monotherapy.

3.4 If the patient fails to respond to monotherapy and continues to experience sub-threshold symptoms or relapses, consider long-term combination treatment.

- a. When the burden of disease is mania, it may be logical to combine predominantly anti-manic agents (e.g. lithium, valproate with an antipsychotic).
- b. When the burden is depressive, lamotrigine or quetiapine may be more appropriate. In bipolar-I disorder, lamotrigine may require combination with an anti-manic long-term agent (e.g. quetiapine).
- c. Lamotrigine and quetiapine may be effective as monotherapy in bipolar-II disorder.
- d. The role of antidepressants in long-term treatment is not established by controlled trials, but they appear to be used effectively in a small minority of patients.
- e. Consider clozapine in treatment refractory patients (unlicensed).
- f. Lamotrigine is unlicensed for bipolar depression.

3.5 Discontinuation of long-term treatment

- a. If stopping long-term pharmacological treatment:
 - Discuss with the person how to recognise early signs of relapse and what to do if symptoms recur

- Stop treatment gradually (see section 1.10) and monitor the person for signs of relapse.
- b. Following discontinuation of medicines, the risk of relapse remains, even after years of sustained remission. Continue monitoring symptoms, mood and mental state for 2 years after medication has stopped entirely.
- c. Discontinuation of any long-term medicine should normally be tapered over at least 2 weeks and preferably longer, especially with lithium.
- d. Early relapse of mania is a risk of abrupt lithium discontinuation.
- e. Clinical monitoring during treatment withdrawal is desirable.
- f. Discontinuation of medicines should not be equated with withdrawal of services to patients.

3.6 Transferring patients

- a. Whenever a patient is transferred between settings and a review of medication is needed after transfer, the date of the review and what needs reviewing must be clearly communicated to the receiving GP, community team or ward. This information must also be shared with the patient and if appropriate the carer.

4. Rapid cycling (4 or more acute episodes in a year) poses particular long-term management problems because of the associated illness intensity.^{1,2}

- a. Identify and treat conditions such as hypothyroidism or substance misuse that may contribute to cycling.
- b. Taper off and discontinue antidepressants that may contribute towards switching from one pole to another.
- c. There is little data on which to base initial treatment beyond extrapolation or secondary analysis of acute and long-term efficacy data for bipolar-I patients in general. Equally, there is no basis yet for identifying rapid cycling as a particular sub-group requiring a different approach to treatment.
- d. Treatment should be as for manic and depressive episodes. Optimise treatments and continue for at least 6 months as full benefits may not be apparent for several months.
- e. For many patients, combinations of mood stabilizers and antipsychotics are necessary.
- f. Evaluate anti-cycling effects over periods of 6 months or more by tracking mood states longitudinally. Discontinue treatments if ineffective or if compliance is poor.
- g. Whenever a patient is transferred between settings and a review of medication is needed after transfer, the date of the review and what needs reviewing must be clearly communicated to the receiving GP, community team or ward. This information must also be shared with the patient and if appropriate the carer.

5. Physical health

- a. Severe bipolar disorder is associated with poor physical health and potentially with poor access to relevant screening and treatment.

- b. It is of growing concern that many of the long-term treatments that appear to be required for bipolar disorder may add to this burden of physical disease.
- c. Take all possible steps to protect and improve the physical health of patients in your care through active screening and treatment of risk factors or confirmed disease. Develop and use practice case registers to monitor the physical and mental health of people with bipolar disorder in primary care.
- d. The health check should be comprehensive, including all the checks recommended below and focusing on physical health problems such as cardiovascular disease, diabetes, obesity and respiratory disease. A copy of the results should be sent to the care coordinator and psychiatrist, and put in the secondary care records.
- e. Ensure that the physical health check for people with bipolar disorder, performed at least annually, includes:
 - Weight or BMI
 - Diet and nutritional status
 - Level of physical activity
 - Cardiovascular status, including pulse and blood pressure
 - Metabolic status, including fasting blood glucose, glycosylated haemoglobin (HbA1c)
 - Blood lipid profile,
 - Liver function
 - Renal function
 - Thyroid function
 - Calcium levels, for people taking long-term lithium.
- f. Identify people with bipolar disorder who have hypertension, have abnormal lipid levels, are obese or at risk of obesity, have diabetes or are at risk of diabetes (as indicated by abnormal blood glucose levels), or are physically inactive, at the earliest opportunity.
- g. Follow NICE guidance on hypertension, lipid modification, prevention of cardiovascular disease, obesity, physical activity and preventing type 2 diabetes.
- h. Offer treatment to people with bipolar disorder who have diabetes and/or cardiovascular disease in primary care in line with the NICE clinical guidelines on type 1 diabetes, type 2 diabetes, type 2 diabetes – newer agents and lipid modification.
- i. Healthcare professionals in secondary care should ensure, as part of the care programme approach, that people with bipolar disorder receive physical healthcare from primary care after responsibility for monitoring has been transferred from secondary care.
- j. People with bipolar disorder, especially those taking antipsychotics and long-term medication, should be offered a combined healthy eating and physical activity programme by their mental healthcare provide.
- k. If a person has rapid or excessive weight gain, abnormal lipid levels or problems with blood glucose management, take into account the effects of medication, mental state, other physical health and lifestyle factors in the development of these problems and offer interventions in line with the NICE guidance on obesity, lipid modification or preventing type 2 diabetes.
- l. Routinely monitor weight and cardiovascular and metabolic indicators of morbidity in people with bipolar disorder. These should be audited in the annual team report.

- m. Trusts should ensure that they take account of relevant guidelines on the monitoring and treatment of cardiovascular and metabolic disease in with bipolar disorder through board-level performance indicators.

6. Treatment in special situations

6.1 In pregnancy

- a. Always obtain up to date advice and treat each case individually. Experience with newer drugs is growing and a change in treatment may not be necessary or advisable.
- b. Contact Medicines Information department on 01903 285075 option 2 during working hours or via email medicines.information@wsht.nhs.uk or contact the UK Teratology Information Service (UKTIS) for specialist advice (0844 892 0909). The clinical pharmacist can also access these services, so can be contacted in the first instance.**
- c. The UKTIS use case reports of drug exposure during pregnancy in order to expand their evidence base and should be contacted for further advice regarding reporting individual cases.
- d. Contraception and the risks of pregnancy (including relapse, risks associated with stopping or changing medication and risk to the foetus) should be discussed with all women of childbearing potential who have a mental disorder and/or who are taking a mood stabilizer. As many pregnancies are unplanned this discussion should take place on first prescription.
- e. Information on the background abnormality rate (abnormality rate in women not diagnosed with a mental illness) which is quoted as 2-3% should also be discussed as 1 in 40 pregnancies have an abnormality.
- f. Medicines contra-indicated in pregnancy (e.g. sodium valproate) should be avoided in women of child bearing potential.
- g. For women who have had a long period without relapse, consideration should be given to switching to a safer drug or withdrawing slowly before conception and during the first trimester.
- h. Do not introduce medication during pregnancy unless clearly necessary and only after careful consideration of the risk/benefit. Consider non drug treatments first line.
- i. The risk of prescribing in pregnancy must be weighed against the risk of not prescribing. The risks for prescribing, in some cases, may be lower than the risks of not prescribing.
- j. In women with history of mental illness, especially bipolar affective disorder, the risk of relapse in the post natal period is high. The deterioration in this period is more rapid than usual and hence it is important to initiate appropriate medication promptly. This may avoid, in some cases, admission to a Mother and Baby Unit.
- k. Due to the higher risk of relapse, treatment may need to be maintained during and after pregnancy. The risk of relapse is not eliminated even if medication is continued throughout pregnancy and postpartum. The risk is very high if medication is stopped abruptly.
- l. As a general prescribing principle, the lowest effective dose should be used. Polypharmacy should be avoided whenever possible.

- m. In the management of mania associated with bipolar disorder, a low dose first generation antipsychotic or second generation antipsychotic is recommended as the treatment of choice by NICE.
- n. Antidepressants should be avoided if possible.
- o. If folic acid 5mg is prescribed (for prevention of neural tube defects), inform the patient that there is an associated risk of multiple births and consideration of a lower dose may be appropriate.

