

# Appendix A: Summary of evidence from surveillance

4-year surveillance (2017) – [Bipolar disorder: assessment and management](#) (2014) NICE guideline CG185

## Summary of evidence from surveillance

### *Improving the experience of carers\**

- Q – 01** What factors improve or diminish the experience of health and social services for carers of people with severe mental illness?
- Q – 02** What modification to health and social services improve the experience of using services for carers of adults with severe mental illness?

\* These review questions are incorporated from NICE guideline CG178 [psychosis and schizophrenia in adults](#).

## Recommendations derived from these review questions

### *Support for carers of people with bipolar disorder*

- 1.1.12 Offer carers of people with bipolar disorder an assessment (provided by mental health services) of their own needs and discuss with them their strengths and views. Develop a care plan to address any identified needs, give a copy to the carer and their GP and ensure it is reviewed annually <sup>[10]</sup>.
- 1.1.13 Advise carers about their statutory right to a formal carer's assessment provided by social care services and explain how to access this <sup>[11]</sup>.
- 1.1.14 Give carers written and verbal information in an accessible format about:
- diagnosis and management of bipolar disorder
  - positive outcomes and recovery
  - types of support for carers
  - role of teams and services
  - getting help in a crisis.
- When providing information, offer the carer support if necessary <sup>[10]</sup>.
- 1.1.15 As early as possible negotiate with the person with bipolar disorder and their carers about how information about the person will be shared. When discussing rights to confidentiality, emphasise the importance of sharing information about risks and the need for carers to understand the person's perspective. Foster a collaborative approach that supports both people with bipolar disorder and their carers, and respects their individual needs and interdependence <sup>[10]</sup>.
- 1.1.16 Review regularly how information is shared, especially if there are communication and collaboration difficulties between the person and their carer <sup>[11]</sup>.
- 1.1.17 Include carers in decision-making if the person agrees <sup>[10]</sup>.
- 1.1.18 Offer a carer-focused education and support programme, which may be part of a family intervention for bipolar disorder, as early as possible to all carers. The intervention should:
- be available as needed
  - have a positive message about recovery <sup>[10]</sup>.

- 1.1.19 Identify children, young people and adults at risk of abuse or neglect who are dependent on, living with or caring for a person with bipolar disorder and:
- review the need for an assessment according to local safeguarding procedures for children or adults as appropriate
  - offer psychological and social support as needed.

<sup>[10]</sup> Adapted from [Psychosis and schizophrenia in adults](#) (NICE clinical guideline 178).

<sup>[11]</sup> From [Psychosis and schizophrenia in adults](#) (NICE clinical guideline 178).

### Surveillance decision

These review questions should not be updated.

#### *Carer support*

##### **4-year surveillance summary**

No relevant evidence was identified.

##### **Topic expert feedback**

A topic expert highlighted ongoing studies related to online self-management for relatives of people with bipolar disorder. These will be considered when published.

##### **Impact statement**

No new evidence was identified at the surveillance review to impact on recommendations. Ongoing studies will be considered when results publish.

New evidence is unlikely to change guideline recommendations.

### *Case identification and assessment in adults, children and young people*

- Q – 03 For adults at risk of or suspected as having bipolar disorder, what identification instruments when compared with a gold standard diagnosis (based on DSM or ICD criteria) have adequate clinical utility (that is, clinically useful with good sensitivity and specificity) and reliability?**
- Q – 04 For children (less than 13 years) and young people (13 to 18 years) at risk of or suspected of having bipolar disorder, what identification instruments when compared with a gold standard diagnosis (based on DSM or ICD criteria) have adequate clinical utility (that is, clinically useful with good sensitivity and specificity) and reliability?**
- Q – 05 For people with possible bipolar disorder, what are the key components of, and the most effective structure for, a diagnostic assessment?**

#### **Subquestion**

What amendments, if any, need to be made for (i) particular cultural or minority ethnic groups, (ii) gender, (iii) children and young people, (iv) older adults?

## Recommendations derived from these review questions

### *Recognising bipolar disorder in primary care and referral*

- 1.2.1 When adults present in primary care with depression, ask about previous periods of overactivity or disinhibited behaviour. If the overactivity or disinhibited behaviour lasted for 4 days or more, consider referral for a specialist mental health assessment.
- 1.2.2 Refer people urgently for a specialist mental health assessment if mania or severe depression is suspected or they are a danger to themselves or others.
- 1.2.3 Do not use questionnaires in primary care to identify bipolar disorder in adults

### *Assessing suspected bipolar disorder in adults in secondary care*

- 1.3.1 Assessment of suspected bipolar disorder, and subsequent management, should be conducted in a service that can:
- offer the full range of pharmacological, psychological, social, occupational and educational interventions for people with bipolar disorder consistent with this guideline
  - be competent to provide all interventions offered
  - place emphasis on engagement as well as risk management
  - provide treatment and care in the least restrictive and stigmatising environment possible, and in an atmosphere of hope and optimism in line with the NICE clinical guidance on [service user experience in adult mental health](#).

This might be an early intervention in psychosis service, a specialist bipolar disorder team, or a specialist integrated community-based team.

- 1.3.2 When assessing suspected bipolar disorder:
- undertake a full psychiatric assessment, documenting a detailed history of mood, episodes of overactivity and disinhibition or other episodic and sustained changes in behaviour, symptoms between episodes, triggers to previous episodes and patterns of relapse, and family history
  - assess the development and changing nature of the mood disorder and associated clinical problems throughout the person's life (for example, early childhood trauma, developmental disorder or cognitive dysfunction in later life)
  - assess social and personal functioning and current psychosocial stressors
  - assess for potential mental and physical comorbidities
  - assess the person's physical health and review medication and side effects, including weight gain
  - discuss treatment history and identify interventions that have been effective or ineffective in the past
  - encourage people to invite a family member or carer to give a corroborative history
  - discuss possible factors associated with changes in mood, including relationships, psychosocial factors and lifestyle changes
  - identify personal recovery goals.
- 1.3.3 Take into account the possibility of differential diagnoses including schizophrenia spectrum disorders, personality disorders, drug misuse, alcohol-use disorders, attention deficit hyperactivity disorder and underlying physical disorders such as hypo- or hyperthyroidism.
- 1.3.4 If bipolar disorder is diagnosed, develop a care plan in collaboration with the person with bipolar disorder based on the assessment carried out in recommendation 1.3.2 as soon as possible after assessment and, depending on their needs, using the care programme approach. Give the person and their GP a copy of the plan, and encourage the person to share it with their carers <sup>[10]</sup>.
- 1.3.5 Carry out a risk assessment in conjunction with the person with bipolar disorder, and their carer if possible, focusing on areas that are likely to present possible danger or harm, such as

self-neglect, self-harm, suicidal thoughts and intent, risks to others, including family members, driving, spending money excessively, financial or sexual exploitation, disruption in family and love relationships, disinhibited and sexualised behaviour, and risks of sexually transmitted diseases. For the management of risk, follow the recommendations in section 1.4.

### *Improving the experience of care*

- 1.1.1 Use this guideline in conjunction with the NICE clinical guidance on [service user experience in adult mental health](#) to improve the experience of care for adults with bipolar disorder using mental health services, and for adults, children and young people:
- promote a positive recovery message from the point of diagnosis and throughout care
  - build supportive and empathic relationships as an essential part of care.

### *Treatment and support for specific populations*

- 1.1.3 Follow the recommendations in [race, culture and ethnicity](#) in the NICE clinical guideline on psychosis and schizophrenia in adults when working with people with bipolar disorder from black, Asian and minority ethnic groups.
- 1.1.4 See the NICE clinical guideline on [antenatal and postnatal mental health](#) for guidance on the management of bipolar disorder during pregnancy and the postnatal period and in women and girls of childbearing potential.
- 1.1.5 Ensure that people with bipolar disorder and a coexisting learning disability are offered the same range of treatments and services as other people with bipolar disorder.
- 1.1.6 Ensure that older people with bipolar disorder are offered the same range of treatments and services as younger people with bipolar disorder.
- 1.1.7 Offer people with bipolar disorder and coexisting disorders, such as personality disorder, attention deficit hyperactivity disorder, anxiety disorders or substance misuse, treatment in line with the relevant NICE clinical guideline, in addition to their treatment for bipolar disorder. See the NICE clinical guidelines on [antisocial personality disorder](#), [borderline personality disorder](#), [attention deficit hyperactivity disorder](#), [generalised anxiety disorder](#) and [psychosis with coexisting substance misuse](#), be alert to the potential for drug interactions and use clinical judgement.
- 1.1.8 Offer people with rapid cycling bipolar disorder the same interventions as people with other types of bipolar disorder because there is currently no strong evidence to suggest that people with rapid cycling bipolar disorder should be treated differently.

### *Information and support*

- 1.1.9 Consider identifying and offering assistance with education, financial and employment problems that may result from the behaviour associated with bipolar disorder, such as mania and hypomania. If the person with bipolar disorder agrees, this could include talking directly with education staff, creditors and employers about bipolar disorder and its possible effects, and how the person can be supported.
- 1.1.10 Encourage people with bipolar disorder to develop advance statements while their condition is stable, in collaboration with their carers if possible.
- 1.1.11 Explain and discuss making a lasting power of attorney with adults with bipolar disorder and their carers if there are financial problems resulting from mania or hypomania.

