Birmingham and Solihull Mental Health NHS Foundation Trust

Guidance for the Pharmacological Management of Bipolar Affective Disorder

Guideline No & Category	AD 01	Affective Disorders
Version No	2	
Formulated Via	Pharmacological Therapies Committee	
Ratifying Committee	Trust Clinical Governance Committee	
Date Ratified	July 2021	
Next Review Date	Extended July 2026	
Guideline Author	XXXX Associate Medical Director (Pharmacological Therapies) and Chair of the Pharmacological Therapies Committee XXXX, Consultant Psychiatrist XXXX, Chief Pharmacist	

Guideline Context

- This guideline gives advice on prescribing pharmacological treatments for bipolar affective disorder including treatment of acute episodes and prevention of relapse. It reflects NICE guidance, BAP guidance and more recent evidence.
- This guideline does not address the issues of psychological therapies that are used alongside medicines. Both are important in the effective management of this disorder.

Guideline Requirement

These are prescribing guidelines so are of particular relevance to prescribers. However, it is essential that all clinical staff be aware of the guideline

MANAGEMENT OF AN ACUTE MANIC / MIXED EPISODE

If a person develops mania or hypomania and is taking an antidepressant as monotherapy:

- consider stopping the antidepressant and

- Regardless of whether the antidepressant is stopped, offer haloperidol, olanzapine, quetiapine or risperidone, taking into account any advance statements, the person's preference and clinical context (including physical comorbidity, previous response to treatment and side effects). Ensure all necessary baseline checks and ongoing monitoring are undertaken (see appendix 2)

If a person develops mania or hypomania and is not taking an antipsychotic or mood stabiliser

- offer haloperidol, olanzapine, quetiapine or risperidone, taking into account any advance statements, the person's preference and clinical context (including physical comorbidity, previous response to treatment and side effects). Ensure all necessary baseline checks and ongoing monitoring are undertaken (see appendix 2)

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 (choosing from haloperidol, olanzapine, quetiapine or risperidone), taking into account any advance statements, the person's preference and clinical context (including physical comorbidity, previous response to treatment and side effects).

If an alternative antipsychotic is not sufficiently effective at the maximum licensed dose

- consider adding lithium. Ensure all baseline and ongoing monitoring are undertaken (see appendix 3)

- 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 prescribed, valproate should be titrated quickly for rapid effect (e.g. Semi-sodium valproate 750mg on day 1, increase to 20mg/kg day 2).

- However, do not offer valproate to women of childbearing potential for long-term treatment or to treat an acute episode. If a woman of childbearing potential is already taking valproate, unless a decision has been taken to continue valproate (as no other treatment options are suitable), advise her to gradually stop the drug because of the risk of foetal malformations and adverse

neurodevelopmental outcomes after any exposure in pregnancy (see appendix 4)

If a person develops mania or hypomania and is taking an antidepressant in combination with a mood stabiliser

- consider stopping the antidepressant.

- If the person is already taking lithium, check plasma lithium levels to optimise treatment.

- Consider adding haloperidol, olanzapine, quetiapine or risperidone, depending on the person's preference and previous response to treatment.
  Ensure all necessary baseline checks and ongoing monitoring are undertaken (see appendix 2)

If a person develops mania or hypomania and is already taking valproate or another mood stabiliser as prophylactic treatment

- consider increasing the dose, up to the maximum level, if necessary, depending on clinical response.

- However, Do not offer valproate to women of childbearing potential for long term treatment or to treat an acute episode. If a woman of childbearing potential is already taking valproate, unless a decision has been taken to continue valproate (as no other treatment options are suitable), advise her to gradually stop the drug because of the risk of foetal malformations and adverse neurodevelopmental outcomes after any exposure in pregnancy (see appendix 4)

- If there is no improvement, consider adding haloperidol, olanzapine, quetiapine or risperidone, depending on the person's preference and previous response to treatment.

If the clinical presentation is of a mixed affective state, characterised by both manic and depressive symptoms

- follow recommendations for the treatment of mania, and monitor closely for the emergence of depression.

Do not offer lamotrigine to treat mania.

Benzodiazepines and Rapid Tranquillisation

- For the treatment of agitated behaviour refer to the BSMHFT Rapid Tranquillisation policy

- To promote sleep for agitated, overactive patients in the short term, follow the BSMHFT insomnia guideline, including considering adjunctive treatment with hypnotic medication, such as temazepam or zopiclone.

- It is better to use benzodiazepines for sedation than high-dose antipsychotic.