Summary of the use of mood stabilisers in pregnancy – This guidance should not take the place of the latest specialist advice

Medication (5, 6, 7, 8)	Comment
Lithium	<p>Should be avoided in pregnancy if possible. Slowly discontinue, if deemed necessary, due to risk of relapse. Consider changing to an antipsychotic if there is a high risk of relapse on withdrawal or the woman is unwell. The main abnormalities with lithium are cardiac (Ebsteins disorder) and as the heart is formed early in pregnancy stopping lithium when pregnancy is confirmed is of little benefit. If lithium is continued high resolution ultrasound and ECG ⁽⁴⁾ should be carried out to identify any abnormalities. Lithium levels alter in pregnancy due to increased renal clearance and fluid retention, therefore monitoring needs to be more frequent (at least monthly).</p>
Sodium valproate	<p>Should not be offered to women of child bearing potential (see Trust guidance).</p> <p>Evidence is mainly from pregnant women with epilepsy who have an increased risk of complications due to teratogenic and neurogenic effects including; spina bifida, atrial septal defect, cleft palate, hypospadias, polydactylism and craniosynostosis. If deemed necessary, then the lowest possible dose is advisable, dividing the dose to 2-3 times a day and also the use of modified release, as the teratogenic effect may be dose related. NICE recommend the dose is limited to 1000mg daily. Prescribe folic acid 5mg daily. Folate supplementation before the pregnancy may decrease the risk of neural tube defects common to all pregnancies; however the available evidence does not suggest it prevents the birth defects or malformations due to valproate exposure.</p>
Carbamazepine	<p>Teratogenic, but this may be a low risk. Neural tube defects (including spina bifida) therefore folic acid 5mg is recommended Use in the third trimester may necessitate maternal and neonatal vitamin K.</p>
Lamotrigine	<p>Low risk when used as monotherapy, although risk of cleft palate.</p>

	Plasma levels change throughout pregnancy with the clearance of lamotrigine significantly increased during pregnancy. Average dose increases can be up to 250% (2.5 times).
Haloperidol, chlorpromazine, trifluoperazine	There is most experience with these FGAs. Chlorpromazine can cause sedation and constipation, which may be a problem.
Olanzapine, quetiapine, risperidone	<p>If an atypical antipsychotic agent is required, then olanzapine or quetiapine are preferred because there is more experience with these agents.</p> <p>Low folate levels have been associated with the SGAs, therefore dietary advice and supplementation with 5mg folic acid (see note m. above) should be considered.</p> <p><u>Olanzapine</u> – consider the risk factors for gestational diabetes and weight gain.</p> <p><u>Quetiapine</u> - If a clinical decision is made to prescribe, there is more experience with the immediate release preparation (rather than XL) and this should be used in preference. The incidence of hyperglycaemia in patients exposed to quetiapine appears to be lower than that for olanzapine or risperidone.</p> <p><u>Risperidone</u> - Consider the risk factors for dose dependent hyperprolactinaemia and EPSE.</p>
SSRI antidepressants	<p>Antidepressants should be avoided if possible.</p> <p>Increased risk of decreased gestational age & birth weight and spontaneous abortion.</p> <p>Some (but not all) studies have reported significantly increased risks of cardiovascular malformations (septal heart defects). These are most consistently demonstrated with paroxetine but have also been reported for citalopram, fluoxetine, and sertraline. A causative relationship has not been established for any SSRI.</p> <p>Persistent pulmonary hypertension in the newborn (PPHN) has been associated with SSRIs if used after 20 weeks of pregnancy.</p> <p>Neonatal withdrawal symptoms may also occur.</p>
Tricyclic antidepressants	<p>Antidepressants should be avoided if possible.</p> <p>See note l above</p> <p>Most evidence for amitriptyline and imipramine (although constipation and sedation can be a problem).</p> <p>Neonatal withdrawal effects.</p>

6.2 In Breast-feeding

- a. Up to date advice should be obtained and the lowest effective dose used.
- b. **Contact Medicines Information department on 01903 285075 option 2 during working hours or via email medicines.information@wsht.nhs.uk. The clinical pharmacist can also access these services, so can be contacted in the first instance.**

- c. The benefits of breast-feeding to the mother and infant must be weighed against the risks due to exposure in the infant. A treatment that allows breast-feeding should be explored rather than recommending not breast-feeding.
- d. The treatment regime established during pregnancy should be continued after delivery if clinically indicated. All psychotropics are detected in the milk. Drug exposure to an infant whilst breast-feeding is less than when in utero.
- e. Infant exposure can be reduced by timing feeds to avoid peak drug levels and avoiding long acting medications or taking the dose just before the longest sleep.
- f. When prescribing medication to breast-feeding women, consideration should be given to the health of the neonate. Premature infants are at greater risk from exposure due to immature excretory function. Drugs should be avoided if an infant is premature or has renal, hepatic, cardiac or neurological impairment.
- g. The infant should be monitored for any specific adverse effects of the drug as well as feeding patterns and also growth & development ⁽⁴⁾.

Summary of the use of mood stabilisers in breast- feeding - This guidance should not take the place of the latest specialist advice

Medicine (5, 6, 7)	Comment
Lithium	Breast milk levels may be approximately 40% (24-72%) with infant serum levels range from 5-200% of the maternal serum concentrations. Adverse effects reported in infants exposed to lithium during breast feeding include cyanosis, lethargy, hypothermia, hypotonia and a heart murmur all of which stopped within 3 days of stopping breast feeding. There have also been reports of no adverse effects. Monitor baby for signs of toxicity ⁽⁴⁾ .
Valproate	Infant levels reported as undetectable to 40% of maternal serum levels. Thrombocytopenia and anaemia reported in an infant, this reversed when breast feeding was discontinued. Hepatotoxicity due to valproate. Monitor LFTs and FBC in baby.
Carbamazepine	Infant serum levels range from 6-65% of the maternal serum levels. Adverse effects reported include cholestatic hepatitis & hepatic dysfunction, seizure like activity, drowsiness, irritability, high-pitched crying, hyperexcitability and poor feeding.
Lamotrigine	Infant serum levels range form 18-50% of maternal serum levels. No adverse events reported and no changes in hepatic or electrolyte profiles. But due to the theoretical risk of life-threatening rash it is advisable to avoid lamotrigine whilst breast feeding.
Antipsychotics	Sulpiride, olanzapine and quetiapine appear to be lower risk. Possible risk of drowsiness in the child with olanzapine and quetiapine.
Antidepressants	Consider continuing the antidepressant used in pregnancy. Nortriptyline and imipramine may be considered the agents of choice due to less sedation, relatively low milk levels and lack of adverse events reported. Sertraline is considered to be the SSRI of choice.

6.3 In Older adults

It is estimated that up to 10% of bipolar patients do not actually develop the disease until they are over 50 years of age. The burden of bipolar disorder on the elderly population will therefore increase as the general population lives to increasing old age in the future.

The use of drug therapy for elderly patients with bipolar disorder follows the same principles as for other bipolar patient groups, although there are very few published studies that look specifically at the use of mood stabilizers in the elderly. Basic principles must therefore be considered – such as elderly patients are likely to have altered pharmacodynamics and pharmacokinetics compared to younger adults and will therefore be more prone to adverse effects of drug therapy. In addition, this patient group will usually be co-prescribed a larger amount of physical healthcare medicines than younger patients and this will increase the risk of drug-drug interactions with psychotropic drugs they may also be prescribed. In general, bipolar treatment doses will be lower than those used in younger adults and may need to be more carefully titrated and monitored.

a. **General principles for prescribing:**

- Use drugs only when absolutely necessary.
- Avoid drugs that block alpha-adrenoreceptors (risk of hypotension, dizziness, falls etc), block acetylcholine (impact of cognitive functioning and mobility, constipation, urinary retention etc), are sedating (risk of confusion, ataxia, falls etc) or are potent hepatic enzyme inhibitors (risk of drug interactions).
- When titrating doses, “start low and go slow”, but be careful not to under-treat. (Optimum dose may still be in the younger adult range).
- Avoid treating drug side-effects with other drugs. Take into account increased risk of drug interactions.
- Keep treatment regimes simple. Prescribe the minimum number of drugs in the minimum number of daily doses wherever possible.
- Consider co-morbidities such as cardiac, renal and hepatic and consult relevant sections.

Summary of the use of mood stabilizers in older adults

Medication	Comment
Lithium	Increased volume of distribution and compromised renal function in the elderly means that reduced clearance and increased risk of toxicity commonly occurs. Because of this, doses of lithium often only need to be 50% of those used in younger adult populations. Starting doses should also be 50% lower. Consideration should be given to more frequent monitoring of lithium plasma levels in elderly patients. In particular, levels should be very closely monitored following lithium dose changes or changes to co-prescribed drugs. Effective maintenance plasma levels can often be lower in the elderly than in younger adult patients and toxic plasma levels (e.g. > 1.5mmol/l) are much more likely to have serious consequences.

