Bipolar Disorder (Update)

Bipolar disorder: the assessment and management of bipolar disorder in adults, children and young people in primary and secondary care

National Clinical Guideline Number X

National Collaborating Centre for Mental Health
Commissioned by the
National Institute for Health and Care Excellence

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ACKNOWLEDGEMENTS

The Guideline Development Group and the National Collaborating Centre for Mental Health review team would like to thank the **Clinical Guidelines Technical Support Unit** and specifically the following people:

Professor Tony Ades (PhD)
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Dr Sofia Dias (PhD)
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The Guideline Development Group and the National Collaborating Centre for Mental Health review team would also like to thank the **Trimbos Instituut** and specifically the following people:

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APPENDICES

1 PREFACE

This guideline, which updates the 2006 NICE guideline (NCCMH, 2006b; NICE, 2006), has been developed to advise on the assessment and management of bipolar disorder in adults, children (aged under 13 years) and young people (aged 13 to 18 years) in primary and secondary care. It applies to people with bipolar I, bipolar II, mixed affective and rapid cycling disorders. Non-bipolar affective disorders are not covered because these are addressed by other guidelines.

Since the publication of the previous guideline on bipolar disorder in 2006, there have been some important advances in our knowledge of the care pathway and treatment approaches that are most likely to benefit people with bipolar disorder. All areas of the 2006 guideline have therefore been updated. It should be noted that because the NICE guideline on *Service User Experience in Adult Mental Health* (NICE, 2011c) covers the experience of care for people accessing mental health services (including people with bipolar disorder), this guideline update does not specifically cover service user experience of care; it does however include a review of carers' experience of care because carer experience was not the explicit focus of *Service User Experience in Adult Mental Health.* This guideline is published contemporaneously with *Psychosis and Schizophrenia in Adults* (NICE, 2014) and *Psychosis and Schizophrenia in Children and Young People* (NICE, 2013c) and the Guideline Development Group (GDG) for the guideline on bipolar disorder sought to maintain consistency with both of these guidelines where appropriate – the method of incorporation and adaptation (see Section 3.7) was used where relevant, and in each case full details are provided in the relevant chapter.

The guideline recommendations have been developed by a multidisciplinary team of healthcare professionals, people with bipolar disorder and guideline methodologists after careful consideration of the best available evidence. It is intended that the guideline will be useful to clinicians and service commissioners in providing and planning high-quality care for people with bipolar disorder (see Appendix 1 for more details on the scope of the guideline).

Although the evidence base is rapidly expanding, there are a number of major gaps. The guideline makes a number of research recommendations specifically to address gaps in the evidence base. In the meantime, it is hoped that the guideline will assist clinicians, and people with bipolar disorder and their carers by identifying the merits of particular treatment approaches where the evidence from research and clinical experience exists.

1.1 NATIONAL CLINICAL GUIDELINES

1.1.1 What are clinical guidelines?

Clinical guidelines are 'systematically developed statements that assist clinicians and service users in making decisions about appropriate treatment for specific conditions' (Mann, 1996). They are derived from the best available research evidence, using predetermined and systematic methods to identify and evaluate the evidence relating to the specific condition in question. Where evidence is lacking, the guidelines include statements and recommendations based upon the consensus statements developed by the Guideline Development Group (GDG).

Clinical guidelines are intended to improve the process and outcomes of healthcare in a number of different ways. They can:

- provide up-to-date evidence-based recommendations for the management of conditions and disorders by healthcare professionals
- be used as the basis to set standards to assess the practice of healthcare professionals
- form the basis for education and training of healthcare professionals
- assist service users and their carers in making informed decisions about their treatment and care
- improve communication between healthcare professionals, service users and their carers
- help identify priority areas for further research.

1.1.2 Uses and limitations of clinical guidelines

Guidelines are not a substitute for professional knowledge and clinical judgement. They can be limited in their usefulness and applicability by a number of different factors: the availability of high-quality research evidence, the quality of the methodology used in the development of the guideline, the generalisability of research findings and the uniqueness of individuals.

Although the quality of research in this field is variable, the methodology used here reflects current international understanding on the appropriate practice for guideline development (AGREE Collaboration, 2003), ensuring the collection and selection of the best research evidence available and the systematic generation of treatment recommendations applicable to the majority of people with bipolar disorder. However, there will always be some people and situations where clinical guideline recommendations are not readily applicable. This guideline does not, therefore, override the individual responsibility of healthcare professionals to make appropriate decisions in the circumstances of the individual, in consultation with the person with bipolar disorder or their carer.

In addition to the clinical evidence, cost-effectiveness information, where available, is taken into account in the generation of statements and recommendations in

clinical guidelines. While national guidelines are concerned with clinical and cost effectiveness, issues of affordability and implementation costs are to be determined by the National Health Service (NHS).

In using guidelines, it is important to remember that the absence of empirical evidence for the effectiveness of a particular intervention is not the same as evidence for ineffectiveness. In addition, and of particular relevance in mental health, evidence-based treatments are often delivered within the context of an overall treatment programme including a range of activities, the purpose of which may be to help engage the person and provide an appropriate context for the delivery of specific interventions. It is important to maintain and enhance the service context in which these interventions are delivered, otherwise the specific benefits of effective interventions will be lost. Indeed, the importance of organising care in order to support and encourage a good therapeutic relationship is at times as important as the specific treatments offered.

1.1.3 Why develop national guidelines?

The National Institute for Health and Care Excellence (NICE) was established as a Special Health Authority for England and Wales in 1999, with a remit to provide a single source of authoritative and reliable guidance for service users, professionals and the public. NICE guidance aims to improve standards of care, diminish unacceptable variations in the provision and quality of care across the NHS, and ensure that the health service is person-centred. All guidance is developed in a transparent and collaborative manner, using the best available evidence and involving all relevant stakeholders.

NICE generates guidance in a number of different ways, four of which are relevant here. First, national guidance is produced by the Technology Appraisal Committee to give robust advice about a particular treatment, intervention, procedure or other health technology. Second, NICE commissions public health intervention guidance focused on types of activity (interventions) that help to reduce people's risk of developing a disease or condition, or help to promote or maintain a healthy lifestyle. Third, NICE commissions the production of national clinical guidelines focused upon the overall treatment and management of a specific condition. To enable this latter development, NICE has established four National Collaborating Centres in conjunction with a range of professional organisations involved in healthcare. Fourth, NICE has a new responsibility, from April 2013, to develop guidelines and quality standards for social care in England. This provides an opportunity to apply an evidence-based system to decision-making in the social care sector, similar to that provided for the NHS. It will also allow guidelines to be produced that promote better integration between health, public health and social care services.

1.1.4 From national clinical guidelines to local protocols

Once a national guideline has been published and disseminated, local healthcare groups will be expected to produce a plan and identify resources for

implementation, along with appropriate timetables. Subsequently, a multidisciplinary group involving commissioners of healthcare, primary care and specialist mental health professionals, service users and carers should undertake the translation of the implementation plan into local protocols, taking into account both the recommendations set out in this guideline and the priorities in the National Service Framework for Mental Health (Department of Health, 1999) and related documentation. The nature and pace of the local plan will reflect local healthcare needs and the nature of existing services; full implementation may take a considerable time, especially where substantial training needs are identified.

1.1.5 Auditing the implementation of clinical guidelines

This guideline identifies key areas of clinical practice and service delivery for local and national audit. Although the generation of audit standards is an important and necessary step in the implementation of this guidance, a more broadly-based implementation strategy will be developed. Nevertheless, it should be noted that the Care Quality Commission in England, and the Healthcare Inspectorate Wales, will monitor the extent to which commissioners and providers of health and social care and Health Authorities have implemented these guidelines.

1.2 THE NATIONAL BIPOLAR DISORDER (UPDATE) GUIDELINE

1.2.1 Who has developed this guideline?

This guideline has been commissioned by NICE and developed within the National Collaborating Centre for Mental Health (NCCMH). The NCCMH is a collaboration of the professional organisations involved in the field of mental health, national service user and carer organisations, a number of academic institutions and NICE. The NCCMH is funded by NICE and is led by a partnership between the Royal College of Psychiatrists and the British Psychological Society's Centre for Outcomes Research and Effectiveness, based at University College London.

The GDG was convened by the NCCMH and supported by funding from NICE. The GDG included people with bipolar disorder and carers, and professionals from psychiatry, clinical psychology, general practice, nursing, occupational therapy, psychiatric pharmacy, and the private and voluntary sectors.

Staff from the NCCMH provided leadership and support throughout the process of guideline development, undertaking systematic searches, information retrieval, appraisal and systematic review of the evidence. Members of the GDG received training in the process of guideline development from NCCMH staff, and the service users and carers received training and support from the NICE Public Involvement Programme. The NICE Guidelines Technical Adviser provided advice and assistance regarding aspects of the guideline development process.

All GDG members made formal declarations of interest at the outset, which were updated at every GDG meeting. The GDG met a total of 13 times throughout the process of guideline development. It met as a whole, but key topics were led by a national expert in the relevant topic. The GDG was supported by the NCCMH technical team, with additional expert advice from special advisers where needed. The group oversaw the production and synthesis of research evidence before presentation. All statements and recommendations in this guideline have been generated and agreed by the whole GDG.

1.2.2 For whom is this guideline intended?

This guideline will be relevant for adults and young people with bipolar disorder and covers the care provided by primary, community, secondary, tertiary and other healthcare professionals who have direct contact with, and make decisions concerning the care of, adults and young people with bipolar disorder.

The guideline will also be relevant to the work, but will not cover the practice, of those in:

- occupational health services
- social services
- the independent sector.

1.2.3 Specific aims of this guideline

The guideline makes recommendations for the assessment and management of bipolar disorder. It aims to:

- improve access and engagement with treatment and services for people with bipolar disorder
- evaluate the role of specific psychological, psychosocial and pharmacological interventions in the treatment of bipolar disorder
- evaluate the role of psychological and psychosocial interventions in combination with pharmacological interventions in the treatment of bipolar disorder
- evaluate the role of specific service-level interventions for people with bipolar disorder
- integrate the above to provide best-practice advice on the care of individuals throughout the course of their treatment
- promote the implementation of best clinical practice through the development of recommendations tailored to the requirements of the NHS in England and Wales.

1.2.4 The structure of this guideline

The guideline is divided into chapters, each covering a set of related topics. The first three chapters provide a general introduction to guidelines, an introduction to the topic of bipolar disorder and to the methods used to develop them. Chapter 4 to Chapter 10 provide the evidence that underpins the recommendations about the treatment and management of bipolar disorder.

Each evidence chapter begins with a general introduction to the topic that sets the recommendations in context. Depending on the nature of the evidence, narrative reviews or meta-analyses were conducted, and the structure of the chapters varies accordingly. Where appropriate, details about current practice, the evidence base and any research limitations are provided. Where meta-analyses were conducted, information is given about both the interventions included and the studies considered for review. Clinical summaries are then used to summarise the evidence presented. Finally, recommendations related to each topic are presented at the end of each chapter. Full details about the included studies can be found in Appendices 11, 12, 16, 18, 22 and 26. Where meta-analyses were conducted, the data are presented using forest plots in Appendix 13, Appendix 21, Appendix 25 and Appendix 29. See Table 1 for details of what is included in the appendices.

Table 1: Clinical and economic evidence appendices

Evidence tables for economic studies	Appendix 31, 32, 33
Clinical study characteristics tables	Appendix 11, 12, 16, 19, 23, 27
Clinical evidence forest plots	Appendix 13, 21, 25, 29
GRADE evidence profiles	Appendix 14, 18, 22, 26, 30

2 INTRODUCTION TO BIPOLAR DISORDER

2.1 THE DISORDER

2.1.1 Overview

The concept of bipolar disorder grew out of Emil Kraepelin's classification of what he termed as 'manic depressive insanity' at the end of the 19th century. In 1957 Leonhard coined the term 'bipolar' for those patients who experienced both depression and mania, the polar opposites of mood. In 1966 Angst and Perris independently demonstrated that unipolar depression and bipolar disorder could be differentiated in terms of clinical presentation, evolution, family history and therapeutic response. Their ideas became assimilated in both the two main modern systems of classification for the diagnosis of mental disorder: the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) published by the American Psychiatric Association and the *International Classification of Disease* (ICD) published by the World Health Organization. In 1980 the name bipolar disorder was adopted to replace the older term manic depressive psychosis because not all people who experience mania and depression become psychotic.

Nowadays, bipolar disorder is conceptualised as a cyclical mood disorder involving periods of profound disruption to mood and behaviour, interspersed with periods of full recovery or much improved function. The key feature of bipolar disorder is the experience of hypomania or mania – grandiose and expansive or irritable affect associated with increased drive and decreased sleep, which ultimately can culminate in psychosis and exhaustion if left untreated. There is some heterogeneity between the major diagnostic classification systems in the criteria for bipolar disorder (see Section 2.3 below). ICD-10 requires two discrete mood episodes, at least one of which must be hypomania or mania. In DSM-V a single episode of mania without any episode of depression, or a single episode of hypomania with one major depressive episode, would warrant a diagnosis of bipolar disorder.

The bipolar spectrum

Far from being a discrete diagnostic entity, there is increasing recognition of a spectrum of bipolar disorders that ranges from marked and severe mood disturbance into milder mood variations that become difficult to distinguish from normal mood fluctuation. In terms of classification, in DSM-V a distinction is drawn between bipolar I disorder, in which the person experiences full-blown manic episodes (most commonly interspersed with episodes of major depression), and bipolar II disorder, in which the person has depressive episodes and less severe manic symptoms, classed as hypomanic episodes (ICD-10 does not draw this distinction). Cyclothymia is the term given to recurrent hypomanic episodes and subclinical episodes of depression. The depressive episodes do not reach sufficient severity or duration to merit a diagnosis of a major depressive episode, but mood

disturbance is a continuing problem and interferes with everyday functioning almost continuously for at least 2 years. 'Softer' forms of bipolar disorder have been proposed, including recurrent depressive episodes with a hyperthymic temperament and a family history of bipolar disorder (Akiskal et al., 2000), or recurrent depression with antidepressant-induced mania. However, these are not currently part of official diagnostic classifications. There are problems with establishing satisfactory inter-rater reliability in the assessments of the 'softer' end of the bipolar spectrum. The clinical utility of these proposed diagnoses has yet to be established and there is currently no indication whether treatment is necessary or effective. Furthermore the bipolar spectrum, apart from bipolar I and bipolar II disorder, does not form part of the scope for this guideline and recommendations on its management will not be made.

2.1.2 Symptoms and presentation

Depression

Although mania or hypomania are the defining characteristics of bipolar disorder, throughout the course of the illness depressive symptoms are more common than manic symptoms. People with bipolar disorder spend a substantial proportion of time with syndromal or subsyndromal depressive symptoms. The outcome of a 12-year prospective longitudinal study, in which 146 patients with bipolar I disorder completed weekly mood ratings, reported that depressive symptoms were three times more common than manic or hypomanic symptoms (Judd et al., 2002a). Patients spent 32% of weeks with symptoms of depression. In a separate study of 86 patients with bipolar II disorder this proportion was much higher at 50% (Judd et al., 2003a). A similar study by the Stanley Foundation Bipolar Network monitored 258 bipolar patients (three quarters of whom had bipolar I disorder) for 1 year using the National Institute for Mental Health (NIMH) Life Chart Method (LCM). On average, patients spent 33% of the time depressed and a large proportion (60%) had four or more mood episodes in a year (Post et al., 2003). However, the proportion of time spent depressed did not differ between those with bipolar I disorder and those with bipolar II disorder. Four- and 8-year follow-up studies of children and young people with bipolar I disorder (aged from 7 to 17 years) in contact with mental health services in the USA suggest that 60% of the time they were symptomatic with mood symptoms with more mood cycling between depression and mania than is usually seen in adult follow-up studies (Birmaher et al., 2009; Geller et al., 2008). People with bipolar I disorder continued to show a similar course even after reaching age 18 years.

Major depressive episodes in bipolar disorder are similar to those experienced in unipolar major depression. People experience depressed mood and a profound loss of interest in activities, coupled with other symptoms such as fatigue, weight loss or gain, difficulty sleeping or staying awake, psychomotor slowing, feelings of worthlessness, excessive guilt and suicidal thoughts or actions. Sometimes symptoms of mania such as elation or racing thoughts are seen briefly for a few hours at a time in bipolar depression but not always (Bauer et al., 2005). For those

presenting with a first episode of depression, it may not be possible to distinguish between those who will go on to have recurrent unipolar depression and those who will develop bipolar disorder. Individuals experiencing a first episode of depression, who have a family history of bipolar disorder, may be at increased risk of developing bipolar disorder. Subsyndromal depressive symptoms are common in people with bipolar disorder (especially those with bipolar II disorder) and are often associated with significant interpersonal or occupational disability. A prospective study in 253 patients (94% with bipolar I disorder) followed over 18 months demonstrated that subsyndromal depressive symptoms had marked effects on role performance and interpersonal behaviour, while detrimental effects of mild hypomania symptoms were confined to interpersonal friction (Morriss et al., 2013).

The treatment of these chronic, low-grade depressive symptoms may seem less urgent and important to clinicians and carers than the management of the more dramatic, alarming and challenging symptoms of mania. However, subsyndromal depression may be more distressing in the long-term and may carry a greater risk of suicide. So the treatment of these chronic depressive symptoms is therefore of major importance, but it is also a substantial treatment challenge.

The risk of suicide is greatly elevated during depressive episodes. Approximately 17% of people with bipolar I disorder and 24% with bipolar II disorder attempt suicide during the course of their illness (Rihmer & Kiss, 2002). Around 8% men and 5% women with bipolar disorder died by suicide at 40-year follow-up (Angst et al., 2003; Nordentoft et al., 2011). Annually around 0.4% of people with bipolar disorder will die by suicide, which is vastly greater than the international population average of 0.017% (Tondo et al., 2007). The standardised mortality ratio (SMR) for suicide in bipolar disorder is estimated to be 15 for men and 22.4 for women in those who have been hospitalised for bipolar disorder (Osby et al., 2001). Most suicide attempts and most completed suicides occur in the depressed phase of the illness and those with bipolar II disorder are at especially high risk (Baldessarini et al., 2003). Compared with other mental disorders, the risk of completed suicide is higher in those with recent contact with mental health services (Clements et al., 2013) possibly because the condition causes such dramatically changeable mental states. The extreme contrasts between the euphoria of mania and deep depression makes bipolar disorder all the harder to endure. Other reasons for the higher risk of suicide include the failure to recognise the severity of depression (Isometsä, 2005), and impulsivity (rapid actions with little planning or consideration of the consequences) coupled with hopelessness (Swann et al., 2008).

Mania and hypomania

The longitudinal study of bipolar symptomatology mentioned above reported that people with bipolar I disorder experienced syndromal or subsyndromal manic or hypomanic symptoms approximately 9% of the time over 12 years (Judd et al., 2002a). For those with bipolar II disorder, approximately 1% of weeks were spent hypomanic (Judd et al., 2003a). Similarly, the 1-year prospective follow-up study conducted by the Stanley Foundation Bipolar Network reported that on average

syndromal manic symptoms were experienced approximately 10% of the time (Post et al., 2003).

However, there was no significant difference in the proportion of time spent with manic symptoms between people with bipolar I or II disorder. The majority of individuals with bipolar disorder will experience both manic and depressive episodes throughout the course of their illness, although one epidemiological survey identified a subpopulation of approximately 20% who had never experienced a depressive episode (Kessler et al., 1997). For those who have both depressive and manic episodes, the evidence above indicates that mania is much less common than depression in those with bipolar disorder. However, the extreme behaviours associated with it can be devastating and people with mania often require hospitalisation to minimise harm to themselves or others. Some individuals, however, even when well, may disagree with clinicians and carers about how necessary involuntary hospitalisations were for their own recovery, reporting that detention under section is distressing, is of little therapeutic value and can cause long-term emotional trauma.

People in the manic phase exhibit expansive, grandiose affect, which may be predominantly euphoric or irritable. Although dysphoric mood is more frequently associated with depressive episodes, factor analytic studies of symptoms in those with pure mania suggest dysphoric mood (such as depression, guilt and anxiety) can be prominent during manic episodes at times (Cassidy & Carroll, 2001; Cassidy et al., 1998). In bipolar I disorder, mania symptoms and depression symptoms appear to be independent except in full episodes (Johnson et al., 2011) when some symptoms of mania can be seen in bipolar depression and symptoms of depression are often seen in mania.

The clinical presentation of mania is marked by several features, which can lead to significant impairment of functioning. These may include inflated self-esteem and disinhibition, for example, over-familiar or fractious and outspoken behaviour. To the observer, an individual with mania might appear inappropriately dressed, unkempt or dishevelled. The person may have an urge to talk incessantly, and their speech may be pressured, faster or louder than usual, and difficult for others to interrupt. In severe forms of mania, the flight of ideas can render speech incoherent and impossible to understand. The person may find that racing thoughts or ideas can be difficult to piece together into a coherent whole. People with mania often describe increased activity, productivity and creativity during the early stages of mania, which is normally, enjoyable, satisfying and rewarding. However, as the episode progresses, severe distractibility, restlessness, and difficulty concentrating can render the completion of tasks impossible. A decreased need for sleep and sleeping less without feeling tired is often experienced. After prolonged periods with little or no sleep the individual can become physically exhausted with no desire to rest. The person may find it hard to stay still or remain seated and other forms of psychomotor restlessness may be apparent, such as excessive use of gestures or

fidgeting. Appetite may also increase, although food intake does not always increase to compensate.

There might be an increase in impulsive risk-taking behaviour in mania with a high potential for negative consequences. However, there is no excess risk of bipolar disorder with violent crime except when it is comorbid with substance-use disorders (Fazel et al., 2010). There is an increase risk of shoplifting, impulsive overspending and motor accidents in bipolar disorder, particularly during mania (Blanco et al., 2008; Chamorro et al., 2012; Christopher et al., 2012). Libido may rise, with increased interest in sexual activity, which may culminate in risky sexual practices. In severe episodes individuals may develop psychotic symptoms such as grandiose or religious delusions and mood-congruent hallucinations. For example, a person with religious delusions may believe that they are on a mission from God, are Jesus Christ or can hear the voice of God. Delusions when manic are very compelling. Later they may struggle to make sense of religious delusions, in particular, find the memory of them distressing or disturbing, or regret that their belief in these 'visions' fading with the passage of time.

Alternatively, persecutory delusions may develop, but are usually consistent with a general grandiose theme such as the belief that others are actively trying to thwart the person's plans or remove their power. Full insight is lost in mania – the individual is unaware that their behaviour is abnormal and does not consider him or herself to be in need of treatment. Clinical interventions may be seen as attempts to undermine the person's esteem and power and could provoke or worsen irritability even in those who are predominantly euphoric. All the features reported in mania – except psychotic symptoms – can also occur in hypomania to a less severe extent. Generally insight is better preserved, although the person may not feel in need of help. Increased productivity and decreased need for sleep can be experienced as a positive enhancement of everyday functioning. Hypomania is accompanied by a change in functioning that is not characteristic of the person when well and the change is noticed by others, but it is not associated with marked impairment in social or occupational function. According to the DSM-V diagnostic criteria, symptoms must last at least 4 days to merit the diagnosis of a hypomanic episode. However, there is considerable debate about how long hypomanic symptoms should be present to merit a diagnosis of bipolar II disorder (see Section 2.3.2 below).

Mixed states

Mixed affective episodes occur when the symptoms of depression and mania or hypomania occur at the same time to a marked degree with a change in overall function. In DSM-V, a manic or hypomanic episode must be present together with three of a list of six symptoms out of the nine used for major depression (depressed mood, diminished interest or pleasure, psychomotor retardation observable to others, fatigue or loss of energy, feelings of worthlessness or guilty and recurrent thoughts of death or suicide) at the same time during the manic or hypomanic episode. Alternatively a major depressive episode must be present with at least three of the seven symptoms required for a manic or hypomanic episode (American

Psychiatric Association, 2013). Previously in DSM-IV criteria for a mixed affective episode are met for a depressive episode and a manic episode nearly every day for at least 1 week (American Psychiatric Association, 1994). People with bipolar disorder rarely meet these criteria so little research on treatment of mixed affective episodes has been performed. It is common to see some hypomanic symptoms in a depressive episode and some depression symptoms in a hypomanic or manic episode (Bauer et al., 2005), and based on these data, the change in criteria from DSM-IV to DSM-V would double the number of episodes described as mixed affective episodes. There is a danger that the diagnosis of mixed affective episodes becomes non-specific and people are misdiagnosed with bipolar disorder because of the relaxed diagnostic criteria for mixed affective episodes (Mahli, 2013). Mixed affective episodes may also be misdiagnosed as anxiety or personality disorders, as they may present with perplexity, anxiety and agitation and only prospective observation reveals the mixed affective bipolar nature of the mental state (Hantouche et al., 2006). Furthermore, there is little evidence that the presence of such symptoms of the other pole changes management. However, the combination of morbid, depressed affect with over activity and racing thoughts makes mixed affective states a risk in terms of suicide and impulsive acts with the potential for harm (Rihmer & Kiss, 2002). People who experience mixed affective episodes also tend to experience rapid cycling (Judd et al., 2002a).

Rapid cycling

There is a large amount of variation in how often people experience mood episodes and no criteria exist to define 'normal' cycle frequency. Some have discrete episodes that occur rarely (for example, no more than one episode per year) with full recovery in between, others experience episodes more often, and some may not fully recover between episodes. A subset of individuals have rapid cycling bipolar disorder, which is defined as the experience of at least four syndromal depressive, manic, hypomanic or mixed episodes within a 12-month period. Ultra-rapid and ultra-ultra-rapid (or ultradian) cycling variants have also been identified, in which mood fluctuates markedly from week to week or even within the course of a single day (Kramlinger & Post, 1996). Whether the differentiation of subtypes of rapid cycling is of clinical significance is currently not known. A cross-national study in over 54,000 respondents found that rapid cycling participants had a younger age of onset, more anxiety disorder, greater severity and impairment from depressive symptoms, greater impairment from mania and hypomania, and an increased likelihood of using health services than participants with no history of rapid cycling bipolar disorder (Lee et al., 2010). However, there were no clear cut associations with sociodemographic factors, childhood, family or other psychiatric comorbidity factors in this sample or another large US community sample (Lee et al., 2010; Nierenberg et al., 2010). Although rapid cycling has a reputation for being difficult to treat, most follow-up studies also suggest more than half of those with rapid cycling bipolar disorder will no longer be rapid cycling after 2 years. Furthermore there is little evidence from randomised controlled trials that the presence of rapid cycling requires a different treatment approach of a mood episode than non-rapid cycling in the same episode. The issue of whether antidepressant use increases cycling

frequency as well as switches into mania and hypomania remain unresolved, partly because frequent cycling represents significant challenges in terms of valid and reliable measurement of outcome and analysis.

2.1.3 Incidence and prevalence

In 2010, bipolar disorder was one of the most prevalent of disabling health conditions ranked 18th in all health conditions in years lived with disability in the world (Vos et al., 2012). Community-based epidemiological studies reporting lifetime prevalence rates in European studies vary from 0.1% to 2.4% (Faravelli et al., 1990; Pini et al., 2005; Regeer et al., 2004; Szadoczky et al., 1998; ten Have et al., 2002). However, the most recent and largest study in the USA confirms the most widely accepted estimates that lifetime and 12-month prevalence of bipolar I disorder are 1.0% and 0.6% respectively (Merikangas et al., 2007b).

Estimates of the lifetime prevalence of bipolar II disorder in the community also vary widely owing to differences in diagnostic practices both over time and geography, with European studies producing estimates between 0.2 and 2.0% (Faravelli et al., 1990; Szadoczky et al., 1998). The most widely accepted estimate of lifetime prevalence of bipolar II disorder in adults based on a cross-national epidemiological study of 11 countries is 0.4% (Merikangas & Lamers, 2012).

Measurement of the incidence of bipolar disorder is fraught with difficulty as subclinical symptoms of the disorder are common, there can be substantial delays of many years duration before presentation to services, and presentation to services is often initially with depression, ill-defined psychotic symptoms or an impulse control problem so the nature of the bipolar disorder is only diagnosed some years after the initial presentation. Most recent estimates based on integrated primary records from 800,000 patients in the Netherlands suggest an overall incidence rate of 0.70/10,000 person-years (95% confidence intervals 0,57-0.83) with incidence rates of 0.43 for bipolar I disorder (95% confidence intervals 0.34-0.55) and 0.19 for bipolar II disorder (95% confidence intervals 0.13-0.27) (Kroon et al., 2013).

Age at onset

Bipolar disorder has a fairly early age of onset, with the first episode usually occurring before the age of 30 years, although there may be a second smaller peak of onset of bipolar I and II disorder in later life (45 to 54 years) (Kroon et al., 2013; Merikangas et al., 2007b). A peak in onset rate occurs between the ages of 15 and 19 years according to a recent large-scale US survey and Dutch primary care records study (Kroon et al., 2013; Merikangas et al., 2007b). A large retrospective study of patients with bipolar disorder reported that there was an average 8 years' delay from a person's first recollected mood episode to receiving a diagnosis of bipolar disorder (Mantere et al., 2004). A review of 14 prospective and retrospective studies suggest that one reason for this is that the period between first symptoms and diagnosis tends to be characterised by a long period of gradual build up of intensity and duration of subsyndromal symptoms such as depression, irritability and

switching from depression to brief periods of manic symptoms short of a full episode (Howes et al., 2011).

Gender

Bipolar I disorder occurs approximately equally in both sexes (Kroon et al., 2013; Lloyd et al., 2005). There is disputed evidence that bipolar II disorder is more common in females than males. Large samples of patients with bipolar disorder found a significantly higher incidence of bipolar II disorder in women than men (Angst et al., 2003; Baldassano et al., 2005) but these studies have been criticised for using broad criteria for measurement of bipolar II disorder. In a general population survey using DSM-III-R criteria (which require a minimum of 4 days of hypomanic symptoms for a hypomanic episode) there was no reported gender difference in the prevalence of bipolar II disorder (Szadoczky et al., 1998). A recent large-scale primary record study also suggests an equal gender distribution between men and women (Kroon et al., 2013). For some women, the experience of psychosis in the postnatal period may be the first indicator of bipolar illness. In studies of mothers with bipolar affective puerperal psychosis, around two thirds went on to experience a non-puerperal mood episode (Blackmore et al., 2013; Robertson et al., 2005). The risk of puerperal psychosis in future pregnancies was also significant with 57% of those who had further children experiencing another episode postnatally. Likewise, for those with an established illness, childbirth brings an increased risk of puerperal psychosis (Chaudron & Pies, 2003) and represents a substantial clinical challenge.

Ethnic minorities

There is evidence of an increased incidence of bipolar disorder in people from black and minority ethnic groups. The Aesop Study (Lloyd et al., 2005), which examined the incidence of bipolar disorder in three cities in the UK, reported a higher incidence among black and minority ethnic groups than in a comparable white population and this finding is consistent with other UK-based studies (Leff et al., 1976; Van Os et al., 1996). The evidence for the increased incidence of bipolar disorder in black and minority ethnic groups is similar to that for schizophrenia. In addition to the increased prevalence of bipolar disorder in these populations, there is also evidence of differences in the manner of presentation. Kennedy and colleagues (2004) in an epidemiological study of first presentations of bipolar disorder in the UK, which compared African and African-Caribbean groups with white Europeans, suggested that the former were more likely to present with a first episode of mania (13.5% versus 6%). The African and African-Caribbean groups were also more likely to present with severe psychotic symptoms when first presenting with mania. A study in the USA looking at the experience of African Americans with bipolar disorder (Kupfer et al., 2005) reported that they were more likely to be hospitalised than white populations (9.8% versus 4.4%) and have a higher rate of attempted suicide (64% versus 49%). Another American study, from the Veterans' Health Administration System (Kilbourne et al., 2005), looked at the clinical presentations of people from minority ethnic groups with bipolar disorder. Again, this confirmed a picture of increased number of psychotic episodes (37% versus 30%) along with

increased use of cocaine or alcohol. They also reported that people from black and minority ethnic groups were more likely to be formally admitted to hospital.

The mechanisms underlying the increased prevalence and increased rates of mania and drug misuse among people from black and minority ethnic groups presenting to services with bipolar disorder are not well understood, although it has been suggested that social exclusion and lack of social support may be important factors (Bentall, 2004; Leff, 2001). However, it is possible that many of the features described above may be associated with later presentation of the disorder resulting, in part, from the difficulties that people from black and minority ethnic groups have in accessing services. Kennedy and colleagues (2004), also raised the possibility that the nature of the problems on initial presentation may contribute to greater diagnostic difficulties and the possibility that people from black and minority ethnic groups may be seen as having schizoaffective or other schizophrenia spectrum disorders rather than bipolar disorder. Although there is now reasonable evidence to show an increased incidence and a difference in the style of presentation of people from black and minority ethnic groups to services, there is little evidence on the outcomes of treatment interventions. Clinicians responsible for the assessment and provision of services for people with severe mental illness should be aware of the increased incidence of bipolar disorder in black and minority ethnic groups. The presentation is more likely to be accompanied by mania, possible psychotic symptoms and associated suicidal behaviour.

Treatment of people with learning difficulties with bipolar disorder

Some studies report an association between extremes of intelligence, both the lowest level of intelligence and higher than average intelligence and the future onset of bipolar disorder (Gale et al., 2013), but others (Sorensen et al., 2012) have not confirmed this. In contrast to early reports, bipolar disorder is found at a similar rate in both neurodevelopmental disorder and Down's syndrome to the general population (Morgan et al., 2008). However, establishing a diagnosis of a mental disorder in people with an intellectual disability can be difficult when the individual's capacity to participate in a clinical assessment is limited (White et al., 2005). The clinical features of mania in individuals with learning difficulties can be identified with the aid of informants and clinical observation but such people can be particularly sensitive to adverse effects of medication. Given the uncertainty around treatment options, the most important point is that the disorder is appropriately recognised in people with a learning difficulty and treated effectively.

2.2 AETIOLOGY

Despite its long history, little is known about what causes bipolar disorder. Recent research has concentrated on identifying possible biological underpinnings of the disorder including genetic components, neurohormonal abnormalities and structural brain differences, and psychosocial research, including life events and social rhythm (Malkoff-Schwartz et al., 1998), and the behavioural activation system (Depue et al., 1987). However, there is no overarching explanation and the

heterogeneous clinical presentation of bipolar disorder suggests the possibility that a number of different mechanisms might be involved.

2.2.1 Genetics

Bipolar disorder occurs substantially more often in families and twins, indicating that the risk for developing it is often inherited. In 60% or more people, there is evidence of heritability of mood disorder from other family members (Baldessarini et al., 2012) suggesting a potentially large genetic contribution to the illness. However both the genetics and the expression of these genetics (phenotype) in terms of the presentation of a person's illness are complex. The inheritance pattern is not simple and is not consistent with a single gene model of bipolar disorder, except in a small proportion of families. Instead it is likely that many genes of small effect accrue to convey susceptibility to a spectrum of psychiatric illnesses, including bipolar disorder, therefore families may have individuals with psychiatric disorders of many different types. There may also be genes that reduce the risk of developing bipolar disorder. Increasingly large-scale association studies point to a complex picture that may only be understood in terms of gene x environment interactions.

Familial inheritance and linkage studies

Family studies report that first-degree relatives of an individual with bipolar disorder face a lifetime risk of developing the illness that is five to ten times greater than the general population (Craddock & Jones, 2001). However, they also face approximately double the risk of developing unipolar major depression, suggesting the two disorders may share some degree of genetic susceptibility. Studies in monozygotic and dizygotic twins where at least one twin is affected by bipolar disorder provide further support for genetic transmission. Monozygotic twins of bipolar probands face a 40 to 70% risk of developing bipolar disorder and the concordance rate of approximately 60% is markedly higher than that for dizygotic twins (Craddock & Jones, 2001). The difference in concordance rates between monozygotic and dizygotic twins can be used to estimate the size of the genetic contribution to the illness. A large twin study reported a heritability estimate of 85%, suggesting almost all of the variance in diagnosis of bipolar disorder was accounted for by genetic factors (McGuffin et al., 2003). However, the concordance rate for monozygotic twins is not 100%, which leaves room for environmental influences. McGuffin and colleagues (2003) found that non-shared environmental influences accounted for the remaining 15% of variance and the influence of shared family environment was negligible.

Attempts to identify candidate genes using families with multiple members with or having had bipolar disorder have suggested several potential areas of interest but have been superseded to some extent by much larger association studies.

Association studies

Using groups of unrelated individuals with bipolar disorder and appropriately matched control groups, association studies have attempted to identify genes that occur more commonly in affected individuals than unaffected individuals. Robust

and replicated findings from large sample size genome-wide studies indicate the importance of the CACNA1C gene (acting on calcium channels), the ODZ4 gene (possibly involved in reward processing) and NCAN (forming neurocan involved in cell adhesion and migration) (Craddock & Sklar, 2013). An important observation is the overlap between bipolar disorder and schizophrenia in terms of similar variation in genes at several loci and their additive effect (polygenic risk) (Craddock et al., 2005; Craddock & Sklar, 2013; Van Snellenberg & de Candia, 2009). Both disorders show small polymorphisms in genes but large deletions and duplications of genes are more likely to occur in schizophrenia than bipolar disorder (Lee et al., 2012). Identification of susceptibility genes may have a major impact on our understanding of pathophysiology, and may eventually lead to changes in classification and perhaps management.

2.2.2 Neurohormonal abnormalities

Much attention recently has focused on the role of the endocrine system in mood disorders. Interest has centred on two biological systems: the hypothalamic-pituitary-adrenal (HPA) axis, one of the major hormonal systems activated during stress, and the hypothalamic-pituitary-thyroid (HPT) axis.

HPA axis dysfunction

In response to stress, neurons in the hypothalamus secrete the chemical messenger corticotropin-releasing hormone (CRH) to the anterior pituitary gland to stimulate the production of adrenocorticotropic hormone (ACTH), which in turn stimulates the adrenal glands to produce cortisol. Cortisol influences immune system function, has a potent anti-inflammatory action and is a major regulator of the physiological stress response. Importantly, it provides negative feedback to the hypothalamus, which shuts down the stress response and eventually returns cortisol to normal, pre-stress levels. One of the most consistent findings in depression (especially psychotic depression) is a marked elevation in cortisol levels, which is suggestive of a dysfunctional HPA axis. More sensitive tests of HPA axis function have been developed in which the response of the system to a pharmacological challenge is measured. If the negative feedback system is functioning normally, cortisol production should be suppressed in response to a drug that blocks the corticosteroid receptors in the hypothalamus. A number of studies have reported abnormalities in this system in people with bipolar disorder, which are consistent with reduced HPA axis feedback (Rybakowski & Twanrdowska, 1999; Schmider et al., 1995; Watson et al., 2004). Chronically elevated levels of cortisol can have deleterious consequences, including effects on mood and memory. Signs of HPA axis dysfunction have been observed in all stages of bipolar disorder, including during remission. Prospective studies will determine if such dysfunction is either an epiphenomenon of the illness or might underlie susceptibility to future episodes, accounting at least in part for the often chronic course of bipolar disorder.

HPT axis and rapid cycling

The HPT axis is also of interest in bipolar disorder. Abnormalities of thyroid function are noted in people with depression and mania. Subclinical hypothyroidism

is seen in a significant proportion of individuals with treatment-resistant depression as well as a high proportion of those with a rapid cycling course. Along with evidence of mild hypothyroidism, people in the manic state may show reduced responsiveness of the pituitary gland to the chemical messenger thyrotropin-releasing hormone, which stimulates activity of the thyroid gland. Approximately 25% of those with rapid cycling bipolar disorder have evidence of hypothyroidism, which contrasts with only 2 to 5% of people with depression (Muller, 2002). Since thyroid hormones have profound effects on mood and behaviour, dysfunction in the HPT axis may either be a consequence of severe mood disorder or maintain or exacerbate some of the presenting symptoms of bipolar disorder.

2.2.3 Neuroimaging.

Neuroimaging studies are starting to make a contribution to our understanding of the aetiology and mechanisms of action of treatment in mood disorder, perhaps more so in unipolar depression with possible application to bipolar disorder than in bipolar disorder itself. Structural brain imaging using magnetic resonance imaging (MRI) looks at the gross neuroanatomy of the brain and does not require any stimulus or activation. Functional brain imaging also uses MRI but requires a stimulus, often a psychological task, to activate changes in blood flow in the brain. Increasingly other forms of brain imaging examining electrical activity or the chemical structure of the brain are also being applied.

2.2.4 Structural brain differences

In comparison with work on schizophrenia, there have been relatively few studies investigating structural brain differences in people with bipolar disorder and findings have been contradictory. A systematic review of 98 structural brain imaging studies (Kempton et al., 2011) identified robust but non-specific changes in the brain in people with bipolar disorder compared with controls, notably lateral ventricle enlargement, increased rates of deep white matter hyperintensities but not periventricular hyperintensities. Grey matter volume increased compared with controls in studies when the proportion of participants using lithium increased. People at genetic risk of bipolar disorder show increased grey matter volume compared with those with established bipolar disorder in another systematic review (Fusar-Poli et al., 2012). One study reported that the number of white matter lesions correlated negatively with functional outcome (Moore et al., 2001). On the whole the functional significance of these findings remains unclear. Prospective longitudinal studies of people at risk of and diagnosed with bipolar disorder will be required to determine the functional significance of these structural brain changes.

2.2.5 Functional brain imaging

Compared with schizophrenia, in bipolar disorder there are important differences in activation in the medial temporal lobe and associated limbic regions that are known to be important in emotional processing (Whalley et al., 2012). In particular, compared with healthy controls, the amygdala, a structure within the limbic system, is activated more during mood episodes, while the prefrontal cortex of the brain is

persistently less activated during mood episodes (Townsend & Altshuler, 2012). Mania and depression might be related to a disruption of the normal regulatory control that the prefrontal cortex has over the limbic system when the amygdala and other parts of the limbic system are most activated. Bipolar disorder might be a developmental or acquired disorder of the failure of the prefrontal cortex of the brain to modulate the limbic brain regions (Schneider et al., 2012; Strakowski et al., 2012). However, these hypotheses are based largely on cross-sectional studies and require prospective longitudinal investigation.

2.2.6 Psychosocial influences

Although much recent research has focused on biological factors, a number of psychosocial factors have also been identified that may be relevant to understanding the development and progression of bipolar disorder or a particular individual's presentation. Antecedent factors, such as childhood maltreatment, may act as predisposing factors for developing the disorder, whereas concurrent factors such as social class, social support and self-esteem, or variation in self-esteem, may act as course modifiers or precipitants for episodes.

A potential role for psychosocial stressors in both the aetiology and exacerbation of acute episodes has been identified in bipolar disorder. Prolonged psychosocial stressors during childhood, such as neglect or abuse, are associated with HPA axis dysfunction in later life which may result in hypersensitivity to stress. In future years such dysregulation may predispose an individual to affective disturbance, and those who develop bipolar disorder may experience an earlier onset, increased rates of self-harm and psychotic symptoms. Likewise, acutely stressful life situations and hostility or criticism in a family may trigger episodes in those with an established illness. In turn, illness in itself is stressful, which may lead to further destabilisation, creating the possibility of a self-perpetuating cycle. The degree of negative emotionality expressed by close family members (termed 'expressed emotion') has been shown to predict future depressive episodes in people with bipolar disorder (Yan et al., 2004) and levels of depressive and manic symptoms (Kim & Miklowitz, 2004; Miklowitz et al., 2005).

Traumatic experiences in childhood have been associated with an adverse course of bipolar disorder and the development of comorbid post-traumatic stress disorder (PTSD) in adult life (Goldberg & Garno, 2005). Retrospective studies have shown an association between a history of childhood abuse and an earlier age at illness onset, increased comorbid substance-use disorders, increased Axis I and II comorbidities, and a rapid cycling course (Garno et al., 2005; Leverich et al., 2002). Studies of the impact of childhood abuse on the illness course of adults with bipolar disorder found that those who reported both sexual and physical abuse had higher rates of current PTSD and lifetime alcohol-use disorders, a poorer level of social functioning, a greater number of lifetime depressive episodes, an increased likelihood of at least one suicide attempt, and increased psychotic symptoms (Brown et al., 2005; Hammersley et al., 2003).

Theories of the psychology of bipolar disorder have identified factors such as self-esteem and explanatory style that may contribute to mood symptoms. The manic defence hypothesis explains the appearance of symptoms of mania as an attempt to avoid the negative and ego-destroying thought patterns associated with depression and anxiety. The ascent into feelings of omnipotence and triumph are thought to over compensate for feelings of worthlessness and underlying depression which are seen as the backdrop to the manic syndrome. People with bipolar disorder have a negative self-concept, highly variable self-esteem and increased drive even during the remitted state with an absence of depressive symptoms (Lyon et al., 1999; Van der Gucht et al., 2009; Winters & Neale, 1985). Moreover self-esteem is a predictor of time to depressive relapse even when treatment, sociodemographic, comorbidity and illness course are taken into account (Pavlickova et al., 2012). Bipolar disorder and mania symptoms may relate to an increased willingness to expend effort toward rewards and to increases in energy and goal pursuit after an initial reward (Johnson et al., 2012; Van der Gucht et al., 2009). Overly optimistic or pessimistic beliefs about the consequences and controllability of extremes of mood (depression and mania) may be associated with switching from depression to hypomania (Stange et al., 2013), severity of depressive symptoms and reduced time to the next bipolar episode (Lobban et al., 2013). Psychological theories of bipolar disorder may help observers understand some of the ideas and beliefs held by those with mania and depression, and may in the future inform the design of more effective psychological interventions for bipolar disorder.

2.3 DIAGNOSIS OF ADULTS

2.3.1 Criteria for diagnosis

Both the DSM-V and ICD-10 outline diagnostic criteria for bipolar disorder; however the two criteria sets are not identical. Crucial differences centre on the number of episodes required for a diagnosis and the distinction between bipolar I and II disorders.

DSM-V

DSM-V recognises a spectrum of bipolar disorders including bipolar I disorder, bipolar II disorder and cyclothymia (a chronic mood disturbance with depression and hypomania symptoms that do not meet a full episode), but only bipolar I and II disorder are covered in this guideline. A diagnosis of bipolar I disorder requires the experience of at least one manic episode. Frequently, people with bipolar disorder will have experienced one or more depressed episodes or sometimes mixed episodes, but this is not required for a diagnosis. The type of current or most recent mood episode can be specified as hypomanic, manic, depressed or mixed. The severity of the episode should be classified as mild, moderate or severe, with psychotic features, in partial or full remission. Other classifiers can also be specified relating to the presence of anxiety, type of depression, type of psychosis, rapid cycling, catatonia, seasonal or postnatal onset. Mixed affective episodes are no longer used for diagnostic purposes but are merely a course specifier. A diagnosis of bipolar II disorder requires the experience of at least one major depressive episode

and at least one hypomanic episode. Any history of a manic episode rules out a diagnosis of bipolar II disorder. Mood specifiers are the same as for bipolar I disorder.

ICD-10

A diagnosis of bipolar affective disorder requires the experience of at least two mood episodes, one of which must be mania or hypomania. Unlike DSM-V, a single episode of mania does not merit a diagnosis of bipolar disorder until another mood episode (of any type) is experienced. Episodes can be specified as hypomanic, manic without psychotic symptoms, manic with psychotic symptoms, mild or moderate depression, severe depression without psychotic symptoms, severe depression with psychotic symptoms, mixed or in remission. ICD-10 does not provide specific criteria for bipolar II disorder as a separate diagnostic entity but it can be coded as F.31.8 (other bipolar disorders).

2.3.2 Diagnostic issues

Hypomania

A matter of considerable and ongoing debate in bipolar disorder is the definition of hypomania. In both DSM-V and ICD-10 the diagnosis of a hypomanic episode requires symptoms of hypomania to last for at least 4 days, which was reduced from the 7 days required by earlier versions. DSM-V now also requires the change in mood in hypomania to be accompanied also by persistently increased activity and energy as well as three other symptoms of hypomania (four if irritability only) over the same period. Those who have hypomanic symptoms lasting between 1 and 3 days can be diagnosed with 'bipolar disorder not otherwise specified'. However, short-lived periods of hypomania may go unnoticed (especially if their absence from official diagnostic nomenclature means they are not enquired about), yet still be an indicator of bipolar illness. Furthermore it might be difficult for clinicians to make a decision about whether the current elevated mood and increased activity levels might be within normal limits or warrant a diagnosis of hypomania (Bruchmuller & Meyer, 2009; Wolkenstein et al., 2011). A longitudinal prospective study of a community cohort of individuals at high risk of developing psychopathology identified no differences between those who experienced hypomanic symptoms for fewer than 4 days versus those who had episodes of 4 days or longer with respect to the number of hypomanic symptoms experienced, previous diagnosis or treatment of depression and family history of depression (Angst et al., 2003). In a similar vein, the same study concluded that the core feature of hypomania should be over activity rather than mood change, as hypomanic episodes often occur without associated elation or grandiosity. Reducing the length criterion for hypomanic episodes would increase lifetime prevalence estimates of bipolar II disorder to approximately 11%, but arguably would identify more unipolar depressed service users with subtle signs of bipolarity. There is no evidence that a personal history of brief hypomania episodes in people with depression determine the effectiveness of treatments demonstrated to be effective in unipolar depression (Perlis et al., 2011). There are problems with establishing satisfactory inter-rater reliability in these assessments

and the clinical utility of such a diagnostic change in terms of treatment outcome has yet to be established.

Diagnostic uncertainty

Diagnostic uncertainty in the early stages of bipolar disorder – especially after the first episode – is common. Where bipolar disorder is suspected, a provisional diagnosis can be made and the individual should be monitored appropriately for further signs of mood disturbance and the provisional diagnosis updated as necessary. A recent national prospective study suggests that over 3 years one in 25 people with unipolar major depressive episode transition to bipolar disorder (Gilman et al., 2012); modest predictive features of such transition were the presence of comorbid social anxiety disorder, generalised anxiety disorder, childhood abuse and past year problems with the person's own social support group. These results require confirmation before they are utilised in clinical practice.

2.3.3 Distinguishing bipolar disorder from other diagnoses

The mania and hypomania stages of bipolar disorder may resemble other conditions and care should be taken during assessment to rule out other possible diagnoses.

Cyclothymia

Careful attention to illness history and duration of episodes is necessary to differentiate bipolar II disorder from cyclothymia. Both disorders are associated with hypomanic episodes, but in cyclothymia depressive symptoms are less severe and do not meet full severity or duration criteria for a diagnosis of a depressive episode. In practice, it may be very difficult to differentiate the two disorders without monitoring the condition for a long period of time and gathering information from other sources such as family members.

Schizophrenia and schizoaffective disorder

Mania resembles schizophrenia in its acute phases. Between one tenth and one fifth of people with mania exhibit classic signs of schizophrenia and both disorders can involve severe psychotic symptoms such as thought disorder, delusions and hallucinations. Typically, however, the delusions and hallucinations in mania are less stable than those in schizophrenia, the content of them is usually congruent or in keeping with the mood of the person and auditory hallucinations may be in the second rather than the third person. Sometimes the content of delusions and hallucinations is mood incongruent and auditory hallucinations are in the third person, like schizophrenia. Bipolar disorder is more likely if the individual has previously experienced episodes of depression, hypomania or mania, or has a family history of bipolar disorder. The diagnosis of bipolar disorder should be employed when there are clear-cut episodes of mania and depression, and there are no psychotic symptoms lasting for more than 2 weeks before or after the symptoms of a mood episode have resolved. The diagnosis of schizoaffective disorder should be used when there is at least one episode when psychotic symptoms dominate the

clinical picture and mood symptoms are fleeting, or the psychotic symptoms persist for more than 2 weeks without the presence of any mood symptoms.

Substance misuse

Mania-like symptoms can be the result of using stimulant drugs such as cocaine, khat, ecstasy or amphetamine. Typically, symptoms dissipate within 7 days after the substance is withdrawn, whereas mania symptoms last much longer. Since substance misuse is a common comorbidity in bipolar disorder (see Section 2.3.5), differentiating mania from the effects of substance misuse can be problematic. The clinician must pay close attention to the severity and duration of symptoms to differentiate between a mania episode and the effects of substance use. A clear history of stimulant drug use preceding any mania symptoms with no previous history of mania, hypomania or mixed affective episodes not preceded by stimulant drug use could point to this episode being drug induced. However, the clinician must ensure a positive diagnosis is made fully informed by the severity and duration of the presenting symptoms. There is a possibility that the first presentation of bipolar disorder may be triggered by use of drugs. Urine screening may be necessary to rule out the use of illicit substances, as part of a care plan agreed with the service user.

Personality disorders

Personality disorders may be both a differential diagnosis and a comorbidity of bipolar disorder. Based on strict DSM-IV criteria for Axis II disorders, one study reported a comorbidity rate of 38% in euthymic people with bipolar disorder (Kay et al., 1999). Diagnosis of personality disorder must never be made just on current behaviour alone and requires a longitudinal history from an informant who has known the person when they have not had affective symptoms. There must be a history of continuous symptoms of the personality disorder from before the age of 15 years for the person to be considered to have a personality disorder.

Cluster B (dramatic and emotional) and C (anxious and fearful) disorders are the most common personality disorder comorbidities in people with bipolar disorder. However, care must be taken not to mistake behaviour and personal experience as a result of frequently occurring bipolar episodes and subsyndromal depression and hypomania symptoms with more persistent abnormal personality traits. On the whole, symptoms of bipolar disorder are more readily treated than enduring personality traits so misdiagnosis of personality disorder at the expense of bipolar disorder can lead to under treatment of subsyndromal symptoms and episodes of mood disorder. Borderline personality disorder, the hallmark of which is affective instability owing to markedly reactive mood, shares some features in common with bipolar disorder, particularly with the ultra-rapid cycling variant. However, people with borderline personality disorder will consistently have problems with role identity, fear of abandonment and episodic panic attacks and paranoia in the absence of mood episodes. Borderline personality disorder is a relatively common comorbidity in those with bipolar disorder and some argue it belongs on the bipolar spectrum (Deltito et al., 2001).

Organic brain syndromes

Certain types of organic pathology can present with disinhibited, manic-like behaviour. Progressive frontal lobe dementia, cerebrovascular insult, encephalitis, epilepsy, demyelinating white matter lesions, such as those seen in multiple sclerosis and HIV infection, and space-occupying lesions can all produce affective disturbance that may be difficult to differentiate from a non-organic mood disorder. In people with a late-onset disorder who have shown no previous signs of affective illness, the possibility of organic pathology should be fully investigated. Thorough cognitive assessment may indicate cognitive disturbances consistent with an organic disorder. Family history of affective disorder, dementia, cerebral tumour or medical illnesses that increase the risk of cerebrovascular events may jointly inform a diagnosis. Organic pathology should be investigated in people who have developed the illness only after a significant head injury.

Metabolic disorders

Occasionally hyperthyroidism, Cushing's disease, Addison's disease, vitamin B12 deficiency and dialysis can cause manic symptoms. In all these instances, the medical problem must precede the onset of the manic symptoms, which resolve within a week or so following treatment of the underlying medical disorder.

Iatrogenic causes

Medications such as corticosteroids (especially in high doses), L-Dopa, and prescribed stimulants (such as methylphenidate) can cause manic-like symptoms. Antidepressants can cause a switch to mania in some people and those predisposed to bipolar disorder. Close attention to the time course of the development of affective symptoms could indicate whether prescribed medications were a precipitant.

2.3.4 Assessment methods

Diagnosis

In research, the most widely used and validated instrument for generating a DSM-IV Axis I diagnosis has been the Structured Clinical Interview for DSM-IV (SCID), which also generates diagnoses on the other DSM-IV axes. It is currently being adapted for use with DSM-V. The structured interview covers a wide range of possible different disorders, and the SCID is thus comprehensive and its validity in clinical samples is high. The reliability of diagnoses is generally higher when symptoms of bipolar I disorder are inquired about, as opposed to bipolar II or cyclothymia (Baldassano, 2005; Bruchmuller & Meyer, 2009). ICD diagnoses must be generated by a semi-structured interview, none of which has been validated, so clinical experience and judgement are essential.

Monitoring

The Life Chart Method (LCM) is the most widely used and researched and has recently been developed further by the creation of an electronic version. While it has been developed for professionals, it can be used by service users and can be very

useful as a therapeutic tool (Denicoff et al., 2000). Other instruments have been developed for the self-rating of the severity of mania include the Altman Self-Rating Mania Scale (Altman et al., 1997), the Self-Rating Mania Inventory (Shugar et al., 1992) or the Internal State Scale (ISS) (Bauer et al., 1991). It is important, however, to be aware that these scales are meant to assess the severity of symptoms in individuals experiencing bipolar disorder and not to screen for hypomanic or manic symptoms. There are also some concerns over their validity as some people with mania do not recognise the presence of mania symptoms that are evident to others; in such individuals these self-rating scales may be misleading.

2.3.5 Comorbidity

Comorbidity is the norm rather than the exception in bipolar disorder, and is associated with worse outcomes than bipolar disorder alone. A study of 288 participants with bipolar disorder found 65% had had at least one other Axis I disorder at some point in their lifetime and one third had at least one current comorbid Axis I diagnosis (McElroy et al., 2001). The most common comorbid Axis I disorders are anxiety and substance-use disorders, in up to 60% and 40%, respectively, of people with bipolar disorder. Care should always be taken when diagnosing comorbid illnesses. A diagnosis should only be made on the basis of symptoms present during euthymic periods or once bipolar disorder symptoms are well managed.

In those with concurrent substance-use disorders, it may be difficult to distinguish symptoms and effects of the illness from the effects of the misused substance. Likewise, causality may be difficult to establish: substance misuse may play a role in the aetiology of affective disturbance, be an attempt at self-medication, or substances may simply be used for social and recreational reasons (Healey et al., 2009). In general, substance misuse is approximately twice as common in men with bipolar disorder as women. However, rates of substance-use disorders are four to seven times higher in women with bipolar disorder than rates derived from community samples (Krishnan, 2005). Mixed episodes and rapid cycling mania are more common in people with bipolar disorder and comorbid substance-use disorder, as are medical disorders, suicide and suicide attempts (Krishnan, 2005; Potash et al., 2000). Alcohol-use disorders are sometimes missed as there is a high proportion of binge drinking rather than constant drinking. Generally, substance misuse destabilises the illness, increases the time taken to recover and/or triggers relapse.

People with bipolar disorder and comorbid substance-use disorders tend to have a higher rate of personality disorder comorbidity than those without substance-use difficulties. Comorbid personality disorder may also affect outcome in people with bipolar disorder, for example increasing the severity of residual mood symptoms during remission periods.

2.3.6 Risk assessment

Self-harm is more common in bipolar disorder than in most other psychiatric disorders and is comparable to that found in other mood and psychotic disorders.

Psychological autopsy studies suggest that suicide occurs when depression is under diagnosed and undertreated, especially in bipolar II disorder, and when there is no long-term maintenance treatment. Suicide may occur with little warning, especially in people with bipolar disorder comorbid with other impulse control disorders such as substance-use disorders, borderline personality disorder and eating disorders. A recent national study showed that 60% of people in contact with secondary care mental health services who died by suicide had been reviewed by a mental health professional in the previous week and half of these in the last 24 hours compared with 40% in all other diagnostic groups including schizophrenia and unipolar depression (Clements et al., 2013). The rapid switch from mania or hypomania to depression may also be a particular risk for suicide. Risk assessments are carried out in the same way as in other groups but in addition healthcare professionals should be aware that mental state and suicide risk can change quickly in bipolar disorder. Therefore an assessment of the degree to which mood has been changeable in the preceding days, weeks and months, and the degree of risk in each of these mood states is required if risk assessment is to be accurate. Some people with bipolar disorder will report that they do not wish to die by suicide but feel unsafe because they recognise that they are in an impulsive mood that has led to previous acts of self-harm or violence. Immediate action is required if a person with bipolar disorder is assessed to be at high or immediate risk of suicide, such as those with a definite suicide plan or persistent suicidal ideation. Similarly, the disinhibited, changeable and impulsive nature of people with bipolar disorder, particularly in a manic or a mixed state, means that healthcare professionals need to exercise caution when there is a risk of harm to self or others through violent or reckless behaviour.

Other types of risk should also be considered. Irritability and impulsive risk taking behaviour are common in mania, depression, mixed affective and rapid cycling mood states with the risk of aggression to others or reckless behaviour and vulnerability of exploitation by others. Severe depression and mania can lead to the neglect of self-care and dependent others.

2.4 DIAGNOSIS OF CHILDREN AND YOUNG PEOPLE

There is considerable international controversy regarding the validity of broadly defined early-onset bipolar disorder. However, epidemiological surveys using structured assessments report a fairly similar rate of early-onset bipolar disorder of 1.8% cross-nationally (Van Meter et al., 2011). Less uniformity is found when adopting broader diagnostic criteria, including bipolar disorder not otherwise specified (NOS), where the rates of early-onset bipolar disorder rise to 5.5% and 6.7% in the USA (Van Meter et al., 2011). Furthermore, there have been differences in conceptualisation, with some viewing irritability, not euphoria, as the hallmark symptom of mania in children (Wozniak & Biederman, 1997). In contrast to the episodic nature of adult bipolar disorder, some authorities maintain that early-onset bipolar is characterised by non-episodic, chronic, ultra-rapid cycling, mixed irritable and manic states (Biederman et al., 2000; Geller et al., 2008); indeed, the latter phenotype appears to be considerably more common in children than episodic

bipolar disorder (Brotman et al., 2006). However, a more conservative diagnostic approach is supported by the findings from longitudinal studies, which show that children with these characteristics do not go on to develop bipolar disorder, rather they are at increased risk of developing unipolar depression and anxiety disorders (Brotman et al., 2006; Stringaris et al., 2010a). Furthermore, irritability is a non-specific symptom in childhood, associated with a wide range of childhood diagnoses. It is not predictive of later bipolar disorder (Stringaris et al., 2010a), and, therefore, it should not be regarded as the core mood symptom of bipolar disorder in this age group.

The diagnosis of mania in a person aged under 18 years requires a distinct period of abnormally and persistently elevated or expansive mood. There has to be a change in the person's normal pattern of behaviour, which is not developmentally appropriate, and which is associated with impairment. The stipulation that the behaviour is 'developmentally inappropriate' is crucial: open and excitable displays of high spirits, periods of feeling invulnerable and occasional boastfulness are all normal during childhood (for example, for a child to plan to be prime minister might be unrealistic but not pathological). Talking to adults in an inappropriately adult way (for instance, berating the teacher) might reflect the testing of limits rather than delusional grandiosity (Taylor, 2009).

In the UK the narrowly defined bipolar disorder phenotype is accepted, however, there remains uncertainty regarding the length of the manic episodes required to make a diagnosis. Currently this is 7 days. In children and young people rapid changes in mood within short time periods are seen; indeed episodes of shorter duration (between 1 and 3 days) are more common than classical mania or hypomania in general population samples (Stringaris et al., 2010b). Importantly, longitudinal clinical studies suggest that up to 40% of people who experience these shorter episodes (often termed bipolar disorder NOS) may go on to develop classical bipolar disorder (Birmaher et al., 2009).

The symptoms of bipolar mania are largely similar when examined by both age of onset and current age, with the exception of psychotic symptoms, which become more prevalent in adolescence (Topor et al., 2013). However, some regard children as more often having mixed, rapid cycling states (Birmaher, 2013), while the clinical presentation of bipolar disorder in mid - to late-adolescence is regarded as fairly similar to that of adults (McClellan & Hamilton, 2006).

Early-onset bipolar disorder more often presents with depression than in adult-onset (Suominen et al., 2007). It is, therefore, important to recognise children and young people at risk of early-onset bipolar, particularly those with recurrent depression, treatment-resistant depression and those with family histories, or a hypomanic response to antidepressant treatment. Specialist advice may need to be sought in these circumstances, particularly where there are multiple risk factors. Children and young people with bipolar depression appear to have more severe depressive episodes, associated with greater suicidality, hopelessness, and anhedonia compared

with children and young people with unipolar depression, although in general differentiation between unipolar depression and bipolar depression remains problematic (DeFilippis & Wagner, 2013).

2.5 COURSE AND PROGNOSIS

For most people, bipolar disorder is chronic and recurrent. There is a large variation between individuals in the number of episodes experienced, but the average is ten (Mackin & Young, 2005). Episodes of mania and depression tend to cluster together, so typically people may experience a number of illness episodes together followed by a more quiescent period and then another cluster of episodes. This pattern with hypomanic and depressive episodes is especially common in bipolar II disorder. The risk of recurrence in the 12 months after a mood episode is especially high (50% in 1 year, 75% at 4 years, and afterwards 10% per year) compared with other psychiatric disorders. Time to relapse is three times earlier in people who have residual symptoms of mania or depression affecting function after recovery from an episode of mania or depression compared with those who make a full recovery (Judd et al., 2008a). The rate of relapse in those who made a full recovery from the index episode and have not relapsed in 4 years is about 10% per year; unfortunately very few with residual symptoms from the index episode reached 4 years without having at least one further episode. Such data have implications for considering how long a person may need to take a long-term pharmacological intervention along with considerations of risk, alternative strategies to managing relapse, adverse effects of medication and personal choice.

Furthermore, compared with unipolar depression, bipolar disorder is much more changeable in severity of the mood episode. In those with a recurrent illness pattern, the length of euthymia between episodes may shorten over time suggesting increased frequency of episodes (Kessing et al., 2004). The length of episodes remains fairly constant for an individual over time, although later episodes may begin more abruptly.

The all-cause SMR is elevated in people with bipolar disorder relative to the general population. Bipolar disorder is associated with a higher burden of physical illnesses such as diabetes and heart disease and the SMR for premature deaths from natural causes is estimated at 1.9 for males and 2.1 for females (Osby et al., 2001) or possibly higher in a study of 1 million men (Gale et al., 2012). Recent large prospective national studies confirm that bipolar disorder and schizophrenia have a higher than expected prevalence of vascular disease such as heart disease, heart attack or stroke in women with bipolar disorder (Fiedorowicz et al., 2011), diabetes and hyperlipidemia (Bai et al., 2013), and possibly the incidence of cancer (Lin et al., 2013; McGinty et al., 2012), compared with both the general population and other psychiatric disorder even when all other risk factors for these conditions are controlled. The reasons for this may be complex but there is some evidence that people with bipolar disorder do not receive health promotion or treatment as readily as the general population (Thornicroft, 2011). The SMR for suicide is much higher at

approximately 15 for males and 22.4 for females (Osby et al., 2001), with the greatest risk of suicide attempts occurring during depressed or mixed episodes.

