



*National Institute for
Health and Clinical Excellence*

Quick reference guide

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Bipolar disorder

The management of bipolar disorder in adults, children and adolescents, in primary and secondary care

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Patient-centred care

Treatment and care should take into account patients' individual needs and preferences. Good communication is essential, supported by evidence-based information, to allow patients to reach informed decisions about their care. Carers and relatives should have the chance to be involved in discussions unless the patient thinks it inappropriate.

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This guidance is written in the following context

This guidance represents the view of the Institute, which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. The guidance does not, however, override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Key priorities for implementation

Treating bipolar disorder with drugs

- Valproate should not be prescribed routinely for women of child-bearing potential. 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, olanzapine or valproate* should be considered for long-term treatment of bipolar disorder. The choice should depend on:
 - response to previous treatments
 - the relative risk, and known precipitants, of manic versus depressive relapse
 - physical risk factors, particularly renal disease, obesity and diabetes
 - the patient's preference and history of adherence
 - gender (valproate should not be prescribed for women of child-bearing potential)
 - a brief assessment of cognitive state (such as the Mini-Mental State Examination) if appropriate, for example, for older people.
- If the patient has frequent relapses, or symptoms continue to cause functional impairment, switching to an alternative monotherapy or adding a second prophylactic agent (lithium, olanzapine, valproate*) should be considered. Clinical state, side effects and, where relevant, blood levels should be monitored closely. Possible combinations are lithium with valproate*, lithium with olanzapine, and valproate* with olanzapine. The reasons for the choice and the discussion with the patient of the potential benefits and risks should be documented.
- If a trial of a combination of prophylactic agents proves ineffective, the following should be considered:
 - consulting with, or referring the patient to, a clinician with expertise in the drug treatment of bipolar disorder
 - prescribing lamotrigine* (especially if the patient has bipolar II disorder) or carbamazepine.
- If a patient is taking an antidepressant at the onset of an acute manic episode, the antidepressant should be stopped. This may be done abruptly or gradually, depending on the patient's current clinical need and previous experience of discontinuation/withdrawal symptoms, and the risk of discontinuation/withdrawal symptoms of the antidepressant in question.
- After successful treatment for an acute depressive episode, patients should not routinely continue on antidepressant treatment long-term, because there is no evidence that this reduces relapse rates, and it may be associated with increased risk of switching to mania.

*Drugs marked with asterisks do not have UK marketing authorisation for the use in question at the time of publication of this clinical guideline.

Key priorities for implementation *continued*

Monitoring physical health

- People with bipolar disorder should have an annual physical health review, normally in primary care, to ensure that the following are assessed each year:
 - lipid levels, including cholesterol in all patients over 40 even if there is no other indication of risk
 - plasma glucose levels
 - weight
 - smoking status and alcohol use
 - blood pressure.

Diagnosis in adolescents

- When diagnosing bipolar I disorder in adolescents the same criteria should be used as for adults except that:
 - mania must be present
 - euphoria must be present most days, most of the time (for at least 7 days)
 - irritability can be helpful in making a diagnosis if it is episodic, severe, results in impaired function and is out of keeping or not in character; however, it should not be a core diagnostic criterion.

Using this quick reference guide

Recommendations on prescribing

At the time of publication, drugs marked with an asterisk (*) do not have UK marketing authorisation for the use in question.

Bipolar II disorder

The evidence on treating bipolar II disorder is limited. The recommendations for treating bipolar I disorder should be cautiously applied to treating bipolar II disorder.

The term mood stabiliser

This guideline does not use the term mood stabiliser because there is no agreed definition. Instead the following are used:

- antimanic drugs (or medication), for antipsychotics, carbamazepine, lithium, valproate when used in the treatment of acute mania
- prophylactic drugs (or medication), for any medication used for long-term treatment.

General principles

Working with patients and their families

- Establish and maintain collaborative relationships with patients, families and carers (within the bounds of confidentiality):
 - respect the patient's knowledge and experience of the illness
 - encourage patients to involve their families and carers if appropriate
 - give patients, families and carers information (including information on medication) at every stage of assessment, diagnosis and treatment
 - encourage patients, family and carers to join self-help and support groups.
- Advise patients on:
 - self-monitoring of symptoms, including triggers and early warning signs
 - lifestyle, including sleep hygiene and work patterns
 - coping strategies.
- Write advance statements (directives) on mental and physical healthcare with patients – especially if they have severe episodes or have been treated under the Mental Health Act. Document these in care plans, and give copies to the patient, and their care coordinator and GP.
- Consider the needs of the patient's family members or carers, including:
 - the impact on relationships
 - the welfare of dependent children, siblings and vulnerable adults
 - carers' physical, social and mental health needs.
- Be accessible to family members and carers in times of crisis.

Specific groups of patients with bipolar disorder

- **People with learning disabilities:** offer the same care for their bipolar disorder as to other patients; consider possible drug interactions.
- **People with personality disorder:** offer the same care for their bipolar disorder as to other patients.
- **People with harmful drug and/or alcohol use:** consider a psychosocial intervention targeted at the drug and/or alcohol use, delivered by general mental health services, working with specialist substance use services where appropriate.
- **Older people:** there should be a robust protocol for transferring patients to services for people older than 65 years. Base referral decisions on the patient's needs first, rather than simply their chronological age.
- When treating older people with bipolar disorder:
 - use medication at lower doses
 - be alert to the increased risk of drug interactions
 - address medical comorbidities.

Assessment, recognition and diagnosis

Bipolar disorder in primary care

New or suspected presentations of bipolar disorder

- **Refer urgently** patients with mania or severe depression who are a danger to themselves or other people.
- **Refer** for assessment and development of a care plan, patients with either:
 - periods of overactive, disinhibited behaviour lasting at least 4 days, with or without periods of depression, or
 - three or more depressive episodes and a history of overactive, disinhibited behaviour.
- **Ask about** hypomanic symptoms when assessing a patient with depression and overactive, disinhibited behaviour.

