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Bipolar disorder

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

NICE clinical guideline 38

Bipolar disorder: the management of bipolar disorder in adults, children and adolescents, in primary and secondary care

Ordering information

You can download the following documents from www.nice.org.uk/CG038

- The NICE guideline (this document) – all the recommendations.
- A quick reference guide – a summary of the recommendations for healthcare professionals.
- ‘Understanding NICE guidance’ – information for patients and carers.
- The full guideline – all the recommendations, details of how they were developed, and summaries of the evidence they were based on.

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

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

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.

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Patient-centred care

This guideline offers best practice advice on the care of people with bipolar disorder.

Treatment and care should take into account people's individual needs and preferences. People with bipolar disorder should have the opportunity to make informed decisions about their care and treatment. Where patients do not have the capacity to make decisions, healthcare professionals should follow the Department of Health guidelines – 'Reference guide to consent for examination or treatment' (2001) (available from www.dh.gov.uk). From April 2007 healthcare professionals will need to follow a code of practice accompanying the Mental Capacity Act (summary available from www.dca.gov.uk/menincap/bill-summary.htm).

Good communication between healthcare professionals and patients is essential. When talking to people with bipolar disorder and their carers, healthcare professionals should use everyday, jargon-free language to give a full and clear explanation of bipolar disorder and its treatment. Written, evidence-based information about the condition and its treatment should also be provided. All information should be tailored to the needs of the individual patient. The treatment, care and information provided should be culturally appropriate and in a form that is accessible to people who have additional needs, such as people with physical, cognitive or sensory disabilities, and people who do not speak or read English.

Unless specifically excluded by the patient, carers and relatives should have the opportunity to be involved in decisions about the patient's care and treatment.

Carers and relatives should also be provided with the information and support they need.

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^{a*} 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.

^a In this guideline, drug names are marked with an asterisk if they do not have UK marketing authorisation for the indication in question at the time of publication (July 2006). Prescribers should check each drug's summary of product characteristics for current licensed indications.

- 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.

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.

Diagnosing bipolar disorder 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.

1 Guidance

The following guidance is based on the best available evidence. The full guideline ('Bipolar disorder: the management of bipolar disorder in adults, children and young people, in primary and secondary care') gives details of the methods and the evidence used to develop the guidance (see section 5 for details).

This guideline makes recommendations for the identification, treatment and management of bipolar disorder for children, adolescents, and adults in primary and secondary care, including those covered by prison medical services. Bipolar disorder is a serious mental illness that often has a long course and is characterised by both episodes of depressed mood and episodes of elated mood (mania or hypomania). However, for many people the predominant experience is of low mood. In its more severe forms, bipolar disorder is associated with significant impairment of personal and social functioning.

It has been estimated that the annual societal cost of bipolar disorder in the UK is about £2 billion. Cases of bipolar disorder often remain unrecognised (mainly misdiagnosed as unipolar depression), resulting in suboptimal treatment and an increase in the overall total healthcare costs.

The peak age of onset is in late adolescence or early adult life, with a further small increase in incidence in mid to late life. This guideline draws a distinction between bipolar I disorder (in which episodes of both depression and mania are required for diagnosis) and bipolar II disorder (in which episodes of both depression and hypomania, but no evidence of mania, are required for diagnosis).

The guideline draws on the best available evidence on bipolar disorder. However, there are significant limitations to the evidence base, including limited data on the differential response of individuals to specific treatments, on the long-term benefits of pharmacological and psychosocial interventions,

on side effects such as switching into mania, and on quality of life and social functioning.

The guideline makes evidence-based recommendations for the diagnosis and treatment of bipolar I disorder. There is less evidence on treatments for bipolar II disorder than for bipolar I disorder. Therefore, except where specific recommendations for the treatment of bipolar II disorder have been made, healthcare professionals should consider cautiously applying the recommendations for treating bipolar I disorder to treating bipolar II disorder. There are also significant limitations to the evidence base for both under 18s and older adults (older than 65 years).

At the date of publication (July 2006) the following drugs have UK marketing authorisation for use in bipolar disorder:

- for treatment of mania – lithium, olanzapine, quetiapine, risperidone, and valproic acid (as valproate semisodium)
- for prophylaxis – lithium and olanzapine
- for prophylaxis of bipolar disorder unresponsive to lithium – carbamazepine.

This guideline recommends some drugs for indications for which they do not have UK marketing authorisation at the date of publication, if they are already in use in the NHS for that indication, and there is evidence to support that use.

Drug names are marked with an asterisk if they do not have UK marketing authorisation for the indication in question at the time of publication.

Prescribers should check each drug's summary of product characteristics for current licensed indications.

The guideline avoids the term 'mood stabiliser', because there is no agreed definition. The terms 'antimanic agent' or 'antimanic medication' are used for treatment of an acute episode, and 'prophylactic agent' or 'prophylactic medication' for long-term maintenance treatment.

1.1 *General recommendations for the care of people with bipolar disorder*

1.1.1 All patients

The provision of information about the nature, course and treatment of bipolar disorder is important in promoting access to services, and understanding and collaboration between patients, close family members, paid and unpaid carers and healthcare professionals.

- 1.1.1.1 Healthcare professionals should establish and maintain collaborative relationships with patients and their families and carers (within the normal bounds of confidentiality), be respectful of the patient's knowledge and experience of the illness, and provide relevant information (including written information) at every stage of assessment, diagnosis and treatment (including the proper use and likely side-effect profile of medication).
- 1.1.1.2 Patients, family and carers should be informed of self-help and support groups and be encouraged to take part in them, particularly at initial diagnosis, and regularly after that. Such groups may provide information on early warning signs, treatment and side effects, and support in time of crisis.
- 1.1.1.3 Healthcare professionals should aim to develop a therapeutic relationship with all patients with bipolar disorder, and advise them on careful and regular self-monitoring of symptoms (including triggers and early warning signs), lifestyle (including sleep hygiene and work patterns) and coping strategies.
- 1.1.1.4 Advance statements (directives) covering both mental and physical healthcare should be developed collaboratively by people with bipolar disorder and healthcare professionals, especially by people who have severe manic or depressive episodes or who have been treated under the Mental Health Act. These should be documented

in care plans, and copies given to the person with bipolar disorder, and to his or her care coordinator and GP.

1.1.1.5 Healthcare professionals should encourage patients to involve their families and carers in assessment and treatment plans if appropriate and make themselves accessible to family members and carers in time of crisis. The needs of patients' family members or carers should be taken into account, including:

- the impact of the disorder on relationships
- the welfare of dependent children, siblings and vulnerable adults
- the regular assessment of carers' physical, social and mental health needs.

1.1.2 Special groups

1.1.2.1 People with bipolar disorder who have learning difficulties should receive the same care as others, taking into account the risk of interactions with any other medication they are prescribed.

1.1.2.2 People with bipolar disorder and comorbid personality disorder should receive the same care as others with bipolar disorder, because the presence of a personality disorder does not preclude the delivery of effective treatments for bipolar disorder.

1.1.2.3 For people with bipolar disorder and comorbid harmful drug and/or alcohol use, a psychosocial intervention targeted at the drug and/or alcohol use (for example, psychoeducation and motivational enhancement) should be considered. This should normally be delivered by general mental health services, working with specialist substance use services where appropriate.

1.1.2.4 Local services should have a robust protocol for transferring patients from services for adults of working age to those for older people (usually those older than 65 years). This should include agreement about the clinical parameters to take into account (for example, medical comorbidity or cognitive deterioration) and what

to do if the patient is no longer in contact with services for adults of working age. Referral or re-referral should be based on the needs of the patient first, rather than simply their chronological age.

1.1.2.5 When treating older people with bipolar disorder, healthcare professionals should:

- be aware of the need to use medication at lower doses
- be alert to the increased risk of drug interactions when prescribing psychotropic medication to older adults
- ensure that medical comorbidities have been recognised and addressed.

1.2 *The assessment, recognition and diagnosis of bipolar disorder in adults*

The diagnosis and recognition of bipolar disorder in adults, particularly in those first presenting to services, can be difficult. Many people have periods of considerable psychological and social disturbance before diagnosis. First presentation of bipolar disorder in later life is more likely to be associated with comorbid physical disorders.

To achieve a diagnosis of bipolar disorder in adults, ICD-10 requires at least two episodes (one of which must be mania or hypomania) in which the person's mood and activity levels are significantly disturbed. (By contrast, DSM-IV requires only a single manic or mixed episode.) The disturbance consists of either an elevation of mood and increased energy and activity (mania or hypomania), or a lowering of mood (depression). Episodes can be further classified as hypomanic, manic without psychotic symptoms, manic with psychotic symptoms, mild or moderate depression, severe depression without psychotic symptoms, severe depression with psychotic symptoms or mixed. Manic episodes usually begin abruptly and last for between 2 weeks and 4–5 months (median duration about 4 months). Depressions tend to last longer (median duration about 6 months). Recovery may or may not be complete between episodes. The pattern of remissions and relapses is very

variable, although remissions tend to get shorter as time goes on and depressions to become commoner and longer lasting.

1.2.1 Recognising bipolar disorder in primary care

New or suspected presentations of bipolar disorder

- 1.2.1.1 Primary care clinicians should normally refer patients with suspected bipolar disorder for a specialist mental health assessment and development of a care plan, if either of the following are present:
- periods of overactive, disinhibited behaviour lasting at least 4 days with or without periods of depression, or
 - three or more recurrent depressive episodes in the context of a history of overactive, disinhibited behaviour.
- 1.2.1.2 Primary care clinicians should urgently refer patients with mania or severe depression who are a danger to themselves or other people, to specialist mental health services.
- 1.2.1.3 Primary care clinicians should ask about hypomanic symptoms when assessing a patient with depression and overactive, disinhibited behaviour.