2.5.1 Early warning signs

Early detection of the development of the first symptoms and signs of mania, hypomania, mixed affective states or bipolar depression is aimed at reducing the duration, severity and consequences of these episodes and minimising harm caused by repeated episodes (Jackson et al., 2003; Morriss et al., 2007; Perry et al., 1999). Individuals are often able to identify precipitating changes in mood and/or behaviour that indicate the early stages of an episode because each episode starts with a similar pattern of symptoms that is idiosyncratic and typical for that individual. Hence the early warning signs of relapse in to mania or depression are sometimes called 'relapse signatures'. In each individual, the relapse signature of mania differs from that of depression. Checklists of early warning symptoms and signs for mania and depression greatly improve the recognition of these early warning signs (Lobban et al., 2011).

There is greater consistency from episode to episode of mania over time than episode to episode of depression. Relapse signatures can be helpful indicators to individuals themselves, family members, close friends, or clinicians that increased support may be necessary to prevent escalation into a full episode. Identifying particular stressors that are associated with relapse, such as specific psychosocial stressors or events associated with circadian rhythm disturbance, can help individuals learn ways of reducing the risk of triggering episodes. Although triggering events may be identified before some episodes, others will have no obvious trigger. Great care must be given to history taking to establish whether triggering events such as sleep disruption or life stress preceded the mood episode, or were the symptoms or consequences of it.

2.5.2 Neuropsychological function

Many people with bipolar disorder have significant psychological impairments characterised by a combination of declarative memory deficits as well as changes in executive functions such as attention, planning and working memory (Ferrier & Thompson, 2003). These impairments tend to be worse when the person has depression or mania symptoms or episodes but can also persist into euthymia (Thompson et al., 2005). This latter observation, together with evidence of similar impairments in first degree relatives suggest that these deficits may be trait markers of bipolar disorder. These neuropsychological impairments may relate to structural changes in the brain (see Section 2.2.4) or to some other unknown biological or psychological process such as rumination. The impairments worsen as the illness progresses and are particularly associated with the number of manic episodes (Robinson et al., 2006). The impact of these impairments on rehabilitation, engagement in therapy, compliance and quality of life is uncertain but may be significant.

2.5.3 Late-onset bipolar disorder

Mania or hypomania that first appears in later life (after age 40 years) usually follows many years of repeated episodes of unipolar depression or is secondary to other factors such as steroid medication, infection, neuroendocrine disturbance or neurological problems. However, only 15% of people with bipolar disorder presenting for the first time to mental health services are precipitated by a medical problem. Late-onset bipolar disorder is less likely to be associated with a family history of the disorder than if it is earlier-onset. The prognosis for late-life depression is generally poor due to a high mortality rate, mainly due to a greater burden of physical illness, especially cardiovascular and cerebrovascular disease, rather than suicide. There is also an increased prevalence of dementia in bipolar disorder in some studies except in participants treated with lithium (Kessing et al., 2010).

2.6 THE TREATMENT AND MANAGEMENT OF BIPOLAR DISORDER

2.6.1 Service needs of adults with bipolar disorder

Community surveys reveal that around 25% of people with bipolar disorder have never sought help from health services (ten Have et al., 2002). Those that have sought help may not receive a correct diagnosis of bipolar disorder for at least 6 years from the first appearance of symptoms (Morselli et al., 2003). Service users with bipolar disorder have identified a range of difficulties in accessing services that meet their needs (Highet et al., 2004):

- lack of awareness and understanding about bipolar disorder in the community leading to delays in seeking medical assessment
- the burden of illness is exacerbated by difficulties obtaining an accurate diagnosis and optimal treatment
- inappropriate crisis management
- difficulties accessing hospital care
- inappropriate exclusion of carers and families from management decisions
- frequent discontinuities of medical and psychological care.

In the UK, the needs of people with bipolar disorder have largely been regarded as similar to the needs of other service users with severe mental illness. Four features of bipolar disorder have been identified that distinguish the service needs of service users with bipolar disorder from other service users (Morriss et al., 2002):

- Most service users with bipolar disorder have the potential to return to normal function with optimal treatment, but with suboptimal treatment have a poor long-term outcome and become a burden to families and society (Ogilvie et al., 2005; Simon & Unützer, 1999).
- Optimal treatment of bipolar disorder is challenging and requires long-term commitment from health services.
- Bipolar disorder is characterised by high rates of episodic recurrence (after a manic episode, it is typically 50% recurrence within 12 months (Tohen et al.,

1990)), with high rates of disabling mood symptoms between recurrences (Judd et al., 2002a) and suicide attempts (Simon et al., 2007).

- Relatives of service users with bipolar disorder are not only subject to the usual stresses of caring but are also at a particularly high risk of developing bipolar disorder or unipolar depressive disorder themselves (McGuffin & Katz, 1989).

The only forms of specific service provision that have been developed for bipolar disorder have been lithium clinics or collaborative care models, either sharing care across the primary care and secondary care divide (Bauer et al., 2006b; Simon et al., 2006) or creating bipolar disorder pathways in secondary care mental health services (Kessing et al., 2013). Lithium clinics are rarely found in the UK because treatment for bipolar disorder often involves antipsychotic and anticonvulsant medication rather than lithium. Collaborative care for bipolar disorder involves a case manager who coordinates the care that is required, psychoeducation for the service user (usually delivered in groups), medical input in terms of the diagnosis, medical and psychiatric comorbidity and medication. Medication is usually given according to treatment algorithms. Progress and other service needs are reviewed by the case manager. The approach aims to support and reinforce the strategies that service users with bipolar disorder already adopt to stay well. These include acceptance of the diagnosis or the problems presented by the disorder if the person does not accept the diagnosis, education about the condition, identifying both triggers and early warning signs of mania and depression, having adequate amounts of sleep, managing stress, taking medication and using support networks and crisis resolution (Russell & Browne, 2005). Specialist bipolar disorder pathways include care given by psychiatrists and other mental health professionals with particular training in the assessment and management of bipolar disorder, and groups for those who are newly diagnosed or recently admitted followed by more intensive psychoeducation groups (Kessing et al., 2013).

However, most mental health organisations in England provide generic care for people with bipolar disorder as one form of severe mental illness along pathways outlined by National Health Service (NHS) tariffs for psychosis (10-17). These may involve community mental health teams, early intervention in psychosis (for people presenting in their first or second episode), dual diagnosis teams when there is a comorbid substance-use disorder, assertive outreach teams when people are difficult to engage and repeatedly require intensive input, and crisis resolution and home treatment teams as an alternative to mental health inpatient admission.

2.6.2 Service needs of children and young people with bipolar disorder

The process of care and provision of treatment for children and young people in England and Wales is through the four-tier model of child and adolescent mental health services (CAMHS) (NHS Health Advisory Service, 1995). Tier 1 services include those that have direct contact with children and young people for primary reasons other than mental health. These include general practitioners (GPs), health

visitors, paediatricians, social workers, teachers, youth workers and juvenile justice workers. Alongside tier 2 specialist trained mental health professionals, working primarily in a community-based setting, they are the first point of contact with the child or young person presenting with a mental health problem. At this level, an important role is to detect those at high risk for bipolar disorder and those who are presenting with depression or mania.

Children and young people suspected of developing, or having, bipolar disorder are usually referred for a diagnostic evaluation in CAMHS tier 3. Tier 3 services comprise multidisciplinary teams of specialist CAMHS professionals working in (secondary care) specialist CAMHS facilities. They provide specialist co-ordinated assessments and treatments, including a full range of appropriate psychological and pharmacological interventions. Children and young people presenting with mania, mixed affective states or moderate to severe depression are typically assessed by tier 3 specialist CAMHS. Outreach services need to be available to those young people who, as result of their presentation, are unable to access the clinic base of the tier 3 service and to young people who require outreach work as part of an outpatient treatment plan. Early intervention in psychosis services are likely to be involved in those young people presenting with first episode psychosis.

For children and young people with suspected or actual bipolar disorder who are also at risk of harm to themselves or others hospital admission at tier 4 may be considered. Tier 4 services are highly specialised tertiary CAMHS in inpatient, day patient or outpatient settings for children and young people with severe and/or complex problems requiring a combination or intensity of interventions that cannot be provided by tier 3 CAMHS. A child or young person presenting with possible bipolar disorder will usually require assessment and treatment by tier 3 or 4 services depending on risks associated with their presentation. Following tier 4 intervention, young people are usually discharged to tier 3 CAMHS or adult mental health services.

2.6.3 Pharmacological interventions

Pharmacological treatments are commonly used during episodes of mania and bipolar depression. Over time these episodes, particularly depression, tend to become more frequent and as repeated episodes are associated with increased functional impairment, effective maintenance treatment is clearly a priority.

Manic episodes have traditionally been effectively treated with antipsychotic drugs often supplemented with a benzodiazepine. Concerns over the neurological side effects of the older, so-called, 'first-generation' antipsychotics have seen these largely replaced by 'second-generation' agents. These newer drugs are generally better tolerated with respect to extrapyramidal side effects but are associated with a range of other side effects including clinically significant weight gain. These side effects are not clearly class effects; each antipsychotic drug has its own side-effect profile. Lithium was previously commonly used in the management of episodes of mania but its slow onset of action, concerns over its side-effect profile and the risk of

relapse into mania after abrupt withdrawal have seen lithium largely replaced by valproate for this indication.

The treatment of bipolar depression is both more challenging and more diverse. Treatments used during acute episodes include antidepressants, some antipsychotic drugs such as quetiapine, the anticonvulsant drug lamotrigine, and lithium. Response to these agents both acutely and during maintenance treatment is often partial. There are concerns about the potential for switching into mania and more frequent cycling mood with antidepressant treatment; the risk of switching may be less with selective serotonin reuptake inhibitors (SSRIs) than with other antidepressants

With respect to relapse prevention, lithium has been traditionally used, and after a decline in its use for reasons outlined above, it's possible effects against suicide has encouraged its use again for this purpose. Polypharmacy is common in relapse prevention. This is inevitable given the differing efficacy profiles of available drugs and the need to protect against both poles of the illness. The efficacy and tolerability of many of the combinations in common use have been poorly evaluated.

2.6.4 Psychological interventions

The development of effective psychological interventions for bipolar disorder is relatively recent. Historically, individuals with this diagnosis were sometimes seen as poor candidates for psychotherapy because of potentially challenging interactions with therapists (Yalom, 1975). However, there has been a growing awareness that psychological factors play an important role in bipolar disorder and that treatment approaches that address these factors can improve clinical outcomes.

There are a number of types of psychological interventions for which there is a current evidence base as described below. A common aim of these approaches is to provide the service user with a set of mood regulation and self-management skills to address the challenges of living with bipolar disorder more effectively after the psychological intervention. The main approaches currently employed for bipolar disorder are:

Enhanced relapse prevention/individual psychoeducation (Lobban et al., 2010), a relatively brief intervention in which the individual is trained in strategies to identify and cope effectively with early warning signs of mania and depression.

Cognitive behavioural therapy (CBT) (Lam et al., 2005a; Meyer & Hautzinger, 2012), a form of talking therapy focusing on the role our thinking and behaviour has on our emotions, and how they reciprocally influence each other.

Interpersonal and social rhythm therapy (Frank et al., 2005), an adaption of interpersonal therapy (IPT) (Klerman et al., 1984a) for bipolar disorder emphasising the role of: (a) interpersonal factors such as losses, role conflicts, role changes or long-standing

interpersonal problems, and (b) circadian rhythm stability such as sleep-wake cycle, work-life balance, and daily routines for the course of bipolar disorder.

Group psychoeducation (Castle et al., 2010; Colom et al., 2003a), a structured intervention of high frequency and intensity (up to 21 sessions, each of 2 hours' duration) to help individuals experiencing bipolar disorders to become experts in their own condition to improve medication adherence, mood stability and self-management.

Family-focused therapy (Miklowitz et al., 2003), a psychoeducational programme for individual families in which one member experiences bipolar disorder; it incorporates a strong behavioural component by focusing on understanding disorder-specific risks, communication and problem-solving skills in the family. Each of these approaches is primarily focused on reduction of relapse and recurrence of mania or depression.

As a secondary outcome, psychological interventions often result in improvement in residual or subsyndromal symptoms, but there is now also some evidence that episodes of bipolar depression can be treated by CBT, family-focused therapy and interpersonal and social rhythm therapy (Miklowitz et al., 2007b).

Despite their different theoretical backgrounds there are common features of all these psychological interventions:

- providing essential information about the condition ideally linked to the individual biography
- identifying early warning signs and prodromal symptoms (an individual relapse signature)
- helping to develop coping strategies to deal with early warning symptoms, mood instability, or situations which might trigger changes in mood and activity levels
- developing a crisis plan and a post-treatment 'staying well' plan.

Psychological interventions for bipolar disorder in the NHS are normally offered through secondary care services. Delivery of interpersonal and social rhythm therapy and family-focused therapy are uncommon although some individuals do receive family therapy (but not specifically family-focused therapy). These are often delivered by clinical psychologists or other clinicians trained in specific approaches, who either form part of secondary care teams or more specialist services depending on the local service context. Specialist services for bipolar disorder in particular are rare in the NHS although there are some exceptions. The extent to which the therapies offered match the specific evidence-based treatments above is very varied. Recent audits in South London and Maudsley NHS Foundation Trust and Manchester Mental Health and Social Care Trust indicate that rates of access to structured psychological interventions for eligible individuals with severe mental illness are very low (7 to 10%). It is likely that access for individuals with bipolar disorders is especially poor as services are not configured to meet their fluctuating

needs. In addition many individuals with bipolar disorder are not seen routinely in secondary care services. These individuals may receive a psychological intervention for discrete episodes of depression or anxiety through primary care services. Often the therapists delivering such therapies will not have specific training in psychological interventions for bipolar disorder. In such circumstances the treatment offered is likely to be generic and lacks an evidence base for this condition. The lack of training of NHS staff in the psychology and psychological treatment of bipolar disorder is increasingly being recognised. In response to this there is a current initiative from Department of Health as part of the Increasing Access to Psychological Therapies programme (IAPT)[1] to increase clinician training and client access for psychological interventions for bipolar disorder. There is also increasing awareness that a primary focus on relapse prevention may be inappropriate. The importance of personal recovery outcomes is recognised at a national level (Department of Health, 2011) and among service users (Slade, 2009). Recent research indicates that the concept of recovery is meaningful and measureable in bipolar disorder and future work will report on interventions designed to enhance recovery outcomes (Johnson et al., 2011). In addition to specific interventions, the British Psychological Society report 'Understanding Bipolar Disorder' (British Psychological Society, 2010) has highlighted the importance of adopting a psychological perspective that goes beyond the delivery of individual therapies to consider how services as a whole can be delivered more sensitively.

2.6.5 Issues of consent for children and young people

Consent should always be sought from the child or young person, and depending on their age, from parents as well. Where a young person over 16 has capacity, they can consent and this cannot be overridden by the parents, although it is always wise to work co-operatively with all involved. Where the child or young person is not competent or lacks capacity (as a result of immaturity, age or mental illness) the parents can consent to treatment, proved they are understand the treatment proposed, that is, it is within the zone of parental control as defined in the Mental Health Act 1983 amended in 2007.

The Mental Heath Act (1983; amended in 2007; (HMSO, 2007) may be required particularly if the person needs to be admitted to hospital. There is no lower age limit for the use of the Mental Health Act.

2.7 ECONOMIC COSTS

Bipolar disorder is a relatively rare affective disorder when compared with unipolar depression, with a lifetime prevalence estimated at approximately 1%. Despite its low lifetime risk, in the recent Global Burden of Disease analysis by Murray and colleagues (2012), bipolar disorder is the sixth biggest cause of disability adjusted life years (DALYs) worldwide among selected mental and behavioural disorders after unipolar depressive disorders, anxiety disorders, substance-use disorders, alcohol-use disorders, and schizophrenia. From 1990 to 2010 there was a 40.9% increase in

[1] http://www.iapt.nhs.uk/smi-/

DALYs attributable to bipolar disorder worldwide. Similarly, in the UK sub-analysis of the Global Burden of Disease Study, Murray and colleagues (2013) found bipolar disorder to be one of the leading causes of years lived with disability (YLDs) with approximately 5% increase in YLDs and 4% increase in DALYs from 1990 to 2010.

A study by Das Gupta and Guest (2002) estimated the annual cost of bipolar disorder in the UK. The study adopted a societal perspective and evaluated direct health service (NHS) costs of managing bipolar disorder, non-healthcare costs borne by other statutory agencies such as social care authorities and the criminal justice system, and indirect costs to society, related to productivity losses owing to unemployment, absenteeism from work and premature mortality resulting from suicide. Cost estimates were based on national statistics data published by the Department of Health and a 0.5% prevalence of bipolar disorder in the UK, translating into 297,000 people with the condition.

The total annual societal cost of bipolar disorder was estimated at £2.055 billion in 1999/2000 prices, consisting of £199 million (10% of total costs) incurred by NHS resource use, £86 million (4%) associated with non-healthcare resource use and £1.77 billion (86%) related to productivity losses. Regarding costs borne by healthcare resource use, £14.9 million (7% of health service costs) was associated with management of bipolar disorder in primary care including drug prescriptions, £69.4 million (35% of health service costs) resulted from inpatient episodes, £57.9 million (29% of health service costs) was borne by day hospital, outpatient and ward attendances, £53.2 million (27% of health service costs) was attributed to community health service resource use, and the rest (£3.4 million – 2% of health service costs) was related to other services, such as high-security hospital authorities and ambulance transport.

Indirect costs represented by far the most important driver of total costs associated with bipolar disorder. The largest amount of these was attributed to unemployment: an excess of 76,500 people annually were considered to be unemployed as a result of having bipolar disorder, bearing a financial burden of productivity losses approximating £1.51 billion per year (that is, 85% of total indirect costs). Other indirect costs due to absenteeism from work and suicide were estimated at £152 million and £109 million per year, respectively.

Another study by McCrone and colleagues (2008) assessed the total societal cost associated with bipolar disorder in 2007, and projected to 2026, using prevalence data from a national community survey conducted in the USA (Merikangas et al., 2007a). The elements used to estimate total costs for bipolar disorder consisted of prescribed drugs, inpatient care, other NHS services, supported accommodation, day care, other social services, informal care and lost employment. Total service costs associated with bipolar disorder in 2007 were estimated to be £1.6 billion (comprising 50% staff costs associated with time spent with psychiatrists, GPs and other doctors, therapists, community mental health nurses and social workers; 28%informal care; 9% inpatient care;6% day care; 2% medication; and 5% residential

care). Productivity losses were estimated at £3.6 billion, so that the total cost of bipolar disorder reached £5.2 billion in 2007, 69% of which was attributable to lost employment. Projected costs for 2026 were estimated at £2.6 billion for services and £5.6 billion for lost employment, reaching a total cost of £8.2 billion associated with bipolar disorder by 2026.

A more recent study revisited the estimated annual cost associated with bipolar disorder to the NHS using a prevalence of 0.15% (Young et al., 2011). The study used various national sources including a database of GP practices, the Hospital Episode Statistics, and NHS data on inpatient, outpatient and community mental healthcare. The authors estimated the annual NHS cost of bipolar disorder at £342 million in 2009/2010 prices. The most significant component of this cost was attributed to hospitalisations (60.4%); outpatient and community mental health accounted for 26.7% of the cost, medication prescribed in primary care accounted for 7.4%, while GP consultations and GP-initiated tests together accounted for the remaining 5.5% of the overall direct healthcare cost associated with bipolar disorder. The authors attributed the differences in costs (especially proportional costs) between their study and the studies by Das Gupta and Guest (2002) and McCrone and colleagues (2008) to differences in methodology, data sources and reported care elements in each of the three analyses.

Similar studies, estimating total costs attributable to bipolar disorder from a societal perspective, have also been conducted in Germany (Runge & Grunze, 2004), the Netherlands (Hakkaart-van Roijen et al., 2004), Sweden (Ekman et al., 2013), Australia (Fisher, 2007) and the USA (Begley et al., 2001; Wyatt & Henter, 1995).

Runge and Grunze (2004) estimated the total annual cost of bipolar disorder in Germany at €5.8 billion in 2002 prices, of which 98% was associated with productivity losses. In the Netherlands, the respective total annual cost was reported to reach approximately US$1.8 billion, also in 2002 prices, based on an estimated prevalence of bipolar disorder equal to 5.2%. Indirect costs were found to be high in this study too, reaching 75% of total costs (Hakkaart-van Roijen et al., 2004). In Sweden, Ekman and colleagues (2013) estimated the average annual cost per patient at approximately €28,000 in 2008. Indirect costs due to sick leave and early retirement represented 75%, inpatient costs 13%, outpatient costs 8%, medication 2% and community care another 2% of the total cost.

In Australia, the total actual excess costs as a result of bipolar disorder were estimated to reach $380 million in 2004, using a 2.5% lifetime prevalence (Fisher et al., 2007). Examined by health sector and individual costs, the actual excess costs were $51 million and $329 million, respectively. The areas of highest excess health sector costs were hospital inpatient services (69.6% of all health sector excess costs), hospital outpatient services (14.1%), specialist services (11.3%) and GPs (3.4%). The highest excess individual costs were days unable to work (60.2%), days of reduced work (39.3%) and specialist services (0.3%) (Fisher et al., 2007).

In the USA, Wyatt and Henter (1995) calculated the total annual cost of bipolar disorder in 1991 using a lifetime prevalence of bipolar disorder equal to 1.3% (that is, 2,500,000 people diagnosed with the disorder at some point during their lives). The total annual cost reached US$45.2 billion, consisting of US$7.6 billion direct costs (mainly health service costs but also costs related to the criminal system, research on bipolar disorder, and so on), and US$37.6 billion indirect costs, which amounted to 83% of total costs.

Begley and colleagues (2001) adopted a different methodology in order to calculate costs attributable to bipolar disorder; based on the incidence rate of the condition, they estimated the lifetime cost of bipolar disorder for all new cases in 1998. The study took into account the fact that only a small number of people (assumed at 20% per year) would be diagnosed and treated for the disorder, whereas the remaining undiagnosed individuals would still incur health service costs, but their treatment would not be specific to bipolar disorder. Besides the above costs, estimates included comorbidity costs from alcohol and substance-use disorders, as well as indirect costs associated with excess unemployment, reduced earnings because of disability and suicide. The lifetime cost of new cases of bipolar disorder in the USA in 1998 was estimated to be as high as US$24 billion, of which US$13.3 billion (55%) referred to medical costs; indirect costs reached US$10.7 billion, equalling 45% of total costs, a proportion significantly lower than that reported in other studies. This divergence was attributed by the authors to differences in the methodology used and in categories of indirect costs included.

Dilsaver (Dilsaver, 2011) provided the most recent total cost estimates for bipolar disorder I and II in the USA. The direct and indirect costs of bipolar I and II disorder were estimated to reach US$30.7 and US$120.3 billion, respectively, totallingUS$151 billion in 2009. The author attributed the increase in costs between 1991 (as reported by (Wyatt & Henter, 1995) and 2009 not only to inflation, but also to the increased prevalence of bipolar disorder reported in epidemiological studies over the years.

Little is known about the healthcare cost of paediatric bipolar disorder. Berry and colleagues (2011) attempted to estimate the annual hospitalisation cost incurred by children and young people with bipolar disorder in the US, using a large national paediatric database. The authors reported more than 40,000 hospitalisations of children and young people with bipolar disorder in 2006, with total associated costs of US$233 million. The mean cost per hospitalisation was US$5,725, while the mean length of stay was 9 days. Among factors associated with higher costs were young age (lower than 13 years), being from a high-income family and the presence of comorbidities.

Unemployment is a considerable burden for people with bipolar disorder. A systematic review by Marwaha and colleagues (2013) found that approximately 40 to 60% of people with bipolar disorder are in employment. However, bipolar disorder appears to lead to workplace underperformance and 40 to 50% of employees with bipolar disorder may experience a decline in their occupational status over time; this

fact is reflected in the observation that employment levels in early bipolar disorder are higher than in more established illness.

A significant number of studies undertaken in the USA analysed the financial burden of bipolar disorder from the perspective of a third-party payer, such as Medicaid (a public insurance plan for individuals and families on low incomes), or a private insurer (paid by the employer). Bipolar disorder was found to be among the most costly mental disorders from an employer's point of view (Goetzel et al., 2003; Goetzel et al., 2000; Peele et al., 1998; Peele et al., 2003). Employees with bipolar disorder were found to incur significantly higher treatment costs compared with employees with other mental disorders (Brook et al., 2006; Rajagopalan, 2006; Stensland et al., 2007) as well as compared with several chronic physical health problems (Williams et al., 2011). They also incurred higher absence costs (related to sick leave, short- and long-term disabilities as well as workers' compensation) compared with employees with other mental disorders, and demonstrated an annual productivity level approximately 20% lower than that of the latter (Kleinman et al., 2005). Regarding direct treatment costs, these were mainly driven by high hospitalisation rates, resulting in substantial inpatient resource use (Bryant-Comstock et al., 2002; Hu & Rush, 1995; Peele et al., 2003; Simon & Unützer, 1999; Stender et al., 2002).

Goetzel and colleagues (2003; 2000) found that bipolar disorder was associated with a lower cost per person compared with schizophrenia; however, because a significantly higher number of employees (dependents also included) were affected by bipolar disorder rather than schizophrenia, the total costs to the insurance plans associated with bipolar disorder were approximately 25 times higher than costs incurred by employees with schizophrenia. Furthermore, the costs to the employers associated with management of people with bipolar disorder were almost four times higher than the respective costs incurred by those with unipolar depression, despite the similar numbers of employees affected by the two disorders, as the cost per person with bipolar disorder was higher than that of person with depression. Consequently, it can be inferred that bipolar disorder, despite its rather low lifetime prevalence, can be a relatively common condition within the population in employment, and a significant financial burden to the payers of health services and absenteeism/disability compensations (such as private insurance plans in the USA and the public sector in the UK).

Comorbidity of bipolar disorder with other mental disorders and medical conditions is an additional factor contributing to the high treatment costs associated with the disorder (Guo et al., 2007; Guo et al., 2008; Peele et al., 2003). An important part of such comorbidities comprises metabolic comorbidities, such as weight gain and diabetes, resulting from service users' lifestyle and receiving antipsychotic medication (Centorrino et al., 2009). Delayed diagnosis and management of unrecognised and/or misdiagnosed bipolar disorder, characterised by overuse of antidepressants and underuse of potentially effective medications, are important factors also adding to the total cost of treatment mainly owing to increased rates of

hospitalisation and emergency room visits (Birnbaum et al., 2003; Li et al., 2002; Matza et al., 2005; McCombs et al., 2007; Shi et al., 2004b; Stang et al., 2006; Stensland et al., 2008; Stensland et al., 2010), suggesting that early diagnosis of bipolar disorder not only offers a benefit to the service users who receive appropriate treatment for their condition, but also results in a considerable reduction in total healthcare costs.

Family members and friends often provide care and support to those with bipolar disorder, which places significant burdens on them that impact upon their health, leisure time, employment and financial status. Evidence from the US suggests that families with a member with bipolar disorder bear higher healthcare costs compared with matched families without a severe mental illness (Chatterton et al., 2008) as well as with families with a member with schizophrenia (Gianfrancesco et al., 2005).

The above review demonstrates the major economic burden that bipolar disorder places on the healthcare system and, more substantially, through productivity losses, to society as a whole. Apart from financial implications, bipolar disorder is associated with a significant psychological burden not only to service users, but also to families and carers (Dore & Romans, 2001; Perlick et al., 1999; Zendjidjian et al., 2012),. Efficient use of available healthcare resources is required to maximise the health benefit for people with bipolar disorder and, at the same time, reduce the financial and psychological burden to society.

3 METHODS USED TO DEVELOP THIS GUIDELINE

3.1 OVERVIEW

The development of this guideline followed *The Guidelines Manual* (NICE, 2012). A team of health and social care professionals, lay representatives and technical experts known as the Guideline Development Group (GDG), with support from the NCCMH staff, undertook the development of a person-centred, evidence-based guideline. There are seven basic steps in the process of developing a guideline:

1. Define the scope, which lays out exactly what will be included (and excluded) in the guidance.
2. Define review questions that cover all areas specified in the scope.
3. Develop a review protocol for each systematic review, specifying the search strategy and method of evidence synthesis for each review question.
4. Synthesise data retrieved, guided by the review protocols.
5. Produce evidence profiles and summaries using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.
6. Consider the implications of the research findings for clinical practice and reach consensus decisions on areas where evidence is not found.
7. Answer review questions with evidence-based recommendations for clinical practice.

The clinical practice recommendations made by the GDG are therefore derived from the most up-to-date and robust evidence for the clinical and cost effectiveness of the interventions and services covered in the scope. Where evidence was not found or was inconclusive, the GDG discussed and attempted to reach consensus on what should be recommended, factoring in any relevant issues. In addition, to ensure a service user and carer focus, the concerns of service users and carers regarding health and social care have been highlighted and addressed by recommendations agreed by the whole GDG.

3.2 THE SCOPE

Topics are referred by the Secretary of State and the letter of referral defines the remit, which defines the main areas to be covered (see *The Guidelines Manual* [NICE, 2012] for further information). The NCCMH developed a scope for the guideline based on the remit (see Appendix 1). The purpose of the scope is to:

- provide an overview of what the guideline will include and exclude
- identify the key aspects of care that must be included

- set the boundaries of the development work and provide a clear framework to enable work to stay within the priorities agreed by NICE and the National Collaborating Centre, and the remit from the Department of Health/Welsh Assembly Government
- inform the development of the review questions and search strategy
- inform professionals and the public about expected content of the guideline
- keep the guideline to a reasonable size to ensure that its development can be carried out within the allocated period.

An initial draft of the scope was sent to registered stakeholders who had agreed to attend a scoping workshop. The workshop was used to:

- obtain feedback on the selected key clinical issues
- identify which population subgroups should be specified (if any)
- seek views on the composition of the GDG
- encourage applications for GDG membership.

The draft scope was subject to consultation with registered stakeholders over a 4-week period. During the consultation period, the scope was posted on the NICE website (www.nice.org.uk). Comments were invited from stakeholder organisations The NCCMH and NICE reviewed the scope in light of comments received, and the revised scope was signed off by NICE.

3.3 THE GUIDELINE DEVELOPMENT GROUP

During the consultation phase, members of the GDG were appointed by an open recruitment process. GDG membership consisted of: professionals in psychiatry, clinical psychology, nursing, social work, and general practice; academic experts in psychiatry and psychology; and service users. The guideline development process was supported by staff from the NCCMH, who undertook the clinical and health economic literature searches, reviewed and presented the evidence to the GDG, managed the process, and contributed to drafting the guideline.

3.3.1 Guideline Development Group meetings

Thirteen GDG meetings were held between October 2012 and June 2014. During each day-long GDG meeting, in a plenary session, review questions and clinical and economic evidence were reviewed and assessed and, at later meetings, recommendations formulated. At each meeting, all GDG members declared any potential conflicts of interest (see Appendix 2), and service user and carer concerns were routinely discussed as a standing agenda item.

3.3.2 Service users and carers

Individuals with direct experience of services gave an integral service-user focus to the GDG and the guideline. The GDG included service users. They contributed as full GDG members to writing the review questions, providing advice on outcomes most relevant to service users and carers, helping to ensure that the evidence

addressed their views and preferences, highlighting sensitive issues and terminology relevant to the guideline, and bringing service user research to the attention of the GDG. In drafting the guideline, they contributed to the chapter on experience of carers and to writing the guideline's introduction and identified recommendations from the service user and carer perspective.

3.3.3 Special advisors

Special advisors, who had specific expertise in one or more aspects of treatment and management relevant to the guideline, assisted the GDG, commenting on specific aspects of the developing guideline and making presentations to the GDG. Appendix 3 lists those who agreed to act as special advisors.

3.3.4 National and international experts

National and international experts in the area under review were identified through the literature search and through the experience of the GDG members. These experts were contacted to identify unpublished or soon-to-be published studies, to ensure that up-to-date evidence was included in the development of the guideline. They informed the GDG about completed trials at the pre-publication stage, systematic reviews in the process of being published, studies relating to the cost effectiveness of treatment and trial data if the GDG could be provided with full access to the complete trial report. Appendix 6 lists researchers who were contacted.

3.4 REVIEWPROTOCOLS

Review questions drafted during the scoping phase were discussed by the GDG at the first few meetings and amended as necessary. The review questions were used as the starting point for developing review protocols for each systematic review (described in more detail below). Where appropriate, the review questions were refined once the evidence had been searched and, where necessary, sub-questions were generated.

For questions about interventions, the PICO (Population, Intervention, Comparison and Outcome) framework was used to structure each question (see Table 2).

Table 2: Features of a well-formulated question on the effectiveness of an intervention – PICO

Population:	Which population of service users are we interested in? How can they be best described? Are there subgroups that need to be considered?
Intervention:	Which intervention, treatment or approach should be used?
Comparison:	What is/are the main alternative/s to compare with the intervention?
Outcome:	What is really important for the service user? Which outcomes should be considered: intermediate or short-term measures; mortality; morbidity and treatment complications; rates of relapse; late morbidity and readmission; return to work, physical and social functioning and other measures such as quality of life; general health status?

Questions relating to diagnosis or case identification do not involve an intervention designed to treat a particular condition, and therefore the PICO framework was not used. Rather, the questions were designed to pick up key issues specifically relevant to clinical utility, for example their accuracy, reliability, safety and acceptability to the service user.

To help facilitate the literature review, a note was made of the best study design type to answer each question. There are four main types of review question of relevance to NICE guidelines. These are listed in Table 3. For each type of question, the best primary study design varies, where 'best' is interpreted as 'least likely to give misleading answers to the question'. For questions about the effectiveness of interventions, where RCTs were not available, the review of other types of evidence was pursued only if there was reason to believe that it would help the GDG to formulate a recommendation.

However, in all cases, a well-conducted systematic review (of the appropriate type of study) is likely to always yield a better answer than a single study.

Table 3: Best study design to answer each type of question

Type of question	Best primary study design
Effectiveness or other impact of an intervention	Randomised controlled trial (RCT); other studies that may be considered in the absence of RCTs are the following: internally/externally controlled before and after trial, interrupted time-series
Accuracy of information (for example, risk factor, test, prediction rule)	Comparing the information against a valid gold standard in an RCT or inception cohort study
Rates (of disease, service user experience, rare side effects)	Prospective cohort, registry, cross-sectional study
Experience of care	Qualitative research (for example, grounded theory, ethnographic research)

3.5 CLINICAL REVIEW METHODS

The aim of the clinical literature review was to systematically identify and synthesise relevant evidence from the literature in order to answer the specific review questions developed by the GDG. Thus, clinical practice recommendations are evidence-based, where possible, and, if evidence is not available, informal consensus methods are used to try and reach general agreement between GDG members (see Section 3.5.6) and the need for future research is specified.

3.5.1 The search process

Scoping searches

A broad preliminary search of the literature was undertaken in August 2011 to obtain an overview of the issues likely to be covered by the scope, and to help define

key areas. Searches were restricted to clinical guidelines, Health Technology Assessment (HTA) reports, key systematic reviews and RCTs. A list of databases and websites searched can be found in Appendix 8.

Systematic literature searches

After the scope was finalised, a systematic search strategy was developed to locate as much relevant evidence as possible. The balance between sensitivity (the power to identify all studies on a particular topic) and specificity (the ability to exclude irrelevant studies from the results) was carefully considered, and a decision made to utilise a broad approach to most of the searches to maximise retrieval of evidence to all parts of the guideline. Searches were restricted to certain study designs if specified in the review protocol, and conducted in the following databases:

- Cochrane Database of Abstracts of Reviews of Effects (DARE)
- Cochrane Database of Systematic Reviews (CDSR)
- CENTRAL
- Embase
- HTA database (technology assessments)
- MEDLINE/MEDLINE In-Process
- Psychological Information Database (PsycINFO).

The search strategies were initially developed for MEDLINE before being translated for use in other databases/interfaces. Strategies were built up through a number of trial searches and discussions of the results of the searches with the review team and GDG to ensure that all possible relevant search terms were covered. The search terms for each search are set out in full in Appendix 8.

Reference Management

Citations from each search were downloaded into reference management software and duplicates removed. Records were then screened against the eligibility criteria of the reviews before being appraised for methodological quality (see below). The unfiltered search results were saved and retained for future potential re-analysis to help keep the process both replicable and transparent.

Search filters

To aid retrieval of relevant and sound studies, filters were used to limit a number of searches to randomised controlled trials and systematic reviews. Both of these search filters are adaptations of filters designed by the Health Information Research Unit of McMaster University. Each filter comprises index terms relating to the study type(s) and associated text words for the methodological description of the design(s).

Date and language restrictions

Systematic database searches were initially conducted in July 2012 up to the most recent searchable date. Search updates were generated on a 6-monthly basis, with the final re-runs carried out in January 2014 ahead of the guideline consultation.

After this point, studies were only included if they were judged by the GDG to be exceptional (for example, if the evidence was likely to change a recommendation).

Although no language restrictions were applied at the searching stage, foreign language papers were not requested or reviewed, unless they were of particular importance to a review question.

For review questions that update Bipolar disorder (NICE clinical guideline 38), searching was limited to updating pre-existing reviews, covering the time period since the searches for the published reviews were conducted. For new review questions, no date restriction was imposed.

Other search methods

Other search methods involved: (a) scanning the reference lists of all eligible publications (systematic reviews, stakeholder evidence and included studies) for more published reports and citations of unpublished research; (b) sending lists of studies meeting the inclusion criteria to subject experts (identified through searches and the GDG) and asking them to check the lists for completeness, and to provide information of any published or unpublished research for consideration (see Appendix 6 and *Unpublished evidence* below); (c) contacting included study authors for unpublished or incomplete datasets. Searches conducted for existing NICE guidelines were updated where necessary.

Full details of the search strategies and filters used for the systematic review of clinical evidence are provided in Appendix 8.

Study selection and assessment of methodological quality

All primary-level studies included after the first scan of citations were acquired in full and re-evaluated for eligibility at the time they were being entered into the study information database. More specific eligibility criteria were developed for each review question and are described in the relevant clinical evidence chapters. The eligibility of each study was confirmed by at least one member of the GDG.

For some review questions, it was necessary to prioritise the evidence with respect to the UK context (that is, external validity). To make this process explicit, the GDG took into account the following factors when assessing the evidence:

- participant factors (for example, gender, age and ethnicity)
- provider factors (for example, model fidelity, the conditions under which the intervention was performed and the availability of experienced staff to undertake the procedure)
- cultural factors (for example, differences in standard care and differences in the welfare system).

It was the responsibility of the GDG to decide which prioritisation factors were relevant to each review question in light of the UK context.

Unpublished evidence

Stakeholders, authors and principle investigators were approached for unpublished evidence (see Appendices 4 and 6). The GDG used a number of criteria when deciding whether or not to accept unpublished data. First, the evidence must have been accompanied by a trial report containing sufficient detail to properly assess risk of bias. Second, the evidence must have been submitted with the understanding that data from the study and a summary of the study's characteristics would be published in the full guideline.

3.5.2 Evidence synthesis

Study characteristics, aspects of methodological quality, and outcome data were extracted from all eligible studies, using Microsoft Excel and Review Manager 5.2 (The Cochrane Collaboration).

The method used to synthesize evidence depended on the review question and availability and type of evidence (see below for full details). In the absence of high-quality research, an informal consensus process was used (see 3.5.6).

Synthesising the evidence from test accuracy studies

Meta-analysis

Review Manager was used to summarise test accuracy data from each study using forest plots and summary ROC plots.

Sensitivity and specificity

The sensitivity of an instrument refers to the probability that it will produce a true positive result when given to a population with the target disorder (as compared to a reference or "gold standard"). An instrument that detects a low percentage of cases will not be very helpful in determining the numbers of service users who should receive further assessment or a known effective intervention, as many individuals who should receive the treatment will not do so. This would lead to an under-estimation of the prevalence of the disorder, contribute to inadequate care and make for poor planning and costing of the need for treatment. As the sensitivity of an instrument increases, the number of false negatives it detects will decrease.

The specificity of an instrument refers to the probability that a test will produce a true negative result when given to a population without the target disorder (as determined by a reference or "gold standard"). This is important so that people without the disorder are not offered further assessment or interventions they do not need. As the specificity of an instrument increases, the number of false positives will decrease.

To illustrate this: from a population in which the point prevalence rate of anxiety is 10% (that is, 10% of the population has anxiety at any one time), 1000 people are given a test that has 90% sensitivity and 85% specificity. It is known that 100 people

in this population have anxiety, but the test detects only 90 (true positives), leaving 10 undetected (false negatives). It is also known that 900 people do not have anxiety, and the test correctly identifies 765 of these (true negatives), but classifies 135 incorrectly as having anxiety (false positives). The positive predictive value of the test (the number correctly identified as having anxiety as a proportion of positive tests) is 40% (90/90+135), and the negative predictive value (the number correctly identified as not having anxiety as a proportion of negative tests) is 98% (765/765 +10). Therefore, in this example, a positive test result is correct in only 40% of cases, while a negative result can be relied upon in 98% of cases.

The example above illustrates some of the main differences between positive predictive values and negative predictive values in comparison with sensitivity and specificity. For both positive and negative predictive values, prevalence explicitly forms part of their calculation (see Altman & Bland, 1994a). When the prevalence of a disorder is low in a population this is generally associated with a higher negative predictive value and a lower positive predictive value. Therefore although these statistics are concerned with issues probably more directly applicable to clinical practice (for example, the probability that a person with a positive test result actually has anxiety) they are largely dependent on the characteristics of the population sampled and cannot be universally applied (Altman & Bland, 1994a).

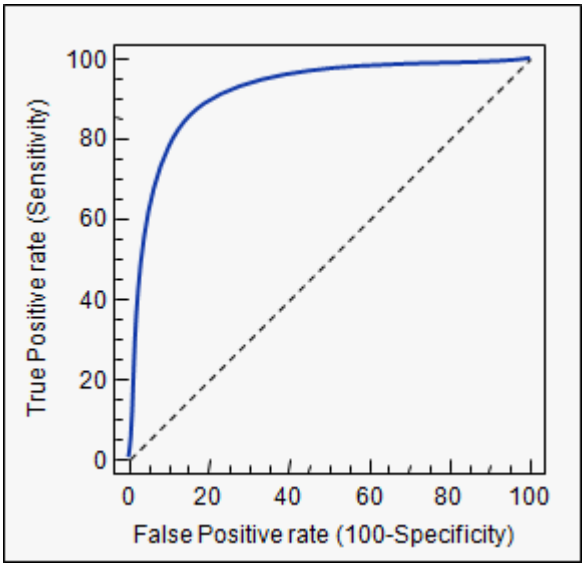
On the other hand, sensitivity and specificity do not necessarily depend on prevalence of anxiety (Altman & Bland, 1994b). For example, sensitivity is concerned with the performance of an identification instrument conditional on a person having anxiety. Therefore the higher false positives often associated with samples of low prevalence will not affect such estimates. The advantage of this approach is that sensitivity and specificity can be applied across populations (Altman & Bland, 1994b). However, the main disadvantage is that clinicians tend to find such estimates more difficult to interpret.

When describing the sensitivity and specificity of the different instruments, the GDG defined values above 0.9 as 'excellent', 0.8 to 0.9 as 'good', 0.5 to 0.7 as 'moderate', 0.3 to 0.4 as 'low', and less than 0.3 as 'poor'.

Receiver operator characteristic curves

The qualities of a particular tool are summarised in a receiver operator characteristic (ROC) curve, which plots sensitivity (expressed as a per cent) against (100-specificity) (see Figure 1).

Figure 1: Receiver operator characteristic (ROC) curve



A test with perfect discrimination would have an ROC curve that passed through the top left hand corner; that is, it would have 100% specificity and pick up all true positives with no false positives. While this is never achieved in practice, the area under the curve (AUC) measures how close the tool gets to the theoretical ideal. A perfect test would have an AUC of 1, and a test with AUC above 0.5 is better than chance. As discussed above, because these measures are based on sensitivity and 100-specificity, theoretically these estimates are not affected by prevalence.

Negative and positive likelihood ratios

Positive (LR+) and negative (LR-) likelihood ratios are thought not to be dependent on prevalence. LR+ is calculated by sensitivity/(1-specificity) and LR- is (1-sensitivity)/specificity. A value of LR+ >5 and LR- <0.3 suggests the test is relatively accurate (Fischer *et al.*, 2003).

Heterogeneity

Heterogeneity is usually much greater, and is to be expected, in meta-analyses of test accuracy studies compared with meta-analyses of RCTs (Macaskill et al., 2010). Therefore, a higher threshold for acceptable heterogeneity in such meta-analyses is required. However, when pooling studies resulted in $I^2 > 90\%$, meta-analyses were not conducted.

Synthesising the evidence for the effectiveness of interventions

Pairwise meta-analysis

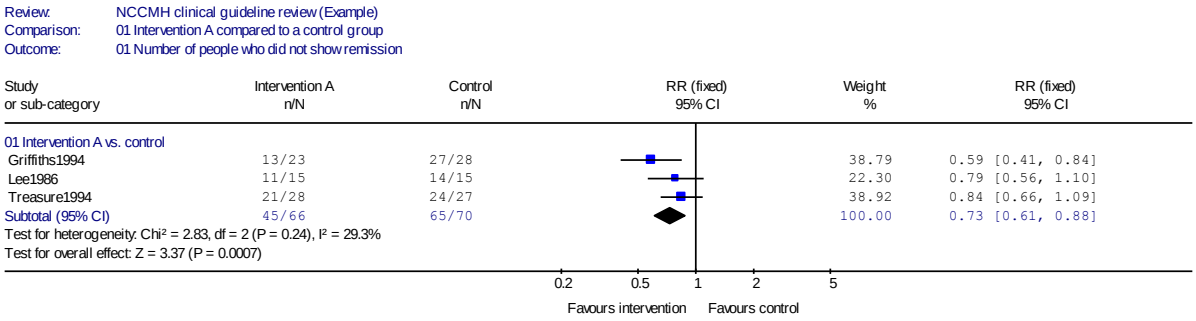
Where appropriate, meta-analysis was used to synthesise evidence for the effectiveness of interventions using Review Manager Version 5.2. If necessary, re-analyses of the data or sub-analyses were used to answer review questions not addressed in the original studies or reviews.

Dichotomous outcomes were analysed as relative risks (RR; also called a risk ratio) with the associated 95% CI (see Figure 2 for an example of a forest plot displaying

dichotomous data). An RR is the ratio of the treatment event rate to the control event rate. An RR of 1 indicates no difference between treatment and control. In Figure 2, the overall RR of 0.73 indicates that the event rate (in this case, rate of non-remission) associated with intervention A is about three-quarters of that of the control intervention or, in other words, the reduction in the relative risk is 27%.

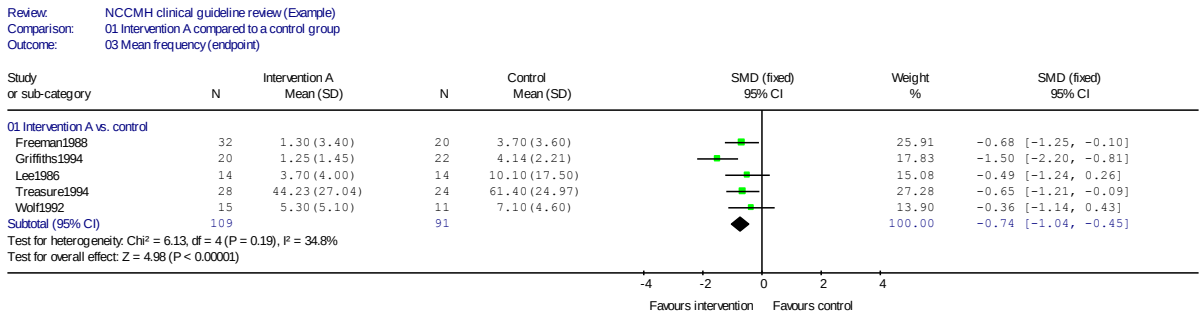
The CI shows a range of values within which it is possible to be 95% confident that the true effect will lie. If the effect size has a CI that does not cross the 'line of no effect', then the effect is commonly interpreted as being statistically significant.

Figure 2: Example of a forest plot displaying dichotomous data



Continuous outcomes were analysed using the mean difference (MD) or standardised mean difference (SMD) when different measures were used in different studies to estimate the same underlying effect (see Figure 3 for an example of a forest plot displaying continuous data). If reported by study authors, ITT data, using a valid method for imputation of missing data, were preferred over data only from people who completed the study.

Figure 3: Example of a forest plot displaying continuous data



Heterogeneity

To check for consistency of effects among studies, both the I^2 statistic and the chi-squared test of heterogeneity, as well as a visual inspection of the forest plots were used. The I^2 statistic describes the proportion of total variation in study estimates that is due to heterogeneity (Higgins & Thompson, 2002). For meta-analyses of comparative effectiveness studies, the I^2 statistic was interpreted in the following way based on guidelines from the Cochrane Collaboration (Higgins & Green, 2011):

- 0% to 40%: might not be important
- 30% to 60%: may represent moderate heterogeneity
- 50% to 90%: may represent substantial heterogeneity
- 75% to 100%: considerable heterogeneity.

The Cochrane Collaboration advice suggests that overlapping categories are less misleading than simple thresholds since the importance of inconsistency depends on (1) the magnitude and direction of effects, and (2) the strength of evidence for heterogeneity (for example, *p* value from the chi-squared test, or a CI for I^2).

Network meta-analysis

Standard models for network meta-analysis (NMA) with binary outcomes were used for two outcomes: a) discontinuation, and b) response given no discontinuation. Information on the log-odds ratio of response in trials reporting on more than one scale was combined and information on the standardised mean difference on different symptoms scales was used to inform the log-odds ratio of response. Baseline probabilities of discontinuation and response given no discontinuation were calculated based on all trials with a Placebo arm reporting these outcomes. Further information about the method used and the winBUGS code can be found in Appendix 15.

3.5.3 Grading the quality of evidence

For questions about the effectiveness of interventions, the GRADE approach[2] was used to grade the quality of evidence for each outcome (Guyatt et al., 2011). For questions about the experience of care and the organisation and delivery of care, methodology checklists (see Section 3.5.1) were used to assess the risk of bias, and this information was taken into account when interpreting the evidence. The technical team produced GRADE evidence profiles (see below) using GRADEprofiler (GRADEpro) software (Version 3.6), following advice set out in the GRADE handbook (Schünemann et al., 2009).

Evidence profiles

A GRADE evidence profile was used to summarise both the quality of the evidence and the results of the evidence synthesis for each 'critical' outcome. The GRADE approach is based on a sequential assessment of the quality of evidence, followed by judgment about the balance between desirable and undesirable effects, and subsequent decision about the strength of a recommendation.

Within the GRADE approach to grading the quality of evidence, the following is used as a starting point:

- RCTs without important limitations provide high quality evidence

[2] For further information about GRADE, see www.gradeworkinggroup.org

- observational studies without special strengths or important limitations provide low quality evidence.

For each outcome, quality may be reduced depending on five factors: limitations, inconsistency, indirectness, imprecision and publication bias. For the purposes of the guideline, each factor was evaluated using criteria provided in Table 4.

For observational studies without any reasons for down-grading, the quality may be up-graded if there is a large effect, all plausible confounding would reduce the demonstrated effect (or increase the effect if no effect was observed), or there is evidence of a dose-response gradient (details would be provided under the 'other' column).

Table 4: Factors that decrease quality of evidence

Factor	Description	Criteria
Limitations	Methodological quality/ risk of bias.	Serious risks across most studies (that reported a particular outcome). The evaluation of risk of bias was made for each study using NICE methodology checklists (see Section 3.5.1).
Inconsistency	Unexplained heterogeneity of results.	Moderate or greater heterogeneity
Indirectness	How closely the outcome measures, interventions and participants match those of interest.	If the comparison was indirect, or if the question being addressed by the GDG was substantially different from the available evidence regarding the population, intervention, comparator, or an outcome.
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of the effect.	If either of the following two situations were met: • the optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) was not achieved • the 95% confidence interval around the pooled or best estimate of effect included both 1) no effect and 2) appreciable benefit or appreciable harm
Publication bias	Systematic underestimate or an overestimate of the underlying beneficial or harmful effect due to the selective publication of studies.	Evidence of selective publication. This may be detected during the search for evidence, or through statistical analysis of the available evidence.

3.5.4 Presenting evidence to the Guideline Development Group

Study characteristics tables and, where appropriate, forest plots generated with Review Manager Version 5.2 and GRADE summary of findings tables (see below) were presented to the GDG.

Where meta-analysis was not appropriate and/or possible, the reported results from each primary-level study were reported in the study characteristics table and presented to the GDG. The range of effect estimates were included in the GRADE profile, and where appropriate, described narratively.

Summary of findings tables

Summary of findings tables generated from GRADEpro were used to summarise the evidence for each outcome and the quality of that evidence. The tables provide illustrative comparative risks, especially useful when the baseline risk varies for different groups within the population.

3.5.5 Extrapolation

When answering review questions, if there is no direct evidence from a primary dataset,[3] based on the initial search for evidence, it may be appropriate to extrapolate from another data set. In this situation, the following principles were used to determine when to extrapolate:

- a primary dataset is absent, of low quality or is judged to be not relevant to the review question under consideration, and
- a review question is deemed by the GDG to be important, such that in the absence of direct evidence, other data sources should be considered, and
- non-primary data source(s) is in the view of the GDG available, which may inform the review question.

When the decision to extrapolate was made, the following principles were used to inform the choice of the non-primary dataset:

- the populations (usually in relation to the specified diagnosis or problem which characterises the population) under consideration share some common characteristic but differ in other ways, such as age, gender or in the nature of the disorder (for example, a common behavioural problem; acute versus chronic presentations of the same disorder), and
- the interventions under consideration in the view of the GDG have one or more of the following characteristics:
    - share a common mode of action (e.g., the pharmacodynamics of drug; a common psychological model of change - operant conditioning)
    - be feasible to deliver in both populations (e.g., in terms of the required skills or the demands of the health care system)
    - share common side effects/harms in both populations, and
- the context or comparator involved in the evaluation of the different datasets shares some common elements which support extrapolation, and
- the outcomes involved in the evaluation of the different datasets shares some common elements which support extrapolation (for example, improved mood or a reduction in challenging behaviour).

[3]A primary data set is defined as a data set which contains evidence on the population and intervention under review

When the choice of the non-primary dataset was made, the following principles were used to guide the application of extrapolation:

- the GDG should first consider the need for extrapolation through a review of the relevant primary dataset and be guided in these decisions by the principles for the use of extrapolation
- in all areas of extrapolation datasets should be assessed against the principles for determining the choice of datasets. In general the criteria in the four principles set out above for determining the choice should be met
- in deciding on the use of extrapolation, the GDG will have to determine if the extrapolation can be held to be reasonable, including ensuring that:
    - the reasoning behind the decision can be justified by the clinical need for a recommendation to be made
    - the absence of other more direct evidence, and by the relevance of the potential dataset to the review question can be established
    - the reasoning and the method adopted is clearly set out in the relevant section of the guideline.

3.5.6 Method used to answer a review question in the absence of appropriately designed, high-quality research

In the absence of appropriately designed, high-quality research (including indirect evidence where it would be appropriate to use extrapolation), an informal consensus process was adopted.

The process involved a group discussion of what is known about the issues. The views of GDG were synthesised narratively by a member of the review team, and circulated after the meeting. Feedback was used to revise the text, which was then included in the appropriate evidence review chapter.

3.6 HEALTH ECONOMICS METHODS

The aim of the health economics was to contribute to the guideline's development by providing evidence on the cost effectiveness of interventions for adults, children and young people with bipolar disorder covered in the guideline. This was achieved by:

- systematic literature review of existing economic evidence
- decision-analytic economic modelling.

Systematic reviews of economic literature were conducted in all areas covered in the guideline. Economic modelling was undertaken in areas with likely major resource implications, where the current extent of uncertainty over cost effectiveness was significant and economic analysis was expected to reduce this uncertainty, in accordance with *The Guidelines Manual* (NICE, 2012). Prioritisation of areas for economic modelling was a joint decision between the Health Economist and the GDG. The rationale for prioritising review questions for economic modelling was set

out in an economic plan agreed between NICE, the GDG, the Health Economist and the other members of the technical team. The following economic questions were selected as key issues that were addressed by economic modelling:

- Cost effectiveness of pharmacological interventions for adults with bipolar disorder in a manic episode
- Cost effectiveness of pharmacological interventions for adults with bipolar disorder in an acute depressive episode
- Cost effectiveness of pharmacological interventions for the maintenance treatment of adults with bipolar disorder.

In addition, literature on the health-related quality of life of people with bipolar disorder was systematically searched to identify studies reporting appropriate utility values that could be utilised in a cost-utility analysis.

The rest of this section describes the methods adopted in the systematic literature review of economic studies. Methods employed in economic modelling are described in the relevant economic sections of the evidence chapters.

3.6.1 Search strategy for economic evidence

Scoping searches

A broad preliminary search of the literature was undertaken in August 2011 to obtain an overview of the issues likely to be covered by the scope, and help define key areas. Searches were restricted to economic studies and HTA reports, and conducted in the following databases:

- Embase
- MEDLINE/MEDLINE In-Process
- HTA database (technology assessments)
- NHS Economic Evaluation Database (NHS EED).

Any relevant economic evidence arising from the clinical scoping searches was also made available to the health economist during the same period.

Systematic literature searches

After the scope was finalised, a systematic search strategy was developed to locate as much relevant evidence as possible. The balance between sensitivity (the power to identify all studies on a particular topic) and specificity (the ability to exclude irrelevant studies from the results) was carefully considered, and a decision made to utilise a broad approach to most of the searches to maximise retrieval of evidence to all parts of the guideline. Searches were restricted to economic studies and health technology assessment reports, and conducted in the following databases:

- CINAHL

- Embase
- HTA database (technology assessments)
- MEDLINE/MEDLINE In-Process
- NHS EED
- PsycINFO.

Any relevant economic evidence arising from the clinical searches was also made available to the health economist during the same period.

The search strategies were initially developed for MEDLINE before being translated for use in other databases/interfaces. Strategies were built up through a number of trial searches, and discussions of the results of the searches with the review team and GDG to ensure that all possible relevant search terms were covered.

The search terms are set out in full in Appendix 9.

Reference Management

Citations from each search were downloaded into reference management software and duplicates removed. Records were then screened against the inclusion criteria of the reviews before being quality appraised. The unfiltered search results were saved and retained for future potential re-analysis to help keep the process both replicable and transparent.

Search filters

The search filter for health economics is an adaptation of a pre-tested strategy designed by the Centre for Reviews and Dissemination. The search filter is designed to retrieve records of economic evidence (including full and partial economic evaluations) from the vast amount of literature indexed to major medical databases such as MEDLINE. The filter, which comprises a combination of controlled vocabulary and free-text retrieval methods, maximises sensitivity (or recall) to ensure that as many potentially relevant records as possible are retrieved from a search. A full description of the filter is provided in Appendix 9.

Date and language restrictions

Systematic database searches were initially conducted in July 2012 up to the most recent searchable date. Search updates were generated on a 6-monthly basis, with the final re-runs carried out in January 2014 ahead of the guideline consultation. After this point studies were included only if they were judged by the GDG to be exceptional (for example, the evidence was likely to change a recommendation).

For review questions that update Bipolar disorder (NICE clinical guideline 38), searching was limited to updating pre-existing reviews, covering the time period since the searches for the published reviews were conducted. For new review questions, searches were restricted to research published from 1998 onwards in order to obtain data relevant to current healthcare settings and costs.

Other search methods

Other search methods involved scanning the reference lists of all eligible publications (systematic reviews, stakeholder evidence and included studies from the economic and clinical reviews) to identify further studies for consideration.

Full details of the search strategies and filter used for the systematic review of health economic evidence are provided in Appendix 9.

3.6.2 Inclusion criteria for economic studies

The following inclusion criteria were applied to select studies identified by the economic searches for further consideration:

1. Only studies from Organisation for Economic Co-operation and Development countries were included, as the aim of the review was to identify economic information transferable to the UK context.
2. Only studies published from 2003 onwards were included in the review. This date restriction was imposed so that retrieved economic evidence was relevant to current healthcare settings and costs.
3. Selection criteria based on types of clinical conditions and service users as well as interventions assessed were identical to the clinical literature review.
4. Studies were included provided that sufficient details regarding methods and results were available to enable the methodological quality of the study to be assessed, and provided that the study's data and results were extractable. Poster presentations Poster presentations and abstracts in conference proceedings were excluded.
5. Full economic evaluations that compared two or more relevant options and considered both costs and consequences were included in the review.
6. Economic studies were included if they used clinical effectiveness data from RCTs, prospective cohort studies, or systematic reviews and meta-analyses of clinical studies. Studies that had a mirror-image or other retrospective design were excluded from the review. Studies that utilised clinical effectiveness parameters based on expert opinion or assumptions were also excluded.
7. Studies were included only if the examined interventions were clearly described. This involved the dosage and route of administration and the duration of treatment in the case of pharmacological interventions; and the types of health professionals involved as well as the frequency and duration of treatment in the case of psychological interventions. Evaluations in which drugs were treated as a class were excluded from further consideration.
8. Studies that adopted a very narrow perspective, ignoring major categories of costs to the NHS, were excluded; for example studies that estimated exclusively drug acquisition costs or hospitalisation costs were considered non-informative to the guideline development process.

3.6.3 Applicability and quality criteria for economic studies

All economic papers eligible for inclusion were appraised for their applicability and quality using the methodology checklist for economic evaluations recommended by NICE (NICE, 2012). The methodology checklist for economic evaluations was also applied to the economic models developed specifically for this guideline. All studies that fully or partially met the applicability and quality criteria described in the methodology checklist were considered during the guideline development process, along with the results of the economic modelling conducted specifically for this guideline. The completed methodology checklists for all economic evaluations considered in the guideline are provided in Appendix 31**Error! Reference source not found.**.

3.6.4 Presentation of economic evidence

The economic evidence considered in the guideline is provided in the respective evidence chapters, following presentation of the relevant clinical evidence. The references to included studies and the respective evidence tables with the study characteristics and results are provided in Appendix 32. Methods and results of economic modelling undertaken alongside the guideline development process are presented in the relevant evidence chapters. Characteristics and results of all economic studies considered during the guideline development process (including modelling studies conducted for this guideline) are summarised in economic evidence profiles that are presented in Appendix 33.

3.6.5 Results of the systematic search of economic literature

The titles of all studies identified by the systematic search of the literature were screened for their relevance to the topic (that is, economic issues and information on health-related quality of life). References that were clearly not relevant were excluded first. The abstracts of all potentially relevant studies (250 references) were then assessed against the inclusion criteria for economic evaluations by the health economist. Full texts of the studies potentially meeting the inclusion criteria (including those for which eligibility was not clear from the abstract) were obtained. Studies that did not meet the inclusion criteria, were duplicates, were secondary publications of one study, or had been updated in more recent publications were subsequently excluded. Economic evaluations eligible for inclusion (20 studies in 19 publications) were then appraised for their applicability and quality using the methodology checklist for economic evaluations. Finally, 17 publications reporting 18 economic analyses that fully or partially met the applicability and quality criteria were considered at formulation of the guideline recommendations.

3.7 USING NICE EVIDENCE REVIEWS AND RECOMMENDATIONS FROM EXISTING NICE CLINICAL GUIDELINES

When review questions overlap and evidence from another guideline applies to a question in the current guideline, it might be desirable and practical to incorporate

or adapt recommendations published in NICE guidelines. Adaptation refers to the process by which an existing recommendation is modified in order to facilitate its placement in a new guideline. Incorporation refers to the placement of a recommendation that was developed for another guideline into a new guideline, with no material changes to wording or structure. Incorporation would be used in relatively rare circumstances, as cross-referring to the other guideline will often be all that is necessary.

Incorporation or adaptation is likely to be substantially more complex where health economics were a major part of the decision making. In these circumstances, these methods are only used rarely after full and detailed consideration.

3.7.1 Incorporation

In the current guideline, the following criteria were used to determine when a recommendation could be incorporated:

- a review question in the current guideline was addressed in another NICE guideline
- evidence for the review question and related recommendation(s) has not changed in important ways
- evidence for the previous question is judged by the GDG to support the existing recommendation(s), and be relevant to the current question
- the relevant recommendation can 'stand alone' and does not need other recommendations from the original guideline to be relevant or understood within the current guideline.

3.7.2 Adaptation

The following criteria were used to determine when a recommendation could be adapted:

- a review question in the current guideline is similar to a question addressed in another NICE guideline
- evidence for the review question and related recommendations has not changed in important ways
- evidence for the previous question is judged by the GDG to support the existing recommendation(s), and be relevant to the current question
- the relevant recommendation can 'stand alone' and does not need other recommendations from the original guideline to be relevant
- contextual evidence, such as background information about how an intervention is provided in the healthcare settings that are the focus of the guideline, informs the re-drafting or re-structuring of the recommendation but does not alter its meaning or intent (if meaning or intent were altered, a new recommendation should be developed).

In deciding whether to choose between incorporation or adaptation of existing guideline recommendations, the GDG considered whether the direct evidence obtained from the current guideline dataset was of sufficient quality to allow

development of recommendations. It was only where (a) such evidence was not available or insufficient to draw robust conclusions and (b) where methods used in other NICE guidelines were sufficiently robust that the 'incorporate and adapt' method could be used. Recommendations were only incorporated or adapted after the GDG had reviewed evidence supporting previous recommendations and confirmed that they agreed with the original recommendations.

When adaptation is used, the meaning and intent of the original recommendation is preserved but the wording and structure of the recommendation may change. Preservation of the original meaning (that is, that the recommendation faithfully represents the assessment and interpretation of the evidence contained in the original guideline evidence reviews) and intent (that is, the intended action[s] specified in the original recommendation will be achieved) is an essential element of the process of adaptation.

3.8 FROM EVIDENCE TO RECOMMENDATIONS

Once the clinical and health economic evidence was summarised, the GDG drafted the recommendations. In making recommendations, the GDG took into account the trade-off between the benefits and harms of the intervention/instrument, as well as other important factors, such as economic considerations, values of the GDG and society, the requirements to prevent discrimination and to promote equality[4], and the GDG's awareness of practical issues (Eccles et al., 1998; NICE, 2012).

Finally, to show clearly how the GDG moved from the evidence to the recommendations, each chapter has a section called 'from evidence to recommendations'. Underpinning this section is the concept of the 'strength' of a recommendation (Schünemann et al., 2003). This takes into account the quality of the evidence but is conceptually different. Some recommendations are 'strong' in that the GDG believes that the vast majority of healthcare professionals and service users would choose a particular intervention if they considered the evidence in the same way that the GDG has. This is generally the case if the benefits clearly outweigh the harms for most people and the intervention is likely to be cost effective. However, there is often a closer balance between benefits and harms, and some service users would not choose an intervention whereas others would. This may happen, for example, if some service users are particularly averse to some side effect and others are not. In these circumstances the recommendation is generally weaker, although it may be possible to make stronger recommendations about specific groups of service users. The strength of each recommendation is reflected in the wording of the recommendation, rather than by using ratings, labels or symbols.