Patients with existing bipolar disorder

- **Consider referring** a new patient with existing bipolar disorder who registers with the practice.
- **Refer urgently** a patient with bipolar disorder managed solely in primary care if there is:
 - an acute exacerbation of symptoms – particularly mania or severe depression
 - an increase in the degree (or change in the nature) of risk to self or others.
- **Consider review** in secondary care, or increased contact in primary care, for a patient managed solely in primary care, if:
 - functioning declines significantly or response to treatment is poor
 - treatment adherence is a problem
 - you suspect alcohol and/or drug misuse
 - the patient is considering stopping prophylactic medication.

Assessment and diagnosis in secondary care

- When making an assessment:
 - take a full history including family history, previous episodes and symptoms between episodes
 - assess the patient's symptom profile, triggers, social and personal functioning, comorbidities including alcohol and/or drug misuse and anxiety, risk, physical health, and psychosocial stressors
 - obtain a corroborative history from a family member or carer – if possible, and within the bounds of confidentiality
 - consider using formal criteria, including self-rating scales such as the Mood Disorder Questionnaire¹.

¹Hirschfeld RM, Williams JB, Spitzer RL et al. (2001) *American Journal of Psychiatry* 158(10):1743-4.

- More pronounced psychotic symptoms, increased suicidal ideation, drug misuse, or more disturbed behaviour may be a late presentation of bipolar disorder and not of a schizophrenia-spectrum disorder, particularly in patients from black and minority ethnic groups, who may have difficulty accessing services.
- Drug or alcohol misuse may induce manic-like symptoms – in inpatient settings, wait 7 days before confirming bipolar disorder if there is evidence of misuse.
- Symptoms may be due to underlying conditions, such as hypothyroidism, cerebrovascular insults or dementia, particularly if age of onset is over 40 years.
- In the differential diagnosis of bipolar disorder and personality disorder:
 - during assessment, consider bipolar disorder before personality disorder if the person has mood swings and functional impairment
 - during treatment, ensure the patient has had adequate treatment to stabilise symptoms before considering a diagnosis of comorbid personality disorder.

Diagnosing rapid-cycling bipolar disorder

- Check for other explanations such as thyroid disease, antidepressant-induced switching, suboptimal medication regimes, the effects of lithium withdrawal, and erratic compliance.
- Consider asking the patient and/or carer to assess mood and behaviour for at least a year.

Assessment and management of risk in primary and secondary care

- Do a risk assessment when:
 - bipolar disorder is first diagnosed
 - there is a significant change in mental state or personal circumstances
 - a person is discharged from or on leave from inpatient care.
- Develop a crisis plan with patients who are at risk of suicide, exploitation or severe self-neglect, are a risk to others, or have a history of recurrent admissions, particularly compulsory admissions.
- The plan should include:
 - a list of the person's triggers and early warning symptoms of relapse
 - for people at risk of rapid onset of mania for whom clear early warning signs can be identified, a protocol for increasing the dose or taking additional medication (which may be given to the patient in advance); monitor the protocol regularly – this is not a substitute for urgent review
 - how primary and secondary care services will respond to increased risk
 - how the patient (and carers) can get help, and the names of staff involved.
- Prescribe limited quantities of psychotropic medication during periods of high suicide risk.

Treatment setting and pathways to care

Continuity of care for people with bipolar disorder

- Where possible, people with bipolar disorder – including those with sub-threshold symptoms – should see the same healthcare professionals regularly.

Service provision in primary and secondary care

- Primary and secondary care organisations should consider integrated care, including:
 - regular reviews of mental state and personal and social functioning, to ensure that symptoms (including sub-threshold symptoms) are treated if they significantly impair social functioning
 - protocols for delivering and monitoring interventions
 - agreements on responsibilities for assessment, monitoring and treatment
 - written treatment plans, promoting self-management, and shared with patients and, if appropriate, families and carers.

- In general practice, include people with bipolar disorder in registers of people with severe mental illness.

- Consider providing telephone support in primary care, using treatment protocols, in particular for monitoring medication regimes.

Specialist mental health services

- Trusts providing specialist mental health services should ensure that all clinicians have access to advice from designated specialists on:
 - managing bipolar disorder in adults (and, if appropriate, separately for children and adolescents)
 - referral to tertiary centres.

Crisis resolution and home treatment teams

- Consider as a way of:
 - managing crises at home or in the community
 - supporting early discharge from hospital.
- Should give particular attention to managing risk, monitoring behavioural disturbance, and the burden on family and carers.

Early intervention services for people with psychosis

- Should provide expertise in diagnosis, and pharmacological, psychological, social, occupational and educational interventions.

Support for returning to work and education

- Consider vocational rehabilitation for people who want help returning to work or getting a job.
- Consider support to return to education or other structured, purposeful activities.

Enhanced multi-professional outpatient clinics (such as lithium clinics)

- Consider for patients who would benefit from close monitoring, and/or have a health risk such as renal damage, and a record of regular attendance.