Existing bipolar disorder in primary care

- 1.2.1.4 When a patient with existing bipolar disorder registers with a practice, the GP should consider referring them for assessment by specialist mental health services and, if appropriate, development of a care plan.

1.2.1.5 When a patient with bipolar disorder is managed solely in primary care, an urgent referral to secondary care services should be made:

- if there is an acute exacerbation of symptoms, in particular the development of mania or severe depression
- if there is an increase in the degree of risk, or change in the nature of risk, to self or others.

1.2.1.6 When a patient with bipolar disorder is managed solely in primary care, a review by secondary care services or increased contact in primary care should be considered if:

- the patient's functioning declines significantly or their condition responds poorly to treatment
- treatment adherence is a problem
- comorbid alcohol and/or drug misuse is suspected
- the patient is considering stopping prophylactic medication after a period of relatively stable mood.

1.2.2 Assessment of bipolar disorder in secondary care

1.2.2.1 When assessing suspected bipolar disorder healthcare professionals should:

- take a full history including family history, a review of all previous episodes and any symptoms between episodes
- assess the patient's symptom profile, triggers to previous episodes, social and personal functioning, comorbidities including substance misuse and anxiety, risk, physical health, and current psychosocial stressors
- obtain where possible, and within the bounds of confidentiality, a corroborative history from a family member or carer

- consider using formal criteria, including self-rating scales such as the Mood Disorder Questionnaire^b.

1.2.2.2 When considering a diagnosis of bipolar disorder healthcare professionals should take into account that:

- more pronounced psychotic symptoms, increased suicidal ideation, drug misuse, or more disturbed behaviour may be symptoms of a later presentation of bipolar disorder and not of a schizophrenia-spectrum disorder – this may be particularly important when assessing patients from black and minority ethnic groups who may have difficulty accessing services
- drug and/or alcohol misuse may induce manic-like symptoms – in inpatient settings, if there is evidence of misuse, wait 7 days before confirming a diagnosis of bipolar disorder
- symptoms may be due to underlying organic conditions, such as hypothyroidism, cerebrovascular insults and other neurological disorders (for example, dementia), particularly in people with late-onset bipolar disorder (older than 40 years).

1.2.2.3 Before diagnosing rapid-cycling bipolar disorder, healthcare professionals should check alternative explanations for the symptoms including problems such as thyroid disease, antidepressant-induced switching, suboptimal medication regimes, the effects of lithium withdrawal, and erratic compliance. They should also consider asking the patient and/or carer to assess mood and behaviour for at least a year.

^b Hirschfeld RM, Williams JB, Spitzer RL et al. (2001) Development and validation of a screening instrument for bipolar spectrum disorder: the Mood Disorder Questionnaire. *American Journal of Psychiatry* 158(10):1743–4.

1.2.2.4 When assessing people with suspected bipolar disorder and/or personality disorder healthcare professionals should:

- during initial assessment, consider a diagnosis of bipolar disorder before a diagnosis of personality disorder in a person with 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.

1.2.3 Assessment of risk in primary and secondary care

1.2.3.1 A risk assessment should be undertaken when:

- bipolar disorder is first diagnosed
- a person with bipolar disorder undergoes significant change in mental state or personal circumstances
- a person with bipolar disorder is discharged from or is on leave from inpatient care.

1.2.4 Crisis and risk management plans

1.2.4.1 If a patient is at risk of suicide, exploitation or severe self-neglect, is a significant risk to others (including neglect of dependents), or has a history of recurrent admissions, particularly compulsory admissions, a crisis plan should be developed in collaboration with the patient, covering:

- a list of identified or potential personal, social or environmental triggers, and early warning symptoms of relapse
- a protocol for increasing the dose of medication or taking additional medication (which may be given to the patient in advance) for patients who are at risk of rapid onset of mania and for whom clear early warning signs can be identified – protocols should be monitored regularly, and are not a substitute for an urgent review

- how primary and secondary healthcare services have agreed to respond to any identified increase in risk, for example by increased contact
- how the patient (and where appropriate their carer) can access help, and the names of healthcare professionals in primary and secondary care who have responsibilities in the crisis plan.

1.2.4.2 A limited quantity of psychotropic medication should be prescribed for patients during periods of high risk of suicide.

1.3 Treatment setting and pathways to care

Bipolar disorder is a long-term illness that needs long-term care. The service needs of a person with bipolar disorder depend on their phase of illness, age, function and recent history. No service will be able to meet all a person's needs throughout their life so care will need to be transferred and shared between services, and good communication is essential.

1.3.1 Continuity of care for people with bipolar disorder

1.3.1.1 People with bipolar disorder (including those with sub-threshold symptoms), whether managed in primary or secondary care, should have continuity of care, and see the same healthcare professionals regularly, where possible, to improve long-term outcomes.

1.3.2 Models of service provision

Service provision in primary and secondary care

1.3.2.1 Primary and secondary care organisations should consider establishing integrated care programmes for people with bipolar disorder. These should include:

- regular reviews in primary and secondary care of mental state, and personal and social functioning, to ensure that symptoms (including sub-threshold symptoms) are treated if they significantly impair social functioning
- clear protocols for the delivery and monitoring of pharmacological, psychosocial and psychological interventions

- clear agreements between healthcare professionals on their responsibilities for assessment, monitoring and treatment
- written treatment plans that promote the principles of self-management, and are shared with the patient and, where appropriate, with families and carers.

1.3.2.2 All GP practices should include people with a diagnosis of bipolar disorder in their case register of people with severe mental illness.

1.3.2.3 Primary care teams should consider providing telephone support to patients with bipolar disorder, by appropriately trained staff using clear protocols, in particular for monitoring medication regimes.

Specialist mental health services

1.3.2.4 Referral to a community mental health team should be considered for people with bipolar disorder who:

- have problems in engaging with, and maintaining regular contact with services such as outpatient care
- experience frequent relapses, poor symptom control, continuing functional impairment, or comorbid anxiety disorders
- are at risk of suicide, or harm to self or others, including self-neglect or exploitation
- have problems adhering to medication regimes or with chronic alcohol and/or drug misuse.

1.3.2.5 Crisis resolution and home treatment teams (which should have prompt access to existing care plans) should be considered for people with bipolar disorder to:

- manage crises at home or in the community
- support early discharge from hospital.

1.3.2.6 When delivering crisis care at home, particular attention should be given to managing risk, monitoring behavioural disturbance

(particularly during episodes of mania), and the burden on family and carers.

- 1.3.2.7 Early intervention services for people with psychosis should be available to people with bipolar disorder and should provide specialist expertise in diagnosis, and pharmacological, psychological, social, occupational and educational interventions.
- 1.3.2.8 Assertive community treatment should be considered for people with bipolar disorder, particularly those who make high use of inpatient services and those who engage poorly with other services and so experience frequent relapse and/or social breakdown.
- 1.3.2.9 Admission to an inpatient unit should be considered for patients with bipolar disorder at significant risk of harm. The unit should provide facilities for containment within a supportive, low-stimulation environment, including access to a psychiatric intensive care unit. The inpatient service should seek to provide an emotionally warm, safe, culturally sensitive and supportive environment, with high levels of positive engagement between staff and patients.
- 1.3.2.10 Acute day hospitals should be considered, as an alternative to inpatient care and to facilitate early discharge from inpatient care.
- 1.3.2.11 Mental health services, in partnership with social care providers and other local stakeholders should consider providing:
 - vocational rehabilitation – specifically, individual supported placements – for people with bipolar disorder who want help returning to work or gaining employment
 - support to return to or engage with education or other structured, purposeful activities.
- 1.3.2.12 Enhanced multiprofessional outpatient clinics, such as lithium clinics, should be considered for patients who would benefit from

close monitoring, and/or have a physical health risk such as renal damage, and have a record of regular attendance without the need for outreach services.

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

1.4 *The treatment and management of bipolar disorder*

The treatment of bipolar disorder is based primarily on psychotropic medication to reduce the severity of symptoms, stabilise mood and prevent relapse. Individual variation in response to medication will often determine the choice of drug, as will the side effects and potential harms associated with each drug. For example, the teratogenic and neurobehavioral toxicity associated with valproate severely limit its use in women of child-bearing potential. However, a range of psychological and psychosocial interventions can also have a significant impact.

1.4.1 **General recommendations**

- 1.4.1.1 Healthcare professionals should fully involve patients in decisions about their treatment and care, and determine treatment plans in collaboration with the patient, carefully considering the experience and outcome of previous treatment(s) together with patient preference.
- 1.4.1.2 Contraception and the risks of pregnancy (including the risks of relapse, damage to the fetus, and the risks associated with stopping or changing medication) should be discussed with all women of child-bearing potential, regardless of whether they are planning a pregnancy. They should be encouraged to discuss pregnancy plans with their doctor.

- 1.4.1.3 People experiencing a manic episode, or severe depressive symptoms, should normally be seen again within a week of their first assessment, and then regularly at appropriate intervals, for example, every 2–4 weeks in the first 3 months and less often after that, if response is good.

1.4.2 The management of acute episodes: mania and hypomania^c

The drug treatment of an acute manic or hypomanic episode depends on the severity of symptoms and whether patients are currently taking antimanic drugs. Clinicians should be guided by current medication doses and previous response. Only lithium, olanzapine, quetiapine, risperidone and valproate semisodium are licensed for the treatment of acute mania in the UK.

Valproate is available in other forms including sodium valproate and valproic acid. The active element in all formulations is the valproate ion. This guideline uses the generic term 'valproate'.

General advice

- 1.4.2.1 To help reduce the negative consequences of manic symptoms, healthcare professionals should consider advising patients to avoid excessive stimulation, to engage in calming activities, to delay important decisions, and to establish a structured routine (including a regular sleep pattern) in which the level of activity is reduced.
- 1.4.2.2 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.

^c This section includes recommendations that update *NICE technology appraisal guidance* no. 66 (see section 6 for details).