	<p>The diet and in particular the fluid intake of elderly patients should be carefully considered, as dehydration (common in the elderly population) can quickly lead to raised plasma levels.</p> <p>Co-prescription of other drugs is common in the elderly, especially for physical health conditions and the potential for drug-drug interactions with lithium is high. For example, serious interactions can occur with:</p> <ul style="list-style-type: none"> ➤ Diuretics, especially thiazides and to a lesser extent loop diuretics ➤ Non-steroidal anti-inflammatory drugs (NSAIDs), including COX-II inhibitors and NSAIDs purchased without prescription (e.g. ibuprofen/ Nurofen®). ➤ Angiotensin-converting enzyme (ACE) inhibitors such as lisinopril and ramipril, and angiotensin-II antagonists such as losartan and valsartan.
Valproate	<p>The elimination half-life of valproate may be considerably extended in the elderly, which may increase the risk of toxicity. Wherever possible dose titration should be slow and lower therapeutic doses aimed for than in younger adults.</p> <p>Confusion, tremor and ataxia may all occur with valproate treatment. These effects are more common in the elderly and in particular during dose titration if this is performed too rapidly.</p> <p>Valproate exerts a high hepatic load that obviously may have more serious consequences in the elderly. Pancreatitis is also linked to valproate use so patients/carers should be counselled on identification of signs and symptoms.</p> <p>The metabolism of valproate is inhibited by erythromycin.</p>
Carbamazepine	<p>Although there are no clear recommendations to use reduced doses of carbamazepine in the elderly, lower doses should always be considered based on potential pharmacokinetic changes.</p> <p>Carbamazepine can induce neutropenia and chronic leucopenia. Blood parameters (including LFTs) should be monitored at least 6-monthly in all patients. Consideration should be given to more frequent monitoring in elderly patients.</p> <p>Carbamazepine is known to cause hyponatraemia in many patients. The elderly are more at risk of developing this condition so consideration should be given to closer monitoring.</p> <p>Carbamazepine is a potent inhibitor of hepatic enzymes and its own metabolism is also significantly affected by several other medicines. For example, serious interactions can occur with:</p> <ul style="list-style-type: none"> ➤ Some antibiotics e.g. clarithromycin and erythromycin ➤ Antidepressants e.g. tricyclics ➤ Many antipsychotics ➤ Antifungals such as fluconazole and ketoconazole ➤ Calcium channel blockers such as felodipine and diltiazem ➤ Corticosteroids such as prednisolone ➤ Warfarin and other oral anticoagulants e.g. acenocoumarol

Lamotrigine	<p>The elimination half-life of lamotrigine may be considerably extended in the elderly, which may increase the risk of toxicity. Wherever possible dose titration should be slow and lower therapeutic doses aimed for than in younger adults.</p> <p>Lamotrigine can induce anaemia, leucopenia and other blood disorders. Blood parameters (along with renal function and LFTs) should be monitored at least 6-monthly in all patients. Consideration should be given to more frequent monitoring in elderly patients.</p> <p>Lamotrigine can also exacerbate Parkinson's disease so patients and carers should be warned to monitor for any worsening of symptoms.</p>
Fluoxetine	<p>Less risk when compared with other antidepressants such as cardiac risks but can cause weight loss and hyponatremia. Increased risk of falls and osteoporotic fractures in the over 50s.</p>
Aripiprazole	<p>The effectiveness of aripiprazole in the treatment of schizophrenia and Bipolar I Disorder in patients aged 65 years and older has not been established. Owing to the greater sensitivity of this population, a lower starting dose should be considered when clinical factors warrant.</p>
Haloperidol	<p>Treatment should start with half the dosage stated for adults and adjusted according to the results if necessary.</p>
Olanzapine	<p>A lower starting dose (5 mg/day) is not routinely indicated but should be considered for those 65 and over when clinical factors warrant.</p> <p>Periodic blood pressure monitoring is recommended and there maybe a slightly higher seizure risk in the elderly.⁽⁶⁾</p>
Quetiapine	<p>As with other antipsychotics, quetiapine should be used with caution in the elderly, especially during the initial dosing period. The rate of dose titration of extended release preparation (XL) may need to be slower, and the daily therapeutic dose lower, than that used in younger patients.</p> <p>Elderly patients should be started on 25 mg/day IR. The dose should be increased daily, in increments of 25 to 50 mg, to an effective dose.</p> <p>Alternatively elderly patients should be started on 50 mg/day XL. The dose can be increased in increments of 50 mg/day to an effective dose, depending on the clinical response and tolerability of the individual patient.</p> <p>The mean plasma clearance of quetiapine was reduced by 30% to 50% in elderly patients when compared to younger patients. Therefore monitoring of blood pressure during titration maybe appropriate.</p> <p>Efficacy and safety have not been evaluated in patients over 65 years with depressive episodes in the framework of bipolar disorder.</p>
Risperidone	<p>A starting dose of 0.5 mg twice daily is recommended. This dosage can be individually adjusted with 0.5 mg twice daily increments to 1 to 2 mg twice daily. Blood pressure monitoring during titration maybe appropriate.</p>

Asenapine	Asenapine should be used with care in the elderly. Limited data on efficacy in patients 65 years of age and older are available. Postural hypotension maybe 30-40% higher than younger adults.
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6.4 In children and adolescents.

This guideline is not intended to serve as an absolute standard of pharmacological treatment, but to guide the prescriber in making the necessary decisions in the treatment of bipolar affective disorder (BPAD) in children and adolescents. The evidence base for the treatment of BPAD in the under 18 year old age group is limited when compared with the adult population and the evidence that is available is of open label design trials with few double blind placebo controlled trials conducted. ⁽⁵⁾ Also of note is that the evidence that has been collected is predominantly for the adolescent age group.

The recent NICE guidance recommended that psychological interventions should form the foundation of therapy for adolescents and children, as medicines used in bipolar disorder can have a damaging effect on children's growth and development. If pharmacological intervention is required then follow the recommendations for adults (section 1, 2 and 3).

6.4.1 Diagnosis Issues

Estimates for the prevalence of BPAD in the children and adolescent population vary, and have been reported as 2% in one meta-analysis. ⁽⁹⁾ General UK guidelines and current practice adheres to a relatively narrow definition of BPAD compared to the US. Current UK guidance suggests that clinicians need to be aware of significant mood elation for periods greater than 7 days compared to normal baseline features. ^(1, 2) Interestingly bipolar depression according to NICE should not normally be diagnosed in those under 18 years due to the insufficiency in the diagnostic criteria, which is not well enough established for routine use. ⁽¹⁾

Another factor for clinicians to consider when diagnosing BPAD in this age group is that it is frequently co-morbid, having some symptom(s) overlap with other psychiatric conditions presenting in children and adolescents. NICE does suggest that ADHD, conduct disorders, substance misuse, previously undiagnosed learning disabilities, abuse (sexual, physical & emotional) and organic causes should be a differential diagnosis from BPAD.

6.4.2 Choice of Medication

Mania

a. Acute Treatment of Mania

Both the current NICE guidance ⁽¹⁾ and the BAP ⁽²⁾ evidence based guidance on the use of medication in BPAD in children & adolescents suggest that adult treatment guidelines should be followed due to the limited evidence base available in the under 18 age group. Further to this the treatment guideline by Kowatch et al ⁽¹⁰⁾ also states that it is sensible to follow adult guidelines, with potential first line options in the treatment of mania being both the mood stabilisers; lithium, valproate and carbamazepine with the antipsychotics; aripiprazole,

olanzapine, quetiapine and risperidone. Irrespective of the choice of medication used the accepted practice is to start with monotherapy at a dose at the lower end of the dosing range. (1, 2, 10)

The choice of medication in the treatment for BPAD will often come down to the severity of the condition presented. The actual medication prescribed should be based on patient specific factors such as physical history, previous response (if applicable), medications prescribed as well as family and patient preferences so affecting compliance. (1, 2, 5)

To treat mania or hypomania in young people see NICE's technology appraisal guidance on aripiprazole for treating moderate to severe manic episodes in adolescents with bipolar I disorder and also consider the recommendations for adults (section 2, 3 and 4). Refer to the BNF for children to modify drug treatments, be aware of the increased potential for a range of side effects, and do not routinely continue antipsychotic treatment for longer than 12 weeks.

Do not offer valproate to girls or young women of childbearing potential ([see Trust guidance](#)).

b. Severe Mania with psychotic features

In patients who present with severe behavioural disturbance or if psychotic symptoms are present, antipsychotics should be considered first due to the more rapid anti-manic response compared to lithium (2, 5). If there is no response after a suitable trial treatment period then switching to another antipsychotic or valproate in such patients is appropriate.

c. Mild to Moderate Mania

Where there is less severe behavioural disturbance and lack of psychotic symptoms valproate or lithium should be considered as well as antipsychotics as first-line treatments. (2, 5)

d. Partial Response

Patients who have partially responded to monotherapy may be augmented with another medication from the other class of medications e.g. if an antipsychotic has been used initially then the use of a mood stabiliser as a second line agent is a suitable treatment strategy. (2, 5, 10)

e. Treatment Duration

Again there is little evidence on the smallest effective treatment duration in youth populations so treatment duration of 18 months or greater has been suggested. (5)

Bipolar depression

a. Treatment of Bipolar depression

The evidence base for antidepressant use in bipolar II depression in adults is moderate at best, with such antidepressant use in those under 18 years old being very limited. Further to this due to the increased potential of antidepressant induced manic switches in younger people

compared to the general population, current guidance from NICE and BAP recommends that antidepressants should only be prescribed in the presence of a mood stabiliser. ^(1, 2)

The antidepressants with the greatest likelihood of mania switching are those with a noradrenergic effect such as tricyclic antidepressants and the SNRI's; venlafaxine and duloxetine ^(2, 6, 8). These medications should be avoided in youth populations due to lack of evidence of efficacy and also the increased potential side effect burden. ^(2, 4, 6, 10)

Bipolar depression

Offer a structured psychological intervention (individual cognitive behavioural therapy or interpersonal therapy) to young people with bipolar depression. The intervention should be of at least 3 months' duration and have a published evidence-based manual describing how it should be delivered

b. Medication options

Suitable options with a reasonable evidence base in adult populations with bipolar depression are quetiapine ^(2, 11) and lamotrigine ^(2, 12), with lithium as a second line therapy. ^(1, 2, 5) Carandang et al ⁽¹³⁾ have shown some evidence of lamotrigine in children and adolescents being effective.

