Bipolar Disorder - Medication Pathway for Adults

The aim of this pathway is to encourage safe and effective prescribing for bipolar disorder by advising the best evidence-based pharmacological treatments.

Patients aged over 65 years: Any doses stated refer to adult dosing and the prescriber should consult the BNF for advice on doses for elderly patient groups.
This patient group has an increased risk of drug-drug interactions and increased sensitivity to anticholinergic effects (which can decrease cognitive function and increase risk of falls). Ensure comorbidities are recognised & treated.

Key prescribing considerations

- Consider non-pharmacological options at all steps.
- Utilise HIE (Health Information Exchange) viewer to view medical problems & medication from the GP before prescribing and consider underlying physical health issues (request this from GP if HIE viewer not available).
- Ensure pre-treatment and ongoing monitoring is carried out per Trust psychotropic medication monitoring guidance, including an annual physical health review.
- Ensure prescribing decisions account for advance directives, the person's preference and clinical context (including physical comorbidity, previous response to treatment and side effects) where possible.
- **Refer to MHRA advice & Trust guidance regarding the use of valproate in patients of childbearing potential** (see also perinatal prescribing guidance). Utilise the decision support tool "Bipolar disorder: is valproate the right treatment for me?" when considering valproate for such patients [N.B. Valproate is AMBER (shared care) for safe transfer of prescribing in this patient cohort}.
- Be aware of potential drug interactions when prescribing combination therapy.
- For lamotrigine initiation, follow BNF/SmPC prescribing recommendations regarding dose escalation. This differs with other medicines, e.g. valproate and carbamazepine. Advise the patient of the risks associated with rash and further actions if required.
- Note BNF warning re: antiepileptics and risk of suicidal thoughts and behaviour
- Please note that for bipolar disorder, lurasidone and asenapine are both **PURPLE** (non-formulary) drugs as per the safe transfer of prescribing guidelines. These require an application for use which must be approved by a panel, and prescribing cannot be transferred to primary care.
- Consider toxicity in overdose when prescribing during periods of high suicide risk. Assess the need to limit the quantity of medication prescribed (e.g. 7-day prescriptions) to reduce the risk.
- **Deprescribing -** 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 and monitor the person for signs of relapse.
  - Discontinuation of any medicine should normally be tapered over at least 4 weeks, preferably longer
  - The risk of relapse remains even after years of sustained remission
- TEWV Level 1 & 2 NMPs cannot initiate lithium or clozapine. Level 2 NMPs may adjust clozapine and lithium doses if this is specified in their scope of practice and the consultant is aware of dose changes.

BIPOLAR MEDICATION PATHWAY FOR ADULTS

NHS
Tees, Esk and Wear Valleys
NHS Foundation Trust

BIPOLAR MANIA/HYPOMANIA

Secondary Care Guidelines for Acute Management in Adults

New Diagnosis
- No current medication

New Diagnosis
- Prescribed Antidepressant

STOP ANTIDEPRESSANT

Existing Diagnosis
- Prescribed ANTIDEPRESSANT + non-antipsychotic mood stabiliser

OPTIMISE MOOD STABILISER

Existing Diagnosis
- Taking a non-antipsychotic mood stabiliser

Consider (in any order, based on patient preference/past history of response/non-response):

- **OLANZAPINE (N)** Initially 10-15 mg/day; max 20 mg/day
- **QUETIAPINE (IMMEDIATE RELEASE) (N)** Initiate 50 mg BD; ↑ by 50 mg BD until day 4, then ↑ by 200 mg/day according to response. Max 800 mg/day
- **QUETIAPINE (MR) (N)** *if faster titration/response required* 300 mg OD for day 1, 600 mg OD for day 2. Then adjust according to response, usual dose 400–800 mg OD (see page 10)
- **RISPERIDONE (N)** 2 mg daily; ↑ steps of 1 mg/day if required. Max 6 mg/day
- **HALOPERIDOL (N)** 2-10 mg/daily (1-2 divided doses); adjust every 1-3 days; max 15 mg/day
- **ARIPIPRAZOLE** 15 mg/day; increased to 30 mg/day if required; consider if comorbidities.