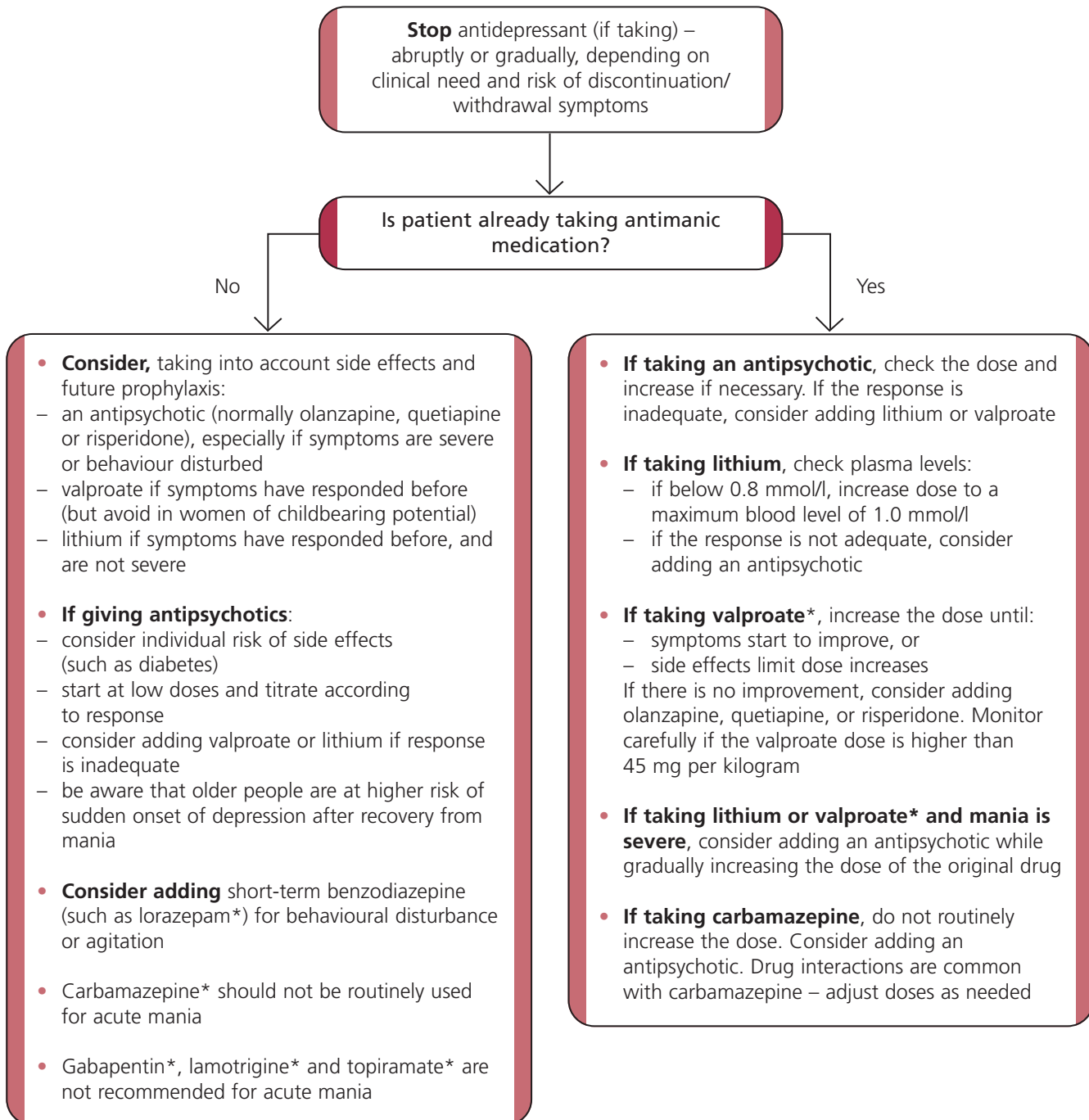
For more details, see the NICE guideline (www.nice.org.uk/CG038).

Managing acute episodes

General recommendations

- Decide treatment plans in collaboration with patients, considering the outcome of previous treatment(s) and the patient's preference.
- With all women of child-bearing potential, discuss contraception and the risks of pregnancy (including relapse, damage to the fetus and risks associated with stopping and changing medication). Encourage women to discuss pregnancy plans with their doctor (see pages 24–26 for more information).
- See people having a manic episode or severe depressive symptoms again within a week of their first assessment. Continue to see them regularly – for example, every 2–4 weeks in the first 3 months, then less often if response is good.

Managing episodes of mania and hypomania



Advise all patients on:

- avoiding excessive stimulation
- calming activities
- delaying important decisions
- a structured routine with a lower activity level

Managing depressive symptoms

Patients not taking antimanic medication

- Patients who are prescribed an antidepressant should also be prescribed an antimanic drug. Base the choice of antimanic drug on:
 - decisions about future prophylactic treatment
 - likely side effects
 - whether the patient is a woman of child-bearing potential.
- When starting an antidepressant:
 - explain the risks of switching to mania and the benefits of taking an adjunctive antimanic agent
 - monitor carefully people who are unwilling to take an antimanic drug
 - start the antidepressant treatment at a low dose and increase gradually if necessary.

Patients taking antimanic medication

- Check the patient is taking the antimanic drug at the appropriate dose and adjust it if necessary.

Patients with mild depressive symptoms

- Arrange a further assessment, normally within 2 weeks, if:
 - the patient's previous episodes of mild depression have not developed into chronic or more severe depression, or
 - a more severe depression is not likely.
- If symptoms do not improve, follow the advice for moderate or severe depression.

Patients with moderate or severe depressive symptoms

- Consider:
 - prescribing an SSRI (but not paroxetine in pregnant women), or
 - adding quetiapine, if the patient is already taking an antimanic drug that is not an antipsychotic.
- For moderate depression, if there is no significant improvement after an adequate trial of drugs, consider a structured psychological therapy focused on depressive symptoms, problem solving, improving social functioning, and medication concordance.

- Do not use routinely:
 - lamotrigine* as a single first-line drug in bipolar I disorder
 - transcranial magnetic stimulation*.

Antidepressant treatment and risk monitoring

- Avoid antidepressants for patients who have:
 - rapid-cycling bipolar disorder
 - a recent hypomanic episode
 - recent functionally impairing rapid mood fluctuations.
- Instead, consider increasing the dose of the antimanic drug or adding a second one (including lamotrigine*).

Starting antidepressants

- Address patients' concerns about taking antidepressants; for example, craving and tolerance do not occur.
- When starting antidepressant treatment, tell patients:
 - manic or hypomanic switching may occur
 - onset of effect is not immediate, and improvement is gradual and fluctuating
 - about the need to take medication as prescribed and the risk of discontinuation/withdrawal symptoms
 - to look out for signs of akathisia, suicidal ideation (normally anyone under 30 should be reviewed within 1 week of initiation of treatment), and increased anxiety and agitation (particularly at the beginning of treatment)
 - to seek help promptly if side effects are distressing.
- If a patient develops marked and/or prolonged akathisia or agitation while taking an antidepressant, urgently review the use of the drug.
- Take care when prescribing SSRIs to people – particularly older people – taking medication that can cause intestinal bleeding, such as non-steroidal anti-inflammatory drugs (NSAIDs). Consider using a gastroprotective drug.

