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A summary of prescribing recommendations from NICE guidance

Bipolar disorder

NICE CG185; 2014

This guideline covers the recognition, assessment and management of bipolar disorder in children, young people and adults. It applies to people with bipolar I, bipolar II, mixed affective and rapid cycling disorders.

Definition of terms

ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
LFT	liver function test
HbA_{1c}	glycosylated haemoglobin
BMI	body mass index
CV	cardiovascular
CVD	cardiovascular disease
NSAID	non-steroidal anti-inflammatory drug
CAMHS	child and adolescent mental health services
CBT	cognitive behavioural therapy
U	unlicensed indication
BNF	British National Formulary

See NICE pathway:Bipolar disorder

Adults

Recognising bipolar disorder in primary care

- When adults present with depression, ask about previous periods of overactivity or disinhibited behaviour. If these lasted for ≥4 days, consider referral for a specialist mental health assessment.
- Refer people urgently for a specialist mental health assessment if mania or severe depression is suspected or they are a danger to themselves or others.
- **Do NOT** use questionnaires to identify bipolar disorder.

Managing bipolar disorder in primary care

Psychological interventions

- Offer people with bipolar depression:
  - a psychological intervention developed specifically for bipolar disorder with a published evidence-based manual describing how it should be delivered, **OR**
  - a high-intensity psychological intervention (CBT, interpersonal therapy or behavioural couples therapy). See NICE pathway:Depression.
- Discuss possible benefits and risks of psychological interventions and the person's preference. Monitor mood and if any signs of hypomania or deterioration of the depressive symptoms, liaise with/refer the person to secondary care. If the person develops mania or severe depression, refer urgently to secondary care.
- If bipolar disorder is managed solely in primary care, re-refer to secondary care if any one of the following applies:
  - there is a poor or partial response to treatment,
  - the person's functioning declines significantly,
  - treatment adherence is poor,
  - the person develops intolerable or medically important side effects from medication,
  - comorbid alcohol or drug misuse is suspected,
  - the person is considering stopping any medication after a period of relatively stable mood,
  - a woman with bipolar disorder is pregnant or planning a pregnancy.

Pharmacological interventions

- **Do NOT** start lithium for people who have not taken lithium before, except under shared-care arrangements.
- **Do NOT** start valproate in primary care.

Monitoring physical health – see NICE pathway

Secondary care

Assessing suspected bipolar disorder – see NICE pathway

Management: psychological interventions – see managing bipolar disorder in primary care.

Pharmacological interventions (also see Box 1)

For people with moderate or severe bipolar depression:

- If treatment naïve offer:
  - fluoxetine[U] combined with olanzapine,[U] or quetiapine monotherapy,* **OR**
    if the person prefers, consider either olanzapine,[U] or lamotrigine[U] monotherapy.
  - if no response to fluoxetine combined with olanzapine, or quetiapine, consider lamotrigine[U] monotherapy.
- If already taking lithium, check the plasma lithium level:
  - if it is inadequate, increase the dose,
  - if it is at maximum level, add either fluoxetine[U] combined with olanzapine[U] or add quetiapine,* **OR**
    if the person prefers, consider adding olanzapine[U] or lamotrigine[U] to lithium.
  - if no response to adding fluoxetine combined with olanzapine, or adding quetiapine, stop the additional treatment and consider adding lamotrigine[U] to lithium.
- If already taking valproate:
  - consider increasing the dose within the therapeutic range,
  - if the maximum tolerated dose, or top of the therapeutic range, has been reached and there is a limited response to valproate, add fluoxetine[U] combined with olanzapine[U] or add quetiapine,* **OR**
    if the person prefers, consider adding olanzapine[U] or lamotrigine,[U]
  - if no response to adding fluoxetine combined with olanzapine, or adding quetiapine, stop the additional treatment and consider adding lamotrigine.[U] .

Recommendations – wording used such as 'offer' and 'consider' denote the strength of the recommendation.
Drug recommendations – the guideline assumes that prescribers will use a drug's Summary of Product Characteristics (SPC) to inform treatment decisions.

*depending on the person's preference and previous response to treatment.
** take into account any advance statements, person's preference and clinical context.

***available formulations:sodium valproateU, valproic acid (as semi-sodium salt). Semi-sodium valproate is licenced for treatment of mania if lithium is not tolerated/contraindicated, acute mania and continuation treatment for mania that has responded to treatment with semi-sodium valproate.