IF FIRST ANTIPSYCHOTIC POORLY TOLERATED (at any dose) OR INEFFECTIVE (at max. licensed dose) OFFER AN ALTERNATIVE FROM THE LIST ABOVE (N)

IF INEFFECTIVE, CONSIDER ADDING

LITHIUM (N)
- **ADD** if alternative antipsychotic insufficient at max dose
- Adjust dose to serum lithium concentration
- Target: 0.8-1.0 mmol/L

IF INEFFECTIVE/NOT TOLERATED, CONSIDER

VALPROATE (N) off-label
750 mg/day (2-3 divided doses); usual dose 1-2 g/day
RESTRICTED USE IN PATIENTS OF CHILDBEARING POTENTIAL

ECT severe or treatment-resistant mania, severe mania in pregnancy or expressed preference

Aim to calm agitated and overactive patients, help promote sleep

Discontinue as soon as symptoms improve

ADJUNCT MEDICINES – SHORT TERM ONLY

see Rapid Tranquilisation Policy for further details

- **LORAZEPAM** 1-2 mg per dose; max 4 mg/24h; higher doses under consultant advice
- **DIAZEPAM off-label** 2-10 mg in divided doses; can increase to max 30 mg/day when prolonged sedation required
- **ZOPICLONE** 7.5 mg/night; higher doses under consultant advice
- **PROMETHAZINE off-label** 25-50 mg per dose; max 100 mg/24h [NB can potentiate QT interval prolongation]

Title	Bipolar Medication Pathway For Adults		
Approved by	Drug & Therapeutics Committee	Date of Approval	28th September 2023
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BIPOLAR MEDICATION PATHWAY FOR ADULTS

Tees, Esk and Wear Valleys NHS Foundation Trust

BIPOLAR DEPRESSION
Acute Phase Management

Not taking lithium or valproate

Already taking:
- **LITHIUM** or
- **VALPROATE** **RESTRICTED USE IN PATIENTS OF CHILDBEARING POTENTIAL**

→ **OPTIMISE MOOD STABILISER**

Consider (in any order, based on patient preference):
- **OLANZAPINE** 5-20 mg/day; Max 20 mg/day **+ FLUOXETINE (N)** 20 mg daily; Max 60 mg/day
- **QUETIAPINE (N) (IMMEDIATE RELEASE)** Titrate to 300 mg over 4 days, then adjust according to response. Max 600 mg/day
- **QUETIAPINE (MR) (N)** *if faster titration/response required* 300 mg OD for day 1, 600 mg OD for day 2. Then adjust according to response, usual dose 400–800 mg OD (see page 10)
- **OLANZAPINE (N)** 10 mg daily; max 20 mg daily

IF INEFFECTIVE, CONSIDER

LAMOTRIGINE (N)
- Slow titration to 200 mg/day; max 400 mg/day; unsuitable if rapid response required
- NB lower dose needed if prescribed VALPROATE
- CAN BE USED FIRST LINE IF PATIENT PREFERS; may be preferable in bipolar II with prominent depressive episodes

IF INEFFECTIVE/ NOT TOLERATED CONSIDER

ECT
- Poor oral intake, high suicide risk or patient preference

ARIPIPRAZOLE (off-label)
- Formulary option with similar side-effect profile to lurasidone; to try before lurasidone considered

LURASIDONE (off-label)
- Prescribing responsibility must remain with TEWV; requires panel approval
- Must be taken with a meal (>300kcal) for optimal absorption

Prescribing antidepressants in bipolar depression
- Avoid antidepressants without a mood stabiliser as there is a risk of "switching" to mania and inducing rapid cycling, particularly in bipolar I
- Studies suggest mood stabilisers alone are as effective as a mood-stabiliser-antidepressant combination; evidence for antidepressants in bipolar depression is much weaker than in unipolar
- SSRIs preferred over TCA's, MAOIs and SNRIs (the latter two are more likely to induce a manic switch)- prescribe if past history of response, or discontinuation led to depression.