Stopping antidepressants after an episode

- If a patient is in remission from depressive symptoms, or symptoms have been significantly less for 8 weeks, consider stopping the antidepressant by reducing the dose gradually (particularly with paroxetine and venlafaxine) over several weeks, while maintaining the antimanic medication.

Incomplete response to treatment for acute depression

- If symptoms do not fully respond to an antidepressant, reassess for substance misuse, psychosocial stressors, physical health problems, comorbid disorders such as anxiety or severe obsessional symptoms, and poor adherence.
- Then consider:
 - increasing the dose of the antidepressant within 'BNF' limits
 - individual psychological therapy focused on depressive symptoms
 - switching to a different antidepressant, such as mirtazapine or venlafaxine
 - adding quetiapine* or olanzapine, if the patient is not already taking them, or
 - adding lithium if the patient is not already taking it.
- If symptoms fail to respond to at least three adequate courses of antidepressant treatment, consider referring to (or seeking advice from) a specialist in bipolar disorder.
- For persistent depressive symptoms in patients with no recent history of rapid cycling (including those not taking an antidepressant), consider structured psychological therapy.

Concurrent depressive and psychotic symptoms

- For concurrent depressive and psychotic symptoms, consider augmenting treatment with an antipsychotic such as olanzapine, quetiapine or risperidone, or using electroconvulsive therapy (ECT, see box on page 14) if depression is severe.

Continued on page 15

The use of ECT in severe manic and depressive episodes

- Consider ECT only for rapid and short-term improvement of severe symptoms after other treatments have proved ineffective or if the condition is life-threatening, in people with:
 - severe depressive illness
 - a prolonged or severe manic episode.
 - catatonia.
- When making the decision, assess and document the risks and potential benefits, including:
 - the risks associated with the anaesthetic
 - current comorbidities
 - anticipated adverse events, particularly cognitive impairment
 - the risks of not having treatment.
- When using ECT to treat bipolar disorder, consider:
 - stopping or reducing lithium or benzodiazepines before giving ECT
 - monitoring the length of fits carefully if the patient is taking anticonvulsants
 - monitoring mental state for evidence of switching to the opposite pole.

Managing rapid-cycling bipolar disorder

Acute episodes

- Manage episodes in secondary care.
- Treat as for manic and depressive episodes, but in addition:
 - review previous treatments and consider a further trial of any that were inadequately delivered or adhered to
 - focus on optimising long-term treatment rather than treating individual episodes and symptoms; trials of medication should usually last at least 6 months
 - encourage patients to keep a mood diary to monitor the impact of interventions.

Long-term management

- Consider:
 - as first-line treatment a combination of lithium and valproate*
 - lithium monotherapy as second-line treatment, or increasing the dose if already taking lithium
 - combinations of lithium or valproate* with lamotrigine*, especially in bipolar II disorder.
- Check thyroid function every 6 months, and thyroid antibodies if indicated.
- Avoid using antidepressants, except on advice from a specialist.

Additional advice on managing depressive symptoms

- Advise about techniques such as structured exercise, activity scheduling, engaging in pleasurable and goal-directed activities, ensuring adequate diet and sleep, and seeking appropriate social support.
- Increase monitoring and formal support.

Managing acute mixed episodes

- Consider treating patients as if they had an acute manic episode, and avoid prescribing an antidepressant.
- Monitor patients at least weekly, particularly for suicide risk.

Preventing and managing behavioural disturbance

- When patients with bipolar disorder exhibit seriously disturbed behaviour, or are at risk of doing so:
 - place them in the least stimulating, most supportive environment available
 - review their safety and physical status, including hydration, and take appropriate action
 - consider using distraction techniques.

Pharmacological management of severe behavioural disturbance

Read this section in conjunction with the NICE clinical guideline on the short-term management of disturbed/violent behaviour in inpatient psychiatric settings and emergency departments (www.nice.org.uk/CG025).

- Use oral medication first – for example, lorazepam*, or an antipsychotic, or an antipsychotic and a benzodiazepine. Orodispersible formulations of risperidone and olanzapine are easier to take and more difficult to spit out.
- If rapid tranquillisation is needed, consider intramuscular olanzapine (10 mg), lorazepam* (2 mg) or haloperidol (2–10 mg), wherever possible as a single agent. Take into account:
 - that olanzapine and lorazepam* are preferable to haloperidol because of the risk of movement disorders with haloperidol
 - olanzapine and benzodiazepines should not be given intramuscularly within 1 hour of each other
 - intramuscular doses can be repeated up to 20 mg per day (olanzapine), 4 mg per day (lorazepam*) or 18 mg per day (haloperidol), within 'BNF' daily dose limits, including concurrent oral medication
 - the patient's previous response and tolerability, their current regular medication, and the availability of flumazenil.
- For behaviour disturbance, do not give routinely:
 - any psychotropic drug intravenously
 - diazepam* or chlorpromazine intramuscularly
 - paraldehyde*
 - zuclopenthixol acetate.

Long-term management of bipolar disorder

Drug treatment after recovery from an acute episode

Consider long-term treatment for bipolar disorder:

- after a manic episode involving significant risk and adverse consequences
- if a patient with bipolar I disorder has had two or more acute episodes
- if a patient with bipolar II disorder has significant functional impairment, is at significant risk of suicide or has frequent episodes.

Choice of drug

- Consider lithium, olanzapine or valproate* for long-term treatment of bipolar disorder, depending on:
 - response to previous treatments
 - the relative risk, and precipitants, of manic versus depressive relapse
 - physical risk factors, particularly renal disease, obesity and diabetes
 - the patient's preference and history of adherence
 - gender (valproate* should not normally be prescribed for women of child-bearing potential)
 - a brief assessment of cognitive state if appropriate, for example, for older people.
- If the patient has frequent relapses, or continuing functional impairment:
 - consider switching to a different prophylactic drug (lithium, olanzapine or valproate*)
 - adding a second; possible combinations are lithium with valproate*, lithium with olanzapine, valproate* with olanzapine
 - discuss with the patient (and document) the potential benefits and risks, and reasons for the choice
 - monitor closely clinical state, side effects and, where relevant, blood levels.
- If a combination of prophylactic agents proves ineffective, consider:
 - consulting, or referring the patient to, a specialist
 - prescribing lamotrigine* (especially if the patient has bipolar II disorder) or carbamazepine.
- Do not use long-acting intramuscular injections of antipsychotics routinely. But they may be considered for people whose mania has responded to oral antipsychotics, but have had a relapse because of poor adherence.