Drug treatment for acute mania for people not taking antimanic medication

- 1.4.2.3 If a patient develops acute mania when not taking antimanic medication, treatment options include starting an antipsychotic, valproate or lithium. When making the choice, prescribers should take into account preferences for future prophylactic use, the side-effect profile, and consider:
- prescribing an antipsychotic if there are severe manic symptoms or marked behavioural disturbance as part of the syndrome of mania
 - prescribing valproate or lithium if symptoms have responded to these drugs before, and the person has shown good compliance
 - avoiding valproate in women of child-bearing potential
 - using lithium only if symptoms are not severe because it has a slower onset of action than antipsychotics and valproate.
- 1.4.2.4 In the initial management of acute behavioural disturbance or agitation, the short-term use of a benzodiazepine (such as lorazepam*) should be considered in addition to the antimanic agent.
- 1.4.2.5 If treating acute mania with antipsychotics, olanzapine, quetiapine or risperidone should normally be used, and the following should be taken into account:
- individual risk factors for side effects (such as the risk of diabetes)
 - the need to initiate treatment at the lower end of the therapeutic dose range recommended in the summary of product characteristics and titrate according to response
 - that if an antipsychotic proves ineffective, augmenting it with valproate or lithium should be considered
 - that older people are at greater risk of sudden onset of depressive symptoms after recovery from a manic episode.

1.4.2.6 Carbamazepine* should not be routinely used for treating acute mania, and gabapentin*, lamotrigine* and topiramate* are not recommended.

Drug treatment of acute mania for people taking antimanic medication

1.4.2.7 If a patient already taking an antipsychotic experiences a manic episode, the dose should be checked and increased if necessary. If there are no signs of improvement, the addition of lithium or valproate should be considered.

1.4.2.8 If a patient already taking lithium experiences a manic episode, plasma lithium levels should be checked. If levels are suboptimal (that is, below 0.8 mmol per litre), the dose should normally be increased to a maximum blood level of 1.0 mmol per litre. If the response is not adequate, augmenting lithium with an antipsychotic should be considered.

1.4.2.9 If a patient already taking valproate* experiences a manic episode, the dose should be increased until:

- symptoms start to improve, or
- side effects limit further dose increase.

If there are no signs of improvement, the addition of olanzapine, quetiapine, or risperidone should be considered. Patients on doses higher than 45 mg per kilogram should be monitored carefully.

1.4.2.10 For patients who present with severe mania when already taking lithium or valproate*, adding an antipsychotic should be considered at the same time as gradually increasing the dose of lithium or valproate.

1.4.2.11 For patients who present with mania when already taking carbamazepine, the dose should not routinely be increased. Adding an antipsychotic should be considered, depending on the severity of mania and the current dose of carbamazepine. Interactions with

other medication are common with carbamazepine, and doses should be adjusted as necessary.

1.4.3 The management of acute episodes: depressive symptoms

Managing acute depressive symptoms in bipolar disorder has some similarities to managing unipolar depression. However, in bipolar disorder antidepressants carry the risk of 'switching' to manic states, and they may be involved in cycle acceleration (mood destabilisation). There is only a limited role for maintenance treatment with antidepressants in bipolar depression; prophylactic medication has a greater role. When prescribing an antidepressant, an antimanic agent should also be prescribed.

Patients with bipolar disorder typically experience more fluctuations in both the severity and duration of symptoms than people with unipolar depression, but there is little evidence on which to base guidance on treating symptoms of different severities. When severity should be taken into account (for example, to avoid unnecessary initiation of medication), the terms 'mild', 'moderate' and 'severe' are used.

Treatment of depressive symptoms

Patients not taking antimanic medication

- 1.4.3.1 A patient who is prescribed antidepressant medication should also be prescribed an antimanic drug. The choice of antimanic drug should be compatible with decisions about future prophylactic treatment, the likely side effects and whether the patient is a woman of child-bearing potential.
- 1.4.3.2 When initiating antidepressant treatment for a patient who is not already taking antimanic medication, prescribers should explain the risks of switching to mania and the benefits of taking an adjunctive antimanic agent. People who are not willing to take antimanic medication should be monitored carefully. Antidepressant treatment should begin at a low dose and be increased gradually if necessary.

Patients taking antimanic medication

- 1.4.3.3 If a person has an acute depressive episode when taking antimanic medication, prescribers should first check they are taking the antimanic agent at the appropriate dose and adjust the dose if necessary.

Patients with mild depressive symptoms

- 1.4.3.4 For patients with acute mild depressive symptoms, a further assessment should be arranged, normally within 2 weeks ('watchful waiting') if:

- previous episodes of mild depression have not developed into chronic or more severe depression in this patient, or
- the patient is judged not to be at significant risk of developing a more severe depression.

If the patient is judged to be at significant risk of worsening or on review continues to be unwell, they should be managed as for moderate or severe depression, particularly if functional impairment is evident.

Patients with moderate or severe depressive symptoms

- 1.4.3.5 For patients with moderate or severe depressive symptoms, prescribers should normally consider:

- prescribing an SSRI antidepressant (but not paroxetine in pregnant women), because these are less likely than tricyclic antidepressants to be associated with switching, or
- adding quetiapine, if the patient is already taking antimanic medication that is not an antipsychotic.

- 1.4.3.6 If a trial of drug treatment at an adequate dose and with adequate compliance does not produce a significant improvement for moderate depressive symptoms, a structured psychological treatment should be considered. This should focus on depressive

symptoms, problem solving, promoting social functioning, and education about medication.

Antidepressant treatment and risk monitoring

1.4.3.7 Antidepressants should be avoided for patients with depressive symptoms who have:

- rapid-cycling bipolar disorder
- a recent hypomanic episode
- recent functionally impairing rapid mood fluctuations.

Instead, consider increasing the dose of the antimanic agent or the addition of a second antimanic agent (including lamotrigine*).

1.4.3.8 Patients' concerns about taking antidepressants should be addressed. For example, they should be advised that craving and tolerance do not occur, and that taking medication should not be seen as a sign of weakness.

1.4.3.9 When antidepressant treatment is started, patients should be told about:

- the possibility of manic or hypomanic switching
- the delay in onset of effect, and the gradual and fluctuating nature of improvement
- the need to take medication as prescribed and the risk of discontinuation/withdrawal symptoms
- the need to monitor 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 in the initial stages of treatment)
- the need to seek help promptly if these side effects are distressing.

1.4.3.10 If a patient with bipolar disorder develops marked and/or prolonged akathisia or agitation while taking an antidepressant, the use of the drug should be reviewed urgently.

1.4.3.11 Care should be taken when prescribing SSRIs to people – particularly older people – taking other medication that can cause intestinal bleeding, such as non-steroidal anti-inflammatory drugs. The use of a gastroprotective drug may be considered.

Stopping antidepressants after an acute depressive episode

1.4.3.12 When a patient is in remission from depressive symptoms (or symptoms have been significantly less severe for 8 weeks), stopping the antidepressant medication should be considered, to minimise the risks of switching to mania and increased rapid cycling. The dose of antidepressant should be gradually reduced over several weeks, while maintaining the antimanic medication. Particular care is needed with paroxetine and venlafaxine because they are associated with a higher risk of discontinuation/withdrawal symptoms.

Treatments not recommended for routine use

1.4.3.13 The following treatments should not be routinely used for acute depressive episodes in people with bipolar disorder:

- lamotrigine* as a single, first-line agent in bipolar I disorder
- transcranial magnetic stimulation*.

Treatment resistance and psychotic symptoms

Incomplete response to the treatment for acute depression

1.4.3.14 When a patient's depressive symptoms do not fully respond to an antidepressant, the patient should be reassessed for evidence of substance misuse, psychosocial stressors, physical health problems, comorbid disorders, such as anxiety or severe obsessional symptoms, and inadequate adherence to medication. Prescribers should then consider:

- increasing the dose of the antidepressant within 'British national formulary' ('BNF') limits
- individual psychological therapy focused on depressive symptoms
- switching to an alternative antidepressant (for example, mirtazapine or venlafaxine)
- adding quetiapine* or olanzapine if the patient is not already taking one of these, or
- adding lithium if the patient is not already taking it.

1.4.3.15 If a patient's depressive symptoms have failed to respond to at least three courses of treatment for depression of adequate dose and duration, seeking the advice of, or referral to, a clinician with a specialist interest in treating bipolar disorder should be considered.

Concurrent depressive and psychotic symptoms

1.4.3.16 For patients with a diagnosis of bipolar disorder experiencing concurrent depressive and psychotic symptoms, prescribers should consider augmenting the current treatment plan with antipsychotic medication, such as olanzapine, quetiapine, or risperidone, or the use of electroconvulsive therapy (see section 1.4.6) if the depressive illness is severe.

Persistent depressive symptoms

1.4.3.17 For patients with persistent depressive symptoms and no history of recent rapid cycling, including those who have declined an antidepressant, structured psychological therapy may be considered. This should focus on depressive symptoms, problem solving, improving social functioning, and further discussion of medication concordance.

Additional advice

1.4.3.18 Patients with depressive symptoms should be advised about techniques such as a structured exercise programme, activity scheduling, engaging in both pleasurable and goal-directed activities, ensuring adequate diet and sleep, and seeking appropriate social support, and given increased monitoring and formal support.

1.4.4 The management of acute mixed episodes

An acute mixed episode is the presence of a mixture, or rapid alternation (usually within a few hours), of manic/hypomanic and depressive symptoms. Both sets of symptoms should be prominent for the greater part of the current episode of illness, usually for at least 2 weeks. It should be distinguished from rapid-cycling bipolar disorder (see below).

1.4.4.1 Prescribers should consider treating patients with an acute mixed episode as if they had an acute manic episode, and avoid prescribing an antidepressant.

1.4.4.2 Prescribers should monitor patients with an acute mixed episode closely (at least weekly), particularly for suicide risk.