Produced for healthcare professionals by North West Medicines Information Service, The Pharmacy Practice Unit, 70 Pembroke Place, Liverpool, L69 3GF. Editor: Lindsay Banks. Telephone 0151 794 8117. E-mail: nwmedinfo@nhs.net

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Box 1

Prescribing (see also Prescribing:individual drugs)

Starting antipsychotic drug treatment

- Before starting treatment, measure and record the person's:
  - weight or BMI,
  - pulse and blood pressure,
  - fasting blood glucose or HbA_{1c},
  - blood lipid profile.
- Before starting treatment, offer the person an ECG if:
  - specified in the drug's SPC, **OR**
  - a physical examination has identified a specific CV risk (such as hypertension), **OR**
  - there is a family history of CVD, a history of sudden collapse, or other CV risk factors such as cardiac arrhythmia or the person is being admitted as an inpatient.
- Consider treatment with antipsychotic medication as an explicit individual therapeutic trial. Carry out the following:
  - discuss and record side effects the person is most willing to tolerate,
  - record indications, expected benefits and risks, expected time for a change in symptoms and appearance of side effects,
  - at the start of treatment prescribe a dose that is appropriate for the phase and severity of the illness,
  - **Do NOT** routinely prescribe a dose above the maximum recommended in the BNF or SPC. Justify and record reasons for doses outside this range and inform the person that such treatment is unlicensed,
  - record the rationale for continuing, changing or stopping medication, and the effects of such changes.
- 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.
- When offering psychotropic medication to older people take into account:
  - its impact on cognitive functioning,
  - the increased risk of drug interactions,
  - the negative impact that anticholinergic medication, or drugs with anticholinergic activity, can have on cognitive function and mobility.
- In older people use lower doses and ensure that medical comorbidities have been recognised and treated.
- **Do NOT** offer gabapentin or topiramate to treat bipolar disorder.

Monitoring

- Monitor and record the following during dose titration and then regularly and systematically throughout treatment:
  - pulse and blood pressure after each dose change,
  - weight or BMI weekly for the first 6 weeks, then at 12 weeks,
  - blood glucose or HbA_{1c} and blood lipid profile at 12 weeks,
  - response to treatment, including changes in symptoms and behaviour,
  - impact of side effects on physical health and functioning,
  - the emergence of movement disorders,
  - adherence.

Stopping treatment

- Reduce the dose gradually over at least 4 weeks to minimise the risk of relapse.

Managing crisis, risk and behaviour that challenges – see NICE pathway

Managing mania or hypomania in secondary care

- Ensure that people with mania or hypomania have access to calming environments and reduced stimulation. Advise them not to make important decisions until they have recovered, and encourage them to maintain relationships with their carers if possible.

Pharmacological interventions: mania (also see Box 1)

- If a person is taking an antidepressant as monotherapy:
  - consider stopping the antidepressant, **AND**
  - offer an antipsychotic, regardless of whether the antidepressant is stopped.
- If a person is not taking an antipsychotic or mood stabiliser:
  - offer haloperidol, olanzapine, quetiapine or risperidone.**
- 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.**
- If an alternative antipsychotic is not sufficiently effective at the maximum licensed dose, consider adding lithium.U
- If adding lithium is ineffective, or if lithium is not suitable (e.g. the person does not agree to routine blood monitoring), consider adding valproate.***
- If a person 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.*
- 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.*
- **Do NOT** offer lamotrigine to treat mania.

Reviewing treatment

Bipolar disorder or mania

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

Electroconvulsive therapy – see NICE pathway

Long term management in secondary care

- After each episode of mania or bipolar depression, discuss with the person, and their carers if appropriate, long-term management. Help people to 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:
  - the nature and variable course of bipolar disorder,
  - the role of psychological and pharmacological interventions to prevent relapse and reduce symptoms,
  - the risk of relapse after reducing or stopping medication for an acute episode,
  - potential benefits and risks of long-term interventions, and the need to monitor mood and medication,
  - potential benefits and risks of stopping medication, including for women who wish to become pregnant,
  - 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,

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- potential triggers for relapse, early warning signs, and self-management strategies,
- possible duration of treatment, and when and how often this should be reviewed.

Long term management: psychological interventions – see NICE pathway

Pharmacological interventions (also see Box 1)

First-line: offer lithium

- If lithium:
  - is ineffective, consider adding valproate,***
  - is poorly tolerated, or is not suitable e.g. because the person does not agree to routine blood monitoring, consider valproate or olanzapine[U] instead **OR**, if it has been effective during an episode of mania or bipolar depression, consider quetiapine.
- 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.
- Continue monitoring symptoms, mood and mental state for two years after medication has stopped entirely. This may be undertaken in primary care.