If an antidepressant is deemed clinically necessary, then fluoxetine is the treatment of choice starting at 10mg daily and increasing to 20mg daily if necessary. ⁽¹⁾ Second line options are sertraline or citalopram after a suitable treatment trial has been ineffective. ⁽¹⁾

c. Long Term Treatment

Lithium monotherapy has been shown to decrease the risk of suicide in bipolar populations and monotherapy is probably effective against both manic and depressive relapse. ^(1, 5, 10) It is likely to be more effective at preventing manic relapse. Bearing this in mind lithium should be considered as long term therapy. If an antipsychotic is considered for long term prevention then NICE has suggested the use of a 2nd generation antipsychotic such as quetiapine or aripiprazole that is associated with lower weight gain and non-elevation of prolactin levels. ^(1, 2)

6.4.3 General principles of prescribing antipsychotics

For general guidance on prescribing of antipsychotics please see the [Trust Guidance on the prescribing of antipsychotics](#), which can be found at the following web address:

Antipsychotics are also less well tolerated in children and adolescents than in adults. This population appears to have a higher risk of experiencing/developing adverse effects including extrapyramidal symptoms (EPSEs), prolactin elevation, sedation, weight gain and metabolic side-effects. ^(14, 15, 16) This makes the choice of antipsychotic challenging. Olanzapine has been particularly associated with weight gain, whilst risperidone has a higher incidence of elevated prolactin. ^(6, 8, 15, 16) The following general recommendations can be made for all patients prescribed antipsychotics, irrespective of diagnosis:

- Patient and/or parent(s) or carer(s) should be directly involved in the choice of medication.
- Antipsychotics should only be used where their use has been fully explained (verbally and written), and consent sought from the patient's parent(s) or carer(s) where appropriate.
- Choice of antipsychotic should be based on the limited efficacy data available and side-effect profile.
- Symptoms should be treated, not the diagnosis.
- Low starting doses should be used, then increase gradually according to response.
- Only one antipsychotic should be used at one time, except when switching from one antipsychotic to another.
- Ensure an adequate trial of medication before changing. (8-12 weeks is a reasonable time for adequate benefits of treatment to be witnessed in children and adolescents).
- Only one medication should be changed at a time.
- Effect, tolerability and dose should be regularly reviewed.

Suggested mood stabilizer dosing recommendations in children and adolescents

Medication ⁽¹⁷⁾	Comment
Lithium	<p>The carbonate salt of lithium is licensed in the UK for the treatment and prophylaxis of mania, bipolar disorder in 12 years and over. See guidance on monitoring of lithium serum concentrations – target of 0.6-1.0 mmol/l</p> <p>Camcolit® (250mg I/R tablets & 400mg M/R tablets): Initial prophylactic dose of 300-400mg daily, increasing to 1-1.5g daily (according to plasma levels).</p> <p>Liskonum® (M/R tablets): Treatment, initially 225-675mg twice daily, with initial prophylactic dose of 225-400mg twice daily</p> <p>Note: Preparations vary widely in bioavailability hence prescribe by brand. If changing brand, the same precautions as initiation should be adhered to.</p>
Carbamazepine	<p>Licensed in the prophylaxis of bipolar disorder, unresponsive to lithium.</p> <p>Immediate release formulation:</p> <p>Child 1 month to 12 years: initially 5mg/kg at night or 2.5mg kg twice daily; increased as necessary by 2.5mg-5mg/kg every 3-7 days. Usual maintenance dose is 5mg/kg 2-3 times daily, with doses up to 20mg/kg daily having been used.</p> <p>Child 12-18 years: Initially 100-200mg 1-2 times daily, increased slowly to usual maintenance dose of 200-400mg 2-3 times daily. Maximum of 1.8g daily.</p> <p>Modified release formulation:</p> <p>Child 5-18 years: follow as indicated above starting at 400mg daily in 2 divided doses aiming for symptom control or daily maximum of 1600mg.</p>

Valproate	<p>Unlicensed in children and adolescents for BPAD.</p> <p>Child 12-18 years: Initially 600mg daily in 1-2 divided doses, increased gradually in steps of 150-300mg every three days. Usual maintenance 1-2g daily. Maximum of 2.5g daily in 2 divided doses.</p>
Lamotrigine ⁽¹³⁾ (for bipolar depression)	<p>Unlicensed in children and adolescents for BPAD.</p> <p>Child 12-18 years: Initially 25mg daily for 14 days, increased to 50mg daily for another 14 days, with further increases of a maximum of 100mg over 7-14 days. Usual maintenance of 100-200mg daily in divided doses. Maximum of 500mg daily.</p> <p>Up to 12 weeks of treatment for moderate to severe manic episodes in bipolar I disorder in adolescents aged 13 and older).¹⁸</p>
Fluoxetine	<p>Unlicensed in children and adolescents for BPAD.</p> <p>Licensed for major depression</p> <p>Child 8–18 years 10 mg daily increased after 1–2 weeks if necessary, max. 20 mg daily</p> <p>Long duration of action Consider the long half-life of fluoxetine when adjusting dosage (or in overdose)</p> <p>Note Daily dose may be administered as a single or divided dose</p>
Aripiprazole	<p>Indicated for the treatment up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older.</p> <p>Child 13- 18 years: Suggested starting dose is 2mg (as aripiprazole liquid), increasing to 5mg daily after 2 days, and after a further 2 days increased to 10mg daily. If necessary increase in steps of 5mg to a maximum of 30mg daily.</p>
Haloperidol	<p>Unlicensed in children and adolescents for BPAD.</p> <p>Licensed for schizophrenia (under specialist supervision)</p> <p>By mouth</p> <p>Child 3–13 years initially 500 micrograms daily in 2–3 divided doses; usual target dose 1–4 mg daily in 2–3 divided doses; max. 6 mg daily in 2–3 divided doses</p> <p>Child 13–18 years initially 500 micrograms daily in 2–3 divided doses; usual target dose 1–6 mg daily in 2–3 divided doses; max. 10 mg daily in 2–3 divided doses</p>
Olanzapine	<p>Unlicensed in children and adolescents (under 18 years).</p> <p>Child 12-18 years: 15mg daily, adjusted to dose range of 5-20mg daily. Doses above 15mg daily should be prescribed after reassessment. Max 20mg daily.</p>
Quetiapine	<p>Unlicensed in children and adolescents (under 18 years).</p> <p>Immediate release formulation:</p> <p>Child 12-18 years: 25mg twice daily on day 1, then 50mg twice daily on day 2, then 100mg twice daily on day 3, then 150mg twice daily on day 4, then 200mg twice daily on day 5. Usual dose range of 400mg-600mg daily, with daily increases limited to 100mg. Maximum dose of 750mg daily.</p>

Risperidone	Unlicensed for mania or schizophrenia in children and adolescents Child 12-18 years: Initially 0.5mg (500mcg) once daily, increasing in steps of 0.5mg-1mg daily according to response. Usual dose of 2.5mg daily in 1-2 divided doses. Maximum of 6mg daily.
Asenapine ⁽⁴⁰⁾	The safety and efficacy of asenapine in children aged below 18 years has not been established.

Note: These are suggested dosing regimens taken from the BNFC, but it is recognised that it may be necessary in some younger patients to titrate doses up more slowly.

6.5 Learning disabilities:

The diagnosis of BPAD in this patient population is compounded by difficulty in communication. The presentation of BPAD in an individual with Learning Disability (LD) may vary to the general population, with symptoms more likely to present as biological (alteration in sleep pattern), changes in motor activity or behavioural disturbance.

LD specific easy read patient information on bipolar can be accessed via the following site; <http://www.rcpsych.ac.uk/pdf/Bipolar%20ld%20final.pdf>

It should be noted that there are no systematic controlled trials of medication for the treatment of bipolar depression or mania in this patient population ⁽¹⁹⁾.