1.4.5 The management of an acute episode in rapid-cycling bipolar disorder

A patient who has four or more acute episodes in a year is defined as having rapid-cycling bipolar disorder. A key aspect of treatment should be to avoid medication-induced switching from one pole to another, particularly with antidepressants.

1.4.5.1 Acute episodes in patients with rapid-cycling bipolar disorder should normally be managed in secondary mental health services. Treatment should be as for manic and depressive episodes, but in addition healthcare professionals should do the following.

- Review the patient's previous treatments for bipolar disorder, and consider a further trial of any that were inadequately delivered or adhered to.
- Focus on optimising long-term treatment rather than on treating individual episodes and symptoms; trials of medication should usually last at least 6 months.
- Adopt a psychoeducational approach and encourage patients to keep a regular mood diary to monitor changes in severity and frequency of symptoms, and the impact of interventions.

1.4.6 The use of ECT in severe manic and depressive episodes

1.4.6.1 Electroconvulsive therapy (ECT) is recommended only to achieve rapid and short-term improvement of severe symptoms after an adequate trial of other treatment options has proven ineffective and/or when the condition is considered to be potentially life-threatening, in individuals with:

- severe depressive illness
- catatonia
- a prolonged or severe manic episode^d.

1.4.6.2 The decision as to whether ECT is clinically indicated should be based on a documented assessment of the risks and potential benefits to the individual, including:

- the risks associated with the anaesthetic
- current comorbidities
- anticipated adverse events, particularly cognitive impairment
- the risks of not having treatment^d.

1.4.6.3 When using ECT to treat bipolar disorder, prescribers should 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 carefully for evidence of switching to the opposite pole.

^d This recommendation is from *NICE technology appraisal guidance* no. 59 (see section 6 for details), and has been incorporated into this guideline in line with NICE procedures for the development of clinical guidelines.

1.4.7 The prevention and management of behavioural disturbance

The management of disturbed behaviour in bipolar disorder should start with psychosocial and environmental interventions aiming to de-escalate any potential violent situations. Restraint and drug interventions should be used only when these approaches are insufficient.

1.4.7.1 If a patient with bipolar disorder exhibits seriously disturbed behaviour, or is judged to be at risk of doing so, healthcare professionals should:

- place the patient in the least stimulating and confrontational, and most supportive environment available
- review the patient's safety and physical status, including hydration levels, and take appropriate action
- consider using distraction techniques and diverting the patient's energy into less risky or more productive activities to prevent or reduce behavioural disturbance.

Drug treatment of severe behavioural disturbance

This section on the drug treatment of severe behavioural disturbance should be read in conjunction with the NICE clinical guideline on the short-term management of disturbed/violent behaviour in inpatient psychiatric settings and emergency departments (see section 6 for details).

1.4.7.2 Severe behavioural disturbance in people with bipolar disorder should normally be treated first with oral medication, such as lorazepam* or an antipsychotic, or a combination of an antipsychotic and a benzodiazepine. Risperidone and olanzapine are available in orodispersible formulations that are easier for patients to take and are more difficult to spit out.

1.4.7.3 If a severely disturbed patient with bipolar disorder cannot be effectively managed with oral medication and rapid tranquilisation is needed, intramuscular olanzapine (10 mg), lorazepam* (2 mg) or haloperidol (2–10 mg) should be considered, wherever possible as a single agent. When making the choice of drug, prescribers should take into account:

- that olanzapine and lorazepam* are preferable to haloperidol because of the risk of movement disorders (particularly dystonia and akathisia) with haloperidol
- that olanzapine and benzodiazepines should not be given intramuscularly within 1 hour of each other
- that repeat intramuscular doses can be given up to 20 mg per day (olanzapine), 4 mg per day (lorazepam*) or 18 mg per day (haloperidol) – the total daily dose including concurrent oral medication should not normally exceed 'BNF' limits
- the patient's previous response and tolerability, their current regular medication, and the availability of flumazenil.

1.4.7.4 Intravenous preparations of any psychotropic drug, intramuscular diazepam*, intramuscular chlorpromazine, paraldehyde* and zuclopenthixol acetate are not recommended for routine use for managing behavioural disturbances in people with bipolar disorder.

1.5 *The long-term management of bipolar disorder*

Bipolar disorder is a chronic relapsing and remitting disorder. Long-term treatment and support are required to minimise the risk of recurrence and optimise quality of life, and social and personal functioning. The primary long-term treatments are pharmacological, but psychological and psychosocial interventions have an important part to play. A coordinated care programme, with rapid access to support at times of crisis, is essential.

1.5.1 Drug treatment after recovery from an acute episode

1.5.1.1 Prescribers should consider starting long-term treatment for bipolar disorder:

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

1.5.1.2 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.

1.5.1.3 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.

- 1.5.1.4 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.
- 1.5.1.5 Long-term drug treatment should normally continue for at least 2 years after an episode of bipolar disorder, and 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. This should be discussed with the patient and there should be regular reviews. Patients who wish to stop medication early should be encouraged to discuss this with their psychiatrist.
- 1.5.1.6 If, after careful discussion, a patient with bipolar disorder declines long-term medication, they should still be offered regular contact and reassessment with primary or secondary care services.
- 1.5.1.7 Long-acting intramuscular injections of antipsychotics ('depots') are not recommended for routine use in bipolar disorder. They may be considered for people who were treated successfully for mania with oral antipsychotics, but have had a relapse because of poor adherence.

After an acute depressive episode

- 1.5.1.8 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.

Treatment for chronic and recurrent depressive symptoms

1.5.1.9 The following treatments should be considered, in discussion with the patient, for people who have an established diagnosis of bipolar disorder and chronic or recurrent depressive symptoms, but who are not taking prophylactic medication and have not had a recent manic or hypomanic episode:

- long-term treatment with SSRIs at the minimum therapeutic dose in combination with prophylactic medication
- cognitive behavioural therapy (16–20 sessions) in combination with prophylactic medication
- quetiapine*, or
- lamotrigine*.

1.5.1.10 For patients with bipolar II disorder with recurrent depression, lamotrigine* alone should be considered for long-term treatment.

1.5.2 Long-term management of rapid cycling

1.5.2.1 For the long-term management of rapid-cycling bipolar disorder prescribers should:

- consider as first-line treatment a combination of lithium and valproate*
- consider lithium monotherapy as second-line treatment; for patients already taking lithium consider increasing the dose
- avoid the use of an antidepressant, except on advice from a specialist in bipolar disorder
- consider combinations of lithium or valproate* with lamotrigine*, especially in bipolar II disorder
- check thyroid function every 6 months together with levels of thyroid antibodies if clinically indicated, for example, by the thyroid function tests.

1.5.3 Comorbid anxiety disorders

1.5.3.1 For patients with significant comorbid anxiety disorders, psychological treatment focused on anxiety or treatment with a drug such as an atypical antipsychotic should be considered.

1.5.4 Promoting a healthy lifestyle and relapse prevention

1.5.4.1 Patients with bipolar disorder should be given 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 routinely working excessively long hours, particularly for patients with a history of relapse related to poor sleep hygiene or irregular lifestyle
- ways to monitor their own physical and mental state.

1.5.4.2 People with bipolar disorder should be given additional support after significant life events, such as loss of job or a close bereavement. This should include increased monitoring of mood and general well-being, and encouraging the patient to discuss difficulties with family and friends.

1.5.4.3 Healthcare professionals, in collaboration with patients, should develop a plan to identify the symptoms and indicators of a potential exacerbation of the disorder, and how to respond (including both psychosocial and pharmacological interventions).

1.5.5 Psychological therapy after recovery from an acute episode

- 1.5.5.1 Individual structured psychological interventions should be considered for people with bipolar disorder who are relatively stable, but may be experiencing mild to moderate affective symptoms. The therapy should be in addition to prophylactic medication, should normally be at least 16 sessions (over 6–9 months) and should:
- include psychoeducation about the illness, and the importance of regular daily routine and sleep and concordance with medication
 - include monitoring mood, detection of early warnings and strategies to prevent progression into full-blown episodes
 - enhance general coping strategies.
- 1.5.5.2 Structured psychological interventions should be delivered by people who are competent to do this and have experience of patients with bipolar disorder.
- 1.5.5.3 Healthcare professionals should consider offering a focused family intervention to people with bipolar disorder in regular contact with their families, if a focus for the intervention can be agreed. The intervention should take place over 6–9 months, and cover psychoeducation about the illness, ways to improve communication and problem solving.

1.5.6 Psychosocial support

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

1.6 *The physical care of people with bipolar disorder*

People with bipolar disorder have higher levels of physical morbidity and mortality than the general population, but often receive suboptimal healthcare. (Appendix D contains a list of physical monitoring tests.)

1.6.1 Initial physical assessment

1.6.1.1 As soon as practicable after initial presentation of a patient with bipolar disorder, healthcare professionals should:

- establish the patient's smoking status and alcohol use
- perform thyroid, liver and renal function tests, blood pressure, and measure full blood count, blood glucose, lipid profile
- measure weight and height
- consider EEG, CT scan or MRI scan if an organic aetiology or a relevant comorbidity is suspected
- consider drug screening, chest X-ray and ECG if suggested by the history or clinical picture.

1.6.2 Initiating, monitoring and stopping drug treatments

Many drugs used to treat bipolar disorder can result in significant weight gain, particularly olanzapine. Careful monitoring of weight is needed with all antipsychotics, lithium and valproate.

The long-term use of antipsychotics

Initiating antipsychotics

1.6.2.1 When initiating long-term treatment of bipolar disorder with antipsychotics, weight and height, plasma glucose and lipids should be measured in all patients, and an ECG arranged for patients with cardiovascular disease or risk factors for it. Prolactin levels should be measured when initiating risperidone* in patients with low libido, sexual dysfunction, menstrual abnormalities, gynaecomastia or galactorrhea.