Refractory illness

- Consider clozapine in more refractory illness

- Electro-convulsive therapy (ECT) may be considered 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

MANAGEMENT OF A DEPRESSIVE EPISODE

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. Ensure that necessary baseline and ongoing monitoring for antipsychotics is undertaken (see appendix 2)

- If the person prefers, consider either olanzapine (without fluoxetine) or lamotrigine on its own. Ensure that necessary baseline and ongoing monitoring for antipsychotics is undertaken (see appendix 2)

- If there is no response to fluoxetine combined with olanzapine, or quetiapine, consider lamotrigine on its own.

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. Ensure that necessary baseline and ongoing monitoring for antipsychotics is undertaken (see appendix 2)

- If the person prefers, consider adding olanzapine (without fluoxetine) or lamotrigine to lithium. Ensure that necessary baseline and ongoing monitoring for antipsychotics is undertaken (see appendix 2)

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

If a person develops moderate or severe bipolar depression and is already taking valproate

- Consider increasing the dose within the therapeutic range.

- However, if a woman of childbearing potential is already taking valproate, unless a decision has been taken to continue valproate (as no other treatment options are suitable), advise her to gradually stop the drug because of the risk of foetal malformations and adverse neurodevelopmental outcomes after any exposure in pregnancy (see appendix 4)

- 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. Ensure that necessary baseline and ongoing monitoring for antipsychotics is undertaken (see appendix 2)

- If the person prefers, consider adding olanzapine (without fluoxetine) or lamotrigine to valproate. Ensure that necessary baseline and ongoing monitoring for antipsychotics is undertaken (see appendix 2)

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

- Be aware of the potential interactions between valproate and fluoxetine, lamotrigine and olanzapine.

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.

- If the person decides to continue psychological or pharmacological treatment for bipolar depression, offer it for a further 3–6 months, and then review.

ECT

Trials of ECT in depression have not tended to exclude bipolar patients, and evidence for its efficacy is good. Consider ECT for patients with high suicidal risk, psychosis, or severe depression during pregnancy.

Treatment-Resistant Bipolar Depression

There is little evidence to inform the management of patients with treatment resistant bipolar depression. Therefore in such cases, consider treatments used in resistant unipolar depression (see guidelines for the pharmacological management of depression).

PHARMACOLOGICAL ASPECTS OF LONG-TERM TREATMENT (RELAPSE PREVENTION)

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.

When planning long-term pharmacological treatment to prevent relapse

- Take into account drugs that have been effective during episodes of mania or bipolar depression.

- Discuss with the person whether they prefer to continue this treatment or switch to lithium, and **explain that lithium is the most effective long-term treatment for bipolar disorder.**

- Offer lithium as a first-line, long-term pharmacological treatment for bipolar disorder

- If lithium is ineffective, consider adding valproate. However, if a woman of childbearing potential is already taking valproate, unless a decision has been taken to continue valproate (as no other treatment options are suitable), advise her to gradually stop the drug because of the risk of foetal malformations and adverse neurodevelopmental outcomes after any exposure in pregnancy (see appendix 4)

- 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. However, if a woman of childbearing potential is already taking valproate, unless a decision has been taken to continue valproate (as no other treatment options are suitable), advise her to gradually stop the drug because of the risk of foetal malformations and adverse neurodevelopmental outcomes after any exposure in pregnancy (see appendix 4)

- The role of antidepressants in long-term treatment is not established by controlled trials, but they appear to be used effectively, in combination with other preventative treatments, in a small minority of patients in the long term.
- Consider clozapine in treatment refractory patients. It also has evidence in combination with lithium or an anticonvulsant.

Pharmacological management of rapid cycling (4+ episodes per year)

- Identify and treat conditions such as hypothyroidism or substance misuse that may contribute to cycling.

- Taper and discontinue antidepressants that may contribute to cycling

- 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.

- For many patients, combinations of medicines are required

- Evaluate anti-cycling effects over periods of 6 months or more by tracking mood states longitudinally.

- Discontinue ineffective treatments.

If stopping long-term pharmacological treatment:

- When a patient has accepted treatment for several years and remains very well, they should be strongly advised to continue indefinitely, because the risks of relapse remain high.

- discuss with the person how to recognise early signs of relapse and what to do if symptoms recur
- stop treatment gradually and monitor the person for signs of relapse.
- Continue monitoring symptoms, mood and mental state for 2 years after medication has stopped entirely. This may be undertaken in primary care.

Pharmacological management of early warning signs or high risk situations

- 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.

- The Trust's Mood on Track programme encourages patients to identify early warning signs of relapse, and to plan actions to be taken in the event that they occur. This includes advice to ask their treating team to discuss shortterm changes to medications.