Length of treatment

- Normally, long-term pharmacological treatment should last for:
 - at least 2 years after an episode of bipolar disorder
 - up to 5 years if the person has risk factors for relapse, such as a history of frequent relapses or severe psychotic episodes, comorbid substance misuse, ongoing stressful life events, or poor social support.

- Discuss this with the patient and arrange regular reviews.
- Encourage patients to talk to their psychiatrist if they want to stop medication early.
- Offer regular contact and reassessment if, after careful discussion, a patient with bipolar disorder declines long-term medication.

After an acute depressive episode

- After successful treatment, patients should not normally continue on antidepressant treatment long-term – there is no evidence it reduces relapse rates, and it may increase the risk of switching.

Chronic and recurrent depressive symptoms

- For patients who are not taking prophylactic medication and have not had a recent manic or hypomanic episode, consider:
 - long-term treatment with SSRIs at the minimum therapeutic dose, and prophylactic medication
 - cognitive behavioural therapy (16–20 sessions) and prophylactic medication
 - quetiapine*, or
 - lamotrigine*.
- Consider lamotrigine* for patients with bipolar II disorder and recurrent depression.

Comorbid anxiety disorders

- For patients with significant comorbid anxiety disorders, consider psychological treatment focused on anxiety, or a drug such as an atypical antipsychotic.

Psychological therapy after an acute episode

- Consider individual structured psychological interventions, such as cognitive behavioural therapy, in addition to prophylactic medication for people who are relatively stable, but may have mild to moderate affective symptoms.
- The therapy should normally be at least 16 sessions over 6–9 months and:
 - include psychoeducation, the importance of a regular routine and concordance with medication
 - cover monitoring mood, detecting early warnings and strategies to prevent progression into full-blown episodes
 - enhance general coping strategies
 - be delivered by people who have experience of patients with bipolar disorder.
- Consider a focused family intervention if appropriate. This should last 6–9 months, and cover psychoeducation, ways to improve communication and problem solving.

Psychosocial support

- Consider offering befriending to people who would benefit from additional social support, particularly those with chronic depressive symptoms.
- This should be in addition to pharmacological and psychological treatments, and should be by trained volunteers providing, typically, at least weekly contact for between 2 and 6 months.

Promoting a healthy lifestyle and relapse prevention

- Give patients advice (including written information) on:
 - the importance of good sleep hygiene and a regular lifestyle
 - the risks of shift work, night flying and flying across time zones, and working long hours
 - ways to monitor their own physical and mental state.
- Provide extra support after life events such as loss of job or a bereavement, and encourage patients to talk to family and friends.
- In collaboration with patients, identify the symptoms and indicators of an exacerbation, and make a plan of how to respond (including both psychosocial and pharmacological interventions).

Physical care of people with bipolar disorder

Physical monitoring

- People with bipolar disorder have higher levels of physical morbidity and mortality than the general population.
 - A schedule for physical monitoring, covering checks to be done as soon as practicable after initial presentation, at an annual check up, and for monitoring specific drugs, is on pages 19–20.
- Give results of the annual check up to the patient and healthcare professionals in primary and secondary care (including whether the person refused any tests). A clear agreement should be made about responsibility for treating any problems.

If a person gains weight during treatment:

- Review their medication.
- Consider:
 - dietary advice from primary care and mental health services
 - advising regular aerobic exercise
 - referral to weight management programmes in mental health services
 - referral to a dietitian if there are comorbidities, such as coeliac disease.
- Drug treatments to promote weight loss are not recommended.

Schedule for physical monitoring

Test or measurement	Monitoring for all patients				Monitoring for specific drugs		
	Initial health check	Annual check up	Antipsychotics	Lithium	Valproate*	Carbamazepine	
Thyroid function	✓	✓ ^a		At start and every 6 months; more often if evidence of deterioration			
Liver function	✓				At start and at 6 months	At start and at 6 months	
Renal function	✓			At start and every 6 months; more often if there is evidence of deterioration or the patient starts taking drugs such as ACE inhibitors, diuretics or NSAIDs		Urea and electrolytes every 6 months	
Full blood count	✓			Only if clinically indicated	At start and at 6 months	At start and at 6 months	
Blood (plasma) glucose	✓	✓	At start and at 3 months (and at 1 month if taking olanzapine); more often if there is evidence of elevated levels				
Lipid profile	✓	Over 40s only	At start and at 3 months; more often if evidence of elevated levels				
Blood pressure	✓	✓					
<p>For patients on lamotrigine*, do an annual health check, but no special monitoring tests are needed</p> <p>^a Every 6 months for people with rapid-cycling bipolar disorder, plus thyroid antibody levels if indicated, for example by thyroid function tests ACE, angiotensin-converting enzyme; NSAID, non-steroidal anti-inflammatory drug</p>							

continued

Monitoring for all patients			Monitoring for specific drugs			
Test or measurement	Initial health check	Annual check up	Antipsychotics	Lithium	Valproate*	Carbamazepine
Prolactin	Children and adolescents only		Risperidone only: at start and if symptoms of raised prolactin develop			
ECG	If indicated by history or clinical picture		At start if there are risk factors for or existing cardiovascular disease	At start if there are risk factors for or existing cardiovascular disease		
Weight and height	✓	✓ ^b	At start and every 3 months for first year; more often if the patient gains weight rapidly	At start and when needed if the patient gains weight rapidly	At start and at 6 months if the patient gains weight rapidly	At start and at 6 months if the patient gains weight rapidly
Drug screening and chest X-ray						
EEG, MRI or CT scan						
Smoking/ alcohol	✓	✓				
Serum levels of drug				1 week after initiation and 1 week after every dose change until levels stable, then every 3 months	Only if there is evidence of ineffectiveness, poor adherence or toxicity	Every 6 months ^c

^b For children and adolescents, monthly for 6 months, then every 6 months

^c Note therapeutic and toxic levels of carbamazepine are close

Long-term treatment: starting, stopping and risks

See table on pages 19–20 for advice on monitoring before and during treatment.