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BIPOLAR MEDICATION PATHWAY FOR ADULTS

LONG-TERM TREATMENT

Discuss within 4 weeks of symptom resolution
(both depression and mania)

CONSIDER

LITHIUM(N)

- See shared care procedure before prescribing
- Consider long-term adherence. May be less suitable if ongoing adherence issues due to increased risk of relapse when stopped abruptly
- Offer MHRA purple lithium book
- Consider if patient is of childbearing potential; will need extra counselling around risks and preconception advice prior to pregnancy
- Levels- 0.4-0.8 mmol/L optimal for prophylaxis; 0.6-0.8mmol/L for mania prophylaxis

IF POORLY TOLERATED/UNSUITABLE

REPLACE WITH:

- **VALPROATE*(N) NB** Valproate monotherapy is less effective than Lithium monotherapy or the combination of Valproate and Lithium
  RESTRICTED USE in patients of childbearing potential

or

- **OLANZAPINE** if previously effective; may be better for mania prophylaxis

or

- **QUETIAPINE** if previously effective; evidence for prophylaxis of manic and depressive episodes

IF INEFFECTIVE

ADD:

- **VALPROATE*(N)** check lithium levels and adherence are optimised before considering addition
  RESTRICTED USE in patients of childbearing potential

or

- **ATYPICAL ANTIPSYCHOTIC** choice based on previous response in acute phase

or

- Consider **PALIPERIDONE LAI, HALOPERIDOL DECANOATE** or **ARIPIPRAZOLE LAI** if adherence to oral medication is erratic or injection preferred

or

- CARBAMAZEPINE licensed for bipolar prophylaxis but not recommended by NICE. Number of clinically significant interactions with many psychotropics (reduced plasma concentration) limits use.

*Guidance surrounding Valproate's place in therapy is subject to change and under review with the MHRA

Supporting Information

Acute Manic Episode
Acute depressive episode
Rapid Cycling
Long-term management
Guidelines for the use of quetiapine XL

Definitions

- Off-label - prescribing a licensed medication for a condition outside its marketing authorisation (licence)
- Unlicensed - prescribing a medicine that does not have a UK marketing authorisation (licence)

Off-label and Unlicensed Medicines

Before prescribing off-label or unlicensed medicines the following conditions must be met:

- The medicine is better suited to the patient/client's needs than an appropriately licensed alternative
- There is a sufficient evidence base and/or experience of using the medicine to demonstrate its safety and efficacy
- The reasons why medicines are not licensed for their proposed use should be explained to the patient/client, or parent/carer
- A clear and accurate record of medicines and the rational for use should be documented on patient record (unless the medication is included in TEWV off-label permissions) as part of the Medication Treatment Plan
- Prescribing & monitoring arrangements for "off-label" and unlicensed medications are likely to remain in secondary care unless transfer has been agreed

NMPs may prescribe a medicine for use outside the terms of its licence (off label) providing they are satisfied that there is a sufficient evidence base and/or experience of using the medicine to demonstrate its safety, efficacy and benefit to the patient (NMC, 2007, HPCP, 2016). All use of unlicensed and off label medications **must** be in accordance with the trust Drug & Therapeutic Committee's approved off licence use and within the scope of practice and level of practice of the NMP.

Useful links

NICE Guideline

Bipolar disorder – assessment and management, (updated 2018). Clinical guideline 185.

BAP Guidelines

Evidence based guidelines for treating bipolar disorder, (2016)
Guidelines for the management of weight gain. (2016)

Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD)

Guidelines for the management of patients with bipolar disorder (2018)

The Maudsley Prescribing Guidelines

Taylor, D., Barnes, T.R.E. & Young A.H. (2021). Chapter 2 – Bipolar disorder. The Maudsley Prescribing Guidelines in Psychiatry, 14th Edition. London: CRC Press. lib.myilibrary.com/Open.aspx (Athens account & login needed; contact library services if needed)

Medication Information

The Choice and Medication website has helpful information in agreeing choice of medication for bipolar disorder with patients www.choiceandmedication.org.uk/tees-esk-and-wear-valleys/ including information on driving whilst taking medication.