Where the GDG identified areas in which there are uncertainties or where robust evidence was lacking, they developed research recommendations. Those that were identified as 'high priority' were developed further in the NICE version of the guideline, and presented in Appendix 10.

[4]See NICE's equality scheme: www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp

3.9 STAKEHOLDER CONTRIBUTIONS

Professionals, service users, and companies have contributed to and commented on the guideline at key stages in its development. Stakeholders for this guideline include:

- service user and carer stakeholders: national service user and carer organisations that represent the interests of people whose care will be covered by the guideline
- local service user and carer organisations: but only if there is no relevant national organisation
- professional stakeholders' national organisations: that represent the healthcare professionals who provide the services described in the guideline
- commercial stakeholders: companies that manufacture drugs or devices used in treatment of the condition covered by the guideline and whose interests may be significantly affected by the guideline
- providers and commissioners of health services in England and Wales
- statutory organisations: including the Department of Health, the Welsh Assembly
- Government, NHS Quality Improvement Scotland, the Care Quality Commission and the National Patient Safety Agency
- research organisations: that have carried out nationally recognised research in the area.

NICE clinical guidelines are produced for the NHS in England and Wales, so a 'national' organisation is defined as one that represents England and/or Wales, or has a commercial interest in England and/or Wales.

Stakeholders have been involved in the guideline's development at the following points:

- commenting on the initial scope of the guideline and attending a scoping workshop held by NICE
- contributing possible review questions and lists of evidence to the GDG
- commenting on the draft of the guideline.

3.10 VALIDATION OF THE GUIDELINE

Registered stakeholders had an opportunity to comment on the draft guideline, which was posted on the NICE website during the consultation period. Following the consultation, all comments from stakeholders and experts (see Appendix 5) were responded to, and the guideline updated as appropriate. NICE also reviewed the guideline and checked that stakeholders' comments had been addressed.

Following the consultation period, the GDG finalised the recommendations and the NCCMH produced the final documents. These were then submitted to NICE for a quality assurance check. Any errors were corrected by the NCCMH, then the

guideline was formally approved by NICE and issued as guidance to the NHS in England and Wales.

4 IMPROVING THE EXPERIENCE OF CARERS

4.1 INTRODUCTION

This chapter is concerned specifically with the experience of carers. The experience of people with mental disorders, including bipolar disorder, is covered by another NICE guideline, *Service User Experience in Adult Mental Health* (NICE, 2011; NCCMH, 2012), which provides evidence-based recommendations for improving mental health services, but did not cover carers' experience. The GDG therefore saw the value in a review of carers' experience of supporting people with bipolar disorder for this guideline update.

Features of bipolar disorder, particularly extreme mood swings from mania to depression, impose particular stresses and demands on service users and their carers (Perlick et al., 1999). Coping with such extremes of mood, with the changes often happening relatively quickly, can be very challenging, and the depressive episodes of the disorder are associated with a higher risk of suicide than with other severe mental illnesses (Clements et al., 2013). Symptoms such as grandiosity, irritability, and inappropriate or excessive behaviour can have very damaging consequences not only for service users, but also for the quality life of their families and their carers (Zendjidjian et al., 2012). Relationships can be put under particular pressure, especially from sexual indiscretions during manic episodes, irritability and from extravagant spending, which may lead to relationships breaking down irrevocably (Hosang et al, 2012; Fletcher et al, 2013; Morriss et al, 2013). Partners and other family members have also reported significant impact on their own employment, finances, legal affairs, parenting roles, other social relationships ((Dore & Romans, 2001; Perlick et al., 1999; Zendjidjian et al., 2012)) and psychological wellbeing (Zendjidjian et al., 2012). However, caring for people with bipolar disorder can also be a positive experience as they often have positive attributes, like drive and creativity (Maskill et al, 2010; Grover et al, 2012), although obviously this is not a typical experience for many service users and carers.

Even more moderate symptoms can be damaging in a different, more insidious way. Milder symptoms may not be obviously recognisable as mental illness, given that everyone experiences changes in mood to some degree. For this reason, it can be difficult for partners, families, carers, employers and others to recognise behaviours that are milder symptoms of the illness and simply attribute it to 'bad behaviour' by the service user. This can have damaging long-term consequences for family dynamics and at work, for example, if symptoms are interpreted as misconduct at work, resulting in loss of income for the family.

The assessment and management of bipolar disorder should ideally involve partners, families and carers contributing to the assessment process (by attesting to the patterns of symptoms and behaviour, for example), managing acute episodes,

promoting long-term recovery (for example, through family intervention) and preventing relapse (carers may be very knowledgeable about the particular triggers that precipitate episodes of illness). People with bipolar disorder may, or may not, want their partners to be involved in shared decision-making. But whatever their relationship, carers' ability to provide effective support may improve outcomes for people with bipolar disorder. Carers may benefit from support to improve how they function in their caring role. Improving their access to, and experience of, health services, may also improve their wellbeing, and in turn benefit service users.

Since bipolar disorder is a lifelong disorder, presenting quite commonly after puberty and lasting into old age, the people who provide informal care, and the nature of that care, will change, with the role of carer likely to pass first from parent to partner, friend or other family member. As servicer users grow older, there are a range of specific age and developmental-related needs that health and social care professionals may need to provide support for. Both information needs and responsibility for self-management will develop and evolve over time, with service users increasingly appreciating the benefits of self-management as their experience of the illness grows. Also, in older age, physical health and cognitive factors will become increasingly important. There is some evidence that people with mania from black and minority ethnic (BME) groups can present late and in a more severe episode of illness, so are disproportionately detained formally (Kennedy et al, 2004; Lloyd et al, 2005). There is a particular need to work with such families to build trust and to intervene earlier in the course of bipolar episodes so that admission and formal detention are less necessary.

4.2 REVIEW OF THE EVIDENCE

4.2.1 Review strategy

Carers of people with serious mental illness may have shared experiences and concerns regardless of the service user's diagnosis (for example, bipolar disorder or schizophrenia. For this reason, the GDG wished to investigate ways to improve the experience of caring for people with bipolar disorder by considering a wide body of evidence about caring for people with serious mental illness. Reviews for this guideline were thus undertaken in conjunction with a NICE guideline being developed at the same time, *Psychosis and Schizophrenia in Adults* (NICE, 2014), which includes the full methods and results of those reviews. The studies included in these reviews included carers of people with bipolar disorder, and the results are directly relevant to this guideline. Before making any recommendations, the GDG were presented with the evidence and draft recommendations made by the *Psychosis and Schizophrenia in Adults* GDG. The method of incorporation and adaptation (see Section 3.7) was followed to ensure that the recommendations were appropriate for people with bipolar disorder. Further information about shared recommendations and the reason for incorporating or adapting each one can be found in the next section.

4.2.2 Summary of findings

A thematic synthesis of qualitative studies identified five themes that carers of adults with severe mental illness believed would improve their experience of health and social care services and reduce carers' burden. These were: (1) building trusting relationships with healthcare providers; (2) valuing the identity and experience of the carer; (3) sharing decision making and involvement; (4) providing clear and comprehensible information; and (5) access to health services. Carers in the included studies valued carer-focused interventions such as a self-management toolkit, group psychoeducation and carer support groups as useful means of receiving information. Group psychoeducation and carer support groups were also considered to be useful for sharing experiences with others.

A systematic review of interventions to improve the experience of caring for a person with serious mental illness found limited evidence that psychoeducation may be effective in reducing carers' burden and these effects are maintained at long-term follow-up. Furthermore, evidence suggests that although no immediate benefit can be found at the end of the intervention, psychoeducation may reduce psychological distress in the long term. Support groups may also be effective in improving carers' experience of caring and reducing psychological distress. However, these findings should be viewed with caution as the studies included in this review are based in East Asia and the services provided there are not directly comparable to the UK. In addition, there was limited evidence that enhanced psychoeducation (providing information, as well as focusing on self-carer skills, coping skills and problem-solving) was more effective than standard psychoeducation (information only) in improving the experience of caring and self-care behaviour at the end of the

intervention. However, longer-term effects are not known. Self-management was not found to be beneficial over control on any critical outcomes. However, this was based on a single high quality study and a trend favouring self-management was observed. Problem-solving bibliotherapy was not found to be effective at improving any critical outcomes at the end of the intervention, however, it was found to improve quality of life at short-term follow-up. Finally, there was no detectable difference in effectiveness between psychoeducation delivered by post or delivered by a practitioner, or between group and individual psychoeducation.

A simple cost analysis estimated that the cost of group psychoeducation aiming to improve carers' experience of caring and of health and social care services ranges between £190 and £1,095 (mean of £582) in 2011/12 prices, depending on the type of health professional (clinical psychologist, psychiatric nurse or consultant psychiatrist) that delivers the intervention.

Table 5 contains the original recommendations from *Psychosis and Schizophrenia in Adults* (NICE, 2014) in column 1 and the associated review question(s) and evidence base in column 2. The adapted/incorporated recommendations are shown in column 3 and reasons for doing so are provided in column 4.

Table 5: Recommendations incorporated or adapted from another NICE guideline

Original recommendation from *Psychosis and Schizophrenia Update* (NICE, 2014)	**Review question and evidence base of existing recommendation**	**Recommendation following adaptation/ incorporation for this guideline**	**Reasons for adaptation/ incorporation**
1.1.5.1 Offer carers of people with psychosis or schizophrenia 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	Review questions: What factors improve or diminish the experience of health and social services for carers of people with severe mental illness? What modification to health and social services improve the experience of using services for carers of adults with severe mental illness? Evidence base: Health and social services to improve the experience of using services for carers of adults with severe mental illness (based on a review of 31 qualitative studies and 20 quantitative studies). See Chapter 4 of *Psychosis and Schizophrenia in Adults* (NCCMH, 2014)	1.1.13 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.	The GDG considered issues that can affect carers of an adult with severe mental illness. The GDG reviewed the evidence in conjunction with the *Psychosis and Schizophrenia in Adults* guideline and judged that this recommendation was relevant to people with bipolar disorder. The GDG adapted this recommendation by changing 'psychosis or schizophrenia' to 'bipolar disorder'.
1.1.5.2 Advise carers about their statutory right to a formal carer's assessment provided by social care services and explain how to access this.	Review questions: What factors improve or diminish the experience of health and social services for carers of people with severe mental illness? What modification to health and social services improve the experience of	1.1.14 Advise carers about their statutory right to a formal carer's assessment provided by social care services and explain how to access this.	The GDG considered issues that can affect carers of an adult with severe mental illness. The GDG reviewed the evidence in conjunction with the *Psychosis and Schizophrenia in Adults* guideline and judged that this recommendation was relevant to people with bipolar disorder. The GDG adapted this recommendation by changing 'psychosis or

	using services for carers of adults with severe mental illness? Evidence base: Health and social services to improve the experience of using services for carers of adults with severe mental illness (based on a review of 31 qualitative studies and 20 quantitative studies). See Chapter 4 of *Psychosis and Schizophrenia in Adults* (NCCMH, 2014)		schizophrenia' to 'bipolar disorder'.
1.1.5.3 Give carers written and verbal information in an accessible format about: · diagnosis and management of psychosis and schizophrenia · 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.	Review questions: What factors improve or diminish the experience of health and social services for carers of people with severe mental illness? What modification to health and social services improve the experience of using services for carers of adults with severe mental illness? Evidence base: Health and social services to improve the experience of using services for carers of adults with severe mental illness (based on a review of 31 qualitative studies and 20 quantitative studies). See Chapter 4 of *Psychosis and Schizophrenia in Adults* (NCCMH, 2014)	1.1.15 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.	The GDG considered issues that can affect carers of an adult with severe mental illness. The GDG reviewed the evidence in conjunction with the *Psychosis and Schizophrenia in Adults* guideline and judged that this recommendation was relevant to people with bipolar disorder. The GDG adapted this recommendation by changing 'psychosis or schizophrenia' to 'bipolar disorder'.
1.1.5.4 As early as possible negotiate with service users and carers about	Review questions:	1.1.16 As early as possible negotiate with the person with bipolar	The GDG considered issues that can affect carers of an adult with severe

how information about the service user will be shared. When discussing rights to confidentiality, emphasise the importance of sharing information about risks and the need for carers to understand the service user's perspective. Foster a collaborative approach that supports both service users and carers, and respects their individual needs and interdependence.	What factors improve or diminish the experience of health and social services for carers of people with severe mental illness? What modification to health and social services improve the experience of using services for carers of adults with severe mental illness? Evidence base: Health and social services to improve the experience of using services for carers of adults with severe mental illness (based on a review of 31 qualitative studies and 20 quantitative studies). See Chapter 4 of *Psychosis and Schizophrenia in Adults* (NCCMH, 2014)	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.	mental illness. The GDG reviewed the evidence in conjunction with the *Psychosis and Schizophrenia in Adults* guideline and judged that this recommendation was relevant to people with bipolar disorder. The GDG adapted this recommendation by changing 'psychosis or schizophrenia' to 'bipolar disorder'.
1.1.5.5 Review regularly how information is shared, especially if there are communication and collaboration difficulties between the service user and carer.	Review questions: What factors improve or diminish the experience of health and social services for carers of people with severe mental illness? What modification to health and social services improve the experience of using services for carers of adults with severe mental illness? Evidence base: Health and social services to	1.1.17 Review regularly how information is shared, especially if there are communication and collaboration difficulties between the person and their and carer.	The GDG considered issues that can affect carers of an adult with severe mental illness. The GDG reviewed the evidence in conjunction with the *Psychosis and Schizophrenia in Adults* guideline and judged that this recommendation was relevant to people with bipolar disorder. The GDG incorporated this recommendation.

	improve the experience of using services for carers of adults with severe mental illness (based on a review of 31 qualitative studies and 20 quantitative studies). See Chapter 4 of *Psychosis and Schizophrenia in Adults* (NCCMH, 2014)		
1.1.5.6 Include carers in decision-making if the service user agrees.	Review questions: What factors improve or diminish the experience of health and social services for carers of people with severe mental illness? What modification to health and social services improve the experience of using services for carers of adults with severe mental illness? Evidence base: Health and social services to improve the experience of using services for carers of adults with severe mental illness (based on a review of 31 qualitative studies and 20 quantitative studies). See Chapter 4 of *Psychosis and Schizophrenia in Adults* (NCCMH, 2014)	1.1.18 Include carers in decision-making if the person agrees.	The GDG considered issues that can affect carers of an adult with severe mental illness. The GDG reviewed the evidence in conjunction with the *Psychosis and Schizophrenia in Adults* guideline and judged that this recommendation was relevant to people with bipolar disorder. The GDG incorporated this recommendation.
1.1.5.7 Offer a carer-focused education and support programme, which may be part of a family intervention for psychosis and schizophrenia, as early as possible to all carers. The intervention should: • be available as needed	Review questions: What factors improve or diminish the experience of health and social services for carers of people with severe mental illness?	1.1.20 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	The GDG considered issues that can affect carers of an adult with severe mental illness. The GDG reviewed the evidence in conjunction with the *Psychosis and Schizophrenia in Adults* guideline and judged that this recommendation was relevant to

• have a positive message about recovery.	What modification to health and social services improve the experience of using services for carers of adults with severe mental illness? Evidence base: Health and social services to improve the experience of using services for carers of adults with severe mental illness (based on a review of 31 qualitative studies and 20 quantitative studies). See Chapter 4 of *Psychosis and Schizophrenia in Adults* (NCCMH, 2014)	· have a positive message about recovery.	people with bipolar disorder. The GDG adapted this recommendation by changing 'psychosis or schizophrenia' to 'bipolar disorder'.

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4.3 LINKING EVIDENCE TO RECOMMENDATIONS

4.3.1 Relative value placed on the outcomes considered

Based on a review of qualitative studies and the expert consensus of the GDG, the critical issues in designing services and measuring the outcomes of interventions to improve the carers' experience of caring for a person with bipolar disorder include:

- quality of life
- mental health (anxiety or depression)
- burden of care (including 'burnout', stress and coping)
- financial impact
- impact on family life
- satisfaction with services
- physical and emotional safety.

4.3.2 Trade-off between clinical benefits and harms

The factors identified by the qualitative review revealed a broad range of issues that resonated with the experience of the carers, service users and healthcare professional members of the GDG.

The qualitative analysis revealed that carers thought a key determinant of their experience of services and experience of caring was building trusting relationships with healthcare professionals. An empathic and understanding healthcare professional allows the carer to build confidence in their role as a carer and reduces feelings of stress and burden. The GDG felt that these issues were particularly important in the context of bipolar disorder, especially during acute episodes.

Two linked themes were identified in the qualitative literature. Carers felt that services should identify and value their experience and involve them in decision making. Carers felt that confidentiality was often used as a reason to exclude them from receiving important information about the service user's care and treatment, resulting in a stressful, burdensome and isolated experience for them. This theme was prevalent throughout the care pathway and specifically during and after acute episodes. The GDG noted that acute episodes may have serious consequences for partners, other carers and for dependent children. The GDG wished to emphasise that families and carers ought to be involved in decision making, especially during periods of mania, because an acute episode might have direct consequences for them. Consent of the service user would be necessary unless there was a risk to themselves or others, including dependent children or young people and vulnerable adults.

The GDG used these findings to make recommendations about the involvement of carers and the negotiation of information sharing among the service user, carers and healthcare professionals. Furthermore, in taking a broad overview of all the themes

identified, combined with the collective experience of the whole GDG, the GDG came to the view that the guideline should explicitly support collaboration among through all phases of care, where this is possible, while respecting the independence of the service user.

Importantly, a theme affecting both carers and service users is access to services. Carers expressed a need to have easy access to services, interventions and support for the service user, which thus reduces the carer's own burden and stress. Carers discussed the importance of swift access to reliable services at all points in the care pathway but particularly during a crisis and following the service user's diagnosis. Carers stated that other practical concerns such as flexible services in terms of times and dates, and appropriate location of services also reduced carers' burden and stress. Furthermore, carers stressed the need for access to support for themselves. Carer support groups were said to be of great value as an informal way of receiving regular support from others who have had similar experiences.

Carers valued the provision of clear and comprehensible information. However, what was also evident from the literature was that carers valued the information more at certain points in the care pathway. For example, carers stated they needed more information around the time of diagnosis, but the information should be neither overwhelming nor too brief (and therefore of little use). Furthermore, carers stressed that an individualised approach to providing information should be used and that the information given to them should be in a format and delivered at times tailored to the specific needs of the carer and the service user.

A key point identified throughout was that carers, like service users, would like services and healthcare professionals to adopt an optimistic and hopeful approach when working with them too. The GDG considered this important and decided to reflect this in the recommendations.

Carers were generally positive about, and suggested components for, a self-management toolkit. They were concerned, however, that healthcare professionals might see the toolkit as a reason to disengage with them. Carers' experience of group psychoeducation was positive overall, but carers stated that the aim of a group should be very clear in order to avoid disappointment if the group did not meet individual needs. Carer support groups were found to be very useful and valued by carers.

The literature evaluating the effectiveness of the carer-focused interventions was limited but promising. Psychoeducation and support groups both provided evidence of benefits on carers' experience of care, quality of life and satisfaction. A self-management toolkit and bibliotherapy intervention did not statistically show any benefit over control, although a trend favouring the interventions was observed. The review of carer-focused interventions included trials of carers of people with serious mental illness, including bipolar disorder, and the GDG believed that many

issues faced by carers of adults with other serious mental illness would be applicable to carers of adults with bipolar disorder.

On the basis of the quantitative review of interventions for carers, the GDG decided that interventions specifically aimed to help carers should be provided. The evidence did not permit a recommendation of a particular type of intervention. However, it was evident, from both the qualitative and quantitative literature, that carers require support, education and information and therefore the GDG made a recommendation that states the components of an intervention that should be provided for the carer.

4.3.3 Trade-off between net health benefits and resource use

No economic studies assessing the cost effectiveness of interventions aimed at improving carers' experience were identified. The cost of providing such interventions was estimated at roughly between £190 and £1,095 (mean of £582) in 2011/12 prices. The GDG judged this cost to be small taking into account the effects of the intervention, leading to a reduction in carers' burden, potential depression and other health vulnerabilities which may be costly to other parts of the NHS, especially considering that the burden of care can last for many years and increase carer morbidity and stress. In addition, increased knowledge and improved confidence helps carers to contribute to care more effectively. Despite the small, emerging evidence base, interventions that aim to improve carers' experience of caring and of services were judged by the GDG to represent good value for money and be worth the investment.

4.3.4 Quality of the evidence

The evidence ranged from very low to moderate quality across critical outcomes. Reasons for downgrading included: risk of bias in the included studies and high heterogeneity or lack of precision in confidence intervals. Wide confidence intervals were also a major concern when evaluating the evidence. However, although variance was observed in the effect size across studies, the direction of effect was consistent across most and the small number of participants in the included trials could have contributed to the lack of precision. Furthermore, some of the included studies for support groups were based in settings that may not be appropriate to the UK healthcare setting (for example, East Asia). In these instances, the evidence was downgraded for indirectness. The evidence showed a benefit of support groups for the carer, but the GDG was cautious about making a recommendation specifically for support groups for this reason. However, the GDG believed that there was also qualitative evidence of great benefits of support groups and therefore could still be considered when drafting recommendations.

4.3.5 Other considerations

The GDG noted that carers, children and other people in the household may be dependent on a person with bipolar disorder and that healthcare providers have a duty to ensure that appropriate safeguarding and other services are provided to

such people. There might be a particular cause for concern during times of high risk (for example, in acute episodes). In addition to safeguarding, the GDG saw value in recommending that children, young people and vulnerable adults who are dependent on or living with a person with bipolar disorder be offered psychological and social support as needed. These issues should be considered during assessment and throughout the care pathway.

4.4 RECOMMENDATIONS

4.4.1 Clinical practice recommendations

Support for carers of people with bipolar disorder

4.4.1.1 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.[5]

4.4.1.2 Advise carers about their statutory right to a formal carer's assessment provided by social care services and explain how to access this.[6]

4.4.1.3 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.[7]

4.4.1.4 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. [8]

4.4.1.5 Review regularly how information is shared, especially if there are communication and collaboration difficulties between the person and their and carer.[9]

4.4.1.6 Include carers in decision-making if the person agrees.[10]

4.4.1.7 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.[11]

[5] Adapted from Psychosis and schizophrenia in adults (NICE clinical guideline 178).
[6] From Psychosis and schizophrenia in adults (NICE clinical guideline 178).
[7] Adapted from Psychosis and schizophrenia in adults (NICE clinical guideline 178).
[8] Adapted from Psychosis and schizophrenia in adults (NICE clinical guideline 178).
[9] From Psychosis and schizophrenia in adults (NICE clinical guideline 178).
[10] From Psychosis and schizophrenia in adults (NICE clinical guideline 178).
[11] Adapted from Psychosis and schizophrenia in adults (NICE clinical guideline 178).

4.4.1.8 Identify children, young people and vulnerable adults 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.

5 CASE IDENTIFICATION AND ASSESSMENT IN ADULTS, CHILDREN AND YOUNG PEOPLE

5.1 INTRODUCTION

Despite some advances in the field of case identification, bipolar disorder is often unrecognised outside specialist settings focusing on mood disorders. This raises the issue as to whether specific instruments should be used for screening the general population, at risk populations such as those in prison or those already diagnosed with depression in primary care settings or even in generalist mental health services.

Lack of recognition or delayed diagnosis can be associated with negative consequences for the individual, their families and society, for example, a high risk of attempted suicide in people with undiagnosed bipolar disorder (Shi et al., 2004b). Furthermore, delayed diagnosis is highly likely to affect treatment and lead to suboptimal outcomes. There are also wider social and economic consequences such as increased medical costs and loss of productivity because of an inability to work (Matza et al., 2005).

Several reasons are often put forward as explanations as to why bipolar disorder might be missed as a diagnosis. Most important of these is that an individual with bipolar disorder often presents in primary care with a depressive episode. Additionally, during a hypomanic or manic phase, people may often feel that they do not need to contact a healthcare professional, or if they are already using mental health services, they may not spontaneously report their symptoms (Bruchmuller & Meyer, 2009; Dunner, 2003; Hirschfeld & Vornik, 2004). In children and young people, correct identification and diagnosis of bipolar disorder can be particularly problematic. There is little evidence about case identification in this population (Waugh et al., 2013), and the precursors of bipolar disorder in this age range are varied and include anxiety disorders, mood disorders and externalising behavioural disorders (Nurnberger et al., 2011).

To decrease the likelihood of not recognising bipolar disorder in clinical practice several screening instruments have been developed over the last few years and evaluated to identify potential bipolar disorder. Some focus more on trait-like features of bipolarity or cyclothymia such as the General Behaviour Inventory (Depue et al., 1989) or the Hypomanic Personality Scale (Eckblad & Chapman, 1986), while others, such as the Mood Disorder Questionnaire (MDQ) (Hirschfeld et al., 2000)), the Bipolar Spectrum Diagnostic Scale (BSDS) (Ghaemi et al., 2005b) or the Hypomania Checklist-32 (HCL-32) (Angst et al., 2005a), ask about lifetime history of mania or hypomania. The latter instruments are shorter than the scales assessing trait-like features. They are easy-to-use self-report tools, which have been validated

in adult samples against diagnoses made using structured clinical interviews (for example, (Meyer et al., 2011; Smith et al., 2011a; Waugh et al., 2013). None of these screening tools is meant as the sole means used to diagnose bipolar disorder, but rather to prompt further assessment.

There is a large number of rating scales but there has been little development specifically of brief instruments suitable for screening in a non-specialist environment. Primary care practices are increasingly using technology-based solutions so screening tests need to be simple and easy to complete by patients without assistance.

5.2 CASE IDENTIFICATION

5.2.1 Clinical review protocol

The review protocol summary, including the review questions, can be found in Table 6 (a complete list of review questions and full review protocols can be found in Appendix 7; further information about the search strategy can be found in Appendix 8)

Table 6: Review protocol summary for the review of case identification instruments

Topic	Interventions
Review question(s)	RQ 1.1: For adults at risk of or suspected as having bipolar disorder, what identification instruments when compared to a gold standard diagnosis (based on DSM or ICD criteria) have adequate clinical utility (i.e. clinically useful with good sensitivity and specificity) and reliability? RQ 1.2: 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 to a gold standard diagnosis (based on DSM or ICD criteria) have adequate clinical utility (i.e. clinically useful with good sensitivity and specificity) and reliability?
Objectives	To identify brief screening instruments to assess need for further assessment of people with suspected bipolar disorder and to assess their diagnostic accuracy.
Criteria for considering studies for the review	
• Intervention	Brief screening questionnaires (<15 items) identified by the GDG
• Comparator	Gold standard: DSM or ICD diagnosis of bipolar disorder.
• Types of participants	Children and young people (aged 18 years and younger) and adults with suspected bipolar disorder
• Outcomes	• Sensitivity (percentage of true cases identified) • Specificity (percentage of non-cases excluded).

• Study design	Studies had to include participants with and without bipolar disorder completing a case-identification instrument and a diagnostic interview.
Note. DSM = Diagnostic and Statistical Manual of Mental Disorders; ICD = International Classification of Diseases.	

For the purposes of this review, pooled diagnostic accuracy meta-analyses on the sensitivity and specificity of specific case identification instruments for bipolar disorder were conducted (dependent on available data). In the absence of adequate data, it was agreed by the GDG that a narrative review of case identification instruments would be conducted and guided by a pre-defined list of consensus-based criteria (for example, the clinical utility of the instrument, administrative characteristics, and psychometric data evaluating its sensitivity and specificity).

The GDG advised that the review should focus on case identification instruments that are relevant to non-specialist settings such as primary care given that bipolar disorder is often unrecognised outside of specialist settings (see Section 5.1). Furthermore, when evaluating case identification instruments, the following criteria were used to decide whether an instrument was eligible for inclusion in the review:

Clinical utility: the instrument should be feasible and implementable in a routine clinical care, especially primary care. The instrument should contribute to the identification of further assessment needs and inform decisions about referral to other services.

Instrument characteristics and administrative properties: A case identification instrument should be brief, easy to administer and score and be able to be interpreted without extensive and specialist training. The GDG agreed that, in order to support its use in a range of non-specialist settings such as primary care, it should contain no more than 15 items and take no more than 5 minutes to administer.

Non-experts from a variety of care settings (for example, primary care, general medical services, and educational, residential or criminal justice settings) should be able to complete and interpret the instrument with relative ease. The instrument should be available in practice, and free to use where possible.

Psychometric data: The instrument should have established reliability and validity (although this data will not be reviewed here). It must have been validated against a gold standard diagnostic instrument such as DSM-IV or ICD-10 and it must have been reported in a paper that described its sensitivity and specificity (see Section 3.5.2 for a description of diagnostic test accuracy terms).

5.2.2 Studies considered[12]

[12]Here and elsewhere in the guideline, each study considered for review is referred to by a study ID in capital letters (primary author and date of study publication, except where a study is in press or only submitted for publication, then a date is not used).

The literature search yielded 6,954 citations. Of those, 165 were potentially relevant. Twenty-two were excluded (see Appendix 34). Studies conducted only in specialist mental health populations, or special groups, were not considered because it would make it difficult to generalise to the general population attending primary care, which is the focus of this review. Studies that did not use instruments in English were also excluded, to ensure greatest applicability to the UK. Only studies where there was evidence that the reference standard included a structured diagnostic interview were included.

Four studies met all of the eligibility criteria. References of included studies were hand searched. Two studies evaluated case identification instruments for adults and two for children. They were published in peer-review journals between 2003 and 2009. The four included studies (N=2,125) evaluated one instrument for adults and two for children and included 100 to 1066 participants receiving both a screening instrument and a diagnostic interview. Case identification instruments included between ten and thirteen questions. Studies were conducted in the community and in psychiatric settings (for further information about each study see Table 7).

Of the four studies, two evaluated the Mood Disorder Questionnaire (MDQ): DODD2009 (Dodd et al., 2009), HIRSCHFELD2003 (Hirschfeld et al., 2003). One study evaluated the CMRS-P: HENRY2008 (Henry et al., 2008), and one study evaluated the Conners' Abbreviated Parent Questionnaire: TILLMAN2005 (Tillman & Geller, 2005).

5.2.3 Clinical evidence review

Overall, the studies were assessed as having a low risk of bias, but information about the timing of the index test and reference standard was generally not described (for further information see Appendix 11). The index tests (case identification instruments) were conducted independently of the reference tests (diagnostic interviews) and the time between case identification and diagnostic interview was not relevant given the stability of the diagnosis. Only one study evaluated the instrument in the general population (HIRSCHFELD2003); one in a general population of women only (DODD2009); the other two were undertaken in clinical settings (see Table 7).

Review Manager 5 (Cochrane Collaboration, 2011) was used to summarise the test accuracy data reported in each study using forest plots and summary ROC plots. The three instruments varied in their specificity and sensitivity. As shown in

Figure **4**, the area under the curve varied reflecting differences in the effectiveness of the measures (see Section 3.5.2 for more information about how this was interpreted). The sensitivity and specificity of each measure is included in Table 7.

Figure 4: Summary ROC plot of brief case identification instruments

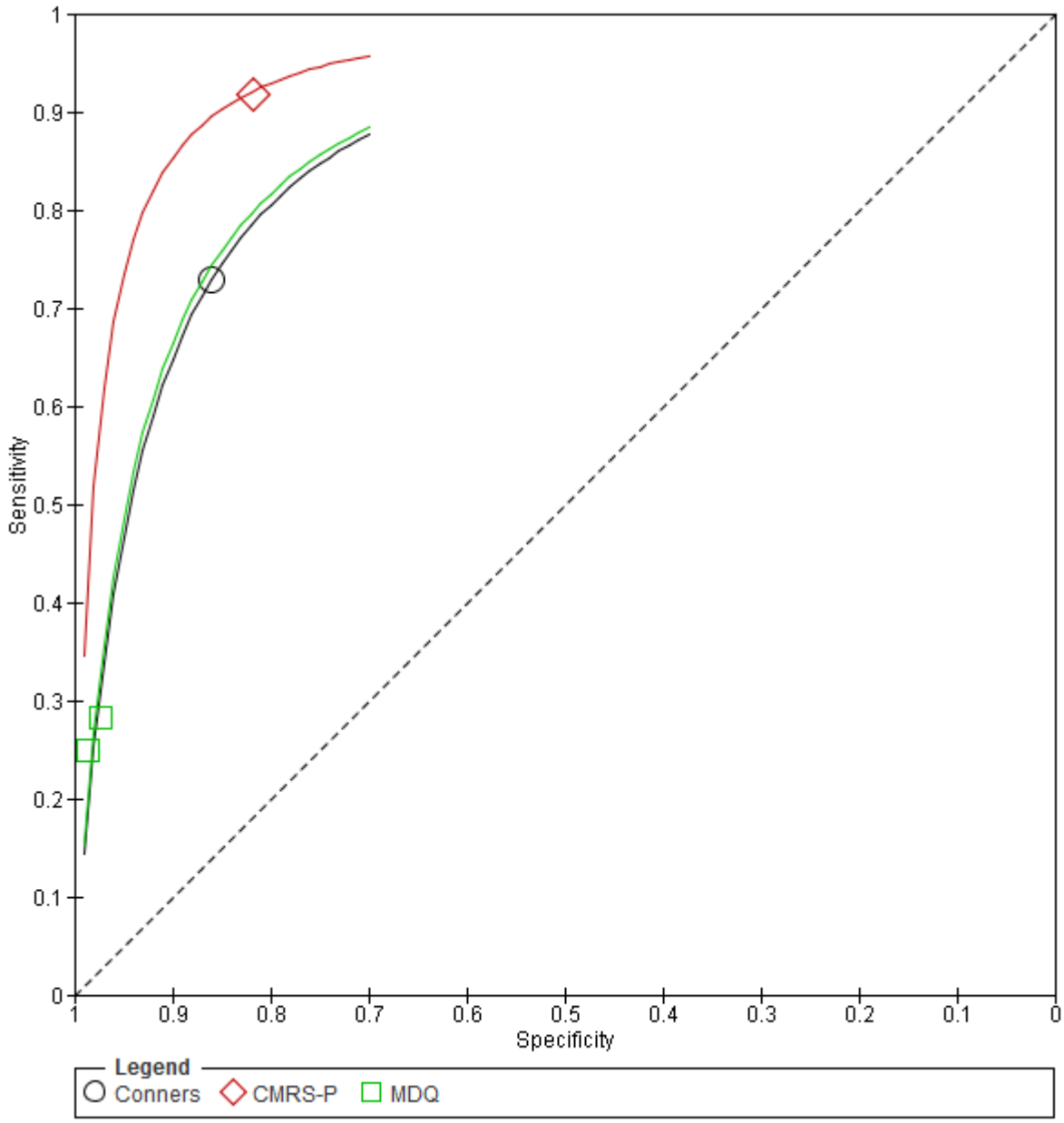


Table 7: Study information table for trials comparing a brief identification instrument with a 'gold standard' clinical interview

Study	Instrument	No. of items	Range (cut-off)	Recruitment	N	Female, n (%)	Age	Country	Prevalence	Sensitivity	Specificity
DODD2009	MDQ	13	Yes/no (7)	Community	1066	1066 (100%)	51	Australia	2.3%	0.25	0.99
HENRY2008	CMRS-P	10	4 point Likert scale. 4-40 (10)	Community and psychiatric settings	100	45 (45%)	10	USA	50%	0.92	0.82
HIRSCHFELD2003	MDQ	13	Yes/no (7)	Community (General population)	695	NR	46	USA	11.2%	0.28	0.97
TILLMAN2005	Conners' Abbreviated Parent Questionnaire	10	4 possible answers per question. 4-40 (9 for 7-8y, 8 for 9-10y, 6 for 11-16y)	Community and psychiatric settings	264	89 (34%)	11	USA	34.9%	0.73	0.86

Note. MDQ = Mood Disorder Questionnaire; CMRS-P = Child Mania Rating Scale – Parent version;

Evidence about the sensitivity and specificity of instruments to identify people with bipolar disorder comes from only a few studies, and only one instrument has been evaluated in more than one study. No study was conducted in the UK.

The MDQ is a self-rated tool and has 13 items with a yes/no answer, plus a further two assessing the temporal clustering of symptoms and functional impairment (4-point scale). It may not be very useful as a screening tool in the general population because screening test sensitivities in a primary care setting would likely be intermediate between those obtained in psychiatric populations and the general community.

The child and adolescent instruments were evaluated in populations that included participants with ADHD, which is an important differential diagnosis in this age group. The Child Mania Rating Scale – Parent (CMRS-P) brief version, is a 10-item instrument, with four possible answers per question and showed accuracy comparable to the full scale. The Conner's abbreviated Parent Questionnaire, is an instrument to assess ADHD in children and adolescents, has 10 items, each with four possible answers. None of these measures had satisfactory properties for identifying bipolar disorder in primary care.

5.2.4 Health economics evidence

Systematic literature review

The systematic search of the economic literature undertaken for the guideline identified one eligible study on case identification that was conducted in the US (Menzin et al., 2009). Full references and evidence tables for all economic evaluations included in the systematic literature review are provided in Appendix 32. Completed methodology checklists of the studies are provided in Appendix 31. Economic evidence profiles of studies considered during guideline development (i.e. studies that fully or partly met the applicability and quality criteria) are presented in Appendix 33.

The study by Menzin and colleagues (2009) assessed the cost effectiveness of MDQ versus no screening in adults presenting for the first time with symptoms of major depressive disorder in primary care; people who screened positive were subsequently referred to psychiatrists. The study, which was based on decision analytic modelling, adopted a third-party payer perspective. Costs included the cost of administration of MDQ by a nurse or physician, the cost of referral to psychiatrists for adults that were screened positive, costs of inpatient and outpatient care, and medication costs. The primary measure of outcome was the number of people correctly diagnosed with bipolar disorder or unipolar depression. Cost data were taken from published literature. Clinical input parameters were based on a literature review and expert opinion. The time horizon of the analysis was 5 years.

According to the results of the analysis, MDQ resulted in a higher number of correctly diagnosed people compared with no screening (440 versus 402 correct

diagnoses per 1000 people screened, respectively) and also in a lower total cost per person ($34,107 versus $36,044, respectively, in 2006 prices). Consequently screening with MDQ was the dominant option. Probabilistic analysis showed that the probability of screening with MDQ being cost-saving reached 76%. Results were robust under various alternative scenarios that considered a range of values for the prevalence of bipolar disorder, sensitivity/specificity of MDQ, costs of treatment, as well as a different time horizon.

The study is only partially applicable to the UK context, as it was conducted in the US where clinical practice, resource use and unit costs differ from those in the NHS. Moreover, the study has potentially serious limitations, as a number of clinical input parameters relating to no screening as well as to further assessment of people with a false positive MDQ result were based on expert opinion.

Economic evidence statement

There is some evidence indicating that the MDQ may be cost-saving in adults presenting for the first time with symptoms of major depression in primary care. This evidence is partially applicable to the UK, but has potentially serious limitations.

5.3 ASSESSMENT

5.3.1 Clinical review protocol

The review protocol summary, including the review questions, can be found in Table 8 (a complete list of review questions and full review protocols can be found in Appendix 7; further information about the search strategy can be found in Appendix 8)

Table 8: Review protocol summary for the review of the assessment of bipolar disorder

Topic	Interventions
Review question(s)	RQ 1.3: For people with possible bipolar disorder, what are the key components of, and the most effective structure for, a comprehensive assessment? 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?
Objectives	To identify the key components of a comprehensive assessment
Criteria for considering studies for the review	
• Intervention	Comprehensive assessment
• Comparator	Any comparator
• Types of participants	Children and young people (aged 18 years and younger) and adults with suspected bipolar disorder
• Outcomes	Any reported outcome
• Study design	Any design

Note. DSM = Diagnostic and Statistical Manual of Mental Disorders; ICD = International Classification of Diseases.

For the purposes of this review it was decided that a narrative synthesis of available evidence would be conducted, and in the absence of adequate data, a consensus-based approach to identify the key components of an effective assessment would be used.

5.3.2 Studies considered

The GDG was unable to identify any formal evaluations of the structure and content of the overall clinical assessment process for people with possible bipolar disorder other than the data on the various case identification instruments described above.

5.3.3 Clinical evidence review

As there was an absence of evidence the GDG drew up a list of the following components of an assessment to consider when making recommendations:

- the person's symptom profile, including a history of mood, episodes of overactivity, disinhibition or other episodic and sustained changes in behaviour, symptoms between episodes, triggers to previous episodes and patterns of relapse, and family history
- social and personal functioning and current psychosocial stressors
    - potential mental and physical comorbidities
    - general physical health and side effects of medication, including weight gain
    - involvement of a family member or carer to give a corroborative history
    - treatment history and interventions that have been effective or ineffective in the past
    - possible factors associated with changes in mood, including relationships, psychosocial factors and lifestyle changes
- risk to self and to others.

The GDG also discussed the components of a long-term management plan in the context of assessment. They considered that the plan should cover possible triggers and early warning signs of relapse, a protocol for increasing medication for those at risk of onset of mania, agreements between primary and secondary care about how to respond to an increase in risk and how service users and carers can access help in a crisis, with a named professional.

The GDG also considered the service configuration best suited to provide assessment of people with suspected bipolar disorder. In common with the guideline *Psychosis and Schizophrenia in Adults* (NICE, 2014), the GDG judged that this would be an early intervention in psychosis service.

5.3.4 Health economic evidence review

No studies assessing the cost effectiveness of assessment systems or instruments for people with bipolar disorder were identified by the systematic search of the economic literature.

5.4 IMMEDIATE POST-ASSESSMENT PERIOD

In addition to conducting the reviews on identification and assessment, the GDG discussed the immediate post-assessment period and the process/issues that would need to be considered when planning treatment and care for people across all phases of the disorder.

The GDG discussed this topic using informal consensus methods (see Section 3.5.6) and their expert knowledge and experience. They considered that the following would need to be considered when making recommendations in this area:

- experience of care
- the care of certain groups of people, or 'special populations'.

Regarding the experience of care, the GDG acknowledged the existing guideline on *Service User Experience in Adult Mental Health* (NICE, 2011; NCCMH, 2012), which provides evidence-based recommendations for improving experience of mental health services in the following main areas: care and support across all points on the care pathway, access to care, assessment, community care, assessment and referral in a crisis, hospital care, discharge and transfer of care, and assessment and treatment under the Mental Health Act. The GDG identified specific areas not explicitly covered by the *Service User Experience in Adult Mental Health* guideline that they considered important to include in this current guideline on bipolar disorder. This included identifying any problems related to the service user's education, employment or finances that may have resulted directly from features of their bipolar disorder, such as extravagant spending and reckless behaviour and decision-making during episodes of mania. Related to this topic, the GDG recognised the need for people with bipolar disorder to consider a lasting power of attorney and developing advance statements.

Bearing in mind the reviews undertaken earlier in this chapter and in chapters 6, 7 and 8, the GDG also considered the care of special populations across all phases of the disorder. They judged that the following groups may need special attention:

- older people
- people with a learning disability
- people with a coexisting disorders, such as personality disorder, anxiety disorders and substance use-disorders
- people with rapid-cycling disorder
- women of child-bearing potential.

The GDG recognised potential inequalities in the way older people with bipolar disorder could be treated, and saw the need to ensure that they are offered the same range of treatments and services as young people. Given that people with a learning disability may be at increased risk of developing comorbid serious mental illness, and due to the uncertainty around treatment options, the GDG was keen to ensure that they were also offered the same range of treatments and services as other people with bipolar disorder. Bipolar disorder also commonly coexists with anxiety disorders, substance-use disorders and personality disorder, therefore the GDG judged that any additional treatment for these disorders should be undertaken according to the related NICE guideline. The GDG bore in mind the reviews undertaken in this chapter on identification, and in subsequent chapters on interventions, and acknowledged that there was very little evidence that people who have sometimes been described as 'rapid cycling' can be reliably identified, and there was no evidence to suggest they respond differently to treatment, therefore the GDG determined that these people should also be offered the same treatment as people with other types of bipolar disorder.

The GDG also considered the service configuration best suited to provide early management of people with bipolar disorder in the first 3 years following diagnosis. In common with the guideline *Psychosis and Schizophrenia in Adults* (NICE, 2014), the GDG judged that this would be an early intervention in psychosis service.

5.5 LINKING EVIDENCE TO RECOMMENDATIONS

5.5.1 Relative value placed on the outcomes considered

In considering case identification instruments, the primary outcome was the accurate detection of bipolar disorder. For assessment, no limits were initially placed on the outcomes that would be considered.

5.5.2 Trade-off between benefits and harms

A number of case identification instruments were identified, but the GDG determined that there was little evidence to support their use as screening

instruments in primary care (both general practice and primary care based psychological therapy services) for those already diagnosed with depression. There is some rationale but the GDG were not aware of evidence for use of the instruments to support provisional diagnosis in those already suspected of bipolar disorder. Through consensus, the GDG developed new recommendations about the identification of bipolar disorder in primary care and what should happen if it is suspected.

There was little evidence about case identification in children and young people (Waugh et al., 2013). The GDG noted that DSM-V has been revised in light of concerns about over-diagnosis of children. Bipolar disorder is extremely rare in children, and although it can begin in adolescence, this is also rare. The reviewed evidence evaluated two instruments with at least 10 items in relatively small sample sizes. The GDG concluded that brief case identification instruments are probably ineffective for children and young people, and the GDG agreed that no questionnaires should be recommended for identifying children and young people with suspected bipolar disorder. The GDG developed recommendations based on a careful consideration of the available evidence and their expert consensus about the best way to manage children and young people with serious psychiatric symptoms that could be indicative of bipolar disorder.

The GDG wished to stress the importance of having specialist input in the diagnosis of bipolar disorder or another serious mental health problem in this population.

The GDG considered evidence for the MDQ and determined that its poor sensitivity in large samples suggests the MDQ is not appropriate for case identification and that it would be better to refer people with suspected bipolar disorder for a full assessment. The GDG wished to emphasise that health and social care professionals who are concerned that an adult may be exhibiting symptoms of mania or psychosis should refer the service user for assessment by a qualified professional.

The GDG also considered the comorbidity of bipolar disorder with other problems in children and young people, the risks associated with bipolar disorder and the impact of bipolar disorder on individuals and their families.

Regarding assessment, the GDG was unable to identify any high-quality evidence that related to the process of assessment for people with bipolar disorder. As a result the GDG drew on their expert knowledge and experience using informal consensus methods. During discussion, the GDG identified several key principles for assessing people with suspected bipolar disorder. They also discussed risk assessment and the components of a risk management plan. The GDG noted that self-harm is common in bipolar disorder and that healthcare professionals should be aware that mental state and suicide risk can change quickly. Similarly, the disinhibited, changeable and impulsive nature of patients with bipolar disorder, particularly in a manic or a mixed state, means that healthcare professionals should exercise caution when there is a risk of harm to others. The GDG determined that there was very little evidence

that people who have sometimes been described as 'rapid cycling' can be reliably identified, and there was no evidence to suggest they respond differently to treatment, so the GDG determined that this specifier is of little clinical utility at present.

Regarding the immediate post-treatment period, the GDG were concerned that certain groups of people with bipolar disorder received the most appropriate treatment and care from other NICE guidelines following assessment, including older people, women of childbearing potential and those with coexisting disorders, such as personality disorder, anxiety and substance misuse. People with a learning disability may be at increased risk of developing comorbid serious mental illness. However, co-existing conditions often overlooked. Given the uncertainty around treatment options, the GDG argued that people with a learning disability should receive the same care as other people with bipolar disorder. A similar recommendation was issued for older people; while adjustments might need to be made to their medication regimes (see Chapter 7), they should be offered the same range of treatments and services as younger people with bipolar disorder

As part of the discussions around the assessment and post-assessment period, the GDG also considered other aspects of care, and the support people should receive when first diagnosed and throughout treatment, including having the same high standard of care as set out in *Service User Experience in Adult Mental Health* (NICE clinical guidance 136) (NICE, 2011a). The GDG also wished to make sure that people with bipolar disorder receive help with problems related to their education, employment or finances that may have resulted from their bipolar disorder, that they are encouraged to consider a lasting power of attorney (especially if they have experienced serious financial problems), and that they develop an advance statement, setting out their preferences, wishes, beliefs and values regarding their future care if, at any point, they are unable to make decisions.

The GDG judged that in common with the guideline *Psychosis and Schizophrenia in Adults* (NICE, 2014), assessment and early management (the first 3 years) of people with bipolar disorder should be conducted in early intervention in psychosis services.

With regards to children and young people, the GDG wished to make recommendations about diagnosis in this age group. The GDG for the 2014 guideline acknowledged the consensus conference undertaken for the previous guideline, which had international representation. The impact of the conference on the diagnosis of children and young people had lasting effects in the UK and the US on diagnostic practices. Most importantly, the conference participants came to the consensus view, now widely held, that bipolar II disorder should not be diagnosed in children and young people because almost invariably this condition does not occur before adulthood. In addition, diagnosing bipolar II disorder before adulthood is likely to delay a child or young person getting the right treatment and care for conditions underlying the symptomatic and behavioural manifestations mistakenly

diagnosed as bipolar II disorder. The GDG therefore decided to uphold the recommendation that a diagnosis of bipolar II disorder should not be made in children and young people.

The GDG further noted that bipolar disorder in children and young people is rare, and they considered that it should not be diagnosed by professionals who do not have specialist training in its assessment and management in young people. For these reasons, the GDG determined that children and young people with suspected bipolar disorder should be referred to appropriate services depending on their age. If they are under 14 years, they should be referred to CAMHS; if they are aged 14 or over they could be referred to either a specialist early intervention in psychosis service or to specialist CAMHS (tiers 3 or 4). The GDG judged that both specialist EIS and CAMHS should be multidisciplinary (comprising professionals who are trained and competent in working with young people with bipolar disorder) and have access to structured psychological interventions and pharmacological interventions. Vocational and educational interventions should also be available. In addition family involvement and family intervention are particularly important to support the diagnosis and ongoing treatment. Engagement and assertive outreach approaches should also be employed to build trusting and supportive relationships, particularly in children and young people who might be difficult to engage (such as those from the looked-after care system).

The GDG also noted a few important differences between the diagnosis of bipolar disorder in adults and in children/young people (namely, that mania must be present, as should euphoria most days and for most of the time, but that irritability is not a core diagnostic criterion); failing to appreciate these differences might have contributed to the historical over-diagnosis of the condition in this population.

5.5.3 Trade-off between net health benefits and resource use

The GDG considered evidence from the US indicating that the MDQ may be cost-saving in adults presenting for the first time with symptoms of major depression in primary care. It also took into account the substantial costs associated with delayed diagnosis and management of unrecognised and/or misdiagnosed bipolar disorder, resulting from overuse of antidepressants and underuse of potentially effective medications. The GDG recognised that early diagnosis of bipolar disorder offers a benefit to the service users who receive appropriate treatment for their condition, and may also result in a considerable reduction in healthcare resource use. Regarding assessment, the GDG acknowledged that appropriate assessment of people with bipolar disorder enables them to receive suitable treatment according to their needs, thus ensuring efficient use of available healthcare resources.

5.5.4 Quality of the evidence

For case identification instruments, overall, the studies were assessed as having a low risk of bias. No formal evaluations were identified that examined the structure

and content of the overall clinical assessment process for people with possible bipolar disorder.

5.6 RECOMMENDATIONS

5.6.1 Clinical practice recommendations

Recognising and managing bipolar disorder in adults in primary care

Recognising bipolar disorder in primary care and referral

5.6.1.1 When adults present in primary care with depression, ask about previous periods of overactivity or disinhibited behaviour. If the overactivity or disinhibited behaviour has lasted for 4 days or more, consider referral for a specialist mental health assessment.

5.6.1.2 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.

5.6.1.3 Do not use questionnaires in primary care to identify bipolar disorder in adults.

Assessing suspected bipolar disorder in adults in secondary care

5.6.1.4 Assessment of people with suspected bipolar disorder should be conducted in early intervention in psychosis services.

5.6.1.5 When assessing suspected bipolar disorder in secondary care:

- undertake a full psychiatric assessment, documenting a detailed history of mood, episodes of overactivity, disinhibition or other episodic and sustained changes in behaviour, symptoms between episodes, triggers to previous episodes and patterns of relapse, and family history
- 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.

5.6.1.6 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.

5.6.1.7 Carry out a risk assessment in conjunction with the person, 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.

5.6.1.8 Following diagnosis, the management of bipolar disorder should be conducted in early intervention in psychosis services for the first 3 years.

Care for across all phases of bipolar disorder

Improving the experience of care

5.6.1.9 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.

Treatment and support for specific populations

5.6.1.10 See the NICE clinical guideline on antenatal and postnatal mental health for guidance on the management of bipolar disorder in women of childbearing potential.

5.6.1.11 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.

5.6.1.12 Ensure that older people with bipolar disorder are offered the same range of treatments and services as younger people with bipolar disorder.

5.6.1.13 Offer people with bipolar disorder and coexisting disorders, such as personality 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, generalised anxiety disorder and psychosis with coexisting substance misuse.

5.6.1.14 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

5.6.1.15 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.

5.6.1.16 Consider encouraging people with bipolar disorder to develop advance statements while their condition is stable, in collaboration with their carers if possible.

5.6.1.17 Consider providing information and discussing 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

Recognition and referral

5.6.1.18 Do not use questionnaires in primary care to identify bipolar disorder in children or young people.

5.6.1.19 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).

5.6.1.20 If bipolar disorder is suspected in primary care in young people aged 14 years and over, refer them to a specialist early intervention in psychosis service or specialist CAMHS. Both services should be multidisciplinary and have:

- engagement or assertive outreach approaches
- family involvement and family intervention
- access to structured psychological interventions and psychologically informed care
- vocational and educational interventions
- access to pharmacological interventions
- professionals who are trained and competent in working with young people with bipolar disorder.

Diagnosis and assessment

5.6.1.21 Diagnosis of bipolar disorder in children and young people should be made only after intensive monitoring and by a specialist in bipolar disorder in children or young people.

5.6.1.22 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.

5.6.1.23 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.

5.6.1.24 Do not diagnose bipolar II disorder in children or young people.

5.6.1.25 When assessing suspected bipolar disorder in children or young people, follow recommendation 5.6.1.5 for adults, but involve parents or carers routinely and take into account the child or young person's educational functioning.

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

5.6.1.26 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 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.

6 PHARMACOLOGICAL AND MEDICAL INTERVENTIONS FOR ACUTE EPISODES

6.1 INTRODUCTION

Pharmacological interventions are commonly used to manage acute episodes in bipolar disorder. Acute episodes may carry significant risk of suicide, neglect, disinhibition, recklessness, irritability and sometimes threats to others. Therefore the settings in which pharmacological interventions are carried out, and the wishes and abilities of service users and families to manage episodes safely, require careful consideration in relation to risk assessment.

On average, people with bipolar disorder experience more depressive than manic episodes, and depressive episodes last longer than mania (Judd et al., 2003a; Judd et al., 2002a; Morriss et al., 2013). The effective treatment of bipolar depression is therefore a clinical priority for the NHS. The main aims of the treatment of bipolar depression are response (that is. resolution of symptoms) and return to a premorbid level of social functioning.

The management of mania in the community can be particularly challenging for carers. During a manic episode, the service user may sleep for only a few hours and be driven to move from one activity to another. Mania involving high levels of restlessness, irritability and insomnia often requires inpatient admission. Similarly, agitated episodes of depression or mixed affective episodes, particularly in people expressing suicidal intent or with a history of self-harm, may require inpatient admission.

The management of acute bipolar episodes is complex because of the propensity to be highly changeable in both the severity of symptoms and the polarity of the episode (mania, hypomania, mixed affective or depression episode). Practitioners often consider all mental states displayed within recent days, not just the one displayed at the time of interview, in making a risk assessment. Furthermore, bipolar disorder tends to be associated with other comorbid mental disorders, and medication may be associated with physical side effects. The management of acute episodes should also consider the risk of switching into a different episode in the short to medium term. Most people who have an acute episode will have another within 12 months, so treatment of acute episodes should consider long-term management as well.

6.1.1 Definitions

Lithium

Lithium is an element that is present in a normal diet, and is handled by the body in a similar way to sodium. The ubiquitous nature of sodium in the human body, its involvement in a wide range of biological processes, and the potential for lithium to alter these processes have made it extremely difficult to ascertain the key mechanism(s) of lithium in regulating mood (for a review see (Marmol, 2008).

Lithium is licensed for the treatment of mania and recurrent depression and the prevention of further mood episodes in people with bipolar disorder. A meta-analysis and at least two large database studies have concluded that lithium treatment is associated with a reduced risk of suicide (Cipriani et al., 2013c; Collins & McFarland, 2008; Goodwin et al., 2003).

Lithium has a narrow therapeutic range, meaning that levels below 0.4mmol/L are unlikely to be effective in the majority of patients and levels above 1.0mmol/L are associated with increasing toxicity (muscle weakness, course tremor, disorientation, seizures, and loss of consciousness). Some commonly used medicines such as non-steroidal anti-inflammatory drugs, diuretics and ACE inhibitors can increase lithium levels in the blood and therefore cause toxicity. Lithium has adverse effects on the kidneys, thyroid and parathyroid (McKnight et al., 2012). Lithium is a known human teratogen, that is, it is potentially harmful to an unborn child.

Antipsychotics

Antipsychotic medication is thought to exert its effects by blocking dopamine (D_2) receptors in the brain. These drugs have been in common use to treat schizophrenia and mania for over 60 years, although few were originally licensed for the latter indication. Over the past 10 years or so, there have been an increasing number of studies examining the efficacy and tolerability of newer antipsychotic drugs in the treatment of both mania and bipolar depression, resulting in some being specifically licensed for these indications. Antipsychotics have long been used to prevent or reduce the severity of new mood episodes in people with bipolar disorder, although the relative effectiveness of these drugs against each pole of the illness is thought to differ (Gitlin & Frye, 2012). The use of antipsychotics in people with bipolar disorder has increased significantly in the UK over recent years (Hayes et al., 2011).

Antipsychotic drugs are variably associated with a range of side effects, the most problematic of which is probably weight gain. Other side effects include dry mouth, blurred vision, sedation, sexual dysfunction, extrapyramidal side effects (tremor, stiffness, restlessness, and abnormal movements) and dizziness.

Anticonvulsants

Valproate is a simple branched-chain fatty acid that is commonly used for the treatment of epilepsy. Although it is known to exert a large range of effects on brain functioning, its exact mechanism of action in bipolar disorder remains unclear. (For a review, see (Rosenberg, 2007).

Valproate is available in various forms including sodium valproate, valproic acid and valproate semi sodium, although only valproate semi-sodium has UK marketing authorisation for the treatment of manic episodes in the context of bipolar disorder. This guideline uses the generic term 'valproate', as it is the active element in all formulations.

Valproate in all formulations is used for the treatment of mania and bipolar depression and for the prevention of new mood episodes. Valproate is associated with a number of side effects including tremor, weight gain, and rarely, liver damage. It can interact with a number of commonly prescribed medicines and notably is known to decrease plasma levels of olanzapine (Haslemo et al., 2012), an antipsychotic drug that is commonly prescribed in people with bipolar disorder. Valproate is a known major human teratogen. There are significant risks associated with taking valproate during pregnancy for the unborn child, including risk of autism (Christensen et al., 2013; NICE, 2014) and its use is best avoided completely in women of child-bearing age.

Carbamazepine is structurally related to the tricyclic antidepressants. It has been used as an anticonvulsant in people with epilepsy since 1974 (Israel & Beaudry, 1988), and it is licensed for the treatment of people with bipolar disorder who are intolerant of lithium or in whom lithium is ineffective.

Although carbamazepine is known to reduce both neuronal firing and the release of excitatory neurotransmitters in the brain, the exact mechanism by which it exerts its effects in people with bipolar disorder is not understood.

The main side effects associated with carbamazepine are dizziness, drowsiness, nausea and headaches, and it can cause a low white blood count, hyponatraemia (low level of sodium in the blood) and rarely, liver damage. Carbamazepine is a potent inducer of hepatic cytochrome enzymes and this can lead to increased metabolism so lower plasma levels of a number of commonly prescribed medicines. For example standard dose combined oral contraceptives can be rendered ineffective due to the increased metabolism of oestrogen. Carbamazepine is also a known human teratogen.

Lamotrigine is another anticonvulsant that is commonly used in people with bipolar disorder, where it is licensed for the prevention of episodes of depression. Its mechanism of action in people with bipolar disorder is not fully understood.

Lamotrigine is associated with rash which can be serious and to minimise the risk of this occurring, the dose of lamotrigine has to be increased very slowly at the start of treatment. Lamotrigine can also cause drowsiness, dizziness and blurred vision and it can depress the bone marrow. Lamotrigine too is a known human teratogen, although it is considerably safer in pregnancy than valproate.

Dosage recommendations are complex, particularly when lamotrigine is used with other anticonvulsant drugs.

Anticonvulsant drugs can interact with each other and if more than one of these drugs is prescribed, the BNF should be checked to ensure doses are adjusted if required.

Antidepressants

Antidepressants all exert their effect by increasing levels of one or more of serotonin, noradrenaline and dopamine within the brain.

Despite having a relatively modest effect size in the treatment of unipolar depression (NICE, 2009), antidepressants are widely prescribed for this indication. Antidepressants are also commonly prescribed for people with bipolar depression (Sidor & McQueen, 2011) but their use is controversial for two reasons. First, there is considerable doubt about whether antidepressants have any efficacy in bipolar depression (Sachs et al., 2007; Sidor & McQueen, 2012), and second there are concerns that these drugs could induce switching into mania (Tondo et al., 2010) or accelerate cycling so that the time to the next relapse decreases and the time spent in relapse increases. However, there is considerable uncertainty whether antidepressants do in fact cause such switching or cycle acceleration given the natural propensity for bipolar disorder to be highly changeable (Altshuler et al., 2004).

There are a number of different types of antidepressants and of these, the selective serotonin reuptake inhibitors (SSRIs) are the most frequently prescribed. These drugs are generally well tolerated although they can cause headache, gastrointestinal upset and sexual dysfunction. SSRIs can also cause hyponatraemia (low blood sodium) and they increase the risk of bleeds, particularly in the gastrointestinal tract. Further background information about the different types of antidepressants and their relative side effects can be found in the NICE guideline for the management of depression (NICE, 2009) or the British National Formulary (BNF)[13].

Nutritional interventions

Adequate intake of dietary omega-3 fatty acids (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]) is essential for the maintenance of good physical health. Western diets may contain insufficient quantities of these fatty acids. Supplements containing omega-3 fatty acids are widely available from health food shops and are commonly taken for their perceived health benefits. The majority of those who take such complementary therapies have mental health problems (Werneke, 2009). This suggests that these treatments are considered to be acceptable by many patients.

[13]British National Formulary (BNF 2013): http://www.bnf.org/bnf/index.htm

Fatty acids are essential components of cell membranes, and omega-3 fatty acids are known to be anti-inflammatory. There is also some evidence to suggest that they alter the structure and function of cell membranes, which in turn, impacts on the functioning of monoamine neurotransmitters (Chalon, 2006). These properties have led to widespread interest in the use of omega-3 fatty acids in a wide range of psychiatric conditions, including mood disorders (Bloch & Hannestad, 2012; Sarris et al., 2012).

Herbal preparations

Herbal preparations are rarely recommended for bipolar depression. It is likely that St John's wort, a treatment for unipolar depression is being used by a small proportion of people with bipolar disorder but there is no evidence concerning its efficacy and it can have some potentially toxic interactions with some medicines with high serotonergic activity such as antidepressants, or anticoagulants such as warfarin. Other herbal preparations (such as valerian) are also often used as hypnotics during depression, again with little evidence of efficacy but there is less concern about interactions with prescribed drugs.

6.2 PHARMACOLOGICAL AND NUTRITIONAL INTERVENTIONS FOR MANIA, HYPOMANIA AND MIXED EPISODES

6.2.1 Introduction

The main aim in treating mania, hypomania and mixed episodes (a mood state in which manic and depressive symptoms are both exhibited) is to achieve rapid control of affective symptoms. More commonly, mania may cause people to act in a disinhibited manner, and such behaviour may have long-term adverse repercussions for the individual's career and relationships. Mixed episodes are reported to be associated with an increased risk of suicide. As indicated above, an important treatment aim is to prevent further affective episodes occurring immediately after the current episode, including switching into a depressive episode, when the risk of suicide is greater. Service users may have long stays in hospital if their mood repeatedly switches from mania into depression and back again. Therefore the management of manic, hypomanic and mixed affective episodes needs to consider the risk of further episodes within days, weeks or months after improvement in the acute phase.

6.2.2 Clinical review protocol

The review protocol summary, including the review question and the eligibility criteria used for this section of the guideline, can be found in Table 9 (a complete list of review questions and protocols can be found in Appendix 7; further information about the search strategy can be found in Appendix 8)

Table 9: Clinical review protocol summary for the review of pharmacological and nutritional interventions for mania, hypomania and mixed episodes

Topic	Interventions
Review question	RQ2.1: For adults with bipolar disorder, what are the relative benefits and harms of pharmacological and nutritional interventions for mania, hypomania and mixed episodes? 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+)?
Objectives	To estimate the efficacy of interventions to treat mania, hypomania and mixed episodes.
Criteria for considering studies for the review	
• Intervention	All licensed oral medications (and their combinations). Nutritional interventions will be analysed separately.
• Comparator	Placebo Other interventions
• Types of participants	Adults (18+) with bipolar disorder who are experiencing an acute episode. Special consideration will be given to the groups above.
• Outcomes	1) Response (50% reduction in symptoms) 2) Discontinuation (due to side effect, other)
• Time	The main analysis will include outcomes at the end of the acute treatment phase.
• Study design	Randomised controlled trials (RCTs) and cluster RCTs with a parallel group design in which providers and participants were blind to treatment. Quasi-RCTs, such as trials in which allocation is determined by alternation or date of birth, and single-blind studies will be excluded.
• Dosage	Fixed or flexible doses within the therapeutic range (BNF recommended).
• Study setting	Primary, secondary, tertiary, health and social care
Note. BNF = British National Formulary.	

6.2.3 Studies considered[14]

The search for systematic reviews identified a recent review that included a network meta-analysis of pharmacological interventions for mania (Cipriani et al., 2011). The review reported the critical outcomes identified by the GDG, and the results were directly relevant to treatment of bipolar mania in the UK. To determine if new studies could change the conclusions of the review, the GDG conducted a search.