Promoting recovery and return to primary care – see NICE pathway

Prescribing: individual drugs

Lithium

Starting treatment

When starting lithium:

- advise the person that poor adherence or rapid discontinuation may increase the risk of relapse,
- measure the person's weight or BMI and arrange tests for urea and electrolytes including calcium, eGFR, thyroid function and a full blood count,
- arrange an ECG for people with or at risk of CVD,
- ensure the person is given appropriate information on taking lithium safely,
- establish a shared-care arrangement with the GP for prescribing lithium and monitoring side effects.

- Measure plasma lithium levels one week after starting lithium, one week after every dose change, and weekly until the levels are stable. Aim to maintain plasma lithium level between 0.6 and 0.8mmol/ litre in people being prescribed lithium for the first time.
- Consider maintaining plasma lithium levels at 0.8 to 1.0mmol/ litre for a trial period of at least 6 months for people who:
  - have had a relapse while taking lithium in the past, **OR**
  - are taking lithium and have subthreshold symptoms with functional impairment.
- Advise people taking lithium to:
  - seek medical attention if they develop diarrhoea or vomiting or become acutely ill,
  - ensure they maintain their fluid intake, particularly after sweating e.g. after exercise, in hot climates or if they have a fever, if they are immobile for long periods or if they develop a chest infection or pneumonia,
  - talk to their doctor as soon as possible if they become pregnant or are planning a pregnancy.
- Warn people taking lithium not to take over-the-counter NSAIDs and avoid prescribing these drugs for people with bipolar disorder if possible; if prescribed, this should be on a regular (not as required) basis and lithium levels monitored monthly until a stable level is reached, then 3 monthly.

Monitoring

- Measure plasma lithium levels every 3 months for the first year.
- After the first year, measure plasma lithium levels every 6 months, or every 3 months for people:
  - who are older,
  - taking drugs that interact with lithium,
  - at risk of impaired renal or thyroid function, raised calcium levels or other complications,
  - who have poor symptom control,
  - with poor adherence,
  - whose last plasma lithium level was ≥0.8 mmol/litre.
- Measure weight or BMI, arrange tests for urea and electrolytes including calcium, eGFR and thyroid function every 6 months, and more often if there is evidence of impaired renal or thyroid function, raised calcium levels or an increase in mood symptoms that might be related to impaired thyroid function.
- Monitor lithium dose and plasma levels more frequently if urea and creatinine levels become elevated, or eGFR falls over two or more tests, and assess rate of deterioration of renal function. See NICE pathways: chronic kidney disease and acute kidney injury.
- When discussing whether to continue lithium, take into account clinical efficacy, other risk factors for renal impairment and CVD, and degree of renal impairment; if needed seek advice from a renal specialist and a clinician with expertise in managing bipolar disorder.
- Monitor the person at every appointment for symptoms of neurotoxicity, including paraesthesia, ataxia, tremor and cognitive impairment, which can occur at therapeutic levels.

Stopping treatment

- Reduce the dose gradually over at least 4 weeks, and preferably up to 3 months, even if the person has started taking another drug for mania.
- During dose reduction and for 3 months after stopping monitor closely for early signs of mania and depression.

Valproate

Starting treatment

- When starting valproate, measure the person's weight or BMI, carry out a full blood count and LFTs.
- **Do NOT** offer valproate to women of childbearing potential for long-term treatment or to treat an acute episode.
- Advise people taking valproate, and their carers, how to recognise the signs and symptoms of blood and liver disorders and to seek immediate medical help if any of these develop.
- Stop valproate immediately if abnormal liver function[α] or blood dyscrasia is detected.
- When prescribing valproate, be aware of interactions with other anticonvulsants (particularly carbamazepine and lamotrigine) and with olanzapine and smoking.

α Absolute values of liver enzymes are a poor indicator of the extent of hepatic damage. It is generally accepted that if LFTs are persistently elevated to >3 times the upper normal limit, continuing to rise or accompanied by clinical symptoms, the suspected drug should be withdrawn. Raised LFTs of any magnitude accompanied by reduced albumin or impaired clotting suggest severe liver disease.

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Monitoring

- **Do NOT** routinely measure plasma valproate levels unless there is evidence of ineffectiveness, poor adherence or toxicity.
- Measure the person's weight or BMI and carry out LFTs and a full blood count again after 6 months of treatment and repeat annually.
- Monitor sedation, tremor and gait disturbance carefully in older people.