### *Recognising, diagnosing and managing bipolar disorder in children and young people*

- 1.11.1 Do not use questionnaires in primary care to identify bipolar disorder in children or young people.
- 1.11.2 If bipolar disorder is suspected in primary care in children or young people aged under 14 years, refer them to child and adolescent mental health services (CAMHS).
- 1.11.3 If bipolar disorder is suspected in primary care in young people aged 14 years or over, refer them to a specialist early intervention in psychosis service or a CAMHS team with expertise in the assessment and management of bipolar disorder in line with the recommendations in this guideline. The service should be multidisciplinary and have:
- engagement or assertive outreach approaches

- family involvement and family intervention
  - access to structured psychological interventions and psychologically informed care
  - vocational and educational interventions
  - access to pharmacological interventions
  - professionals who are trained and competent in working with young people with bipolar disorder.
- 1.11.4 Diagnosis of bipolar disorder in children or young people should be made only after a period of intensive, prospective longitudinal monitoring by a healthcare professional or multidisciplinary team trained and experienced in the assessment, diagnosis and management of bipolar disorder in children and young people, and in collaboration with the child or young person's parents or carers.
- 1.11.5 When diagnosing bipolar disorder in children or young people take account of the following:
- mania must be present
  - euphoria must be present on most days and for most of the time, for at least 7 days
  - irritability is not a core diagnostic criterion.
- 1.11.6 Do not make a diagnosis of bipolar disorder in children or young people on the basis of depression with a family history of bipolar disorder but follow them up.
- 1.11.7 When assessing suspected bipolar disorder in children or young people, follow recommendations 1.3.2–1.3.4 for adults, but involve parents or carers routinely and take into account the child or young person's educational and social functioning.

#### *Managing crisis, risk and behaviour that challenges in adults with bipolar disorder in secondary care*

- 1.4.1 Develop a risk management plan jointly with the person, and their carer if possible, covering:
- identifiable personal, social, occupational, or environmental triggers and early warning signs and symptoms of relapse
  - a protocol for applying the person's own coping strategies and increasing doses of medication or taking additional medication (which may be given to the person in advance) for people at risk of onset of mania or for whom early warning signs and symptoms can be identified
  - agreements between primary and secondary care about how to respond to an increase in risk or concern about possible risk
  - information about who to contact if the person with bipolar disorder and, if appropriate, their carer, is concerned or in a crisis, including the names of healthcare professionals in primary and secondary care who can be contacted.

Give the person and their GP a copy of the plan, and encourage the person to share it with their carers.

<sup>[10]</sup> Adapted from [Psychosis and schizophrenia in adults](#) (NICE clinical guideline 178).

#### **Surveillance decision**

These review questions should not be updated.

#### *Identification instruments for adults*

##### **4-year surveillance summary**

A systematic review and meta-analysis<sup>1</sup> found 53 studies reporting the accuracy of the Bipolar Spectrum Diagnostic Scale (BSDS),

Hypomania Checklist (HCL-32) and the Mood Disorder Questionnaire (MDQ). The analysis found all 3 instruments to be generally consistent in sensitivity and specificity. However, the HCL-32 was found to be most

accurate in detecting bipolar II disorder in mental health care centres.

#### Topic expert feedback

A topic expert commented that it would potentially be worthwhile to consider the impact and adoption of DSM-V in practice.

#### Impact statement

A search for the level of impact and adoption of DSM-V in practice was beyond the scope of the surveillance review.

Evidence was identified on the accuracy of diagnostic tools for bipolar disorder in adults. CG185 currently recommends a detailed assessment to diagnose bipolar disorder and advises against using questionnaires. The evidence identified through surveillance which compared diagnostic questionnaires with interview was limited, and so is unlikely to impact on recommendations.

New evidence is unlikely to change guideline recommendations.

### *Pharmacological and medical interventions for acute episodes*

**Q – 06** For adults with bipolar disorder, what are the relative benefits and harms of pharmacological and nutritional interventions for mania, hypomania and mixed episodes?

**Q – 07** For adults with bipolar disorder, what are the relative benefits and harms of pharmacological and nutritional interventions for acute episodes of acute bipolar depression?

**Q – 08** For adults with bipolar disorder, what are the relative benefits and harms of acupuncture, bright light therapy, transcranial magnetic stimulation (TMS), and vagus nerve stimulation for mania, hypomania, and mixed episodes?

**Q – 09** For adults with bipolar disorder, what are the relative benefits and harms of acupuncture, bright light therapy, transcranial magnetic stimulation (TMS), and vagus nerve stimulation for depressive episodes?

#### Subquestions

What amendments, if any, need to be made for (i) particular cultural or minority ethnic groups, (ii) gender, (iii) adults (18 to 64) and older adults (65+)?

#### Recommendations derived from these review questions

##### *Managing mania or hypomania in adults in secondary care*

- 1.5.1 Ensure that people with mania or hypomania have access to calming environments and reduced stimulation. Advise them not to make important decisions until they have recovered from mania or hypomania and encourage them to maintain their relationships with their carers if possible.
- 1.5.2 If a person develops mania or hypomania and is taking an antidepressant (as defined by the [British national formulary \(BNF\)](#)) as monotherapy:
  - consider stopping the antidepressant and
  - offer an antipsychotic as set out in recommendation 1.5.3, regardless of whether the antidepressant is stopped.

- 1.5.3 If a person develops mania or hypomania and is not taking an antipsychotic or mood stabiliser, offer haloperidol, olanzapine, quetiapine or risperidone, taking into account any advance statements, the person's preference and clinical context (including physical comorbidity, previous response to treatment and side effects). Follow the recommendations on using antipsychotics in section 1.10.
- 1.5.4 If the first antipsychotic is poorly tolerated at any dose (including rapid weight gain) or ineffective at the maximum licensed dose, offer an alternative antipsychotic from the drugs listed in recommendation 1.5.3, taking into account any advance statements, the person's preference and clinical context (including physical comorbidity, previous response to treatment and side effects).
- 1.5.5 If an alternative antipsychotic is not sufficiently effective at the maximum licensed dose, consider adding lithium <sup>[12]</sup>. If adding lithium is ineffective, or if lithium is not suitable (for example, because the person does not agree to routine blood monitoring), consider adding valproate <sup>[13]</sup> instead (see the recommendations on valproate in section 1.10).
- 1.5.6 If a person develops mania or hypomania and is taking an antidepressant (as defined by the [BNF](#)) in combination with a mood stabiliser, consider stopping the antidepressant.
- 1.5.7 If the person is already taking lithium, check plasma lithium levels to optimise treatment (see section 1.10). Consider adding haloperidol, olanzapine, quetiapine or risperidone, depending on the person's preference and previous response to treatment.
- 1.5.8 If the person is already taking valproate or another mood stabiliser as prophylactic treatment, consider increasing the dose, up to the maximum level in the [BNF](#) if necessary, depending on clinical response. If there is no improvement, consider adding haloperidol, olanzapine, quetiapine or risperidone, depending on the person's preference and previous response to treatment. Follow the recommendations on using antipsychotics and valproate in section 1.10.
- 1.5.9 If the clinical presentation is of a mixed affective state, characterised by both manic and depressive symptoms, follow recommendations 1.5.1–1.5.8 for the treatment of mania, and monitor closely for the emergence of depression.
- 1.5.10 Do not offer lamotrigine to treat mania.
- 1.5.11 For the treatment of severe mania that has not responded to other interventions, see NICE's technology appraisal [guidance on the use of electroconvulsive therapy](#).
- 1.5.12 Within 4 weeks of resolution of symptoms, discuss with the person, and their carers if appropriate, whether to continue treatment for mania or start long-term treatment (see section 1.7). Explain the potential benefits of long-term treatment and the risks, including side effects of medication used for long-term treatment.
- 1.5.13 If the person decides to continue treatment for mania, offer it for a further 3-6 months, and then review.

#### *Managing bipolar depression in adults in secondary care*

- 1.6.3 If a person develops moderate or severe bipolar depression and is not taking a drug to treat their bipolar disorder, offer fluoxetine <sup>[14]</sup> combined with olanzapine <sup>[15]</sup>, or quetiapine on its own, depending on the person's preference and previous response to treatment.
- If the person prefers, consider either olanzapine (without fluoxetine) or lamotrigine <sup>[16]</sup> on its own.
  - If there is no response to fluoxetine combined with olanzapine, or quetiapine, consider lamotrigine on its own.
- Follow the recommendations on using antipsychotics and lamotrigine in section 1.10.
- 1.6.4 If a person develops moderate or severe bipolar depression and is already taking lithium, check their plasma lithium level. If it is inadequate, increase the dose of lithium; if it is at maximum level, add either fluoxetine <sup>[14]</sup> combined with olanzapine <sup>[15]</sup> or add quetiapine, depending on the person's preference and previous response to treatment.
- If the person prefers, consider adding olanzapine (without fluoxetine) or lamotrigine <sup>[16]</sup> to lithium.

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

Follow the recommendations in section 1.10 on using lithium, antipsychotics and lamotrigine.

- 1.6.5 If a person develops moderate or severe bipolar depression and is already taking valproate, consider increasing the dose within the therapeutic range. If the maximum tolerated dose, or the top of the therapeutic range, has been reached and there is a limited response to valproate, add fluoxetine <sup>[14]</sup> combined with olanzapine <sup>[15]</sup> or add quetiapine, depending on the person's preference and previous response to treatment.
- If the person prefers, consider adding olanzapine (without fluoxetine) or lamotrigine <sup>[16]</sup> to valproate.
  - If there is no response to adding fluoxetine combined with olanzapine, or adding quetiapine, stop the additional treatment and consider adding lamotrigine to valproate.

Follow the recommendations in section 1.10 on using valproate, antipsychotics and lamotrigine.

- 1.6.6 Follow the recommendations on using antipsychotics in section 1.10 and be aware of the potential interactions between valproate and fluoxetine, lamotrigine and olanzapine.
- 1.6.7 Take into account toxicity in overdose when prescribing psychotropic medication during periods of high suicide risk. Assess the need to limit the quantity of medication supplied to reduce the risk to life if the person overdoses.
- 1.6.8 Within 4 weeks of resolution of symptoms, discuss with the person, and their carers if appropriate, whether to continue psychological or pharmacological treatment for bipolar depression or start long-term treatment (see section 1.7). Explain the potential benefits of long-term treatment and the risks, including side effects of medication used for long-term treatment.
- 1.6.9 If the person decides to continue psychological or pharmacological treatment for bipolar depression, offer it for a further 3–6 months, and then review.