The search for new studies identified five RCTs: ASTRAZENECA2011 (Astrazeneca, (unpublished) 2011b), BEHZADI2009 (Behzadi et al., 2009), CHIU2005 (Chiu et al., 2005), KANBA2012 (Kanba et al., 2012) and SZEGEDI2012 (Schering-Plough, 2007; Szegedi et al., 2012). Two studies about 'bipolar anxiety' were excluded from all reviews: SHEEHAN2009 (Sheehan et al., 2009), SHEEHAN2013 (Sheehan et al., 2013). Two open-label studies: SCHAFFER2013 (Schaffer et al., 2013), SINGH2013

[14]Here and elsewhere in the guideline, each study considered for review is referred to by a study ID in capital letters (primary author and date of study).

(Singh et al., 2013); and three trials of medications neither routinely used nor licensed for the treatment of mental health problems: ZHANG2007 (Zhang et al., 2007), KULKARNI2006 (Kulkarni et al., 2005; Kulkarni et al., 2006), MCELROY2011 (McElroy et al., 2011) were also excluded from this review. Results could not be obtained for five studies: BOSE2012 (Bose et al., 2012), BRISTOLMYERSSQUIBB2011 (Bristol-Myers Squibb, (unpublished) 2011), FOREST2012 (Forest, 2012), KNESEVICH2009 (Knesivich et al., 2009), YANG2009 (Yang, 2009); although they have published several papers about the drug, the manufacturer of cariprazine has not reported the results of clinical trials, and they refused requests from the NCCMH for data.

Of the five new RCTs, three (N = 940; ASTRAZENECA2011, KANBA2012, SZEGEDI2012) could have been considered for the network meta-analysis (had they been available at the time the analysis was conducted). The new studies were analysed and their results compared with the results of the network meta-analysis for the critical outcomes. Two additional RCTs (N = 103), which did not meet inclusion criteria for the network meta-analysis were also identified. These were a trial of folic acid added to valproate (BEHZADI2009) and a trial of omega-3 polyunsaturated fatty acids added to valproate (CHIU2005).

Further information about both included and excluded studies can be found in **Error! Reference source not found.** and **Error! Reference source not found.**.

6.2.4 Clinical evidence review

The GDG considered the findings of the network meta-analysis (Cipriani et al., 2011) alongside new trials (see Table 10). The network meta-analysis found robust evidence that several pharmacological interventions are efficacious. Furthermore, the network meta-analysis found evidence of differential effectiveness among medications, which is a unique strength of this method. Examining the results of several trials reported after the publication of the network meta-analysis, the GDG concluded that the most recent evidence is consistent with the results of the network meta-analysis and that the inclusion of new studies would not change the conclusions of that review. One study of folic acid added to valproate reported effects that the GDG considered implausibly large and insufficient to lead to a recommendation (BEHZADI2009). In one study of omega-3 polyunsaturated fatty acids, it was not possible to extract outcomes, however the authors reported no effect of the intervention on manic symptoms. For these reasons, the GDG used the results of the network meta-analysis when considering what recommendations to make.

Table 10: Comparison between new studies and network meta-analysis (all results compared with placebo)

	New study result		Network result (Cipriani 2011)	
Mean change (YMRS)	**SMD (95% CI)**	**k (N)**	**SMD (95% CrI)**	**k (N)**
Aripiprazole (KANBA2012)	-0.63 (-0.88, -0.37)	1 (122)	-0.37 (-0.51, -0.23)	7 (2436)
Asenapine (SZEGEDI2012)	-0.24 (-0.46, -0.02)	1 (155)	-0.30 (0.53, -0.07)	2 (960)

Lithium with quetiapine (ASTRAZENECA2011)	-0.29 (-0.50, -0.08)	1 (173)	-0.37 (-0.50, -0.25)	2 (370)
Response	**OR (95% CI)**	**k (N)**	**OR (95% CrI)**	**k (N)**
Aripiprazole (KANBA2012)	0.51 (0.31, 0.85)	1 (128)	0.50 (0.38, 0.66)	7 (2571)
Asenapine (SZEGEDI2012)	0.72 (0.44, 1.15)	1 (159)	0.59 (0.31, 1.13)	1 (480)
Lithium with quetiapine (ASTRAZENECA2011)	0.50 (0.31, 0.81)	1 (173)	0.55 (0.38, 0.79)	2 (370)
Discontinuation	**OR (95% CI)**	**k (N)**	**OR (95% CrI)**	**k (N)**
Aripiprazole (KANBA2012)	0.75 [0.46, 1.23)	1(128)	0.76 [0.55, 1.06)	7 (2631)
Asenapine (SZEGEDI2012)	0.79 [0.50, 1.24)	1(159)	0.98 [0.57, 1.71)	2 (977)
Lithium with quetiapine (ASTRAZENECA2011)	0.65 [0.38, 1.13)	1(173)	1.05 [0.78, 1.43)	2 (402)

Note. CI = confidence interval; Crl = credibility interval; k = Number of trials. N = Number of participants receiving the treatment listed. Numbers represent all trials of the investigational drug and all participants assigned to that drug (that is, excluding those assigned to placebo or other comparators).

Of the drugs included in the network meta-analysis (Cipriani et al., 2011) without new evidence, seven were shown on the primary outcome to have an advantage over placebo: carbamazepine (SMD = -0.36, 95% CrI = -0.60 to -0.11), valproate (SMD = -0.20, 95% CrI = -0.37 to -0.04), haloperidol (SMD = -0.56, 95% CrI = -0.68 to -0.43), lithium (SMD = -0.37, 95% CrI = -0.50 to -0.25), olanzapine (SMD = -0.43, 95% CrI = -0.54 to -0.32), quetiapine (SMD = -0.37, 95% CrI = -0.51 to -0.23), risperidone (SMD = -0.50, 95% CrI = -0.63 to -0.38). A further three we shown on the primary outcome to be little better than placebo: gabapentin (SMD = 0.32, 95% CrI = -0.18 to 0.82), lamotrigine (SMD = -0.08, 95% CrI = -0.34 to 0.18), topiramate (SMD = 0.07, 95% CrI = -0.09 to 0.24), ziprasidone (SMD = -0.19, 95% CrI = -0.37 to -0.03).

6.2.5 Health economics evidence

Systematic literature review

The systematic search of the economic literature undertaken for the guideline identified no study on the cost effectiveness of nutritional interventions and 4 eligible studies on the cost effectiveness of pharmacological treatments for adults with bipolar disorder in a manic, hypomanic or mixed episode (Bridle et al., 2004; Caro et al., 2006; Revicki et al., 2003; Zhu et al., 2005). Of these, only the study by Bridle and colleagues was conducted in the UK, while the rest three studies were conducted in the US. References to included studies and evidence tables for all economic evaluations included in the systematic literature review are provided in Appendix 32. Completed methodology checklists of the studies are provided in Appendix 31. Economic evidence profiles of studies considered during guideline development (that is, studies that fully or partly met the applicability and quality criteria) are presented in Appendix 33.

Olanzapine versus valproate semisodium

Revicki and colleagues (2003) evaluated the cost effectiveness of valproate semisodium versus olanzapine in adults with bipolar I disorder in a manic episode in the US. The economic analysis was conducted alongside a multi-centre RCT

(ZAJECKA2002). The study was a cost consequence analysis; the RCT outcomes considered in the analysis were the participants' clinical improvement based on the Mania Rating Scale (MRS) from the Schedule for Affective Disorders and Schizophrenia (SADS) Change Version and the Hamilton Rating Scale for Depression (HAM-D), and the participants' Health Related Quality of Life (HRQoL) measured by the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) and the number of days with restricted activity. The perspective of the analysis was that of a third-party payer. Costs included hospitalisation costs, physicians' fees, costs of emergency room, costs of psychiatric, physician, psychologist or other mental health provider visits, home health service visit costs and medication costs. HRQoL and resource use data were collected via telephone interviews; a number of resource use data, such as the number of inpatient physician visits and type of outpatient visits, were based on assumptions. National unit costs were used. The time horizon of the analysis was 12 weeks. Participants in the RCT discontinued treatment if they did not improve after 3 weeks, but data were still collected for a total period of 12 weeks.

The results of the analysis showed that there were no significant differences between the two drugs in terms of clinical, HRQoL and economic outcomes over the 12-week period. Valproate semisodium was associated with significantly lower outpatient costs compared with olanzapine; nevertheless, total direct medical costs associated with the two drugs were similar (mean total cost per person $13,703 for valproate semisodiumand$15,180 for olanzapine, p = 0.88, cost year not stated). The study is partially applicable to the UK context as it was conducted in the US. Moreover, it is characterised by potentially serious limitations, relating to the short time horizon of the analysis (12 weeks), the use of assumptions for some resource use data, and potential conflicts of interest.

Zhu and colleagues (2005) also conducted a cost consequence analysis alongside a multi-centre RCT (TOHEN2002) to evaluate the cost effectiveness of olanzapine versus valproate semisodium in adults with bipolar I disorder that were hospitalised for a manic or mixed episode in the US. The time horizon of this analysis was 47 weeks, comprising 3 weeks of acute phase and 44 weeks of maintenance phase. Only participants who entered the maintenance phase of the RCT were included in the economic analysis (59% of the initial study sample). The clinical outcomes considered were the clinical improvement based on the Young Mania Rating Scale (YMRS) and the rate of symptom remission (defined as YMRS score ≤12) at 3 weeks, and the median time to remission of manic symptoms. The perspective of the analysis was that of a third-party payer. Cost elements included hospitalisation (full and partial), outpatient psychiatric physician and other mental health provider visits, emergency room visits, home visits by healthcare professionals, medication and laboratory tests. Effectiveness and resource use data were taken from the RCT; resource use data were collected from hospital and other medical records and family reports. National unit costs were used.

According to the analysis, total costs were similar between the two drugs (mean total cost per person $14,967 for olanzapine, $15,801 for valproate semisodium, p > 0.05, cost year 2000). Olanzapine was found to be significantly better than valproate semisodium in improving manic symptoms at 3 weeks and in the percentage of people achieving remission (54.4% versus 42.3%, respectively). The median time to remission was 14 days for olanzapine and 62 days for valproate semisodium. The results of the analysis suggest that olanzapine is a more effective treatment option that valproate semisodium for people with bipolar disorder experiencing mania at no extra cost. The study is partially applicable to the NHS context as it was conducted in the US. Moreover, it is characterised by potentially serious limitations including the design of the study regarding collection of resource use data and potential conflicts of interest.

Quetiapine versus usual care

Caro and colleagues (2006) developed a discrete event simulation model to evaluate the cost effectiveness of quetiapine versus usual care in adults with bipolar I disorder experiencing a manic episode in the US. Usual care comprised 45% monotherapy with lithium, 25% lithium plus risperidone, 25% lithium plus olanzapine, and 5% lithium plus quetiapine. The time horizon of the analysis was 100 days. The analysis adopted a third-party payer perspective. Cost elements consisted of hospitalisation and physician fees, emergency room and intensive care units, routine physician and psychiatrist visits, laboratory tests, medication and management of side effects. The outcome measures used were the percentage of people responding at 21 days and the percentage of people remitting at 84 days. Clinical data for the economic model were taken from a literature review, whereas resource use data were derived from administrative databases; national unit costs were used.

Quetiapine was found to be overall less costly than usual care (mean total cost per person $5,525 for quetiapine and $6,912 for quetiapine in 2004 prices). It was also found to be more effective than usual care: the percentage of people responding at 21 days was 54% for quetiapine and 43% for usual care; the percentage of people remitting at 84 days was 80% for quetiapine and 74% for usual care. Consequently quetiapine was the dominant treatment option. Results were sensitive to drug prices, discharge criteria and side-effect management costs. The study is partially applicable to the UK context as it was conducted in the US; the definition of usual care may not reflect usual care in the UK. The analysis is characterised by a number of potentially serious limitations including the source of cost and effectiveness data and potential conflicts of interest.

Antipsychotic drugs (olanzapine, quetiapine and haloperidol) compared with lithium and valproate semisodium

The economic analysis by Bridle and colleagues (2004) was the only study undertaken in the UK. The objective of the study, which informed a previous NICE Technology Appraisal on the use of newer anti-manic drugs (NICE, 2003), was to evaluate the cost effectiveness of quetiapine, olanzapine and valproate semisodium

in the treatment adults with bipolar disorder experiencing an manic episode. The study was based on decision-analytic modelling. Effectiveness data were derived from a systematic review and network meta-analysis. The availability of effectiveness data in the network meta-analysis determined the choice of drugs included in the economic analysis. The following drugs were thus considered in the analysis: quetiapine, olanzapine, valproate semisodium, haloperidol and lithium.

The primary measure of outcome was the number of responders to treatment; response was defined as ≥50% improvement in manic symptoms, expressed in changes in YMRS scores. The time horizon was equal to 3 weeks in the base-case analysis, to reflect the most commonly reported length of follow-up for which effectiveness data were provided in the clinical trials. Estimated costs, expressed in 2001–2002 prices, included direct medical costs from the NHS perspective; these consisted of hospitalisation and drug-acquisition costs, as well as costs of diagnostic and laboratory tests required for monitoring. Resource use data were based on expert opinion, information from manufacturers and further assumptions. Unit costs were taken from national sources. Costs of treating adverse events were not included in the analysis, because of lack of relevant data reported in the literature. However, the authors' opinion was that the majority of adverse events associated with the drugs compared were unlikely to have significant resource use implications in the 3-week time horizon of the model. Hospitalisation costs were estimated to be the same for all drug treatment options, as all people experiencing a manic episode were assumed to be hospitalised at the start of the model and to remain hospitalised for the total 3-week period, regardless of response to treatment.

The base-case results of the analysis showed that mean response rates for olanzapine (0.54) and haloperidol (0.52) were higher than for lithium (0.50), quetiapine (0.47) and valproate semisodium (0.45). Haloperidol had the lowest mean total costs per person (£3,047) in comparison to valproate semisodium (£3,139), olanzapine (£3,161), lithium (£3,162) and quetiapine (£3,165). In terms of cost effectiveness, lithium, valproate semisodium and quetiapine were dominated by haloperidol as they were all less effective and more costly than haloperidol. Compared with haloperidol, olanzapine was more effective and resulted in higher total costs, demonstrating an incremental cost effectiveness ratio (ICER) equal to £7,179 per additional responder. This means that if decision-makers are prepared to pay less than £7,179 per additional responder, then haloperidol is the optimal decision; however, if they are prepared to pay at least £7,179 per additional responder, then olanzapine is the most cost-effective option.

One-way sensitivity analyses showed that results relating to dominance of haloperidol were robust to alternative assumptions tested, such as discharge of non-responders at a later time than responders, treatment of non-responders with second and third-line pharmacological therapies, reductions in diagnostic and laboratory costs, inclusion of effectiveness data for people initially excluded from analysis according to a modified intention-to-treat approach, and inclusion of treatment costs for extrapyramidal symptoms because of haloperidol use. Under these scenarios, the

ICER of olanzapine compared with haloperidol ranged between £1,236 (when longer hospitalisation was assumed for non-responders) and £7,165 (when second and third-line treatment was assumed for non-responders) per additional responder. Base-case results were sensitive only to the entire exclusion of diagnostic and laboratory costs from the analysis, which constituted a rather extreme scenario.

Probabilistic analysis demonstrated that, for a willingness to pay (WTP) equal to £20,000 per additional responder, the probabilities of each drug being cost-effective were: olanzapine 0.44, haloperidol 0.37, lithium 0.16, quetiapine 0.02 and valproate semisodium 0.01. The probability that olanzapine was cost-effective increased as the WTP increased: for a maximum WTP £10,000 per additional responder this probability reached 0.42, increasing to 0.45 if the maximum WTP rose to £40,000. When the WTP for an additional responder was zero, haloperidol was the most cost-effective option (with probability equalling 1), as this was the least costly option of those assessed.

Although the study was conducted in the UK, it is only partially applicable to the NICE context because its primary measure of outcome was the rates of response and not the quality-adjusted life year (QALY), which is the preferred outcome measure by NICE, due to lack of appropriate utility data. As a result, the reported ICERs are difficult to interpret as there is no set threshold for the WTP per additional responder to anti-manic therapy. In addition, although the study was well conducted, it is characterised by potentially serious limitations: first of all, the model had a very short time horizon of 3 weeks, which was nevertheless dictated by the time horizon of the RCTs included in the network meta-analysis. This means that potential differences across drugs regarding benefits and resource use, including the overall length of hospitalisation (beyond 3 weeks), were not taken into account. However, potential differences in the length of hospitalisation among drugs may affect significantly their relative cost effectiveness, as inpatient care is the major driver of total medical costs associated with treatment of mania. Cost differences between drugs were found to be very small and were attributed exclusively to differences in acquisition and monitoring costs, as hospitalisation costs were assumed to be the same across drugs over the time period of 3 weeks. Finally, omission of costs and HRQoL aspects of side effects from the analysis was also acknowledged by the authors as a further limitation of their study.

Overall conclusions from existing economic evidence

The existing economic evidence on drugs for the treatment of mania in people with bipolar disorder is rather limited and not directly applicable to the NICE decision-making context. All studies included in the review are characterised by potentially serious limitations. Evidence from the US suggests that olanzapine and valproate semisodium are associated with similar overall costs; in terms of effectiveness one study showed superiority of olanzapine, and the other study found no difference in effectiveness. Another US study indicated that quetiapine was dominant (more effective and less costly) than usual care. The only UK study included in the review showed that haloperidol was dominant over lithium, valproate semisodium and

quetiapine. Olanzapine was more effective and more costly than haloperidol, with an ICER equal to £7,179 per additional responder. However, the study is characterised by potentially serious limitations and its results are not easy to interpret due to lack of use of QALYs as a measure of outcome.

It needs to be noted that quetiapine and olanzapine are now available in generic form, and therefore their acquisition cost is lower than the cost of the patented forms evaluated in the studies included in the systematic review. Thus their relative cost effectiveness is likely higher than that suggested in the literature.

Economic modelling

Introduction – objective of economic modelling

The cost effectiveness of pharmacological interventions for the treatment of adults with bipolar disorder experiencing a manic episode was identified by the GDG as an area with potentially major resource use implications that should be addressed by economic modelling. However, the availability of clinical and cost data did not allow the development of a model with a time horizon longer than 3 weeks that would overcome the limitations characterising the study by Bridle and colleagues (2004). Therefore, a simple economic analysis was attempted, which updated the costs and clinical data reported by Bridle and colleagues (2004) and allowed the GDG to consider the costs associated with pharmacological interventions for mania alongside their clinical effectiveness as reported in Cipriani and colleagues (2011). In addition, a cost-utility analysis was conducted, using available utility data that allowed outcomes to be expressed in the form of QALYs.

Economic modelling methods

Interventions assessed

The interventions that were assessed in this economic analysis were determined by the availability of data reported in the network meta-analysis by Cipriani and colleagues (2011). Only drugs that were found to be effective in this study and licensed in the UK were considered in the economic analysis. Cipriani and colleagues (2011) evaluated the following drugs: aripiprazole, asenapine, carbamazepine, valproate, gabapentin, haloperidol, lamotrigine, lithium, olanzapine, quetiapine, risperidone, topiramate and ziprasidone. Paliperidone was not assessed separately, but relevant data were pooled with risperidone data, as paliperidone is the main active metabolite of risperidone. The economic analysis did not consider ziprasidone, because this is not licensed in the UK. Moreover, gabapentin, lamotrigine and topiramate were found to be not significantly better than placebo in the network meta-analysis and were thus excluded from the economic analysis. Thus the economic analysis assessed the costs and outcomes of the following nine drugs: aripiprazole, asenapine, carbamazepine, valproate, haloperidol, lithium, olanzapine, quetiapine and risperidone.

Costs and outcomes considered in the analysis

The economic analysis adopted the NHS and personal social services (PSS) perspective, as recommended by NICE (2012). Costs included hospitalisation costs, drug acquisition costs and costs of laboratory testing. The measures of effectiveness were determined by the outcome measures reported in Cipriani and colleagues (2011), which included the change scores on the YMRS as a primary outcome, and the proportion of people who responded to treatment as a secondary outcome. Moreover, the economic analysis estimated the number of QALYs gained associated with each pharmacological treatment.

Time horizon of the analysis

The time horizon of the economic analysis was 3 weeks, the same as in the study by Bridle and colleagues (2004), which reflected the time horizons of the RCTs included in the network meta-analysis that provided the effectiveness data.

Clinical input parameters

All clinical input parameters were taken from the study by Cipriani and colleagues (2011). These included the SMDs of YMRS scores and the ORs of response rates, as well as the baseline probability of response for placebo. The latter was estimated by pooling the data from all placebo arms included in the network meta-analysis and found to equal 31.1%. This baseline probability of response was used in order to estimate the probability of response for each drug using the following formulae:

$$p_x = odds_x / (1 + odds_x)$$

and

$$odds_x = (1/OR_{b,x}) * p_b/(1-p_b)$$

where p_b the probability of response for placebo (baseline), $OR_{b,x}$ the odds ratio for response of placebo versus each drug as reported in Cipriani and colleagues (2011) and $odds_x$ the odds of each drug to achieve response.

Utility data and estimation of quality-adjusted life years

In order to express outcomes in the form of QALYs, the health states of the economic model need to be linked to appropriate utility scores. Utility scores represent the HRQoL associated with specific health states on a scale from 0 (death) to 1 (perfect health). More details on the estimation of utility scores, the NICE criteria on selection of available utility data and on the systematic review of the literature that aimed to identify utility scores associated with distinct health states experienced by adults with bipolar disorder are provided in section 6.4.5. This analysis considered utility scores corresponding to the health states of 'mania' equalling 0.44, and 'full response – euthymia' equalling 0.90, as reported in Table 20; the difference in utility between these states (0.46) was estimated using data reported in Revicki and colleagues (2005a). The utility score for mania was used for all people at the start of the model and for people not responding to treatment; the utility score for euthymia was used

for people responding to treatment. The model assumed linear increase in utility in those responding to treatment between the start of the model and the point where response was achieved.

Cost data

Similar to the economic analysis by Bridle and colleagues (2004), people in all arms of the economic model were assumed to be hospitalised over the 3-week time horizon of the analysis. Therefore, hospitalisation costs were the same across all drugs and were excluded from the guideline analysis.

The drug daily dosage was determined according to optimal levels of administration (based on the BNF and the GDG expert opinion) and was consistent with the dosage range reported in the RCTs included in the network meta-analysis by Cipriani and colleagues (2011). Drug acquisition costs were taken from the NHS Electronic Drug Tariff, February 2014 (NHS Business Services Authority, 2014a).

Required laboratory testing was determined by the GDG expert opinion. It was agreed that at initiation of all drugs a number of tests should be undertaken, including electrocardiogram (ECG), assessment of renal function (creatinine, blood urea and electrolytes), glucose, lipid profile and thyroid function tests. The costs of these tests were not included in the analysis, as they were common to all arms of the model. In addition to these tests, the GDG expressed the opinion that liver function should be tested at initiation of all drugs except lithium; for lithium, 3 tests of serum lithium concentration were required to determine optimal dose. The cost of liver function testing was taken from data reported in the economic analysis described in the previous NICE guideline (NCCMH, 2006a). The cost of serum lithium concentration testing was taken from the Newcastle upon Tyne Hospitals NHS trust biochemistry laboratory services tariff for 2006-7.

All costs were uplifted to 2014 prices using the Hospital and Community Health Services (HCHS) pay and prices inflation index (Curtis, 2013). The inflation index for the year 2014 was estimated using the average value of the HCHS pay and prices indices of the previous 3 years.

The drug daily dosages and the associated acquisition costs, as well the laboratory testing costs that were utilised in the model are reported in Table 11.

Table 11: Average daily dosage, daily and 3-week acquisition costs, and additional required laboratory testing costs of pharmacological interventions for the treatment of adults with bipolar disorder experiencing a manic episode included in the economic analysis (2014 prices)

Drug	Daily dosage	Daily drug cost	3-week drug cost	Laboratory test and cost
Aripiprazole	15 mg	£6.86	£144.06	Liver function: £4.37
Asenapine	10 mg twice daily	£3.42	£71.82	Liver function: £4.37
Carbamazepine	500 mg	£0.32	£6.77	Liver function: £4.37

Valproate	1500 mg	£0.97	£20.41	Liver function: £4.37
Haloperidol	5 mg twice daily	£0.23	£4.76	Liver function: £4.37
Lithium	1400 mg	£0.12	£2.59	Lithium concentration: 3 x £3.25
Olanzapine	15 mg	£0.08	£1.61	Liver function: £4.37
Quetiapine	300 mg twice daily	£0.17	£3.55	Liver function: £4.37
Risperidone	4 mg	£0.04	£0.79	Liver function: £4.37
Drug acquisition costs from the NHS Electronic Drug Tariff, February 2014 (NHS Business Services Authority, 2014a). Liver function testing cost from (NCCMH, 2006a). Serum lithium concentration testing cost from the Newcastle upon Tyne Hospitals NHS trust biochemistry laboratory services tariff for 2006-7.				

Data analysis

Estimated costs of pharmacological interventions are presented alongside effectiveness data (SMDs of YMRS scores and ORs of response as reported in Cipriani and colleagues (2011)) and the mean QALY gain per person. Formal synthesis of costs and SMDs in an ICER was not attempted, as the resulting figures would be difficult to interpret and therefore would not be useful in decision-making. On the other hand, ICERs expressing cost per additional responder were estimated despite the fact that they were difficult to interpret, to enable comparisons with the results reported in Bridle and colleagues (2004). In addition, incremental analysis where the ICER was expressed as cost/QALY was undertaken. Probabilistic analysis was not possible to undertake using the summarised efficacy data (mean and 95% CIs) that were reported in Cipriani and colleagues (2011). The cost data used in this analysis were very limited and were not subject to uncertainty, as the drug and laboratory testing unit prices are determined. Therefore, other sensitivity analysis was not attempted.

Economic modelling results

Results of the economic analysis using the SMDs and the ORs of response of each drug versus placebo are presented in Table 12 and Table 13, respectively. Table 13 also presents the QALY gains per person associated with each drug. In both tables, drugs have been ordered from the most to the least effective. As shown in Table 12, the 3 most effective drugs in terms of SMD are haloperidol, risperidone and olanzapine; these drugs have also the lowest costs, all below £10 per person. These drugs are followed by quetiapine and lithium, which have comparable costs, as well as aripiprazole, which, however, has a total acquisition and laboratory testing cost of £148.

Table 12: Results of the economic analysis of pharmacological interventions for the treatment of adults with bipolar disorder experiencing a manic episode: effectiveness expressed by the standardised mean difference (SMD) of YMRS scores compared with placebo and costs

Drug	Effectiveness: SMD Mean (95% CIs)	Cost per person
Haloperidol	–0.56 (–0.68 to –0.43)	£9.12
Risperidone	–0.50 (–0.63 to –0.38)	£5.16
Olanzapine	–0.43 (–0.54 to –0.32)	£5.97

Quetiapine	–0.37 (–0.51 to –0.23)	£7.92
Lithium	–0.37 (–0.50 to –0.25)	£12.34
Aripiprazole	–0.37 (–0.51 to –0.23)	£148.43
Carbamazepine	–0.36 (–0.60 to –0.11)	£11.14
Asenapine	–0.30 (–0.53 to –0.07)	£76.19
Valproate	–0.20 (–0.37 to –0.04)	£24.77

In terms of ORs of response and QALYs, the 4 most effective drugs were carbamazepine, haloperidol, olanzapine and risperidone, all with comparable costs. These are followed by quetiapine, which has also comparable costs, valproate, which has somewhat higher costs, and aripiprazole, which is by far the most costly drug of the analysis. According to formal incremental analysis, all drugs below the 4 most effective drugs are dominated by absolute dominance, as they are less effective and more costly than one of more of the 4 most effective drugs. Haloperidol and olanzapine are dominated by rules of extended dominance (the latter occurs when an option is less effective and more costly than a linear combination of two alternative options). The ICER of carbamazepine versus risperidone is £149 per additional responder or £3,842/QALY. It needs to be noted that carbamazepine was not among the most effective drugs in the analysis of YMRS change scores, which was the primary analysis of efficacy data in Cipriani and colleagues (2011). If carbamazepine is excluded from incremental analysis, then haloperidol and olanzapine are not dominated anymore. The ICER of haloperidol versus olanzapine is £283 per additional responder or £7,333/QALY and the ICER of olanzapine versus risperidone is £151 per additional responder or £3,918/QALY. Using the NICE cost effectiveness threshold of £20,000-£30,000/QALY, haloperidol becomes the most cost-effective option if carbamazepine is excluded from analysis. This is followed by olanzapine and then risperidone. Quetiapine is the next most cost-effective option, as it dominates all the remaining drugs in the analysis.

The ICERs expressing cost per additional responder are difficult to interpret, as there is no set threshold regarding the WTP per additional responder to treatment for mania. Nevertheless, they were estimated to enable comparison with respective ICERs reported in Bridle and colleagues (2004). The comparison reveals that the ICERs estimated in this analysis are much lower than those reported by Bridle and colleagues, who estimated an ICER of olanzapine versus haloperidol equal to £7,179 per additional responder; this discrepancy may be attributable to the very different drug acquisition costs between the guideline analysis and the analysis by Bridle and colleagues (2004), as, since the latter, many of the drugs considered have become available in generic form. It should also be noted that the total costs reported in this analysis are substantially lower than those reported by Bridle and colleagues (2004), because this analysis did not include costs of hospitalisation, which, in both analyses, were assumed to be common across all arms and were thus cancelled out.

Table 13: Results of the economic analysis of pharmacological interventions for the treatment of adults with bipolar disorder experiencing a manic episode: effectiveness expressed by the odds ratios (ORs) of response rates of placebo

versus each drug, QALYs, costs and incremental cost effectiveness ratios

Drug	Effectiveness: OR Mean (95% CIs)	Probability of response	QALYs/ person	Cost/ person	ICER
Carbamazepine	0.40 (0.22 to 0.77)	0.530	0.0205	£11.14	Versus risperidone: £149/extra responder £3,842/QALY
Haloperidol	0.44 (0.33 to 0.58)	0.506	0.0196	£9.12	£283/extra responder £7,333/QALY - dominated by ED
Olanzapine	0.46 (0.36 to 0.58)	0.495	0.0191	£5.97	£151/extra responder £3,918/QALY - dominated by ED
Risperidone	0.47 (0.35 to 0.61)	0.490	0.0189	£5.16	
Quetiapine	0.50 (0.37 to 0.66)	0.474	0.0183	£7.92	Dominated
Valproate	0.50 (0.36 to 0.70)	0.474	0.0183	£24.77	Dominated
Aripiprazole	0.50 (0.38 to 0.66)	0.474	0.0183	£148.43	Dominated
Lithium	0.55 (0.38 to 0.79)	0.451	0.0174	£12.34	Dominated
Asenapine	0.59 (0.31 to 1.13)	0.433	0.0168	£76.19	Dominated

ED = extended dominance

The methodology checklist and the economic evidence profile of the analysis are provided in Appendix 31 and Appendix 33, respectively.

Discussion – limitations of the analysis

The results of the economic analysis suggest that haloperidol, olanzapine, risperidone and quetiapine may be more cost-effective options compared with the other drugs assessed in the analysis. Carbamazepine was shown to be the most effective (and cost-effective) option when ORs of response and QALYs were used, but not in the analysis that utilised SMDs. After excluding carbamazepine from the cost-utility analysis, haloperidol became the most cost-effective treatment option, followed by olanzapine, risperidone and quetiapine. It has to be noted that the efficacy and cost differences between haloperidol, olanzapine, risperidone and quetiapine were overall shown to be rather small.

The economic analysis is very simplistic and has taken into account only costs associated with drug acquisition and additional laboratory tests required for each drug over a period of 3 weeks. This short time horizon was imposed by the short time horizons of the RCTs that were included in the meta-analysis that provided the effectiveness data. Side effects and their impact on costs and HRQoL were not considered in the analysis, due to the short time horizon and the lack of relevant data. Hospitalisation costs were assumed to be the same for all drugs over 3 weeks, as all people with bipolar disorder experiencing an acute episode were estimated to be hospitalised over the first 3 weeks of acute treatment. However, the total length of hospitalisation and outcomes of drugs beyond 3 weeks were not taken into account in the analysis due to lack of relevant data. If some drugs result in better outcomes beyond the period of the 3 weeks and reduce the total length of hospitalisation, then they are expected to be more cost-effective, as hospitalisation is the most substantial driver of costs in the treatment of mania (the mean cost of Mental Health Care

Clusters per bed-day was £344 in 2013, according to NHS reference costs (NHS Department of Health, 2013)).

Another limitation of the analysis is the use of utility data from Revicki and colleagues (2005a) owing to the lack of more relevant utility data for the state of mania. The study described hypothetical health states using vignettes, which were valued by stable outpatients with bipolar disorder in the US. As discussed in section 6.3.7, these utility values do not meet NICE criteria on use of utility values and do not reflect the UK general population's preferences. The results of the cost-utility analysis should be therefore interpreted with caution.

In conclusion, the analysis has not overcome many of the limitations characterising previous studies. Factors such as acceptability, rate and type of side effects associated with each drug should also be considered when making recommendations.

Economic evidence statement

The existing economic evidence is rather limited and not directly applicable to the NICE decision-making context; all reviewed studies are characterised by potentially serious limitations. In the economic analysis conducted for this guideline, haloperidol, olanzapine, risperidone and quetiapine appear to be more cost-effective options than other drugs included in the analysis. However, this analysis is also characterised by potentially serious limitations.

6.3 PHARMACOLOGICAL AND NUTRITIONAL INTERVENTIONS FOR ACUTE EPISODES OF BIPOLAR DEPRESSION

6.3.1 Introduction

People with bipolar disorder spend considerably more time depressed than manic; for those with bipolar I disorder, it has been estimated that for two-thirds of the time that they are unwell, it is with depression (Judd et al., 2003a; Judd et al., 2002a). For those with bipolar II disorder, over 90% of unwell days are due to depression. Bipolar disorder is associated with a high prevalence of suicide with most of these occurring during the depressed phase (Novick et al., 2010). A number of medications have been used for bipolar depression, alone and in combination, including antidepressants used for unipolar depression (SSRIs, tricyclics, MAOIs) as well as antipsychotics, anticonvulsants and lithium.

6.3.2 Clinical review protocol

The review protocol summary, including the review question and the eligibility criteria used for this section of the guideline, can be found in Table 14 (a complete list of review questions and protocols can be found in Appendix 7; further information about the search strategy can be found in Appendix 8).

Table 14: Clinical review protocol summary for the review of pharmacological and nutritional interventions for acute episodes of bipolar depression

Topic	Interventions
Review question	RQ2.2: For adults with bipolar disorder, what are the relative benefits and harms of pharmacological and nutritional interventions for acute episodes of acute bipolar depression? 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+)?
Objectives	To estimate the efficacy of interventions to treat acute episodes of bipolar depression.
Criteria for considering studies for the review	
• Intervention	All licensed oral medications (and their combinations). Nutritional interventions will be analysed separately.
• Comparator	Placebo Other interventions
• Types of participants	Adults (18+) with bipolar disorder who are experiencing an acute episodes of bipolar depression. Special consideration will be given to the groups above.
• Outcomes	1) Response (50% reduction in symptoms) 2) Discontinuation (due to side effect, other)
• Time	The main analysis will include outcomes at the end of the acute treatment phase.
• Study design	Randomised controlled trials (RCTs) and cluster RCTs with a parallel group design in which providers and participants were blind to treatment. Quasi-RCTs, such as trials in which allocation is determined by alternation or date of birth, and single-blind studies, will be excluded.
• Dosage	Fixed or flexible doses within the therapeutic range (BNF recommended).
• Minimum sample size	To be included in a network meta-analysis, drugs must have been evaluated in at least 20 participants.
• Study setting	Primary, secondary, tertiary, health and social care
Note. BNF = British National Formulary.	

6.3.3 Studies considered

Twenty-seven RCTs (N = 9,006) published between 1999 and 2012 compared eligible interventions and reported outcomes that could be used for network meta-analysis: BRISTOLMYERSSQUIB2006 (Bristol-Myers Squibb, (unpublished) 2006; Thase et al., 2008), BRISTOLMYERSSQUIB2007 (Bristol-Myers Squibb, (unpublished) 2007; Thase et al., 2008), BROWN2006 (Brown et al., 2009; Brown et al., 2006; Nierenberg, 2007), CALABRESE1999 (Bowden, 1999; Calabrese et al., 1999; GlaxoSmithKline, (unpublished) 2005a; GlaxoSmithKline, (unpublished) 2005d; McElroy et al., 2004; Preston et al., 2004; Rudd et al., 1998), CALABRESE2005 (Calabrese et al., 2005a; Cookson et al., 2007; Endicott et al., 2008; Endicott et al., 2007; Hirschfeld et al., 2006; Tohen et al., 2013; Weisler et al., 2008a), CALABRESE2008a (Calabrese et al., 2008; Geddes et al., 2009; GlaxoSmithKline, (unpublished) 2005b; GlaxoSmithKline,

(unpublished) 2005e; Goldsmith et al., 2004), CALABRESE2008b (Calabrese et al., 2008; Geddes et al., 2009; Goldsmith et al., 2004), CALABRESE2008c (Calabrese et al., 2008; Geddes et al., 2009), CALABRESE2008d (Calabrese et al., 2008; Geddes et al., 2009), DAVIS2005 (Davis et al., 2005), GHAEMI2007 (Ghaemi et al., 2005a; Ghaemi et al., 2007), MCELROY2010 (McElroy et al., 2010; Young et al., 2012; Young et al., 2008), MUZINA2011 (Muzina, 2008; Muzina et al., 2011), NEMEROFF2001 (GlaxoSmithKline, (unpublished) 2005c; Nemeroff et al., 2001), PFIZER2009a (Gao et al., 2013; Lombardo et al., 2012; Pfizer, (unpublished) 2009a), PFIZER2009b (Gao et al., 2013; Lombardo et al., 2012; Pfizer, (unpublished) 2009b), QUANTE2010 (Quante et al., 2010), SACHS2011 (Sachs et al., 2011), SILVERSTONE2001 (Silverstone, 1997; Silverstone, 2001), SUNOVION2012a (Citrome et al., 2014; Ketter et al., 2012; Sunovion, (unpublished) 2012), SUNOVION2012b (Citrome et al., 2014; Ketter et al., 2012; Sunovion, 2012), SUPPES2010 (Suppes et al., 2010), THASE2006 (Endicott et al., 2008; Goodwin, 2007; Thase, 2007; Thase et al., 2006; Tohen et al., 2013; Weisler et al., 2008a), TOHEN2003 (Corya et al., 2006; Dube et al., 2007; Shi et al., 2004a; Tohen et al., 2007a; Tohen et al., 2003; Vieta et al., 2009a), TOHEN2012 (Katagiri et al., 2013; Tohen et al., 2012a), VANDERLOOS2009 (Van der Loos et al., 2010; Van der Loos et al., 2011; Van der Loos et al., 2009), YOUNG2010 (Grunze, 2010; Young et al., 2010). Six of these were unpublished (BRISTOLMYERSSQUIB2006, BRISTOLMYERSSQUIB2007, PFIZER2009a, PFIZER2009b, SUNOVION2012a, SUNOVION2012b). Studies included in the network meta-analysis were analysed by comparing discontinuation (for any reason) and response, given not discontinued.

A joint network meta-analysis on discontinuation and number of responders given not discontinued was carried out by subtracting the number of patients who had discontinued from the total number of patients randomised. A separate network meta-analysis to estimate relative effects of response out of all randomised patients (that is, not conditional on discontinuation) was also carried out.

All studies reported the number of patients discontinuing, out of the total number randomised, but only 25 studies reported a useable measure of response on a dichotomous or continuous scale (BRISTOLMYERSSQUIB2006 and BRISTOLMYERSSQUIB2007 did not report response).

Data on response were reported in different formats. The relative effect of interest was the odds ratio of response, so the following approach was taken to incorporate as much of the available data as possible:

(1) For studies reporting the number of responders on ***only one*** of the HAMD or MADRS scales, those data were used in the analysis.
(2) For studies reporting the number of responders on ***both*** the HAMD and MADRS the log-odds ratio of response, given not discontinued, given by each measure was averaged and the standard error of the log-odds ratios was calculated as the average of the standard errors on each scale
(3) For studies not reporting the number of responders but reporting the mean and standard deviation (SD) on one of the scales (HAMD or MADRS), the

within-study standardised mean difference (SMD) and its variance were calculated according to the Hedges' g formula and used in the analysis.

(4) For studies not reporting the number of responders but reporting the mean and SD on both the HAMD and MADRS scales, the within-study SMD on each scale and their standard errors were calculated as above, and then averaged. This combined SMD and its variance (the standard error squared) were used in the analysis.

One additional three-arm study (N = 174; POST2006) was a comparison of three drugs that could not be connected to the network. Therefore, the pairwise comparisons are reported separately below.

An additional 29 studies were excluded; eight were open-label studies: AMSTERDAM2009 (Amsterdam & Shults, 2009), ASTRAZENECA2012a (Astrazeneca, (unpublished) 2012a), ASTRAZENECA2012b (Astrazeneca, (unpublished) 2012b), NIERENBERG2006 (Nierenberg et al., 2006), NOLEN2007 (Nolen et al., 2007), TAMAYO2009 (Tamayo et al., 2009), WANG2010 (Wang et al., 2010), YONGNING2005 (Yong Ning & Hui, 2005); seven trials were of medications neither routinely used nor licensed for the treatment of mental health problems: CHENGAPPA2000 (Chengappa et al., 2000), DENICOFF2005 (Denicoff et al., 2005) DIAZGRANADOS2010 (Diazgranados et al., 2010), FUREY2013 (Furey & Zarate, 2013), STAMM2011 (Stamm et al., 2011), SZUBA2005 (Szuba et al., 2005), WATSON2012 (Watson et al., 2012), YOUNG2004 (Young et al., 2004), ZARATE2012; and four trials included people who did not have bipolar disorder: FIEVE1968 (Fieve et al., 1968), KESSELL1975 (Kessell & Holt, 1975), SMITH1978 (Smith et al., 1978), SPEER2009 (Speer et al., 2009). Three studies were excluded because did not include a sufficient number of participants to be included; one was a study of pramipexole as a second-line intervention: GOLDBERG2004 (Goldberg et al., 2004); one was a study of pramipexole: ZARATE2004B (Zarate et al., 2004); one was a study of paroxetine and mood stabilisers: YOUNG2000; and one was a study of risperidone and paroxetine: SHELTON2004 (Shelton & Stahl, 2004). One study was excluded because it involved a comparison of antidepressants as a class (rather a specific drug) with placebo: SACHS2007. One study of tranylcypromine was excluded because it did not report response on an accepted measure: HIMMELHOCH1991 (Himmelhoch et al., 1991). Two studies were excluded because they did not report usable outcomes; one compared olanzapine and fluoxetine alone or in combination: AMSTERDAM2005a (Amsterdam & Shults, 2005a); one compared valproate with lithium: OQUENDO2011 (Oquendo et al., 2011). One study of eicosapentaenoic acid was excluded because there were only six participants in each group: OSHER2005 (Osher et al., 2005). One was excluded because participants were not acutely depressed: FRANGOU2006 (Frangou et al., 2006). Results could not be obtained for eight studies: AHUJA2011 (Ahuja et al., 2011), COLOMBO2000 (Colombo et al., 2000), FOREST2010 (Forest, 2010), FRYE2000, GAO2008 (Gao et al., 2008), MCELROY2013 (McElroy et al., 2013), PATKAR2012, SACHS2002; although they have published several papers about the drug, the manufacturer of cariprazine has not reported the results of clinical trials, and they refused requests for data.

Further information about both included and excluded studies can be found in Appendix 16and Appendix 34.

6.3.4 Network meta-analysis of pharmacological interventions for acute episodes of bipolar depression

Trials included in the network meta-analysis included between 19 and 833 participants at baseline (median 298). Where known, participants were on average (median of means) aged 40 years and about 58% of them were female. Fourteen trials included only participants with bipolar I disorder; one trial included only participants with bipolar II disorder (CALABRESE2008c), and only 37% of participants in another had bipolar II disorder (MUZINA2011).

Studies of medication alone or as an addition to another treatment were included. All participants were taking a mood stabiliser in six studies (QUANTE2010, SACHS2011, NEMEROFF2001, VANDERLOOS2009, SUNOVION2012a, SUNOVION2012b). Twelve studies reported that participants were not taking mood stabilisers at baseline (BRISTOLMYERSSQUIB2006, BRISTOLMYERSSQUIB2007, CALABRESE1999, CALABRESE2005, CALABRESE2008a, CALABRESE2008b, CALABRESE2008c, CALABRESE2008d, DAVIS2005, GHAEMI2007, MCELROY2010, MUZINA2011, PFIZER2009a, PFIZER2009b, SUPPES2010, THASE2006, TOHEN2003, YOUNG2010), though participants in some of these studies could be taking other medications including anxiolytics or hypnotics. Nine studies included a mix of participants taking or not taking mood stabilisers, or did not report their use.

Quality of the evidence

To rate the quality of evidence, guidelines may use GRADE profiles for critical outcomes. However, GRADE has not yet been adapted for use in network meta-analyses. To evaluate the quality of the evidence from the network meta-analysis, information about the factors that would normally be included in a GRADE profile will be reported (that is, risk of bias, publication bias, imprecision, inconsistency and indirectness).

Risk of bias

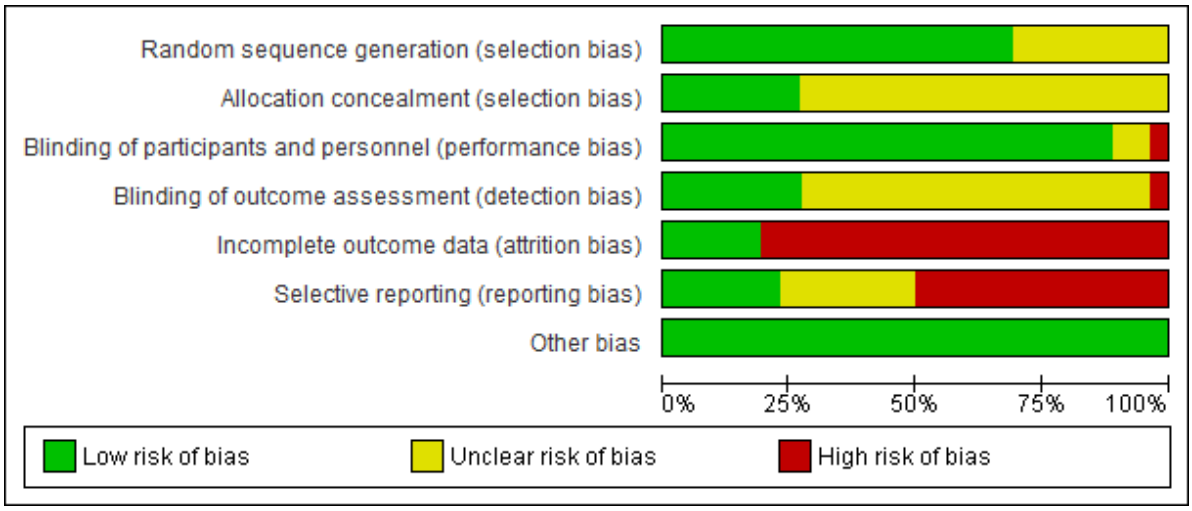
All included trials were assessed for risk of bias (Appendix 17). Of those in the network meta-analysis, 21 were at low risk for sequence generation and nine of these were at low risk of bias for allocation concealment. Allocation concealment was unclear in 18 trials. All trials were double-blind and were rated as low risk of bias for participant and provider blinding, although effects of medication, including side effect, may make it difficult to maintain participant and provider blinding, particularly at higher doses. Assessor blinding was considered separately for all trials; seven were at low risk of bias and assessors were aware of treatment conditions in one trial. For incomplete outcome data, response was analysed assuming that participants who discontinued treatment did not respond. Because of

the high rate of missing data and/or the handling of missing data, continuous outcomes were at high risk of bias in 22 trials.

Selective outcome reporting and publication bias

Several methods were employed to minimise risk of selective outcome reporting and publication bias. The NCCMH review team wrote to all authors to request trial registrations and unpublished outcomes, and all authors of included trials, all stakeholders, and pharmaceutical manufacturers were asked to provide unpublished trials. Nonetheless, only six were at low risk of selective outcome reporting bias, the remaining 14 and seven were at unclear and high risk of bias, see Figure 5.

Figure 5: Risk of bias summary



Inconsistency

Inconsistency was assessed by fitting an unrelated mean effects model (Dias et al., 2012) and comparing the fit of this model to the fit of the full network meta-analysis model using the residual deviance (Dias et al., 2012). The posterior mean of the residual deviance for discontinuation was 63.5, very close to the respective 64 data points of the model; the posterior mean of the total residual deviance for response was 58.44, moderately high compared with the respective 51 data points. This finding may be attributable to one study (THASE2006) that did not fit the model well regarding response. Only one loop in the network had the potential for inconsistency, and there was no evidence of inconsistency for response and for discontinuation.

Indirectness

All evidence in the network meta-analysis is direct insofar as it relates to the population, interventions and outcomes of interest.

Effects of interventions

In the network meta-analysis, all interventions except aripiprazole ranked higher than placebo for response given no discontinuation, but only six were statistically

superior to placebo (lurasidone, valproate, quetiapine, the combination of fluoxetine and olanzapine, olanzapine alone, and lamotrigine) (see Table 15). Quetiapine and lurasidone were less well tolerated than placebo; for discontinuation, the combination of fluoxetine and olanzapine, valproate, olanzapine alone and lamotrigine ranked higher than placebo. When response for all randomised participants (that is, assuming the dropouts did not respond) were compared, moclobemide and ziprasidone were also ranked below placebo. Other interventions that were included in the network but were not statistically superior to placebo were imipramine, lithium, moclobemide, paroxetine and ziprasidone. Excluding valproate, which only 48 people received, the five efficacious interventions were received by 292 to 1867 participants.

Table 15: Pharmacological interventions for acute episodes of bipolar depression (results from network meta-analysis)

Intervention	N	Response[1]	Conditional response[2]	Discontinuation	Study ID(s)
Aripiprazole	385	0.41 (0.04, 3.38)	0.17 (0.00, 5.97)	1.58 (1.09, 2.31)	BRISTOLMYERSSQUIB2006, BRISTOLMYERSSQUIB2007, QUANTE2010
Fluoxetine and olanzapine	292	2.25 (1.58, 3.18)	2.37 (1.37, 4.29)	0.66 (0.43, 0.99)	BROWN2006, TOHEN2003,
Imipramine	111	1.06 (0.43, 2.48)	1.67 (0.49, 6.02)	1.36 (0.56, 3.37)	NEMEROFF2001, SILVERSTONE2001,
Lamotrigine	810	1.42 (1.13, 1.77)	1.44 (1.07, 2.00)	0.96 (0.74, 1.27)	BROWN2006, CALABRESE1999, CALABRESE2008d, CALABRESE2008c, CALABRESE2008b, CALABRESE2008a, VANDERLOOS2009,
Lithium	136	1.35 (0.88, 2.07)	1.77 (0.95, 3.32)	1.03 (0.60, 1.74)	YOUNG2010
Lurasidone	518	2.15 (1.58, 2.94)	3.00 (1.92, 4.72)	1.16 (0.78, 1.74)	SUNOVION2012a, SUNOVION2012b
Moclobemide	81	0.78 (0.26, 2.20)	1.17 (0.25, 5.81)	1.66 (0.51, 5.46)	SILVERSTONE2001
Olanzapine	713	1.41 (1.09, 1.83)	1.54 (0.98, 2.45)	0.86 (0.61, 1.20)	TOHEN2003, TOHEN2012
Paroxetine	155	1.21 (0.81, 1.80)	1.38 (0.77, 2.51)	0.97 (0.60, 1.51)	MCELROY2010, NEMEROFF2001,
Quetiapine	1867	1.69 (1.39, 2.06)	2.59 (1.94, 3.55)	1.03 (0.82, 1.29)	CALABRESE2005, MCELROY2010, SUPPES2010, THASE2006, YOUNG2010,
Valproate	48	2.7 (1.08, 7.56)	3.37 (1.07, 11.02)	0.62 (0.26, 1.45)	DAVIS2005, GHAEMI2007, MUZINA2011,
Ziprasidone	675	0.99 (0.77, 1.26)	1.27 (0.87, 1.91)	1.44 (1.06, 1.96)	PFIZER2009a, PFIZER2009b, SACHS2011,

Note. All effects (median OR and 95% CI) compared with placebo (N = 3215), which was included in BRISTOLMYERSSQUIB2006, BRISTOLMYERSSQUIB2007, CALABRESE1999, CALABRESE2005, CALABRESE2008a, CALABRESE2008b, CALABRESE2008c, CALABRESE2008d, DAVIS2005, GHAEMI2007, MCELROY2010, MUZINA2011, NEMEROFF2001, PFIZER2009a, PFIZER2009b, QUANTE2010, SACHS2011, SUNOVION2012a, SUNOVION2012b, SUPPES2010, THASE2006, TOHEN2003, TOHEN2012, VANDERLOOS2009, YOUNG2010.

[1]Effect calculated using the number of participants *randomised to treatment* as the denominator.

[2]Effect calculated using the number or participants *who did not discontinue treatment* as the denominator.

6.3.5 Pharmacological interventions for acute episodes of bipolar depression that could not be included in the network meta-analysis

One RCT (N = 174; POST2006) published in 2006 compared bupropion, sertraline and venlafaxine in outpatients. In the total sample, mean age was 42 years, 50% were female and 73% were diagnosed with bipolar I disorder. Little difference was found between any of the groups on response and discontinuation.

6.3.6 Nutritional interventions for acute episodes of bipolar depression

One RCT (N = 116) published in 2006 compared medication as usual with or without eicosapentaenoic acid supplementation (KECK2006b (Keck et al., 2006b). There was very low quality evidence that eicosapentaenoic acid supplementation was not associated with a reduction in depressive symptoms (see Appendix 16).

6.3.7 Health economics evidence

Systematic literature review

The systematic search of the economic literature undertaken for the guideline identified one eligible study on the cost effectiveness of pharmacological interventions (Ekman et al., 2012) and one eligible study on the cost effectiveness of nutritional interventions (Cheema et al., 2013) for adults with bipolar disorder in an acute depressive episode. References to included studies and evidence tables for all economic evaluations included in the systematic literature review are provided in Appendix 32. Completed methodology checklists of the studies are provided in Appendix 31. Economic evidence profiles of studies considered during guideline development (that is, studies that fully or partly met the applicability and quality criteria) are presented in Appendix 33.

The study by Ekman and colleagues (2012) assessed the cost effectiveness of quetiapine versus a number of pharmacological treatment options in adults with bipolar disorder (I or II) in the UK. The study was based on decision-analytic modelling. Two separate analyses were undertaken: one where the study population entered the model in an acute episode of bipolar depression, and another one where the study population entered the model in remission. Both analyses had a 5-year time horizon and considered the following treatment options: quetiapine; quetiapine added to a mood stabiliser (lithium or valproate semisodium); olanzapine; olanzapine plus lithium, with olanzapine replaced by venlafaxine in acute depression; olanzapine plus lithium, with olanzapine replaced by paroxetine in acute depression; aripiprazole that was replaced by olanzapine and venlafaxine in acute depression; and a mixed scenario where risperidone was administered in mania, venlafaxine and lithium were administered in acute depression, and olanzapine was administered as maintenance treatment.

The study adopted the NHS perspective. Costs included hospitalisation costs, costs of outpatient care, costs associated with crisis teams, staff costs (senior house officer, GP, community psychiatric nurse, practice nurse, dietician), drug acquisition costs, laboratory test costs, and costs of adverse events. Indirect costs (productivity losses) were considered in a sensitivity analysis. The measure of outcome was the QALY. Relative effects across drugs were taken from RCTs and published meta-analyses of trials. Resource use data were taken from published sources, which, however, reported estimates based on expert opinion. Unit costs were taken from national sources.

The study is directly applicable to the UK. However, evidence synthesis was based on indirect comparisons between drugs, using placebo as baseline; however, as the authors acknowledged, the meta-analyses used to derive the relative effects were not similar in terms of the phase of the disorder examined and the measures of outcome used. Moreover, it is not clear whether the study populations and designs across all RCTs used in evidence synthesis (including those considered in the published meta-analyses) were similar enough to allow indirect comparisons of drugs. Overall, it appears that methods of evidence synthesis were inappropriate, introducing bias in the economic analysis. For this reason, the study was judged to suffer from very serious limitations and was therefore not considered further when making recommendations.

Cheema and colleagues (2013) evaluated the cost effectiveness of ethyl-eicosapentaenoic acid (ethyl-EPA) adjunctive to mood stabilisers versus mood stabilisers alone in adults with bipolar I disorder in a stable (euthymic) state, from the perspective of the UK NHS. The study, which was based on decision-analytic modelling, is described here because it has utilised effectiveness data from a 12-week RCT that assessed the efficacy of ethyl-EPA in people with bipolar depression (FRANGOU2006). This RCT was excluded from the guideline systematic review because participants were not acutely depressed. The economic analysis extrapolated the efficacy data from this trial to stable adults with bipolar disorder experiencing acute episodes, over 1 year; efficacy of ethyl-EPA in reducing depressive symptoms over 12 weeks was assumed to correspond to efficacy in preventing acute manic and depressive episodes over 1 year. This was considered a very serious limitation of the analysis; consequently the study was not considered further when formulating guideline recommendations.

Economic modelling

Introduction – objective of economic modelling

The cost effectiveness of pharmacological interventions for adults with bipolar disorder experiencing an acute depressive episode was considered by the GDG as an area with likely significant resource implications. Existing economic evidence in this area was limited to one study that was conducted in the UK. The study was characterised by potentially serious limitations and did not assess the whole range of interventions that are available in the UK for the treatment of acute depression in adults with bipolar disorder. The clinical evidence in this area was judged to be sufficient and of adequate quality to inform primary economic modelling. Based on the above considerations, this area was prioritised for further economic analysis. An economic model was therefore developed to assess the relative cost effectiveness of pharmacological interventions for adults with bipolar disorder experiencing an acute depressive episode in the UK.

Economic modelling methods

Interventions assessed

The guideline economic analysis assessed pharmacological interventions that were included in the relevant network meta-analysis conducted for this guideline. The economic model considered interventions that were found to be effective in the network meta-analysis and are available in the UK. Aripiprazole was excluded from the economic analysis, since the network meta-analysis indicated that it is ineffective in the treatment of acute depression in adults with bipolar disorder. Lurasidone and ziprasidone were not considered in the economic analysis because they are not available in the UK.

Based on the above criteria the following pharmacological interventions were included in the economic analysis: imipramine, lamotrigine, lithium, moclobemide, olanzapine, paroxetine, quetiapine, valproate semisodium, and the combination of fluoxetine and olanzapine.

The model also considered no pharmacological treatment (reflected in treatment with placebo) consisting, in terms of resource use, of visits to healthcare professionals only, in order to assess the cost effectiveness of active interventions versus a non-specific medical management (used as a benchmark).

Model structure

A decision-analytic model in the form of a decision-tree was constructed using Microsoft Office Excel 2010. The model estimated the total costs and benefits associated with provision of each of the 10 treatment options (including no pharmacological treatment) to adults with bipolar disorder experiencing an acute depressive episode. The structure of the model, which aimed to simulate the course of acute bipolar depression and relevant clinical practice in the UK, was also driven by the availability of clinical data.

According to the model structure, hypothetical cohorts of adults with bipolar disorder in acute depression were initiated on each of the 10 treatment options assessed. People initiated on a pharmacological treatment option could either continue treatment for 6 weeks or discontinue for any reason (for example because of intolerable side effects). Drug discontinuation was estimated to occur on average at 3 weeks form initiation of drug treatment. At the end of 6 weeks, people continuing treatment either responded to treatment fully or partially, or they did not respond. Assessment of response was undertaken at this point because 6 weeks was the median (and mode) time horizon of the studies considered in the guideline network meta-analysis that provided the response data for the model. People who responded to the initiated drug fully or partially continued their drug treatment for another 12 weeks at the same dosage, at the end of which they either experienced a manic or depressive relapse or did not relapse.

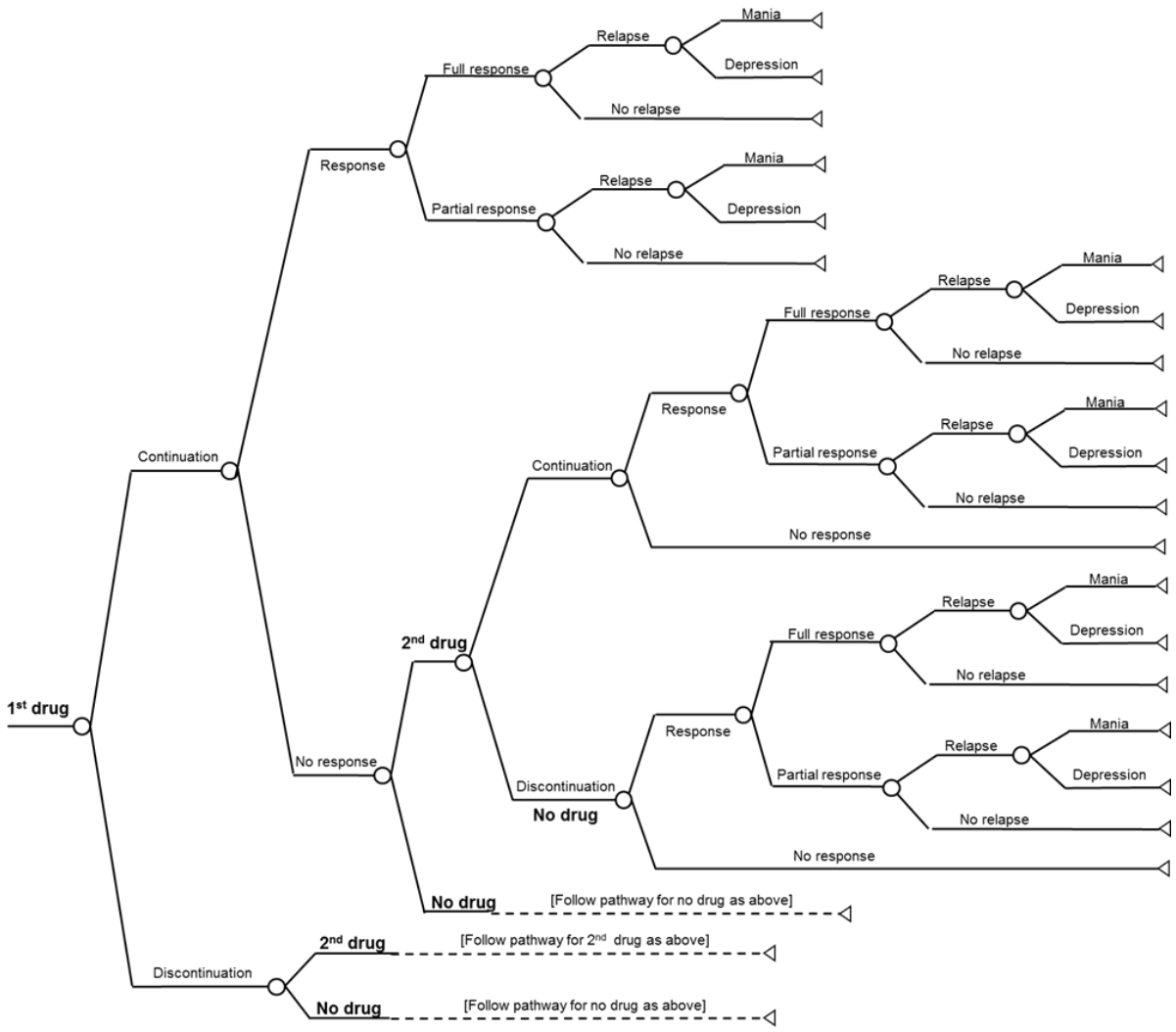
People discontinuing their initiated drug treatment at 3 weeks or not responding to this treatment after 6 weeks either stopped drug treatment (that is, they moved to no pharmacological treatment) or moved to a second drug treatment option; this was assumed to be a non-weighted ‘average’ mixture of all other drug treatment options

assessed in the economic analysis (in terms of intervention costs and clinical outcomes), excluding the initiated drug treatment option. People initiated on the combination of fluoxetine and olanzapine could move to a mixture of all other drugs evaluated in the model except monotherapy with olanzapine, since the combination of the latter with fluoxetine had already failed. People under the second drug treatment option either continued the drug treatment or discontinued after 3 weeks and moved to no pharmacological treatment. Those continuing the second drug followed the same pathway as people who continued the first drug (that is, no response or response, either full or partial, 6 weeks later, after which they could relapse to a manic or depressive episode or not relapse). People receiving a second drug treatment and not discontinuing remained on this drug for the remaining of the time horizon, whether they responded to this treatment or not.

People under no pharmacological treatment (either as initial treatment, or following discontinuation of, or no response to, their initiated drug treatment option) either responded to treatment, fully or partially, and could experience a manic or depressive relapse, or did not respond to treatment.

The time horizon of the analysis was 18 weeks, which consisted, for people responding to their initiated drug, of 6 weeks of treatment until assessment of the clinical outcome (6 weeks was the median time horizon of trials considered in the guideline network meta-analysis), and another 12 weeks of continuation of the drug, prior to initiation of long-term pharmacological maintenance treatment. The GDG expressed the opinion that people with acute bipolar depression that show responsiveness to a drug normally continue the drug as acute treatment, and at full dosage, for another 8 weeks and then they either take the drug as long-term maintenance treatment at the same dosage, or they receive the drug at gradually reduced dosages over a period of another 4 weeks, during which they start long-term maintenance treatment with another drug. For simplicity purposes as well as for consistency across model arms (as some drugs in the model are not suitable for long-term maintenance treatment), it was assumed that all people responding to a drug received its full dosage for the remaining of the model. The 18-week time horizon enabled capturing the full course of acute drug treatment for people who responded at 6 weeks (6 + 8 + 4 weeks), and was long enough to allow moving to second drug treatment and assessing response in cases where the 6-week initiated drug treatment failed; the model did not extend beyond 18 weeks because this would mean that some people in the model (those who responded at 6 weeks) would start maintenance treatment whereas others would be still receiving acute treatment for their depressive episode. Maintenance treatment was not considered in the model due to lack of appropriate and relevant data that were required to populate a longer-term economic model, as discussed in Chapter 7. A schematic diagram of the decision-tree is presented in Figure 6.