1.6.2.2 When initiating quetiapine*, the dose should be titrated gradually (in line with the summary of product characteristics), to help maintain normal blood pressure.

Monitoring antipsychotics

1.6.2.3 Patients taking antipsychotics should have their weight checked every 3 months for the first year, and more often if they gain weight rapidly. Plasma glucose and lipids (preferably fasting levels) should be measured 3 months after the start of treatment (and within 1 month if taking olanzapine), and more often if there is evidence of elevated levels. In patients taking risperidone*, prolactin levels should be measured if symptoms of raised prolactin develop; these include low libido, sexual dysfunction, menstrual abnormalities, gynaecomastia and galactorrhea.

Stopping antipsychotics

1.6.2.4 If a patient with bipolar disorder is stopping antipsychotic medication, the antipsychotic:

- should be stopped gradually over at least 4 weeks if the patient is continuing with other medication
- should be stopped over a period of up to 3 months if the patient is not continuing with other medication, or has a history of manic relapse.

Risks associated with the use of antipsychotics

1.6.2.5 Healthcare professionals should discuss with patients the risk of weight gain, and be aware of the possibility of worsening existing diabetes, malignant neuroleptic syndrome and diabetic ketoacidosis with the use of antipsychotic medication; particular caution is needed when treating patients with mania.

The long-term use of lithium

Initiating lithium

1.6.2.6 Lithium should not be initiated routinely in primary care for the treatment of bipolar disorder.

1.6.2.7 When initiating lithium as long-term treatment, prescribers should:

- advise patients that erratic compliance or rapid discontinuation may increase the risk of manic relapse
- measure height and weight, and arrange tests for urea and electrolytes and serum creatinine, and thyroid function
- arrange an ECG for patients with cardiovascular disease or risk factors for it
- arrange a full blood count if clinically indicated
- establish a shared-care protocol with the patient's GP for prescribing and monitoring lithium and checking for adverse effects
- be aware that patients should take lithium for at least 6 months to establish its effectiveness as a long-term treatment.

1.6.2.8 Serum lithium levels should be checked 1 week after starting and 1 week after every dose change, and until the levels are stable. The aim should be to maintain serum lithium levels between 0.6 and 0.8 mmol per litre in people being prescribed it for the first time.

1.6.2.9 For people who have relapsed previously while taking lithium or who still have sub-threshold symptoms with functional impairment while receiving lithium, a trial of at least 6 months with serum lithium levels between 0.8 and 1.0 mmol per litre should be considered.

Monitoring lithium

1.6.2.10 For patients with bipolar disorder on lithium treatment, prescribers should do the following.

- Monitor serum lithium levels normally every 3 months.
- Monitor older adults carefully for symptoms of lithium toxicity, because they may develop high serum levels of lithium at doses

in the normal range, and lithium toxicity is possible at moderate serum lithium levels.

- Monitor weight, especially in patients with rapid weight gain.
- Undertake more frequent tests if there is evidence of clinical deterioration, abnormal results, a change in sodium intake, or symptoms suggesting abnormal renal or thyroid function such as unexplained fatigue, or other risk factors, for example, if the patient is starting medication such as ACE inhibitors, non-steroidal anti-inflammatory drugs, or diuretics.
- Arrange thyroid and renal function tests every 6 months, and more often if there is evidence of impaired renal function.
- Initiate closer monitoring of lithium dose and blood serum levels if urea and creatinine levels become elevated, and assess the rate of deterioration of renal function. The decision whether to continue lithium depends on clinical efficacy, and degree of renal impairment; prescribers should consider seeking advice from a renal specialist and a clinician with expertise in the management of bipolar disorder on this.
- Monitor for symptoms of neurotoxicity, including paraesthesia, ataxia, tremor and cognitive impairment, which can occur at therapeutic levels.

Stopping lithium

1.6.2.11 Lithium should be stopped gradually over at least 4 weeks, and preferably over a period of up to 3 months, particularly if the patient has a history of manic relapse (even if they have been started on another antimanic agent).

1.6.2.12 When lithium treatment is stopped or is about to be stopped abruptly, prescribers should consider changing to monotherapy with an atypical antipsychotic or valproate*, and then monitor closely for early signs of mania and depression.

Risks associated with the use of lithium

- 1.6.2.13 Patients taking lithium should be warned not to take over-the-counter non-steroidal anti-inflammatory drugs. Prescribing non-steroidal anti-inflammatory drugs for such patients should be avoided if possible, and if they are prescribed the patient should be closely monitored.
- 1.6.2.14 Patients taking lithium should be advised to:
- seek medical attention if they develop diarrhoea and/or vomiting
 - ensure they maintain their fluid intake, particularly after sweating (for example, after exercise, in hot climates, or if they have a fever), if they are immobile for long periods or – in the case of older people – develop a chest infection or pneumonia
 - consider stopping lithium for up to 7 days if they become acutely and severely ill with a metabolic or respiratory disturbance from whatever cause.

The long-term use of valproate

Initiating valproate

- 1.6.2.15 Valproate should not be routinely initiated in primary care for the treatment of bipolar disorder.
- 1.6.2.16 When initiating valproate* as long-term treatment, patients should have their height and weight measured, and have a full blood count and liver function tests.
- 1.6.2.17 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.
- 1.6.2.18 Valproate* should not be prescribed for young women with bipolar disorder who are younger than 18 years because of the risk of polycystic ovary syndrome and unplanned pregnancy in this age group.

*Monitoring valproate**

1.6.2.19 Routine measurement of valproate* blood levels is not recommended unless there is evidence of ineffectiveness, poor adherence or toxicity.

1.6.2.20 Liver function tests and a full blood count should be done after 6 months' treatment with valproate*, and weight should be monitored in patients who gain weight rapidly.

*Stopping valproate**

1.6.2.21 When stopping valproate* in patients with bipolar disorder, the dose should be reduced gradually over at least 4 weeks to minimise the risk of destabilisation.

*Risks associated with the use of valproate**

1.6.2.22 Patients on valproate*, and their carers, should be advised how to recognise the signs and symptoms of blood and liver disorders and to seek immediate medical help if these develop. If abnormal liver function or blood dyscrasia is detected the drug should be stopped immediately.

1.6.2.23 When prescribing valproate*, prescribers should be aware of:

- its interactions with other anticonvulsants
- the need for more careful monitoring of sedation, tremor and gait disturbance in older people.

Lamotrigine

Initiating lamotrigine

1.6.2.24 Lamotrigine should not be routinely initiated in primary care for the treatment of bipolar disorder.

1.6.2.25 The dose of lamotrigine* should be titrated gradually to minimise the risk of skin rashes, including Stevens–Johnson syndrome. Titration should be slower in patients also taking valproate.

- 1.6.2.26 When offering lamotrigine* to women taking oral contraceptives, prescribers should explain that the drug may decrease the effectiveness of the contraceptive and discuss alternative methods of contraception. If a woman taking lamotrigine* stops taking an oral contraceptive, the dose of lamotrigine* may need to be reduced by up to 50%.

Monitoring lamotrigine

- 1.6.2.27 Routine monitoring of blood levels of lamotrigine* is not needed.

Stopping lamotrigine

- 1.6.2.28 When stopping lamotrigine*, the dose should be reduced gradually over at least 4 weeks to minimise the risk of destabilisation.

Risks associated with the use of lamotrigine

- 1.6.2.29 Patients taking lamotrigine* should be advised, particularly when starting the drug, to seek medical attention urgently if a rash develops. The drug should be stopped unless it is clear that the rash is not related to the use of lamotrigine*. If an appointment cannot be arranged within a few days or if the rash is worsening, the patient should be advised to stop the drug and then restart if lamotrigine* is not implicated in the development of the rash.

Carbamazepine

Initiating carbamazepine

- 1.6.2.30 Carbamazepine should be used for the long-term treatment of bipolar disorder only after consulting a specialist.
- 1.6.2.31 The dose of carbamazepine should be increased gradually to reduce the risk of ataxia.
- 1.6.2.32 When initiating carbamazepine as long-term treatment, patients should have their height and weight measured, and have a full blood count and liver function tests.

Monitoring carbamazepine

- 1.6.2.33 Plasma levels of carbamazepine should be measured every 6 months to exclude toxicity, because therapeutic levels and toxic levels are close.
- 1.6.2.34 Liver function tests and a full blood count should be repeated after 6 months' treatment with carbamazepine, and weight should be monitored in patients who gain weight rapidly.
- 1.6.2.35 Blood urea and electrolytes should be measured every 6 months after starting treatment with carbamazepine to check for hyponatraemia.
- 1.6.2.36 Possible interactions of carbamazepine with other drugs, including oral contraceptives, should be monitored closely, particularly if the patient starts a new medication.

Stopping carbamazepine

- 1.6.2.37 The dose of carbamazepine should be reduced gradually over at least 4 weeks to minimise the risk of destabilisation.

Risks associated with the use of carbamazepine

- 1.6.2.38 When prescribing carbamazepine for patients taking concomitant medications – for example, people older than 65 years and people with multiple physical problems – prescribers should be aware that carbamazepine has a greater potential for drug interactions than other drugs used to treat bipolar disorder.

Annual review of physical health

- 1.6.2.39 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.

1.6.2.40 The results of the annual review should be given to the person, and to 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.

1.6.3 Weight gain management

1.6.3.1 If a person gains weight during treatment their medication should be reviewed, and the following considered:

- dietary advice and support from primary care and mental health services
- advising regular aerobic exercise
- referral to mental health services for specific programmes to manage weight gain
- referral to a dietitian if the person has complex comorbidities (for example, coeliac disease).

1.6.3.2 Drug treatments such as high-dose antidepressants, sibutramine or topiramate* are not recommended to promote weight loss.