#### *Managing crisis, risk and behaviour that challenges in adults with bipolar disorder in secondary care*

- 1.4.2 Offer crisis services to support people with bipolar disorder who are in crisis, in line with recommendations 1.4.1.1–1.4.1.4 in the NICE clinical guideline on psychosis and schizophrenia in adults.
- 1.4.3 If people with bipolar disorder pose an immediate risk to themselves or others during an acute episode, see the NICE guidance on:
- [violence](#) and [service user experience in adult mental health](#) for advice on managing agitation, challenging behaviour and imminent violence, and on rapid tranquillisation or
  - [self-harm](#) for advice on managing acts of self-harm and suicide risk.

#### *How to use medication*

- 1.10.1 When using any psychotropic medication for bipolar disorder ensure that:
- the person is given information that is suitable for their developmental level about the purpose and likely side effects of treatment including any monitoring that is required, and give them an opportunity to ask questions
  - the choice of medication is made in collaboration with the person with bipolar disorder, taking into account the carer's views if the person agrees
  - the overall medication regimen is regularly reviewed so that drugs that are not needed after the acute episode are stopped.
- 1.10.2 Discuss the use of alcohol, tobacco, prescription and non-prescription medication and illicit drugs with the person, and their carer if appropriate. Explain the possible interference of



these substances with the therapeutic effects of prescribed medication and psychological interventions [\[10\]](#).

- 1.10.3 When offering psychotropic medication to older people, take into account its impact on cognitive functioning in older people and:
- use medication at lower doses
  - take into account the increased risk of drug interactions
  - take into account the negative impact that anticholinergic medication, or drugs with anticholinergic activity, can have on cognitive function and mobility
  - ensure that medical comorbidities have been recognised and treated.
- 1.10.4 Do not offer gabapentin or topiramate to treat bipolar disorder.
- 1.10.5 Before starting antipsychotic medication, measure and record the person's:
- weight or BMI
  - pulse
  - blood pressure
  - fasting blood glucose or HbA1c
  - blood lipid profile [\[10\]](#).
- 1.10.6 Before starting antipsychotic medication, offer the person an electrocardiogram (ECG) if:
- it is specified in the drug's summary of product characteristics (SPC) or
  - a physical examination has identified a specific cardiovascular risk (such as hypertension) or
  - there is a family history of cardiovascular disease, a history of sudden collapse, or other cardiovascular risk factors such as cardiac arrhythmia or
  - the person is being admitted as an inpatient [\[10\]](#).
- 1.10.7 Treatment with antipsychotic medication should be considered an explicit individual therapeutic trial. Carry out the following:
- Discuss and record the side effects that the person is most willing to tolerate.
  - Record the indications and expected benefits and risks of antipsychotic medication, and the expected time for a change in symptoms and appearance of side effects.
  - At the start of treatment prescribe a dose that is appropriate for the phase and severity of the illness.
  - Do not routinely prescribe a dose above the maximum recommended in the [BNF](#) or SPC.
  - Justify and record reasons for doses outside the range given in the [BNF](#) or SPC, and inform the person that such treatment is unlicensed.
  - Record the rationale for continuing, changing or stopping medication, and the effects of such changes [\[10\]](#).

#### *Monitoring antipsychotic medication*

- 1.10.8 Monitor and record the following during dose titration and then regularly and systematically throughout treatment:
- pulse and blood pressure after each dose change
  - weight or BMI weekly for the first 6 weeks, then at 12 weeks
  - blood glucose or HbA1c and blood lipid profile at 12 weeks
  - response to treatment, including changes in symptoms and behaviour
  - side effects and their impact on physical health and functioning
  - the emergence of movement disorders
  - adherence [\[10\]](#).

- 1.10.9 The secondary care team should maintain responsibility for monitoring the efficacy and tolerability of antipsychotic medication for at least the first 12 months or until the person's condition has stabilised, whichever is longer. Thereafter, the responsibility for this monitoring may be transferred to primary care under shared-care arrangements [\[10\]](#).
- 1.10.10 If out-of-range test results are reported at any stage of treatment, the healthcare professional who ordered the tests should ensure that the person is offered further investigations and treatment as needed.
- 1.10.11 'As required' (p.r.n.) prescriptions of antipsychotic medication should be made as described in recommendation 1.10.7. Review clinical indications, frequency of administration, therapeutic benefits and side effects each week or more often if needed. Ensure that p.r.n. prescriptions have not unintentionally led to a total antipsychotic dosage above the maximum specified in the [BNF](#) or [SPC](#) [\[10\]](#).
- 1.10.12 Do not start regular combined antipsychotic medication, except for short periods (for example, when changing medication) [\[11\]](#).

### *Stopping antipsychotic drugs*

- 1.10.13 If stopping an antipsychotic drug, reduce the dose gradually over at least 4 weeks to minimise the risk of relapse.

### *Using lithium*

- 1.10.14 When starting lithium:
- advise the person that poor adherence or rapid discontinuation may increase the risk of relapse
  - measure the person's weight or BMI and arrange tests for urea and electrolytes including calcium, estimated glomerular filtration rate (eGFR), thyroid function and a full blood count
  - arrange an ECG for people with cardiovascular disease or risk factors for it
  - ensure the person is given appropriate national information (or a locally available equivalent) on taking lithium safely
  - establish a shared-care arrangement with the person's GP for prescribing lithium and monitoring adverse effects.
- 1.10.15 Measure plasma lithium levels 1 week after starting lithium and 1 week after every dose change, and weekly until the levels are stable. Aim to maintain plasma lithium level between 0.6 and 0.8 mmol per litre in people being prescribed lithium for the first time.
- 1.10.16 Consider maintaining plasma lithium levels at 0.8–1.0 mmol per litre for a trial period of at least 6 months for people who:
- have had a relapse while taking lithium in the past or
  - are taking lithium and have subthreshold symptoms with functional impairment.
- 1.10.17 Advise people taking lithium to:
- seek medical attention if they develop diarrhoea or vomiting or become acutely ill for any reason
  - 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 if they develop a chest infection or pneumonia
  - talk to their doctor as soon as possible if they become pregnant or are planning a pregnancy.
- 1.10.18 Warn people taking lithium not to take over-the-counter non-steroidal anti-inflammatory drugs and avoid prescribing these drugs for people with bipolar disorder if possible; if they are prescribed, this should be on a regular (not p.r.n.) basis and the person should be monitored monthly until a stable lithium level is reached and then every 3 months.
- 1.10.19 Measure the person's plasma lithium level every 3 months for the first year.
- 1.10.20 After the first year, measure plasma lithium levels every 6 months, or every 3 months for people in any of the following groups:

- older people
  - people taking drugs that interact with lithium
  - people who are at risk of impaired renal or thyroid function, raised calcium levels or other complications
  - people who have poor symptom control
  - people with poor adherence
  - people whose last plasma lithium level was 0.8 mmol per litre or higher.
- 1.10.21 Measure the person's weight or BMI and arrange tests for urea and electrolytes including calcium, estimated glomerular filtration rate (eGFR) and thyroid function every 6 months, and more often if there is evidence of impaired renal or thyroid function, raised calcium levels or an increase in mood symptoms that might be related to impaired thyroid function.
- 1.10.22 Monitor lithium dose and plasma lithium levels more frequently if urea levels and creatinine levels become elevated, or eGFR falls over 2 or more tests, and assess the rate of deterioration of renal function. For further information see NICE's guidance on [chronic kidney disease](#) and [acute kidney injury](#).
- 1.10.23 When discussing whether to continue lithium, take into account clinical efficacy, other risk factors for renal impairment and cardiovascular disease, and degree of renal impairment; if needed seek advice from a renal specialist and a clinician with expertise in managing bipolar disorder.
- 1.10.24 Monitor the person at every appointment for symptoms of neurotoxicity, including paraesthesia, ataxia, tremor and cognitive impairment, which can occur at therapeutic levels of lithium.
- 1.10.25 If stopping lithium, reduce the dose gradually over at least 4 weeks, and preferably up to 3 months, even if the person has started taking another antimanic drug.
- 1.10.26 During dose reduction and for 3 months after lithium treatment is stopped, monitor the person closely for early signs of mania and depression.

#### *Using valproate*

- 1.10.27 When starting valproate, measure the person's weight or BMI and carry out a full blood count and liver function tests.
- 1.10.28 Advise people taking valproate, and their carers, how to recognise the signs and symptoms of blood and liver disorders and to seek immediate medical help if any of these develop. Stop valproate immediately if abnormal liver function <sup>[19]</sup> or blood dyscrasia is detected.
- 1.10.29 When prescribing valproate, be aware of its interactions with other anticonvulsants (particularly carbamazepine and lamotrigine) and with olanzapine and smoking.
- 1.10.30 Do not routinely measure plasma valproate levels unless there is evidence of ineffectiveness, poor adherence or toxicity.
- 1.10.31 Measure the person's weight or BMI and carry out liver function tests and a full blood count again after 6 months of treatment with valproate and repeat annually.
- 1.10.32 Monitor sedation, tremor and gait disturbance carefully in older people.
- 1.10.33 If stopping valproate, reduce the dose gradually over at least 4 weeks to minimise the risk of relapse.

#### *Valproate in women of childbearing potential*

- 1.10.34 Do not offer valproate to women of childbearing potential for long-term treatment or to treat an acute episode <sup>[20]</sup>
- 1.10.35 If a woman of childbearing potential is already taking valproate, advise her to gradually stop the drug because of the risk of fetal malformations and adverse neurodevelopmental outcomes after any exposure in pregnancy <sup>[20]</sup>.