Figure 6: Schematic diagram of the economic model constructed for the evaluation of the relative cost effectiveness of pharmacological interventions for acute depression in adults with bipolar disorder



Costs and outcomes considered in the analysis

The economic analysis adopted the perspective of the NHS and personal social services (PSS), as recommended by NICE (NICE, 2012). Costs consisted of drug acquisition costs, laboratory testing costs, healthcare professional visit costs, as well as costs of hospitalisation and crisis resolution and home treatment teams (CRHTTs) for a proportion of people not responding to treatment. The measure of outcome was the QALY.

Clinical input parameters

Clinical model input parameters consisted of the probabilities of discontinuation and conditional response (in those not discontinuing) following first and second

treatment; the probability of response in people under no pharmacological treatment; the probability of moving to no pharmacological treatment following discontinuation or no response to first pharmacological treatment; the probability of partial response in those responding; the probability of relapse in those responding fully or partially; and the probability of a manic episode in those relapsing.

The probabilities of discontinuation and response in those not discontinuing were taken from the network meta-analysis conducted for this guideline, the methods of which are reported in Appendix 15. For the economic analysis the first 50,000 iterations undertaken in WinBUGS were discarded and another 300,000 were run, thinned by 30, so as to obtain 10,000 iterations that populated the economic model. The results of the network meta-analysis that were used to populate the economic model are provided in Table 16. The table shows the mean probability of discontinuation and conditional response (that is, response in those not discontinuing) for each intervention considered in the economic analysis at the end of treatment (6 weeks).

For no pharmacological treatment (placebo), the data on probability of discontinuation and conditional response were combined in order to provide an overall probability of response in those under no pharmacological treatment (placebo), since the probability of discontinuation was not meaningful in an economic model that assumed that people were already under no pharmacological treatment. Thus, people discontinuing placebo were counted as non-responders.

Table 16: Results of network meta-analysis that were utilised in the economic model: probability of discontinuation and conditional response in adults with acute bipolar depression at end of treatment

Intervention	Mean probability of discontinuation (95% credible intervals)	Mean probability of conditional response (95% credible intervals)
Imipramine	0.41 (0.17 to 0.69)	0.64 (0.26 to 0.92)
Lamotrigine	0.33 (0.16 to 0.53)	0.62 (0.33 to 0.85)
Lithium	0.35 (0.16 to 0.58)	0.66 (0.35 to 0.89)
Moclobemide	0.45 (0.16 to 0.77)	0.56 (0.16 to 0.91)
Olanzapine	0.31 (0.15 to 0.51)	0.63 (0.34 to 0.87)
Paroxetine	0.33 (0.15 to 0.55)	0.61 (0.30 to 0.86)
Quetiapine	0.35 (0.18 to 0.55)	0.74 (0.48 to 0.91)
Valproate	0.25 (0.08 to 0.50)	0.77 (0.43 to 0.95)
Fluoxetine and olanzapine	0.26 (0.11 to 0.45)	0.72 (0.43 to 0.91)

The probability of discontinuation remained the same for each drug when used as second drug option. The probability of conditional response for each drug, however, was assumed to be lower when the drug was used as second option. This reduction in probability of conditional response was assumed to be the same across all drugs and was estimated using data from a longitudinal study on adults with unipolar major depression receiving one to four successive pharmacological treatment options (Rush et al., 2006), owing to the lack of relevant data on people with bipolar

disorder. The reduction in response was also applied to no pharmacological treatment (placebo) for people moving to it after discontinuation of, or no response to, a pharmacological treatment option. It was estimated that the probability of response of each treatment option used as second choice was 0.59 of the probability of response for this option if used as first choice.

The probability of moving to no pharmacological treatment following discontinuation of, or no response to, first pharmacological treatment was based on the GDG expert opinion; the GDG estimated that 25% of people discontinuing their first drug and 10% of people not responding to their first drug moved to no pharmacological treatment.

The probability of partial response in those responding to treatment was assumed to be the same across all treatments and was estimated based on data reported in a pragmatic trial that compared a mood stabiliser plus adjunctive antidepressant therapy versus a mood stabiliser plus a matching placebo in adults with acute bipolar depression (bipolar depression I or II) (Sachs et al., 2007). According to data reported in this trial, out of 366 participants with acute depression, 165 achieved either transient remission or durable recovery (defined as euthymia for a minimum of 8 weeks) following treatment. The percentage of people achieving a transient remission was 43.6% (72/165), and this figure was used in the model to represent the probability of partial response in those responding to treatment.

The probability of relapse following full or partial response was estimated based on data reported in a prospective naturalistic study that followed 223 adults with bipolar disorder I or II for up to 20 years (Judd et al., 2008b). The study reported the probability of relapse to a major acute episode following full and partial recovery from a previous acute episode (which could be manic or depressive), and these data were used to model the probability of relapse at the end of the 18 weeks for all people in the model that had responded to treatment, taking into account that the point at which response occurred differed across the various pathways in each cohort, so that the probability of relapse at the end of 18 weeks, which was assumed to be time-dependent, differed across the various pathways, too.

The probability of a manic episode in those relapsing was also estimated using data reported in Judd and colleagues (2008b). The study reported that in 126 people with bipolar disorder who had recovered from an acute depressive or manic episode and experienced a relapse, 66 had a major depressive episode (52.4%), 26 had a manic episode (20.6%) and 34 had a mixed/cycling polarity episode (27.0%). For simplicity, the GDG advised that half of the mixed/cycling episodes should be considered manic and half should be considered depressive, resulting in a ratio of manic to depressive acute relapses 34.1:65.9, and a probability of a manic episode in those relapsing of 0.341.

Utility data and estimation of quality-adjusted life years

In order to express outcomes in the form of QALYs, the health states of the economic model need to be linked to appropriate utility scores. Utility scores represent the HRQoL associated with specific health states on a scale from 0 (death) to 1 (perfect health); they are estimated using preference-based measures that capture people's preferences on the HRQoL experienced in the health states under consideration. Preference-based measures are instruments consisting of a health state classification system, that is, an instrument that allows determination of the health state of the respondent, and an algorithm that links every health state described by the instrument with a utility score. Utility scores can also be estimated using vignettes that describe hypothetical health states including symptoms, functioning, side effects from treatment, and so on. Utility scores (which express preferences) can be elicited from various population groups (for example, service users, their parents and carers, healthcare professionals or members of the general population). The main methods of valuation are the Visual Analogue Scale (VAS), the Time Trade-Off (TTO) and the Standard Gamble (SG) (Brazier et al., 2007).

The systematic search of the literature identified 3 studies that reported utility scores associated with distinct health states experienced by adults with bipolar disorder (Depp, 2006; Hayhurst, 2006; Revicki et al., 2005a).

Depp and colleagues (2006) reported utility data generated using responses to the Quality of Well-Being Scale (QWB) (Kaplan & Anderson, 1988) derived from 50 community-dwelling adults with bipolar I disorder (according to DSM-IV) aged 45 years or older; of these, 14 were in a depressive episode at the time of the evaluation, 11 in a hypomanic or manic episode, 13 in a mixed episode and 12 were in full or partial remission. The QWB scores were converted into utility scores using an algorithm that has been generated by eliciting preferences from 866 community members in the US using VAS (Kaplan & Anderson, 1988).

Hayhurst and colleagues (2006) reported EQ-5D utility values for bipolar disorder-related health states derived from 204 people with bipolar disorder participating in a multi-centre, pragmatic RCT of CBT [SCOTT2006]; participants had been recently or were still in an acute episode. The definition of health states was based on Longitudinal Interval Follow-up Evaluation (LIFE-II) Depression and Mania ratings on a 6-point scale (from l = no symptoms to 6 = DSM-IV major depressive episode, or mania with psychotic symptoms or severe impairment of function). Participants scoring 1 on both LIFE scales were considered to be in a euthymic state; those with a score of 1 or 2 on one LIFE scale and 2 on the other were considered to have residual symptoms. Adults with a score of 3 or 4 on LIFE Depression and 1 on LIFE Mania were categorised as having subsyndromal depression; those with a score of 5 or 6 on LIFE Depression and 1 on LIFE Mania were diagnosed as depressed. No hypomanic or manic subgroup was identified within the study sample (there were only two instances of a LIFE Mania score of 5 or 6). The utility values were generated using participant responses on EQ-5D. The algorithm linking EQ-5D data to utility values has been developed following a valuation survey of 3,337 members of the general UK population using TTO (Dolan, 1997; Dolan et al., 1996).

Revicki and colleagues (2005a) reported utility values of various hypothetical bipolar disorder-related health states, elicited from 96 clinically stable outpatients with bipolar I disorder in the US, using SG (values elicited using VAS were also reported). Fifty-five hypothetical health states (vignettes) were constructed for this purpose, based on reviews of psychiatric literature and consultation with psychiatrists experienced in treating bipolar disorder. Each health state described bipolar symptom severity, functioning and well-being, as well as side effects related to treatment. The study provided utility values for stable state, inpatient mania, outpatient mania and severe depression, varying with respect to the kind of pharmacological treatment obtained in each vignette and the presence or absence of side effects.

Table 17 summarises the methods used to derive and value health states associated with bipolar disorder and the resulting utility scores, as reported in the 3 studies identified in the systematic literature search conducted for this guideline.

According to NICE guidance on the selection of utility values for use in cost-utility analysis, the measurement of changes in HRQoL should be reported directly from people with the condition examined, and the valuation of health states should be based on public preferences elicited using a choice-based method, such as the TTO or SG, in a representative sample of the UK population. When changes in HRQoL cannot be obtained directly by the people with the condition examined, then data should be obtained from their carers. NICE recommends EQ-5D (Dolan, 1997) for use in cost-utility analyses of interventions for adults. When EQ-5D scores are not available or are inappropriate for the condition or effects of treatment, the institute recommends that the valuation methods be fully described and comparable to those used for the EQ-5D (NICE, 2013b).

Of the three utility studies, only the one by Hayhurst and colleagues (2006) reported utility data for bipolar disorder-related health states based on EQ-5D and therefore complied with the NICE criteria on selection of appropriate utility data. However, the study reported utility values relating to depressive health states only; no relevant data on manic states were available. The study by Revicki and colleagues (2005a) reported utility data associated with various bipolar disorder-related health states, including mania, acute depression and stable state. These data referred to hypothetical health states (vignettes) and were elicited from service users in the US rather than the general population, using SG, and therefore did not satisfy NICE criteria. Finally, the study by Depp and colleagues (2006), which generated utility data from QWB scores that have been valued by members of the US general population also do not meet NICE criteria.

The GDG reviewed the available utility data against the NICE criteria, considered the limitations of each study and decided to use data from the study by Hayhurst and colleagues (2006) where possible. The reported utility value for euthymia was used for people fully responding to treatment in the economic model; the reported

utility value for subsyndromal depression was used for people partially responding; and the reported utility value for depression was used for all people at the start of the model and for people not responding to treatment or relapsing to acute depression in the economic analysis.

The GDG decided to use relevant utility data from Revicki and colleagues (2005a) for people relapsing to mania, due to lack of any other relevant and more appropriate data. It was decided to use for this purpose the utility values reported for inpatient mania in the study. However, the GDG noted that there were discrepancies between the values reported in Hayhurst and colleagues (2006) and Revicki and colleagues (2005a) corresponding to similar health states, likely attributable to differences in the methods used by each study. For example, Revicki and colleagues (2005) reported a utility of 0.80 for the current (apparently stable) state of study participants with SG and a value of 0.67 when EQ-5D was used. The mean utility value reported for the hypothetical stable state was 0.70, that is, 0.20 lower that the respective utility value reported in Hayhurst and colleagues (2006). In addition, Revicki and colleagues (2005a) reported a utility value of 0.29 for severe depression, which was again almost 0.20 lower than the utility value reported for depression in the study by Hayhurst and colleagues (2006). From the above examples it can be concluded that participants in the study by Revicki and colleagues (2005a) systematically under-reported the utility of bipolar disorder health states compared with participants in the study by Hayhurst and colleagues (2006). It was thus decided to add this difference of 0.20 to the utility value reported in Revicki and colleagues for inpatient mania, and utilise this adjusted value in the economic model.

It was assumed that all improvements and decrements in utility occurred linearly over the time period of the change in utility.

Side effects from medication are expected to result in a reduction in utility scores of adults with bipolar disorder. Disutility due to side effects was not considered in the analysis, as the model structure did not incorporate side effects. This was due to inconsistent reporting of specific side effect rates across the studies included in the network meta-analysis. This is acknowledged as a limitation of the analysis.

Table 17: Summary of studies reporting utility scores for health states experienced by adults with bipolar disorder

Study	Definition of health states	Valuation method	Population valuing	Health states and corresponding utility scores	
(Depp, 2006)	QWB data on 50 community-dwelling adults aged 45 years or older with bipolar I disorder (diagnosis based on DSM-IV)	VAS	866 community members in the US	All (n = 50) Mania or hypomania (n = 11) Mixed episode (n = 13) Depression (n = 14) Remission (n = 12)	0.54 (sd 0.09) 0.53 (sd 0.11) 0.52 (sd 0.08) 0.52 (sd 0.08) 0.59 (sd 0.10)
(Hayhurst, 2006)	EQ-5D data on 204 adults with bipolar disorder recently or still in episode participating in a multi-centre, pragmatic RCT of CBT [SCOTT2006] Definition of health states: based on LIFE-II ratings of Depression and Mania, using a 6 point scale (from l = no symptoms to 6 = DSM-IV major depressive episode or mania with psychotic symptoms or severe impairment of function). Euthymic: score = 1 on both LIFE scales Residual Symptoms: score = 1or2 on one LIFE scale and 2 on the other Subsyndromal Depression: score = 3 or 4 on LIFE Depression; 1 on LIFE Mania Depressed: score = 5 or 6 on LIFE Depression; 1 on LIFE Mania	TTO	3,337 members of the general UK population	Euthymic (n = 76) Residual symptoms (n = 55) Subsyndromal depression (n = 40) Depression (n = 33)	0.90 (sd 0.16) 0.83 (sd 0.16) 0.76 (sd 0.21) 0.47 (sd 0.30)

(Revicki et al., 2005a)	Hypothetical health state descriptions (vignettes) constructed based on reviews of psychiatric literature and consultation with psychiatrists experienced in treating bipolar disorder.	SG	96 clinically stable adult outpatients with DSM-IV bipolar I disorder	Current state		0.80 (sd 0.22)
				Stable state – no weight gain: mean (95% CI)		
				Lithium		0.71 (0.56 to 0.86)
				Valproate		0.74 (0.58 to 0.89)
				Risperidone		0.83 (0.74 to 0.91)
				Olanzapine		0.82 (0.72 to 0.92)
				Lithium & haloperidol		0.61 (0.45 to 0.78)
				Valproate & haloperidol		0.62 (0.46 to 0.78)
				MS & risperidone		0.70 (0.62 to 0.79)
				MS & olanzapine		0.58 (0.48 to 0.68)
				MS & haloperidol		0.62 (0.51 to 0.72)
				No medication		0.74 (0.63 to 0.85)
				Stable, no medication, tardive dyskinesia		0.76 (0.64 to 0.88)
				Disutility because of weight gain		-0.066
				Severe depression		0.29 (0.16 to 0.42)
					Mild symptoms/SE Mean (95% CI)	Moderate symptoms/SE Mean (95% CI)
				Inpatient mania	0.26 (0.19 to 0.34)	0.23 (0.16 to 0.31)
				Outpatient mania		
				Lithium	0.56 (0.39 to 0.73)	0.54 (0.42 to 0.65)
				Valproate	0.47 (0.30 to 0.63)	0.44 (0.27 to 0.62)
				Risperidone	0.54 (0.40 to 0.67)	0.52 (0.40 to 0.63)
				Olanzapine	0.64 (0.52 to 0.76)	0.53 (0.40 to 0.66)
				Lithium & haloperidol	0.37 (0.25 to 0.48)	0.44 (0.32 to 0.56)
				Valproate & haloperidol	0.63 (0.48 to 0.78)	0.29 (0.13 to 0.44)
				MS & risperidone	0.54 (0.45 to 0.65)	0.41 (0.31 to 0.51)
				MS & olanzapine	0.56 (0.48 to 0.66)	0.53 (0.44 to 0.63)
				MS & haloperidol	0.49 (0.39 to 0.60)	0.37 (0.28 to 0.46)

MS = mood stabiliser; TTO = Time Trade-Off; SE = side effects; SG = Standard Gamble; VAS = Visual Analogue Scale

Cost data

Costs considered in the economic model consisted of drug acquisition costs, laboratory testing costs, healthcare professional visit costs, and costs of hospitalisation and CRHTTs incurred by a proportion of people not responding to treatment. Costs associated with the management of manic or depressive relapses were not considered, because these were expected to be incurred beyond the time horizon of the analysis (that is, the model was constructed in such a way that the time horizon expanded up to the point where a relapse might occur). This was decided because treatment of relapses requires a minimum of 6 to 7 weeks, and if the model was extended to include this period, people in other pathways who responded to treatment early (at 6 weeks) would be starting maintenance treatment, introducing inconsistency across different part of the model. Costs were calculated by combining resource use estimates with respective national unit costs.

The mean daily dosage of each drug that was used in the model matched the average dosage for this drug of those reported in the relevant RCTs included in the guideline network meta-analysis, and was within the optimal dosage range according to the GDG expert opinion. Drug acquisition costs were taken from the NHS Electronic Drug Tariff, February 2014 (NHS, Business Services Authority, 2014); for lithium, drug acquisition costs were derived from BNF, December 2013 (British Medical Association and the Royal Pharmaceutical Society of Great Britain, 2013). For each drug the lowest reported price was selected and used in the analysis; where available, costs of generic forms were considered. Initial treatment with drugs was estimated to last 6 weeks, while people responding to treatment were assumed to receive the drug until the end of the time horizon of the analysis, that is, for 18 weeks in total, at the same daily dosage. The drug acquisition cost for no pharmacological treatment (placebo) was zero. Details on the total drug acquisition costs associated with pharmacological interventions for the treatment of acute depression in adults with bipolar disorder that were included in the economic analysis are presented in Table 18.

Table 18: Average daily dosage, acquisition costs, and 6-week and 18-week drug costs of pharmacological interventions for the management of acute depression in adults with bipolar disorder included in the economic model (2014 prices)

Drug	Mean daily dosage	Drug acquisition cost*	Total drug cost	
			6 weeks	18 weeks
Imipramine	175mg	28 x 25mg tb£1.23	£12.92	£38.75
Lamotrigine	200mg	56 x 200mg tb£3.77	£2.83	£8.48
Lithium	1000mg	100 x 200mg tb £2.30 (Priadel) 100 x 400mg tb £3.35 (Priadel)	£3.78	£11.34
Moclobemide	600mg	30 x 300mg tb £13.99	£39.17	£117.52
Olanzapine	10mg	28 x 10mg tb £1.67	£2.51	£7.52
Paroxetine	30mg	30 x 30mg tb £2.17	£3.04	£9.11
Quetiapine	50% 300mg/ 50% 600mg	60 x 300mg tb £5.07	£5.32	£15.97
Valproate semisodium	2000mg	90 x 500mg tb £29.15 (Depakote)	£54.41	£163.24

Fluoxetine and olanzapine	40mg and 10mg	30 x 20mg caps £1.10 28 x 10mg tb £1.67	£5.59	£16.76

*NHS Electronic Drug Tariff, February 2014 (NHS 2014); BNF December 2013 (British Medical Association and the Royal Pharmaceutical Society of Great Britain, 2013)

People moving from first to second drug treatment following failure of first drug treatment (discontinuation or non-response) were assumed to receive the first drug at gradually reduced dosages (50% of the full dosage) for another 2 weeks following discontinuation or non-response, while the second drug was started at gradually increasing dosages (50% of the full dosage) over this 2-week period.

People moving to no pharmacological treatment following discontinuation of first drug were assumed to reduce the dosage of the discontinued drug gradually over a period of 4 weeks (each week they received 80%, 60%, 40% and 20% of the full drug dosage).

Regarding laboratory tests, according to the GDG expert opinion all cohorts in the model (including the cohort initiated on placebo) should undergo a number of tests at baseline, regardless of the initiated drug; these tests include ECG, renal function tests (urea, electrolytes and creatinine), a glucose test, a lipid profile test, thyroid function tests and a pregnancy test in women of childbearing potential. Associated costs are part of the monitoring and are not specific to the initiated drug; thus these costs do not need to be included in the model as they are common to all arms. It was estimated that all drugs except lithium require liver function testing. There are also a number of other tests that need to be undertaken over the 18-week time horizon of the analysis that are specific to each drug. The costs of serum lithium concentration and valproate concentration tests were taken from the Newcastle upon Tyne Hospitals NHS trust biochemistry laboratory services tariff for 2006-7. All other laboratory testing costs were based on data reported in the economic analysis described in the previous NICE guideline (NCCMH, 2006a). All laboratory tests considered in the analysis together with their unit costs are presented in Table 19.

Table 19: Laboratory tests and associated unit costs required for each pharmacological intervention received over 18 weeks for the treatment of depression in adults with bipolar disorder in the economic analysis (2014 prices)

Drug	Laboratory testing over 18 weeks	Unit costs*
Imipramine	Baseline: liver function	Glucose test £0.87 Lipid profile test £2.62 Liver function £4.37 Serum lithium concentration £3.25 Urea £0.87 Electrolytes £1.75 Creatinine £2 Valproate level £7.01
Lamotrigine	Baseline: liver function	
Lithium	Baseline: 3 x serum lithium concentration At 12 weeks: lithium concentration, renal function (urea, electrolytes and creatinine)	
Moclobemide	Baseline: liver function	
Olanzapine	Baseline: liver function At 4 weeks: glucose test At 12-16 weeks: glucose test, liver function and lipid profile test	

Paroxetine	Baseline: liver function	
Quetiapine	Baseline: liver function At 12-16 weeks: glucose test, liver function and lipid profile test	
Valproate semisodium	Baseline: liver function At 12 weeks: valproate level	
Fluoxetine and olanzapine	Baseline: liver function At 4 weeks: glucose test At 12-16 weeks: glucose test, liver function and lipid profile test	

* Newcastle upon Tyne Hospitals NHS trust biochemistry laboratory services tariff for 2006-7 and (NCCMH, 2006a)

All people in the model contacted Community Mental Health Teams (CMHTs), including those receiving no pharmacological treatment (placebo). CMHTs consist of a variety of healthcare professionals including consultants, community nurses, social workers, occupational therapists, physiotherapists, staff providing carer support, and other types of healthcare professionals (Curtis, 2013). All cohorts were assumed to have 6 CMHT contacts over the period of 18 weeks. Cohorts receiving lithium had one extra CMHT contact. In addition, people not responding to treatment or responding only partially had one additional CMHT contact. The unit cost of a CMHT visit was taken from the NHS reference costs for 2013 (NHS Department of Health, 2013). The mean total cost of CMHT contacts over 18 weeks for people responding to treatment (6 visits) was £892.

A proportion of people with bipolar disorder in acute depression are treated in hospital or by CRHTTs. Hospitalisation and CRHTT treatment rates relate to the severity of the acute episode, lack of response to treatment, and the risk of suicide and are independent of specific drug use. CRHTTs are considered is an alternative to hospitalisation. According to the GDG expert opinion, the rate of hospitalisation / CRHTT treatment is approximately 10% in this population. Based on data reported by Glover and colleagues (2006), it was estimated that the ratio of people with acute bipolar depression who are treated in hospital to those that are managed by CRHTTs is 77:23.

The GDG estimated that the probability of hospitalisation/CRHTT management is twice as much in people who don't respond to their first drug treatment (including those who discontinued treatment) compared with those who do. Based on these estimates and the mean number of people responding to first treatment among all cohorts receiving pharmacological treatment in the model it was possible to estimate the percentage of people that are hospitalised or managed by CRHTTs among those responding and those not responding to treatment, using the formulae:

$$Prob_H\text{-nr} = 2 \times Prob_H\text{-r}$$

$$Prob\text{-r} \times Prob_H\text{-r} + Prob\text{-nr} \times Prob_H\text{-nr} = Prob_H$$

$$Prob\text{-r} = (1 - Prob_D) \times Prob_{CR}$$

where $Prob_H$-nr the probability of hospitalisation/CHRTT management in non-responders to first treatment (including those who discontinue their first treatment); $Prob_H$-r the probability of hospitalisation/CRHTT management in responders to first treatment, $Prob_H$ the probability of hospitalisation/CRHTT management in the total study population of adults with acute bipolar depression, estimated at 0.10, Prob-r the mean probability of response to first treatment across all cohorts in the model receiving pharmacological treatment (averaged across drug treatment options); Prob-nr the mean probability of non-response to first treatment across all cohorts, including people who discontinued treatment; and $Prob_D$ and $Prob_{CR}$ the mean probabilities of discontinuation conditional response, respectively, across all cohorts receiving their first pharmacological treatment, as estimated from the network meta-analysis.

Based on the above, it was estimated that the probability of hospitalisation/CRHTT management in those responding to treatment was 0.064, and in those not responding was 0.128. Every person in the model was allowed to have only one incident of hospitalisation/CRHTT treatment over the time horizon of the analysis.

The mean length of hospitalisation (7 weeks) was taken from relevant data reported in the Hospital Episode Statistics for England in 2012 (NHS, 2012). Management by CRHTTs was also estimated to occur over 7 weeks, according to GDG expert opinion. This was broadly consistent with the duration of CRHTT management in a RCT comparing CRHTT with standard care (inpatient services and CMHTs) for people in a psychiatric crisis in the UK (Johnson et al., 2005). People managed by CRHTT in the model had 2 contacts per week, according to relevant resource use reported for that trial (McCrone et al., 2009). The unit cost per CRHTT contact was based on data reported in (Curtis, 2013). Based on these data, the total hospitalisation cost over 7 weeks was £17,274 and the total CRHTT cost was £2,818.

People that were hospitalised or managed by CRHTTs were estimated to have 2 fewer contacts with CMHTs over the duration of the model, as they were not expected to be seen by CMHTs during the period of hospitalisation or CRHTT attendance.

Costs of treating side effects of drugs were not considered in the economic analysis, due to lack of consistency in reported appropriate side effect data across all drugs. Nevertheless, the model did consider the implications of discontinuation, which is partly caused by the development of intolerable side effects. Moreover, it was estimated that the costs associated with management of side effects over the 18-week time horizon of the model were not substantial as most side effects could be dealt with during the planned contacts with the health services.

All costs have been expressed in 2014 prices, uplifted, where required, using the HCHS pay and prices inflation index (Curtis, 2013). The inflation index for year 2014 was estimated using the average value of HCHS pay and prices indices of the

previous 3 years. As the time horizon of the analysis was less than 1 year, no discounting of costs and outcomes was necessary.

Table 20 reports the values of all input parameters utilised in the economic model and provides information on the distributions assigned to specific parameters in probabilistic analysis, as described in the next section.

Handling uncertainty

Model input parameters were synthesised in a probabilistic analysis. This means that the input parameters were assigned probabilistic distributions (rather than being expressed as point estimates), to reflect the uncertainty characterising the available clinical and cost data. Subsequently, 10,000 iterations were performed, each drawing random values out of the distributions fitted onto the model input parameters. Results (mean costs and QALYs for each intervention) were averaged across the 10,000 iterations. This exercise provides more accurate estimates than those derived from a deterministic analysis (which utilises the mean value of each input parameter ignoring any uncertainty around the mean), by capturing the non-linearity characterising the economic model structure (Briggs et al., 2006).

The distributions of the probability of discontinuation and conditional response for all pharmacological treatments as well as the probability of response for no pharmacological treatment were obtained from the network meta-analysis, defined directly from values recorded in each of the 10,000 respective iterations performed in WinBUGS. All other probabilities utilised in the economic model were given a beta distribution based on available data in the published sources of evidence and other assumptions. Utility values were also given a beta distribution using the method of moments on data reported in the relevant literature.

Drug acquisition and laboratory testing costs were not given a probabilistic distribution as these costs are set. Uncertainty in costs associated with CMHT and CRHTT contacts was taken into account by assigning different probabilities to the number of contacts, based on expert opinion. Unit costs of CMHT, CRHTT and hospitalisation were assigned a normal distribution, after considering the range of values reported in the relevant data sources.

Table 20 provides details on the types of distributions assigned to each input parameter and the methods employed to define their range.

Table 20: Input parameters and utility data used to populate the economic model of pharmacological interventions for acute depression in adults with bipolar disorder

Input parameter	Mean value	Probabilistic distribution	Source of data - comments
Clinical input parameters			
Probability of discontinuation, all pharmacological treatments	See Table 16	Distribution based on network meta-analysis	Guideline network meta-analysis; distribution formed by 10,000 iterations
Probability of conditional response, all pharmacological treatments	See Table 16	Distribution based on network meta-analysis	Guideline network meta-analysis; distribution formed by 10,000 iterations
Probability of response, no pharmacological treatment (placebo)	0.35	Network meta-analysis 95% CrI: 0.16 to 0.57	Guideline network meta-analysis
		Beta distributions	
Ratio of probability of response: second / first line of treatment, all interventions	0.59 = 0.284/0.484	$\alpha = 408, \beta = 1031$ / $\alpha = 1776, \beta = 1895$	Rush et al., 2006
Probability of moving to no drug following discontinuation	0.25	$\alpha = 25, \beta = 75$	GDG expert opinion; distribution based on assumption
Probability of moving to no drug following no response	0.10	$\alpha = 10, \beta = 90$	GDG expert opinion; distribution based on assumption
Probability of partial response in responders	0.44	$\alpha = 72, \beta = 93$	Sachs et al., 2007
3-month probability of relapse in full responders 3-month probability of relapse in partial responders	0.08 0.20	$\alpha = 16, \beta = 184$ $\alpha = 40, \beta = 160$	Judd et al., 2008; time-dependent probabilities for each model pathway estimated from these data assuming exponential increase over time
Probability of mania in those relapsing	0.34	$\alpha = 43, \beta = 83$	Judd et al., 2008

Utility values		**Beta distributions**	
Depression (baseline, no response, depressive relapse)	0.47	$\alpha = 16, \beta = 17$	Hayhurst et al., 2006; distribution estimated using method of moments
Full response - euthymia	0.90	$\alpha = 68, \beta = 8$	
Partial response - sub depression	0.76	$\alpha = 30, \beta = 10$	
Mania (weighted)	0.44	$\alpha = 54, \beta = 69$	Revicki et al. 2005, adjusted (see text for details); distribution estimated using method of moments
Resource use and costs			
Drug acquisition costs	See Table 18	No distributions assigned	NHS, 2014; BNF, 2013
Laboratory testing costs	See Table 19		Newcastle Upon Tyne Hospitals NHS trust biochemistry laboratory services tariff for 2006-7 and NCCMH, 2006
Number of CMHT contacts		Probabilities assigned to number of contacts	
All pathways (including placebo)	6	70%: 6; 15%: 7; 15%: 5	GDG expert opinion; distribution based on assumption
Extra visits: non-responders and partial responders	1	70%: 1; 15%: 2; 15%: 0	
Extra visits: lithium	1	70%: 1; 25%: 2; 5%: 0	
Number of CRHTT contacts over 7 weeks	14	50%: 14; 40%: 15-21; 10%: 7-13	McCrone et al., 2009
		Normal distribution	NHS, 2013; Curtis, 2013; unit cost per hospital day based on weighted mean of mental health care clusters; distributions based on assumption after considering lower-upper value quartiles
Unit cost of CMHT (2014)	£149	mean = 149, SE = 29.72	
Unit cost per hospital day (2014)	£353	mean = 353, SE = 17.63	
Unit cost per CRHTT contact (2014)	£201	mean = 201, SE = 10.07	
Probability of hospitalisation/CRHTT	0.10	Beta distribution $\alpha = 10, \beta = 90$	GDG expert opinion; distribution based on assumption
Probability of hospitalisation/CRHTT in responders	0.064	Determined by other distributions	Depending on distributions of probability of hospitalisation/CRHTT, and of discontinuation and conditional response (see text for details)
Probability of hospital/CRHTT in non-responders	0.128		
Proportion of CRHTT in hospitalisation/CRHTT	0.23	Beta distribution $\alpha = 23, \beta = 77$	Glover et al., 2006
Duration of hospitalisation/CRHTT (weeks)	7	No distribution	NHS, The Information Centre, 2012

A number of deterministic one-way sensitivity analyses were undertaken to explore the impact of alternative hypotheses on the results. The following scenarios were explored:

- A change in the probability of moving to no drug following discontinuation of, or no response to, the first drug treatment option (values tested 0-1)
- A change in the probability of response to a drug if this used as second option (values tested ranged from 20% to 100% of respective probability if the drug was used as first choice)
- A change in the probability of partial response (values tested 0-1)
- A change in the probability of relapse following full or partial response (values tested 0.01-0.40 for a 3-month probability of relapse)
- A change in the overall probability of hospitalisation/CRHTT management in the study population (values tested 0.02-0.20)

Presentation of the results

Results of the economic analysis are presented as follows:

For each intervention mean total costs and QALYs are presented, averaged across 10,000 iterations of the model. An incremental analysis is provided, where all options have been ranked from the most to the least effective (in terms of QALYs gained). Options that are dominated by absolute dominance (that is, they are less effective and more costly than one or more other options) or by extended dominance (that is, they are less effective and more costly than a linear combination of two alternative options) are excluded from further analysis. Subsequently, incremental cost-effectiveness ratios (ICERs) are calculated for all pairs of consecutive options remaining in analysis.

ICERs are calculated by the following formula:

$$ICER = \Delta C / \Delta E$$

where ΔC is the difference in total costs between two interventions and ΔE the difference in their effectiveness (QALYs). ICERs express the extra cost per extra unit of benefit (that is, QALY in this analysis) associated with one treatment option relative to its comparator. The treatment option with the highest ICER below the NICE lower cost effectiveness threshold of £20,000/QALY (NICE, 2008) is the most cost-effective option.

In addition to ICERs, the mean net monetary benefit (NMB) of each intervention is presented. This is defined by the following formula:

$$NMB = E \cdot \lambda - C$$

where E and C are the effectiveness (number of QALYs) and costs associated with the treatment option, respectively, and λ is the level of the willingness-to-pay per unit of effectiveness, set at the NICE lower cost effectiveness threshold of £20,000/QALY (NICE, 2008). The intervention with the highest NMB is the most cost-effective option (Fenwick et al., 2001). Moreover, for the most cost-effective intervention, the probability that this is the most cost-effective option is also provided, calculated as the proportion of iterations (out of the 10,000 iterations run) in which the intervention had the highest NMB among all interventions considered in the analysis.

Validation of the economic model

The economic model (including the conceptual model and the excel spreadsheet) was developed by the health economist working on this guideline and checked by a second modeller not working on the guideline. The model was tested for logical consistency by setting input parameters to null and extreme values and examining whether results changed in the expected direction. The results were discussed with the GDG for their plausibility.

Economic modelling results

The results of the economic analysis are provided in Table 21. This table provides mean QALYs and total costs for each intervention assessed in the economic analysis, as well as costs for each cost element considered in the model. Results are presented per 1000 adults with bipolar disorder in an acute depressive episode. Table 22 presents the results of the incremental analysis, the NMB of each intervention and its ranking by cost effectiveness (with higher NMBs indicating higher cost effectiveness). Interventions have been ordered from the most to the least effective in terms of number of QALYs gained.

Table 21: Results of economic analysis of pharmacological treatments for the management of acute depression in adults with bipolar disorder: mean total QALYs, total costs and detailed costs for each cost element considered in the analysis per 1000 people

Intervention	Total QALYs	Total drug cost	Total lab cost	Total CMHT cost	Total hospital / CRHTT cost	Total cost
Imipramine	213.83	£33,553	£6,676	£986,243	£1,427,093	£2,453,565
Lamotrigine	216.41	£17,118	£6,559	£983,444	£1,394,948	£2,402,070
Lithium	217.93	£18,472	£16,406	£1,149,083	£1,378,991	£2,562,952
Moclobemide	208.56	£70,159	£6,955	£991,267	£1,488,561	£2,556,942
Olanzapine	218.23	£16,180	£10,640	£981,673	£1,373,802	£2,382,295
Paroxetine	215.79	£17,588	£6,327	£984,029	£1,401,684	£2,409,628
Quetiapine	221.90	£20,586	£9,782	£978,313	£1,336,040	£2,344,721
Valproate	229.24	£120,049	£9,767	£971,019	£1,251,864	£2,352,699
Fluoxetine and olanzapine	225.84	21,701	£10,760	£975,581	£1,288,415	£2,296,457
Placebo	198.51	£0	£0	£992,201	£1,447,421	£2,439,821

Table 22: Results of economic analysis of pharmacological treatments for the management of acute depression in adults with bipolar disorder: incremental analysis.

Intervention	Mean QALYs	Mean total costs	Incremental analysis and ICERs (£/QALY)	Mean NMB per person	Ranking by highest NMB
	Per 1000 people				
Valproate	229.24	£2,352,699	£16,572	£2,232	1
Fluoxetine and olanzapine	225.84	£2,296,457		£2,220	2
Quetiapine	221.90	£2,344,721	Dominated	£2,093	3
Olanzapine	218.23	£2,382,295	Dominated	£1,982	4
Lithium	217.93	£2,562,952	Dominated	£1,796	8
Lamotrigine	216.41	£2,402,070	Dominated	£1,926	5
Paroxetine	215.79	£2,409,628	Dominated	£1,906	6
Imipramine	213.83	£2,453,565	Dominated	£1,823	7
Moclobemide	208.56	£2,556,942	Dominated	£1,614	9
Placebo	198.51	£2,439,821	Dominated	£1,530	10

Valproate appears to be the most effective and cost-effective intervention, as it produces the highest number of QALYs and the highest NMB. The combination of fluoxetine and olanzapine is the next (2nd) most effective and cost-effective intervention. It is also the least costly treatment option. The ICER of valproate versus fluoxetine and olanzapine combination is £16,572/QALY, which is below the NICE cost-effectiveness threshold of £20,000-£30,000/QALY. All other interventions are dominated by the combination of fluoxetine and olanzapine (that is, they are less effective and more costly). Quetiapine is the 3rd most cost-effective option, followed by olanzapine (4th) and lamotrigine (5th). These are followed by paroxetine (6th) and imipramine (7th). Lithium and moclobemide are ranked 8th and 9th, respectively, in terms of cost effectiveness. No pharmacological treatment (placebo) is the least cost-effective intervention, ranked 10th.

The probability of valproate being the most cost-effective intervention is 0.47, which reflects the proportion of the 10,000 iterations of the economic model in which the intervention had the highest NMB among all treatment options assessed in the model. The probability of fluoxetine and olanzapine combination being the most cost-effective intervention among those assessed is close, at 0.40. If valproate is not a treatment option, then the probability of fluoxetine and olanzapine combination being the most cost-effective intervention becomes 0.73.

Figure 7 provides the cost effectiveness plane of the analysis. Each intervention is placed on the plane according to its incremental costs and QALYs compared with placebo (which is placed at the origin).

Results were overall robust to alternative scenarios explored in sensitivity analysis. The five most cost-effective treatment options (valproate, combination of fluoxetine and olanzapine, quetiapine, olanzapine and lamotrigine) remained in the group of the five most cost-effective options in all scenarios explored. In a few scenarios, the combination of fluoxetine and olanzapine became more cost-effective than valproate (this happened when the responsiveness to a drug used as second option was assumed to be equal to the responsiveness to this drug when used as first choice; when the probability of partial response was set at 1; and when the overall probability of hospitalisation/CRHTT management was assumed to be 0.02). In some scenarios moclobemide became less cost-effective than placebo (this happened when the probability of moving to no drug following discontinuation of, or no response to, the first drug treatment option was assumed to equal 1; when the probability of response to a drug used as second option was assumed to be 20% of the probability of response to this drug when used as first choice; when the probability of partial response was set at 1; and when the 3-month probability of relapse following response was set at 0.40). Overall, conclusions from the analysis were not affected by the scenarios tested.
The methodology checklist and the economic evidence profile of the analysis are provided in Appendix 31 and Appendix 33, respectively.

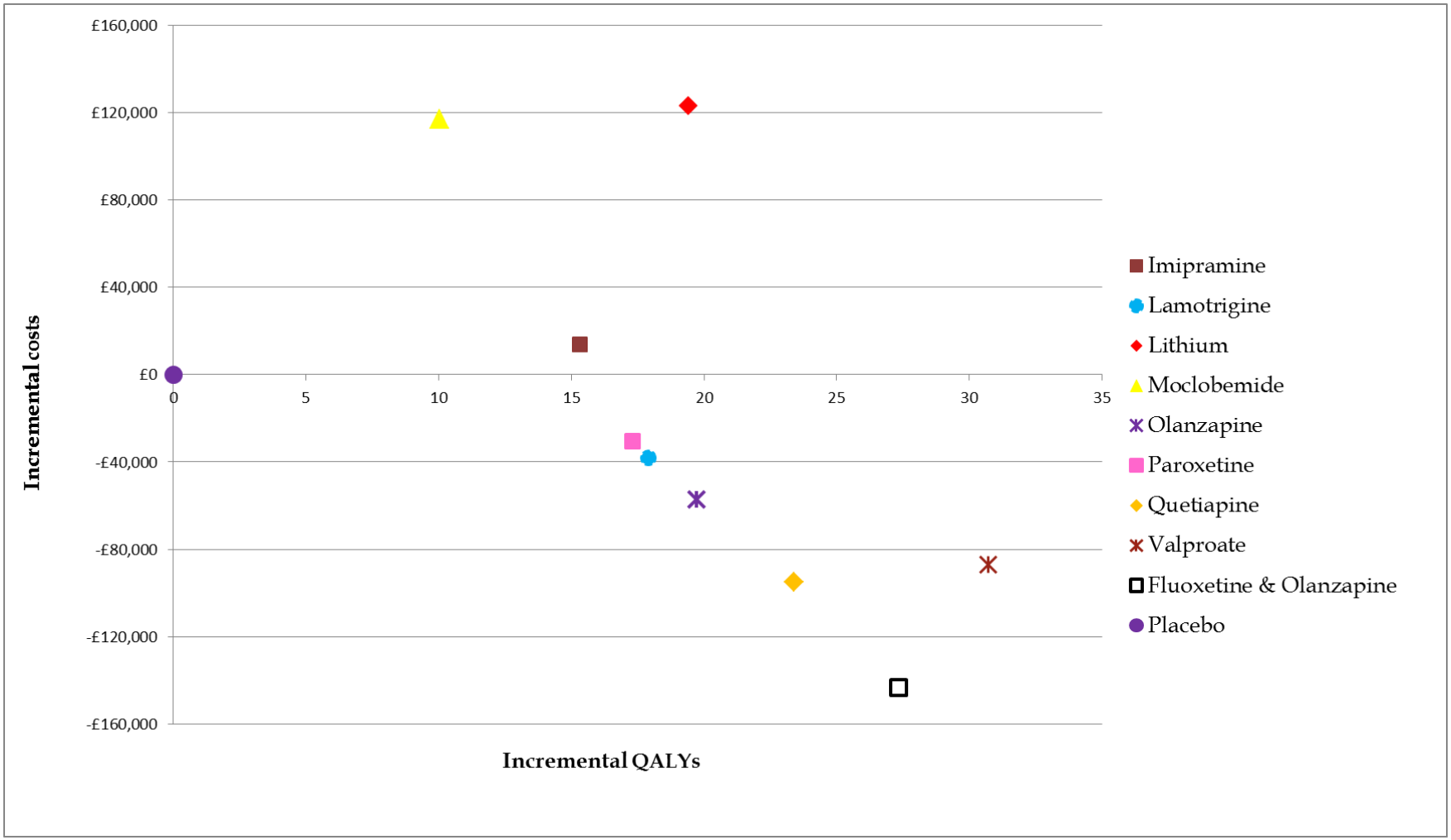
Discussion – limitations of the analysis

The guideline economic analysis assessed the cost effectiveness of a range of pharmacological interventions for the treatment of acute depression in adults with bipolar disorder. The results of the analysis suggest that valproate may be the most cost-effective option, followed by the combination of fluoxetine and olanzapine, quetiapine, olanzapine and lamotrigine. Lithium and antidepressants used as monotherapy (paroxetine, imipramine and moclobemide) appear to be less cost-effective. These findings were not unexpected, given that the network meta-analysis did not show a statistical difference from placebo, in terms of overall response (that is, response in all randomised), for either lithium or any of the antidepressants used as monotherapy. Results were overall robust to different scenarios explored through sensitivity analysis. It should be noted that, as reported in section 6.3.4, clinical data for valproate were derived from a small number of RCT participants receiving valproate (n=48) and therefore cost effectiveness findings for this drug should be interpreted with great caution.

The clinical effectiveness data utilised in the model were derived from the network meta-analysis undertaken for this guideline. This methodology enabled evidence synthesis from both direct and indirect comparisons between interventions, and allowed simultaneous inference on all treatments examined in pair-wise trial comparisons while respecting randomisation (Caldwell et al., 2005; Lu & Ades, 2004). The assumptions and any limitations of the network meta-analysis model, as well as the limitations of individual studies considered in the network meta-analysis, have unavoidably impacted on the quality of the economic model clinical input parameters. For example, both the clinical and economic results may be vulnerable to reporting and publication bias. The assumptions underlying the network meta-

analysis model have been described in detail in Appendix 15; the characteristics and any limitations of the individual studies considered in the guideline network meta-analysis model have been described in 6.3.4.

Figure 7: Cost effectiveness plane of all pharmacological interventions for acute depression in adults with bipolar disorder assessed in the economic analysis plotted against no pharmacological treatment (placebo) – incremental costs and QALYs per 1,000 people



The economic model assumed a maximum of two lines of drugs. The purpose of considering moving to a second drug treatment option was to assess the impact of each initiated drug's non-acceptability (reflected in discontinuation rates) and ineffectiveness (reflected in non-response rates) on cost effectiveness and not to assess specific drug sequences. The clinical and cost parameters for the second pharmacological treatment option were based on the mean probabilities of discontinuation, conditional response and acquisition costs of all drug treatment options considered in the analysis, except the initiated option for each cohort. Ideally, weighted average cost and clinical outcome figures should have been used, according to actual utilisation of these drugs in the treatment of acute depression in people with bipolar disorder in the NHS. However, specific data on actual drug utilisation patterns for adults with acute bipolar depression were not possible to find. Detailed data on all prescriptions dispensed in the community in England are available (Prescribing and Primary Care team, 2013), but these are listed by BNF therapeutic class. The majority of antidepressant prescriptions are dispensed for the treatment of unipolar depression and/or anxiety disorders, while the majority of prescriptions of antipsychotics and lithium are dispensed for the management of schizophrenia, psychosis and mania. No data are available to indicate what proportion of antidepressants, antipsychotics or lithium is prescribed for the management of acute bipolar depression in the UK.

There are indications that treatment with antidepressants may induce switching to mania, although this appears to be a controversial issue (Baldessarini et al., 2013; Sidor & McQueen, 2011; Tondo et al., 2010). The risk of switching to mania associated with antidepressants was not considered in the model due to lack of good quality data in the RCTs included in the guideline network meta-analysis and the wider literature. The GDG suggested that any available data on this issue be considered in a sensitivity analysis. Nevertheless, this analysis proved unnecessary as the base-case analysis demonstrated that antidepressants were not cost-effective. Consideration of switching to mania would only increasing the costs for these drugs (due to high hospitalisation costs associated with mania), thus reducing their relative cost effectiveness even more.

The impact of side effects on quality of life and associated management costs was not considered in the analysis, due to lack of appropriate relevant data. However, omission of important side effects (such as the renal failure associated with lithium and the acute extrapyramidal syndrome and weight gain associated with antipsychotics) from the model structure is unlikely to have affected the results of the analysis due to its short time horizon. Moreover, some short-term side effects have been implicitly been taken into account in the model structure, since discontinuation of treatment occurs to some extent due to the development of intolerable side effects. Also, a number of short-term side effects can be dealt with by routine contacts with health services at no additional cost. In addition, the probabilistic model allowed a small proportion of people to have a higher

number of contacts with CMHTs, which could be relating to management of side effects.
Therefore, although omission of side effects is acknowledged as a limitation of the analysis, it is estimated that it has not impacted considerably on the results.

Some clinical input parameters were taken from studies that were not directly relevant to the model population and condition. For example, data on the potential reduction in responsiveness following second treatment were taken from a study on people with unipolar (rather bipolar) depression (Rush et al., 2006) because of lack of more relevant data. The probability of partial response in those responding was based on relevant recovery (rather than response) data on people with bipolar depression (Sachs et al., 2007); partial recovery in that study was defined by the duration of effect, rather than its intensity. The probability of relapse following response was estimated using data on relapse after recovery (not response) from any acute major episode, not just depressive, in people with bipolar disorder (Judd et al., 2008b). Some data on resource use (especially the overall probability of hospitalisation/CRHTT management in the study population) were based on the GDG expert opinion, due to lack of relevant data. The impact of all these parameters was tested in sensitivity analysis, which suggested that the results were robust under a broad range of alternative values and scenarios.

Costs associated with treatment of relapses were not considered in the model, because the model was constructed in such a way that the time horizon expanded up to the point where a relapse might occur. This was decided so as to avoid introducing long-term maintenance treatment to people in some pathways in the model (which would occur if the model was extended to capture the management of relapses), and thus inconsistency in the treatment received across pathways. It should be clarified that the model did not consider the reduction in utility occurring during a manic or depressive relapse, but it did consider the deterioration in HRQoL from the point of response to treatment and up to the point of (but not including) relapse. This allowed a more realistic representation of the HRQoL during the period following response for people eventually relapsing.

Another limitation of the analysis was its short time horizon. Ideally, the analysis should consider longer-term outcomes of the acute treatment, including modelling of long-term maintenance treatment. However, this was not possible due to lack of relevant long-term data across the drugs considered in the analysis. On the other hand, the time horizon of 18 weeks was adequate as it enabled the full course of acute bipolar depression to be modelled, and the associated costs and benefits from pharmacological treatment to be assessed.

Economic evidence statement

The existing economic evidence in the area of pharmacological interventions for adults with bipolar disorder experiencing an acute depressive episode is very

limited and characterised by potentially serious limitations. The economic analysis undertaken for this guideline suggested that, after excluding valproate, the effectiveness (and cost effectiveness) of which was determined from clinical data on 48 people only, the combination of fluoxetine and olanzapine is likely to be the most cost-effective pharmacological treatment option among those assessed, followed by quetiapine, olanzapine and lamotrigine. These results were overall robust to alternative scenarios considered in sensitivity analysis. The evidence from the guideline economic analysis is directly applicable to the UK context and characterised by minor limitations.

6.4 NON-PHARMACOLOGICAL INTERVENTIONS FOR ACUTE EPISODES

6.4.1 Introduction

Several non-pharmacological interventions have been tested for the treatment of acute episodes, including acupuncture, bright light therapy, transcranial magnetic stimulation and vagus nerve stimulation.

6.4.2 Clinical review protocol

The review protocol summary, including the review questions and the eligibility criteria used for this section of the guideline, can be found in Table 23 (a complete list of review questions and protocols can be found in Appendix 7; further information about the search strategy can be found in Appendix 8).

Table 23: Clinical review protocol summary for the review of non-pharmacological interventions for acute episodes

Topic	Interventions
Review question(s)	RQ 2.3: 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; RQ 2.4: 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; 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+)?
Objectives	To estimate the efficacy of physical interventions for adults with bipolar disorder.
Criteria for considering studies for the review	
• Intervention	Non-pharmacological medical interventions
• Comparator	A credible no-intervention control (for example, sham intervention).
• Types of participants	Adults (18+) with bipolar disorder who are experiencing an acute episode. Special consideration will be given to the groups above.

• Outcomes	1) Change in symptoms (of mania or depression) 2) Response (50% reduction or greater) 3) Discontinuation
• Time	The main analysis will include outcomes at the end of the acute treatment phase.
• Study design	Randomised controlled trials (RCTs) and cluster RCTs with a parallel group design. Quasi-RCTs, such as trials in which allocation is determined by alternation or date of birth, will be excluded.
• Study setting	Primary, secondary, tertiary, health and social care

6.4.3 Studies considered[15]

The search identified two trials that were eligible to be included in the mania review (review question 2.3): DENNEHY2009A (Dennehy et al., 2009) and KAPTSAN2003 (Kaptsan et al., 2003). One additional study was excluded because it had no eligible comparison group: GRISARU1998 (Grisaru et al., 1998); and one study was excluded because it was quasi-randomised (Praharaj et al., 2009). There were no eligible studies of bright light therapy or vagus nerve stimulation.

The search identified four trials that were eligible to be included in the depression review (review question 2.4): DENNEHY2009B (Dennehy et al., 2009), DAUPHINAIS2012 (Dauphinais et al., 2012), NAHAS2003 (Nahas et al., 2003) and WU2009 (Wu et al., 2009). Two additional studies were excluded because they had no eligible comparison group: CAMURI2013 (Camuri, 2013) and DOLBERG2002 (Dolberg et al., 2001). There were no eligible studies of vagus nerve stimulation.

Of the two RCTs included in the mania review, there were comparisons of acupuncture (N = 20; DENNEHY2009A) and transcranial magnetic stimulation (N = 25; KAPTSAN2003).

Of the four RCTs included in the depression review, there were comparisons of acupuncture (N = 26; DENNEHY2009B), bright light therapy (N = 44; DAUPHINAIS2012), transcranial magnetic stimulation (N = 23; NAHAS2003) and chronotherapeutic augmentation (sleep deprivation with bright light therapy as an adjunct to usual medication) (N = 49; WU2009).

Further information about both included and excluded studies can be found in Appendix 16 and Appendix 34.

6.4.4 Clinical evidence review

There was very low quality evidence that neither acupuncture nor transcranial magnetic stimulation were associated with reductions in mania or depression.

[15]Here and elsewhere in the guideline, each study considered for review is referred to by a study ID in capital letters (primary author and date of study).

There was very low quality evidence that bright light therapy was not associated with reduction in depression. There was very low quality evidence from one study that chronotherapeutic augmentation may be associated with reduced symptoms of depression for people who can tolerate the treatment.

6.4.5 Health economics evidence

No study assessing the cost effectiveness of non-pharmacological medical interventions was identified by the systematic search of the literature.

6.5 LINKING EVIDENCE TO RECOMMENDATIONS

6.5.1 Relative value placed on the outcomes considered

The GDG determined that the critical outcomes for acute episodes were response to treatment and treatment discontinuation. Acute episodes of mania and depression may last several weeks or months, and the GDG determined that response (that is, reduction in symptoms of mania or depression) would identify treatments that may be efficacious. Distal consequences of treatment (for example, improved quality of life) are unlikely to be observed during the course of short clinical trials, and the GDG noted that very high dropout from acute treatment made it impossible to interpret effects that could appear over the medium- to long-term. The GDG also determined that discontinuation would identify treatments that are not well tolerated by participants (for example, those with important side effects). Specific reasons for discontinuation may be rare or underreported in clinical trials, so the GDG decided to focus on discontinuation for any reason rather than discontinuation because of side effects.

6.5.2 Trade-off between clinical benefits and harms

Some people who experience acute episodes have been taking inadequate doses of long-term medication (for example, lithium). Considering safety and efficacy, the GDG decided that the dose of current medications should be considered before initiating new treatments. In addition to avoiding harmful interactions, the GDG found that people taking a medication are likely to tolerate it in the future, and through expert consensus they identified circumstances in which it would be better to increase the dose of an existing medication rather than initiate a new treatment. They also identified circumstances in which the addition of another medication would be clinically indicated and supported by the evidence reviewed here.

In reviewing evidence for the treatment of acute mania and depression, the GDG considered several treatments that appear to be efficacious. As all medications may have important side effects, the GDG decided not to recommend interventions that have not been shown to be clinically efficacious for the treatment of acute mania (that is, asenapine, gabapentin, lamotrigine, topiramate, ziprasidone) or depression (that is, aripiprazole, moclobemide, ziprasidone) because these would not have a favourable ratio of benefits to harms.

Considering the remaining interventions, the GDG determined that service users may have different preferences based on prior experience, and they may value side effects differently. For these reasons, the GDG decided to recommend that service users and clinicians choose among several pharmacological interventions with favourable ratios of benefits to harms. For mania, the GDG determined that olanzapine, risperidone, haloperidol and quetiapine had different trade-offs between benefits and harms. The GDG determined that for people not already taking an antipsychotic or mood stabiliser it would be reasonable to choose from among these based on service user preference, previous response to treatment and other clinical factors. There was little evidence about the efficacy of second-line treatments (that is, when an initial treatment has failed because of discontinuation or non-response). The GDG considered that many people with acute episodes have experienced multiple episodes and have tried multiple interventions. They determined that the comparative efficacy of first-line interventions was likely related to their efficacy as second-line interventions, so the GDG recommended that the same group of interventions be considered if an initial intervention failed. If there is still no response, then the GDG considered that lithium first, and then valproate, could be added in combination with an antipsychotic. The combination of valproate with an antipsychotic is off-label, but it is common practice in the UK in the treatment of bipolar disorder. Both valproate and antipsychotics have some efficacy when used alone, but given that their mode of action is different, the GDG judged that it is reasonable to combine these treatments if response to either alone is suboptimal, and is in the service user's best interests.

For people who develop mania who are already taking an antidepressant and a mood stabiliser, the GDG judged that the clinician should consider advising the person to stop taking the antidepressant.

Of the available medications for acute episodes of bipolar depression, with sufficient data, olanzapine combined with fluoxetine, and quetiapine on its own, demonstrated the greatest benefit. There was evidence of smaller benefits for olanzapine alone and for lamotrigine, but the GDG judged that these were less likely to be clinically efficacious, but could be considered if it was the person's preference or if there was no response to first-line treatment. Lurasidone is not currently licensed in the UK, so it could not be recommended for the treatment of acute depression, but the GDG thought it should be considered in future guidelines. For people at a high risk of suicide, the GDG wished to caution that toxicity in overdose should be considered when prescribing psychotropic medication and to limit the quantity of medication supplied at any one time.

The GDG found very limited evidence for lithium and valproate monotherapy for acute episodes, but many participants in clinical trials were taking these medications in addition to investigational treatments, and the expert consensus was that mood stabilisers should normally be continued during acute episodes,

with doses and plasma levels checked to optimise treatment. The GDG discussed side effects of interventions that appear to be efficacious as monotherapies or additional interventions for mania (olanzapine, risperidone, haloperidol and quetiapine) or depression (lamotrigine, lurasidone, quetiapine, olanzapine, and the combination of olanzapine and fluoxetine).

For mixed affective states, the GDG determined that there was no good evidence for treating these differently from manic episodes, but that clinicians should monitor the person closely for signs of depression.

There was little evidence that nutritional interventions reduce symptoms of acute manic or depressive episodes, and very low quality evidence that eicosapentaenoic acid supplementation was not associated with a reduction in depressive symptoms. Therefore, the GDG has not made any recommendations regarding these interventions.

There was also little evidence that non-pharmacological interventions (acupuncture, transcranial magnetic stimulation and bright light therapy) reduce symptoms of manic or depressive episodes. Therefore, the GDG has not made any recommendations regarding these interventions.

Lamotrigine, gabapentin and topiramate were little, or no, better than placebo for treating mania. Gabapentin and topiramate were also without evidence for bipolar depression. Therefore, because of the risk of harm the GDG judged that a negative recommendation advising against their use in bipolar disorder was warranted. Because lamotrigine had some evidence of benefit for bipolar depression, the GDG judged that a negative recommendation advising against its use in bipolar depression was warranted.

6.5.3 Trade-off between net health benefits and resource use

Mania is associated with hospitalisation and with high costs for health services and for service users and their families. Such costs are considerably higher than drug acquisition costs for most medications that have been shown to be effective in the treatment of mania, so that, in general, medications that are most clinically effective and reduce manic symptoms are expected to be also most cost effective. Most efficacious interventions for the treatment of mania have similarly low acquisition costs, which are insubstantial compared with the costs of prolonged mania. Asenapine and aripiprazole are associated with considerably higher drug acquisition costs and may be less efficacious than other medications for mania. Of the medications that were assessed in the guideline economic analysis, haloperidol, risperidone, olanzapine and quetiapine were among the most effective when both YMRS scores and response rates were considered, and had lower drug and laboratory testing costs compared with other drugs. Carbamazepine was shown to be the most clinically and cost-effective option in the cost-utility analysis (that was based on response rates) but not when YMRS

scores were considered, while its cost was slightly higher than the four drugs mentioned above.

Regarding acute depression, the guideline economic analysis suggested that the five most cost-effective pharmacological treatment options among those assessed in the guideline are valproate, the combination of fluoxetine and olanzapine, quetiapine, olanzapine and lamotrigine. These results were robust to alternative scenarios considered in sensitivity analysis. The GDG took into account the fact that the results for valproate were determined based on very limited clinical data. Lurasidone was not considered in the economic analysis as it is currently not available in the UK but future analyses need to evaluate its cost effectiveness should it become available in the UK market.

The economic evidence on nutritional and non-pharmacological medical interventions was very limited and, where available, was characterised by very serious limitations.

6.5.4 Quality of evidence

For the treatment of acute episodes, the GDG considered only pharmacological interventions that have been tested in double-blind clinical trials. Although dropout limits the interpretation of continuous measures in such trials (that is, symptoms), dichotomous measures of response and discontinuation were considered less vulnerable to bias. The GDG considered that reporting bias may lead to overestimates of efficacy, but it was not clear if particular interventions were more vulnerable to reporting bias than others. Only interventions reporting critical outcomes in the populations of interest were considered, so none of the evidence was indirect. Evidence for several interventions was very imprecise because there were few trials with few participants; for this reason, the GDG decided not to recommend some interventions that have been evaluated for acute depression (imipramine, lithium, paroxetine, pramipexole, tranylcypromine, valproate).

6.5.5 Other considerations

People with bipolar disorder may experience multiple episodes of mania or depression, and they may take long-term medication. For these reasons, the expert consensus of the GDG was that experience of previous episodes and response to previous treatment should inform decisions about the treatment of new episodes. Furthermore, the likelihood of specific side effects varies across medications, and the GDG determined that treatment decisions should consider the values and preferences of service users in relation to potential side effects. Preferences about the treatment of manic episodes may be expressed at the time or through advance statements to guide clinicians at times when the service user's ability to make decisions is limited.

After an acute episode has resolved, the GDG judged that at 4 weeks after resolution of symptoms of an acute episode, clinicians should have a discussion

with the person about continuing with treatment for the acute episode or starting long-term treatment, with an emphasis on the benefits of long-term treatment, while also advising them about the risk of side effects. If the person decides to continue with acute treatment, the GDG determined by expert consensus that this should be for between 3 and 6 months and then reviewed.

The GDG did not find any trials that suggest efficacy or tolerability varies across gender, ethnicity or disability. People of different size and age may require different doses of medications, and clinicians should consult manufacturer and BNF guidelines for specific advice.

Finally, the GDG judged that people with bipolar disorder who experience a crisis during an acute episode should have access to the same crisis services as people with schizophrenia, in line with the NICE guideline, *Psychosis and Schizophrenia in Adults* (NICE, 2014). This would include crisis resolution and home treatment teams and other acute services, such as acute community treatment, crisis houses and acute day hospitals. For those people in crisis how pose an immediate risk to themselves or others during an acute episode, the GDG wished to ensure that professionals followed the advice in the NICE guideline on *Violence* (NICE, 2005b), *Service User Experience in Adult Mental Health* (NICE, 2011c)and *Self-harm* (NICE, 2011b)when managing imminent violence, acts of self harm or suicide risk, and when considering rapid tranquillisation.

6.6 RECOMMENDATIONS

6.6.1 Clinical practice recommendations

Managing mania or hypomania in adults in secondary care

Support and advice

6.6.1.1 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.

Pharmacological interventions

6.6.1.2 If a person develops mania or hypomania and is taking an antidepressant (as defined by the British national formulary [BNF]) as monotherapy, stop the antidepressant and start an antipsychotic as set out in recommendation 6.6.1.3.

6.6.1.3 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 and previous response to treatment). Follow the recommendations on using antipsychotics in section 7.6.1.

6.6.1.4 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 6.6.1.3, taking into account any advance statements, the person's preference and clinical context (including physical comorbidity and previous response to treatment).

6.6.1.5 If an alternative antipsychotic is not sufficiently effective at the maximum licensed dose, consider adding lithium. If adding lithium is ineffective, consider adding valproate[16] instead.

6.6.1.6 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.

6.6.1.7 If the person is already taking lithium, check plasma lithium levels to optimise treatment (see recommendations 7.6.1.17 and 7.6.1.18). Consider adding haloperidol, olanzapine, quetiapine or risperidone, depending on the person's preference and previous response to treatment.

6.6.1.8 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.

6.6.1.9 If the clinical presentation is of a mixed affective state, characterised by both manic and depressive symptoms, follow recommendations 6.6.1.1–6.6.1.8 for the treatment of mania, and monitor closely for the emergence of depression.

6.6.1.10 Do not offer lamotrigine to treat mania.

6.6.1.11 Do not offer gabapentin or topiramate to treat bipolar disorder.

Reviewing treatment for mania

[16] Although its use is common in UK clinical practice, at the time of publication (September 2014), sodium valproate 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. Semi-sodium valproate is licensed for mania if lithium is not tolerated or is contraindicated.

6.6.1.12 At 4 weeks after 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 7.6.1). Explain the potential benefits of long-term treatment and the risks, including side effects of medication used for long-term treatment.

6.6.1.13 If the person decides to continue with treatment for mania, offer it for a further 3–6 months, and then review.

Managing bipolar depression in adults in secondary care

6.6.1.14 If a person develops moderate or severe bipolar depression and is not taking a drug to treat their bipolar disorder, offer fluoxetine combined with olanzapine[17], 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[18] 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 in section 7.6.1.

6.6.1.15 If a person develops moderate or severe bipolar depression and is already taking lithium, check their plasma lithium level and:

- if their plasma lithium level is inadequate, increase the dose of lithium
- if their plasma lithium is at maximum level, add either fluoxetine combined with olanzapine[5] or quetiapine, depending on the person's preference and previous response to treatment. If there is no response or the person prefers, consider olanzapine (without fluoxetine) or lamotrigine[18].

Follow the recommendations in section 7.6.1 on using lithium and antipsychotics.

[17] Although this 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.

[18] Although this 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.

6.6.1.16 If a person develops moderate or severe bipolar depression and is already taking valproate, consider increasing the dose. If the maximum tolerated dose has been reached and there is a limited response to valproate, add fluoxetine combined with olanzapine[19] 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[20] 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 7.6.1 on using valproate.

6.6.1.17 Follow the recommendations on using antipsychotics in section 7.6.1 and be aware of the potential interactions between valproate and fluoxetine, lamotrigine and olanzapine.

6.6.1.18 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.