- 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.

Appendix 1 – Equality Impact Assessment

Equality Analysis Screening Form

A word version of this document can be found on the HR support pages on Connect
http://connect/corporate/humanresources/managementsupport/Pages/default.aspx

Title of Proposal	Guideline for the Pharmacological Management of Bipolar Affective Disorder		
Person Completing this proposal	XXXX/XXXX	**Role or title**	Associate Medical Director/Chief Pharmacist
Division	Medical	**Service Area**	
Date Started	23.3.21	**Date completed**	24/6/2021
Main purpose and aims of the proposal and how it fits in with the wider strategic aims and objectives of the organisation.			
Ensure evidence based prescribing for individuals with bipolar disorder			
Who will benefit from the proposal?			
All patients with bipolar affective disorder			
Impacts on different Personal Protected Characteristics – *Helpful Questions:*			
Does this proposal promote equality of opportunity? *Eliminate discrimination?* *Eliminate harassment? Eliminate victimisation?*		*Promote good community relations?* *Promote positive attitudes towards disabled people?* *Consider more favourable treatment of disabled people?* *Promote involvement and consultation?* *Protect and promote human rights?*	
Please click in the relevant impact box or leave blank if you feel there is no particular impact.			

Personal Protected Characteristic	No/Minimum Impact	Negative Impact	Positive Impact	Please list details or evidence of why there might be a positive, negative or no impact on protected characteristics.
Age	X			
Including children and people over 65 Is it easy for someone of any age to find out about your service or access your proposal? Are you able to justify the legal or lawful reasons when your service excludes certain age groups				
Disability	X			
Including those with physical or sensory impairments, those with learning disabilities and those with mental health issues Do you currently monitor who has a disability so that you know how well your service is being used by people with a disability? Are you making reasonable adjustment to meet the needs of the staff, service users, carers and families?				
Gender		X		Girls and women of child bearing potential should not take valproate preparations unless all other possible treatments have been tried or considered and are not suitable due to efficacy or tolerability. Where valproate preparations are prescribed, this should be in line with the valproate pregnancy prevention programme that requires the woman to understand the risks of taking valproate, give active consent to treatment and to agree to take highly effective contraception (unless not applicable).
This can include male and female or someone who has completed the gender reassignment process from one sex to another Do you have flexible working arrangements for either sex? Is it easier for either men or women to access your proposal?				
Marriage or Civil Partnerships	X			
People who are in a Civil Partnerships must be treated equally to married couples on a wide range of legal matters Are the documents and information provided for your service reflecting the appropriate terminology for marriage and civil partnerships?				

Pregnancy or Maternity		X		Valproate preparations are contra-indicated in pregnancy. Where women on valproate wish to conceive, they should be referred to the perinatal mental health service for advice and supervision of treatment (see gender)
This includes women having a baby and women just after they have had a baby Does your service accommodate the needs of expectant and post natal mothers both as staff and service users? Can your service treat staff and patients with dignity and respect relation in to pregnancy and maternity?				
Race or Ethnicity	X			

Including Gypsy or Roma people, Irish people, those of mixed heritage, asylum seekers and refugees What training does staff have to respond to the cultural needs of different ethnic groups? What arrangements are in place to communicate with people who do not have English as a first language?				
Religion or Belief	X			
Including humanists and non-believers Is there easy access to a prayer or quiet room to your service delivery area? When organising events – Do you take necessary steps to make sure that spiritual requirements are met?				
Sexual Orientation	X			
Including gay men, lesbians and bisexual people Does your service use visual images that could be people from any background or are the images mainly heterosexual couples? Does staff in your workplace feel comfortable about being 'out' or would office culture make them feel this might not be a good idea?				
Transgender or Gender Reassignment	X			
This will include people who are in the process of or in a care pathway changing from one gender to another Have you considered the possible needs of transgender staff and service users in the development of your proposal or service?				
Human Rights	X			

Affecting someone's right to Life, Dignity and Respect? Caring for other people or protecting them from danger? The detention of an individual inadvertently or placing someone in a humiliating situation or position?				
If a negative or disproportionate impact has been identified in any of the key areas would this difference be illegal / unlawful? I.e. Would it be discriminatory under anti-discrimination legislation. (The Equality Act 2010, Human Rights Act 1998)				
	Yes	**No X**		
What do you consider the level of negative impact to be?	**High Impact**	**Medium Impact**	**Low Impact**	**No Impact**
				X The issues highlighted above are intended to keep women safe and
				prevent children born with abnormalities or suffer from neurodevelopmental problems through childhood into adulthood.
If the impact could be discriminatory in law, please contact the **Equality and Diversity Lead** immediately to determine the next course of action. If the negative impact is high a Full Equality Analysis will be required. If you are unsure how to answer the above questions, or if you have assessed the impact as medium, please seek further guidance from the **Equality and Diversity Lead** before proceeding. If the proposal does not have a negative impact or the impact is considered low, reasonable or justifiable, then please complete the rest of the form below with any required redial actions, and forward to the **Equality and Diversity Lead.**				
Action Planning:				
How could you minimise or remove any negative impact identified even if this is of low significance?				
How will any impact or planned actions be monitored and reviewed?				