1.7 *Women with bipolar disorder who are planning a pregnancy, pregnant or breastfeeding*

The treatment and management of bipolar disorder in women who are trying to conceive, and during the antenatal and postnatal periods, is challenging and complex. This is largely because the risks of taking medication during pregnancy are not always well understood and because the risk of relapse in women during this time is high. No psychotropic drug is specifically licensed for use during pregnancy or when breastfeeding.

1.7.1 General principles of management for women

- 1.7.1.1 The absolute and relative risks of problems associated with both treating and not treating the bipolar disorder during pregnancy should be discussed with women.
- 1.7.1.2 More frequent contact by specialist mental health services (including, where appropriate, specialist perinatal mental health services), working closely with maternity services, should be considered for pregnant women with bipolar disorder, because of the increased risk of relapse during pregnancy and the postnatal period.
- 1.7.1.3 A written plan for managing a woman's bipolar disorder during the pregnancy, delivery and postnatal period should be developed as soon as possible. This should be developed with the patient and significant others, and shared with her obstetrician, midwife, GP and health visitor. All medical decisions should be recorded in all versions of the patient's notes. Information about her medication should be included in the birth plan and notes for postnatal care.
- 1.7.1.4 If a pregnant woman with bipolar disorder is stable on an antipsychotic and likely to relapse without medication, she should be maintained on the antipsychotic, and monitored for weight gain and diabetes.
- 1.7.1.5 The following drugs should not be routinely prescribed for pregnant women with bipolar disorder:
- valproate – because of risk to the fetus and subsequent child development
 - carbamazepine – because of its limited efficacy and risk of harm to the fetus
 - lithium – because of risk of harm to the fetus, such as cardiac problems
 - lamotrigine* – because of the risk of harm to the fetus

- paroxetine – because of the risk of cardiovascular malformations in the fetus
- long-term treatment with benzodiazepines – because of risks during pregnancy and the immediate postnatal period, such as cleft palate and floppy baby syndrome.

1.7.2 Women planning a pregnancy

- 1.7.2.1 Women with bipolar disorder who are considering pregnancy should normally be advised to stop taking valproate, carbamazepine, lithium and lamotrigine*, and alternative prophylactic drugs (such as an antipsychotic) should be considered.
- 1.7.2.2 Women taking antipsychotics who are planning a pregnancy should be advised that the raised prolactin levels associated with some antipsychotics reduce the chances of conception. If prolactin levels are raised, an alternative drug should be considered.
- 1.7.2.3 If a woman who needs antimanic medication plans to become pregnant, a low-dose typical or atypical antipsychotic should be considered, because they are of least known risk.
- 1.7.2.4 If a woman taking lithium plans to become pregnant, the following options should be considered:
- if the patient is well and not at high risk of relapse – gradually stopping lithium
 - if the patient 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 the woman 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 of the risks, while trying to conceive and throughout the pregnancy, if manic episodes have complicated the woman's previous

pregnancies, and her symptoms have responded well to lithium.

1.7.2.5 If a woman remains on lithium during pregnancy, serum lithium levels should be monitored every 4 weeks, then weekly from the 36th week, and less than 24 hours after childbirth. The dose should be adjusted to keep serum levels within the therapeutic range. The woman should maintain adequate fluid intake.

1.7.2.6 If a woman planning a pregnancy becomes depressed after stopping prophylactic medication, psychological therapy (CBT) should be offered in preference to an antidepressant because of the risk of switching associated with antidepressants. If an antidepressant is used, it should usually be an SSRI (but not paroxetine because of the risk of cardiovascular malformations in the fetus) and the woman should be monitored closely.

1.7.3 Women with an unplanned pregnancy

1.7.3.1 If a woman with bipolar disorder has an unplanned pregnancy:

- the pregnancy should be confirmed as quickly as possible
- the woman should be advised to stop taking valproate, carbamazepine and lamotrigine*
- if the pregnancy is confirmed in the first trimester, and the woman is stable, lithium should be stopped gradually over 4 weeks, and the woman informed that this may not remove the risk of cardiac defects in the fetus
- if the woman remains on lithium during pregnancy serum lithium levels should be checked every 4 weeks, then weekly from the 36th week, and less than 24 hours after childbirth; the dose should be adjusted to keep serum levels within the therapeutic range, and the woman should maintain adequate fluid intake
- an antipsychotic should be offered as prophylactic medication

- offer appropriate screening and counselling about the continuation of the pregnancy, the need for additional monitoring and the risks to the fetus if the woman stays on medication.

1.7.3.2 If a woman with bipolar disorder continues with an unplanned pregnancy, the newborn baby should have a full paediatric assessment, and social and medical help should be provided for the mother and child.

1.7.4 Pregnant women with acute mania or depression

Acute mania

1.7.4.1 If a pregnant women who is not taking medication develops acute mania, an atypical or a typical antipsychotic should be considered. The dose should be kept as low as possible and the woman monitored carefully.

1.7.4.2 If a pregnant woman develops acute mania while taking prophylactic medication, prescribers should:

- 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 to changes in dose or drug and the patient has severe mania, consider the use of ECT, lithium and, rarely, valproate.

1.7.4.3 If there is no alternative to valproate the woman should be informed of the increased risk to the fetus and the child's intellectual development. The lowest possible effective dose should be used and augmenting it with additional antimanic medication (but not carbamazepine*) considered. The maximum dosage should be 1 gram per day, in divided doses and in the slow-release form, with 5 mg/day folic acid.

Depressive symptoms

- 1.7.4.4 For mild depressive symptoms in pregnant women with bipolar disorder the following should be considered:
- self-help approaches such as guided self-help and computerised CBT
 - brief psychological interventions
 - antidepressant medication.
- 1.7.4.5 For moderate to severe depressive symptoms in pregnant women with bipolar disorder the following should be considered:
- psychological treatment (CBT) for moderate depression
 - combined medication and structured psychological interventions for severe depression.
- 1.7.4.6 For moderate to severe depressive symptoms in pregnant women with bipolar disorder, quetiapine* alone, or SSRIs (but not paroxetine) in combination with prophylactic medication should be preferred because SSRIs are less likely to be associated with switching than the tricyclic antidepressants. Monitor closely for signs of switching and stop the SSRI if patients start to develop manic or hypomanic symptoms.
- 1.7.4.7 Women who are prescribed an antidepressant during pregnancy should be informed of the potential, but predominantly short-lived, adverse effects of antidepressants on the neonate.
- 1.7.5 Care in the perinatal period**
- 1.7.5.1 Women taking lithium should deliver in hospital, and be monitored during labour by the obstetric medical team, in addition to usual midwife care. Monitoring should include fluid balance, because of the risk of dehydration and lithium toxicity.
- 1.7.5.2 After delivery, if a woman with bipolar disorder who is not on medication is at high risk of developing an acute episode,

prescribers should consider establishing or reinstating medication as soon as the patient is medically stable (once the fluid balance is established).

- 1.7.5.3 If a woman maintained on lithium is at high risk of a manic relapse in the immediate postnatal period, augmenting treatment with an antipsychotic should be considered.
- 1.7.5.4 If a woman with bipolar disorder develops severe manic or psychotic symptoms and behavioural disturbance in the intrapartum period rapid tranquillisation with an antipsychotic should be considered in preference to a benzodiazepine because of the risk of floppy baby syndrome. Treatment should be in collaboration with an anaesthetist.

1.7.6 Breastfeeding

- 1.7.6.1 Women with bipolar disorder who are taking psychotropic medication and wish to breastfeed should:
- have advice on the risks and benefits of breastfeeding
 - be advised not to breastfeed if taking lithium, benzodiazepines or lamotrigine*, and offered a prophylactic agent that can be used when breastfeeding – an antipsychotic should be the first choice (but not clozapine*)
 - be prescribed an SSRI if an antidepressant is used (but not fluoxetine or citalopram).

1.7.7 Care of the infant

Symptoms including irritability, constant crying, shivering, tremor, restlessness, increased tone, feeding and sleeping difficulties and rarely seizures have been reported in neonates of mothers taking SSRIs. Many of these symptoms are mild and self-limiting. In many cases these symptoms appear causally related to antidepressant exposure although there is debate about to what extent they represent serotonergic toxicity or a withdrawal reaction.

1.7.7.1 Babies whose mothers took psychotropic drugs during pregnancy should be monitored 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). If the mother was prescribed antidepressants in the last trimester, such symptoms may be a serotonergic toxicity syndrome rather than withdrawal, and the neonate should be monitored carefully.

1.8 Children and adolescents with bipolar disorder

The diagnosis of bipolar disorder in children and adolescents, particularly prepubescent children, presents a challenge because current diagnostic criteria developed for adults have limitations when applied to them. The evidence for drug and psychological treatments of bipolar disorder in children and adolescents is also extremely limited. At the date of publication (July 2006), 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 older. 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. General management principles for the drug treatment of bipolar disorder in children and adolescents include starting at lower doses than in adults. Closer monitoring is needed because children and adolescents may be more prone to adverse effects of medication, including sedation, obesity, extrapyramidal symptoms, metabolic changes and raised prolactin.

1.8.1 Special considerations

1.8.1.1 Healthcare professionals working in specialist services with children and adolescents with bipolar disorder should:

- be familiar with local and national guidelines on confidentiality and the rights of the child

- ensure appropriate consent is obtained, considering the adolescent's understanding (including Gillick competence), parental consent and responsibilities, child protection matters, and the use of the Mental Health Act and of the Children Act (1989).

1.8.1.2 When planning the care of children and adolescents with bipolar disorder, healthcare professionals should consider:

- stressors and vulnerabilities in their social, educational and family environments, including the quality of interpersonal relationships
- the impact of any comorbidities, such as attention deficit hyperactivity disorder (ADHD) and anxiety disorders
- the impact of the disorder on their social inclusion and education
- their vulnerability to exploitation, for example, as a result of disinhibited behaviour.

1.8.1.3 Parents or carers (and possibly other family members) should be involved in developing care plans so that they can give informed consent, support the psychological goals of treatment, and help to ensure treatment adherence.