Reviewing treatment for bipolar depression

6.6.1.19 At 4 weeks after resolution of symptoms, discuss with the person, and their carers if appropriate, whether to continue treatment for bipolar depression or start long-term treatment (see section 7.6.1). Explain the potential benefits of long-term treatment and the risks, including side effects of medication used for long-term treatment.

6.6.1.20 If the person decides to continue with acute treatment, 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

6.6.1.21 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.

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[19] Although this 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

[20] Although this 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.

6.6.1.22 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 imminent violence and on rapid tranquillisation **or**
- self-harm for advice on managing acts of self-harm or suicide risk.

6.6.2 Research recommendations

6.6.2.1 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?

7 INTERVENTIONS AND SERVICES FOR LONG-TERM MANAGEMENT

7.1 INTRODUCTION

Effective treatment of bipolar disorder requires treatment of depressive and manic or hypomanic episodes together with long-term management to enhance mood stability and to prevent further episodes and hospitalisation. The prevention of acute episodes of illness does not represent fully effective treatment for most people with bipolar disorder and is unlikely to be considered as recovery from illness. Long-term management aims to improve social and occupational functioning, and to reduce direct and indirect economic costs.

On average, people with bipolar disorder spend more time experiencing depressive symptoms than from manic symptoms. This is particularly the case in bipolar II disorder in which in one study (Judd et al., 2003b), the ratio of time depressed to hypomanic was 37 to 1 compared with 3 to 1 in bipolar I disorder (Judd et al., 2002b). The long-term amelioration of depression is therefore a key aim for most people with bipolar disorder. However, tolerability of side effects will often be a bigger concern for people during long-term management, as opposed to acute treatment.

Several pharmacological agents are used in the long-term management of bipolar disorder. These include lithium, valproate (in various forms), lamotrigine and antipsychotic drugs.

Service-level interventions, and communication technologies for monitoring symptoms, are also reviewed in this chapter.

7.2 SERVICE-LEVEL INTERVENTIONS

7.2.1 Introduction

The GDG considered the efficacy of service-level interventions specifically for bipolar disorder (for example, mood clinics, lithium clinics and collaborative care). In addition, the GDG also considered the organisation of services in the UK and the evidence reviewed in related NICE guidelines, including *Psychosis and Schizophrenia in Adults* (NICE, 2014). The method of incorporation and adaptation (Section 3.7) was used where considered appropriate by the GDG when drafting recommendations.

7.2.2 Clinical review protocol

The review protocol summary, including the review question, can be found in Table 24 (a complete list of review questions and protocols can be found in

Appendix 7; further information about the search strategy can be found in Appendix 8).

Table 24: Clinical review protocol for the review of service-level interventions for bipolar disorder

Topic	Interventions
Review question(s)	RQ3.1: For adults with bipolar disorder, what are the relative benefits and harms of service-level interventions that are designed specifically for people bipolar disorder? 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+)?
Objectives	To estimate the efficacy of services in treating bipolar disorder.
Criteria for considering studies for the review	
• Intervention	Lithium clinics Mood clinics Collaborative care
• Comparator	Treatment as usual Other services
• Types of participants	Adults (18+) with suspected bipolar disorder. Special consideration will be given to the groups above.
• Outcomes	1) Relapse (all, mania/mixed, depression) 2) Hospitalisation (rate, duration) 3) Quality of life 4) Mortality
• Time	At least 1 year after initiating treatment.
• Study design	Randomised controlled trials (RCTs) and cluster RCTs with a parallel group design. We will exclude quasi-RCTs, such as trials in which allocation is determined by alternation or date of birth.

7.2.3 Studies considered[21]

One RCT (N = 158) providing relevant clinical evidence met the eligibility criteria for this review, KESSING2013 (Kessing et al., 2013). The study took place in Denmark and it evaluated a mood clinic that provided a structured psychological intervention and protocols for the pharmacological management of acute episodes compared to usual care. Duration of treatment was 104 weeks. The participants had a mean age of 36 years and 54% were female.

7.2.4 Clinical evidence review

One trial examined the effects of mood clinics for people with bipolar disorder, and this trial suggests that services providing coordinated, evidence-based psychological and pharmacological interventions are likely to reduce relapse and hospitalisation (see Table 25).

[21]Here and elsewhere in the guideline, each study considered for review is referred to by a study ID in capital letters (primary author and date of study).

Table 25: Summary of evidence for service-level interventions for adults with bipolar disorder

Comparison	N	k	Hospitalisations: number admitted (95% CI)	Time to hospitalisation (95% CI)	Number of relapses (95% CI)	Study ID
Mood clinic compared with usual care	158	1	RR = 0.66 (0.46, 0.95)	HR = 0.60 (0.37, 0.97)	RR = 1.10 (0.85, 1.42)	KESSING2013
Note. k = Number of studies; CI = Confidence interval; N = Sample size; RR = Relative risk.						

Owing to the lack of evidence regarding service-level interventions, the GDG therefore considered the organisation of services in the UK as set out in the NICE guideline *Psychosis and Schizophrenia in Adults* (NICE, 2014) regarding continued access to an early intervention in psychosis service, referral to a specialist integrated community-based team, or intensive case management for people likely to disengage from services, access to supported employment programmes, and returning to primary care for further management once symptoms had resolved or stabilised.

7.2.5 Health economics evidence

Systematic literature review

The systematic search of the economic literature undertaken for the guideline identified one eligible study assessing the cost effectiveness of service-level interventions specifically for bipolar disorder (Kessing et al., 2013). References to included studies and evidence tables for all economic evaluations included in the systematic literature review are provided in Appendix 32. Completed methodology checklists of the studies are provided in Appendix 31. Economic evidence profiles of studies considered during guideline development (that is, studies that fully or partly met the applicability and quality criteria) are presented in Appendix 33.

Kessing and colleagues (2013) assessed the cost effectiveness of a specialised out-patient mood disorder clinic versus standard decentralised psychiatric treatment for adults with recently diagnosed bipolar disorder in Denmark. The economic analysis was conducted alongside a RCT (KESSING2013). The study participants were recruited in the trial following discharge from one of their first 3 psychiatric hospital admissions for a manic episode. The study adopted the perspective of the health service; costs consisted of intervention costs, costs of mental health centre, costs of private psychiatrists, outpatient treatment costs at the local psychiatric hospital, medication costs and costs of inpatient care. The primary measure of outcome, taken from the RCT, was the rate of first readmission to hospital. Resource use data were derived from the RCT, published literature and further assumptions. National published data were used to estimate unit costs. The cost year was not reported but it was likely to be 2012. The time horizon of the analysis was 2 years.

The mood disorder clinic was overall less costly than standard care (mean cost per person €25,953 versus €29,147, respectively), although the level of statistical significance was not provided. In addition, the mood disorder clinic was significantly more effective than standard care (percentage of first readmission to hospital 36.1% versus 54.7%, p=0.034). Thus the mood disorder clinic was found to dominate standard care, as it was more effective at no additional cost. Cost results were sensitive to intervention costs and the length of hospital re-admission. The study is partially applicable to the UK context as it was conducted in Denmark. QALYs were not estimated in the study, but this did not affect conclusions on cost effectiveness as the intervention was dominant according to the outcome measure used. The study suffers from potentially serious limitations, including the fact that a number of resource use data were based on assumptions, and also that statistical analysis was done only for the clinical outcomes; cost results were subject to sensitivity analysis but their level of significance was not estimated. The study was funded by pharmaceutical industry but this created no apparent conflict of interest.

Economic evidence statement

There is limited evidence that mood disorder clinics may be cost effective compared with standard care, as they improve outcomes at no additional cost. This evidence is partially applicable and is characterised by potentially serious limitations.

7.3 COMMUNICATION TECHNOLOGIES

7.3.1 Introduction

Regularly monitoring symptoms of bipolar disorder may help service users and clinicians identify periods when there is a high risk of relapse. If effective, monitoring could facilitate early intervention to reduce the duration of acute episodes.

7.3.2 Clinical review protocol

The review protocol summary, including the review question, can be found in Table 26**Error! Reference source not found.** (a complete list of review questions and protocols can be found in Appendix 7; further information about the search strategy can be found in Appendix 8).

Table 26: Review protocol summary for the review of communication technologies for monitoring the symptoms of bipolar disorder

Topic	Interventions
Review question(s)	RQ3.3: What are the relative benefits and harms of information and communication technologies (for example, text messaging) for monitoring and managing symptoms? 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+)?
Objectives	To estimate the efficacy of communication technologies for monitoring symptoms.
Criteria for considering studies for the review	
• Intervention	Internet and computer programs, automated telephone systems, and text messaging.
• Comparator	Waitlist, no-intervention and other interventions.
• Types of participants	People with bipolar disorder. Special consideration will be given to the groups above.
• Outcomes	1) Relapse (all, mania/mixed, depression) 2) Hospitalisation (rate, duration) 3) Mortality (all cause, suicide attempts, suicides completed)
• Time	Outcomes will be grouped by time point.
• Study design	Randomised controlled trials (RCTs) and cluster RCTs with a parallel group design. We will exclude quasi-RCTs, such as trials in which allocation is determined by alternation or date of birth.
• Study setting	Primary, secondary, tertiary, health and social care

7.3.3 Studies considered

The search identified no eligible studies and therefore the GDG was unable to make any recommendations about communication technologies for monitoring symptoms, such as internet and computer programs, automated telephone systems, and text messaging.

7.4 PHARMACOLOGICAL AND NUTRITIONAL INTERVENTIONS

7.4.1 Introduction

Of the drugs reviewed in this section, in the UK, lithium carbonate is licensed for the 'treatment and prophylaxis of mania, manic depressive illness and recurrent depression'[22]; olanzapine is licensed for the 'treatment of moderate to severe manic episode…In patients whose manic episode has responded to olanzapine treatment, olanzapine is indicated for the prevention of recurrence in patients with bipolar disorder'[23] and carbamazepine is indicated for the 'prophylaxis of manic-depressive psychosis in patients unresponsive to lithium therapy'[24].

7.4.2 Clinical review protocol

Long-term trials in bipolar disorder include multiple types of studies. Some assign people who are not in an acute episode to receive a new long-term treatment;

[22] http://www.medicines.org.uk/emc/medicine/1239/SPC/CAMCOLIT+250/
[23] http://www.medicines.org.uk/emc/medicine/27661/SPC/Olanzapine++10+mg+tablets/
[24] http://www.medicines.org.uk/emc/medicine/27629/SPC/Carbamazepine+100+mg+5+ml+Oral+Suspension/

others randomise participants to discontinue or to continue treatment that was effective in an acute phase (Cipriani et al., 2013a). The GDG considered both types of studies in this review.

The GDG determined that the purpose of long-term management is to prevent new mood episodes and to keep people out of hospital. For this reason, they determined that trials would need to include controlled results at 1 year or more to provide evidence of effects on long-term outcomes. Given the goals of long-term management, the GDG did not consider the use of additional medication to be indicative of treatment failure. They noted that studies may not report the number of people who return to hospital or relapse according to accepted criteria (that is, for a major depressive episode or manic episode), and they considered evidence of effects for other definitions of 'relapse' to be of limited clinical utility, primarily because many studies include in their definition the use of additional medication, which is extremely common in bipolar and may be used to prevent symptoms from escalating into a full episode (a treatment success) rather than treat a full episode (a failure).

The review protocol summary, including the review questions, can be found in Table 27 (a complete list of review questions and protocols can be found in Appendix 7; further information about the search strategy can be found in Appendix 8).

Table 27: Clinical review protocol for the review of pharmacological intervention for long-term management

Topic	Interventions
Review question(s)	RQ3.4: For adults with bipolar disorder, what are the relative benefits and harms of starting a new pharmacological or nutritional intervention outside of an acute episode? RQ3.5: For adults with bipolar disorder, what are the relative benefits and harms of continuing an acute treatment for 1 year or more? 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+)?
Objectives	To estimate the efficacy of interventions for the long-term management of bipolar disorder.
Criteria for considering studies for the review	
• Intervention	All licensed oral medications (and their combinations) delivered for 1 year or more
• Comparator	Pill placebo Other pharmacological interventions
• Types of participants	Adults (18+) with bipolar disorder. Special consideration will be given to the groups above.
• Outcomes	1) Relapse (all, mania/mixed, depression) (for the purposes of the guideline, relapse was defined as a new episode meeting criteria for MDD or mania) 2) Discontinuation (due to side effect, other) 3) Hospitalisation (rate) 4) Quality of life 5) Mortality (all cause, suicides completed) 6) Weight
• Time	Included studies must have included controlled measures of outcomes at 12 months or later.
• Study design	Randomised controlled trials (RCTs) and cluster RCTs with a parallel group design. Quasi-RCTs, such as trials in which allocation is determined by alternation or date of birth, will be excluded.
• Include unpublished data?	Unpublished research may be included.
• Restriction by date?	No limit.
• Dosage	Fixed or flexible doses within the therapeutic range (BNF recommended).
• Minimum sample size	10 participants per group
• Study setting	Primary, secondary, tertiary, health and social care

7.4.3 Studies considered

Thirty-six RCTs (N = 8,326) met the eligibility criteria for this review: BERWAERTS2012 (Berwaerts et al., 2012), BOBO2011B (Bobo, 2011; Bobo et al., 2011), BOWDEN2000 (Bowden et al., 2000; Bowden et al., 2005; Bowden et al., 1997; Gyulai et al., 2003; Keck et al., 2005), BOWDEN2003 (Bowden et al., 2006;

Bowden et al., 2003; Sajatovic et al., 2005), CALABRESE2003 (Bowden et al., 2006; Calabrese et al., 2003; Sajatovic et al., 2005), CALABRESE2005C (Calabrese et al., 2005b), CARLSON2012 (Carlson et al., 2012; Kemp et al., 2013; Rahman, 2011), COXHEAD1992 (Coxhead et al., 1992), DENICOFF1997, DUNNER1976 (Dunner et al., 1976; Mendlewicz et al., 1973), GEDDES2010 (Geddes et al., 2010), GELENBERG1989 (Gelenberg et al., 1989; Keller et al., 1992; Perlis et al., 2002; Solomon et al., 1996), GHAEMI2010 (Ghaemi et al., 2010), HARTONG2003 (Hartong et al., 2003), JENSEN1995 (Jensen et al., 1996a; Jensen et al., 1995; Jensen et al., 1996b), KLEINDIENST2000 (Greil et al., 1986; Greil et al., 1998; Greil et al., 1997; Greil et al., 1993; Kleindienst & Greil, 2000; Kleindienst & Greil, 2004; Thies-Flechtner et al., 1996), LANGOSCH2008 (Langosch et al., 2008), LICHT2010 (Licht et al., 2010), MACFADDEN2009 (Macfadden et al., 2009), MARCUS2011 (Kemp et al., 2013; Marcus, 2011; Marcus et al., 2011; Yatham et al., 2013a), PRIEN1973 (Prien et al., 1973a; Prien et al., 1974), PRIEN1973B (Prien et al., 1973b), PRIEN1984 (Prien et al., 1984; Shapiro et al., 1989), QUIROZ2010 (Quiroz et al., 2010), QUITKIN1981 (Quitkin et al., 1979; Quitkin et al., 1981), STALLONE1973 (Mendlewicz et al., 1973; Mendlewicz & Stallone, 1975; Stallone et al., 1973), SUPPES2009 (Suppes, 2009; Suppes et al., 2009; Vieta et al., 2012b), TOHEN2004 (Tohen et al., 2004; Tohen et al., 2002), TOHEN2005 (Tohen et al., 2005; Tohen et al., 2012b), VIETA2006 (Vieta et al., 2006), VIETA2008 (Vieta et al., 2008a), VIETA2008B (Vieta et al., 2008b; Vieta et al., 2012b), VIETA2012 (Vieta et al., 2012a), WEISLER2011 (Nolen & Weisler, 2013; Weisler et al., 2008b; Weisler et al., 2011), WOLF1997 (Berky et al., 1998; Wolf et al., 1997) and YOUNG2012 (Young et al., 2012).

One trial of lithium, carbamazepine and their combination (N=52; DENICOFF1997) met the inclusion criteria for this review but could not be included because pre cross-over data were unavailable.

No long-term trials of nutritional interventions met the inclusion criteria for this review.

Twenty-seven studies were excluded; four because they evaluated medications that are not indicated for mental disorders and not in common use: BERK2008 (Berk et al., 2008), BERK2012 (Berk et al., 2012), ESPARON1986 (Esparon et al., 1986) and NORRIS2013 (Norris et al., 2013); two could not be included in the review because the results were not available: AHLFORS1981 (Ahlfors et al., 1981) and OKUMA1981 (Okuma et al., 1981); one trial, BAASTRUP1970 (Baastrup et al., 1970), of lithium compared with placebo was excluded because the methods were unsound and unethical; the trial continued to enrol participants until results were statistically significant, and participants did not give consent (participants assigned to placebo were not aware that their existing lithium therapy had been switched to placebo); one study, ALTAMURA2003 (Altamura et al., 2003), could not be included because it compared quetiapine with 'classic mood stabilisers' and did not describe what these were; one was excluded because it included participants who did not have bipolar disorder: SUPPES1999 (Suppes et al., 1999); one trial comparing lithium with valproate was excluded because there were only

six participants in each group: SOLOMON1997 (Solomon et al., 1997); and one trial of omega-3 fatty acids compared with placebo was excluded because there were only ten participants in total: MARANGELL2006 (Marangell et al., 2006); 16 followed participants for less than 12 months: ALTAMURA2004 (Altamura et al., 2004), AMSTERDAM2005b (Amsterdam & Shults, 2005b; Amsterdam et al., 2004), AMSTERDAM2010 (Aigner, 2010; Amsterdam et al., 2013; Amsterdam & Shults, 2010), BOWDEN2010 (B. et al., 2010; Bowden et al., 2010; Dubovsky & Dubovsky, 2012; Kemp, 2012; Vieta et al., 2009b), BOWDEN2012 (Bowden et al., 2012), BURDICK2012 (Burdick et al., 2012), CALABRESE2000 (Calabrese et al., 2000; Goldberg et al., 2008), CUNDALL1972 (Cundall et al., 1972), ELMALLAKH2009 (El-Mallakh et al., 2010; El-Mallakh et al., 2009), GSK2012 (GlaxoSmithKline, (unpublished) 2012; GlaxoSmithKline, (unpublished) 2012), KECK2006a (Keck, 2007; Keck et al., 2006a), MURPHY2012 (Murphy et al., 2012), STOLL1999 (Stoll et al., 1999), TOHEN2006 (Tohen et al., 2006), WOO2011 (Woo et al., 2011) and ZARATE2004 (Zarate & Tohen, 2004).

Included trials were published in peer-reviewed journals between 1973 and 2012. No unpublished reports were located. The GDG determined that it was not possible to conduct a network meta-analysis because of diversity in study designs, outcome measurement, and participant characteristics across the included trials. Pairwise analyses were conducted for all eligible interventions. Further information about both included and excluded studies can be found in Appendix 35.

Study characteristics

Participants were on average aged 40 years (median of means). Approximately half of the included participants were female (54%). Twenty-nine trials reported the proportion of participants with a diagnosis of bipolar I or bipolar II disorder. Of these, 19 included participants with bipolar I only, and one included participants with bipolar II only; nine trials included some participants with each type of bipolar disorder. Included studies lasted 52 to 129 weeks (79 weeks median of means). Participants and providers were blind to group assignment in most trials, but eight trials were open-label.

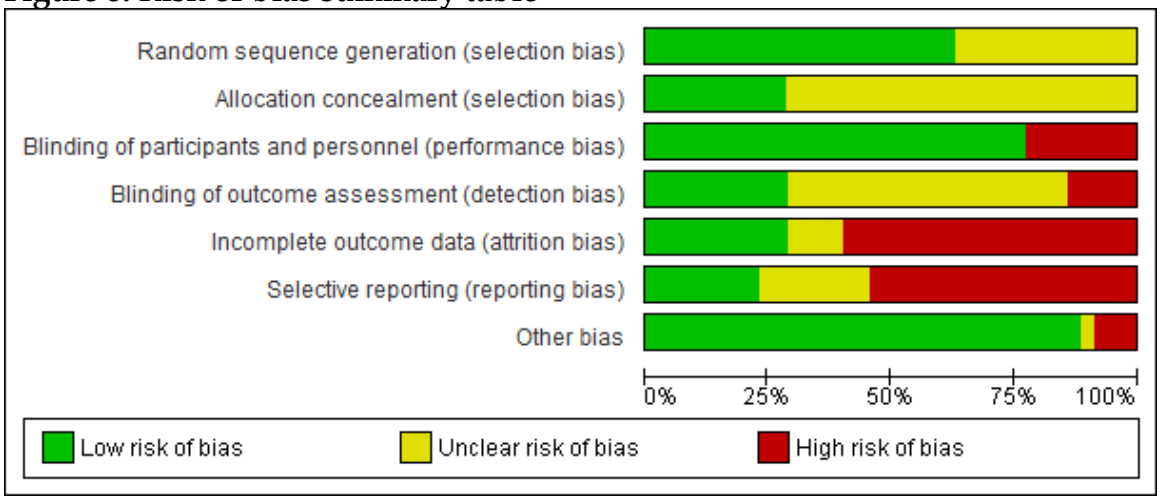
Risk of bias

All included trials were assessed for risk of bias (see Appendix 17). For sequence generation, 22 trials were at low risk of bias and ten of these were at low risk of bias for allocation concealment. Allocation concealment was unclear in 25 trials. For blinding of participants and providers, 27 trials were at low risk of bias and eight were at high risk. Assessor blinding was considered separately for all trials, and nine had a low risk of bias. Four trials had a high risk of bias for assessor blinding and 22 were unclear. For incomplete outcome data, 10 trials were at low risk of bias and 23 trials were at high risk of bias, mostly because of the large amount of missing data.

Selective outcome reporting and publication bias

Several methods were employed to minimise risk of selective outcome reporting and publication bias. All authors were contacted to request trial registrations and unpublished outcomes, and all authors of included studies, all stakeholders, and all pharmaceutical manufacturers were asked to provide unpublished trials. Only sixteen of the included studies were known to be registered and eight were at low risk of selective outcome reporting bias; 18 were at high risk of bias and nine were unclear (see Figure 8). Comparing published reports and unpublished documents for two trials, we found that published reports misrepresent the number of people randomised; we used the unpublished data for our analyses (VIETA2006; VIETA2012).

Figure 8: Risk of bias summary table



7.4.4 Clinical evidence review

Evidence from primary outcomes is presented in Table 28. Additional forest plots and details about the quality of evidence can be found in Appendices 14 to 17.

Lithium

Lithium compared with placebo

Seven trials (N = 1,434) included a comparison of lithium with placebo (STALLONE1973, DUNNER1976, CALABRESE2003, BOWDEN2003, BOWDEN2000, PRIEN1973B, WEISLER2011). Because of differences in study design, data for relapse and discontinuation could not be combined for all trials. Results are summarised for several comparisons.

Two trials (N = 90) compared lithium with placebo for participants who were euthymic (normal non-depressed, reasonably positive mood) at study entry (STALLONE1973, DUNNER1976). The length of follow-up was 121 weeks in STALLONE1973 and 69 weeks in DUNNER1976. There was very low quality evidence that lithium reduced the risk of relapse (RR = 0.41, 95% CI = 0.07 to 2.43), but the estimate is imprecise and the definition of relapse did not meet the

criteria set by the GDG. There was very low quality evidence that lithium might be associated with an increase in the risk of discontinuation for any reason (RR = 1.39, 95% CI = 0.58 to 3.34).

Two trials (N = 358) compared lithium with placebo (CALABRESE2003, BOWDEN2003); both included a third arm that received lamotrigine (comparisons involving lamotrigine are described below). In both trials, which were conducted by the same investigators, participants were euthymic at randomisation following 8 to 16 weeks of active treatment with lamotrigine alone or in addition to another psychotropic medication. Lithium was titrated to serum levels of 0.8-1.1 mEq per litre and participants were followed for approximately 74 weeks. There was very low quality evidence that lithium reduced the risk relapse (RR = 0.71, 95% CI = 0.47 to 1.06), but the estimate is imprecise and the definition of relapse did not meet the criteria set by the GDG. Very low quality evidence suggested that lithium may increase the risk of participants discontinuing for any reason (RR = 1.38, 95% CI = 0.78 to 2.45).

One trial (N = 185) compared lithium with placebo for participants who were not experiencing an acute episode at randomisation, but had experienced the onset of a manic episode within 3 months (BOWDEN2000). The trial included a third arm that received valproate (comparisons involving valproate are described below). Lithium was titrated to serum levels of 0.8 to 1.2 mmol per litre and participants were followed for 1 year. There was very low quality evidence that lithium reduced the risk relapse (RR = 0.80, 95% CI = 0.54 to 1.20), but the estimate is imprecise and the definition of relapse did not meet the criteria set by the GDG. Very low quality evidence suggested that lithium may increase the risk of participants discontinuing for any reason (RR = 1.21, 95% CI = 0.86 to 1.71).

One trial (N = 205) compared lithium (1000 mg) with placebo for participants who had remitted from a manic episode and were receiving stable doses of lithium (PRIEN1973). There was very low quality evidence that continued lithium reduced the risk relapse (RR = 0.53, 95% CI = 0.41 to 0.67), but the definition of relapse did not meet the criteria set by the GDG. Very low quality evidence suggested that lithium reduced the risk of participants discontinuing for any reason (RR = 0.42, 95% CI = 0.28 to 0.62).

One trial (N = 31) compared lithium (1250 mg) with placebo for participants who at randomisation had remitted from a manic episode and were receiving stable doses of lithium (PRIEN1973B). The trial included a third arm that received imipramine (comparisons involving imipramine are described below). Relapse was reported separately for manic and depressive episodes, and the definition of relapse did not meet the criteria set by the GDG. There was very low quality evidence that continued lithium reduced the risk of manic relapse (RR = 0.48, 95% CI = 0.09 to 2.48) and depressive relapse (RR = 0.29, 95% CI = 0.07 to 1.26), but the estimates were imprecise. At 2 years, there was very low quality evidence

that continued lithium reduced the risk of discontinuation for any reason (RR = 0.12, 95% CI = 0.02 to 0.88).

One trial (N = 1,172) compared lithium, quetiapine (600 mg) and placebo (WEISLER2011). Participants were euthymic at randomisation following 4 to 24 weeks of active treatment with quetiapine. Lithium was titrated to serum levels of 0.6-1.2 mEq per litre and participants were followed for 2 years. Relapse was not reported according to the criteria set by the GDG and the number of participants relapsing in each group was not reported. Time to recurrence of a study-defined mood episode was significantly longer for continued quetiapine compared with switching to lithium (HR = 0.66, 95% CI = 0.49 to 0.88). Time to recurrence of a mood episode was significantly longer for switching to lithium compared with placebo (HR = 0.46, 95% CI = 0.36 to 0.59). At 2 years, very low quality evidence indicated evidence of benefit in favour of continued quetiapine in comparison with lithium for participants discontinuing from the study (RR = 1.62, 95% CI = 1.23 to 2.13). The lithium group had more participants discontinuing for any reason compared with placebo (RR = 1.37, 95% CI = 1.06 to 1.78).

Lithium administered at different doses

One trial (N = 94) included two groups receiving lithium at different daily doses. All participants had been euthymic for at least 2 months since the end of their index episode and were receiving lithium (GELENBERG1989). The first group received a standard dose of lithium to achieve serum levels between 0.8 and 1.0 mmol per litre. In the second, they received a low dose to achieve serum levels between 0.4 and 0.6 mmol per litre. At 1 year after randomisation, there was very low quality evidence that low dose lithium increased the risk of relapse (RR = 3.50, 95% CI = 1.55 to 7.89). There was very low quality evidence that the standard dose increased the risk of discontinuation for any reason (RR = 0.46, 95% CI = 0.25 to 0.83).

One trial (N = 50) compared 800 mg of lithium administered daily with 1200 mg administered every other day (JENSEN1995). Participants had all been euthymic for at least 4 months and had completed 3 months of active treatment with lithium administered daily. At 56 weeks after randomisation, there was very low quality evidence that lithium every other day increased the risk of relapse (RR = 2.40, 95% CI = 0.99 to 5.81) and there was very low quality evidence that lithium every other day decreased the risk of discontinuing for any reason (RR = 0.11, 95% CI = 0.01 to 1.96).

Lithium compared with carbamazepine

Three trials (N = 399) compared lithium with carbamazepine (HARTONG2003, KLEINDIENST2000, WOLF1997). At study entry participants were euthymic. In HARTONG2003 serum levels were titrated between 0.6-1.0 mmol per litre for lithium and between 6-10 mg per litre for carbamazepine. In KLEINDIENST2000 lithium serum levels were titrated between 0.6-1.2 mmol per litre and

carbamazepine was administered at daily doses of 600 mg. In WOLF1997 the average daily doses of lithium and carbamazepine were 888 mg and 835 mg respectively. Participants were followed up for 52 to 130 weeks. At post-treatment, very low quality evidence indicated that lithium reduced the risk of relapse (RR = 0.73, 95% CI = 0.56 to 0.95). Two of the three trials (N = 262) reported very low quality evidence of a reduced risk of discontinuation for any reason (RR = 0.75, 95% CI = 0.16 to 3.54).

One trial (N = 31) compared lithium with carbamazepine for participants who were euthymic and had been receiving stable doses of lithium for at least 4 weeks (COXHEAD1992). Lithium was titrated to a serum level between 0.6-1.0 mmol per litre and carbamazepine was titrated to a serum level between 38-51 mmol per litre. There was very low quality evidence that was inconclusive with regard to the risk of relapse (RR = 1.25, 95% CI = 0.57 to 2.75), the study's definition of relapse was not reported. There was very low quality evidence that lithium may reduce the risk of discontinuation for any reason (RR = 0.47, 95% CI = 0.05 to 4.56).

Lithium compared with lamotrigine

One trial (N = 122) compared lithium with lamotrigine (400 mg) for participants who were not experiencing an acute episode at randomisation. Serum levels of lithium were maintained between 0.5-1.0 mmol per litre (LICHT2010). There was very low quality evidence suggesting little difference in the risk of relapse (RR = 0.97, 95% CI = 0.69 to 1.36), but the estimate is imprecise and the definition of relapse did not meet the criteria set by the GDG. There was very low quality evidence suggesting little difference in discontinuation for any reason (RR = 1.09, 95% CI = 0.64 to 1.87).

Lithium compared with valproate

One trial (N = 185) compared lithium with valproate as part of a three-arm trial (BOWDEN2000; see above for the comparison of lithium with placebo). Participants were not experiencing an acute episode at randomisation, but had experienced the onset of a manic episode within 3 months. Serum levels were maintained between 0.8-1.2 mmol per litre for lithium and 71 to 125 ug per mL for valproate. There was very low quality evidence suggesting lithium produced a small increase in the risk of relapse (RR = 1.28, 95% CI = 0.86 to 1.91), but the estimate is imprecise and the definition of relapse did not meet the criteria set by the GDG. There was very low quality evidence suggesting little difference in discontinuation for any reason (RR = 1.19, 95% CI = 0.89 to 1.59).

One trial (N = 60) compared lithium (1400 mg) with valproate (1600 mg) for participants who were euthymic and had been receiving active treatment with lithium and valproate for 6 months (CALABRESE2005C). There was very low quality evidence suggesting little difference in the risk of relapse (RR = 1.13, 95% CI = 0.70 to 1.82), and a possible increase in the risk of discontinuation for any reason (RR = 1.46, 95% CI = 0.61 to 3.50).

Lithium compared with valproate and lithium and valproate combined

One three-arm trial (N = 330) compared lithium, valproate and the combination of lithium and valproate for participants who were not experiencing an acute episode following active treatment of lithium and valproate in combination for four to 8 weeks (GEDDES2010). Lithium serum levels were maintained between 0.4-1.0 mmol per litre for lithium and 750-1250 mg of valproate were administered daily for a total of 2 years. At post-treatment, there was low quality evidence favouring lithium over valproate for study-defined relapse (RR = 0.85, 95% CI = 0.70 to 1.05) and hospitalisation (RR = 0.88, 95% CI = 0.53 to 1.46), and little evidence of a difference in discontinuation for any reason (RR = 1.02, 95% CI = 0.78 to 1.34). For lithium compared with the combination therapy, there was low quality evidence of a small difference favouring continued combination therapy for study-defined relapse (RR = 1.10, 95% CI = 0.87 to 1.40) and hospitalisation (RR = 1.38, 95% CI = 0.76 to 2.47), and there was little evidence of a difference in discontinuation for any reason (RR = 0.96, 95% CI = 0.74 to 1.26). There was low quality evidence favouring continued combination therapy over valproate alone for study-defined relapse (RR = 1.29, 95% CI = 1.04 to 1.61) and hospitalisation (RR = 1.56, 95% CI = 0.88 to 2.76), and little evidence of a difference in discontinuation for any reason (RR = 0.95, 95% CI = 0.72, 1.24).

Olanzapine compared with lithium

One trial (N = 431) compared olanzapine (10 mg) with lithium (1000 mg) for participants who were no longer experiencing an acute episode following 6 to 12 weeks of active treatment with olanzapine and lithium (TOHEN2005). At 1 year after randomisation, there was very low quality evidence suggesting continued olanzapine reduced the risk of relapse (RR = 0.76, 95% CI = 0.56 to 1.03) and discontinuation due to any reason (RR = 0.79, 95% CI = 0.68 to 0.93).

Antipsychotics

Aripiprazole compared with placebo

One trial (N = 351) compared aripiprazole (20 mg) with placebo for participants who were taking lamotrigine (CARLSON2012). At randomisation, participants had been euthymic for 8 weeks following active treatment with aripiprazole and lamotrigine for 9 to 24 weeks. There was very low quality evidence suggesting aripiprazole reduced the risk of relapse (RR = 0.69, 95% CI = 0.49 to 0.98), but the definition of relapse did not meet the criteria set by the GDG. There was very low quality evidence suggesting little difference in discontinuation for any reason (RR = 0.92, 95% CI = 0.79 to 1.06).

One trial (N = 337) compared aripiprazole (15 mg) with placebo for participants who were taking lithium or valproate (MARCUS2011). All participants had not responded to initial treatment with lithium or valproate for a manic or mixed episode. Subsequently, they were administered aripiprazole in addition to lithium or valproate, and participants who were symptom free for 12 consecutive weeks were randomised. There was very low quality evidence suggesting

aripiprazole reduced the risk of relapse (RR = 0.58, 95% CI = 0.38 to 0.91), but the definition of relapse did not meet the criteria set by the GDG. There was very low quality evidence suggesting that aripiprazole may decrease the risk of discontinuation for any reason (RR = 0.82, 95% CI = 0.64 to 1.05).

Olanzapine compared with placebo

One trial (N = 68) compared olanzapine with placebo for participants who were all taking lithium or valproate (TOHEN2004). Participants were euthymic following 6 weeks of active treatment with olanzapine and either lithium or valproate. There was very low quality evidence that olanzapine might be associated with a reduction relapse (RR = 0.66, 95% CI = 0.38 to 1.15), but the estimate is imprecise and the definition of relapse did not meet the criteria set by the GDG. There was very low quality evidence that olanzapine reduces the risk of discontinuation (RR = 0.77, 95% CI = 0.62 to 0.94).

One trial (VIETA2012; N = 278) compared olanzapine (10 mg) with placebo as part of a three-arm trial that also included risperidone long-acting injectable). (Additional comparisons are described below.) Participants were randomised once euthymic following 12 weeks of active treatment with risperidone long-acting injectable. There was low quality evidence that olanzapine reduced the risk of relapse (RR = 0.42, 95% CI = 0.30 to 0.59), but the definition of relapse did not meet the criteria set by the GDG. There was low quality evidence of no difference or a small difference in discontinuation for any reason (RR = 1.10, 95% CI = 0.66 to 1.85). The GDG noted that the published report for the trial is not consistent with unpublished company reports[25].

Paliperidone compared with placebo

One trial (N = 68) compared paliperidone extended release (6 mg) with placebo for participants who were euthymic following 6 weeks of active treatment with paliperidone (BERWAERTS2012). At 129 weeks after randomisation there was very low quality evidence that continued paliperidone was not associated with a reduction in relapse (RR = 0.83, 95% CI = 0.66 to 1.06), but the estimate is imprecise and the definition of relapse did not meet the criteria set by the GDG. There was very low quality evidence of no difference in discontinuation (RR = 1.05, 95% CI = 0.78 to 1.42).

Quetiapine compared with placebo

One trial (N = 585) compared quetiapine (300 mg or 600 mg) with placebo for participants who were euthymic following 8 weeks of active treatment with quetiapine (YOUNG2012). At 1 year after randomisation there was very low quality evidence that continued quetiapine may be associated with a reduction in relapse (RR = 0.59, 95% CI = 0.46 to 0.76), but the definition of relapse did not meet the criteria set by the GDG. There was very low quality evidence suggesting

[25] http://clinicaltrials.gov/ct2/show/study/NCT00391222

that quetiapine increased the risk of discontinuation (RR = 1.23, 95% CI = 1.05 to 1.43).

One trial (WEISLER2011; N = 808) compared quetiapine with placebo as part of a three-arm trial that also included lithium (see above). Participants were randomised if they were euthymic for at least 4 weeks following 4 to 24 weeks of active treatment quetiapine. Relapse was not reported according to the criteria set by the GDG and the number of participants relapsing in each group was not reported. The authors reported that time to recurrence of a mood episode was significantly longer for the continued quetiapine group compared with placebo (HR = 0.29, 95% CI = 0.23 to 0.38). At 2 years, very low quality evidence indicated that continued quetiapine when compared with placebo increased the risk of discontinuing for any reason (RR = 1.23, 95% CI = 1.05 to 1.43).

Two trials (N = 1,326) compared quetiapine with placebo for participants who were also taking lithium or valproate (SUPPES2009, VIETA2008B). Participants were randomised if they were euthymic for at least 12 weeks following active treatment with quetiapine and either lithium or valproate for 12 to 36 weeks. At 2 years after randomisation there was low quality evidence that continued quetiapine may be associated with a reduction in relapse (RR = 0.38, 95% CI = 0.32 to 0.46), but the definition of relapse did not meet the criteria set by the GDG. There was low quality evidence continued quetiapine may increase the risk of discontinuation for any reason (RR = 1.53, 95% CI = 1.24 to 1.89).

Quetiapine compared with valproate

One trial (LANGOSCH2008; N = 38) compared quetiapine (500 mg) with valproate (1300 mg) for participants with rapid-cycling bipolar disorder who had remitted or partly remitted from an acute episode. At 1 year after randomisation, there was very low quality evidence of no difference in discontinuation for any reason (RR = 0.95, 95% CI = 0.64 to 1.41). Relapse was not reported; however, the authors reported the mean number of mood swings per month, defined as (1) a change from a (sub)depressive to a manic or hypomanic state and vice versa, or (2) a change from an euthymic to an acute state and vice versa. Over the 12-month study period, the authors report there was no significant difference between groups in the frequency of mood swings. The quetiapine group had significantly fewer days with moderate to severe depressive symptoms.

Risperidone long-acting injectable compared with placebo

One trial (VIETA2012; N = 273) compared risperidone long-acting injectable (25 mg) with placebo as part of a three-arm trial (see above). Participants were randomised when euthymic following 12 weeks of active treatment with risperidone long-acting injectable. At 78 weeks after randomisation there was very low quality evidence that risperidone may be associated with a reduction in relapse (RR = 0.69, 95% CI = 0.53 to 0.90), but the definition of relapse did not meet the criteria set by the GDG. There was very low quality evidence that risperidone may increase the risk of discontinuation for any reason (RR = 1.33,

95% CI = 0.82 to 2.17). The GDG noted that the published report for the trial is not consistent with unpublished company reports.

One trial (N = 303) compared risperidone long-acting injectable (25 mg) for participants who were euthymic following 3 weeks of active treatment with oral risperidone and 12 weeks with risperidone long-acting injectable (QUIROZ2010). At 2 years after randomisation there was very low quality evidence that risperidone may be associated with a reduction in relapse (RR = 0.56, 95% CI = 0.42 to 0.75), but the definition of relapse did not meet the criteria set by the GDG. There was very low quality evidence of a small effect in favour of risperidone on discontinuation for any reason (RR = 0.89, 95% CI = 0.61 to 1.32).

Risperidone long-acting injectable in addition to treatment as usual compared treatment as usual

One trial (N = 124) compared risperidone long-acting injectable (12.5 mg) with a placebo injection for participants who were receiving treatment as usual (MACFADDEN). Participants were randomised when euthymic for at least 4 weeks following 16 weeks of active treatment with risperidone long-acting injectable. At 1 year after randomisation, there was very low quality evidence that risperidone may be associated with a reduction in relapse (RR = 0.50, 95% CI = 0.30 to 0.85), but the definition of relapse did not meet the criteria set by the GDG. There was very low quality evidence that risperidone may increase the risk of discontinuation for any reason (RR = 1.27, 95% CI = 0.61 to 2.64).

One trial (BOBO2011B; N = 50) compared risperidone long-acting injectable (27 mg) in addition to treatment as usual with treatment as usual alone. Participants were randomised when not in acute episode, and participants were required a history of four or more episodes in the previous year. Relapse was not reported according to the criteria set by the GDG and the number of participants relapsing in each group was not reported. The authors reported a higher mean number of study-defined mood events in the treatment as usual group between baseline and 12 months, however the authors report that this was not statistically significant. There was very low quality evidence that risperidone may increase the risk of discontinuation (RR = 1.50, 95% CI = 0.63 to 3.59).

Anticonvulsants

Oxcarbazepine compared with placebo

One trial (N = 55) compared oxcarbazepine (1200 mg) with placebo for participants who had been euthymic for 6 months (VIETA2008). During the trial, all participants were also taking lithium. At 1 year after randomisation, there was very low quality evidence that oxcarbazepine may be associated with a reduction in relapse (RR = 0.50, 95% CI = 0.26 to 0.94), but the definition of relapse did not meet the criteria set by the GDG. There was very low quality evidence of no effect or a small increase in discontinuation for any reason (RR = 1.12, 95% CI = 0.55 to 2.24).

Gabapentin compared with placebo

One trial (N = 25) compared gabapentin (300 mg) with placebo for participants who were euthymic but had experienced an acute episode within 6 months (VIETA2006). All participants continued taking lithium, valproate, carbamazepine or any combination of these medications. The number of people in each group who experienced a relapse was not reported. The authors reported no significant difference between groups for time to first new episode (HR = 1.34, p=0.67). There was very low quality evidence of no difference in discontinuation for any reason (RR = 1.08, 95% CI = 0.51 to 2.30). The GDG noted that the published report for the trial is not consistent with unpublished company reports (Vedula et al., 2013).

Lamotrigine compared with placebo

Two trials (BOWDEN2003, CALABRESE2003; N = 471) compared lamotrigine (200 mg) as part of a three-arm trial (also including lithium as described above). Participants were euthymic at randomisation following 8 to 16 weeks of active treatment with lamotrigine alone or in addition to other psychotropic medication. At approximately 74 weeks after randomisation there was low quality evidence that continued lamotrigine may be associated with a reduction in relapse (RR = 0.82, 95% CI = 0.59 to 1.14), but the estimate is imprecise and the definition of relapse did not meet the criteria set by the GDG. There was low quality evidence of a small or no effect of lamotrigine on discontinuation (RR = 1.14, 95% CI = 0.64 to 2.06).

Valproate compared with placebo

One trial (BOWDEN2000; N = 281) compared valproate with placebo as part of a three-arm trial (also including lithium as described above). Participants were not experiencing an acute episode at randomisation, but had experienced the onset of a manic episode within 3 months. Valproate was titrated to serum levels of 71 to 125 ug per millilitre and participants were followed for 1 year. There was low quality evidence that valproate was associated with a reduction in the risk of relapse (RR = 0.63, 95% CI = 0.44 to 0.90). There was very low quality evidence of little effect of valproate on discontinuation for any reason (RR = 1.02, 95% CI = 0.74 to 1.40).

Antidepressants

Imipramine compared with placebo

One trial (PRIEN1973B; N = 26) compared imipramine (125 mg) with placebo as part of a three-arm trial (also including lithium as described above). At randomisation, participants had remitted from a manic episode and were receiving stable doses of lithium. Study-defined relapse was reported separately for manic and depressive episodes, but the definition of relapse did not meet the criteria set by the GDG. Estimates were very imprecise for study-defined manic (RR = 2.00, 95% CI = 0.63 to 6.34) and depressive relapses (RR = 0.09, 95% CI =

0.01 to 1.49). At 2 years, there was very low quality evidence of little effect on discontinuation (RR = 1.17, 95% CI = 0.54 to 2.53).

One three-arm trial (PRIEN1984; N = 78) compared lithium, imipramine (150 mg) and the combination of lithium and imipramine. At randomisation participants were euthymic following 2 months of active treatment with combined lithium and imipramine. Lithium serum levels were maintained between 0.4 to 1.0 mmol per litre. At 2 years after randomisation, there was very low quality evidence that imipramine when compared with lithium increased the risk of relapse (RR = 1.47, 95% CI = 1.07 to 2.02), but the definition of relapse did not meet the criteria set by the GDG. Only the number of participants discontinuing due to side effects was reported and no one withdrew for this reason in either the lithium or imipramine groups. For the combination therapy compared with imipramine, very low quality evidence indicated that the combination therapy may be associated with a reduction in the risk of study-defined relapse (RR = 0.62, 95% CI = 0.43 to 0.89), but for a possible increase in the risk of discontinuation for any reason (RR = 5.81, 95% CI = 0.29 to 117.23). For the combination therapy compared with lithium there was little evidence of an important effect for study-defined relapse (RR = 0.91, 95% CI = 0.60 to 1.40). For discontinuation, the results were inconclusive (RR = 5.81, 95% CI = 0.29 to 117.23).

One trial (QUITKIN1981; N = 75) compared imipramine (125 mg) with placebo for participants who were all taking lithium. At randomisation participants had been euthymic for at least 6 weeks while receiving stable doses of lithium. At 129 weeks after randomisation in the results were inconclusive for relapse (RR = 1.54, 95% CI = 0.71 to 3.33) and discontinuation for any reason (RR = 0.86, 95% CI = 0.65 to 1.13), but the quality of the evidence was very low.

Antidepressants compared with placebo

One trial (GHAEMI2010; N = 70) compared antidepressant continuation with discontinuation for participants who were also taking mood stabilisers. All participants had responded to active treatment with antidepressants and mood stabilisers for an acute depressive episode and had been euthymic for at least 2 months when randomised. Outcomes were reported in insufficient detail to allow extraction and analysis. The authors reported no difference between groups in the occurrence of manic, depressive or mixed episodes from baseline to 12 months. There was no difference in time to the occurrence of a manic episode, however the delay in occurrence of a depressive episode was significantly longer for the continuation group (HR = 2.13, 95% CI = 1.00 to 4.56).

Table 28: Summary of evidence for pharmacological interventions for the long-term management of bipolar disorder

Comparison	N	k	Relapse, any (95% CI)†	Definition of relapse‡	Discontinuation for any reason (95% CI)†	Length of follow-upΔ	Study ID
Pharmacological Interventions							
Lithium							
Lithium (low dose) compared with lithium (standard dose)	94	1	RR = 3.50 (1.55, 7.89)	Research diagnostic criteria or DSM-III criteria for mania or depression	RR = 0.46 (0.25, 0.83)	52	GELENBERG1989
Lithium every other day compared with lithium daily)	50	1	RR = 2.40 (0.99, 5.81)	Manic or depressive relapse was defined as the DSM-III-R criteria for mania or major depression and a BRMAS score ≥10 or a BRMES score ≥10, respectively	RR = 0.11 (0.01, 1.96)	56	JENSEN1995
Lithium compared with placebo (participants were euthymic at study entry)	92	2	RR = 0.41 (0.07, 2.43)	Extra medication required to treat symptoms	RR = 1.39 (0.58, 5.08)	121, 69	STALLONE1973, DUNNER1976
Lithium compared with placebo (participants first received open-label lamotrigine – alone or in combination with other psychotropic drugs - for 8 to 16 weeks and were randomised once euthymic)	358	2	RR = 0.71 (0.47, 1.06)	An intervention - addition of ECT or pharmacotherapy, including antidepressants, antipsychotics, anticonvulsants/mood stabilisers, or benzodiazepines (exceeding doses of rescue medication)	RR = 1.38 (0.78, 2.45)	72, 76	CALABRESE2003, BOWDEN2003
Lithium compared with placebo (participants were randomised when euthymic and within 3 months of the onset of the index manic episode)	185	1	RR = 0.80 (0.54, 1.20)	A manic episode was defined as one accompanied by an MRS score of 16 or more or requiring hospitalisation. A depressive episode was defined as one requiring antidepressant use or premature discontinuation from the study because of symptoms	RR = 1.21 (0.86, 1.71)	52	BOWDEN2000

Comparison	N	k	Relapse, any (95% CI)†	Definition of relapse‡	Discontinuation for any reason (95% CI)†	Length of follow-upΔ	Study ID
Lithium compared with placebo (following remission of a manic episode and prior to discharge patients were stabilised on maintenance doses of lithium)	205	1	RR = 0.53 (0.41, 0.67)	Manic or depressive attack requiring hospitalisation or supplementary drugs	RR = 0.42 (0.28, 0.62)	104	PRIEN1973
Lithium compared with placebo (following remission from a depressive episode, patients were stabilised on lithium or imipramine)	31	1	NR	Manic or depressive attack requiring hospitalisation or supplementary drugs	RR = 0.12 (0.02, 0.88)	104	PRIEN1973B
Lithium compared with placebo (participants received open-label quetiapine for 4 to 24 weeks and were randomised once euthymic)	768 δ	1	NR	One or more of the following: initiation of any other medication to treat mania/hypomania or depression, including an antipsychotic, antidepressant mood stabilising agent, or anxiolytic other than lorazepam; hospitalisation for depression and/or mania or hypomania; a YMRS or MADRS total score of at least 16 or 20, respectively; or discontinuation due to depression and/or mania or hypomania	RR = 1.37 (1.06, 1.78)	104	WEISLER2011
Lithium compared with carbamazepine (participants were euthymic and were ready to start prophylactic treatment)	399	3	RR = 0.73 (0.56, 0.95)	Recurrence of an affective episode	RR = 0.75 (0.16, 3.54)	52, 104, 130	WOLF1997, HARTONG2003, KLEINDIENST2000
Lithium compared with carbamazepine (participants were euthymic and all on stable doses of lithium)	31	1	RR = 1.25 (0.57, 2.75)	Not defined	RR = 0.47 (0.05, 4.56)	52	COXHEAD1992

Comparison	N	k	Relapse, any (95% CI)†	Definition of relapse‡	Discontinuation for any reason (95% CI)†	Length of follow-upΔ	Study ID
Lithium compared with quetiapine (participants received open-label quetiapine for 4-24 weeks and were randomised once euthymic)	768δ	1	NR	One or more of the following: initiation of any other medication to treat mania/hypomania or depression, including an antipsychotic, antidepressant mood stabilising agent, or anxiolytic other than lorazepam; hospitalisation for depression and/or mania or hypomania; a YMRS or MADRS total score of at least 16 or 20, respectively; or discontinuation due to depression and/or mania or hypomania	RR = 1.62 (1.23, 2.13)	104	WEISLER2011
Lithium compared with valproate (participants were randomised when euthymic and within 3 months of the onset of the index manic episode)	278	1	RR = 1.28 (0.86, 1.91)	A manic episode was defined as one accompanied by an MRS score of 16 or more or requiring hospitalisation. A depressive episode was defined as one requiring antidepressant use or premature discontinuation from the study because of symptoms	RR = 1.19 (0.89, 1.59)	52	BOWDEN2000
Lithium compared with valproate (participants were randomised when euthymic and after 6 months of active treatment with lithium and valproate)	60	1	RR = 1.13 (0.70, 1.82)	Patients who met criteria for mania (a total Young Mania Rating Scale score ≥20 for up to 8 weeks) or depression (a 24-item Hamilton depression scale score ≥20 for 8 weeks) were considered to have relapsed.	RR = 1.46 (0.61, 3.50)	80	CALABRESE2005C
Lithium compared with valproate (participants were randomised whilst euthymic and after 4 to 8 weeks of active treatment with lithium and valproate)	220β	1	RR = 0.85 (0.70, 1.05)	New intervention for an emerging mood episode (including drug treatment) or admission to hospital	RR = 1.02 (0.78, 1.34)	104	GEDDES2010
Lithium compared with lithium and valproate combination	220β	1	RR = 1.10 (0.87, 1.40)	New intervention for an emerging mood episode (including drug treatment) or admission to hospital	RR = 0.96 (0.74, 1.26)	104	GEDDES2010
Valproate compared with lithium and valproate combination	220β	1	RR = 1.29 (1.04, 1.61)	New intervention for an emerging mood episode (including drug treatment) or admission to hospital	RR = 0.95 (0.72, 1.24)	104	GEDDES2010

Comparison	N	k	Relapse, any (95% CI)†	Definition of relapse‡	Discontinuation for any reason (95% CI)†	Length of follow-upΔ	Study ID
Olanzapine compared with lithium	431	1	RR = 0.76 (0.56, 1.03)	DSM-IV criteria for a depressive, manic or mixed episode.	RR = 0.79 (0.68, 0.93)	52	TOHEN2005
Antipsychotics							
Aripiprazole compared with placebo (all participants taking lamotrigine)	351	1	RR = 0.69 (0.49, 0.98)	One or more of the following events: hospitalisation for a manic or mixed episode; a serious adverse event or worsening disease during the study; or discontinuation due to a lack of efficacy (as determined by the investigator). For the latter two criteria, patients also needed to have a YMRS total score ≥14 and a MADRS total score ≤16 for a relapse to a manic episode; a YMRS total score ≥14 and a MADRS total score ≥16 for a relapse to a mixed episode; and a YMRS total score ≤14 and a MADRS total score ≥16 for a relapse to a depressive episode	RR = 0.92 (0.79, 1.06)	52	CARLSON2012
Aripiprazole compared with placebo (all participants taking lithium or valproate)	337	1	RR = 0.58 (0.38, 0.91)	One or more of the following: hospitalisation for a manic, mixed or depressive episode; a serious adverse event of worsening disease accompanied by a YMRS total score ≥16 and/or a MADRS total score ≥16; discontinuation due to lack of efficacy, as determined by the investigator, accompanied by a YMRS total score ≥16 and/or a MADRS total score ≥16	RR = 0.82 (0.64, 1.05)	52	MARCUS2011
Olanzapine compared with placebo (all participants taking lithium or valproate)	68	1	RR = 0.66 (0.38, 1.15)	YMRS total score ≥15, symptomatic relapse of depression defined as an HRSD–21 total score ≥15	RR = 0.77 (0.62, 0.94)	78	TOHEN2004

Comparison	N	k	Relapse, any (95% CI)†	Definition of relapse‡	Discontinuation for any reason (95% CI)†	Length of follow-upΔ	Study ID
Olanzapine compared with placebo	278	1	RR = 0.42 (0.30, 0.59)	*1*) Fulfilled DSM-IV-TR criteria for a manic, hypomanic, mixed, or depressive episode; 2) required treatment intervention with any mood stabiliser, antipsychotic medication (other than study drug), benzodiazepine (beyond the dosage allowed), or antidepressant medication; 3) hospitalisation for any bipolar mood episode; 4) had YMRS score ≥12, MADRS score ≥12, or CGI-S scale score ≥4 at any visit	RR = 1.10 (0.66, 1.85)	78	VIETA2012
Paliperidone compared with placebo	300	1	RR = 0.83 (0.66, 1.06)	(1) YMRS ≥15 and CGI-BP-S for mania ≥4 ; YMRS ≥15, MADRS ≥16 and CGI-BP-S for depression ≥4; voluntary or involuntary hospitalisation for any mood symptoms; therapeutic intervention to prevent or treat an impending mood episode; another therapeutic measure; any other clinically relevant event suggestive of a recurrent mood episode*	RR = 1.05 (0.78, 1.42)	129	BERWAERTS2012
Quetiapine compared with placebo (participants were randomised when euthymic after 8 weeks of active treatment with quetiapine)	585	1	RR = 0.59 (0.49, 0.76)	One or more of the following: initiation of any other medication to treat mania/hypomania or depression, including an antipsychotic, antidepressant mood stabilising agent, or anxiolytic other than lorazepam; hospitalisation for depression and/or mania or hypomania; a YMRS or MADRS total score of at least 16 or 20, respectively; or discontinuation due to depression and/or mania or hypomania	RR = 1.23 (1.05, 1.43)	52	YOUNG2012

Comparison	N	k	Relapse, any (95% CI)†	Definition of relapse‡	Discontinuation for any reason (95% CI)†	Length of follow-upΔ	Study ID
Quetiapine compared with placebo (participants were randomised when euthymic after 4 to 24 weeks of active treatment with quetiapine)	808δ	1	NR	One or more of the following: initiation of any other medication to treat mania/hypomania or depression, including an antipsychotic, antidepressant mood stabilising agent, or anxiolytic other than lorazepam; hospitalisation for depression and/or mania or hypomania; a YMRS or MADRS total score of at least 20; or discontinuation due to depression and/or mania or hypomania	RR = 0.85 (0.63, 1.14)	104	WEISLER2011
Quetiapine compared with placebo (all participants were taking lithium or valproate)	1,326	2	RR = 0.38 (0.29, 0.48)	Initiation of any medication to treat mixed, manic, or depressive symptoms, including an antipsychotic, antidepressant, or mood-stabilising agent other than lithium or divalproex or an anxiolytic other than lorazepam; psychiatric hospitalisation; YMRS or MADRS total scores ≥20 at two consecutive assessments; or discontinuation from the study because of a mood event (as determined by the investigator)	RR = 1.53 (1.24, 1.89)	104	SUPPES2009, VIETA2008B
Risperidone long-acting injectable compared with placebo (participants were randomised when euthymic after 8 weeks of active treatment with risperidone)	273	1	RR = 0.69 (0.53, 0.90)	1) Fulfilled DSM-IV-TR criteria for a manic, hypomanic, mixed, or depressive episode; 2) required treatment intervention with any mood stabiliser, antipsychotic medication (other than study drug), benzodiazepine (beyond the dosage allowed), or antidepressant medication; 3) hospitalisation for any bipolar mood episode; 4) had YMRS score ≥12, MADRS score ≥12, or CGI-S scale score ≥4 at any visit	RR = 1.33 (0.82, 2.17)	78	VIETA2012

Comparison	N	k	Relapse, any (95% CI)†	Definition of relapse‡	Discontinuation for any reason (95% CI)†	Length of follow-upΔ	Study ID
Risperidone long-acting injectable compared with placebo (participants were randomised when euthymic after 3 weeks of active treatment with oral risperidone and 26 weeks of risperidone long-acting injectable)	303	1	RR = 0.63 (0.51, 0.77)	1) Fulfilled DSM-IV-TR criteria for a manic, hypomanic, mixed, or depressive episode; 2) required treatment intervention with any mood stabiliser, antipsychotic medication (other than study drug), benzodiazepine (beyond the dosage allowed), or antidepressant medication; 3) hospitalisation for any bipolar mood episode; 4) had YMRS score ≥12, MADRS score ≥12, or CGI-S scale score ≥4 at any visit	RR = 0.89 (0.61, 1.32)	104	QUIROZ2010
Risperidone long-acting injectable compared with placebo injection (all participants received treatment as usual and were euthymic as randomisation following 16 weeks of active treatment with risperidone long-acting injectable)	124	1	RR = 0.50 (0.30, 0.85)	DSM-IV-TR criteria for an acute mood episode in the setting of adequate compliance with oral TAU. Additionally, at least one of the following three conditions was satisfied: (i) Clinical worsening, with the addition of a new mood stabiliser, antidepressant or antipsychotic or a > 20% dose increase of existing oral TAU medication, and meeting the following criteria: (a) YMRS score > 15 or MADRS score > 15 and (b) CGI-BP-S score ≥ 4 or CGI-BP-C score ≥ 6 or GAF score decreased by > 10 points from baseline; (ii) hospitalisation for worsening of manic or depressive symptoms and meeting the following criteria: (a) YMRS score > 15 or MADRS score > 15 and (b) CGI-BP-S score ≥ 4 or CGI-BP-C score ≥ 6 or GAF score decreased by > 10 points from baseline; (iii) hospitalisation for worsening of manic or depressive symptoms and having significant suicidal ideation	RR = 1.27 (0.61, 2.64)	52	MACFADDEN2009

Comparison	N	k	Relapse, any (95% CI)†	Definition of relapse‡	Discontinuation for any reason (95% CI)†	Length of follow-upΔ	Study ID
Risperidone long-acting injectable in addition to treatment as usual compared with treatment as usual (all participants had rapid cycling bipolar disorder and were not in an acute episode at randomisation)	50	1	NR	Occurrence of any of the following at any study visit: (1) a YMRS score >14 or a MADRS score >15; (2) 20% or greater increase in YMRS or MADRS scores from the previous study visit for patients with a MADRS score ≥10 or a YMRS score ≥8 at the current study visit; (3) urgent care visit/referral (psychiatric hospitalisation; emergency department visit; or referral for respite care, partial hospitalisation, or intensive outpatient treatment) due to worsening mood symptoms; (4) a CGI-S score ≥4; (5) syndromal relapse (DSM-IV-TR criteria for manic, hypomanic, major depressive, or mixed episode met); (6) withdrawal from the study due to inefficacy; and (7) necessary clinical medication adjustments	RR = 1.50 (0.63, 3.59)	52	BOBO2011B
Anticonvulsants							
Oxcarbazepine compared with placebo	55	1	RR = 0.50 (0.26, 0.94)	DSM-IV-TR criteria for a manic, hypomanic, mixed or depressive episode or scoring ≥12 in the YMRS or ≥20 in the MADRS	RR = 1.12 (0.55, 2.24)	52	VIETA2008
Gabapentin compared with placebo	25	1	NR	NR	RR = 1.08 (0.51, 2.30)	52	VIETA2006
Lamotrigine compared with placebo	471	2	RR = 0.82 (0.59, 1.14)	An intervention - addition of ECT or pharmacotherapy, including antidepressants, antipsychotics, anticonvulsants/mood stabilisers, or benzodiazepines (exceeding doses of rescue medication)	RR = 1.14 (0.64, 2.06)	76, 78	CALABRESE2003, BOWDEN2003

Comparison	N	k	Relapse, any (95% CI)†	Definition of relapse‡	Discontinuation for any reason (95% CI)†	Length of follow-upΔ	Study ID
Valproate compared with placebo	281	1	RR = 0.63 (0.44, 0.90)	A manic episode was defined as one accompanied by an MRS score of 16 or more or requiring hospitalisation. A depressive episode was defined as one requiring antidepressant use or premature discontinuation from the study because of symptoms	RR = 1.02 (0.74, 1.40)	52	BOWDEN2000
Antidepressants							
Imipramine compared with placebo (all participants were taking lithium)	75	1	RR = 1.54 (0.71, 3.33)	Research diagnostic criteria for mania or major depressive disorder	RR = 0.86 (0.65, 1.13)	129	QUITKIN1981
Imipramine compared with placebo	26	1	RR = 0.75 (0.36, 1.55)	Manic or depressive attack requiring hospitalisation or supplementary drugs (that is, psychopharmacologic agents other than the patient's assigned treatment)	RR = 1.17 (0.54, 2.53)	104	PRIEN1973B
Imipramine and lithium combination compared with lithium	78[µ]	1	RR = 0.68 (0.49, 0.93)	A recurrence was declared if the clinical condition satisfied the research diagnostic criteria for definite major depressive disorder or mania and yielded a GAS rating of 60 or less.	RR[∂]= 5.81 (0.29, 117.23)	104	PRIEN1984
Imipramine and lithium combination compared with imipramine	72[µ]	1	RR = 0.62 (0.43, 0.89)	A recurrence was declared if the clinical condition satisfied the research diagnostic criteria for definite major depressive disorder or mania and yielded a GAS rating of 60 or less.	RR[∂] = 5.81 (0.29, 117.23)	104	PRIEN1984
Imipramine compared with lithium	78[µ]	1	RR = 1.47 (1.07, 2.02)	A recurrence was declared if the clinical condition satisfied the research diagnostic criteria for definite major depressive disorder or mania and yielded a GAS rating of 60 or less.	There was no discontinuation in either group.	104	PRIEN1984
Antidepressants compared with placebo	70	1	NR	NR	NR	52	GHAEMI2010

Comparison	N	k	Relapse, any (95% CI)†	Definition of relapse‡	Discontinuation for any reason (95% CI)†	Length of follow-upΔ	Study ID

Note. CI = Confidence interval; k = Number of studies; N = Sample size; NR = Not reported; RR = Relative risk.
†A relative risk (RR) of less than 1 favours the first treatment named
‡Cells containing definitions of relapse which do not meet the criteria set by the GDG have been shaded grey
ΔLength of follow-up reported in number of weeks

[β]GEDDES2010 is a three-arm trial including lithium, valproate and the combination of lithium and valproate. The overall number of participants is 330. All three comparisons have been included in this table so the number of participants has been double-counted.

[δ]WEISLER2011 is a three-arm trial including lithium, quetiapine and placebo. The overall number of participants is 1,172. All three comparisons have been included in this table so the number of participants has been double-counted.

[μ]PRIEN1984 is a three-arm trial including imipramine, lithium and the combination of imipramine and lithium. The overall number of participants is 114. All three comparisons have been included in this table so the number of participants has been double-counted.

[∂] Discontinuation due to side effects. No other reasons for discontinuation were reported.

7.4.5 Previous reviews

In making their recommendations, the GDG considered the results of several previous reviews identified through the search for evidence. These reviews were particularly useful for identifying evidence of side effects and rare events that are specific to each medication.

Other reviews confirm that lithium has the strongest evidence for long-term relapse prevention; the evidence for other pharmacological interventions is less robust and there is much uncertainty about the longer term benefits of other types of medication. Lithium is associated with a reduction of the risk of manic relapses by 38% and depressive relapse by 28% (Geddes et al., 2004) and it is the only known anti-suicidal treatment with randomised evidence of a reduction in the risk of suicide of more than 50% (Cipriani et al., 2013b). However, the benefits of lithium are restricted by adverse effects, the risk of rebound phenomena and a low therapeutic index (McKnight et al., 2012). In addition to known effects of lithium on the thyroid, the risk of hyperparathyroidism is increased and some evidence exists of a clinically substantial reduction in renal function in some patients. By contrast, the risk of end-stage renal failure remains unclear and the risk of congenital malformations is uncertain, but probably lower than previously thought.

Antipsychotic drugs are the most potent treatments in mania (Cipriani et al., 2011), and in many clinical situations, it will seem reasonable to continue them after remission from the acute episode (Yatham et al., 2013b). Unfortunately, most trials do not provide information about the relative effects of different drugs that could be used for acute treatment and continued long-term.