Patients with LD are more likely to have altered sensitivity to the effects of medication and changes in the effects of any given medication which leads to difficulty in determining the correct dose. ⁽¹⁸⁾ As such the recommendation would be to treat as per Trust guidelines, **lower starting doses and slower titrations** are considered to be best practice in this patient population, due to the increased sensitivity of these individuals to the effects and side effects of medication, particularly cognitive dulling.

The possibility of co-morbid epilepsy +/- cardiovascular abnormalities in this patient population should be borne in mind when deciding on drug therapy, as psychotropic medications have the potential to decrease seizure threshold and adversely affect QTc interval. Please refer to Trust guidance, Maudsley Prescribing Guidelines, The Psychotropic Drug Directory or pharmacists for further information.

Individuals with LD are more likely to experience drug-drug interactions, as often more than one medication is prescribed. ⁽¹⁹⁾ Medication regimens should take into account the potential for interaction. ⁽¹⁾

Difficulties in communication should be considered when assessing for the side effect burden of medication. Pictorial representation of possible side effects may aid in assessment for some individuals. Please see the link to LD specific medication leaflets:

<http://www.rcpsych.ac.uk/mentalhealthinfo/problems/learningdisabilities.aspx>

If an individual exhibits challenging behaviour soon after a change of medication or a dose change, the potential for this to be a communication of the presence of side effects should be considered, and an appropriate screening tool used.

Particular care should be taken to monitor for EPSE, tardive dyskinesia, hyperprolactinaemia and metabolic syndrome.

The formulation of medication used in this patient population may be important due to the relatively high rate of dysphagia. Care should be taken if converting between tablet and liquid form as not all preparations are equivalent e.g. lithium carbonate tablets and lithium citrate liquid.

6.6 Cardiac dysfunction

General principles in cardiac disease. ^(5, 6, 27)

1. Polypharmacy should be avoided where possible, particularly with drugs likely to affect the cardiac rate and electrolyte balance.
2. Awareness of QT prolongation is increasing and so care is essential with drugs likely to increase the QTc interval. Also consult the Trust antipsychotic guidance as this has much more detail on QTc prolongation and comparison between antipsychotics.
3. Avoid drugs specifically contraindicated.
4. Start low and go slow is, as ever, good advice. Rapid dose escalation should be avoided.

The summary table below is not exhaustive and the advice of a clinical pharmacist can be sought to aid the patient and clinician in the decision making process.

	Contra indication	Precautions
Lithium	<p>Cardiac disease associated with rhythm disorder or cardiac insufficiency.</p> <p>Brugada syndrome or family history of Brugada syndrome.</p>	<p>Cardiac function should be assessed prior to initiation especially in patients with cardiovascular disease or a risk factor(s) for cardiovascular disease. ECG should be carried out in patients with risk factors. ⁽¹⁾</p> <p>As a precautionary measure, lithium should be avoided in patients with congenital long QT syndrome. Caution should be exercised in patients with risk factors such as QT interval prolongation (e.g. uncorrected hypokalaemia, bradycardia), and in patients concomitantly treated with drugs that are known to prolong the QTc interval.</p> <p>Drugs affecting the renin angiotensin system (ACE inhibitors, Angiotensin II receptor antagonists) and diuretics can interact – see appendix 5.</p>

Carbamazepine	Patients with atrioventricular block.	Rare side effects include cardiac conduction disturbances. ⁽²⁾
Valproate	None	None
Lamotrigine	None	None
Fluoxetine	None	<p>Cases of QT interval prolongation and ventricular arrhythmia including torsade de pointes have been reported during the post-marketing period.</p> <p>Fluoxetine should be used with caution in patients with conditions such as congenital long QT syndrome, a family history of QT prolongation or other clinical conditions that predispose to arrhythmias (e.g., hypokalemia and hypomagnesemia, bradycardia, acute myocardial infarction or uncompensated heart failure) or increased exposure to fluoxetine (e.g., hepatic impairment).</p> <p>If patients with stable cardiac disease are treated, an ECG review should be considered before treatment is started. If signs of cardiac arrhythmia occur during treatment with fluoxetine, the treatment should be withdrawn and an ECG should be performed.</p>
Aripiprazole	None	<p>Use with caution in patients with known cardiovascular disease (history of myocardial infarction or ischaemic heart disease, heart failure, or conduction abnormalities), cerebrovascular disease, conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medicinal products) or hypertension, including accelerated or malignant.</p> <p>The incidence of QT prolongation is comparable to placebo. As with other antipsychotics, aripiprazole should be used with caution in patients with a family history of QT prolongation.</p> <p>Uncommon side effects include tachycardia and orthostatic hypotension, QT prolongation, ventricular arrhythmias, sudden unexplained death, cardiac arrest, torsades de pointes and bradycardia.</p>
Haloperidol	Patients with clinically significant cardiac disorders (see SmPC for more details) or with other QT prolonging drugs.	The risk-benefit of haloperidol treatment should be fully assessed before treatment is commenced and patients with risk factors for ventricular arrhythmias such as cardiac disease, family history of sudden death and/or QT prolongation; uncorrected electrolyte disturbances; subarachnoid haemorrhage, starvation or alcohol abuse should be monitored carefully (ECGs and

		<p>potassium levels), particularly during the initial phase of treatment to obtain steady plasma levels.</p> <p>The risk of QT prolongation and/or ventricular arrhythmias may be increased with higher doses or with parenteral use, particularly intravenous administration.</p> <p>ECG monitoring should be performed for QT interval prolongation and for serious cardiac dysrhythmias if haloperidol is administered intravenously.</p> <p>Baseline ECG is recommended prior to treatment in all patients, especially in the elderly and patients with a positive personal or family history of cardiac disease or abnormal findings on cardiac clinical examination. During therapy, the need for ECG monitoring (e.g. at dose escalation) should be assessed on an individual basis. Whilst on therapy, the dose should be reduced if QT is prolonged, and haloperidol should be discontinued if the QTc exceeds 500 ms.</p> <p>Periodic electrolyte monitoring is recommended, especially for patients taking diuretics, or during intercurrent illness.</p>
Olanzapine	None	<p>In clinical trials, clinically meaningful QTc prolongations ≥ 500 milliseconds [msec] were uncommon (0.1% to 1%) in patients treated with olanzapine, with no significant differences in associated cardiac events compared to placebo.</p> <p>However, as with other antipsychotics, caution should be exercised when olanzapine is prescribed with medicines known to increase QTc interval, especially in the elderly, in patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalaemia or hypomagnesaemia.</p>
Quetiapine	None	<p>Use with caution in patients with known cardiovascular disease, cerebrovascular disease, or other conditions predisposing to hypotension.</p> <p>May induce orthostatic hypotension, especially during the initial dose-titration period and therefore dose reduction or more gradual titration should be considered if this occurs. A slower titration regimen could be considered in patients with underlying</p>

		<p>cardiovascular disease.</p> <p>QT prolongation has been reported with quetiapine at therapeutic doses and in overdose. As with other antipsychotics, caution should be exercised when quetiapine is prescribed in patients with cardiovascular disease or family history of QT prolongation. Also, caution should be exercised when quetiapine is prescribed either with medicines known to increase QTc interval, or with concomitant neuroleptics, especially in the elderly, in patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalaemia or hypomagnesaemia.</p>
Risperidone	None	<p>Use with caution in patients with known cardiovascular disease (e.g. heart failure, myocardial infarction, conduction abnormalities, dehydration, hypovolemia, or cerebrovascular disease), and the dosage should be gradually titrated as recommended. A dose reduction should be considered if hypotension occurs.</p> <p>QTc prolongation has been reported. Common side effects include tachycardia.</p> <p>Uncommon side effects include atrioventricular block, bundle branch block, atrial fibrillation, sinus bradycardia, bradycardia and palpitations</p>
Asenapine	None	<p>Asenapine may induce orthostatic hypotension. Elderly patients are particularly at risk for experiencing orthostatic hypotension.</p> <p>Caution in patients with known cardiovascular disease (e.g. heart failure, myocardial infarction or ischemia, conduction abnormalities), cerebrovascular disease, or conditions that predispose the patient to hypotension (e.g., dehydration and hypovolemia).</p> <p>Clinically relevant QT prolongation does not appear to be associated with asenapine. Caution should be exercised when asenapine is prescribed in patients with known cardiovascular disease or family history of QT prolongation, and in concomitant use with other medicinal products thought to prolong the QTc interval.</p>

6.7 Renal dysfunction

Classification for chronic kidney disease (CKD) has changed, now being described as stages 1–5. Each stage is defined by the patient's eGFR (or estimated GFR) which is calculated using the MDRD equation (modification of diet in renal disease). One point to note is that the eGFR is normalised to a standard body surface area of 1.73 m². There is relatively good correlation between the two equations for calculating renal function in patients of average weight, and either could be used for the majority of drugs. However, eGFR should not be used for calculating drug doses in patients at extremes of body weight nor for drugs with a narrow therapeutic window unless it is first corrected to the actual GFR for that patient. ⁽⁴¹⁾

At extremes of body weight neither the MDRD nor the Cockcroft-Gault equation are particularly accurate.