Antipsychotics

Starting

- If using quetiapine*, titrate the dose gradually to help maintain normal blood pressure.

Stopping

- Reduce the dose gradually:
 - over at least 4 weeks if the patient is continuing on other drugs
 - over up to 3 months if the patient is not continuing with other drugs, or has a history of manic relapse.

Risks

- Discuss with patients the risk of weight gain.
- Be aware of the possibility of worsening diabetes, malignant neuroleptic syndrome and diabetic ketoacidosis, particularly with patients with mania.

Lithium

Starting

- Do not start routinely in primary care.
- When starting lithium as long-term treatment:
 - tell patients that erratic compliance or stopping the drug suddenly may increase the risk of relapse
 - establish a shared-care protocol with the patient's GP for prescribing and monitoring
 - continue a trial for at least 6 months to establish effectiveness.

Monitoring

- Aim for:
 - 0.6–0.8 mmol per litre normally, or
 - 0.8–1.0 mmol per litre if the patient has relapsed previously on lithium or has sub-syndromal symptoms.
- Monitor older adults carefully for symptoms of lithium toxicity.
- Do tests more often if there is clinical deterioration, abnormal results, a change in sodium intake, symptoms of abnormal renal or thyroid function, or other risk factors, such as starting ACE inhibitors, NSAIDs, or diuretics.
- Monitor lithium dose and blood levels more closely if urea and creatinine levels rise, and assess the rate of deterioration of renal function. The decision on whether to continue the drug depends on clinical efficacy and the degree of renal impairment. Consider consulting a renal physician and specialist in bipolar disorder about this.
- Monitor for symptoms of neurotoxicity, including paraesthesia, ataxia, tremor and cognitive impairment.

Stopping

- Reduce the dose gradually over at least 4 weeks, and preferably over up to 3 months (even if the patient is taking another antimanic agent).
- If lithium treatment is stopped or is about to be stopped abruptly, consider changing to an atypical antipsychotic or valproate*, and monitor closely for early signs of mania and depression.

Risks

- Advise patients:
 - not to take over-the-counter NSAIDs (and monitor patients closely if these drugs are prescribed)
 - to seek medical attention if they develop diarrhoea and/or vomiting
 - to maintain their fluid intake, particularly after sweating, if they are immobile for long periods, or have a chest infection or pneumonia
 - to consider stopping lithium for up to 7 days if they become severely ill with a metabolic or respiratory disturbance.

Valproate**Starting*

- Do not start routinely in primary care.
- Do not prescribe routinely for women of child-bearing potential. If there is no alternative, ensure the woman is using adequate contraception, and explain risks.
- Do not prescribe for women younger than 18 years because of the risk of polycystic ovary syndrome and unplanned pregnancy.

Stopping

- Reduce the dose gradually over at least 4 weeks.

Risks

- Explain the signs and symptoms of blood and liver disorders and advise patients to seek immediate medical help if these develop.
- Stop the drug if liver function is abnormal or blood dyscrasia is detected.
- Be aware of interactions with other anticonvulsants.
- Monitor sedation, tremor and gait disturbance in older people.

Lamotrigine*

Starting

- Do not start routinely in primary care.
- Titrate the dose gradually to minimise the risk of rashes, including Stevens–Johnson syndrome – more slowly in patients also taking valproate.
- Discuss alternatives to oral contraceptives with women. Reduce the dose of lamotrigine* by up to 50% if a woman stops taking an oral contraceptive.

Stopping

- Reduce the dose gradually over at least 4 weeks.

Risks

- Advise patients to make an urgent appointment if a rash develops. Stop the drug unless it is clear that the rash is not related to lamotrigine*.
- If an appointment can not be arranged within a few days or the rash is worsening, advise patients to stop the drug and then restart it if the rash is not caused by lamotrigine*.

Carbamazepine

Starting

- Consult a specialist before using for long-term treatment.
- Increase the dose gradually to reduce the risk of ataxia.

Stopping

- Reduce the dose gradually over at least 4 weeks.

Risks

- Monitor possible interactions, including with oral contraceptives, because carbamazepine has a greater potential for drug interactions than other drugs used in bipolar disorder.

Managing bipolar disorder in pregnant women

General principles

- Discuss the absolute and relative risks of treating and not treating the bipolar disorder during pregnancy and the postnatal period.
- Consider more frequent contact by specialist mental health services, working with maternity services.
- Develop a written plan for managing a woman's bipolar disorder during the pregnancy, delivery and postnatal period with the patient and significant others, and share it with her obstetrician, midwife, GP and health visitor.
- Record all medical decisions in all versions of the patient's notes, and include information about her medication in the birth plan and postnatal care notes.
- If a pregnant woman is stable on an antipsychotic and likely to relapse without medication, continue treatment and monitor for weight gain and diabetes.

Do not routinely prescribe for pregnant women:

- valproate
- carbamazepine
- lithium
- lamotrigine*
- long-term treatment with benzodiazepines
- paroxetine

Women planning a pregnancy

- Tell women that the raised prolactin levels associated with some antipsychotics reduce the chances of conception. If prolactin levels are raised, consider an alternative drug.
- If a woman who needs antimanic medication is planning a pregnancy, consider a low-dose typical or atypical antipsychotic.
- If a woman taking valproate, carbamazepine, lithium or lamotrigine* is planning a pregnancy, advise her to stop and consider alternative prophylactic drugs (such as an antipsychotic).
- For a woman taking lithium who is planning a pregnancy, consider:
 - if she is well and not at high risk of relapse – gradually stopping lithium
 - if she is not well or is at high risk of relapse:
 - ◆ switching gradually to an antipsychotic, or
 - ◆ stopping lithium and restarting it in the second trimester if she is not planning to breastfeed and her symptoms have responded better to lithium than to other drugs in the past, or
 - continuing with lithium, after full discussion, if manic episodes have complicated her previous pregnancies, and her symptoms have responded well to lithium.
- If a woman remains on lithium during pregnancy, monitor serum levels every 4 weeks, then weekly from the 36th week, and less than 24 hours after childbirth. Adjust the dose to keep serum levels within the therapeutic range, and ensure the woman has an adequate fluid intake.
- If a woman planning a pregnancy becomes depressed after stopping prophylactic medication, offer psychological therapy (CBT) in preference to an antidepressant because of the risk of switching.