In terms of adverse effects, weight gain is a concern with most antipsychotics and particularly olanzapine, which is associated with a higher mean weight increase than other second generation antipsychotics (Allison et al., 1999). Recently, there has been increasing concern about the possible metabolic side effects of second generation antipsychotics including elevation of glucose, cholesterol and triglycerides. The US Federal Drugs Agency has regarded hyperglycaemia and risk of diabetes as a class effect of 'atypical' antipsychotics. The issues of whether (i) second generation antipsychotics differ in their propensity to cause metabolic side effects and (ii) the clinical significance of any such differences are both controversial. This reflects a relative lack of long-term RCTs, with metabolic data plus contradictory results in the existing literature. Much of the data are retrospective and has methodological weaknesses that include potential screening bias, failure to thoroughly assess non-pharmacological risk for diabetes and lack of randomisation, which makes it impossible to separate drug effects from non-pharmacological effects, such as lifestyle and family history, with any confidence. Most of the data concerning metabolic abnormalities in those receiving second generation antipsychotics relates to patients with schizophrenia and not bipolar disorder (Leucht et al., 2013). However, it seems that all atypical antipsychotics can, in some patients, lead to elevation of glucose and indeed this adverse effect was reported with chlorpromazine in the1950s.

Many guidelines now recommend monitoring of glucose and lipid levels for patients prescribed any antipsychotic and this is the view adopted by this guideline. It is also important to note that many people with bipolar disorder may be at high risk of developing diabetes mellitus and dyslipidaemias resulting from aspects of their lifestyle, irrespective of antipsychotic treatment.

Valproate semisodium is licensed for the treatment of mania. Despite the dramatic increase in the use of valproate in the past 2 decades (Hayes et al., 2011), limited evidence supports its efficacy in the long-term prevention of bipolar disorder (Cipriani et al., 2013d). Moreover, there is evidence that combination therapy with lithium plus valproate is more likely to prevent relapse than is monotherapy with valproate and that weight gain with valproate can continue over an entire 12-month period.

Carbamazepine is licensed for the treatment of bipolar disorder in people who are intolerant of lithium or for whom lithium is ineffective. A major complication of carbamazepine is that it can lower the plasma level of concurrently prescribed drugs, including antipsychotics. Both carbamazepine and valproate are teratogenic, being associated with an increased risk of neural tube defects. Sodium valproate is also associated with the development of a range of other major abnormalities including facial dysmorphias and distal digit hypoplasia (Holmes et al., 2001; Morrow et al., 2006; O'Brien & Gilmour-White, 2005). The monotherapy major malformation rate (MMR) for valproate was 5.9% (4.3–8.2), significantly higher than the other commonly used prophylactic agents (carbamazepine 2.3% (1.4–3.7), lamotrigine 2.1% (1.0–4.0)). The risk is thought to be greater in those prescribed >1g valproate per day versus lower doses (Omtzigt et al., 1992). It is important to note that the neural tube closes at day 30 of gestation which will usually be before a pregnancy has been confirmed; for this reason prevention is essential. In addition, there is evidence that the use of valproate is associated with a significant reduction in cognitive functioning of children born to mothers who used valproate during pregnancy (Adab et al., 2004a; Adab et al., 2004b).

Uncertainty about both short and long term efficacy of antidepressants and concerns about the potential for causing mood instability cycle mean that the question of whether to use and, if so, how long to continue, antidepressants is controversial (Sidor & McQueen, 2012). In a meta-analysis that combined data from seven trials with 350 people with bipolar disorder that were prescribed an antidepressant with or without a mood stabiliser for a minimum of 6 months, antidepressant monotherapy showed modest benefit but significantly increased manic symptoms (Ghaemi et al., 2008). As there is evidence of a clinically significant degree of differences in both efficacy and tolerability among antidepressants in unipolar disorder (Cipriani et al., 2009), antidepressants may also vary in the degree to which they cause mood elevation in people with bipolar disorder. A meta-analysis on antidepressants for acute bipolar depression reported significantly higher treatment emergent mania in patients treated with TCAs (Gijsman et al., 2004).

In summary, these reviews identified a heterogeneous group of studies that in few cases could be synthesised using meta-analysis. There is little evidence that any pharmacological intervention is superior to lithium, which remains an agent of first choice in the preventative treatment of bipolar disorder. However, 40% of patients may not respond adequately to it, so alternatives are often needed for long-term treatment in bipolar disorder (Geddes & Miklowitz, 2013). Evidence for other mood stabilisers is limited, but there is some evidence that valproate may be efficacious alone and as an adjunct to lithium.

Most evidence for other types of medication, including antipsychotics, comes from studies in which participants are discontinuing an acute treatment. These trials, usually sponsored by the manufacturer, are not fair tests of the comparator agents. Many of these trials select patients with known acute response to the investigational drug and, following a short period of mood stability, randomly assign participants to either continue the investigational drug or change treatment. In these trials, many people in the comparator group will relapse or experience discontinuation symptoms immediately. There is some evidence that olanzapine may be beneficial for long-term management. For people who have responded to it in the acute phase, there is some evidence that quetiapine may be beneficial.

All pharmacological interventions used for the long-term management of bipolar disorder are associated with serious side effects, which differ across interventions.

7.4.6 Health economics evidence

Systematic literature review

The systematic search of the economic literature undertaken for the guideline identified nine eligible studies on pharmacological interventions for the long-term management of adults with bipolar disorder (Calvert et al., 2006; Ekman et al., 2012; Fajutrao, 2009; McKendrick, 2007; NCCMH, 2006a; Revicki et al., 2005b; Soares-Weiser et al., 2007; Woodward, 2009; Woodward, 2010). Of the nine studies, five were conducted in the UK (Ekman et al., 2012; Fajutrao, 2009; McKendrick, 2007; NCCMH, 2006a; Soares-Weiser et al., 2007), while the remaining 4 studies were all conducted in the US (Calvert et al., 2006; Revicki et al., 2005c; Woodward, 2009; Woodward, 2010). References to included studies and evidence tables for all economic evaluations included in the systematic literature review are provided in Appendix 32. Completed methodology checklists of the studies are provided in Appendix 31. Economic evidence profiles of studies considered during guideline development (that is, studies that fully or partly met the applicability and quality criteria) are presented in Appendix 33.

Valproate semisodium versus lithium

Revicki and colleagues (2005c) examined the cost effectiveness of valproate semisodium versus lithium, both added to usual psychiatric care, for the maintenance

treatment of adults with bipolar I disorder, following discharge after hospitalisation for a manic or mixed episode. The economic study was conducted in the US alongside a pragmatic, multicentre clinical trial. The time horizon of the analysis was 1 year following hospital discharge. The analysis adopted a third-party payer perspective and considered hospitalisation costs, outpatient psychiatric, physician, psychologist and other mental health provider visit costs, costs of emergency room visits, costs of home health service visits and medication costs. Clinical outcomes included the number of months without DSM-IV manic or depressive symptoms, the participant functioning and quality of life measured using the mental component summary (MCS) and the physical component summary (PCS) scores of the SF-36, the Mental Health Index (MHI-17), and a questionnaire on disability days; the rate of adverse events and continuation rates were also measured. Effectiveness and resource use data were derived from the trial, and national unit costs were used. Analysis demonstrated that valproate semisodium and lithium were overall similar in terms of both clinical outcomes and total costs (no statistically significant differences were observed between the two drugs). The study is partially applicable to the UK context and has potentially serious limitations mainly due to potential conflicts of interest and also due to the relatively short time horizon (12 months) that did not allow for long-term side effects and their associated impact on costs and HRQoL to be considered.

Olanzapine versus lithium

McKendrick and colleagues (2007) explored the cost effectiveness of olanzapine versus lithium in adults with bipolar I disorder newly stabilised following response to olanzapine and lithium combination therapy for mania, in the UK. The study, which was based on decision-analytic modelling, adopted the perspective of the NHS. Cost elements included physician's time, medication, laboratory tests, hospitalisation, outpatient care, and home visits. Costs of side effects were not considered. The primary measure of outcome was the number of acute episodes experienced by the study population within the time horizon of the analysis, which was 12 months. Effectiveness data were taken from a double-blind RCT, while resource use data were based on a UK chart review and other published sources; national unit costs were used.

The total cost per person was lower for olanzapine (£3,619; 95% CI £2,941 to £4,385) compared with lithium (£4,419; 95% CI £3,537 to £5,563 - price year 2003). The number of acute episodes was also lower for olanzapine (0.58; 95% CI: 0.53 to 0.64) than for lithium (0.81; 95% CI: 0.71 to 0.91). Olanzapine thus dominated lithium, as it was less costly and more effective. Results were most sensitive to risk and length of hospitalisation for mania, the cost of hospitalisation, and the time horizon. Results of sensitivity analysis ranged from olanzapine being dominant, to an ICER of olanzapine versus lithium equalling £367 per acute episode avoided.

The study is directly applicable to the UK context. Although QALYs were not estimated, interpretation of the results was straightforward as the intervention was found to be dominant. The study is characterised by potentially serious limitations,

including potential conflicts of interest, its relatively short time horizon (12 months), as well as the lack of consideration of the impact of side effects on costs and HRQoL.

Olanzapine versus valproate semisodium versus lithium

The previous NICE guideline on bipolar disorder (NCCMH, 2006a) included a model-based economic analysis that assessed the cost effectiveness of olanzapine, valproate semisodium, lithium and no pharmacological treatment in adults with bipolar I disorder in a stable state following an acute episode (that is in a sub-acute or euthymic state) in the UK. Three sub-populations were assessed: men, women without child-bearing potential, and women with child-bearing potential. The time horizon of the analysis was 5 years. The analysis adopted the NHS perspective; costs included drug acquisition costs, costs of visits to healthcare professionals (consultant psychiatrists, senior house officers, GPs, community psychiatric nurses), laboratory testing costs, costs of treating acute episodes (hospitalisation, crisis teams, enhanced outpatient treatment and additional medication); costs of treating side effects were not considered. Three measures of outcome were used: the number of acute episodes averted; the number of days free from acute episode; and the number of QALYs gained. QALYs were estimated using vignette-based, drug-specific utility values elicited from outpatients with bipolar disorder in the US. Effectiveness data were derived from indirect comparisons of drugs using evidence from placebo-controlled double-blind RCTs. Resource use data were mainly based on expert opinion, supplemented by published data. National unit costs were utilised.

The economic analysis is only partially applicable to the NHS context, as it used exclusively utility values elicited from service users in the US rather than the general population in the UK. More importantly, it suffers from very serious limitations, as the RCTs used to make indirect comparisons across the drugs had very different study designs. This means that the method of evidence synthesis (indirect comparisons) was inappropriate and may have introduced bias in the economic analysis. Therefore, the results of this analysis were not considered when formulating recommendations.

Lamotrigine versus olanzapine versus lithium

Calvert and colleagues (2006) developed a decision-analytic model to assess the cost effectiveness of lamotrigine compared with lithium, olanzapine and 'no maintenance treatment' in adults with bipolar I disorder stabilised after resolution of a mixed or manic episode in the US. The time horizon of the analysis was 18 months. The study adopted the perspective of a direct payer and considered physician time costs, medication costs, costs of laboratory tests and hospitalisation costs; costs of side effects were not included in the analysis. Three measures of outcome were used: the number of acute episodes avoided; the number of euthymic days achieved; and the number of QALYs gained. The source of clinical effectiveness data were three placebo-controlled RCTs (BOWDEN2003, CALABRESE2003 and TOHEN2004). Resource use data were taken from published sources, clinical guidelines and a physician survey. National unit costs were used. The study is partially applicable to the UK and suffers from very serious limitations as the 3 RCTs used to make indirect comparisons across the drugs assessed in the economic analysis had different study designs, so it is possible that the

method of evidence synthesis has introduced bias in the economic analysis. Consequently the results of this analysis were not taken into account when making recommendations.

Quetiapine and quetiapine extended release compared with other pharmacological treatment options

Fajutrao and colleagues (2009) assessed the cost effectiveness of quetiapine added to a mood stabiliser (lithium or valproate) versus a mood stabiliser alone, in adults with bipolar I disorder newly stabilised with a combination of quetiapine and a mood stabiliser, from a UK NHS perspective. The study, which was based on decision-analytic modelling, had a time horizon of 2 years. Cost elements consisted of staff time (psychiatrist, SHO, GP, CPN, laboratory nurse), medication, laboratory testing, hospitalisation, crisis resolution and home treatment teams; costs of treating side effects were not included in the analysis. The primary measures of outcome were the number of acute episodes experienced during the time horizon of the analysis, the percentage of people hospitalised due to acute episodes, and the number of QALYs gained. The study utilised effectiveness data from 2 double-blind placebo-controlled RCTs. Resource use data were taken from clinical guidelines which, however, reported estimates based on expert opinion; national unit costs were used.

Quetiapine added to a mood stabiliser was found to be the dominant option as it was associated with lower total costs per person compared with mood stabiliser alone (£9,130 versus £9,637, respectively, in 2007 prices), while it was more effective in terms of all outcome measures used. Results were most sensitive to risk and length of hospitalisation, cost of hospital stay, and the acquisition cost of quetiapine. The study is directly applicable to the NICE decision-making context, but suffers from potentially serious limitations, including its short time horizon (2 years), the lack of consideration of side effects and their impact on costs and HRQoL, and potential conflicts of interest.

A very similar modelled-based study that assessed the cost effectiveness of quetiapine added to a mood stabiliser (lithium or valproate) versus a mood stabiliser alone, in adults with bipolar I disorder newly stabilised with a combination of quetiapine and a mood stabiliser in the US was conducted by Woodward and colleagues (2009). The study adopted a third-party payer perspective and used the same model structure, time horizon and effectiveness data sources as the study by Fajutrao and colleagues (2009). The study also reported that the combination of quetiapine with a mood stabiliser was the dominant option. The study is partially applicable to the UK, and suffers from the same methodological limitations as Fajutrao and colleagues (2009).

Ekman and colleagues (2012) assessed the cost effectiveness of quetiapine versus a number of pharmacological treatment options in adults with bipolar disorder (I or II) in the UK using decision-analytic modelling. Two separate analyses were undertaken: one where the study population entered the model in acute depression, and another one where the study population entered the model in remission. Both analyses had a 5-year time horizon and considered the following treatment options:

quetiapine; quetiapine added to a mood stabiliser (lithium or valproate semisodium); olanzapine; olanzapine plus lithium, with olanzapine replaced by venlafaxine in acute depression; olanzapine plus lithium, with olanzapine replaced by paroxetine in acute depression; aripiprazole that was replaced by olanzapine and venlafaxine in acute depression; and a mixed scenario where risperidone was administered in mania, venlafaxine and lithium were administered in acute depression, and olanzapine was administered as maintenance treatment.

The study adopted the NHS perspective. Costs included hospitalisation costs, costs of outpatient care, costs associated with crisis teams, staff costs (SHOs, GPs, CPNs, practice nurses, dieticians), drug acquisition costs, laboratory test costs, and costs of extrapyramidal syndrome (EPS), a side effect associated with administration of antipsychotics. Indirect costs (productivity losses) were considered in a sensitivity analysis. The measure of outcome was the QALY. Clinical effectiveness data were based on RCTs and meta-analyses of trials. Resource use data were taken from published sources, which, however, reported estimates based on expert opinion. Unit costs were taken from national sources.

As discussed in Chapter 6, the study is directly applicable to the UK context, but suffers from very serious limitations, as it appears that the methods of evidence synthesis were inappropriate and may have introduced bias in the analysis. For this reason the study was not considered further when making recommendations.

Woodward and colleagues (2010) developed a decision-analytic model to assess the cost effectiveness of quetiapine fumarate extended release (XR) added to a mood stabiliser (lithium or valproate) versus a number of other pharmacological options for the maintenance treatment of adults with stabilised bipolar I disorder in the US. The combination of quetiapine XR with a mood stabiliser was compared with a mood stabiliser alone, olanzapine, lithium, lamotrigine, aripiprazole, and no maintenance treatment. The time horizon of the analysis was 2 years. The study adopted a third-party payer perspective and considered costs associated with hospitalisation, physician's time, medication and laboratory testing; costs of side effects were not considered. A secondary analysis considered a societal perspective. The primary measures of outcomes were the number of acute episodes, the number of hospitalisations due to acute episodes, and the number of QALYs gained. Effectiveness data were based on two double-blind RCTs comparing quetiapine adjunctive to a mood stabiliser versus a mood stabiliser alone, and other RCTs identified via a non-systematic literature review. Resource use data and unit costs were based on published literature, national sources and further assumptions.

The combination of quetiapine XR and mood stabiliser was found to be the most effective option for any of the 3 outcomes considered. Its ICER versus mood stabiliser alone was $22,959/QALY (2009 prices). However, the comparisons with other interventions suffer from very serious limitations as the studies used for evidence synthesis had very different study designs, so that the indirect comparisons made across the drugs were not appropriate and may have introduced bias in the

analysis. For this reason, the study findings, with the exception of the comparison between quetiapine XR plus mood stabiliser versus mood stabiliser alone were not taken into account when making recommendations. It should also be noted that efficacy data for quetiapine XR were taken from RCTs assessing quetiapine. In any case, the study is only partially applicable to the UK context as it was conducted in the US.

Various pharmacological treatments

Soares-Weiser and colleagues (2007) used decision-analytic modelling to evaluate the cost effectiveness of a number of pharmacological treatment options for adults with stabilised bipolar I disorder in the UK; the authors reported two separate analyses, one for adults whose previous acute episode was depressive and another one for adults whose previous acute episode was manic. The following drugs were assessed in the analysis: carbamazepine, imipramine, lamotrigine, lithium, combination of lithium with imipramine, olanzapine and valproate. The time horizon of the analysis was over lifetime. The study adopted the perspective of the NHS. Costs included medication costs, laboratory testing costs, hospitalisation costs, healthcare professionals' time (psychiatric consultant, SHO, GP, CPN, practice nurse), and crisis resolution and home treatment teams; costs associated with management of side effects were not considered in the analysis. The primary measure of outcome was the QALY. Effectiveness data were taken from a systematic review and network meta-analysis. Resource use data were taken from clinical guidelines, which, nevertheless, were based on expert opinion, other published data and further assumptions; national unit costs were used.

The study is directly applicable to the NICE context, but is characterised by very serious limitations. This is because effectiveness data for the analysis were derived by a network meta-analysis of RCTs with very different study designs, so that evidence synthesis was inappropriate. Therefore this study was not further considered when formulating recommendations.

Overall conclusions from the systematic review of economic literature

The systematic economic literature review identified a number of studies that compared a variety of drugs for the long-term maintenance treatment of adults with bipolar disorder in the UK and US. Most of the studies suffered from very serious limitations, owing to the inappropriate methods that were used for evidence synthesis. According to the remaining studies, valproate semisodium and lithium were similar in terms of costs and outcomes in an analysis conducted in the US. Olanzapine was found to dominate lithium in a UK study. Quetiapine in addition to mood stabiliser (including quetiapine in XR formulation) was found to be more cost-effective than a mood stabiliser alone in a number of US and UK studies. These studies were characterised by a number of potentially serious limitations, including overall short time horizons, lack of consideration of side effects and their impact on costs and HRQoL, and potential conflicts of interest.

In general, no safe conclusions could be drawn from the results of this systematic review. It should be noted that quetiapine (but not quetiapine XR) and olanzapine are now available in generic form and therefore their acquisition costs are lower than the economic studies considered. This means that their current cost effectiveness may be higher than that reported in the studies included in the literature review, at least regarding this aspect.

Economic considerations – cost analysis of lithium provision

Introduction and rationale for the cost analysis

The cost effectiveness of pharmacological interventions for the long-term management of adults with bipolar disorder was identified by the GDG as an area with considerable resource use implications that was prioritised for economic modelling. In order to compare all relevant pharmacological treatment options in an economic analysis, a network meta-analysis of the clinical data was required to allow simultaneous inference on all drugs evaluated in trial pairwise comparisons and provide the economic model with appropriate clinical input parameters, enabling the assessment of the relative cost effectiveness of all drugs without breaking the rules of randomisation (Caldwell et al., 2005).

Nevertheless, the review of the clinical evidence in this area suggested that it was not appropriate to synthesise the available clinical data in a network meta-analysis, as there was great heterogeneity across the studies in terms of the study populations (type of bipolar disorder, phase of illness, previous and concurrent treatments received), study designs, time horizons and reported outcomes. Consequently, it was not possible to evaluate the cost effectiveness of drugs using formal economic modelling.

Clinical evidence suggests that lithium is an effective option for the prevention of relapses in the long-term management of bipolar disorder. The long-term studies on lithium were not possible to combine in a pair-wise meta-analysis, because there were differences across the RCTs in terms of study design and definitions of relapse. Given this inability to synthesise available clinical evidence in order to inform an economic model, a simple cost analysis was attempted to explore the magnitude of the costs associated with long-term treatment with lithium and the potential savings resulting from relapse prevention, and to assess whether costs associated with provision of lithium may be offset by savings from relapse prevention. Moreover, other factors that could affect the cost effectiveness of lithium were considered, including benefits of lithium that go beyond the prevention of relapses, and associated long-term side effects.

Resource use elements – cost data considered in the cost analysis

Costs associated with provision of lithium

The costs associated with provision of lithium consist of drug acquisition costs, costs of healthcare professional visits, and costs of laboratory testing. These costs were estimated for a period of 1 year of lithium administration.

The GDG estimated that the daily dosage of lithium used for the maintenance treatment of people with bipolar disorder should be in the range of 800-2000 mg daily, in order to achieve a serum lithium concentration of 0.6-0.8 mEq/L. These figures are consistent with the doses and the levels of lithium concentration that were reported in the RCTs considered in the relevant guideline systematic review. The drug acquisition cost was taken from the NHS Electronic Drug Tariff, February 2014 (NHS Business Services Authority, 2014b).

The GDG estimated that people with bipolar disorder should be typically visiting a healthcare professional nine times over 1 year (roughly at weeks 1, 2, 4, 6, 10, 14, 22, 34, 46), whether they receive long-term pharmacological treatment or not, provided that no relapse occurs. Treatment with lithium normally requires four extra visits per year. The cost analysis thus considered four lithium-specific healthcare professional visits. All four visits were assumed to be made to multidisciplinary community mental health teams (CMHTs), which consist of a variety of healthcare professionals including consultants, community nurses, social workers, occupational therapists, physiotherapists, staff providing carer support, and other types of healthcare professionals (Curtis, 2013). The unit cost of a visit to a CMHT was taken from the NHS reference costs for 2013 (Department of Health, 2013).

According to the GDG expert opinion, laboratory tests that are required specifically for people receiving long-term therapy with lithium include:

- At initiation of treatment: 3 tests of serum lithium concentration in order to establish the drug's therapeutic dose
- Over 1 year: four tests of serum lithium concentration, two tests of renal function (urea, creatinine and electrolytes); two tests of thyroid function; and two tests of calcium levels.

Table 29 shows all costs associated with lithium therapy in adults with bipolar disorder. All costs are expressed in 2014 prices, uplifted, where required, using the Hospital and Community Health Services (HCHS) pay and prices inflation index (Curtis, 2013). The inflation index for year 2014 was estimated using the average value of HCHS pay and prices indices of the previous 3 years.

Table 29: 1-year costs associated with lithium therapy in adults with bipolar disorder (2014 prices)

Cost element	Unit cost (2014)	Source	1-year cost
Lithium 800-2000 mg/day	£0.086-£0.215/day	NHS drug tariff (2014a)	£31.39-£78.48
Contacts with CMHT: 4 lithium-specific	£149 per visit	NHS ref costs (2013)	£594.00

Laboratory testing: Baseline: 3 x lithium concentration Over 1 year: 4 x lithium concentration 2 x urea, creatinine & electrolytes 2 x thyroid function 2x calcium levels	 £3.25 per test £3.25 per test £4.62 per test £19.25 per test £7.02 per test	NCCMH (2006)& Newcastle upon Tyne Hospitals NHS trust biochemistry laboratory services tariff for 2006-7	 £9.75 £13.00 £9.24 £38.50 £14.04 Sub-total: £84.53
MEAN TOTAL COST ASSOCIATED WITH LITHIUM THERAPY			£733.86

Costs associated with the management of relapses (manic or depressive)

The costs associated with the management of relapses include costs of hospitalisation, costs of management by crisis resolution and home treatment teams (CRHTTs), costs of outpatient treatment and costs of medication administered during an acute episode.

Management of treating mania – estimated resource use

The GDG expressed the opinion that all people with bipolar disorder experiencing a manic episode require hospitalisation or management by CRHTTs, which is an alternative to hospitalisation. Based on Glover and colleagues (2006) the cost analysis assumed that 77% of people with bipolar disorder in a manic episode were treated in hospital; the mean length of stay (8 weeks) was taken from relevant data from the Hospital Episode Statistics for 2012 (NHS, 2012). The remaining 23% of people with a manic episode were treated by CRHTTs for the same period as the hospital length of stay (8 weeks), which is consistent with the duration of a CRHTT intervention described in Johnson and colleagues (2005). The analysis assumed two contacts per week (Johnson et al., 2005; McCrone et al., 2009). All people in a manic episode were assumed to be treated with olanzapine at a dose of 15 mg/day.

Management of acute depression – estimated resource use

The GDG estimated that 10% of people with bipolar disorder experiencing an acute depressive episode are hospitalised or managed by CRHTTs, as an alternative to hospitalisation. Based on Glover and colleagues (2006), the cost analysis assumed that 7.7% of people with bipolar disorder in an acute depressive episode were treated in hospital; the mean length of stay (7 weeks) was taken from relevant data from the Hospital Episode Statistics for 2012 (NHS, 2012). Another 2.3% of people with an acute depressive episode were seen by CRHTTs twice per week for the same period as the hospital length of stay (7 weeks). The remaining 90% of people with bipolar disorder in an acute depressive episode were estimated to receive enhanced outpatient care comprising 4 visits to multidisciplinary CMHTs over 7 weeks. All people in an acute episode were assumed to be treated with fluoxetine 40 mg plus olanzapine 10 mg per day.

Unit costs were taken from national sources and were expressed in 2014 prices using the HCHS pay and prices inflation index (Curtis, 2013), as described earlier. Costs per

hospital bed-day were taken from the NHS reference costs (NHS, 2012), using the weighted average value of Mental Health Clusters. The unit cost per CRHTT contact was based on data reported in Curtis (2013). Drug acquisition costs were derived from the NHS Electronic Drug Tariff, February 2014 (NHS Business Services Authority, 2014a)(NHS, 2014).

In order to estimate a mean cost of relapse for people with bipolar disorder, the ratio of manic to depressive relapses is required. This was estimated by data reported in Judd and colleagues (2008b). The study reported that in 126 people with bipolar disorder who had recovered from an acute depressive or manic episode and experienced a relapse, 66 had a major depressive episode (52.4%), 26 had a manic episode (20.6%) and 34 had a mixed/cycling polarity episode (27.0%). For simplicity, the GDG advised that half of the mixed/cycling episodes should be considered manic and half should be considered depressive, resulting in a ratio of manic to depressive acute relapses 34.1:65.9.

Table 30 shows the estimated resource use, unit prices and costs associated with the management of relapses in adults with bipolar disorder and provides an estimated mean cost of relapse.

Table 30: Costs associated with the management of relapse in adults with bipolar disorder (2014 prices)

Type of management	% of people	Details on resource use	Unit cost (2014)	Weighted cost
Mania – management over 8 weeks				
Hospitalisation	77.0		£353/bed-day	£15,202
CRHTT	23.0	2 contacts /week	£201/contact	£741
Olanzapine	100.0	15 mg/day	0.08/day	£4
MEAN COST OF MANAGEMENT OF MANIA				**£15,947**
Acute depression – management over 7 weeks				
Hospitalisation	7.7		£353/bed-day	£1,330
CRHTT	2.3	2 contacts /week	£201/contact	£65
Enhanced outpatient care	90.0	4 visits to CMHT	£149/contact	£535
Fluoxetine & olanzapine	100.0	40 mg & 10 mg	£0.13/day	£7
MEAN COST OF MANAGEMENT OF ACUTE DEPRESSION				**£1,936**
Using a ratio of manic to depressive episodes 34.1:65.9 (extrapolated from Judd and colleagues (2008b):				
MEAN WEIGHTED COST OF MANAGEMENT OF RELAPSE				**£6,714**

Synthesis of lithium costs and cost-savings from relapse prevention

If the ratio of manic to depressive relapses following treatment with lithium is the same with the estimated ratio for the whole population of adults with bipolar disorder (34.1:65.9), then over 1 year the cost of lithium is offset by cost-savings owing to prevention of relapses if lithium has a number needed to treat (NNT) to prevent a relapse versus placebo £6,714/£734 = 9 at maximum (this translates to a minimum required absolute risk reduction 10.93 relapses per 100 people treated over

1 year in order for lithium to be cost neutral). This estimate (NNT=9) is independent of the baseline risk of relapse associated with placebo, as long as this risk is at least 10.93 per 100 people per year.

Evidence reviewed in this chapter suggests that lithium has a higher preventative effect for manic episodes, which are costlier to manage than acute depressive ones. This means that the weighted mean cost associated with management of relapses is lower under lithium treatment compared with the £6,714 estimate. For example, assuming a ratio of manic to depressive episodes of 27:73 for relapses occurring under lithium treatment, the cost of relapse is reduced to £5,719. In this case, and using a 1-year baseline risk of relapse with placebo of 0.35 (Judd et al., 2008; 1-year risk of relapse following full remission), lithium leads to greater cost-savings than estimated above, and its maximum NNT versus placebo in order for lithium to be cost-neutral becomes 15 (minimum absolute risk reduction 6.74 relapses per 100 people treated over 1 year). If the 1-year baseline risk of relapse is 0.20, then the NNT becomes 10 and lithium needs to prevent 9.35 extra relapses to become cost-neutral. If the 1-year baseline risk of relapse is 0.50, then the NNT becomes 24 and lithium needs to prevent only 4.13 extra relapses to be cost-neutral.

The methodology checklist and the economic evidence profile of the analysis are provided in Appendix 31 and Appendix 33, respectively.

Interpretation of the results

The NNT for lithium versus placebo in the long-term maintenance treatment varies across RCTs included in the guideline systematic review. For example, in PRIEN1973B the NNT was 3, in WEISLER2011 the NNT was 5, in DUNNER1976 was 8, and in BOWDEN2000 it reached 14. The estimated NNT for lithium to be cost-neutral is within the range of these values. As already discussed, these studies are characterised by high heterogeneity regarding their design, study populations, and definition of relapse, which may explain the wide range in the estimated NNTs.

Other considerations relating to the cost effectiveness of lithium

Although the cost analysis described in this section examined the maximum NNT for lithium to be cost-neutral, lithium does not need to be cost-neutral to be cost-effective. Lithium is cost-effective versus no pharmacological treatment (placebo) if the total net cost associated with lithium (estimated by adding the acquisition cost, extra contacts with healthcare professionals, required laboratory testing and the relapse cost-savings) divided by the total extra QALYs gained following lithium treatment (reflecting mainly improvement in HRQoL from relapse prevention minus HRQoL impairments due to side effects over time), gives a maximum ICER of £20,000-£30,000/QALY (NICE cost effectiveness threshold).

In addition to the improvement in HRQoL due to relapse prevention, lithium has also a beneficial anti-suicidal effect compared with other drugs and no treatment (Angst et al., 2005b; Cipriani et al., 2013b), which increases the QALY gains associated with lithium. Provision of lithium reduces not only suicidal behaviour,

but also deliberate self-harm as well as all-cause mortality in people with bipolar disorder (Cipriani et al., 2005), resulting in gains in life-years and improvement in HRQoL, thus in extra QALYs compared with no treatment.

Besides benefits associated with lithium therapy, lithium is also associated with side effects, the most important one being chronic kidney disease (Kripalani et al., 2009). Werneke and colleagues (2012) developed a decision-analytic model to establish whether lithium should be preferred over an anticonvulsant for the long-term maintenance treatment of adults with bipolar disorder, by examining whether the benefits of suicide and relapse prevention associated with lithium were cancelled out by the risk of end-stage renal disease. The authors conducted a systematic literature review to obtain relevant epidemiological and clinical data; various events associated with bipolar disorder and lithium therapy were considered in the analysis: occurrence of relapses and their impact on the study population, death from suicide, and the development of chronic kidney disease. Based on the results of their analysis, the authors concluded that lithium should be the treatment of choice at initiation of maintenance therapy, and should remain treatment of choice in the majority of cases in the long-term, even in the presence of long-term adverse renal effects, provided that associated risks of lithium regarding renal function were assessed, monitored, and managed.

On the other hand, chronic kidney disease incurs considerable costs at final stages of the disease: the mean annual healthcare cost of per person on dialysis in England has been crudely estimated at £29,782; the annual healthcare cost per transplant recipient has been estimated at £13,237, while the annual healthcare cost per person not on renal replacement therapy at £259, all figures uplifted to 2014 prices (Kerr et al., 2012). This translated in an average annual cost per person recorded with a diagnosis of chronic kidney disease in the Quality and Outcomes Framework for General Practice (QOF) approximately £877. According to Werneke and colleagues (2012), the risk of chronic kidney disease after 20 years of lithium treatment is 4.3%. From these figures, it can be inferred that the mean weighted total extra cost per person with bipolar disorder treated with lithium after 20 years of lithium treatment is roughly 0.043 x £877 = £38; the actual cost is between the two extremes of 0.043 x £259 = £11 (if none of the people that have developed chronic kidney disease is under dialysis or has undergone transplantation) and 0.043 x £29,782 = £1,281 (if all people that have developed chronic kidney disease after 20 years are under dialysis). This cost is lower than the mean cost of management of an acute depressive episode, and it is not expected to drive the cost effectiveness of lithium in the long-term management of bipolar disorder. Moreover, it is expected the people receiving lithium treatment who develop chronic kidney disease are discontinued from lithium before their condition progresses to renal failure, so that most of them don't incur costs associated with dialysis or transplantation.

Conclusively, although it was not possible to conduct formal economic modelling to assess the cost effectiveness of lithium in the long-term management of adults with bipolar disorder, the simple cost analysis undertaken for this guideline and other

available evidence on the risks and benefits associated with long-term lithium therapy suggest that lithium is likely to be a cost-effective maintenance treatment option for this population.

Other drugs, such as antipsychotics, that are available in generic form are expected to have overall similar to lithium acquisition and laboratory testing costs and lower healthcare visit costs (as lithium requires extra visits for monitoring); thus the total costs associated with their provision is expected to be lower than the cost of lithium. If such drugs have effectiveness in preventing relapses that is comparable to that of lithium, they should also be similarly cost-effective to lithium versus no treatment. It should be noted though, that different drugs have different side effect profiles that may affect their relative cost effectiveness.

Comparison of the cost effectiveness across all drugs that are relevant to the long-term treatment of adults with bipolar disorder was not possible, as discussed, and requires direct comparisons of the clinical effectiveness of drugs and subsequent network meta-analysis of RCTs of similar design. This is an area for future research.

Overall conclusions from economic evidence

The existing economic literature review reports conflicting results and is characterised by serious limitations. Formal economic modelling was not possible to conduct due to the heterogeneity characterising the RCTs included in the guideline systematic review that did not allow synthesis of the available clinical evidence. A simple cost analysis undertaken for this guideline together with available evidence on the risks and benefits associated with long-term lithium therapy suggests that lithium is likely to be a cost-effective maintenance treatment option for this population. Other drugs that are available in generic form and therefore have similar drug acquisition costs with lithium are likely to be cost-effective too, if their effectiveness in relapse prevention is similar to that of lithium.

Economic evidence statement

The existing economic literature review reports conflicting results and is characterised by serious limitations. The guideline cost analysis indicates that lithium may be a cost-effective and potentially cost-saving treatment option for the long-term management of adults with bipolar disorder. This analysis is partially applicable to the guideline and has potentially serious limitations.

7.5 LINKING EVIDENCE TO RECOMMENDATIONS

7.5.1 Relative value placed on the outcomes considered

The GDG determined that long-term management for bipolar disorder should focus on the prevention of new episodes. Effective long-term interventions would also improve functioning and quality of life, but the GDG recognised that these would relate to proximal goals of treatment and that clinical trials would be unlikely to find robust evidence of comparative effectiveness for secondary outcomes in any case. For this reason, they determined that the critical outcomes include relapse and

hospitalisation. Additionally, the GDG identified specific side effects that may be associated with different medications and concluded that individuals may assign different value to these harms. They identified discontinuation for any reason as a critical outcome and determined that clinicians and service users would need to discuss potential harms before initiating any intervention. Because the GDG sought to make recommendations about the long-term use of medication, only studies with controlled follow-up of 1 year of greater were included.

7.5.2 Trade-off between clinical benefits and harms

There is some evidence that mood clinics may help prevent relapse and hospitalisation for adults, and that these services may be no more expensive than alternative services. Furthermore, working closely with specialists may be the best strategy to minimise potential harms.

With regard to medication, because bipolar disorder is characterised by relapsing episodes of mania and depression that may be severely impairing and associated with significant harm (including suicide), the GDG concluded that many people are willing to tolerate important side effects of interventions that prevent the recurrence of acute episodes. Potential side effects vary across medications, and service users who have used particular medications for the treatment of acute episodes or for previous long-term management may have insight into the likely efficacy and side effects of those medications. For these reasons, the GDG determined that any long-term strategy should reflect individual treatment history and preferences.

All drugs used in the treatment of bipolar disorder, either acute or long-term, are associated with common side effects. Some of these side effects are clearly dose related and can be minimised by careful dose titration at the start of treatment. With respect to long-term maintenance treatment it is important to review of the need for each drug after an acute episode has resolved, and if needed to review the dose of that drug. Some side effects can only be detected by blood tests.

Lithium has the longest history of use for long-term management, and it may be associated with adverse effects, such as increased risk of reduced urinary concentrating ability (extent to which the kidneys are able to manufacture urine rich in dissolved wastes yet low in water), hormone disorders, and weight gain (McKnight 2012). Lithium has a narrow therapeutic range meaning that there is a small difference between a dose that is too low to be effective and one that is known to be toxic. Toxic levels of lithium cause a range of symptoms including confusion, neurological disorders, cardiac arrhythmias (irregular heartbeat), and, as levels rise, further convulsions, coma and death. A number of commonly used medicines can increase the concentration in the blood and potentially lead to lithium toxicity. The National Patient Safety Agency (NPSA) produce a patient information pack[26] that contains clear advice for patients about how to use lithium safely and the GDG thought it important that a copy of this pack, or equivalent, should be given to

[26] http://www.nrls.npsa.nhs.uk/alerts/?entryID45=65426

everyone who is prescribed lithium. Rapid discontinuation is associated with a high risk of relapse. However, other medications may also be associated with serious adverse events. For these reasons, the GDG determined that service users should discuss their treatment options with a qualified health service professional before initiating any treatment. Regular blood tests are required to ensure that the concentration of lithium in the blood is likely to be effective and safe. When developing recommendations in this area, the GDG used its clinical judgement and expert knowledge. It is common clinical practice to keep the plasma level below 0.8 mmol per litre initially and only increase this if response is suboptimal. Higher levels are associated with more side effects, including renal side effects, so are used with caution.

Treatment with lithium and possibly valproate should not be stopped abruptly as this has been associated with early relapse. Both drugs, but particularly valproate, are human teratogens, meaning that they may harm an unborn child.

Antipsychotic medication is associated with weight gain and some of the drugs can also adversely affect blood glucose levels and lipid profiles. It is therefore important that people who take antipsychotic medication, particularly in the long term have their body weight monitored as well as their blood pressure, glucose and lipid profile. Antipsychotic drugs can also, rarely, prolong the QTc interval in the heart precipitating potentially dangerous disturbances of cardiac rhythm (arrhythmias).

There is no evidence that high-dose or combined antipsychotic are associated with a better outcome than using a single antipsychotic drug and it is likely that such strategies increase side effects.

Care should be taken, particularly during episodes of mania, to ensure that *pro re nata* (PRN *as required) antipsychotics do not inadvertently lead to exposure to high-dose antipsychotics.

When the GDG formulated recommendations their aim was to optimise the use of medication in people with bipolar disorder because that is how to maximise the efficacy of treatment while screening for side effects. The detailed side-effect profile for each medicine can be found in its Summary of Product Characteristics (SPCs; accessible at www.medicines.co.uk). The management of common side effects is beyond the scope of this guideline and standard texts should be consulted. People with bipolar disorder should always be given information about the treatment options available and where possible, actively participate in treatment choice. The GDG also judged that, to avoid any confusion, where appropriate, the wording of recommendations about using antipsychotic medication should be consistent with the NICE guideline on *Psychosis and Schizophrenia in Adults* (NICE, 2014).

In addition, the GDG considered the benefit of recommending that clinicians should discuss with service users their use of alcohol, tobacco, prescription and non-prescription medication and illicit drugs, particularly their possible interference with

prescribed medication and psychological interventions. When considering what amendments, if any, needed to be made for treatment in older adults, the GDG judged that when prescribing to older people, clinicians needed to take into account the impact of psychotropic medication on their cognitive functioning; this might mean prescribing at lower doses, minimising drug interactions and ensuring medical comorbidities have been identified and treated.

Finally, the GDG judged that because of the risks associated with the use of valproate, it should not be prescribed in primary care. Lithium should also not be started in primary care except under shared-care arrangements.

7.5.3 Trade-off between net health benefits and resource use

The GDG felt that no safe conclusions could be made on the relative cost effectiveness of drugs from the existing economic evidence. Formal economic modelling was not possible to conduct due to limitations in evidence synthesis of efficacy data, but the simple cost analysis undertaken for this guideline suggested that lithium is likely to be a cost-effective (and likely cost-saving) drug in the maintenance treatment of adults with bipolar disorder. Using the findings of this analysis, the GDG noticed that the cost of treating relapses is the most substantial component of the total costs associated with management of bipolar disorder, in particular if people with bipolar disorder receive long-term treatment with drugs available in generic form, which incur low acquisition costs. The GDG expressed the opinion that other medications for long-term management that are available in generic form and have thus similar acquisition and monitoring costs to lithium are likely to be cost-effective if their effectiveness in preventing acute episodes is similar to (or higher than) that of lithium. In general, among drugs with similar acquisition costs, those that are most effective in preventing acute episodes are likely to be most cost-effective as well.

7.5.4 Quality of the evidence

For safety and ethical reasons, the GDG determined that it could be clinically inappropriate to conduct placebo-controlled double-blind studies of long-term pharmacological interventions. Therefore, the GDG considered evidence from single- and double-blind trials. For this reason, results of long-term studies may be more susceptible to bias than studies of interventions for acute episodes, but the critical outcomes (relapse, hospitalisation, discontinuation) may be less influenced by bias than subjective patient reported outcomes. The GDG considered that reporting bias may lead to overestimates of efficacy, but it was not clear if particular interventions were more vulnerable to reporting bias than others.

Only interventions reporting critical outcomes in the populations of interest were considered, so none of the evidence was indirect. However, many studies of pharmacological interventions with long-term outcomes include only people who responded to a drug during an acute episode. These studies generally find that discontinuing treatment is associated with increased relapse, but they do not

provide evidence of comparative effectiveness because the populations are not interchangeable between studies. The GDG determined that studies of new medications for people who are euthymic would provide the best evidence of comparativeness effectiveness for long-term treatment. The GDG also decided to consider evidence from discontinuation studies, however these were interpreted cautiously.

Evidence for several interventions was very imprecise because there were few trials with few participants; for this reason, the GDG decided not to recommend some interventions that have been evaluated for long-term management. Few interventions have been compared with placebo for long-term management, but some have been compared with lithium. The GDG considered evidence that lithium prevents new episodes and reduces hospitalisation, and they considered that little evidence suggests any monotherapies are superior to lithium. They concluded that advances in drug treatment remain quite modest. There are relatively few long-term trials in bipolar disorder; and the best available evidence suggests that lithium is efficacious and that the combination of lithium and valproate may be more efficacious than valproate alone. Studies comparing lithium with valproate had mixed results, but the GDG concluded that it suggests valproate may be more efficacious than placebo, and switching to olanzapine may be efficacious for people who respond to an acute antipsychotic. For these reasons, the GDG determined that lithium has the strongest empirical support as an intervention for the long-term management of bipolar disorder and that it remains the initial treatment of choice for people who can tolerate it. For people who do not respond to lithium, the GDG identified valproate combined with lithium, valproate alone, and olanzapine as empirically supported treatment options. Additionally, quetiapine may reduce relapse for people who respond during the acute phase, and the GDG noted that quetiapine is recommended for the treatment of both manic and depressive episodes. For these reasons, the GDG identified continued quetiapine as a potentially useful option for people with a history of its use.

7.5.5 Other considerations

People with bipolar disorder often have a history of taking medication for acute episodes and for long-term management. The expert consensus of the GDG was that experience of previous episodes and response to previous treatment should inform decisions about the treatment of new episodes. Furthermore, the likelihood of specific side effects varies across medications, and the GDG determined that treatment decisions should consider the values and preferences of service users in relation to potential side effects.

Bipolar disorder and its treatment may have important effects on carers, children, and other people in a service user's life. Furthermore, other people may be able to provide information and insight into a service user's history of illness and treatment. For these reasons, the GDG determined that such people should be involved in decision-making about pharmacological interventions in cases where this is appropriate and desired by the service user. There was no evidence that

pharmacological interventions inhibit or are inhibited by psychological interventions for service users or their families, and the GDG considered that these could be offered simultaneously.

There was little evidence about the efficacy of second-line treatments (that is, when an initial treatment has failed due to discontinuation or non-response). The GDG considered that many people in trials about long-term management have experienced multiple episodes and have tried multiple interventions, and they determined that other interventions used for initial treatment should be considered if an initial intervention was ineffective or not tolerated.

The GDG did not find any trials that suggest efficacy or tolerability varies across gender, ethnicity or disability. People of different size and age may require different doses of medications, and clinicians should consult manufacturer and BNF guidelines for specific advice.

The GDG considered trials with controlled follow-up at least 1 year after initiating treatment. Discontinuation studies suggest that withdrawing pharmacological interventions after recovery from an acute episode is associated with increased relapse and discontinuation symptoms, and the same may be true for people who have taken medication for a longer time. For these reasons, the expert consensus of the GDG was that discontinuation should be agreed and planned whenever possible, and that medication should normally be discontinuing slowly. Because service users will be at increased risk of relapse following discontinuation, clinicians should monitor symptoms carefully during this period for 2 years following the end of treatment.

Because of the prolonged, often lifelong, nature of bipolar disorder, the GDG also considered other aspects of long-term management, including recovery and the services that would support people during and after resolution of symptoms. There was evidence suggesting that services providing coordinated, evidence-based psychological and pharmacological interventions specifically for bipolar disorder are likely to reduce relapse and hospitalisation. The GDG was unable to make a recommendation for clinical practice based on one trial, therefore they decided to make a recommendation for research. Given the lack of evidence relating to specific services for people with bipolar disorder, the GDG took the view that the recovery-oriented services recommended for people with psychosis and schizophrenia would be appropriate for people with bipolar disorder and therefore adapted recommendations from *Psychosis and Schizophrenia in Adults* (NICE, 2014) where appropriate. This includes continued access to an early intervention in psychosis service, referral to a specialist integrated community-based team, or intensive case management for people likely to disengage from services, and access to supported employment programmes. The GDG judged, that as with people with psychosis or schizophrenia, that people with bipolar disorder who have responded to treatment and remain relatively stable should have the option of returning to primary care for

further management. The GDG also developed a recommendation by consensus for primary care professionals working with people with bipolar disorder.

Table 35 contains the original recommendations from *Psychosis and Schizophrenia in Adults* (NICE, 2014) in column 1 and the associated review question(s) and evidence base in column 2. The adapted/incorporated recommendations are shown in column 3 and reasons for doing so are provided in column 4.

Table 31: Recommendations incorporated or adapted from another NICE guideline

Original recommendation from *Psychosis and Schizophrenia Update* (NICE, 2014)	Review question and evidence base of existing recommendation	Recommendation following adaptation/ incorporation for this guideline	Reasons for adaptation/ incorporation
1.5.1.1 Continue treatment and care in early intervention in psychosis services or refer the person to a specialist integrated community-based team. This team should: • offer the full range of psychological, pharmacological, social and occupational interventions recommended in this guideline • be competent to provide all interventions offered • place emphasis on engagement rather than 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 Service user experience in adult mental health (NICE clinical guidance 136).	Review question: Are early detection programmes effective in reducing duration of untreated psychosis and improving pathways to care for people with first episode psychosis? Evidence base: Early detection programmes effective in reducing duration of untreated psychosis and improving pathways to care for people with first episode psychosis (based on 13 quantitative studies). See Chapter 12 of *Psychosis and Schizophrenia in Adults* (NCCMH, 2014)	1.9.1 Continue treatment and care in early intervention in psychosis services or refer the person to a specialist integrated community-based team. This team should: • offer the full range of psychological, pharmacological, social and occupational interventions recommended in this guideline • be competent to provide all interventions offered • place emphasis on engagement rather than 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	Given the lack of evidence relating to specific services for people with bipolar disorder, the GDG took the view that the recovery-oriented services recommended for people with psychosis and schizophrenia would be appropriate for people with bipolar disorder and therefore incorporated this recommendation from the *Psychosis and Schizophrenia in Adults* guideline.
1.5.1.2 Consider intensive case management for people with	Review question: For adults with psychosis and	1.9.2 Consider intensive case management for people with bipolar	Given the lack of evidence relating to specific services for people with

psychosis or schizophrenia who are likely to disengage from treatment or services.	schizophrenia, what are the benefits and/or potential harms of intensive case management compared with non-intensive case management or standard treatment? Evidence base: The benefits and/or potential harms of intensive case management compared with non-intensive case management or standard treatment (based on a review of 38 quantitative studies). See Chapter 12 of *Psychosis and Schizophrenia in Adults* (NCCMH, 2014).	disorder who are likely to disengage from treatment or services	bipolar disorder, the GDG took the view that the recovery-oriented services recommended for people with psychosis and schizophrenia would be appropriate for people with bipolar disorder and therefore adapted this recommendation from the *Psychosis and Schizophrenia in Adults* guideline. The GDG adapted this recommendation by changing 'psychosis or schizophrenia' to 'bipolar disorder'.
1.5.2.1 Offer people with psychosis or schizophrenia whose symptoms have responded effectively to treatment and remain stable the option to return to primary care for further management. If a service user wishes to do this, record this in their notes and coordinate transfer of responsibilities through the care programme approach.	Updated from previous version of guideline. Evidence base: Based on expert opinion of the GDG after reviewing previous versions of guideline. See Chapter 12 of *Psychosis and Schizophrenia in Adults* (NCCMH, 2014)	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.	The GDG judged, that as with people with psychosis or schizophrenia, that people with bipolar disorder who have responded to treatment and remain relatively stable should have the option of returning to primary care for further management. The GDG adapted this recommendation by changing 'psychosis or schizophrenia' to 'bipolar disorder'.
1.5.8.1 Offer supported employment programmes to people with psychosis or schizophrenia 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.	Review question: For adults with psychosis and schizophrenia, what are the benefits and/or potential harms of vocational rehabilitation interventions compared with treatment as usual or another interventions? Evidence base: The benefits and/or potential harms of vocational rehabilitation	1.9.6 Offer supported employment programmes to people with bipolar disorder 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	Given the lack of evidence relating to specific recovery-oriented services for people with bipolar disorder, the GDG took the view that recovery-oriented services recommended for people with psychosis and schizophrenia would be appropriate for people with bipolar disorder and therefore adapted this recommendation from the *Psychosis and Schizophrenia in Adults* guideline.

	interventions compared with treatment as usual or another interventions (based on a review of 18 quantitative studies). See Chapter 13 of *Psychosis and Schizophrenia in Adults* (NCCMH, 2014).		
1.3.6.7 Discuss the use of alcohol, tobacco, prescription and non-prescription medication and illicit drugs with the service user, and carer if appropriate. Discuss their possible interference with the therapeutic effects of prescribed medication and psychological treatments.	Review questions: For people with an acute exacerbation or recurrence of schizophrenia, what are the benefits and downsides of continuous oral antipsychotic drug treatment when compared with another oral antipsychotic drug (when administered within the recommended dose range [BNF 54])? For people with an acute exacerbation or recurrence of schizophrenia, what are the benefits and downsides of psychological/psychosocial interventions when compared with alternative management strategies? Evidence base: Based on expert opinion of the GDG after reviewing the evidence for pharmacological and psychological interventions. See Chapter 9 and 10 of *Psychosis and Schizophrenia in Adults* (NCCMH, 2014)	1.10.1 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.	The GDG judged, that as with people with psychosis or schizophrenia, that people with bipolar disorder have high levels of alcohol and drug use. Given similar review questions about pharmacological and psychological interventions, the GDG decided to incorporate this recommendation from the *Psychosis and Schizophrenia in Adults* guideline.
1.3.6.1 Before starting antipsychotic medication, undertake and record the following baseline investigations:	Review question: For people with an acute exacerbation or recurrence of	1.10.3 Before starting antipsychotic medication, measure and record the person's:	The GDG agreed that side effects from antipsychotics will occur in the same way in people with bipolar disorder

• weight (plotted on a chart) • waist circumference • pulse and blood pressure • fasting blood glucose, glycosylated haemoglobin (HbA1c), blood lipid profile and prolactin levels • assessment of any movement disorders • assessment of nutritional status, diet and level of physical activity.	schizophrenia, what are the benefits and downsides of continuous oral antipsychotic drug treatment when compared with another oral antipsychotic drug (when administered within the recommended dose range [BNF 54])? Evidence base: Based on expert opinion of the GDG after reviewing the evidence for pharmacological interventions. See Chapter 10 of *Psychosis and Schizophrenia in Adults* (NCCMH, 2014)	• weight or BMI • pulse • blood pressure • fasting blood glucose or HbA1c • blood lipid profile.	as they do in people with schizophrenia. As most of the antipsychotic literature will be found in trials of people with psychosis and schizophrenia, the GDG judged it would be appropriate to adapt this recommendation from the *Psychosis and Schizophrenia in Adults* guideline. The recommendation was adapted by the GDG based on their expertise: they judged that it was important to measure BMI as well as weight to indicate risk of developing a physical health problem, but that assessment of movement disorders and nutritional status, diet and level of physical activity were not indicated for most people with bipolar disorder before starting an antipsychotic.
1.3.6.2 Before starting antipsychotic medication, offer the person with psychosis or schizophrenia an electrocardiogram (ECG) if: • specified in the summary of product characteristics (SPC) • a physical examination has identified specific cardiovascular risk (such as diagnosis of high blood pressure) • there is a personal history of cardiovascular disease **or** • the service user is being admitted as an inpatient.	Review question: For people with an acute exacerbation or recurrence of schizophrenia, what are the benefits and downsides of continuous oral antipsychotic drug treatment when compared with another oral antipsychotic drug (when administered within the recommended dose range [BNF 54])? Evidence base: Based on expert opinion of the GDG after reviewing the evidence for pharmacological interventions. See Chapter 10 of *Psychosis and Schizophrenia in Adults* (NCCMH,	1.10.4 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.	The GDG agreed that antipsychotics will have the same metabolic effects on people with bipolar disorder as they do on people with schizophrenia. As most of the antipsychotic literature will be found in trials of people with psychosis and schizophrenia, the GDG judged it would be appropriate to adapt this recommendation from the *Psychosis and Schizophrenia in Adults* guideline. The recommendation was adapted by the GDG based on their expertise: they judged that a family history of cardiovascular disease, a history of sudden collapse, or other cardiovascular risk factors such as

	2014)		cardiac arrhythmia was more relevant to a population with bipolar disorder.
1.3.6.3 Treatment with antipsychotic medication should be considered an explicit individual therapeutic trial. Include 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 oral antipsychotic medication, and the expected time for a change in symptoms and appearance of side effects. • At the start of treatment give a dose at the lower end of the licensed range and slowly titrate upwards within the dose range given in the British national formulary (BNF) or SPC. • Justify and record reasons for dosages outside the range given in the BNF or SPC. • Record the rationale for continuing, changing or stopping medication, and the effects of such changes. • Carry out a trial of the	Review question: For people with an acute exacerbation or recurrence of schizophrenia, what are the benefits and downsides of continuous oral antipsychotic drug treatment when compared with another oral antipsychotic drug (when administered within the recommended dose range [BNF 54])? Evidence base: Based on expert opinion of the GDG after reviewing the evidence for pharmacological interventions. See Chapter 10 of *Psychosis and Schizophrenia in Adults* (NCCMH, 2014)	1.10.5 Treatment with antipsychotic medication should be considered an explicit individual therapeutic trial. Include 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.	The GDG agreed that antipsychotics will have the same metabolic effects on people with bipolar disorder as they do on people with schizophrenia. As most of the antipsychotic literature will be found in trials of people with psychosis and schizophrenia, the GDG judged it would be appropriate to adapt this recommendation from the *Psychosis and Schizophrenia in Adults* guideline. The recommendation was adapted by the GDG based on their expertise: they judged that it should be made clear that doses above the maximum recommended in the BNF and SPC should not be routinely prescribed in people with bipolar disorder. Given that antipsychotics are recommended for mania as well as in the long-term, and therefore might be used for shorter periods, the GDG omitted the bullet point specifying the trial should last for 4-6 weeks.

medication at optimum dosage for 4–6 weeks.			
1.3.6.4 Monitor and record the following regularly and systematically throughout treatment, but especially during titration: • response to treatment, including changes in symptoms and behaviour • side effects of treatment, taking into account overlap between certain side effects and clinical features of schizophrenia (for example, the overlap between akathisia and agitation or anxiety) and impact on functioning • the emergence of movement disorders • weight, weekly for the first 6 weeks, then at 12 weeks, at 1 year and then annually (plotted on a chart) • waist circumference annually (plotted on a chart) • pulse and blood pressure at 12 weeks, at 1 year and then annually • fasting blood glucose, HbA1c and blood lipid	Review question: For people with an acute exacerbation or recurrence of schizophrenia, what are the benefits and downsides of continuous oral antipsychotic drug treatment when compared with another oral antipsychotic drug (when administered within the recommended dose range [BNF 54])? Evidence base: Based on expert opinion of the GDG after reviewing the evidence for pharmacological interventions. See Chapter 10 of *Psychosis and Schizophrenia in Adults* (NCCMH, 2014)	1.10.6 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 functioning • the emergence of movement disorders • adherence.	The GDG agreed that antipsychotics will have the same metabolic effects on people with bipolar disorder as they do on people with schizophrenia. As most of the antipsychotic literature will be found in trials of people with psychosis and schizophrenia, the GDG judged it would be appropriate to adapt this recommendation from the *Psychosis and Schizophrenia in Adults* guideline. The recommendation was adapted by the GDG based on their expertise. The GDG made a separate recommendation about what should be included in an annual physical health check, therefore they omitted that weight, pulse and blood pressure, fasting blood glucose, HbA1c and blood lipid levels should be measured at 1 year in this recommendation. Overall physical health was also omitted because it would be covered by the annual physical health check.

levels at 12 weeks, at 1 year and then annually • adherence • overall physical health.			
1.3.6.5 The secondary care team should maintain responsibility for monitoring service users' physical health and the effects 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.	Review question: For people with an acute exacerbation or recurrence of schizophrenia, what are the benefits and downsides of continuous oral antipsychotic drug treatment when compared with another oral antipsychotic drug (when administered within the recommended dose range [BNF 54])? Evidence base: Based on expert opinion of the GDG after reviewing the evidence for pharmacological interventions. See Chapter 10 of *Psychosis and Schizophrenia in Adults* (NCCMH, 2014)	1.10.7 The secondary care team should maintain responsibility for monitoring the efficacy and tolerability of antipsychotic medication until the person's condition has stabilised.	The GDG judged that the issues relating to use of medication are similar in people with any severe mental illness. When reviewing the *Psychosis and Schizophrenia in Adults* guideline for related recommendations about antipsychotic use, the GDG judged that this recommendation was relevant to people with bipolar disorder. The GDG made a separate recommendation about shared care and an annual physical health check, therefore they omitted the stipulation that the secondary care team should maintain responsibility for monitoring physical health and the effects of antipsychotic medication for at least the first 12 months.
1.3.6.8 'As required' (p.r.n.) prescriptions of antipsychotic medication should be made as described in recommendation 1.3.6.3. Review clinical indications, frequency of administration, therapeutic benefits and side effects each week or as appropriate. Check whether 'p.r.n.' prescriptions have led to a dosage above the maximum specified in the BNF or SPC.	Review question: For people with an acute exacerbation or recurrence of schizophrenia, what are the benefits and downsides of continuous oral antipsychotic drug treatment when compared with another oral antipsychotic drug (when administered within the recommended dose range [BNF 54])? Evidence base:	1.10.9 'As required' (p.r.n.) prescriptions of antipsychotic medication should be made as described in recommendation 1.10.3. 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	The GDG agreed that antipsychotics will have the same metabolic effects on people with bipolar disorder as they do on people with schizophrenia. As most of the antipsychotic literature will be found in trials of people with psychosis and schizophrenia, the GDG judged it would be appropriate to adapt this recommendation from the *Psychosis and Schizophrenia in Adults* guideline. The recommendation was adapted by the

	Based on expert opinion of the GDG after reviewing the evidence for pharmacological interventions. See Chapter 10 of *Psychosis and Schizophrenia in Adults* (NCCMH, 2014)	SPC.	GDG based on their expertise. They judged that minor changes were needed to improve clarity.
1.3.6.10 Do not initiate regular combined antipsychotic medication, except for short periods (for example, when changing medication).	Review question: For people with schizophrenia whose illness has not responded adequately to clozapine treatment, is augmentation of clozapine with another antipsychotic associated with an enhanced therapeutic response? Evidence base: Augmentation of clozapine with another antipsychotic in people with schizophrenia whose illness has not responded adequately to clozapine treatment (based on one quantitative study). See Chapter 10 of *Psychosis and Schizophrenia in Adults* (NCCMH, 2014)	1.10.10 Do not start regular combined antipsychotic medication, except for short periods (for example, when changing medication).	The GDG agreed that antipsychotics will have the same metabolic effects on people with bipolar disorder as they do on people with schizophrenia. As most of the antipsychotic literature will be found in trials of people with psychosis and schizophrenia, the GDG judged it would be appropriate to adapt this recommendation from the *Psychosis and Schizophrenia in Adults* guideline. Minor changes were made to the recommendation in line with the latest NICE style guide.

1

7.6 RECOMMENDATIONS

7.6.1 Clinical practice recommendations

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

Discussing long-term treatment

7.6.1.1 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 stopping medication for an acute episode
- the potential benefits and risks of long-term medication and the need for monitoring
- 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 [hyperlink to be added for final publication], and ensure there is enough time to discuss options and concerns.

Pharmacological interventions

7.6.1.2 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.

7.6.1.3 Offer lithium as a first-line, long-term pharmacological treatment for bipolar disorder and:

- if lithium is ineffective, consider adding valproate[27]
- if lithium is poorly tolerated, consider valproate or olanzapine 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.

7.6.1.4 Before stopping medication, discuss with the person how to recognise early signs of relapse and what to do if symptoms recur.

7.6.1.5 If stopping medication, do so gradually (see recommendations 7.6.1.7-7.6.1.37) and monitor the person for signs of relapse.

7.6.1.6 Continue monitoring symptoms, mood and mental state for 2 years after stopping medication. This may be undertaken in primary care (see recommendation 7.6.1.40).

How to use medication

7.6.1.7 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. [28]

7.6.1.8 When offering psychotropic medication to older people, take into account its impact on cognitive functioning in older people and:

- be aware of the need to use medication at lower doses
- be alert to the increased risk of drug interactions
- be aware of the negative impact that anticholinergic medication, or drugs with anticholinergic activity, can have on cognitive function
- ensure that medical comorbidities have been recognised and treated.

Using antipsychotic medication

Starting antipsychotic medication

7.6.1.9 Before starting antipsychotic medication, measure and record the person's:

- weight or BMI
- pulse
- blood pressure
- fasting blood glucose or HbA_{1c}

[27] Although its use is common in UK clinical practice, at the time of publication (September 2014), sodium valproate 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. Semi-sodium valproate is licensed for this indication if the person responded to treatment for mania.

[28] From Psychosis and schizophrenia in adults (NICE clinical guideline 178).

- blood lipid profile. [29]

7.6.1.10 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. [30]

7.6.1.11 Treatment with antipsychotic medication should be considered an explicit individual therapeutic trial. Include 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.[31]

Monitoring antipsychotic medication

7.6.1.12 Monitor and record the following during dose titration and then regularly and systematically throughout treatment:

- pulse and blood pressure after each dose change
- weight or BMI weekly for the first 6 weeks, then at 12 weeks
- blood glucose or HbA_{1c} and blood lipid profile at 12 weeks
- response to treatment, including changes in symptoms and behaviour
- side effects and their impact on functioning
- the emergence of movement disorders
- adherence. [32]

[29] Adapted from Psychosis and schizophrenia in adults (NICE clinical guideline 178).
[30] Adapted from Psychosis and schizophrenia in adults (NICE clinical guideline 178).
[31] Adapted from Psychosis and schizophrenia in adults (NICE clinical guideline 178).
[32] Adapted from Psychosis and schizophrenia in adults (NICE clinical guideline 178).

7.6.1.13 The secondary care team should maintain responsibility for monitoring the efficacy and tolerability of antipsychotic medication until the person's condition has stabilised. [33]

7.6.1.14 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.

7.6.1.15 'As required' (p.r.n.) prescriptions of antipsychotic medication should be made as described in recommendation 7.6.1.9. 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. [34]

7.6.1.16 Do not start regular combined antipsychotic medication, except for short periods (for example, when changing medication). [35]

Using lithium for long-term treatment

Starting lithium

7.6.1.17 When starting lithium as long-term treatment:

- 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 the information they need to take lithium safely, for example the National Patient Safety Agency's information on lithium or a locally developed equivalent
- establish a shared-care arrangement with the person's GP for prescribing lithium and monitoring adverse effects.

7.6.1.18 Measure serum lithium levels 1 week after starting lithium and 1 week after every dose change, and weekly until the levels are stable. Aim to maintain serum lithium level between 0.6 and 0.8 mmol per litre in people being prescribed lithium for the first time.

7.6.1.19 Consider maintaining serum 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.

[33] Adapted from Psychosis and schizophrenia in adults (NICE clinical guideline 178).
[34] Adapted from Psychosis and schizophrenia in adults (NICE clinical guideline 178).
[35] From Psychosis and schizophrenia in adults (NICE clinical guideline 178).

7.6.1.20 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.

7.6.1.21 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 closely.