#### *Using lamotrigine*

- 1.10.36 When starting lamotrigine:
- carry out a full blood count, urea and electrolytes and liver function tests

- be aware of its interaction with valproate
- follow the instructions for initial dosage and dosage titration outlined in the SPC and [BNF](#), taking into account the need for slow titration in people who have not taken lamotrigine before.

1.10.37 Advise people taking lamotrigine to:

- contact their doctor immediately if they develop a rash while the dose of lamotrigine is being increased
- tell you if they are pregnant or planning a pregnancy.

1.10.38 Do not routinely measure plasma lamotrigine levels unless there is evidence of ineffectiveness, poor adherence or toxicity.

1.10.39 If stopping lamotrigine, reduce the dose gradually over at least 4 weeks to minimise the risk of relapse.

<sup>[10]</sup> Adapted from [Psychosis and schizophrenia in adults](#) (NICE clinical guideline 178).

<sup>[11]</sup> From [Psychosis and schizophrenia in adults](#) (NICE clinical guideline 178).

<sup>[12]</sup> Although its use is common in UK clinical practice, at the time of publication (September 2014) lithium did not have a UK marketing authorisation for this indication, although its use is common in UK clinical practice. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's [Good practice in prescribing and managing medicines and devices](#) for further information.

<sup>[13]</sup> At the time of publication (September 2014) semi-sodium valproate had a UK marketing authorisation for the treatment of mania if lithium is not tolerated or is contraindicated. Sodium valproate did not have a UK marketing authorisation for this indication, although its use is common in UK clinical practice. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's [Good practice in prescribing and managing medicines and devices](#) for further information.

<sup>[14]</sup> Although its use is common in UK clinical practice, at the time of publication (September 2014), fluoxetine did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's [Good practice in prescribing and managing medicines and devices](#) for further information.

<sup>[15]</sup> At the time of publication (September 2014), olanzapine did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's [Good practice in prescribing and managing medicines and devices](#) for further information.

<sup>[16]</sup> Although its use is common in UK clinical practice, at the time of publication (September 2014), lamotrigine did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's [Good practice in prescribing and managing medicines and devices](#) for further information.

<sup>[19]</sup> Although the absolute values of hepatic enzymes are a poor indicator of the extent of hepatic damage, it is generally accepted that if these are persistently elevated to over 3 times the upper normal limit, continuing to rise or accompanied by clinical symptoms, the suspected drug should be withdrawn. Raised hepatic enzymes of any magnitude accompanied by reduced albumin or impaired clotting suggest severe liver disease.

<sup>[20]</sup> February 2016: see also the [MHRA toolkit on the risks of valproate medicines in female patients](#).

## Surveillance decision

These review questions should not be updated.

### *Pharmacological treatment of mania, hypomania or mixed episodes*

#### **4-year surveillance summary**

An RCT<sup>2</sup> (n=497) found significant improvements in Young Mania Rating Scale (YMRS) and Clinical Global Impressions-Severity of illness (CGI-S) scores for

cariprazine 3-6mg or 6-12mg compared to placebo at 3 weeks in people with manic or mixed episodes of bipolar I disorder. However, cariprazine was also associated with greater incidences of treatment-related adverse events.

A systematic review and meta-analysis<sup>3</sup> of 15 studies found treatment with second generation

antipsychotics (aripiprazole, quetiapine or ziprasidone) in conjunction with lithium or valproate significantly reduced the risk of relapse for people with bipolar disorder. No statistical data is available in the abstract for comparisons of antipsychotics as monotherapy.

A network meta-analysis<sup>4</sup> of 33 RCTs analysed 17 pharmacological treatments for bipolar disorder. Aripiprazole, carbamazepine, imipramine and paliperidone were not significantly different to placebo in reducing the risk of mood relapse or recurrence. The analysis supports the use of lithium as first-line maintenance treatment for bipolar disorder.

A systematic review and meta-analysis<sup>5</sup> of 7 trials found significant improvements in preventing manic and depressive episodes with the use of lithium compared with placebo. Also, compared with anticonvulsants, lithium significantly improved prevention of manic episodes but not depressive or overall mood episodes.

An RCT<sup>6</sup> (n=1172) found significant improvements in the time to next manic or depressive episodes for maintenance treatment with quetiapine or lithium compared with placebo in people with bipolar I disorder. Participants were initially stabilised with quetiapine for 4-24 weeks before randomisation to quetiapine, lithium or placebo.

A systematic review and meta-analysis<sup>7</sup> of 19 RCTs found significant improvement at 3 weeks in mania symptoms after combination treatment with mood stabilisers and antipsychotics compared with monotherapy with either type of medication. However, combination therapy was associated with an increase in side effects.

An individual patient data meta-analysis<sup>8</sup> (n=1243) found that early response to antipsychotic treatment for mania within the first 2 weeks significantly improved response and remission rates at weeks 3 and 4.

A meta-analysis<sup>9</sup> found significantly increased risks of polycystic ovary syndrome, menstrual disorder and hyperandrogenism associated with valproate for bipolar disorder in women compared to non-valproate treatments.

#### **Topic expert feedback**

Feedback indicates lithium is licensed for the management of acute manic or hypomanic episodes. It is not licensed for use in combination with other antipsychotics due to a risk of neurotoxicity.

Feedback also indicated that Episenta (prolonged-release sodium valproate) is licensed for bipolar disorder however should be prescribed as monotherapy.

#### **Impact statement**

The evidence on pharmacological treatments for mania, hypomania or mixed episodes is generally consistent with current recommendations.

The evidence suggests lithium is an effective treatment for manic episodes as is recommended in the guideline.

Studies also suggest antipsychotics in conjunction with lithium or valproate are an effective treatment option as is recommended in the guideline.

Other pharmacological treatments have shown inconsistent effects and are generally not licensed for use in this indication. CG185 recognises the common use of medications off-label and advises prescribers to check SPCs and take responsibility for decisions.

Cariprazine, ziprasidone, imipramine and paliperidone are all included as treatment options within the new evidence. However, these are not licensed for treating bipolar disorder in the UK.

Two studies found improvements in response rates for mood stabilisers and antipsychotics. However, these studies do not specify in the abstract the individual medications investigated. Recommendations in the guideline consider individual medications and evidence for the general classification of drugs is unlikely to have an impact.

Lithium, valproate, haloperidol, olanzapine, risperidone and quetiapine are recommended as treatment options for this population. The guideline advises clinicians to consider the benefits and risks of each medication before prescribing.

The evidence indicates various side effects for pharmacological treatments which CG185 advises to account for.

Valproate was found in one study to increase risks in women of childbearing age. Recommendations already take this into account.

Expert feedback highlights that the use of lithium or sodium valproate in conjunction with other medications is not licensed for this indication in the UK. This is in line with current footnotes in the guideline for prescribers to

follow professional guidance and take responsibility for decisions.

New evidence is unlikely to change guideline recommendations.

## *Pharmacological treatment of bipolar depression*

### **4-year surveillance summary**

An RCT<sup>10</sup> in adults with bipolar II depression (n=129) compared the pharmacological effectiveness of venlafaxine and lithium carbonate as monotherapy. Venlafaxine was found to have significantly greater; response rate, remission rate, decline in depression symptom scores, reduction in global severity scores, and improvement in global change scores compared to lithium at 12 weeks.

Using the same study population and treatments, an RCT<sup>11</sup> found that an increase in the number of prior antidepressant treatments was associated with significant step-wise reductions in the likelihood of treatment response and remission.

An RCT<sup>12</sup> (n=571) found significant improvements on the Montgomery-Asberg Depression Rating Scale (MADRS) and CGI-S scores for cariprazine 1.5mg compared with placebo in people with bipolar I depression at 6 weeks. No significant difference was found for cariprazine 0.75mg or 3mg compared with placebo. However, cariprazine was also associated with greater incidences of treatment-related adverse events.

An RCT<sup>13</sup> (n=202) investigated the effect of combining lamotrigine or placebo with quetiapine in people with bipolar depression at 12 and 52 weeks. A significant difference between groups in symptom improvement scores was found only at 52 weeks in favour of the lamotrigine and quetiapine combination. The addition of folic acid was found to significantly reduce the effect of lamotrigine at 12 weeks. It is not stated in the abstract whether symptom improvements for either group were significantly different between baseline and follow-up.

A systematic review and meta-analysis<sup>14</sup> of 11 RCTs found significant improvements in depression symptoms for quetiapine compared with placebo in people with bipolar depression. However, quetiapine was associated with increased side effects including weight gain.

A Cochrane systematic review<sup>15</sup> of 5 studies concluded that there is limited and low quality evidence in favour of a single intravenous administration of ketamine as an addition to mood stabilisers for reducing depressive symptoms in bipolar disorder. However, the effect was only significant at the 24 hour follow-up point.

A meta-analysis<sup>16</sup> of 3 RCTs found significant improvement in depression symptoms at 40 minutes following a single intravenous administration of ketamine treatment compared with placebo for bipolar depression.

A systematic review and meta-analysis<sup>17</sup> of 6 trials found a significant improvement in clinician-rated depression scores for second-generation antidepressants (SGA) as an addition to mood stabilisers or antipsychotics for bipolar depression. No significant differences were found for clinical response or remission rates compared to placebo. Long-term use of SGAs (52 weeks) was associated with a significant increase in risk of mania or hypomania.

A network meta-analysis<sup>18</sup> of 14 RCTs found significantly improved depression symptoms associated with lurasidone compared to placebo, aripiprazole and ziprasidone. Compared with olanzapine and quetiapine, lurasidone was associated with less weight gain but no significant differences in depression symptoms. No significant differences were found between medications for response rates, remission rates or bipolar disorder severity scores.