Classification	
Stage 1	GFR >90ml/min/1.73m ² .
Stage 2	Mild impairment; GFR 60-89ml/min/1.73m ² .
Stage 3	Moderate impairment, GFR 30-59ml/min/1.73m ² .
Stage 4	Severe impairment, GFR 15-29mL/min/1.73m ² .
Stage 5	Established renal failure, GFR <15/min/1.73m ² or on dialysis.

The use of drugs in patients with impaired renal function can give rise to problems for several reasons:

- Altered pharmacokinetics of some drugs, i.e. changes in absorption, tissue distribution, extent of plasma protein binding, metabolism and excretion. In renal impairment these parameters are often variable and interrelated in a complex manner. This may be further complicated if the patient is undergoing renal replacement therapy (dialysis).
- Sensitivity to some drugs is increased, even if elimination is unimpaired.
- The incidence of side-effects is greater in renally impaired patients.
- Some drugs are ineffective when renal function is reduced.
- Renal function generally declines with age, and many elderly patients have a GFR less than 50 ml/min which, because of reduced muscle mass, may not be reflected by an elevated creatinine. Consequently, one can justifiably assume mild renal impairment when prescribing for the elderly.

Dose in renal impairment:

The level of renal function below which the dose of a drug must be reduced depends largely on the extent of renal metabolism and elimination, and on the drug's toxicity. Most drugs are relatively well tolerated, have a broad therapeutic index or are metabolised and excreted

hepatically, so precise dose modification is unnecessary. In such cases, the prescriber is instructed to 'dose as in normal renal function'.

For renally excreted drugs with a narrow therapeutic index, the total daily maintenance dose may be reduced either by decreasing the dose or by increasing the dosing interval, or sometimes by a combination of both. ⁽⁴¹⁾

The summary table below is not exhaustive and the advice of a clinical pharmacist can be sought to aid the patient and clinician in the decision making process.

	Contraindication	Precautions
Lithium	Severe renal impairment (stage 4)	<p>Lithium excretion is reduced in the presence of renal impairment. This increases the risk of toxicity. If patients with mild or moderate renal impairment are being treated with lithium, serum levels should be closely monitored.</p> <p>Older patients, and others with reduced renal function, will require lower doses. ⁽²⁾</p> <p>Renal function should be monitored (more frequently than recommended 6 monthly) in patients with renal impairment, and in patients with polyuria and polydipsia.</p> <p>The possibility of renal dysfunction arising during prolonged treatment should be borne in mind and periodic assessments made.</p> <p>Rare cases of nephrotic syndrome have been reported.</p>
Carbamazepine	None	<p>Baseline and periodic complete urinalysis and blood urea nitrogen (BUN) determinations are recommended.</p> <p>Rare side effects include renal failure. ⁽²⁾</p>
Valproate	None	<p>Renal insufficiency: In patients with renal insufficiency, it may be necessary to decrease dosage. As monitoring of plasma concentrations may be misleading, dosage should be adjusted according to clinical monitoring.</p> <p>Mild to moderate - Reduce dose</p> <p>Severe - Alter dose according to free serum valproic acid concentration.</p>
Lamotrigine	None	<p>Caution should be exercised when administering to patients with renal failure. For patients with end-stage renal failure, lower initial doses of lamotrigine may be required. Reduced maintenance doses may be effective for patients with significant renal functional impairment.</p>

Fluoxetine	None	Fluoxetine is extensively metabolised by the liver and excreted by the kidneys. When given fluoxetine 20mg/day for 2 months, patients with severe renal failure (GFR <10ml/min) requiring dialysis showed no difference in plasma levels of fluoxetine or norfluoxetine compared to controls with normal renal function.
Aripiprazole	None	The pharmacokinetic characteristics were found to be similar in patients with severe renal disease compared to young healthy subjects. Dose adjustment is not usually required.
Haloperidol	None	Caution is advised. There are no apparent problems but accumulation may occur. ⁶
Olanzapine	None	A lower starting dose (5mg) should be considered for renal impairment.
Quetiapine	None	Start low and go slow. ⁽⁵⁾
Risperidone	None	Irrespective of the indication, starting and consecutive dosing should be halved. Dose titration should be slower for patients with renal impairment.
Asenapine	None	The pharmacokinetics of asenapine following a single dose of 5 mg asenapine were similar among subjects with varying degrees of renal impairment and subjects with normal renal function. Dose adjustment is not usually required.

6.8 Hepatic Dysfunction

Many of the medicines used in psychiatry are hepatically metabolised. Hepatic impairment may result in:-

- Impaired metabolism.
 - The higher the severity of the impairment the greater the risk of toxicity or side effects due to impaired drug metabolism. Care is especially required with medicines with a narrow therapeutic window.
 - Waste materials may accumulate leading to confusion and possible hepatic encephalopathy. As constipation can exacerbate encephalopathy and sedation can mask the symptoms, care is required for medicines which can cause constipation or sedation.
- Impaired production of plasma proteins and vitamin K clotting factors.
 - This can lead to increased risk of bleeds.
 - Increase risk of toxicity for highly protein bound medicines.
- Reduced hepatic flow
 - Medicines subject to first pass metabolism may show elevated plasma levels.

Childs-Pugh classification ⁽³¹⁾

Liver function tests (LFTs) are not a good indication of liver impairment. The degree of hepatic impairment is assessed by the Childs-Pugh classification which assesses the severity of liver cirrhosis.

Score	1	2	3
Bilirubin (micromol/l)	<34	34-50	>50
Albumin (g/l)	>35	28-35	<28
PT (prolonged)	<4	4-6	>6
Encephalopathy	none	mild	marked
Ascites	none	mild	marked

If there is primary biliary cirrhosis or sclerosing cholangitis then bilirubin is classified as <68=1; 68-170=2; >170=3.

The individual scores are summed and then grouped as:

- <7 = A grade
- 7-9 = B grade
- >9 = C grade (C grade forecasts a survival of less than 12 months).

The summary table below is not exhaustive and the advice of a clinical pharmacist can be sought to aid the patient and clinician in the decision making process.

	Contra indication	Precautions
Lithium	None	None
Carbamazepine	History of hepatic porphyrias (e.g. acute intermittent porphyria, variegate porphyria, porphyria cutaneatarda).	<p>LFTs should be performed before commencing treatment and periodically thereafter, particularly in patients with a history of liver disease and in elderly patients. The drug should be withdrawn immediately in cases of aggravated liver dysfunction or acute liver disease.</p> <p>Some LFTs in patients receiving carbamazepine may be found to be abnormal, particularly gamma glutamyltransferase (GGT). This is probably due to hepatic enzyme induction. Enzyme induction may also produce modest elevations in alkaline phosphatase. These enhancements of hepatic metabolising capacity are not an indication for the withdrawal of carbamazepine.</p> <p>Severe hepatic reactions to carbamazepine occur very rarely. The development of signs and symptoms of liver dysfunction or active liver disease should be urgently evaluated and treatment suspended pending the outcome of the evaluation. ⁽²⁾</p>
Valproate	Active liver disease Personal or family	Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in patients whose treatment included valproate.

	history of severe hepatic dysfunction, drug related.	<p>Patients most at risk, especially in cases of multiple anticonvulsant therapy, are infants and in particular young children under the age of 3 years and those with severe seizure disorders, organic brain disease, and (or) congenital metabolic or degenerative disease associated with mental retardation.</p> <p>In most cases, such liver damage occurred during the first 6 months of therapy, the period of maximum risk being 2-12 weeks.</p> <p>Liver function should be measured before therapy and then periodically monitored during the first 6 months of therapy, especially in those who seem most at risk, and those with a prior history of liver disease.</p>
Lamotrigine	None	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.
Fluoxetine	None	Fluoxetine is extensively metabolised by the liver and excreted by the kidneys. A lower dose, e.g., alternate day dosing, is recommended in patients with significant hepatic dysfunction.
Aripiprazole	None	Jaundice, hepatitis, increased ALT, increased AST, increased GGT and increased alkaline phosphatase have all been reported.
Haloperidol		Caution is advised in patients with liver disease. Isolated cases of liver function abnormalities or hepatitis, most often cholestatic, have been reported.
Olanzapine	None	<p>In cases of moderate hepatic insufficiency (cirrhosis, Child-Pugh class A or B), the starting dose should be 5mg and only increased with caution.</p> <p>Transient, asymptomatic elevations of alanine transferase (ALT), aspartate transferase (AST) have been seen commonly, especially in early treatment. Caution should be exercised, and follow-up organised, in patients with elevated ALT and/or AST, in patients with signs and symptoms of hepatic impairment, in patients with pre-existing conditions associated with limited hepatic functional reserve and in patients who are being treated with potentially hepatotoxic medicines.</p> <p>In cases where hepatitis (including hepatocellular,</p>

		cholestatic or mixed liver injury) has been diagnosed, olanzapine treatment should be discontinued.
Quetiapine	None	If jaundice develops, quetiapine should be discontinued.
Risperidone	None	<p>Patients with impaired hepatic function have increases in plasma concentration of the free fraction of risperidone.</p> <p>Irrespective of the indication, starting and consecutive dosing should be halved, and dose titration should be slower for patients with hepatic impairment.</p> <p>Uncommon side effects include increased transaminases (ALT and AST) and rarely jaundice.</p>
Asenapine	None	<p>No dose adjustment is required for patients with mild hepatic impairment. The possibility of elevated asenapine plasma levels cannot be excluded in some patients with moderate hepatic impairment (Child-Pugh B) and caution is advised. In subjects with severe hepatic impairment (Child-Pugh C), a 7-fold increase in plasma levels with asenapine exposure was observed. Asenapine is not recommended in patients with severe hepatic impairment.</p> <p>Transient, asymptomatic elevations of hepatic transaminases, ALT, AST have been seen commonly, especially in early treatment.</p>

6.9 Epilepsy ⁽³²⁾

The risks to consider in epilepsy are:-

- Many psychotropic medicines can lower the seizure threshold.
- Interactions between medications.