1.8.1.4 Children and adolescents should be offered separate individual appointments with a healthcare professional in addition to joint meetings with their family members or carers.

1.8.2 Diagnosing bipolar I disorder in prepubescent children

1.8.2.1 When diagnosing bipolar I disorder in prepubescent children the same criteria should be used as in adults except that:

- mania must be present
- euphoria must be present most days, most of the time (for a period of 7 days)
- irritability is not a core diagnostic criterion.

1.8.2.2 Bipolar I disorder should not be diagnosed solely on the basis of a major depressive episode in a child with a family history of bipolar disorder. However, children with a history of depression and a family history of bipolar disorder should be carefully followed up.

1.8.3 Diagnosing bipolar I disorder in adolescents

1.8.3.1 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.

1.8.3.2 Bipolar I disorder should not be diagnosed solely on the basis of a major depressive episode in an adolescent with a family history of bipolar disorder. However, adolescents with a history of depression and a family history of bipolar disorder should be carefully followed up.

1.8.4 Diagnosing bipolar I disorder in older or developmentally advanced adolescents

1.8.4.1 In older or developmentally advanced adolescents, the criteria for establishing a diagnosis of bipolar I disorder in adults should be used.

1.8.5 Bipolar II disorder in both children and adolescents

1.8.5.1 Bipolar II disorder should not normally be diagnosed in children or adolescents because the diagnostic criteria are not well-enough established for routine use.

1.8.5.2 In older or developmentally advanced adolescents, the criteria for diagnosing bipolar II disorder in adults should be used.

1.8.6 Differential diagnosis for children and adolescents

1.8.6.1 The presence of clear-cut episodes of unduly elated mood, inappropriate and impairing grandiosity, and cycles of mood should be used to distinguish bipolar I disorder from attention deficit hyperactivity disorder (ADHD) and conduct disorder.

1.8.6.2 The presence of mood cycles should be used to distinguish bipolar disorder from schizophrenia.

1.8.6.3 Before diagnosing bipolar I disorder in a child or adolescent, other possible explanations for the behaviour and symptoms should be considered, including:

- sexual, emotional and physical abuse if they show disinhibition, hypervigilance or hypersexuality
- the possibility of drug and/or alcohol misuse as a cause of mania-like symptoms; consider a diagnosis of bipolar disorder only after 7 days of abstinence
- previously undiagnosed learning difficulties
- organic causes such as excited confusional states in children with epilepsy, and akathisia resulting from neuroleptic medication.

1.8.7 Children and adolescents with learning difficulties

1.8.7.1 When diagnosing bipolar I disorder in a child or adolescent with learning difficulties, the same criteria as are applied to children and adolescents without learning difficulties should be used.

1.8.8 Children and adolescents with sub-threshold symptoms of bipolar disorder

1.8.8.1 If it is not possible to make a diagnosis in a child or adolescent with sub-threshold symptoms of bipolar disorder, they should be carefully followed up.

1.8.9 Assessment methods for children and adolescents

1.8.9.1 The diagnosis of bipolar disorder in children and adolescents should be made by a clinician with specialist training in child and adolescent mental health.

1.8.9.2 Assessment should include:

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

1.8.9.3 A specialist diagnostic instrument such as the Wash-U-KSADS may be used; scales completed by parents or carers such as the Child Behaviour Checklist, Conners' Abbreviated Rating Scale, Parent Young Mania Rating Scale and Parent General Behaviour Inventory may also be used. These should not replace a full clinical interview.

1.8.9.4 In severely mentally ill children and adolescents with psychotic symptoms, a diagnosis should be attempted as early as practical, and should be subject to regular specialist review.

1.8.10 Drug treatment of acute mania in children and adolescents

1.8.10.1 When prescribing medication for children or adolescents with an acute manic episode, the recommendations for adults with bipolar disorder should be followed except drugs should be initiated at lower doses. In addition, at initial presentation:

- height and weight should be checked (and monitored regularly afterwards – for example, monthly for 6 months then every 6 months)
- prolactin levels should be measured
- when considering an antipsychotic, the risk of increased prolactin levels with risperidone* and weight gain with olanzapine* should be considered
- where there is an inadequate response to an antipsychotic, adding lithium or valproate* should be considered. Valproate should normally be avoided in girls and young women because of risks during pregnancy and risk of polycystic ovary syndrome.

1.8.11 Drug and psychological treatments of depression in children and adolescents

1.8.11.1 Children and adolescents with bipolar disorder experiencing mild depressive symptoms assessed as not requiring immediate treatment should be monitored weekly and offered additional support, for example at home and in school.

1.8.11.2 Children or adolescents with depressive symptoms needing treatment should normally be treated by specialist clinicians (based in at least Tier 3 services^e). Treatment should be as for adults with bipolar disorder except that a structured psychological therapy aimed at treating depression should be considered in addition to prophylactic medication.

^e Specialised 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.

1.8.11.3 If there has been no response to psychological therapy for depression combined with prophylactic medication after 4 weeks, prescribers should consider:

- adding fluoxetine* starting at 10 mg per day, and increasing to 20 mg per day if needed
- using an alternative SSRI (sertraline* or citalopram*) if there is no response to fluoxetine after an adequate trial.

If there is still no response, advice should be sought from a specialist in affective disorders.

1.8.11.4 For developmentally advanced adolescents with depressive symptoms, the recommendations on managing depression in adults with bipolar disorder should be followed.

1.8.12 Long-term treatment of children and adolescents

1.8.12.1 Long-term management of children or adolescents with bipolar disorder should normally be by specialist clinicians (based in at least Tier 3 services). Treatment should be as for adults with bipolar disorder except that:

- an atypical antipsychotic that is associated with lower weight gain and non-elevation of prolactin levels should be the first-line prophylactic agent
- lithium should be considered as the second-line prophylactic agent in female patients and valproate or lithium as the second-line prophylactic agent in male patients
- parents and carers should be given support to help the patient maintain a regular lifestyle
- the school or college should be given advice (with permission of the patient and those with parental responsibility) on managing the patient's bipolar disorder.

1.8.13 Inpatient services for children and adolescents

- 1.8.13.1 Admission as an inpatient or day patient, or more intensive community treatment, should be considered for children and adolescents at risk of suicide or other serious harm. Such care should be provided in specialist units, designed specifically for children and adolescents and able to support their educational, social and personal needs.
- 1.8.13.2 Severe behavioural disturbance in children and adolescents with bipolar disorder should be managed as for adults, except that rapid tranquillisation with haloperidol* is not recommended because of the increased risk of extrapyramidal side effects in this age group.

2 Notes on the scope of the guidance

NICE guidelines are developed in accordance with a scope that defines what the guideline will and will not cover. The scope of this guideline is available from www.nice.org.uk/CG038.

This guideline is relevant to adults, young people and children who meet the standard diagnostic criteria of bipolar disorder, their families or carers, and all healthcare professionals involved in the help, treatment and care of people with bipolar disorder and their families or carers. These include the following.

- Professional groups (including general practitioners, psychiatrists, clinical psychologists, psychotherapists, pharmacists, community psychiatric and practice nurses, occupational therapists and physicians) who share in the treatment and care of people with a diagnosis of bipolar disorder.
- Professionals in other health and non-health sectors who may have direct contact with, or are involved in the provision of health and other public services for, people diagnosed with bipolar disorder. These may include staff from schools and other educational settings, paediatric and community child health services, social services, the voluntary sector and prison doctors, the police, and professionals who work in the criminal justice sectors.

- Those with responsibility for planning services for people with a diagnosis of bipolar disorder and their families or carers, including directors of public health, NHS trust managers and managers in primary care trusts.

This guideline does not specifically address treatments that are not normally available on the NHS.

How this guideline was developed

NICE commissioned the National Collaborating Centre for Mental Health to develop this guideline. The Centre established a Guideline Development Group (see appendix A), which reviewed the evidence and developed the recommendations. An independent Guideline Review Panel oversaw the development of the guideline (see appendix B).

There is more information in the booklet: 'The guideline development process: an overview for stakeholders, the public and the NHS' (second edition, published April 2006), which is available from www.nice.org.uk/guidelinesprocess or by telephoning 0870 1555 455.

3 Implementation in the NHS

The Healthcare Commission assesses the performance of NHS organisations in meeting core and developmental standards set by the Department of Health in 'Standards for better health', issued in July 2004. Implementation of clinical guidelines forms part of the developmental standard D2. Core standard C5 says that national agreed guidance should be taken into account when NHS organisations are planning and delivering care.

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 which support this locally.
- Audit criteria to monitor local practice (see appendix C).

4 Research recommendations

The Guideline Development Group has made the following recommendations for research, based on its review of evidence, to improve NICE guidance and patient care in the future.

4.1 *Treatments for patients in partial remission from depressive symptoms in bipolar disorder*

A randomised placebo-controlled trial should be conducted to investigate the efficacy and cost-effectiveness of an adding an antidepressant (SSRI) to an existing antimanic agent for patients with bipolar disorder in partial remission from a depressive episode. The trial would ideally recruit from both primary and secondary care and outcome measures would include time to recovery from depression, time to prevention of the next episode, social functioning with a 2 year follow-up period.

Why this is important

The treatment of severe mental illness is a key priority in the National Service Framework for mental health, and depression of all kinds is a major cause of long-term disability and unemployment. People with bipolar disorder suffer more depressive episodes than manic episodes. Partial remission from symptoms is common, so successful treatment would greatly improve functioning and quality of life. But there is little evidence on which to base

recommendations for treatment of bipolar depression, and none on treatment after partial remission.