How will you promote equal opportunity and advance equality by sharing good practice to have a positive impact other people as a result of their personal protected characteristic.
Please save and keep one copy and then send a copy with a copy of the proposal to the Senior Equality and Diversity Lead at **bsmhft.hr@nhs.net** . The results will then be published on the Trust's website. Please ensure that any resulting actions are incorporated into Divisional or Service planning and monitored on a regular basis.

Appendix 2 **MONITORING REQUIREMENTS FOR LITHIUM**

Key: = required, Grey = recommended as per notes of if clinically indicated

Medication:	**Lithium**				**Advice if abnormal/Comments**
	Baseline	**months**	**Months**	**Every 6 months thereafter**	**All results should be shared between secondary and primary care – this can be done using the patient-held record book.**
Weight & BMI					**All patients - Exercise & dietary advice.** If BMI >25 and/or weight gain >5kg over 3 months, consider referral to dietician.
Lithium levels	Monitor 1week after initiation and at each dosage change until stable, then every 3 months				Dose according to response and tolerability: Lithium levels should not exceed 1.0mmol/l (therapeutic levels for augmentation of antidepressant medication are usually at or above 0.4mmol/l)
ECG	If additional risk factors exist				Contact specialist if QTc >440msec (men) or >470msec (women).
U&Es *(inc eGFR)*					Contact specialist if significant variations detected.
Calcium					Contact specialist if significant variations detected
TFTs					Contact specialist if significant variations detected
Physical health check	**do annually (usually done by GP)**				Contact specialist or GP if significant variations detected

The lithium shared care agreement can be found here

BSSE APC ESCA Lithium Feb 2020 FINAL.pdf (birminghamandsurroundsformulary.nhs.uk)

Appendix 3 **MONITORING REQUIREMENTS FOR ANTIPSYCHOTICS**

The oral antipsychotics shared care agreement can be found here
[BSSE APC ESCA Oral Antipsychotics Feb 2020 FINAL.pdf (birminghamandsurroundsformulary.nhs.uk)]

Investigations, test results and treatment				
Monitoring stage	**Baseline**	**During Initiation**	**At three months**	**At annual review**
Monitoring setting	**Secondary Care**	**Secondary Care**	**GP or Secondary Care**	**GP or Secondary Care**
Who undertakes the monitoring	Undertaken by specialist initiating medication	Undertaken by specialist initiating medication	Undertaken by specialist initiating medication or by GP if prescribing has already been transferred	Undertaken by GP unless prescribing is retained by the specialist
Parameters	Weight	Weight	Weight	Weight
	BMI	BMI	BMI	BMI
	Pulse	Pulse	Pulse	
	Blood Pressure	Blood Pressure	Blood Pressure	
	Blood Glucose/HbA1C		Blood Glucose/HbA1C	Blood Glucose/HbA1C
	U&Es			U&Es
	Renal Function		Renal Function	Renal Function
	Full Blood Count			Full Blood Count
	Liver Function tests		Liver Function tests	Liver Function tests
	Blood lipids		Blood lipids	Blood lipids

	Prolactin		Prolactin (if indicated e.g. gynaecomastia, menstrual disturbance, galactorrhoea, impaired libido)	Prolactin (if indicated e.g. gynaecomastia, menstrual disturbance, galactorrhoea, impaired libido)
				Side effect assessment
	ECG (if indicated in the SPC)			ECG (if indicated in the SPC)

Appendix 4: Use of Valproate in Women of Childbearing Potential

Up to date information may be found here
Valproate use by women and girls - GOV.UK (www.gov.uk)

Risk acknowledgement form can be found here
Risk-acknowledgment.pdf (publishing.service.gov.uk)

Shared care agreement can be found here
BSSE APC ESCA valproate medicines FINAL.pdf (birminghamandsurroundsformulary.nhs.uk)

This form expires 12 months from this date. A new form should be completed at each annual review

More information can also be found online at www.medicines.org.uk by entering "valproate" in the search box and then clicking on "Risk Materials" next to any of the medicines that appear.