Acute Manic Episode

- Choice of medicine should be based on a review of the benefits of efficacy versus the risks of short term adverse reactions/effects and should take into account any advance statements, the person's preference and clinical context (including physical comorbidity, previous response to treatment and side effects).
- Also take into account the need for prophylactic treatment whilst selecting an anti-manic drug.
- Combination therapy with atypical antipsychotic and lithium/valproate might be considered in patients with a severe manic episode.
- Short-term parenteral administration of anti-psychotics and benzodiazepines may be necessary in the early stages, following agreed Trust protocols and using the lowest doses necessary
- Short term benzodiazepine use may be required to promote sleep for agitated, overactive patients
- Antidepressant drugs (i.e. drugs approved for treatment of unipolar depression) should usually be tapered and discontinued during a manic episode.
- Any medicine used adjunctively for symptomatic effect to promote sleep or sedation should be discontinued as soon as symptoms improve.

- **With regard to specific drugs:**
    - Haloperidol, olanzapine, risperidone and quetiapine are all effective in short-term reduction of symptoms
    - Haloperidol is superior to other agents but there is an increased risk of adverse effects such as EPSE and tardive dyskinesia as well as the potential to cause depression. Risperidone and olanzapine are equipotent and superior to all agents except Haloperidol.
    - Valproate has less risk of adverse motor reactions but should not be prescribed in women of childbearing age.
    - Lithium, quetiapine, valproate, carbamazepine, aripiprazole and asenapine all have similar efficacy, although quetiapine may be better tolerated and the evidence for carbamazepine is not robust
    - Gabapentin, lamotrigine and topiramate are no better than placebo.
    - Olanzapine, risperidone, haloperidol and quetiapine are thought to have the best efficacy and acceptability, although there is a higher risk of side effects with haloperidol.

- **For patients who are already taking long term treatment who suffer a manic episode:**
    - If the current presentation is due to inadequate symptom control, ensure that the highest well-tolerated dose is offered/treatment optimised.
    - If the current episode is due to poor adherence, establish the reasons for this, e.g. if non-adherence is associated with an adverse reaction, consider dose reduction, assuming the adverse effect is dose related, or a switch to a more tolerable alternative regimen.
    - If non-adherence is deliberate, long term use lithium may not be indicated due to the risk of mania and depression on withdrawal.

- The benefit of an antipsychotic-mood stabiliser combination has been established for those relapsing on mood stabilisers but is less clear for those presenting on no treatment.
- If the clinical presentation is of a mixed affective state, characterised by both manic and depressive symptoms, follow the recommendations for treatment of mania, monitoring closely for the emergence of depression. **NB.** Do not offer lamotrigine monotherapy to treat mania.
- Clozapine has been used in refractory mania; this is an off license indication.
- ECT should only be considered if mania is severe, treatment resistant, for patient preference or for severe mania during pregnancy.
- Assess the contribution of substance use to a manic or hypomanic episode and consider if medically assisted withdrawal is required.
- LAI such as risperidone and aripiprazole are unsuitable for acute treatment of mania.
- Drug discontinuation should be planned in relation to the need for long term maintenance treatment. Within four 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. If the person decides to continue treatment for mania, offer it for a further 3-6 months then review.

Acute depressive episode

- There is a risk of a switch to mania or mood instability during treatment for depression, whilst this will often reflect the natural history of the disorder; it may be increased by monotherapy with antidepressants.
- **With regard to specific drugs:**
  - Antidepressants have not been adequately studied in bipolar disorder; the only specific treatment with support is the combination of olanzapine with fluoxetine.
  - The best performers are olanzapine + fluoxetine, olanzapine, quetiapine and lurasidone
  - Also recommended are valproate, SSRIs and Lithium
  - There is little evidence for lamotrigine (stronger evidence for prevention than treatment), MAOIs, aripiprazole and risperidone
  - Minimise antidepressant exposure – switching to manic or mixed states with an antidepressant usually occurs within the first 12 weeks, the risk is lower if the antidepressant is used with a mood stabiliser; dual action monoamine reuptake inhibitors such as venlafaxine, duloxetine, amitriptyline & imipramine carry a greater risk than single action drugs such as SSRIs. Tricyclics are also likely to cause switching and rapid cycling.
  - Although NICE does not differentiate between bipolar I and II, there is much more evidence regarding use of antidepressant drugs in bipolar II. In clinical practice, antidepressant drugs are used more often in this population.
  - Consider discontinuation of antidepressants after as little as 12 weeks in remission.