If an alternative antiepileptic drug (AED) is to be considered discuss with the patient's neurologist and start the second drug and build up to an adequate or maximum tolerated dose and then the first drug should be tapered off slowly. ⁽⁴²⁾

The summary table below is not exhaustive and the advice of a clinical pharmacist can be sought to aid the patient and clinician in the decision making process.

	Contra indication	Precautions
Lithium	None	The risk of convulsions may be increased in case of co-administration of lithium with drugs that lower the seizure threshold, or in epileptic patients.

Carbamazepine	None	<p><i>Abrupt withdrawal of carbamazepine may precipitate seizures:</i></p> <p>If treatment has to be withdrawn abruptly, the changeover to another anti-epileptic drug should, if necessary be effected under the cover of a suitable drug (e.g. diazepam iv or rectal; or phenytoin).</p> <p>May lower other antiepileptic plasma levels.</p>
Valproate	None	None
Lamotrigine	None	<p>In clinical trials, there was no increase in the incidence, severity or type of adverse reactions following abrupt termination of lamotrigine versus placebo. Therefore, patients may terminate lamotrigine without a step-wise reduction of dose.</p> <p>Lamotrigine interacts with other antiepileptics.</p>
Fluoxetine	None	<p>Seizures are a potential risk with antidepressant drugs. Therefore, as with other antidepressants, fluoxetine should be introduced cautiously in patients who have a history of seizures. Treatment should be discontinued in any patient who develops seizures or where there is an increase in seizure frequency. Fluoxetine should be avoided in patients with unstable seizure disorders/epilepsy and patients with controlled epilepsy should be carefully monitored.</p> <p>The probable seizure incidence of 0.2% similar to other antidepressants and may even have a positive effect.⁶</p>
Aripiprazole	None	<p>In clinical trials, uncommon cases of seizure were reported during treatment with aripiprazole. Therefore, aripiprazole should be used with caution in patients who have a history of seizure disorder or have conditions associated with seizures.</p>
Haloperidol	None	<p>It has been reported that seizures can be triggered by haloperidol. Caution is advised in patients suffering from epilepsy and in conditions predisposing to convulsions (e.g., alcohol withdrawal and brain damage).</p> <p>Haloperidol may be a lower risk drug.⁶</p>
Olanzapine	None	<p>Olanzapine should be used cautiously in patients who have a history of seizures or are subject to factors which may lower the seizure threshold. Seizures have been reported to occur rarely in patients when treated with olanzapine. In most of these cases, a history of seizures or risk factors for seizures, were reported.</p>

Quetiapine	None	In controlled clinical trials there was no difference in the incidence of seizures in patients treated with quetiapine or placebo. No data is available about the incidence of seizures in patients with a history of seizure disorder. As with other antipsychotics, caution is recommended when treating patients with a history of seizures.
Risperidone	None	Use cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold.
Asenapine	None	In clinical trials, cases of seizure were occasionally reported during treatment with asenapine. Therefore use with caution in patients who have a history of seizure disorder or have conditions associated with seizures.

7 The Risk of Switching to Mania with Antidepressants ^(1, 2, 3)

Antidepressant-induced mania is well known as is the spontaneous swing from depression to hypomania/mania in bipolar affective disorder.

General management principles in bipolar depression

- a. Avoid inducing a mixed affective state with antidepressants, where the risk of self harm is high.
- b. Use mood-stabilisers or optimise antidepressants with mood stabilizers with the lowest risk drugs (see below).
- c. Minimise antidepressant exposure by attempting a gradual taper after continuation phase, provided the patient is genuinely euthymic.
- d. Consider, however that premature discontinuation of antidepressants within the first 3-6 months of an episode has an up to three times higher relapse rate than those continuing for at least 8 months.

How to prevent switching to mania with antidepressants

- a. Usually occurs within the first 12 weeks.
- b. The risk is highest in bipolar I and bipolar II, lowest with Major Depressive Disorder.
- c. The risk is also lower if antidepressants are used with a mood stabiliser.
- d. Depressed bipolar II patients may be less vulnerable than in bipolar I to switch to mania/hypomania when treated with an antidepressant and an adjunctive mood stabiliser.
- e. If antidepressant-induced mania develops, the antidepressant dose should be reduced immediately and allow the mood to settle for a month or so.
- f. Switch rates in trials have been reported to be:
 - Placebo 7%
 - Sertraline 2%
 - Bupropion 4%
 - Fluoxetine up to 16%

- Venlafaxine 9%
 - Tranylcypromine 24%
 - Clomipramine up to 35%
 - Imipramine and amitriptyline up to 42%
- g. Antidepressant-induced switching may be more common in women.
- h. TCAs have the highest risk of switching compared to non-TCAs (36% v 17%) with amitriptyline, imipramine and clomipramine being the most likely.
- i. Risk factors include
- Increased number of antidepressant trials.
 - History of substance misuse.
 - Higher doses.

8 Psychological interventions and psychoeducation ^(1,2)

- a. Offer a structured psychological intervention (individual, group or family), which has been designed for bipolar disorder and has a published evidence-based manual describing how it should be delivered, to prevent relapse or for people who have some persisting symptoms between episodes of mania or bipolar depression.
- b. Individual and group psychological interventions for bipolar disorder to prevent relapse should:
- provide information about bipolar disorder
 - consider the impact of thoughts and behaviour on moods and relapse
 - include self-monitoring of mood, thoughts and behavior
 - address relapse risk, distress and how to improve functioning
 - develop plans for relapse management and staying well
 - consider problem-solving to address communication patterns and managing functional difficulties.
- c. In addition: individual programmes should be tailored to the person's needs based on an individualised assessment and psychological formulation group programmes should include discussion of the information provided with a focus on its relevance for the participants.
- d. Group psychoeducation appears to be a highly effective adjunct to pharmacotherapy in relapse prevention. Psychoeducation is an umbrella term that includes components of illness awareness, treatment adherence, early detection of prodromal symptoms and recurrences and lifestyle regularity.

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Appendix 1 - Summary of the evidence for medication

	Licensed indication for bipolar affective disorder.	Acute mania	Bipolar depression	Prophylaxis depression most significant	Prophylaxis mania most significant	Rapid Cycling
Lithium	1) Prophylaxis and treatment of mania. 2) Prophylaxis of bipolar disorder 3) Incomplete response to treatment for acute depression in bipolar disorder	++	+	++	++	+
Carbamazepine	Prophylaxis of bipolar disorder unresponsive to lithium	+	-	+	++	+
Valproate (Depakote® only)	Treatment of manic episodes associated with bipolar disorder	++	-	+	+	+
Lamotrigine	Prevention of depressive episodes associated with bipolar disorder	-	+ ⁽²⁴⁾	++ ⁽²⁴⁾	-	+
Fluoxetine with olanzapine	No licensed preparation in the UK.	CI	++	+	-	-
Aripiprazole	Treatment and recurrence prevention of mania	++	-	+	++	+

	Licensed indication for bipolar affective disorder.	Acute mania	Bipolar depression	Prophylaxis depression most significant	Prophylaxis mania most significant	Rapid Cycling
Haloperidol	Mania and hypomania	++	-	-	-	-
Olanzapine	1) Combination therapy for mania 2) Preventing recurrence in bipolar disorder 3) Monotherapy for mania	++ ⁽²⁶⁾	+ ⁽²⁰⁾	+	++	+
Risperidone	Mania	++ ⁽²⁷⁾	-	+	++	+
Quetiapine	1) Treatment of mania in bipolar disorder 2) Treatment of depression in bipolar disorder 3) Prevention of mania and depression in bipolar disorder	++ ⁽²⁸⁾	++	++	++	+
Asenapine (Non – formulary)	Manic episode	++	- (? Mixed)	-	-	-

- = Little or no evidence + = some evidence, unlicensed. ++ = evidence and licensed CI = contra-indicated

MS = mood stabilisers.