A Cochrane review<sup>19</sup> of 6 studies found no significant differences in bipolar depression symptoms when comparing topiramate with placebo at 3 or 12 weeks.

An RCT<sup>20</sup> (n=482) found no significant interaction effects of nonsteroidal anti-inflammatory drugs (NSAID) or paracetamol on treatment outcomes in people using lithium or quetiapine for bipolar disorder.

A meta-analysis<sup>21</sup> of 8 RCTs found a moderate and significant improvement in depression symptoms for NSAID and standard treatment

combination compared with standard treatment alone.

### **Topic expert feedback**

A topic expert commented that lurasidone is now licensed for use in the UK for schizophrenia.

A topic expert commented that current evidence is not strong enough to change recommendations on venlafaxine and lamotrigine.

A topic expert commented that the British Association for Psychopharmacology (BAP) note differences from NICE in approach to treatment for bipolar depression. The BAP recommends quetiapine, lurasidone or olanzapine monotherapy. NICE recommends fluoxetine combined with olanzapine or monotherapy with either quetiapine, olanzapine or lamotrigine.

### **Impact statement**

The new evidence on pharmacological treatments for bipolar depression generally consider medications not contained within current recommendations.

From the medicines considered in the new evidence, only lamotrigine, quetiapine and lithium are recommended as treatment options within the guideline.

Studies on lamotrigine and quetiapine, either as monotherapy or in combination, support recommendations for their use.

New evidence suggests effectiveness of cariprazine and ketamine for improving depressive symptoms. However, neither drug is licensed for this indication in the UK. This evidence is unlikely to impact recommendations due to the short follow-up time for ketamine studies and risks of adverse events with cariprazine.

One study found venlafaxine to be more effective than lithium. However, topic experts indicate that the evidence is not currently strong enough to start prescribing venlafaxine in this population.

A Cochrane review of topiramate found no significant improvement in bipolar depression symptoms. Topiramate is not licensed for use in the UK and recommendation 1.10.4 specifically advises to not offer topiramate to treat bipolar disorder.

Studies on lurasidone generally show effectiveness in improving bipolar symptoms and suggest that this is a well tolerated drug.

However, it is not licensed in the UK for use in this indication. There are more established and well researched treatments (both licensed and unlicensed) for this indication. Patients who have tried other treatments without success, those with particularly severe depression or at high suicide risk, may benefit from lurasidone. However, the prescription would be off-label and prescribers would need to consider whether the slightly better side effect profile of lurasidone is good enough reason to use an unlicensed over licensed drug.

CG185 recognises the common use of medications off-label and advises prescribers to check SPCs and take responsibility for decisions.

The evidence indicates various side effects of pharmacological treatments which CG185 advises clinicians to take into account. The guideline advises clinicians to consider the benefits and risks of each medication before prescribing.

Some of the new evidence investigated the effects of drug classes (antipsychotics and antidepressants) without reporting individual medications. This is unlikely to impact the guideline as drugs within these classes are already specified in recommendations.

There is conflicting new evidence on the interaction effects of NSAIDs with standard treatments for bipolar depression. One trial found no interaction effects whereas a meta-analysis found improvements in depression symptoms.

Current recommendations already advise prescribers to recognise and treat comorbidities using the appropriate related NICE guidance and to discuss the potential interaction effects of medicines with the patient.

Comments from a topic expert indicates differences in treatment approaches with the BAP guidelines. The order in which to offer the alternative medications differs between NICE and BAP guidelines. However, there is consensus in both guidelines that the strongest evidence supports treatment with a fluoxetine and olanzapine combination. Although there are differences between guideline recommendations, NICE has additionally considered economic analyses as part of the decision-making process for recommendations. The BAP also advises prescribers to use the guideline alongside NICE guideline CG185.

New evidence is unlikely to change guideline recommendations.

### *Non-pharmacological interventions*

#### **4-year surveillance summary**

An RCT<sup>22</sup> (n=73) found significant improvements in depression symptoms and response rates for electroconvulsive therapy (ECT) compared with pharmacological treatment for bipolar depression at 6 weeks. Remission rates were not significantly different between groups.

An RCT<sup>23</sup> (n=50) found significant improvements in depression rating scores for deep transcranial magnetic stimulation (dTMS) at 4 weeks following 20 sessions compared with sham treatment for bipolar depression. The effect was no longer significant at 8 week follow-up. Response and remission rates were not significantly different at any measurement point.

#### **Topic expert feedback**

A topic expert commented that there is some evidence for ECT showing effectiveness in serious cases. However no references were provided to support this view.

#### **Impact statement**

Evidence suggests improvements in depression symptoms after treatment with dTMS. However, the effects are limited to treatment end points and remission rates did not improve.

A topic expert also suggested beneficial effects of ECT for serious cases. This is in line with recommendation 1.5.11 which does recommend ECT for the treatment of severe mania that has not responded to other interventions.

New evidence is unlikely to change guideline recommendations.

### *Interventions and services for long-term management*

- Q – 10 For adults with bipolar disorder, what are the relative benefits and harms of service-level interventions that are designed specifically for people bipolar disorder?**
- Q – 11 What are the relative benefits and harms of information and communication technologies (for example, text messaging) for monitoring symptoms?**
- Q – 12 For adults with bipolar disorder, what are the relative benefits and harms of starting a new pharmacological outside of an acute episode?**
- Q – 13 For adults with bipolar disorder, what are the relative benefits and harms of continuing an acute treatment for 1 year or more?**

#### **Subquestion**

What amendments, if any, need to be made for (i) particular cultural or minority ethnic groups, (ii) gender, and (iii) adults (18 to 64) and older adults (65+)?



## Recommendations derived from these review questions

### *Managing bipolar disorder in primary care*

- 1.2.4 When working with people with bipolar disorder in primary care:
- engage with and develop an ongoing relationship with them and their carers
  - support them to carry out care plans developed in secondary care and achieve their recovery goals
  - follow crisis plans developed in secondary care and liaise with secondary care specialists if necessary
  - review their treatment and care, including medication, at least annually and more often if the person, carer or healthcare professional has any concerns.
- 1.2.7 Do not start lithium to treat bipolar disorder in primary care for people who have not taken lithium before, except under shared-care arrangements.
- 1.2.8 Do not start valproate in primary care to treat bipolar disorder.
- 1.2.9 If bipolar disorder is managed solely in primary care, re-refer to secondary care if any one of the following applies:
- there is a poor or partial response to treatment
  - the person's functioning declines significantly
  - treatment adherence is poor
  - the person develops intolerable or medically important side effects from medication
  - comorbid alcohol or drug misuse is suspected
  - the person is considering stopping any medication after a period of relatively stable mood
  - a woman with bipolar disorder is pregnant or planning a pregnancy.

### *Managing bipolar disorder in adults in the longer term in secondary care*

- 1.7.1 After each episode of mania or bipolar depression, discuss with the person, and their carers if appropriate, managing their bipolar disorder in the longer term. Discussion should aim to help people understand that bipolar disorder is commonly a long-term relapsing and remitting condition that needs self-management and engagement with primary and secondary care professionals and involvement of carers. The discussion should cover:
- the nature and variable course of bipolar disorder
  - the role of psychological and pharmacological interventions to prevent relapse and reduce symptoms
  - the risk of relapse after reducing or stopping medication for an acute episode
  - the potential benefits and risks of long-term medication and psychological interventions, and the need to monitor mood and medication
  - the potential benefits and risks of stopping medication, including for women who may wish to become pregnant
  - the person's history of bipolar disorder, including:
    - the severity and frequency of episodes of mania or bipolar depression, with a focus on associated risks and adverse consequences
    - previous response to treatment
    - symptoms between episodes
    - potential triggers for relapse, early warning signs, and self-management strategies
  - possible duration of treatment, and when and how often this should be reviewed.

Provide clear written information about bipolar disorder, including NICE's [information for the public](#), and ensure there is enough time to discuss options and concerns.

- 1.7.5 When planning long-term pharmacological treatment to prevent relapse, take into account drugs that have been effective during episodes of mania or bipolar depression. Discuss with the person whether they prefer to continue this treatment or switch to lithium, and explain that lithium is the most effective long-term treatment for bipolar disorder.
- 1.7.6 Offer lithium as a first-line, long-term pharmacological treatment for bipolar disorder and:
- if lithium is ineffective, consider adding valproate <sup>[17]</sup>
  - if lithium is poorly tolerated, or is not suitable (for example, because the person does not agree to routine blood monitoring), consider valproate or olanzapine <sup>[18]</sup> instead or, if it has been effective during an episode of mania or bipolar depression, quetiapine.
- Discuss with the person the possible benefits and risks of each drug for them, following the recommendations in section 1.10.
- 1.7.7 If stopping long-term pharmacological treatment:
- discuss with the person how to recognise early signs of relapse and what to do if symptoms recur
  - stop treatment gradually (see section 1.10) and monitor the person for signs of relapse.
- 1.7.8 Continue monitoring symptoms, mood and mental state for 2 years after medication has stopped entirely. This may be undertaken in primary care (see recommendation 1.9.3).

#### *Monitoring physical health in secondary care*

- 1.8.1 Healthcare professionals in secondary care should ensure, as part of the care programme approach, that people with bipolar disorder receive physical healthcare from primary care as described in recommendations 1.2.10–1.2.14 after responsibility for monitoring has been transferred from secondary care <sup>[10]</sup>.
- 1.8.2 People with bipolar disorder, especially those taking antipsychotics and long-term medication, should be offered a combined healthy eating and physical activity programme by their mental healthcare provider <sup>[10]</sup>.
- 1.8.3 If a person has rapid or excessive weight gain, abnormal lipid levels or problems with blood glucose management, take into account the effects of medication, mental state, other physical health and lifestyle factors in the development of these problems and offer interventions in line with the NICE guidance on [obesity](#), [lipid modification](#) or [preventing type 2 diabetes](#) <sup>[10]</sup>.
- 1.8.4 Routinely monitor weight and cardiovascular and metabolic indicators of morbidity in people with bipolar disorder. These should be audited in the annual team report <sup>[10]</sup>.
- 1.8.5 Trusts should ensure that they take account of relevant guidelines on the monitoring and treatment of cardiovascular and metabolic disease in people with bipolar disorder through board-level performance indicators <sup>[10]</sup>.