- When depressive symptoms are less severe, lithium may be considered, especially with a view to long-term treatment
- Avoid sudden dose changes and switches
- For patients who suffer a depressive episode whilst taking long-term treatment, ensure that the current choice of drug is likely to protect the patient from manic relapse by checking they are taking adequate doses or checking serum lithium levels (if lithium is prescribed), once these treatments are optimised, initiate additional treatment as above.
- Treatment resistance – Hidaglo-Mazzei et al (2019) defined the criteria for treatment resistant bipolar disorder (TRBD) in bipolar depression as failure to reach sustained symptomatic remission for 8 consecutive weeks after two different treatment trials, at adequate therapeutic doses, with at least two recommended monotherapy treatments or at least one monotherapy treatment and another combination treatment. The definition of multi-therapy- resistant bipolar depression included the same initial definition as TRBD, with the addition of failure of at least one trial with an antidepressant, a psychological treatment and a course of electroconvulsive therapy.
- Augmentation strategies may be translated from experience in unipolar depression, but not before evidence based bipolar options have been exhausted, adequate anti-manic cover may be necessary. Common augmentation strategies include lithium + quetiapine, Thyroid augmentation is uncommon.
- Drug discontinuation should be planned in relation to the need for long term maintenance treatment. Within four weeks of resolution of symptoms, discuss with the person, and their carers if appropriate, whether to continue treatment for bipolar depression or start long-term treatment. If the person decides to continue treatment for bipolar depression, offer it for a further 3-6 months then review.
- Consider ECT for patients with high suicidal risk, treatment resistance, psychosis, severe depression during pregnancy or life-threatening inanition, see NICE guidance for ECT.

References

Hidalgo-Mazzei, D., Berk, M., Cipriani, A., Cleare, A., Florio, A., Dietch, D.,Stokes, P. (2019). Treatment-resistant and multi-therapy-resistant criteria for bipolar depression: Consensus definition. *The British Journal of Psychiatry, 214*(1), 27-35. doi:10.1192/bjp.2018.257

Rapid Cycling

- If rapid cycling is a problem in long-term-management identify and treat conditions that may contribute to cycling e.g. hypothyroidism, substance use
- Consider tapering and stopping antidepressants and stimulants that may contribute to cycling
- There are no specific treatments for rapid cycling; many patients require combinations of medicines. (Lithium + valproate; Lithium + Lamotrigine; Lithium/Valproate + quetiapine/olanzapine/aripiprazole)

- Quetiapine has the best supporting data for use in rapid cycling but there is no evidence of superiority over aripiprazole or olanzapine.
- Anti-cycling effects should be evaluated over periods of 6 months or more
- Discontinue ineffective treatments to avoid unnecessary polypharmacy
- Minimise adverse drug reactions to improve adherence
- Clozapine is approved for off-label use in TEWV treatment of refractory rapid cycling bipolar disorder.

Long-term management

- Maintenance treatment should be considered in most patients, especially if they have frequent episodes and if episodes are associated with significant dysfunction and risks.
- The current preferred strategy is for continuous rather than intermittent treatment with oral medicines to prevent new mood episodes

- **Drugs with evidence for prevention of manic relapse:**
  - Lithium
  - Olanzapine
  - Quetiapine
  - Risperidone LAI
  - Valproate (marginal)

- **Drugs with evidence to prevent depressive relapse:**
  - Lithium
  - Lamotrigine
  - Quetiapine
  - Lurasidone

- Short-term add-ons e.g. benzodiazepines, antipsychotics, may be needed when an acute stressor is imminent or present, early symptoms of relapse (especially insomnia) are present or anxiety becomes prominent. Consider supplying these prospectively with instructions on how and when to use. Higher doses of long-term treatments may also be effective instead of add-ons.
- In addition to relapse prevention study data, data to compare the rates of hospital admission on and off treatment over 4 years are strongly supportive of efficacy for:

  Lithium > Valproate > Olanzapine > Lamotrigine > Quetiapine > Carbamazepine

- Lithium should therefore be considered as the **first line drug**. Monitoring should be completed as per Trust guidance and the patient should be added to the relevant lithium register. On initiation, patients should receive the purple Lithium booklet and counselling on the content. Lithium can be transferred to primary care following the Trust shared care protocol.
- Lithium has also been found to reduce the risk of suicide and decreases the risk of Alzheimer's dementia.