- If an antidepressant is used, it should usually be an SSRI (but not paroxetine because of the risk to the fetus). Monitor the woman closely.

Women with an unplanned pregnancy

- If a woman with bipolar disorder has an unplanned pregnancy:
 - confirm the pregnancy as quickly as possible
 - advise her to stop taking valproate, carbamazepine and lamotrigine*
 - if the pregnancy is confirmed in the first trimester, and the woman is stable, stop lithium gradually over 4 weeks, and explain there is still risk of cardiac defects in the fetus
 - if the woman remains on lithium, check serum levels every 4 weeks, then weekly from the 36th week, and less than 24 hours after childbirth; adjust the dose to keep serum levels within the therapeutic range and ensure the woman has an adequate fluid intake
 - offer an antipsychotic as prophylactic medication
 - if the woman stays on medication, offer screening and counselling about continuing with the pregnancy, the need for additional monitoring and the risks to the fetus.
- The newborn baby should have a full paediatric assessment, and the mother and child should have social and medical help.

Treating acute symptoms in pregnant women

Acute mania

- If the woman is not currently on medication:
 - consider an atypical or a typical antipsychotic
 - keep the dose as low as possible and monitor carefully.
- If the woman is taking prophylactic medication:
 - check the dose of the prophylactic agent and adherence
 - increase the dose if the woman is taking an antipsychotic, or consider changing to an antipsychotic if she is not
 - if there is no response and mania is severe, consider ECT, lithium and, rarely, valproate.
- If there is no alternative to using valproate:
 - tell the woman about risks to the fetus and the child's development
 - use the lowest possible dose, and consider augmenting with additional antimanic medication (but not carbamazepine*)
 - the maximum dosage should be 1 gram per day, in divided doses and slow-release form, with 5 mg/day folic acid.

Depressive symptoms

- For mild symptoms:
 - guided self-help and computerised CBT
 - brief psychological interventions
 - antidepressant medication.
- If symptoms are moderate to severe:
 - consider CBT (moderate symptoms)
 - consider combined medication and structured psychological interventions (severe symptoms)
 - if prescribing, consider quetiapine* alone or SSRIs (but not paroxetine) with prophylactic medication; monitor closely for switching and stop the SSRI if manic or hypomanic symptoms develop
 - tell women taking an antidepressant about the potential short-lived, adverse effects of antidepressants on the neonate.

Care in the perinatal period

- Women taking lithium should deliver in hospital, and be monitored by the obstetric medical team as well as midwives. Fluid balance should be monitored, because of the risk of dehydration and lithium toxicity.
- After delivery, if a woman who is not on medication is at high risk of developing an acute episode, consider establishing or reinstating medication as soon as the fluid balance is established.
- If a woman maintained on lithium is at high risk of a manic relapse in the postnatal period, consider augmenting with an antipsychotic.
- If a woman develops severe manic or psychotic symptoms and behavioural disturbance in the intrapartum period, consider rapid tranquillisation with an antipsychotic in preference to a benzodiazepine because of the risk of floppy baby syndrome. Treatment should be in collaboration with an anaesthetist.

Breastfeeding and care of the infant

- If a woman is taking psychotropic medication:
 - advise on the risks and benefits of breastfeeding
 - advise not to breastfeed if taking lithium, benzodiazepines or lamotrigine* and offer an alternative prophylactic agent that can be used when breastfeeding (normally an antipsychotic, but not clozapine*)
 - prescribe an SSRI if an antidepressant is used (but not fluoxetine or citalopram).
- Monitor babies whose mothers took psychotropic drugs during pregnancy in the first few weeks for adverse drug effects, drug toxicity or withdrawal (for example, floppy baby syndrome, irritability, constant crying, shivering, tremor, restlessness, increased tone, feeding and sleeping difficulties and rarely seizures). These may be a serotonergic toxicity syndrome, rather than a withdrawal reaction.

Children and adolescents with bipolar disorder

The only drug with current UK marketing authorisation for bipolar disorder in patients younger than 18 years is lithium, which is licensed for those aged 12 and over. However, in 2000 the Royal College of Paediatrics and Child Health stated that unlicensed medicines may be prescribed for children and adolescents where there are no suitable alternatives and where the use is justified by a responsible body of professional opinion.

Special considerations

- Staff in specialist services for children and adolescents should:
 - be familiar with guidelines on confidentiality and the rights of the child
 - ensure consent is obtained, considering the adolescent's understanding, parental consent and responsibilities, child protection matters, and the use of the Mental Health Act and of the Children Act (1989).
- In planning the care of children and adolescents consider:
 - stressors and vulnerabilities in their social, educational and family environments
 - the impact of any comorbidities, such as attention deficit hyperactivity disorder and anxiety disorders
 - the impact of the disorder on their social inclusion and education
 - their vulnerability to exploitation.
- Involve parents or carers (and possibly other family members) in developing care plans so that they can give informed consent, support treatment goals, and help ensure adherence.
- Offer children and adolescents separate individual appointments in addition to joint meetings with their family members or carers.

Diagnosis

Bipolar I disorder

- **Prepubescent children:** use the same criteria as in adults except that:
 - mania must be present
 - euphoria must be present most days, most of the time (for 7 days)
 - irritability is not a core diagnostic criterion.
- Do not diagnose solely on the basis of a major depressive episode in a child with a family history of bipolar disorder, but follow up such children carefully.

- **Adolescents:** use the same criteria as in adults except that:
 - mania must be present
 - euphoria must be present most days, most of the time (for 7 days)
 - irritability can be helpful if it is episodic, severe, impairs function and is not in keeping or out of character; however, it should not be a core diagnostic criterion.
- Do not diagnose solely on the basis of a major depressive episode in an adolescent with a family history of bipolar disorder, but follow up such adolescents carefully.