#### *Promoting recovery and return to primary care*

- 1.9.1 Continue treatment and care in an early intervention in psychosis service, a specialist bipolar disorder service or a specialist integrated community-based team. Share physical health monitoring with primary care as outlined in section 1.2 and section 1.8.
- 1.9.2 Consider intensive case management for people with bipolar disorder who are likely to disengage from treatment or services <sup>[10]</sup>.
- 1.9.3 Offer people with bipolar disorder whose symptoms have responded effectively to treatment and remain stable the option to return to primary care for further management. If they wish to do this, record it in their notes and coordinate transfer of responsibilities through the care programme approach <sup>[10]</sup>.
- 1.9.4 When making transfer arrangements for a return to primary care, agree a care plan with the person, which includes:
- clear, individualised social and emotional recovery goals
  - a crisis plan indicating early warning symptoms and triggers of both mania and depression relapse and preferred response during relapse, including liaison and referral pathways

- an assessment of the person's mental state
- a medication plan with a date for review by primary care, frequency and nature of monitoring for effectiveness and adverse effects, and what should happen in the event of a relapse.

Give the person and their GP a copy of the plan, and encourage the person to share it with their carers.

- 1.9.5 Encourage and support the person to visit their GP and discuss the care plan before discharge and transfer.
- 1.9.6 Offer supported employment programmes to people with bipolar disorder in primary or secondary care who wish to find or return to work. Consider other occupational or educational activities, including pre-vocational training, for people who are unable to work or unsuccessful in finding employment <sup>[10]</sup>.

<sup>[10]</sup> Adapted from [Psychosis and schizophrenia in adults](#) (NICE clinical guideline 178).

<sup>[17]</sup> At the time of publication (September 2014) semi-sodium valproate had a UK marketing authorisation for this indication in people who have had mania that has responded to treatment with semi-sodium valproate. Sodium valproate did not have a UK marketing authorisation for this indication, although its use is common in UK clinical practice. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's [Good practice in prescribing and managing medicines and devices](#) for further information.

<sup>[18]</sup> Although its use is common in UK clinical practice, at the time of publication (September 2014), olanzapine did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's [Good practice in prescribing and managing medicines and devices](#) for further information.

## Surveillance decision

These review questions should not be updated.

### *Service-level interventions*

#### **4-year surveillance summary**

No relevant evidence was identified for this question.

#### **Topic expert feedback**

A topic expert highlighted the British Association for Psychopharmacology (BAP) as a source of advice on recommendations for planning service provision.

A topic expert commented that the Access and Waiting Times Directive may have had impact on service structures since the last guideline.

#### **Impact statement**

Comments from topic experts highlight the availability of BAP guidelines for advice on

planning service provision. The BAP suggest their guideline is to be used alongside NICE guideline CG185.

A further comment from a topic expert highlights the potential impact of the Access and Waiting Times Directive on service structures. However, no evidence is provided to support this view and no new evidence relevant to service structures was found from the surveillance review.

New evidence is unlikely to change guideline recommendations.

### *Long-term pharmacological management*

#### **4-year surveillance summary**

An RCT<sup>24</sup> (n=102) investigated the efficacy of 400mg long-acting injectable antipsychotic aripiprazole once-monthly (AOM 400) in people

with a manic episode of bipolar I disorder. Patients were randomised to either AOM 400 or placebo following mood stabilisation with oral aripiprazole and AOM 400. Significant improvements at 52 weeks in rates of and time to recurrence of mood episodes were found for

AOM 400 compared to placebo. However, AOM 400 was also associated with greater incidence of treatment-related adverse events. An RCT<sup>25</sup> (n=159) found no significant difference in time to relapse between placebo and risperidone or olanzapine treatments at 52 weeks in people in remission from bipolar mania. An increase in weight gain was associated with both antipsychotic treatments compared with placebo.

#### **Topic expert feedback**

No relevant feedback was identified for this question.

#### **Impact statement**

Current recommendations advise on the use of lithium, valproate, olanzapine and quetiapine

for the long-term management of bipolar disorder.

New evidence suggests efficacy of aripiprazole injection. However, it was also associated with adverse events and aripiprazole injection is not licensed for long-term use in bipolar disorder.

Olanzapine was not found to be beneficial in preventing relapse in a small RCT. Although the current recommendation is to use olanzapine, the new evidence is unlikely to be sufficient to challenge this.

New evidence is unlikely to change guideline recommendations.

### *Psychological and psychosocial interventions for acute episodes and long-term management in adults*

- Q – 14 For adults with bipolar disorder, what are the relative benefits and harms of psychological and psychosocial interventions for mania, hypomania, and mixed episodes?**
- Q – 15 For adults with bipolar disorder, what are the relative benefits and harms of combined psychological and pharmacological interventions for mania, hypomania, and mixed episodes?**
- Q – 16 For adults with bipolar disorder, what are the relative benefits and harms of psychological and psychosocial interventions for depression?**
- Q – 17 For adults with bipolar disorder, what are the relative benefits and harms of combined psychological and pharmacological interventions for depression?**
- Q – 18 For adults with bipolar disorder, what are the relative benefits and harms of psychological and psychosocial interventions for long-term management?**
- Q – 19 For adults with bipolar disorder, what are the relative benefits and harms of combined psychological and pharmacological interventions for long-term management?**

#### **Subquestions**

What amendments, if any, need to be made for (i) particular cultural or minority ethnic groups, (ii) gender?

Does the effectiveness of treatment vary:

- For people taking a mood stabiliser (for example lithium or valproate) and people not taking a mood stabiliser

- For people whose most-recent episode was depressive and people whose most-recent episode was manic
- For people with bipolar I and bipolar II
- For adults (18 to 64) and older adults (65+)

## Recommendations derived from these review questions

### *Managing bipolar disorder in primary care*

1.2.5 Offer people with bipolar depression:

- a psychological intervention that has been developed specifically for bipolar disorder and has a published evidence-based manual describing how it should be delivered or
- a high-intensity psychological intervention (cognitive behavioural therapy, interpersonal therapy or behavioural couples therapy) in line with recommendations 1.5.3.1–1.5.3.5 in the NICE clinical guideline on depression.

Discuss with the person the possible benefits and risks of psychological interventions and their preference. Monitor mood and if there are signs of hypomania or deterioration of the depressive symptoms, liaise with or refer the person to secondary care. If the person develops mania or severe depression, refer them urgently to secondary care.

1.2.6 Psychological therapists working with people with bipolar depression in primary care should have training in and experience of working with people with bipolar disorder.

### *Managing bipolar depression in adults in secondary care*

1.6.1 Offer adults with bipolar depression:

- a psychological intervention that has been developed specifically for bipolar disorder and has a published evidence-based manual describing how it should be delivered or
- a high-intensity psychological intervention (cognitive behavioural therapy, interpersonal therapy or behavioural couples therapy) in line with recommendations 1.5.3.1–1.5.3.5 in the NICE clinical guideline on depression.

Discuss with the person the possible benefits and risks of psychological interventions and their preference. Monitor mood for signs of mania or hypomania or deterioration of the depressive symptoms.

1.6.2 Psychological therapists working with people with bipolar depression should have training in, and experience of, working with people with bipolar disorder.

### *Managing bipolar disorder in adults in the longer term in secondary care*

1.7.2 Offer a family intervention to people with bipolar disorder who are living, or in close contact, with their family in line with recommendation 1.3.7.2 in the NICE clinical guideline on psychosis and schizophrenia in adults.

1.7.3 Offer a structured psychological intervention (individual, group or family), which has been designed for bipolar disorder and has a published evidence-based manual describing how it should be delivered, to prevent relapse or for people who have some persisting symptoms between episodes of mania or bipolar depression.

1.7.4 Individual and group psychological interventions for bipolar disorder to prevent relapse should:

- provide information about bipolar disorder
- consider the impact of thoughts and behaviour on moods and relapse
- include self-monitoring of mood, thoughts and behaviour
- address relapse risk, distress and how to improve functioning
- develop plans for relapse management and staying well

- consider problem-solving to address communication patterns and managing functional difficulties.

In addition:

- individual programmes should be tailored to the person's needs based on an individualised assessment and psychological formulation
- group programmes should include discussion of the information provided with a focus on its relevance for the participants.

## Surveillance decision

These review questions should not be updated.

### Cost effectiveness

#### 4-year surveillance summary

A cost-effectiveness analysis derived from an RCT<sup>26</sup> (n=304) found group psychoeducation to be less cost-effective than treatment as usual with group peer support.

#### Topic expert feedback

No topic expert feedback was relevant to this evidence.

#### Impact statement

Evidence suggests that group peer support is more cost-effective than group psychoeducation. Psychoeducation is implicitly covered by recommendation 1.7.4, which deals with group therapies. To impact recommendations, further evidence is required which directly compares different types, or programmes, of group therapy with each other.

New evidence is unlikely to change guideline recommendations.

### Psychological interventions for mania, hypomania and mixed episodes

#### 4-year surveillance summary

A meta-analysis<sup>27</sup> of 9 RCTs found no significant improvements in relapse or depression rates for cognitive behaviour therapy (CBT) in people with bipolar disorder. Significant improvements in one of two mania scales was found for CBT. However, the abstract does not specify follow-up times or comparators for these results. A subgroup analysis found significant improvements in relapse and mania scores for CBT at 6 months.