Stopping treatment

- Reduce the dose gradually over at least 4 weeks to minimise the risk of relapse.

Lamotrigine

Starting treatment

- When starting lamotrigine:
  - carry out a full blood count, urea and electrolytes and LFTs,
  - be aware of its interaction with valproate,
  - follow the instructions for initial dosage and dosage titration outlined in the SPC and BNF, taking into account the need for slow titration in people who have not taken lamotrigine before.
- Advise people taking lamotrigine to contact their doctor:
  - immediately if they develop a rash while the dose of lamotrigine is being increased,
  - if they are pregnant or planning a pregnancy.

Monitoring

- **Do NOT** routinely measure plasma lamotrigine levels unless there is evidence of ineffectiveness, poor adherence or toxicity.

Stopping treatment

- Reduce the dose gradually over at least 4 weeks to minimise the risk of relapse.

- The secondary care team should maintain responsibility for monitoring antipsychotic medication for at least the first 12 months or until the person's condition has stabilised. Then responsibility may be transferred to primary care under shared-care arrangements.

Children and young people

Recognising bipolar disorder in primary care

- **Do NOT** use questionnaires to identify bipolar disorder.
- If bipolar disorder is suspected in children aged <14 years, refer them to CAMHS.
- If bipolar disorder is suspected in young people aged ≥14 years, refer to a specialist early intervention in psychosis service or CAMHS team with expertise in the assessment and management of bipolar disorder. The service should be multidisciplinary and have:
  - engagement or assertive outreach approaches,
  - family involvement and family intervention,
  - access to structured psychological interventions and psychologically informed care,
  - vocational and educational interventions,
  - access to pharmacological interventions,
  - professionals who are trained and competent in working with young people with bipolar disorder.
- Diagnosis should be made only after a period of intensive, prospective longitudinal monitoring by a healthcare professional or multidisciplinary team trained and experienced in the assessment, diagnosis and management of bipolar disorder in children and young people, and in collaboration with parents or carers.
- When diagnosing bipolar disorder in children or young people take account of the following:
  - mania must be present,
  - euphoria must be present on most days and for most of the time, for at least 7 days,
  - irritability is not a core diagnostic criterion.
- **Do NOT** make a diagnosis on the basis of depression with a family history of bipolar disorder but follow them up.

Managing bipolar disorder

- When offering treatment to young people, take into account their cognitive ability, emotional maturity, developmental level, capacity to consent to treatment, the severity of their bipolar disorder and risk of suicide or self-harm or any other risks as for adults.

Psychological intervention

- Offer a structured psychological intervention (individual CBT or interpersonal therapy) to young people with bipolar depression. It should be of at least 3 months' duration and have a published evidence-based manual describing how it should be delivered.
- If after 4 to 6 weeks there is no or a limited response to CBT or interpersonal therapy carry out a multidisciplinary review and consider an alternative individual or family psychological intervention.
- If there is a risk of suicide or self-harm or any other risk (as outlined for management of adults in secondary care) carry out an urgent review and develop a risk management plan; see NICE pathway.
- After the multidisciplinary review, if there are coexisting factors such as comorbid conditions, persisting psychosocial risk factors such as family discord, or parental mental ill-health, consider:
  - an alternative psychological intervention for the young person, their parents or other family member, **OR**
  - an additional psychological intervention for any coexisting mental health problems in line with relevant NICE guidance for the young person, their parents or other family member.

Pharmacological intervention (also see Box 1)

- If the young person's bipolar depression is moderate to severe, consider a pharmacological intervention in addition to a psychological intervention. Follow recommendations for adults but refer to the BNF for Children (BNFC) to modify drug treatments.
- At 12 weeks, carry out a full multidisciplinary review of mental and physical health, and consider further management of depression or long-term management.
- **Do NOT** routinely continue antipsychotic treatment for >12 weeks.

Mania

- To treat mania or hypomania in young people follow recommendations as for adults and see NICE TA292; aripiprazole is recommended as a possible treatment (for up to 12 weeks) for moderate to severe manic episodes in adolescents aged ≥13 years with bipolar I disorder.
- Refer to the BNFC to modify drug treatments, be aware of increased potential for a range of side effects. Do not routinely continue antipsychotic treatment for >12 weeks.
- **Do NOT** offer valproate to girls or young women of childbearing potential.

Long-term treatment

- After the multidisciplinary review, consider a structured individual or family psychological intervention for managing bipolar disorder in young people in the longer term.