- Where lithium is ineffective, poorly tolerated or patients are unlikely to be adherent with treatment and monitoring consider alternative e.g. Valproate or antipsychotic. It is worth noting that valproate monotherapy is less effective than lithium and the combination of lithium and valproate.
- In an individual patient, if a medicine leads to prompt remission from the most recent manic or depressive episode, this may be considered evidence in favour of its long term use as monotherapy, however, this may lead to preferential use of antipsychotics due to their short term efficacy. Lithium should be actively considered as a better alternative.
- Carbamazepine may be used as an alternative to lithium monotherapy if lithium is ineffective, especially in patients who do not show the classical pattern of episodic euphoric mania but is less effective in maintenance treatment and pharmacokinetic interactions can be problematic. (Oxcarbazepine has a lower potential for such interactions and could theoretically be considered an option)
- Long-acting depot formulations should be considered if prophylaxis against recurrence of mania is required and adherence to oral medication is erratic, only risperidone LAI has data to support its use, the use of other LAI represents an extrapolation of evidence from oral efficacy or a class effect and clinical experience.
- If a patient fails to respond to monotherapy and continues to experience sub-threshold depressive symptoms or relapses, consider long term combination treatment.
    - Where the burden of disease is **mania**, it may be logical to combine two anti-manic drugs e.g. Lithium, valproate or antipsychotic
    - Where the burden of disease is **depressive** a combination of lithium, lamotrigine, quetiapine, lurasidone or olanzapine may be more appropriate.
- The role of antidepressants in long term treatment is not established, but they appear to be effective in a minority of patients in the long term.
- If clozapine was effective in refractory mania, consider continuation as clozapine may have some significant mood stabilising effects in treatment-resistant bipolar or schizoaffective patients.
- Maintenance ECT may be considered for patients who respond to ECT during an acute episode but respond poorly to all oral agents
- Adjunctive psychotherapy should be considered to address subthreshold symptoms.

Guidelines for the use of quetiapine XL

Quetiapine is available as immediate-release (standard) and modified-release (XL) tablets.

The drug tariff price of generic immediate-release quetiapine tablets is considerably lower than modified-release quetiapine tablets (Seroquel® XL, Biquelle XL, etc). The modified-release tablets should only be used when they offer a clear clinical benefit over the standard tablets. This may be the case in:

- Patients who would benefit from a faster titration before switching to immediate-release tablets (see table below)

- Patients at high risk of adverse events that are related to peak blood levels (e.g. orthostatic hypotension) – the modified-release formulation may be the preferred option for initiation of therapy (see table below)
- Patients on treatment who are experiencing side-effects that are related to peak blood levels
- Patients who are poorly compliant with treatment and would benefit from once-daily dosing

Options for initiation of quetiapine are:

	Using immediate-release tablets				**Using modified-release tablets**
	Schizophrenia		Acute Mania		Schizophrenia or acute mania
	am	pm	am	pm	once daily
Day 1	25 mg	25 mg	50 mg	50 mg	300 mg XL
Day 2	50 mg	50 mg	100 mg	100 mg	600 mg XL
Day 3	100 mg	100 mg	150 mg	150 mg	Switch to twice daily immediate release tablets and adjust dose according to response.
Day 4	150 mg	150 mg	200 mg	200 mg	As above
Day 5 onwards	Adjust dose according to response; usual range 300-450 mg daily in two divided doses; **max. 750 mg daily**		Adjust dose according to response (max. 200 mg increments); usual range 400-800 mg daily in two divided doses; **max. 800 mg daily**		As above

N.B. quetiapine XL is **not** suitable for covert administration to non-compliant patients. The modified-release nature of the formulation is completely dependent upon the tablet being swallowed whole. If tablets need to be crushed, then immediate-release tablets should be used.