A pilot RCT<sup>28</sup> (n=67) found the addition of recovery-focused CBT significantly improved personal recovery and increased time to relapse in adults with a recent onset of bipolar disorder compared to treatment as usual alone.

An RCT<sup>29</sup> (n=304) in adults found no significant difference in time to next bipolar episode between group psychoeducation and unstructured peer support treatments.

#### Topic expert feedback

A topic expert commented that psychological care for bipolar disorder has not significantly improved and this may justify a review of the treatments.

A topic expert commented that there are ongoing problems with very low access to structured psychological care in bipolar disorder despite guideline recommendations.

A topic expert highlighted ongoing studies related to psychological treatments for bipolar disorder. These will be considered when published.

#### Impact statement

The new evidence regarding the effects of CBT is inconsistent. From the evidence, it is unclear whether CBT is effective for relapse rates or symptom management. The current recommendations to offer a psychological intervention with an evidence-based manual is unlikely to be impacted by this inconsistent evidence.

Although some efficacy has been indicated, there is currently not enough evidence beyond the one small pilot trial for recovery-focused CBT to impact recommendations.

Group treatments with clinically relevant content are recommended currently. Further evidence directly comparing group treatments with outcomes relevant to recovery and remission are required to impact recommendations.

Topic experts highlighted the limited advancements in psychological care and the

difficulties with access to treatments for this population. The new evidence focusses primarily on CBT and group psychoeducation. Further evidence on different interventions would benefit this population and potentially advance psychological care. Ongoing research in this area will be considered when results publish.

New evidence is unlikely to change guideline recommendations.

### *Combined interventions for mania, hypomania and mixed episodes*

#### **4-year surveillance summary**

A post hoc analysis of an RCT<sup>30</sup> (n=158) found no significant differences between early intervention with combined pharmacological and group psychoeducation treatment compared with standard care. The population consisted of adults with bipolar mania and the sub-analysis compared the effect in young adults (aged 18 to 25) with those over the age 25.

#### **Topic expert feedback**

A topic expert commented that psychological treatments are of greater value in the early stages of bipolar disorder and less clearly of value later in the course of bipolar disorder. However, they also state it is unclear whether the evidence is sufficient to change recommendations.

#### **Impact statement**

Recommendations do not currently specify any particular stage of bipolar disorder at which to offer psychological treatments.

The new evidence is inconsistent with one trial finding no difference for early intervention and one topic expert suggesting psychological treatments have greater value in the early stages of bipolar disorder.

Further evidence is required to investigate the effects of psychological treatments at different stages of bipolar disorder. Topic experts also commented that the evidence relating to early psychological interventions is currently insufficient to change recommendations.

New evidence is unlikely to change guideline recommendations.

### *Management of physical health in adults\**

**Q – 20 For adults with psychosis and schizophrenia, what are the benefits and/or potential harms of behavioural interventions to promote physical activity (all forms, with or without healthy eating)?**

**Q – 21 For adults with psychosis and schizophrenia what are the benefits and/or potential harms of behavioural interventions to promote healthy eating?**

\* These review questions are incorporated from NICE guideline CG178 [psychosis and schizophrenia in adults](#).

## Recommendations derived from these review questions

### *Monitoring physical health in primary care*

- 1.2.10 Develop and use practice case registers to monitor the physical and mental health of people with bipolar disorder in primary care <sup>[10]</sup>.
- 1.2.11 Monitor the physical health of people with bipolar disorder when responsibility for monitoring is transferred from secondary care, and then at least annually. The health check should be comprehensive, including all the checks recommended in recommendation 1.2.12 and focusing on physical health problems such as cardiovascular disease, diabetes, obesity and respiratory disease. A copy of the results should be sent to the care coordinator and psychiatrist, and put in the secondary care records <sup>[10]</sup>.
- 1.2.12 Ensure that the physical health check for people with bipolar disorder, performed at least annually, includes:
- weight or BMI, diet, nutritional status and level of physical activity
  - cardiovascular status, including pulse and blood pressure
  - metabolic status, including fasting blood glucose, glycosylated haemoglobin (HbA1c) and blood lipid profile
  - liver function
  - renal and thyroid function, and calcium levels, for people taking long-term lithium.
- 1.2.13 Identify people with bipolar disorder who have hypertension, have abnormal lipid levels, are obese or at risk of obesity, have diabetes or are at risk of diabetes (as indicated by abnormal blood glucose levels), or are physically inactive, at the earliest opportunity. Follow NICE guidance on [hypertension](#), [lipid modification](#), [prevention of cardiovascular disease](#), [obesity](#), [physical activity](#) and [preventing type 2 diabetes](#) <sup>[10]</sup>.
- 1.2.14 Offer treatment to people with bipolar disorder who have diabetes and/or cardiovascular disease in primary care in line with the NICE clinical guidelines on [type 1 diabetes](#), [type 2 diabetes](#), [type 2 diabetes – newer agents](#) and [lipid modification](#) <sup>[10]</sup>.

### *Monitoring physical health in secondary care*

- 1.8.1 Healthcare professionals in secondary care should ensure, as part of the care programme approach, that people with bipolar disorder receive physical healthcare from primary care as described in recommendations 1.2.10–1.2.14 after responsibility for monitoring has been transferred from secondary care <sup>[10]</sup>.
- 1.8.2 People with bipolar disorder, especially those taking antipsychotics and long-term medication, should be offered a combined healthy eating and physical activity programme by their mental healthcare provider <sup>[10]</sup>.
- 1.8.3 If a person has rapid or excessive weight gain, abnormal lipid levels or problems with blood glucose management, take into account the effects of medication, mental state, other physical health and lifestyle factors in the development of these problems and offer interventions in line with the NICE guidance on [obesity](#), [lipid modification](#) or [preventing type 2 diabetes](#) <sup>[10]</sup>.
- 1.8.4 Routinely monitor weight and cardiovascular and metabolic indicators of morbidity in people with bipolar disorder. These should be audited in the annual team report <sup>[10]</sup>.
- 1.8.5 Trusts should ensure that they take account of relevant guidelines on the monitoring and treatment of cardiovascular and metabolic disease in people with bipolar disorder through board-level performance indicators <sup>[10]</sup>.

<sup>[10]</sup> Adapted from [Psychosis and schizophrenia in adults](#) (NICE clinical guideline 178).

## Surveillance decision

No new information was identified at any surveillance review.



## *Interventions for children and young people*

- Q – 22** For children and young people with bipolar disorder, what are the relative benefits and harms of service-level interventions that are designed specifically for people bipolar disorder?
- Q – 23** For children and young people with bipolar disorder, what are the relative benefits and harms of pharmacological and nutritional interventions for mania, hypomania and mixed episodes?
- Q – 24** For children and young people with bipolar disorder, what are the relative benefits and harms of pharmacological and nutritional interventions for episodes of bipolar depression?
- Q – 25** For children and young people with bipolar disorder, what are the relative benefits and harms of pharmacological and nutritional interventions for long-term management?
- Q – 26** For children and young people with bipolar disorder, what are the relative benefits and harms of psychological and psychosocial interventions for episodes of bipolar depression?
- Q – 27** For children and young people with bipolar disorder, what are the relative benefits and harms of psychological and psychosocial interventions for long-term management?

### **Subquestions**

What amendments, if any, need to be made for (i) particular cultural or minority ethnic groups, (ii) gender, (iii) for children (younger than 13 years) and young people (13 to 18 years)?

### **Recommendations derived from these review questions**

#### *Improving the experience of care for children and young people with bipolar disorder*

- 1.1.2 Follow the recommendations in [general principles of care](#) in the NICE clinical guideline on psychosis and schizophrenia in children and young people to improve the experience of care for children and young people with bipolar disorder.
- 1.11.8 When offering treatment to young people with bipolar disorder, take into account their cognitive ability, emotional maturity, developmental level, their capacity to consent to treatment, the severity of their bipolar disorder and risk of suicide or self-harm or any other risk outlined in recommendation 1.3.5.

#### *Mania*

- 1.11.9 To treat mania or hypomania in young people see NICE's technology appraisal guidance on [aripiprazole for treating moderate to severe manic episodes in adolescents with bipolar I disorder](#) <sup>[21]</sup> and also consider the recommendations for adults in section 1.5 <sup>[22]</sup>. Refer to the [BNF for children](#) to modify drug treatments, be aware of the increased potential for a range of side effects, and do not routinely continue antipsychotic treatment for longer than 12 weeks.
- 1.11.10 Do not offer valproate to girls or young women of childbearing potential.

## Bipolar depression

- 1.11.11 Offer a structured psychological intervention (individual cognitive behavioural therapy or interpersonal therapy) to young people with bipolar depression. The intervention should be of at least 3 months' duration and have a published evidence-based manual describing how it should be delivered.
- 1.11.12 If after 4 to 6 weeks there is no or a limited response to cognitive behavioural therapy or interpersonal therapy, carry out a multidisciplinary review and consider an alternative individual or family psychological intervention.
- 1.11.13 If there is a risk of suicide or self-harm or any other risk outlined in recommendation 1.3.5, carry out an urgent review and develop a risk management plan as outlined in recommendation 1.4.1.
- 1.11.14 After the multidisciplinary review, if there are coexisting factors such as comorbid conditions, persisting psychosocial risk factors such as family discord, or parental mental ill-health, consider:
- an alternative psychological intervention for bipolar depression for the young person, their parents or other family member or
  - an additional psychological intervention for any coexisting mental health problems in line with relevant NICE guidance for the young person, their parents or other family member.
- 1.11.15 If the young person's bipolar depression is moderate to severe, consider a pharmacological intervention in addition to a psychological intervention. Follow the recommendations for pharmacological interventions for adults in [section 1.6](#) <sup>[23]</sup> but refer to the [BNF for children](#) to modify drug treatments, and do not routinely continue antipsychotic treatment for longer than 12 weeks. At 12 weeks, carry out a full multidisciplinary review of mental and physical health, and consider further management of depression or long-term management.