4.2 *Treatments for depression in bipolar disorder, and their risks*

A sequenced set of randomised controlled trials should be undertaken to investigate the efficacy and cost-effectiveness of antidepressants, in the presence of an antimanic medication, in treating bipolar depression. The studies should address the different stages of depression (acute, continuation and maintenance) and also evaluate the risks, particularly switching to mania and cycle acceleration, associated with antidepressant treatment. Patients with bipolar I and II disorder should be recruited. Outcome measures would include time to recovery from depression, time to prevention of the next episode and social functioning.

Why this is important

People with bipolar disorder suffer more depressive episodes than manic episodes. Depression is the major cause of suicide and the rate of suicide is very high among patients with bipolar disorder (10–15%). Therefore successful treatment would greatly improve functioning and quality of life. There is little evidence on the treatment of bipolar depression, particularly in different phases of the illness. Reducing depression could contribute to meeting the national targets to reduce suicide in bipolar disorder, and to reduce depression as a major cause of long-term disability and unemployment.

4.3 *Choice of prophylactic medication*

A randomised placebo-controlled trial should be undertaken to assess the efficacy and cost-effectiveness of adding an atypical antipsychotic to existing prophylactic medication (either lithium or valproate) in bipolar I disorder and bipolar II disorder. The primary outcome measure at 2 years would be time to the next bipolar episode requiring treatment, and an important secondary outcome measure would be social functioning. The trial should be adequately

powered to investigate tolerability differences and other potential harms such as weight gain and diabetes.

Why this is important

The treatment of severe mental illness is a key priority in the National Service Framework for mental health. Episodes of mania and depression are a significant cause of long-term disability and unemployment. There is insufficient evidence about the use of antipsychotics in the prophylaxis of bipolar disorder treatment, particularly in bipolar II disorder. The results of further research would allow more specific recommendations to be made.

4.4 *Prophylaxis in children and adolescents*

A randomised placebo-controlled trial should be undertaken to assess the efficacy and cost-effectiveness of an atypical antipsychotic plus an antimanic agent of a different class versus antimanic agent alone in children and adolescents in remission from bipolar disorder. The primary outcome measure at 2 years would be time to the next bipolar episode requiring treatment, and an important secondary outcome measure would be social functioning. The trial should also be adequately powered to investigate tolerability differences and other potential harms such as weight gain and diabetes.

Why this is important

Inadequate treatment of psychosis in young people is associated with poor long-term outcomes, including increased risk of suicide. But there is very little evidence of any quality on the drug treatment of bipolar disorder in children and young people. The answer to this question would allow more specific recommendations about the treatment of this group, and would help address standard 9 of the children's National Service Framework.

4.5 *Configuration of services*

A randomised controlled trial should be undertaken to compare the effectiveness of collaborative care for adolescents and adults with bipolar I or bipolar II disorder with treatment as usual in primary and secondary care.

Why this is important

There is very little evidence on effective configuration of services to suit the needs of people with bipolar disorder. The answer to this question would allow more specific recommendations on this topic, and so reduce morbidity.

5 Other versions of this guideline

5.1 *Full guideline*

The full guideline, 'Bipolar disorder: the management of bipolar disorder in adults, children and young people, in primary and secondary care' contains details of the methods and evidence used to develop the guideline. It is published by the National Collaborating Centre for Mental Health, and is available from www.bps.org.uk/publications/core/core_home.cfm, our website (www.nice.org.uk/CG038fullguideline) and the National Library for Health (www.nlh.nhs.uk).

5.2 *Quick reference guide*

A quick reference guide for healthcare professionals is available from www.nice.org/CG038quickrefguide

For printed copies, phone the NHS Response Line on 0870 1555 455 (quote reference number N1076).

5.3 *'Understanding NICE guidance'*

Information for patients and carers ('Understanding NICE guidance') is available from www.nice.org.uk/CG038publicinfo

For printed copies, phone the NHS Response Line on 0870 1555 455 (quote reference number N1077).

6 Related NICE guidance

- 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/CG025
- Guidance on the use of electroconvulsive therapy. *NICE technology appraisal guidance* no. 59 (2003). Available from www.nice.org/TA059

The development of this guideline included a review of the following technology appraisal. The appraisal is therefore now obsolete and has been replaced by this guideline.

- Olanzapine and valproate semisodium in the treatment of acute mania associated with bipolar I disorder. *NICE technology appraisal guidance* no. 66 (2001). Available from www.nice.org.uk/TA066

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.)

7 Updating the guideline

NICE clinical guidelines are updated as needed so that recommendations take into account important new information. 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.

Appendix A: The Guideline Development Group

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Mr Stephen Yorke

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Appendix B: The Guideline Review Panel

The Guideline Review Panel is an independent panel that oversees the development of the guideline and takes responsibility for monitoring adherence to NICE guideline development processes. In particular, the panel ensures that stakeholder comments have been adequately considered and responded to. The Panel includes members from the following perspectives: primary care, secondary care, lay, public health and industry.

Dr Chaand Nagpaul

General Practitioner, Stanmore

Mr John Seddon

Patient representative

Professor Kenneth Wilson

Professor of Psychiatry of Old Age and Honorary Consultant Psychiatrist, Cheshire and Wirral Partnership NHS Trust

Professor Shirley Reynolds

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Dr Roger Paxton

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Dr Paul Rowlands

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Appendix C: Technical detail on the criteria for audit

Criterion	Exception	Definition of terms
1. Valproate has not been routinely prescribed for women of child-bearing potential with bipolar disorder. If it has been prescribed, adequate contraception has been ensured the risks to the health of the unborn child have been explained	None	Any reason for resumption or continuation is in the patient's record.
2. For the long-term management of bipolar disorder prescribers have considered lithium, olanzapine and valproate, depending on response to previous treatments and: A. the relative risk and precipitants of manic versus depressive relapse B. physical risk factors C. the patient's preference and history of adherence D. the patient's gender E. a brief assessment of cognitive state if there is evidence of impairment	None	Physical risk factors include renal disease, obesity and diabetes. Valproate should not be prescribed for women of child-bearing potential. Tests such as the Mini-Mental State Examination may be considered, for example for older adults.
3. For patients who have frequent relapses or continuing functional impairment, alternative monotherapy or adding a second prophylactic drug has been considered. Clinical state, side effects and, where relevant, blood levels have been closely monitored. The reasons for the use of the chosen combination, and the discussion with the patient of the potential benefits and risks, have been documented in the case notes	None	Possible combinations are lithium with valproate*, lithium with olanzapine, and valproate* with olanzapine.

<p>4. If a trial of one of the combination of prophylactic agents proves ineffective, the following have been considered:</p> <p>A. consulting with, or referring the patient to, a clinician with expertise in the drug treatment of bipolar disorder</p> <p>B. prescribing lamotrigine* (especially for patients with bipolar II disorder) or carbamazepine</p>	None	None
<p>5. Antidepressants have been stopped, for patients in an acute manic episode, who were taking an antidepressant at the time of onset.</p> <p>The decision to stop antidepressants abruptly or gradually has been based on current clinical need, previous experience of discontinuation/withdrawal symptoms, and the risk of discontinuation/withdrawal symptoms of the antidepressant in question</p>	None	Evidence of stopping antidepressants, and any reason for resumption or continuation, is in the patient's record.
<p>6. After successful treatment for an acute depressive episode, prescribers have not routinely continued patients on long-term antidepressant treatment</p>	None	None
<p>7. An annual review of the physical health of a person with bipolar disorder has been carried out to ensure that over the course of a year the following have been assessed:</p> <p>A. lipid levels including cholesterol in patients over 40 even where there is no other indication of risk</p> <p>B. plasma glucose levels</p> <p>C. weight</p> <p>D. smoking status and alcohol use</p> <p>E. blood pressure</p>	None	None

<p>8. For all adolescents diagnosed with bipolar I disorder, healthcare professionals have used the same criteria as for the adult disorder, modified as follows:</p> <p>A. mania is present</p> <p>B. euphoria is present most days, most of the time (for at least 7 days)</p> <p>C. irritability, of an episodic, severe nature resulting in impaired function, which is not in character, or is out of keeping with the context, may be present (however, it was not used as a core diagnostic criterion)</p>	<p>Patients who are not adolescent.</p>	<p>Evidence that the patient meets these modified diagnostic criteria should be in the patient's record.</p>
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Appendix D: Schedule for physical monitoring

Table 1 Physical monitoring for people with bipolar disorder

Test or measurement	Monitoring for all patients		Monitoring for specific drugs			
	Initial health check	Annual check up	Antipsychotics	Lithium	Valproate*	Carbamazepine
Thyroid function	Yes	Yes ^a		At start and every 6 months; more often if evidence of deterioration		
Liver function	Yes				At start and at 6 months	At start and at 6 months
Renal function	Yes			At start and every 6 months; more often if there is evidence of deterioration of the patient starts taking drugs such as ACE inhibitors, diuretics or NSAIDs		Urea and electrolytes every 6 months
Full blood count	Yes			Only if clinically indicated	At start and 6 months	At start and at 6 months
Blood (plasma) glucose	Yes	Yes	At start and at 3 months (and at 1 month if taking olanzapine); more often if evidence of elevated levels			
Lipid profile	Yes	Over 40s only	At start and at 3 months; more often if evidence of elevated levels			
Blood pressure	Yes	Yes				

	Monitoring for all patients		Monitoring for specific drugs			
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 risk factors for or existing cardiovascular disease		
Weight and height	Yes	Yes ^b	At start and every 3 months for first year; more often if patient gains weight rapidly	At start and when needed if the patient gains weight rapidly	At start and at 6 months if patient gains weight rapidly	At start and at 6 months if the patient gains weight rapidly
Drug screening and chest X-ray	If suggested by the history or clinical picture					
EEG, MRI, CT scans	If organic aetiology or comorbidity is suspected					
Smoking/ alcohol	Yes	Yes				
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
<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.</p> <p>b For children and adolescents, monthly for 6 months, then every 6 months.</p> <p>c Note that therapeutic levels and toxic levels of carbamazepine are close.</p>						