- **Older or developmentally advanced adolescents:** use the same criteria as in adults.

Bipolar II disorder

- **Children and adolescents:** diagnostic criteria are not well established – do not normally diagnose.
- **Older or developmentally advanced adolescents:** use the same criteria as in adults.

Differential diagnosis in children and adolescents

Comorbidity is common in children and adolescents. When considering a diagnosis of bipolar disorder:

- the presence of clear-cut episodes of elated mood, grandiosity and cycles of mood can help to distinguish it from attention deficit hyperactivity disorder or conduct disorder
- the presence of mood cycles can help to distinguish it from schizophrenia
- consider other explanations, such as:
 - sexual, emotional and physical abuse if they show disinhibition, hypervigilance or hypersexuality
 - drug and/or alcohol misuse as a cause of mania-like symptoms; consider bipolar disorder only after 7 days of abstinence
 - undiagnosed learning difficulties
 - organic causes such as excited confusional states in children with epilepsy, and akathisia due to neuroleptic medication.

Children with learning difficulties

- Use the same criteria for diagnosis as for other children and adolescents.

Sub-threshold symptoms

- If it is not possible to make a diagnosis, follow up the child carefully.

Assessment for children and adolescents

- The diagnosis of bipolar disorder in children and adolescents should be made by a clinician with specialist training in child and adolescent mental health.
- For severely mentally ill children and adolescents with psychotic symptoms attempt a diagnosis as soon as possible and ensure this is subject to regular specialist review.

Assessment should include:

- a detailed mental state examination based on an individual interview
- a medical evaluation to exclude organic causes
- further neuropsychological and neurological evaluation as appropriate
- an account from the child, parents or carers, and other adults such as teachers
- a developmental and neurodevelopmental history, covering birth, speech and language development, behaviour problems, attachment behaviour and any history of abuse.

Specialist diagnostic instruments and scales completed by parents or carers may be used, but should not replace a full clinical interview.

Acute mania and depression in children and adolescents

Acute mania

- Follow the recommendations for treating acute mania in adults (see pages 10–11), except that drugs should be started at lower doses, and at initial presentation:
 - check height and weight (and monitor regularly afterwards)
 - measure prolactin levels
 - if considering an antipsychotic, take into account the risk of increased prolactin levels with risperidone* and weight gain with olanzapine*.
- If response to an antipsychotic is inadequate, consider adding lithium or valproate* – but normally avoid valproate in girls and young women.

Depression

- Monitor weekly if symptoms are mild and do not need immediate treatment, and offer additional support at home and school.
- If treatment is needed, it should normally be by specialist clinicians (based in at least Tier 3 services²). Treat as for adults (see pages 12–15), but consider a structured psychological therapy in addition to prophylactic medication.

²Specialised child and adolescent mental health services for severe, complex or persistent disorders. Staff include child and adolescent psychiatrists, clinical psychologists, nurses and child and adolescent psychotherapists.

- If this does not produce a response after 4 weeks, consider:
 - adding fluoxetine* starting at 10 mg per day, and increasing to 20 mg per day if needed
 - using a different SSRI (sertraline* or citalopram*) if there is no response to fluoxetine.
- If there is still no response, ask for advice from a specialist in affective disorders.
- For developmentally advanced adolescents, follow the recommendations on managing depression in adults (see pages 12–15).

Long-term treatment of children and adolescents

- Long-term management should normally be by specialist clinicians (based in at least Tier 3 services).
- Treat as for adults, but:
 - consider as first line an atypical antipsychotic that is associated with less weight gain and does not increase prolactin levels
 - consider as second line lithium for female patients and valproate or lithium for male patients
 - give parents and carers support to help the patient maintain a regular lifestyle
 - advise the school or college (with permission of the patient and parents or carers) on managing the patient's bipolar disorder.

Inpatient services for children and adolescents

- Consider admission to a specialist unit for children and adolescents – as an inpatient or day patient – or more intensive community treatment, for patients at risk of suicide or other serious harm.
- Manage severe behavioural disturbance as for adults (see page 15), except that rapid tranquillisation with haloperidol* is not recommended because of the increased risk of extrapyramidal side effects.

Implementation

NICE has developed tools to help organisations implement this guidance (listed below).

These are available on our website (www.nice.org.uk/CG038).

- Slides highlighting key messages for local discussion.
- Costing tools
 - Costing report to estimate the national savings and costs associated with implementation.
 - Costing template to estimate the local costs and savings involved.
- Implementation advice on how to put the guidance into practice and national initiatives that support this locally.
- Audit criteria to monitor local practice.

Further information

Ordering information

You can download the following versions of this guideline from www.nice.org.uk/CG038

- The quick reference guide (this document), which has been sent to healthcare professionals in England.
- 'Understanding NICE guidance' – information for patients and carers.
- The NICE guideline – all the recommendations on bipolar disorder.
- The full guideline – all the recommendations, details of how they were developed and summaries of the evidence they are based on.

For printed copies of the quick reference guide and 'Understanding NICE guidance', phone the NHS Response Line on 0870 1555 455 and quote:

- N1076 (quick reference guide)
- N1077 ('Understanding NICE guidance').

Related guidance

For information about NICE guidance that has been issued or is in development, see the website (www.nice.org.uk).

- Guidance on the use of electroconvulsive therapy. *NICE technology appraisal* no. 59 (2003). Available from www.nice.org.uk/TA059
- Violence: the short-term management of disturbed/violent behaviour in in-patient psychiatric settings and emergency departments. *NICE clinical guideline* no. 25 (2005). Available from www.nice.org.uk/CG025

NICE is developing the following guidance (details available from www.nice.org.uk):

- Antenatal and postnatal mental health: clinical management and service guidance. *NICE clinical guideline*. (Publication expected February 2007.)

Updating the guideline

NICE clinical guidelines are updated as needed so that the results of new research can be put into practice. We check for new evidence 2 and 4 years after publication, to decide whether all or part of the guideline should be updated. If important new evidence is published at other times, we may decide to do a more rapid update of some recommendations.

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