## Long-term management

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

<sup>[21]</sup> At the time of publication (September 2014) aripiprazole had a UK marketing authorisation for up to 12 weeks of treatment for moderate to severe manic episodes in bipolar I disorder in young people aged 13 and older.

<sup>[22]</sup> At the time of publication (September 2014), olanzapine, risperidone, haloperidol, quetiapine, lamotrigine, lithium and valproate did not have a UK marketing authorisation for use in children and young people for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's [Good practice in prescribing and managing medicines and devices](#) for further information.

<sup>[23]</sup> At the time of publication (September 2014), olanzapine, quetiapine and lamotrigine did not have a UK marketing authorisation for use in children and young people for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's [Good practice in prescribing and managing medicines and devices](#) for further information.

## Surveillance decision

These review questions should not be updated.

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### *Pharmacological treatments for mania, hypomania and mixed episodes in children and young people*

#### **4-year surveillance summary**

An RCT<sup>31</sup> (n=81) found significant improvements in Young Mania Rating Scale (YMRS) scores for lithium compared to placebo during an 8 week treatment of manic or mixed

episodes of bipolar I disorder in people aged 7-17 years.

#### **Topic expert feedback**

A topic expert commented that a study is due to be published on aripiprazole in children and adolescents. This will be considered when results are published.

A topic expert commented that there is a debate amongst child and adolescent

psychiatrists about the recommendation to treat children with antipsychotics for only 12 weeks. However, no supporting evidence for longer-term treatment was identified.

**Impact statement**

Evidence suggests efficacy of lithium to treat manic or mixed episodes. However, lithium is currently not licensed for this indication and recommendations advise prescribers to follow relevant professional guidance and take responsibility for use of medications as off-label.

The recommendations only specify treatment with aripiprazole as it is licensed for this age

population. Recommendations advise that other pharmacological treatments can be considered in line with those for adults (this includes lithium) however, none of these are licensed for children and young people.

Topic experts commented that the recommendation to limit pharmacological treatment to 12 weeks should be reviewed. However, no relevant evidence was found to support this view.

New evidence is unlikely to change guideline recommendations.

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*Pharmacological treatments for bipolar depression in children and young people*

**4-year surveillance summary**

An RCT<sup>32</sup> (n=144) found no significant differences in Children’s Depression Rating Scale-Revised (CDRS-R) scores between quetiapine and placebo during an 8 week treatment of bipolar depression in people aged 10-17 years. Secondary outcomes also indicated no significant differences between groups for rates of response and remission. Quetiapine was also associated with treatment-related adverse events.

**Topic expert feedback**

No topic expert feedback was relevant to this evidence.

**Impact statement**

The evidence suggests no benefits for quetiapine to treat bipolar depression in children. No recommendations are currently made for quetiapine in this population.

New evidence is unlikely to change guideline recommendations.

### *Editorial and factual corrections identified during surveillance*

During surveillance of the guideline we identified the following issues with the NICE version of the guideline that should be corrected:

- Footnote 18 for recommendation 1.7.6 states that olanzapine does not have a UK marketing authorisation for use as long-term treatment for bipolar disorder. This footnote is to be removed, as the [SPC](#) for olanzapine now states that it is indicated for the prevention of recurrence in patients with bipolar disorder.
- Recommendations 1.10.34 and 1.10.35 to be updated with footnote links to a new [safety alert \(April 2017\)](#) relating to valproate and developmental disorders in women and girls of childbearing potential. The footnote should change to:  
'See also the [MHRA safety alert on the risks of valproate and developmental disorders](#)'
- Link in recommendations cross-referring to related guidelines to be updated with new guideline numbers:
  - Recommendation 1.1.4 referring to NICE guideline CG45 [antenatal and postnatal mental health: clinical management and service guidance](#) should be updated to NICE guideline CG192 [antenatal and postnatal mental health](#)
  - Recommendation 1.2.14 referring to NICE guideline CG66 [type 2 diabetes](#) should be updated to NICE guideline NG28 [type 2 diabetes in adults: management](#)
  - Recommendation 1.2.14 referring to NICE guideline CG15 [diagnosis and management of type 1 diabetes in children, young people and adults](#) should be updated to NICE guideline NG17 [type 1 diabetes in adults: diagnosis and management](#)
  - Recommendation 1.4.3 referring to NICE guideline CG25 [violence: short-term management for over 16s in psychiatric and emergency departments](#) should be updated to NICE guideline NG10 [violence and aggression: short-term management in mental health, health and community settings](#)
- Incorrect link within recommendation to be amended:
  - Recommendation 1.8.3 referring to NICE guideline PH38 [preventing type 2 diabetes](#) incorrectly directs to NICE guideline CG38 [bipolar disorder](#)

## Research recommendations

### *Prioritised research recommendations*

At 4-year and 8-year surveillance reviews of guidelines published after 2011, we assess progress made against prioritised research recommendations. We may then propose to remove research recommendations from the NICE version of the guideline and the [NICE database for research recommendations](#). The research recommendations will remain in the full versions of the guideline. See NICE's [research recommendations process and methods guide 2015](#) for more information.

These research recommendations were deemed priority areas for research by the Guideline Committee; therefore, at this 4-year surveillance review time point a decision will be taken on whether to retain the research recommendations or stand them down.

We applied the following approach:

- New evidence relevant to the research recommendation was found and an update of the related review question is planned.
  - The research recommendation will be removed from the NICE version of the guideline and the NICE research recommendations database. If needed, a new research recommendation may be made as part of the update process.
- New evidence relevant to the research recommendation was found but an update of the related review question is not planned because the new evidence is insufficient to trigger an update.
  - The research recommendation will be retained because there is evidence of research activity in this area.
- New evidence relevant to the research recommendation was found but an update of the related review question is not planned because evidence supports current recommendations.
  - The research recommendation will be removed from the NICE version of the guideline and the NICE research recommendations database because further research is unlikely to impact on the guideline.
- Ongoing research relevant to the research recommendation was found.
  - The research recommendation will be retained and evidence from the ongoing research will be considered when results are published.
- No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
  - The research recommendation will be removed from the NICE version of guideline and the NICE research recommendations database because there is no evidence of research activity in this area.
- The research recommendation would be answered by a study design that was not included in the search (usually systematic reviews or randomised controlled trials).
  - The research recommendation will be retained in the NICE version of the guideline and the NICE research recommendations database.
- The new research recommendation was made during a recent update of the guideline.
  - The research recommendation will be retained in the NICE version of the guideline and the NICE research recommendations database.

**RR – 01 What is the clinical and cost effectiveness of structured psychological interventions for young people with bipolar depression?**

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

**Surveillance decision**

The research recommendation will be removed from the NICE version of guideline and the NICE research recommendations database because there is no evidence of research activity in this area.

**RR – 02 In the maintenance treatment of bipolar disorder, what is the relative effect on quality of life of lithium, an antipsychotic (haloperidol, olanzapine, quetiapine or risperidone), or a combination of lithium and an antipsychotic?**

New evidence relevant to the research recommendation was found but an update of the related review question is not planned because the new evidence is insufficient to trigger an update.

The evidence included under questions [6-9](#) and [10-13](#) generally support the use of lithium as first-line treatment in adults. Specific data on quality of life was not investigated however studies highlighted the increased risks of adverse events associated with all pharmacological interventions.

**Surveillance decision**

The research recommendation will be retained because there is evidence of research activity in this area.

**RR – 03 What is the clinical and cost effectiveness of fluoxetine combined with olanzapine versus an alternative selective serotonin reuptake inhibitor (SSRI) combined with olanzapine in the treatment of moderate to severe bipolar depression?**

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

**Surveillance decision**

The research recommendation will be removed from the NICE version of guideline and the NICE research recommendations database because there is no evidence of research activity in this area.

**RR – 04 What is the clinical and cost effectiveness of a specialised collaborative care service for people admitted to hospital with bipolar disorder compared with usual treatment delivered by generic care services?**

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

**Surveillance decision**

The research recommendation will be removed from the NICE version of guideline and the NICE research recommendations database because there is no evidence of research activity in this area.

**RR – 05 What is the clinical and cost effectiveness of face-to-face cognitive behavioural therapy (CBT) compared with internet-facilitated CBT in the long-term management of bipolar disorder?**

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

### **Surveillance decision**

The research recommendation will be removed from the NICE version of guideline and the NICE research recommendations database because there is no evidence of research activity in this area.

### *Other research recommendations*

The following research recommendations were not deemed as priority areas for research by the guideline committee.

#### **RR – 06 What is the clinical and cost effectiveness of communication technologies for people with bipolar disorder versus treatment as usual?**

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

### **Surveillance decision**

This research recommendation will be considered again at the next surveillance point.

#### **RR – 07 What is the effectiveness and cost effectiveness of structured psychological therapies with respect to clinical and functional outcomes in particular recovery, quality of life, social functioning and work?**

Ongoing research relevant to the research recommendation was found. One trial is currently investigating the effects of a novel psychological treatment for the improvement of quality of life in late stage bipolar disorder. One trial is investigating the clinical and cost-effectiveness of adapted dialectical behaviour therapy for bipolar mood instability in primary care. A feasibility study is investigating the acceptability of delivering recovery-focused CBT to older adults with bipolar disorder. Also, a trial is investigating the effectiveness of psychoeducation and acceptance and commitment therapy for bipolar disorder. Publication dates are currently not available for any of the ongoing trials.

### **Surveillance decision**

This research recommendation will be considered again at the next surveillance point.

#### **RR – 08 What is the clinical and cost effectiveness of individual CBT versus individual psychoeducation in the long-term management of bipolar disorder?**

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

### **Surveillance decision**

This research recommendation will be considered again at the next surveillance point.

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