Appendix 2 – licensed doses for the mood stabilizers ⁽²⁷⁾

Mood stabilizer	Licensed dose Working age adults	Licensed dose Elderly
Lithium*	400mg -1.2g/day (maintenance) Max 2.4g/day	800mg -1.8g/day 3 (treatment) 600mg to 1.2g/day 3 (prophylaxis)
Carbamazepine	Initially 400mg daily, in divided doses, max daily dose 1.6g. Usual maintenance dose is 400-600mg per day	Same as working age adults
Valproate (Depakote ® only)	Initially 250 TDS, increased rapidly to 1 or 2g. Dose is 20-30mg/kg/day. Doses higher than 45mg/kg/day require careful monitoring.**	No different information. Pharmacokinetics may differ. Titrate according to response
Lamotrigine	Week 1 & 2 - 25mg/day Week 3 & 4 – 50mg/day Week 5 – 100mg/day Max 200mg/day When used with valproate, use half the specified dose above	No dosage adjustment from recommended schedule is required.
Fluoxetine		
Aripiprazole	Initiate at 15mg/day and optimise dose according to response. Max dose 30mg/day.	Effectiveness not established in patients over 65. No alternative dosage
Haloperidol	Doses between 2 and 20 mg/day should be administered either as a single dose or in divided doses.	Treatment should start with half the dosage stated for adults and adjusted according to the results if necessary
Olanzapine	Manic episode: starting dose 10-15mg/day as monotherapy (10mg as combination therapy) Max 20mg/day	A lower starting dose (5 mg/day) is not routinely indicated but should be considered for those 65 and over when clinical factors warrant
Risperidone	Starting dose of 2-3mg OD. Dose increases at 1mg per day are acceptable to 6mg/day	A starting dose of 500 micrograms BD is recommended. Increments of 500 micrograms BD to 1 - 2 mg BD are acceptable
Quetiapine	I/R: 100mg/day, increasing to 800mg as required. X/L: 300mg/day increasing to 600mg/day on day 2	25mg/day, increased in increments of 25-50mg/day to effective dose. Max 800mg/day
Asenapine	10mg BD as monotherapy (reduce to 5mg BD if necessary) 5mg BD as combination therapy. ⁽⁴⁰⁾	Same as in working age adults

Notes: * For adults less than 50kg, follow the elderly doses. Doses should be titrated to achieve optimum reference range.

ADULTS: Prophylaxis - 0.5 to 1.0 mmol/l; Treatment - 0.8 - 1.2 mmol/l

ELDERLY: Prophylaxis - 0.4 to 0.8 mmol/l; Treatment - 0.8 to 1.0 mmol/l

** The maximum daily dose in the UK is 30mg/kg/day, whereas in the USA it is 60mg/kg/day

Appendix 3 – side effect profile of the mood stabilizers

Mood stabilizer	Side Effect
Lithium	Common: tremor, stomach upset, polyuria, metallic taste, polydipsia Uncommon: weight gain, oedema, hypothyroidism, Rare: skin rashes Other: blurred vision
Carbamazepine	Common: sleepiness, diplopia, dizziness, stomach upset Uncommon: headache, ataxia, Rare: constipation, confusion, erythematous rash, ankle oedema, SIADH Very Rare: Agranulocytosis and thrombocytopenia
Valproate	Common: increased appetite and weight gain Uncommon: gastric irritation, hair loss, nausea, Rare: sleepiness, impaired liver function, tremor, ataxia, confusion, lethargy, thrombocytopenia, and impaired platelet function, rash
Lamotrigine	Common: sleepiness, dizziness, headache, skin rashes, nausea Uncommon: oedema, blurred vision Rare: bone marrow suppression, seizures
Aripiprazole,	Common: akathisia, stomach upset, constipation, headache, insomnia, blurred vision, tremor Uncommon: postural hypotension, seizures, palpitations
Haloperidol	Very Common: agitation and EPSEs Common: postural hypotension, dry mouth, constipation. Uncommon: Leucocytopenia, altered liver Hepatitis, Jaundice, hyperprolactaemia. Rare: Sexual dysfunction, photosensitivity
Olanzapine,	Very Common: sleepiness, weight gain, Common: postural hypotension, dry mouth, constipation, peripheral oedema, diabetes Rare: altered liver function, photosensitivity
Risperidone,	Very common: postural hypotension, headache, akathisia, movement disorders (EPSEs), Common: hyperprolactinaemia, sleepiness, weight gain, constipation Uncommon: blurred vision, sexual dysfunction, skin rashes
Quetiapine	Common: sleepiness, dizziness, dry mouth, weight gain, postural hypotension Uncommon: headache, akathisia, anticholinergic side effects, stomach upset
Asenapine	Common: restlessness and anxiety, somnolence and sleepiness, oral hypoesthesia or paraesthesia, Uncommon: EPSEs, fatigue, weight gain, akathisia, dizziness, dysgeusia, postural hypotension

Very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare (>1/10,000, <1/1000) and very rare (<1/10,000).

Appendix 4

Summary of Monitoring Requirements for the mood stabilizers

Lithium

The latest [Trust guidelines for the prescribing and monitoring of lithium therapy](#) can be found on the Trust's website.

Valproate

Pre-treatment

- Liver Function Tests (LFTs)
- Full Blood Count (FBC)
- U & Es and serum creatinine
- Weight or Body Mass Index (BMI)

During treatment

- LFTs should be repeated after a minimum of 6 months but more frequently in those at risk or with a prior history of liver disease. Raised liver enzymes are not uncommon and are usually transient and dose related. An abnormally low prothrombin rate, particularly in association with other biological abnormalities (such as significant decrease in fibrinogen and coagulation factors, increased bilirubin level and raised transaminases) requires cessation of treatment.
- FBC should be repeated after a minimum of 6 months. Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations.
- Weight or BMI should be monitored periodically.

Plasma levels

Plasma level monitoring is of limited value but may be used to assess non compliance or toxicity. The target range is 50-100mg/l. Trough levels should be taken immediately prior to the next dose. Time to steady state is 2-3 days.

Signs of toxicity include nausea, vomiting, confusion, stupor and tremor.

Significant interactions - this list is not exhaustive

- Drugs that may raise valproate levels include aspirin, cimetidine, erythromycin and fluoxetine.
- Drugs that may lower valproate levels include carbamazepine, antiretrovirals, rifampicin and carbapenem antibiotics such as panipenem, imipenem and meropenem.
- Valproate possibly enhances the anticoagulant effect of warfarin.
- Valproate may raise levels of benzodiazepines, lamotrigine and quetiapine.
- Valproate may raise or lower clozapine levels.
- The combination of valproate and olanzapine may increase the risk of neutropenia.
- Valproate may raise or lower levels of phenytoin. Phenytoin may reduce valproate levels.

Carbamazepine

Pre-treatment

- FBC
- Urea and electrolytes
- LFTs
- Weight or BMI

During treatment

- Urea and electrolytes, FBC, LFTs and weight or BMI should be repeated after six months.
- Carbamazepine should be discontinued if the patient develops leucopenia which is severe, progressive or accompanied by clinical manifestations or if significant bone marrow depression appears.
- Sodium levels should be performed if symptoms of syndrome of inappropriate antidiuretic hormone (SIADH) secretion occur and treatment should be discontinued.

Plasma levels

Evidence for therapeutic levels in bipolar disorder is limited. Plasma levels > 7mg/l are associated with a therapeutic response in affective disorder.

Trough levels should be taken immediately before the first dose of the day. Carbamazepine is a hepatic enzyme inducer which induces its own metabolism. Therefore time to steady state is 2-4 weeks. Plasma levels may be useful to assess non compliance or suspected toxicity (>12mg/l).

Signs of toxicity include ataxia, dizziness, blurred vision, headache, nausea and diplopia.

Significant interactions

Carbamazepine has an extensive interaction profile and is metabolised by numerous cytochrome P450 enzymes. Further information may need to be obtained from specialist texts such as the SPCs or from specialist pharmacists and Medicine information.

- Drugs that may raise carbamazepine levels include; cimetidine, diltiazem, verapamil, fluoxetine, erythromycin, clarithromycin, fluconazole and ketoconazole.
- Phenytoin may lower carbamazepine levels but phenytoin levels may be increased or decreased by carbamazepine.
- Oral contraceptives– reduced contraceptive effect.
- Variable effects are observed with antiretrovirals and calcium channel blockers. Check individually for interactions.
- Carbamazepine may reduce levels of methadone, paracetamol, warfarin, mirtazapine, trazodone, lamotrigine, valproate, numerous antipsychotics, clonazepam, ciclosporin and simvastatin.
- Carbamazepine may reduce the effects of tramadol and clopidogrel.