Monitoring lithium

7.6.1.22 Measure the person's serum lithium level every 6 months.

7.6.1.23 Consider measuring serum lithium levels every 3 months for:

- older people
- people taking drugs that interact with lithium
- people who are at risk of renal, thyroid or other complications
- people who have poor symptom control
- people with poor adherence.

7.6.1.24 Measure the person's weight or BMI and arrange tests for urea and electrolytes including calcium, eGFR and thyroid function every 6 months, and more often if there is evidence of impaired renal function.

7.6.1.25 Monitor lithium dose and blood serum levels more frequently if urea and creatinine levels become elevated or eGFR declines over 2 or more tests, and assess the rate of deterioration of renal function.

7.6.1.26 When discussing whether to continue lithium, take into account clinical efficacy, other risk factors for renal impairment, and degree of renal impairment; if needed seek advice from a renal specialist and a clinician with expertise in managing bipolar disorder.

7.6.1.27 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.

Stopping lithium

7.6.1.28 Lithium should be stopped gradually over at least 4 weeks, and preferably up to 3 months, even if the person has been started on another antimanic drug.

7.6.1.29 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 for long-term treatment

Starting valproate

7.6.1.30 When starting valproate as long-term treatment, measure the person's weight or BMI and carry out a full blood count and liver function tests.

7.6.1.31 Do not offer valproate to women of childbearing potential.

7.6.1.32 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 or blood dyscrasia is detected.

7.6.1.33 When prescribing valproate, be aware of its interactions with other anticonvulsants (particularly carbamazepine and lamotrigine) and with olanzapine and smoking.

Monitoring valproate

7.6.1.34 Do not routinely measure valproate blood levels unless there is evidence of ineffectiveness, poor adherence or toxicity.

7.6.1.35 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.

7.6.1.36 Be aware of the need for more careful monitoring of sedation, tremor and gait disturbance in older people.

Stopping valproate

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

Promoting recovery and return to primary care

General principles

7.6.1.38 Continue treatment and care in early intervention in psychosis services or refer the person to a specialist integrated community-based team. This team should:

- offer the full range of psychological, pharmacological, social and occupational interventions recommended in this guideline
- be competent to provide all interventions offered
- place emphasis on engagement rather than 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.[36]

[36] From Psychosis and schizophrenia in adults (NICE clinical guideline 178).

7.6.1.39 Consider intensive case management for people with bipolar disorder who are likely to disengage from treatment or services.[37]

Return to primary care

7.6.1.40 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.[38]

7.6.1.41 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 review date, frequency and nature of monitoring for effectiveness and adverse effects, and what should happen in the event of a relapse.

7.6.1.42 Review the need for a meeting with the person's GP before discharge and transfer.

Employment, education and occupational activities

7.6.1.43 Offer supported employment programmes to people with bipolar disorder 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.[39]

Managing bipolar disorder in primary care

7.6.1.44 When working with people with bipolar disorder in primary care:

- engage with and develop an ongoing relationship with them
- 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.

7.6.1.45 Do not start lithium in primary care to treat bipolar disorder, except under shared-care arrangements.

7.6.1.46 Do not start valproate in primary care to treat bipolar disorder.

[37] Adapted from Psychosis and schizophrenia in adults (NICE clinical guideline 178).
[38] Adapted from Psychosis and schizophrenia in adults (NICE clinical guideline 178).
[39] Adapted from Psychosis and schizophrenia in adults (NICE clinical guideline 178).

7.6.1.47 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
- 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.

7.6.2 Research recommendations

7.6.2.1 What is the clinical and cost effectiveness of a specialised collaborative care service for people admitted to hospital with bipolar disorder versus treatment as usual delivered by generic care services?

7.6.2.2 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?

7.6.2.3 What is the clinical and cost effectiveness of communication technologies for people with bipolar disorder versus treatment as usual?

8 PSYCHOLOGICAL AND PSYCHOSOCIAL INTERVENTIONS FOR ACUTE EPISODES AND LONG-TERM MANAGEMENT IN ADULTS

8.1 INTRODUCTION

Background

Individual case reports of psychotherapy for bipolar disorder - then known as manic depression - date to the early 1900s (Abraham, 1927), and a randomised trial of a psychological intervention for increasing adherence to medication was published in 1984 (Cochran, 1984). However, most formal evaluations of talking therapies have been conducted in the last 15 years. Published trials of structured psychological interventions often focus on self-management and relapse prevention strategies, and these are typically provided as an adjunct to pharmacotherapy. There have been no studies of structured psychological therapy in the absence of drug treatment despite high rates of medication non-adherence. Structured psychological interventions are based on psychological models of mood disorders in which links between thoughts, feelings and behaviour are regarded as helping establish stable, normal mood and restore social and other functioning. Some key common features of structured psychological interventions include providing information, developing coping strategies to deal with symptoms, identifying signs of relapse, developing an emergency plan for acute crises and having a staying well plan. Research has focussed on delivering psychological interventions for individuals who are in remission or those who are acutely depressed. Psychological therapy has also been delivered to mixed groups combining euthymic patients and those in an acute episode, but these studies may be difficult to interpret if results are not presented separately. There have been no studies evaluating psychological interventions for mania or hypomania.

Definitions

Cognitive behavioural therapy

Cognitive models of bipolar disorder suggest that dysfunctional thoughts and beliefs may be triggered by both positive and negative life events and influence mood and behaviour (Newman et al, 2003). Cognitive behavioural therapy (CBT; Lam et al., 2010; Meyer & Hautzinger, 2012) is a form of talking therapy that focuses on the role thinking and behaviour has on emotions, and how they reciprocally influence each other. CBT for bipolar disorder typically consists of 12 to 20 individual sessions over a period of 6 months.

Group psychoeducation

Group psychoeducation (Castle et al., 2010; Colom et al., 2003b) is a relatively intensive intervention in which the patient attends weekly group sessions lasting from 90 minutes to 2 hours for up to 21 weeks. Each group session is designed to provide information on a key aspect of bipolar disorder with time allocated for group discussion on the chosen topic. The rationale for these groups is that by learning more about the symptoms, treatment and coping strategies relevant to bipolar disorder, service users will become more skilled in self-managing their condition.

Family-focused therapy

Family-focused therapy (Miklowitz et al., 2003) is a psychoeducational programme for individual families based on behavioural family therapy principles (Falloon et al., 1993), which have previously been applied effectively in the treatment of people with schizophrenia. In family-focused therapy the service user and family members are offered 21 sessions over a 9-month period. Therapy has three phases beginning with psychoeducation and relapse prevention followed by work on improving family communication and, finally, developing problem solving skills for both service user and family.

Self-management training groups

Self-management training groups are typically offered in a group format and facilitated by individuals with personal experience of bipolar disorder. They are informed by both cognitive therapy approaches and by a focus on relapse prevention (Copeland, 1994). Sessions have been delivered in a variety of ways from single intensive weekend courses to weekly group sessions. The focus of self-management training is for service users to learn more about how to avoid relapses by sharing coping skills in the group setting and developing relapse avoidance plans that are used after the group sessions are completed.

Relapse prevention/individual psychoeducation

Relapse prevention is informed by previous work in psychosis on coping strategy enhancement (Lobban et al., 2010; Perry et al., 1999). These approaches involve clinicians teaching service users to detect early changes in mood and to apply helpful strategies to avoid these early changes escalating in full episodes of mania or depression. Service users are typically offered six to 12 sessions over a period of 4 to 6 months. Enhanced relapse prevention (Lobban et al., 2010) has a stronger emphasis on facilitating self-management coping approaches (teaching the service user to use psychological techniques to manage their mood changes) in addition to accessing additional service support.

Interpersonal and social rhythm therapy

People with bipolar disorder often experience disrupted sleep patterns, and the circadian instability and appraisal model suggests that they are particularly sensitive

to disturbances of 24 hour circadian rhythms, which trigger mood disturbances that themselves cause further circadian effect (Goodwin & Jamison, 2007).

Interpersonal and social rhythm therapy (Frank et al., 2005) is based on interpersonal therapy (Klerman et al., 1984b) but adapted for bipolar disorder to try to help people develop more stable social rhythms. It focuses on two areas: (1) supporting service users to discuss experiences of change and loss associated with their bipolar disorder and how to deal with them; and (2) helping service users to learn to monitor their patterns of sleep and activity and stabilise these where required. Interpersonal and social rhythm therapy is an intensive psychological intervention of 39 to 40 individual therapy sessions over a period of 2 years.

8.1.1 Clinical review protocol

The review protocol summary, including the review questions, can be found in Table 32 (a complete list of review questions and protocols can be found in Appendix 7; further information about the search strategy can be found in Appendix 8).

Table 32: Clinical review protocol summary for the review of psychological interventions

Topic	Interventions
Review question(s)	*Mania* RQ 4.1: For adults with bipolar disorder, what are the relative benefits and harms of psychological and psychosocial interventions for mania, hypomania, and mixed episodes; RQ 4.2: For adults with bipolar disorder, what are the relative benefits and harms of combined psychological and pharmacological interventions for mania, hypomania, and mixed episodes; *Depression* RQ 4.3: For adults with bipolar disorder, what are the relative benefits and harms of psychological and psychosocial interventions for depression; RQ 4.4: For adults with bipolar disorder, what are the relative benefits and harms of combined psychological and pharmacological interventions for depression; *Long-term management* RQ 4.5: For adults with bipolar disorder, what are the relative benefits and harms of psychological and psychosocial interventions for long-term management; RQ 4.6: For adults with bipolar disorder, what are the relative benefits and harms of combined psychological and pharmacological interventions for long-term management; What amendments, if any, need to be made for (i) particular cultural or minority ethnic groups, (ii) gender?

Sub-question(s)	Does the effectiveness of treatment vary: 1. For RQ 6.4 to RQ 6.11: For people taking a mood stabiliser (e.g. lithium or valproate) and people not taking a mood stabiliser; 2. For RQ 6.12 to RQ 6.15: For people whose most-recent episode was depressive and people whose most-recent episode was manic; 3. For people with Bipolar I and Bipolar II; 4. For adults (18 to 64) and older adults (65+).
Objectives	To estimate the efficacy of interventions to treat depression.
Criteria for considering studies for the review	
• Intervention	RQ 4.1 to RQ 4.6: All psychological and psychosocial interventions (e.g. cognitive behavioural therapy), all combined psychological with (licensed) pharmacological interventions.
• Comparator	Wait-list, placebo, and other interventions.
• Types of participants	Adults (18+) with bipolar disorder. Special consideration will be given to the groups above.
• Outcomes	**FOR PEOPLE IN AN ACUTE EPISODE** **1)** Change in symptoms of depression **2)** Change in symptoms of mania **3)** Response (50% reduction or greater) **4)** Discontinuation **5)** Quality of life **6)** Psychosocial functioning **FOR PEOPLE WHO ARE EUTHYMIC AT BASELINE** **1)** Relapse **2)** Discontinuation **3)** Hospitalisation **4)** Quality of life **5)** Psychosocial functioning
• Time	The main analysis will include outcomes at the end of treatment. For interventions the GDG considers recommending based on post-treatment results, additional analyses will be conducted for further follow-up data.
• Study design	Randomised controlled trials (RCTs) and cluster RCTs with a parallel group design. We will exclude quasi-RCTs, such as trials in which allocation is determined by alternation or date of birth.
• Study setting	Primary, secondary, tertiary, health and social care

8.1.2 Studies considered[40]

Fifty-five trials of psychological and psychosocial interventions met the inclusion criteria for this review: BALL2006 (Ball et al., 2006), BARROS2012 (De Barros Pellegrinelli et al., 2012; De Barros Pellegrinelli et al., 2013), BAUER2006a (Bauer et al., 2006a; Bauer et al., 2006b), BERNHARD2009 (Bernhard, 2009), BORDBAR2009 (Bordbar, 2009), CASTLE2010 (Castle et al., 2007; Castle et al., 2010), CLARKIN1998 (Clarkin et al., 1998), COCHRAN1984 (Cochran, 1984), COLOM2003a (Colom et al., 2003b), COLOM2003b (Colom et al., 2003a; Colom et al., 2009; Miklowitz, 2009), COSTA2012 (Costa et al., 2012), DIJK2013 (Van Dijk et al., 2013), DOGAN2003

[40]Here and elsewhere in the guideline, each study considered for review is referred to by a study ID in capital letters (primary author and date of study).

(Dogan & Sabanciogullari, 2003), DSOUZA2010 (D'Souza et al., 2010), EKER2012 (Eker & Harkin, 2012), FAGIOLINI2009 (Fagiolini et al., 2009; Kupfer et al., 2009), FRANK1999a (Frank et al., 2005; Frank et al., 1999), GENT1991 (Van Gent & Zwart, 1991), GLICK1993 (Clarkin et al., 1990; Glick et al., 1991; Glick et al., 1993; Glick et al., 1985; Glick et al., 1990; Haas et al., 1988; Spencer et al., 1988), GOMES2011 (Gomes et al., 2011), JAVADPOUR2013 (Javadpour et al., 2013), JONES2013 (Jones et al., 2013), KESSING2013 (Kessing et al., 2013), KILBOURNE2008 (Kilbourne et al., 2008), KILBOURNE2012 (Kilbourne et al., 2012), LAHERA2013 (Lahera et al., 2013), LAM2000 (Lam et al., 2000), LAM2003 (Lam et al., 2005a; Lam et al., 2003), LOBBAN2010 (Lobban et al., 2010), MADIGAN2012 (Madigan et al., 2012), MEYER2012 (Meyer & Hautzinger, 2012), MIKLOWITZ2000 (Miklowitz et al., 2003; Miklowitz et al., 2000; Richards & Miklowitz, 2002), MIKLOWITZ2007b (Miklowitz et al., 2007a; Miklowitz et al., 2007b), MILLER2004 (Miller et al., 2004; Solomon et al., 2008; Uebelacker et al., 2006), PARIKH2012 (Parikh et al., 2012), PERICH2013 (Perich et al., 2013), PERLICK2010 (Perlick et al., 2010), PERRY1999 (Perry et al., 1999), PROUDFOOT2012 (Proudfoot et al., 2012), REA2003 (Rea et al., 2003), REINARES2008 (Reinares et al., 2008; Reinares et al., 2004), SAJATOVIC2009 (Sajatovic et al., 2009), SCHMITZ2002 (Schmitz et al., 2002), SCHWANNAUER2007 (Schwannauer, 2007), SCOTT2001 (Scott et al., 2001), SCOTT2006 (Lam, 2006; Scott et al., 2006), SIMON2005 (Simon et al., 2005), SMITH2011 (Smith et al., 2011b), SWARTZ2012 (Swartz et al., 2012), TODD2012 (Todd et al., 2012), TORRENT2013 (Torrent et al., 2013), WEISS2007 (Weiss et al., 2007), WEISS2009 (Weiss et al., 2009), WILLIAMS2008 (Williams et al., 2008), ZARETSKY2008 (Zaretsky et al., 2008). 47 trials

A further five trials were excluded; three because a minority of participants had bipolar disorder and it was not possible to obtain disaggregated data: JACKSON2008 (Jackson et al., 2008), PICKETTSCHENK2008 (Pickett-Schenk et al., 2008) and STARING2010 (Staring et al., 2010); one because on closer inspection it did not appear to be randomised: COSTA2011 (Costa et al., 2011); and one because the GDG determined it was not relevant to the UK: DASHTBOZORGI2009 (Dashtbozorgi et al., 2009).

Two ongoing studies were also identified: PRASKO2013 (Prasko et al., 2013) and GINDRE2009 (Gindre et al., 2009).

Of the 55 included studies, four were unpublished (BERNHARD2009, TODD2012, JONES2013, SCHWANNAUER2007) and the other 51 were published between 1984 and 2013. Seven were not included in the meta-analysis because the authors did not report useable outcomes, which remained unavailable after contacting authors: CLARKIN1998, BARROS2012, EKER2012, FAGIOLINI2009, GLICK1993, PARIKH2012, and WEISS2007.

Study characteristics

Included studies randomised 6,010 participants, ranging from 19 to 441 per study (a summary of study characteristics can be found in Appendix 23). Studies were

conducted in North America (k = 22), England and Ireland (k = 12), Europe (k = 11), Australia (k = 5), Brazil (k = 3), and Iran (k = 2). Participants were recruited from an outpatient (k = 23) or inpatient setting (k = 12), GP practice (k = 2), community mental health team (k = 2), or via advertising combined with referral (k = 16). In 52 studies a diagnostic interview was used to establish the presence of a bipolar disorder, in one study participants themselves reported if they had a bipolar disorder, another confirmed the diagnosis through a mood questionnaire, while one study only reported that bipolar disorder was an inclusion criteria.

The median of mean age of participants was 40 years (range of 26 to 55 years), 58% were female and 81% had bipolar I disorder. Four studies included participants in a depressed episode at baseline (MIKLOWITZ2007b, SCHMITZ2002, SWARTZ2012, DIJK2013), six studies had a mix of participants in depressed or manic episode (BAUER2006a, CLARKIN1998, FRANK1999a, GLICK1993, MILLER2004, SAJATOVIC2009) and 32 studies included euthymic participants. Twelve studies (FAGIOLINI2009, KILBOURNE2012, KILBOURNE2008, MIKLOWITZ2000, PERLICK2010, PROUDFOOT2012, SCOTT2001, SCOTT2006, SIMON2005, TODD2012, WEISS2009, WEISS2007) included a mix of euthymic and symptomatic participants at baseline, while two (PROUDFOOT2012, TODD2012) provided disaggregated data.

8.1.3 Clinical evidence review

Evidence from each important outcome and overall quality of evidence are presented in Appendices Appendix 23 toAppendix 26.

Risk of bias

No trials were at high risk of bias for sequence generation (not truly random), however, the method of randomisation was unclear (not reported) in 15 trials. Allocation concealment was unclear in 25 trials and low risk in 30 trials. All trials were at high risk of bias for blinding for participants and providers *per se*. Nine trials had no assessors and 31 reporting assessor-rated outcomes used a blind assessor and were at low risk of bias for blinding, but eight studies did not have blind assessors, which was a reason for a high risk of bias. For six studies, blinding of assessors remained unclear. For incomplete outcome data, almost half (k = 25) of the trials were at low risk of bias and the other half (k = 23) were at high risk of bias because of the high amount of dropouts or because dropouts were excluded from the analyses.

There was a risk of outcome reporting bias in 22 trials. Only 11 studies were prospectively registered, but 23 others were assessed to be at low risk of bias because authors provided missing data or confirmed that all outcomes were published. Risk of publication bias could not be assessed by means of funnel plots because of the small number of studies per intervention.

Overall quality of the evidence

Most evidence was of low or very low quality. Nearly all results were downgraded at least one level owing to imprecision because the analyses included few participants or events, and/or the boundaries of the confidence interval (CI) crossed the decision-making threshold. Also, risk of bias in studies and reporting bias had a negative influence on some of the outcomes. Some outcomes were also downgraded for inconsistency when there was evidence of statistical heterogeneity.

Post-treatment data were mostly of low to very low quality. Only relapse data on individual interventions, hospitalisation data on collaborative care and discontinuation on interpersonal and social rhythm therapy were of moderate quality.

Studies also reported controlled comparisons at follow-up, but most outcomes were of very low quality, except for most hospitalisation and relapse outcomes with regards to the comparisons of individual and group psychological interventions, and family psychoeducation with treatment as usual.

Effects of interventions

Across nine comparisons, results of the meta-analyses suggest that psychological interventions may be associated with symptomatic improvement, reduced relapse and hospitalisation. The majority of these moderate to low quality outcomes are summarised per comparison and presented in Table 33 (post-treatment) and Table 34 (follow-up), and additional outcomes are presented in Appendix 26. Reasons for downgrading are given per outcome in the tables.[41]

Individual psychological interventions

The search identified RCTs of face-to-face psychoeducation and interactive online psychoeducation (DOGAN2003, JAVADPOUR2013, LOBBAN2010, PERRY1999, PROUDFOOT2012, SMITH2011, TODD2012), CBT (BALL2006, JONES2013, LAM2000, LAM2003, MIKLOWITZ2007b, SCOTT2001, SCOTT2006, ZARETSKY2008) and medication adherence therapy (COCHRAN1984). Eleven trials started with euthymic participants at baseline, and four had a mix of participants in an acute episode and euthymic (PROUDFOOT2012, SCOTT2001, SCOTT2006, TODD2012).

At post-treatment, seven trials (N = 637) reported low quality evidence that individual psychological interventions when compared with treatment as usual, produced a small effect in symptoms of depression (see Table 33). Six trials (N = 365) reported moderate quality evidence that individual psychological interventions reduced the risk of relapse. One trial with few events was inconclusive regarding the risk of hospitalisation.

At follow-up, seven trials (N = 446) reported moderate quality evidence that individual psychological interventions were associated with a long-term reduction

[41] a Risk of bias, b Inconsistency, c Indirectness, d Imprecision, e Publication/Reporting Bias.

in the risk of relapse (see Table 34). In three studies (N = 214) there was a reduction in the risk of hospitalisations, but the estimate was imprecise.

One study (N = 76) compared individual CBT with supportive therapy for depression (MEYER2012). At follow-up, there was very low quality evidence favouring supportive therapy for symptoms, but the effect on relapse was not conclusive (see Table 34).

Group psychological interventions

The search identified trials of group interventions including psychoeducation, (CASTLE2010, COLOM2003A, COLOM2003B, SAJATOVIC2009, TORRENT2013) CBT (BERNHARD2009, COSTA2012, GOMES2011), mindfulness (PERICH2013, WILLIAMS2008), social cognition and interaction training (LAHERA2013), and dialectical behaviour therapy (DIJK2013). Interventions were compared with treatment as usual, except for two studies that compared psychoeducation with attention control (COLOM2003A, COLOM2003B). In ten trials, participants were euthymic at baseline (BERNHARD2009, CASTLE2010, COLOM2003A, COLOM2003B, COSTA2012, GOMES2011, LAHERA2013, PERICH2013, TORRENT2013, WILLIAMS2008) and two studies included participants experiencing an acute episode (SAJATOVIC2009, DIJK2013).

Eight trials (N = 423) reported very low quality evidence of a small effect on depression outcomes (see Table 33). Furthermore, the two studies comparing psychoeducation with attention control (N = 170) found a reduction in depression and mania relapses. In three trials (N = 205) the effect estimate on the number of hospitalisation was very imprecise.

Long-term results in five studies (N = 333) reported low quality evidence of a reduction in depression relapses (Table 34). Also, four studies (N = 274) reported a reduction of relapses into mixed episodes. However, the effect on depression symptoms and hospitalisation was inconclusive.

Family psychoeducation

Two trials included an intervention on psychoeducation for service users and their family members (DSOUZA2010, MILLER2004) and in five trials psychoeducation was only for family members (BORDBAR2009, MADIGAN2012, PERLICK2010, REINARES2008, GENT1991). Five trials started with euthymic participants at baseline (BORDBAR2009, DSOUZA2010, MADIGAN2012, REINARES2008, GENT1991), one trial had a mix of participants in an acute episode and euthymic (PERLICK2010) and another included only participants in an acute episode (MILLER2004).

In comparison with treatment as usual, one trial (N = 43) found low quality evidence of medium effect in depression symptoms favouring family psychoeducation at post-treatment (see Table 33).

At follow-up, three trials (N = 228) reported low quality evidence of a reduction in the risk of relapse (see Table 34). One trial (N = 113) reported a reduction in the risk of mania relapses, but the effect on depression relapses was inconclusive. One study (N = 57) reported a very large effect on reduction of the number of hospitalisations, but effect estimates were imprecise with only nine events in the study.

Family-focused therapy

Trials of family-focused therapy included participants who were euthymic (REA2003), either in an acute episode and euthymic (MIKLOWITZ2000), only depressed (MIKLOWITZ2007b) or in any type of episode (MILLER2004).

Post-treatment data were of low quality. One study (N = 79) found a medium effect favouring family-focused therapy when compared with treatment as usual on depression symptoms (see Table 33). Furthermore, a study (N = 53) comparing family-focused therapy with psychoeducation found little difference with regard to relapse, but the estimate was imprecise.

The follow-up evidence was of very low quality and found little difference in effects on depression symptoms, relapse and response, but the estimates were imprecise (see Table 34). The evidence suggested family-focused therapy reduced the risk of hospitalisation.

Interpersonal and social rhythm therapy

There were three trials of interpersonal and social rhythm therapy with participants in an acute episode at baseline (FRANK1999a, MIKLOWITZ2007b, SWARTZ2012). At post-treatment, very low quality from one study was inconclusive with regard to symptoms of depression, relapse and response (see Table 33). At follow-up, one trial (N = 41) reported that interpersonal and social rhythm therapy reduced the risk of relapse, but the results were imprecise (see Table 34).

Collaborative care

Two trials of collaborative care started with euthymic participants (BAUER2006a, KESSING2013) and three trials recruited participants in an acute episode (KILBOURNE2012, KILBOURNE2008, SIMON2005).

In comparison with treatment as usual, two trials (N = 123) reported low quality evidence of a small effect favouring collaborative care in depression and mania symptoms at post-treatment, but the effect estimate was imprecise (see Table 33). One trial (N = 234) found no difference in the risk of relapse. However, two trials (N = 572) reported moderate quality evidence suggesting collaborative care reduced the risk of hospitalisation at post-treatment. At follow-up, there was very low quality evidence from one trial suggesting a medium effect favouring collaborative care on symptoms of depression (see Table 34).

Integrated group therapy and group drug counselling

One study (N = 61) included euthymic or depressed participants and compared integrated group therapy with group drug counselling (WEISS2009). Based on very low quality evidence, there was no conclusive evidence of difference between groups at post-treatment (see Table 33) or follow-up (see Table 34).

Integrated cognitive and interpersonal therapy

One trial compared a group of participants that were randomised to integrated cognitive and interpersonal therapy or treatment as usual (SCHWANNAUER2007). Participants in the intervention group could choose to follow individual or group integrated cognitive and interpersonal therapy. Outcome data were presented for the whole intervention group versus treatment as usual.

The trial reported low quality evidence of a medium effect favouring the intervention on depression symptoms at post-treatment (see Table 33).

Table 33: Outcomes at post-treatment

Outcome	Effect size (95% CI)	Heterogeneity: Chi² (p value); I²	Time (weeks)	Quality (GRADE)
1. Individual psychological intervention versus treatment as usual (TAU)				
Depression symptoms	SMD = -0.23 (-0.41, -0.05)	8.55 (P = 0.29); 18%	6-26	Low [a e]
Hospitalisation	RR = 0.14 (0.01, 2.53)	N/A	6	Low [d e]
Relapse	RR = 0.66 (0.48, 0.92)	2.50 (P = 0.78); 0%	6-26	Moderate [d]
Response	RR = 0.71 (0.46, 1.07)	N/A	26	Very Low [d e]
2. Group psychological intervention versus TAU				
Depression symptoms	SMD = -0.24 (-0.64, 0.16)	25.65 (P = 0.0006); 73%	8-52	Very Low [a b d e]
Hospitalisation	RR = 0.45 (0.10, 2.09)	3.94 (P = 0.14); 49%	14-21	Low [d]
Relapse (any)	RR = 0.48 (0.22, 1.04)	2.42 (P = 0.12); 59%	21	Low [d]
Relapse (depression)	RR = 0.39 (0.19, 0.78)	0.45 (P = 0.50); 0%	21	Low [d]
Relapse (mania)	RR = 0.48 (0.28, 0.82)	0.80 (P = 0.37); 0%	21	Low [d]
3. Family psychoeducation versus TAU				
Depression symptoms	SMD = -0.73 (-1.35, -0.10)	N/A	14	Low [d e]
4. Family -focused therapy versus control				
Depression symptoms	SMD = -0.40 (-0.80, 0.00)	N/A	39	Low [a d]
Relapse	RR = 0.89 (0.52, 1.54)	N/A	39	Low [d]
Hospitalisation	RR = 0.71 (0.33, 1.52)	N/A	39	Low [d]
5. CBT versus active control				
Depression symptoms	SMD = 0.41 (0.12, 0.70)	N/A	39	Low [d e]
Relapse	RR = 0.60 (0.34, 1.05)	N/A	39	Low [d e]
6. Interpersonal and social rhythm therapy versus active control				
Depression symptoms	SMD = 0.44 (-0.34, 1.22)	N/A	12	Very Low [a d]
Relapse	RR = 1.55 (0.63, 3.84)	N/A	123	Very Low [a d]
Response	RR = 0.98 (0.60, 1.60)	N/A	12	Very Low [a d]
7. Collaborative care versus TAU				
Depression symptoms	SMD = -0.22 (-0.63, 0.19)	1.32 (P = 0.25); 24%	26-30	Low [a d e]
Hospitalisation	RR = 0.68 (0.49, 0.94)	0.13 (P = 0.72); 0%	52-130	Moderate [d]
Relapse	RR = 0.99 (0.84, 1.17)	N/A	52	Low [d e]
8. Integrated group therapy versus drug counselling (group)				
Depression symptoms	SMD = -0.35 (-0.85, 0.16)	N/A	12	Very Low [c d e]
9. Integrated cognitive and interpersonal therapy versus TAU				
Depression	SMD = -0.64 (-1.19, -	N/A	20	Low [d]

symptoms	0.09)			
[a] Risk of bias, [b] Inconsistency, [c] Indirectness, [d] Imprecision, [e] Publication/Reporting Bias)				

Table 34: Outcomes at follow-up

Outcome	Effect size (95% CI)	Heterogeneity: Chi² (p value); I²	Time (weeks)	Quality (GRADE)
1. Individual psychological intervention versus TAU				
Depression symptoms	SMD = -0.21 (-0.43, 0.01)	6.85 (P = 0.23); 27%	26-52	Low [a d]
Hospitalisation	RR = 0.63 (0.38, 1.02)	2.19 (P = 0.35); 9%	32-52	Low [d]
Relapse	RR = 0.74 (0.63, 0.87)	5.78 (P = 0.57); 0%	32-78	Moderate [d]
Response	RR = 0.46 (0.21, 1.02)	N/A	52	Very Low [a d e]
2. Group psychological intervention versus TAU				
Depression symptoms	SMD = 0.22 (-0.05, 0.49)	0.95 (P = 0.62); 0%	52-61	Very Low [a d e]
Hospitalisation	RR = 0.48 (0.16, 1.45)	2.30 (P = 0.13); 56%	78-124	Very Low [b d e]
Relapse (any)	RR = 0.86 (0.61, 1.20)	21.46 (P = 0.0003); 81%	52-124	Very Low [b d e]
Relapse (depression)	RR = 0.62 (0.45, 0.88)	7.12 (P = 0.13); 44%	52-124	Low [b d]
Relapse (mixed episode)	RR = 0.48 (0.30, 0.77)	2.38 (P = 0.50); 0%	52-124	Low [b d]
3. Family psychoeducation versus TAU				
Depression symptoms	SMD = -0.15 (-0.69, 0.39)	N/A	60	Very Low [a d e]
Hospitalisation	RR = 0.05 (0.00, 0.83)	N/A	60	Low [d]
Relapse (any)	RR = 0.52 (0.32, 0.84)	2.61 (P = 0.27); 23%	52-65	Low [d e]
Relapse (depression)	RR = 0.73 (0.44, 1.21)	N/A	65	Low [d e]
Relapse (mania)	RR = 0.35 (0.15, 0.85)	N/A	65	Low [d]
Response	RR = 0.67 (0.34, 1.32)	N/A	121	Very Low [a d e]
4. Family-focused therapy versus (active) control				
Depression symptoms	SMD = -0.10 (-0.56, 0.36)	N/A	52	Very Low [a d e]
Relapse	RR = 0.67 (0.34, 1.30)	N/A	52	Very Low [a d e]
Response	RR = 1.15 (0.68, 1.94)	N/A	121	Very Low [a d e]
Hospitalisation	RR = 0.24 (0.08, 0.74)	N/A	104	Very Low [a d]
5. CBT versus supportive therapy				
Depression symptoms	SMD = 0.49 (0.04, 0.94)	N/A	143	Very Low [d e]
Relapse	RR = 1.13 (0.81, 1.58)	N/A	143	Very Low [d e]
6. Interpersonal and social rhythm therapy versus active control				
Response (depression)	RR = 0.73 (0.50, 1.07)	N/A	52	Very Low [a d e]
7. Collaborative care versus TAU				
Depression symptoms	SMD = -0.56 (-1.06, -0.07)	N/A	52	Very Low [a d]
8. Integrated group therapy versus drug counselling (group)				
Depression	SMD = 0.11 (-0.39, 0.61)	N/A	26	Very Low [c d e]

symptoms				
[a] Risk of bias, [b] Inconsistency, [c] Indirectness, [d] Imprecision, [e] Publication/Reporting Bias)				

8.1.4 Health economics evidence

Systematic literature review

The systematic search of the economic literature undertaken for the guideline identified two eligible studies on psychological and psychosocial interventions for adults with bipolar disorder (Lam et al., 2005b; Scott et al., 2009). References to included studies and evidence tables for all economic evaluations included in the systematic literature review are provided in Appendix 32. Completed methodology checklists of the studies are provided in Appendix 31. Economic evidence profiles of studies considered during guideline development (i.e. studies that fully or partly met the applicability and quality criteria) are presented in Appendix 33.

Lam and colleagues (2005a) undertook an economic analysis to assess the cost effectiveness of CBT added to TAU versus TAU alone for adult outpatients with bipolar I disorder in the UK. The analysis was conducted alongside a RCT (LAM2003). CBT consisted of 14 sessions on average for 6 months and two booster sessions for the following 6 months. TAU was defined as use of mood stabilisers at a recommended level and regular psychiatric outpatient follow-up. The analysis adopted a NHS and social care perspective. Costs included inpatient care (psychiatric and general), outpatient care, day hospitals, A&E, community mental health care, day centres, medication, staff (psychiatrists, GPs, psychologists, social workers, counsellors, other therapists), residential care and support groups. The primary measure of outcome was the mean number of days in an acute bipolar episode per person. Clinical and resource use data were taken from the RCT; resource use data were based on self-reports and hospital records. Unit costs were derived from national sources. The study considered two time horizons, 12 and 30 months.

CBT added to TAU was significantly more effective than TAU alone over both 12 and 30 months. The mean number of days in an acute episode was 26.6 (SD 46.0) per person for CBT added to TAU and 88.4 (SD 108.9) per person for TAU alone over 12 months; over 30 months these figures became 95.3 (SD 152.1) per person for CBT added to TAU and 201.0 (SD 95.3) per person for TAU alone ($p<0.05$ in both time horizons). Regarding costs, no statistically significant differences were observed between the two interventions: over 12 months, the mean cost per person was £4,383 (SD £5,264) for CBT added to TAU and £5,356 (SD £6,599) for TAU alone; over 30 months, the mean cost per person was £10,352 (SD £13,464) for CBT added to TAU and £11,724 (SD £12,061) for TAU alone (1999-2000 prices). Therefore CBT added to TAU was the dominant option, as it was significantly more effective than TAU alone and it resulted in lower total costs (it has to be noted, though, that cost differences between CBT added to TAU and TAU alone were not statistically significant). Probabilistic analysis showed that the probability of CBT added to TAU being cost

effective at a zero willingness to pay per additional day free from bipolar episodes (that is, the probability of CBT added to TAU being cost-saving) was 0.85 at 12 months and 0.80 at 30 months. When the willingness to pay per additional day free from bipolar episodes was £10, the probability of CBT added to TAU being cost effective became 0.90 at 12 months and 0.85 at 30 months.

The study by Lam and colleagues (2005b) is directly applicable to the NHS and is characterised by minor limitations.

Scott and colleagues (2009) also conducted an economic analysis alongside a RCT (COLOM2003A) to assess the cost effectiveness of group psychoeducation versus unstructured group support, both added to TAU, for adults with bipolar disorder type I or II in Spain. Group psychoeducation consisted of up to 21 sessions over 6 months. TAU comprised administration of mood stabilisers. People participating in the trial had to be euthymic for at least 6 months before entering the study. The perspective of the analysis was that of the Spanish healthcare system. Costs consisted of inpatient, outpatient and emergency visit costs, costs of medication and lab testing, and costs of group and individual psychological therapy. The primary outcomes of the analysis were the percentage of people experiencing at least one relapse, the mean number of relapses per person, and the mean number of days in an acute episode per person over the time horizon of the analysis, which was 5.5 years (6 months of intervention plus 5 years' follow-up). Effectiveness and cost data were taken from the RCT. Resource use was based on self-reports and hospital records. Unit costs were based on hospital prices and other published sources.

Group psychoeducation was significantly better than unstructured group support in two out of the three primary outcomes. Although the percentage of people experiencing at least one relapse was not statistically different between the two groups (85% versus 95%, respectively, $p>0.05$), the mean number of relapses per person was significantly lower for group psychoeducation (3.86, sd 4.18) compared with unstructured group support (8.37, sd 6.02; $p<0.05$); the mean number of days in acute episode was also significantly lower for group psychoeducation (154.73) compared with unstructured group support (586.45; $p= 0.01$). The mean cost per person was €17,582 (sd €16,395) for group psychoeducation and €20,909 (sd €17,392) for unstructured group support ($p>0.05$, cost year not reported but likely 2006). Thus, group psychoeducation was the dominant option, as it was significantly more effective than unstructured group support at no extra cost.

The study by Scott and colleagues (2009) is partially applicable to the UK context as it was conducted in Spain, and is characterised by minor limitations.

Economic evidence statement

There is limited economic evidence suggesting that psychological and psychosocial interventions may be cost-effective treatment options for adults with bipolar disorder. This evidence comes from one directly applicable and one partially applicable study and is characterised by minor methodological limitations.

8.2 LINKING EVIDENCE TO RECOMMENDATIONS

Relative value placed on the outcomes considered

As in studies of pharmacological interventions, the GDG determined that effective psychological interventions for acute episodes would be associated with reductions in symptoms (response to treatment). In contrast to pharmacological interventions, the GDG also felt that effective psychological interventions for acute episodes might have effects that last beyond the end of treatment, including reduced long-term relapse and hospitalisation, so relapse was also designated as an outcome. For people who were euthymic at the start of a clinical trial, the GDG determined that effective psychological interventions would reduce relapse (that is, new mood episodes) and hospitalisation. The GDG noted that psychological interventions for acute episodes and long-term management might also endeavour to improve social and psychological functioning and quality of life; in making their recommendations, the GDG considered available evidence for these secondary outcomes. Evaluation of the impact of psychological intervention on outcomes other than symptoms and relapse was made difficult by incomplete reporting in some studies and inconsistent use of measures across studies. Available evidence indicates possible benefits of psychological interventions for functional and quality of life outcomes that need to be more rigorously tested by better quality research.

Trade-off between clinical benefits and harms

Across all interventions and comparisons, the included studies suggest that structured psychological interventions may have short- and long-term benefits for people with bipolar disorder. That is, evidence suggests that psychological interventions may improve symptoms and reduce the risk of relapse and hospitalisation for people with bipolar depression, though the evidence for particular psychological interventions varies in quality. There is better evidence that individual psychological interventions and collaborative care may be effective. Group interventions, integrated cognitive and interpersonal therapy and psychoeducation for families showed promising results. There is no evidence that interpersonal and social rhythm therapy was superior to no intervention or to other interventions. Interventions appeared to be well tolerated, and there was no evidence of harm.

The GDG also noted that the evidence for psychological interventions for unipolar depression is consistent with the evidence presented here and of much higher quality. Therefore the GDG decided to offer service users a choice between a manualised psychological intervention specifically developed for bipolar disorder or a high-intensity intervention (CBT, IPT or behavioural couples therapy) as recommended in the NICE *Depression* guideline (NICE, 2009). The GDG judged that these could be conducted in primary or secondary care by psychological therapists who have training and expertise in working with people with bipolar disorder.

Regarding the reduction in the risk of relapse, the GDG noted that this benefit would be clinically important even if psychological interventions were ineffective in the

short-term. Similarly, a short-term benefit in more rapid recovery from acute depression is clinically important even without a significant impact on post-therapy relapse rates. The GDG determined that psychological interventions may be beneficial with minimal risk of side effects, and decided to make recommendations on the use of individual, group and family psychological interventions for the long-term management of bipolar disorder in adults. The components of a family intervention were judged by the GDG to be the same for people with bipolar disorder as for people with psychosis and schizophrenia and therefore a cross-reference to the guideline *Psychosis and Schizophrenia in Adults* (NICE, 2014) was deemed appropriate. For individual, family and group interventions specifically to prevent relapse, the GDG considered the components of the interventions used in the trials reviewed in this chapter when drafting their recommendations.

Trade-off between net health benefits and resource use

The limited economic evidence suggests that psychological interventions are cost-effective in adults with bipolar disorder as they appear to improve clinical outcomes and result in potential cost-savings compared with standard care.

Quality of the evidence

When the GDG examined specific therapies and comparisons, the quality of evidence was mostly very low or low quality. Particularly, results were imprecise (that is, trials included few participants and reported large confidence intervals). It was also noted by the GDG that different treatment types shared a range of common elements. Outcome data were therefore evaluated by primarily differentiating between individual, group and family structured psychological interventions. Quality of evidence for these comparisons ranged from very low to moderate. The GDG noted that the evidence was consistently in favour of structured interventions, but the evidence was insufficient to identify specific psychological interventions that should be used rather than others. For these reasons, the GDG decided that while the evidence did not support a specific treatment modality, it did strongly suggest that psychological interventions should be structured and manualised.

Other considerations

In their discussion, the GDG emphasised that many people with bipolar disorder want psychological interventions. Similar services are offered to people with psychosis and to people with other mood disorders (for example, unipolar depression), and the GDG determined that similar services ought to be available to people with bipolar disorder who wish to access them. In addition, the GDG discussed the value placed by service users and government policy on improving personal recovery and functional outcomes in general. The lack of high quality evidence in this area was a notable shortcoming of the research conducted to date.

There was no evidence that psychological interventions differ in efficacy or tolerability across gender, ethnicity or disability.

8.3 RECOMMENDATIONS

8.3.1 Clinical practice recommendations

Managing bipolar disorder in primary care

8.3.1.1 Offer people with bipolar depression:

- a manualised psychological intervention specifically developed for bipolar disorder **or**
- a high-intensity psychological intervention (cognitive behavioural therapy, interpersonal therapy or behavioural couples therapy) in line with the NICE clinical guideline on depression.

Monitor mood carefully 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.

8.3.1.2 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

8.3.1.3 Offer people with bipolar depression:

- a manualised psychological intervention specifically developed for bipolar disorder **or**
- a high-intensity psychological intervention (cognitive behavioural therapy, interpersonal therapy or behavioural couples therapy) in line with the NICE clinical guideline on depression.

Monitor mood carefully for signs of mania or hypomania or deterioration of the depressive symptoms.

8.3.1.4 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

8.3.1.5 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.

8.3.1.6 Offer a structured, manualised psychological intervention (individual, group or family) designed for bipolar disorder to prevent relapse or for people who have some persisting symptoms between episodes of mania or bipolar depression.

8.3.1.7 Individual and group psychological interventions for bipolar disorder to prevent relapse should consist of between 9 and 25 sessions and:

- 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.

8.3.2 Research recommendations

8.3.2.1 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?

8.3.2.2 What is the clinical and cost effectiveness of individual CBT versus individual psychoeducation in the long term management of bipolar disorder?

8.3.2.3What is the clinical and cost effectiveness of face-to-face CBT versus internet-facilitated CBT in the long-term management of bipolar disorder?

9 MANAGEMENT OF PHYSICAL HEALTH IN ADULTS

9.1 INTRODUCTION

People with bipolar disorder seem to be at increased risk of physical health problems, particularly from cardiovascular disease. Overall, 38% of people with bipolar disorder die from cardiovascular disease, about twice the expected standardised mortality rate, compared with 18% by suicide in a national sample from Sweden (Westman et al., 2013). The reasons for this are not entirely clear although lifestyle factors, weight gain and other adverse effects of antipsychotic and other medication, substance misuse including alcohol and tobacco, and reduced use of cardiovascular drugs (such as statins) may all play a role (Crump et al., 2013; Gomes et al., 2013; Kilbourne et al., 2007; Mitchell et al., 2009). Lithium can lead to renal impairment and the greatest risk of this can be cardiovascular disease although there is also evidence that it may reduce mortality other than from suicide (Angst et al., 2013).

In this chapter behavioural interventions to promote physical activity and healthy eating are reviewed. The GDG also considered pharmacological interventions for managing or preventing weight gain but searches of the literature revealed only RCTs in people taking particular antipsychotic drugs for a range of indications or in the general population. The GDG did not believe that a review of these drugs would be informative and for this reason they are not included in this chapter or the guideline as a whole. For a review see *Psychosis and Schizophrenia in Adults* (NICE, 2014). Other interventions to modify risk factors for cardiovascular disease or other physical health problems were not considered as part of the scope of this guideline.

9.2 BEHAVIOURAL INTERVENTIONS TO PROMOTE PHYSICAL ACTIVITY AND HEALTHY EATING

9.2.1 Introduction

For people with bipolar disorder, and people taking antipsychotics in particular, a combination of poor diet and nutrition, weight gain and lack of physical activity contribute to high rates of physical comorbidities such as type 2 diabetes and reduced life expectancy particularly from cardiovascular disease. Excluding suicide, all-cause mortality may be increased by 40 to 50% in people with bipolar disorder not taking antipsychotics when compared with the English general population, but increased by 70 to 80% in people with bipolar disorder taking antipsychotic medication (Murray-Thomas et al., 2012). Even higher rates have been reported for all cause and cardiac mortality (Laursen et al., 2013; Westman et al., 2013). The prevalence of metabolic syndrome is also increased by 70 to 80% with antipsychotic drug use in bipolar disorder (Vancampfort et al., 2013). There is increasing evidence that adverse effects associated with an increased risk of long-term health problems

are prevalent with the use of antipsychotics (Newcomer et al., 2013). Additionally, cardiometabolic risks appear within weeks of commencing antipsychotics, particularly weight gain and hypertriglyceridaemia and later glucose dysregulation and hypercholesterolemia (Foley & Morley, 2011). Moreover weight gain and obesity further contribute to stigma and discrimination and may explain unplanned discontinuation of antipsychotic medication leading to relapse. Limited research has mainly been directed towards weight reduction rather than physical activity programmes, although in practice these approaches may overlap. Weight reduction should not be the only concern since poor nutrition may directly contribute to physical ill health. Moreover studies using actigraphs show that people with bipolar disorder often lead very sedentary lives (Janney et al., 2014).

9.2.2 Clinical evidence review

Review strategy

People with severe mental illness may be taking similar medications and experience similar physical health problems irrespective of diagnosis (for example, bipolar disorder or schizophrenia). For these reasons, the GDG wished to investigate ways to improve the physical health of bipolar disorder by considering a wide body of evidence about interventions for people with severe mental illness. Reviews for this guideline were thus undertaken in conjunction with a NICE guideline being developed at the same time, *Psychosis and Schizophrenia in Adults* (2014) (NICE, 2014), which includes the full methods and results of those reviews. The studies included in these reviews included people with bipolar disorder (subgroup analyses were undertaken where possible) and the results are directly relevant to this guideline. Before making any recommendations, the GDG were presented with the evidence and draft recommendations made by the *Psychosis and Schizophrenia in Adults* GDG. The method of incorporation and adaptation (see Section 3.7) was followed to ensure that the recommendations were appropriate for people with bipolar disorder. Further information about shared recommendations and the reason for incorporating or adapting each one can be found in the next section.

Summary of findings

Several studies suggested that behavioural interventions to promote physical activity and healthy eating may be efficacious in reducing body weight, and these effects may be maintained in the short term. Because no longer-term data were available, effects after 6 months are not known. In addition, there is evidence that an intervention that combines a behavioural approach to promoting both physical activity and healthy eating can improve quality of life when measured at the end of treatment. However, the longer-term benefits are not known. Interventions that aimed to promote physical activity alone were not found to be any more efficacious than control in reducing weight. Additionally there was no evidence of an increase in quality of life at the end of treatment. Limited evidence suggests that a yoga intervention may be more efficacious than aerobic physical activity in improving quality of life in the short term. There is no evidence that outcomes for people with bipolar disorder differ from outcomes for people with other severe mental illness.

No studies assessing the cost effectiveness of behavioural interventions to promote physical health in people with bipolar disorder were identified. The systematic review identified one study (Winterbourne et al., 2013) reporting that a behavioural intervention involving psychoeducation, nutritional and/or exercise counselling was cost-effective in people with first episode psychosis, but the analysis was judged to be partially applicable to this guideline review and to have potentially serious methodological limitations (such as lack of robust long-term clinical evidence).

Table 35 contains the original recommendations from *Psychosis and Schizophrenia in Adults* (NICE, 2014) in column 1 and the associated review question(s) and evidence base in column 2. The adapted/incorporated recommendations are shown in column 3 and reasons for doing so are provided in column 4.

Table 35: Recommendations incorporated or adapted from another NICE guideline

Original recommendation from *Psychosis and Schizophrenia Update* (NICE, 2014)	Review question and evidence base of existing recommendation	Recommendation following adaptation/ incorporation for this guideline	Reasons for adaptation/ incorporation
1.5.3.1 Develop and use practice case registers to monitor the physical and mental health of people with psychosis or schizophrenia in primary care.	Updated from previous version of guideline. Evidence base: Based on expert opinion of the GDG after reviewing previous versions of guideline. See Chapter 12 of *Psychosis and Schizophrenia in Adults* (NCCMH, 2014)	1.2.10 Develop and use practice case registers to monitor the physical and mental health of people with bipolar disorder in primary care.	The GDG considered issues that can affect the physical health of an adult with severe mental illness. These issues relate to when physical health problems should be assessed, how they should be monitored and who should be responsible for both physical and mental health. The GDG reviewed the *Psychosis and Schizophrenia in Adults* guideline and judged that this recommendation was relevant to people with bipolar disorder. The GDG adapted this recommendation by changing 'psychosis or schizophrenia' to 'bipolar disorder'.
1.5.3.2 GPs and other primary healthcare professionals should monitor the physical health of people with psychosis or schizophrenia when responsibility for monitoring is transferred from secondary care, and then at least annually. The health check should be comprehensive, focusing on physical health problems that are common in people with psychosis and schizophrenia. Include all the checks recommended in 1.3.6.1 and refer to relevant NICE guidance on	Review question: 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)? For adults with psychosis and schizophrenia, what are the benefits and/or potential harms of behavioural interventions to promote healthy eating?	1.2.11 GPs and other primary healthcare professionals should 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, focusing on physical health problems that are common in people with bipolar disorder. Include all the checks recommended in recommendation 1.2.13 and refer to relevant NICE guidance on	The GDG considered issues that can affect the physical health of an adult with severe mental illness. These issues relate to when physical health problems should be assessed, how they should be monitored and who should be responsible for both physical and mental health. The GDG reviewed the evidence in conjunction with the *Psychosis and Schizophrenia in Adults* guideline and judged that this recommendation was relevant to people with bipolar disorder. The GDG adapted this recommendation

monitoring for 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 notes.	Evidence base: Benefits and/or potential harms of behavioural interventions to promote physical activity (based on a review of 24 studies). See Chapter 7 of *Psychosis and Schizophrenia in Adults* (NCCMH, 2014).	monitoring for 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	by changing 'psychosis or schizophrenia' to 'bipolar disorder'.
1.5.3.3 Identify people with psychosis or schizophrenia who have high blood pressure, 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 following relevant NICE guidance (see Lipid modification [NICE clinical guideline 67], Preventing type 2 diabetes [NICE public health guidance 38], Obesity [NICE clinical guideline 43], hypertension [NICE clinical guideline 127], Prevention of cardiovascular disease [NICE public health guidance 25] and Physical activity [NICE public health guidance 44]).	Review question: 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)? For adults with psychosis and schizophrenia, what are the benefits and/or potential harms of behavioural interventions to promote healthy eating? Evidence base: Benefits and/or potential harms of behavioural interventions to promote physical activity (based on a review of 24 studies). See Chapter 7 of *Psychosis and Schizophrenia in Adults* (NCCMH, 2014).	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 lipid modification, preventing type 2 diabetes, obesity, hypertension, prevention of cardiovascular disease and physical activity.	The GDG considered issues that can affect the physical health of an adult with severe mental illness. These issues relate to when physical health problems should be assessed, how they should be monitored and who should be responsible for both physical and mental health. The GDG reviewed the evidence in conjunction with the *Psychosis and Schizophrenia in Adults* guideline and judged that this recommendation was relevant to people with bipolar disorder. The GDG adapted this recommendation by changing 'psychosis or schizophrenia' to 'bipolar disorder'.
1.5.3.4 Treat people with psychosis or schizophrenia who have diabetes and/or cardiovascular disease in primary care according to the appropriate NICE guidance (for example, see Lipid modification [NICE clinical guideline 67], Type 1 diabetes [NICE clinical guideline 15],	Updated from previous version of guideline. Evidence base: Based on expert opinion of the GDG after reviewing previous versions of guideline. See Chapter 7 of *Psychosis and Schizophrenia in Adults* (NCCMH,	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 lipid modification, type 1 diabetes, type 2 diabetes and type 2 diabetes – newer agents.	The GDG considered issues that can affect the physical health of an adult with severe mental illness. These issues relate to when physical health problems should be assessed, how they should be monitored and who should be responsible for both physical and mental health. The GDG

Type 2 diabetes [NICE clinical guideline 66], Type 2 diabetes – newer agents [NICE clinical guideline 87]).	2014)		reviewed the evidence in conjunction with the *Psychosis and Schizophrenia in Adults* guideline and judged that this recommendation was relevant to people with bipolar disorder. The GDG adapted this recommendation by changing 'psychosis or schizophrenia' to 'bipolar disorder'.
1.5.3.5 Healthcare professionals in secondary care should ensure, as part of the care programme approach, that people with psychosis or schizophrenia receive physical healthcare from primary care as described in recommendations 1.5.3.1–1.5.3.4.	Updated from previous version of guideline. Evidence base: Based on expert opinion of the GDG after reviewing previous versions of guideline. See Chapter 7 of *Psychosis and Schizophrenia in Adults* (NCCMH, 2014)	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.	The GDG considered issues that can affect the physical health of an adult with severe mental illness. These issues relate to when physical health problems should be assessed, how they should be monitored and who should be responsible for both physical and mental health. The GDG reviewed the evidence in conjunction with the *Psychosis and Schizophrenia in Adults* guideline and judged that this recommendation was relevant to people with bipolar disorder. The GDG adapted this recommendation by changing 'psychosis or schizophrenia' to 'bipolar disorder'.
1.1.3.1 People with psychosis or schizophrenia, especially those taking antipsychotics, should be offered a combined healthy eating and physical activity programme by their mental healthcare provider.	Review question: 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)? For adults with psychosis and schizophrenia, what are the benefits	1.8.2 People with bipolar disorder, especially those taking antipsychotics, should be offered a combined healthy eating and physical activity programme by their mental healthcare provider.	The GDG considered issues that can affect the physical health of an adult with severe mental illness. These issues relate to when physical health problems should be assessed, how they should be monitored and who should be responsible for both physical and mental health. The GDG reviewed the evidence in conjunction with the *Psychosis and Schizophrenia in*

	and/or potential harms of behavioural interventions to promote healthy eating? Evidence base: Benefits and/or potential harms of behavioural interventions to promote physical activity (based on a review of 24 studies). See Chapter 7 of *Psychosis and Schizophrenia in Adults* (NCCMH, 2014).		*Adults* guideline and judged that this recommendation was relevant to people with bipolar disorder. The GDG adapted this recommendation by changing 'psychosis or schizophrenia' to 'bipolar disorder'.
1.1.3.2 If a person has rapid or excessive weight gain, abnormal lipid levels or problems with blood glucose management, offer interventions in line with relevant NICE guidance (see Obesity [NICE clinical guideline 43], Lipid modification [NICE clinical guideline 67] and Preventing type 2 diabetes [NICE public health guidance 38]).	Review question: 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)? For adults with psychosis and schizophrenia, what are the benefits and/or potential harms of behavioural interventions to promote healthy eating? Evidence base: Benefits and/or potential harms of behavioural interventions to promote physical activity (based on a review of 24 studies). See Chapter 7 of *Psychosis and Schizophrenia in Adults* (NCCMH, 2014).	1.8.3 If a person has rapid or excessive weight gain, abnormal lipid levels or problems with blood glucose management, offer interventions in line with the NICE guidance on obesity, lipid modification, or preventing type 2 diabetes.	The GDG considered issues that can affect the physical health of an adult with severe mental illness. These issues relate to when physical health problems should be assessed, how they should be monitored and who should be responsible for both physical and mental health. The GDG reviewed the evidence in conjunction with the *Psychosis and Schizophrenia in Adults* guideline and judged that this recommendation was relevant to people with bipolar disorder. The GDG adapted this recommendation by changing 'psychosis or schizophrenia' to 'bipolar disorder'.
1.1.3.6 Routinely monitor weight, and cardiovascular and metabolic indicators of morbidity in people with psychosis and schizophrenia.	Review question: For adults with psychosis and schizophrenia, what are the benefits and/or potential harms of	1.8.4 Routinely monitor weight and cardiovascular and metabolic indicators of morbidity in people with bipolar disorder. These should	The GDG considered issues that can affect the physical health of an adult with severe mental illness. These issues relate to when physical health

These should be audited in the annual team report.	behavioural interventions to promote physical activity (all forms, with or without healthy eating)? For adults with psychosis and schizophrenia, what are the benefits and/or potential harms of behavioural interventions to promote healthy eating? Evidence base: Benefits and/or potential harms of behavioural interventions to promote physical activity (based on a review of 24 studies). See Chapter 7 of *Psychosis and Schizophrenia in Adults* (NCCMH, 2014).	be audited in the annual team report.	problems should be assessed, how they should be monitored and who should be responsible for both physical and mental health. The GDG reviewed the evidence in conjunction with the *Psychosis and Schizophrenia in Adults* guideline and judged that this recommendation was relevant to people with bipolar disorder. The GDG adapted this recommendation by changing 'psychosis or schizophrenia' to 'bipolar disorder'.
1.1.3.7 Trusts should ensure compliance with quality standards on the monitoring and treatment of cardiovascular and metabolic disease in people with psychosis or schizophrenia through board-level performance indicators.	Review question: 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)? For adults with psychosis and schizophrenia, what are the benefits and/or potential harms of behavioural interventions to promote healthy eating? Evidence base: Benefits and/or potential harms of behavioural interventions to promote physical activity (based on a review of 24 studies). See Chapter	1.8.5 Trusts should ensure compliance with relevant guidelines on the monitoring and treatment of cardiovascular and metabolic disease in people with bipolar disorder through board-level performance indicators.	The GDG considered issues that can affect the physical health of an adult with severe mental illness. These issues relate to when physical health problems should be assessed, how they should be monitored and who should be responsible for both physical and mental health. The GDG reviewed the evidence in conjunction with the *Psychosis and Schizophrenia in Adults* guideline and judged that this recommendation was relevant to people with bipolar disorder. The GDG adapted this recommendation by changing 'psychosis or schizophrenia' to 'bipolar disorder'.

	7 of *Psychosis and Schizophrenia in Adults* (NCCMH, 2014).		

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9.3 LINKING EVIDENCE TO RECOMMENDATIONS

9.3.1 Relative value placed on the outcomes considered

The GDG agreed that the main aims of a physical health and/or healthy eating intervention should be to improve health, reduce weight and improve quality of life (Sattelmair et al., 2011; Tuomilehto et al., 2011). The GDG also considered the importance of engaging the service user in the intervention. Therefore, the GDG decided to focus on the following, which were considered to be critical:

- physical health
- BMI/ weight
- levels of physical activity
- service use
- primary care engagement (for example, GP visits)
- quality of life
- user satisfaction (validated measures only).

9.3.2 Trade-off between clinical benefits and harms

A wealth of research in the general population supports the importance of being physically active and having a healthy, balanced diet. For people with bipolar disorder, interventions that aim to both increase physical activity and to improve healthy eating may be efficacious for multiple outcomes. The GDG considered this evidence of clinical benefit to be of particular importance in a population with greatly increased risk of mortality.

9.3.3 Trade-off between net health benefits and resource use

The health economic evidence on interventions to promote physical health was limited to one UK study. Despite the study's limitations, the results provide evidence that non-pharmacological interventions that include psychoeducation, nutritional and/or exercise counselling may comprise a cost-effective strategy for the prevention of weight gain in the short term in people with serious mental illness. The positive economic finding supports the GDG's view that these interventions are not only of important clinical benefit but also are likely to be cost effective within the NICE decision-making context.

9.3.4 Quality of the evidence

The evidence ranged from very low quality to high quality across interventions. For the combined physical health and healthy eating intervention, evidence was of better quality and rated from low to moderate quality across critical outcomes. Reasons for downgrading included risk of bias, inconsistency (although the direction of effect was consistent across studies) and, for some outcomes, imprecision.

9.3.5 Other considerations

The review of behavioural interventions to promote healthy eating (without a physical activity component) did not identify any studies meeting the inclusion criteria. A behavioural intervention to increase physical activity and healthy eating may be efficacious in reducing weight and improving quality of life in adults with serious mental illness. The GDG considered the possibility of cross-referring to existing guidance in this area for the general population. However, people with severe mental illness are at a high risk of morbidity and mortality because of physical complications such as diabetes, obesity, cardiovascular disease and other related illness. Therefore, the GDG decided it was important to generate recommendations specifically for this population and felt the available evidence assisted in informing these recommendations. They did, however, see the benefit of making specific reference to NICE guidance on obesity and prevention of diabetes and cardiovascular disease.

Evidence suggests that long periods of mild physical activity, for example walking, may be more efficacious than shorter periods of moderate to vigorous exercise in improving insulin action and plasma lipids for people who are sedentary. The GDG purposefully decided to use the terms 'physical activity 'and 'healthy eating' (rather than the potentially stigmatising words 'exercise' and 'diet') in order to take this evidence into consideration and promote a long-term lifestyle change rather than a short-term 'fix' to reduce weight (Duvivier et al., 2013).

The GDG went beyond the evidence of clinical benefit to consider other important issues that can affect the physical health of an adult with severe mental illness. These issues relate to when physical health problems should be assessed, how they should be monitored and who should be responsible for both physical and mental health. The GDG considered and discussed the important role of primary care in monitoring physical health (especially current diabetes and cardiovascular disease) and that this should be made explicit in the care plan. The GDG believed that these issues were of equal importance to the service user's health as the interventions themselves.

9.4 RECOMMENDATIONS

9.4.1 Clinical practice recommendations

Monitoring physical health in primary care

9.4.1.1 Develop and use practice case registers to monitor the physical and mental health of people with bipolar disorder in primary care.[42]

[42] Adapted from Psychosis and schizophrenia in adults (NICE clinical guideline 178).

9.4.1.2 GPs and other primary healthcare professionals should 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, focusing on physical health problems that are common in people with bipolar disorder. Include all the checks recommended in recommendation 9.4.1.3 and refer to relevant NICE guidance on monitoring for 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.[43]

9.4.1.3 Ensure that the physical health check for people with bipolar disorder 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 (HbA_{1c}) and blood lipid profile
- liver function
- renal function for people taking long-term lithium.

9.4.1.4 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 lipid modification, preventing type 2 diabetes, obesity, hypertension, prevention of cardiovascular disease and physical activity.[44]

9.4.1.5 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 lipid modification, type 1 diabetes, type 2 diabetes and type 2 diabetes – newer agents. [45]

Monitoring physical health in secondary care

9.4.1.6 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 9.4.1.1–9.4.1.5.[46]

9.4.1.7 People with bipolar disorder, especially those taking antipsychotics, should be offered a combined healthy eating and physical activity programme by their mental healthcare provider. [47]

[43] Adapted from Psychosis and schizophrenia in adults (NICE clinical guideline 178).
[44] Adapted from Psychosis and schizophrenia in adults (NICE clinical guideline 178).
[45] Adapted from Psychosis and schizophrenia in adults (NICE clinical guideline 178).
[46] Adapted from Psychosis and schizophrenia in adults (NICE clinical guideline 178).
[47] Adapted from Psychosis and schizophrenia in adults (NICE clinical guideline 178).

9.4.1.8 If a person has rapid or excessive weight gain, abnormal lipid levels or problems with blood glucose management, offer interventions in line with the NICE guidance on obesity, lipid modification, or preventing type 2 diabetes. [48]

9.4.1.9 Routinely monitor weight and cardiovascular and metabolic indicators of morbidity in people with bipolar disorder. These should be audited in the annual team report. [49]

9.4.1.10 Trusts should ensure compliance with relevant guidelines on the monitoring and treatment of cardiovascular and metabolic disease in people with bipolar disorder through board-level performance indicators. [50]

[48] From Psychosis and schizophrenia in adults (NICE clinical guideline 178).
[49] Adapted from Psychosis and schizophrenia in adults (NICE clinical guideline 178).
[50] Adapted from Psychosis and schizophrenia in adults (NICE clinical guideline 178).

10 INTERVENTIONS FOR CHILDREN AND YOUNG PEOPLE

10.1 INTRODUCTION

The principal interventions for bipolar disorder in children and young people involve medical and psychological approaches. As for adults the treatment aims are focused on managing acute episodes of mania and bipolar depression, longer-term maintenance and preventing relapse. The treatment of bipolar disorder in children and young people requires a broad, often multimodal approach, because comorbid disorders such as substance misuse and conduct disorders are common. Any treatment plan clearly needs to take account of the developmental level of the child or young person and the differing age presentations of bipolar disorder. Perhaps reflecting practice and diagnostic difficulties in this age group, early age at onset predicts a longer time to first pharmacological treatment (Morken et al., 2009).

Pharmacological interventions

Treatment of mania

The range and types of medication used to treat the various phases of bipolar disorder in children and young people are similar to those used in adults. For mania, pharmacotherapy is the mainstay of treatment. The mechanisms of action of medications such as second generation antipsychotics (SGAs) (e.g., risperidone, olanzapine, quetiapine, aripiprazole) and mood stabilisers (lithium, sodium valproate, lamotrigine, carbamazepine, and so on) are thought to be similar in this age group to that in adults, although differences in dosage and side effects need to be considered, especially in younger patients. SGAs are associated with considerable side effects, particularly weight gain, which is greater in younger people than adults (Correll et al., 2010). Furthermore, the longer-term effects of these medications upon the developing brain remain unclear, although these drugs are increasingly used. A major problem with medication is compliance—a large US study of children and young people treated for bipolar disorder under the Medicaid system found around 50% of those on monotherapy and polytherapy had defaulted within 1 month (Bhowmik et al., 2013). This highlights the need for psychoeducation and close involvement of parents and guardians.

Licensing

There is considerable concern about the licensing and, therefore, use of medication in children and young people. At the time of publication, in the UK only one drug – aripiprazole, which has been subject to a NICE Technology Appraisal (NICE, 2013a) -- is licensed for 12 weeks' treatment of moderate to severe manic episodes in bipolar I disorder in young people aged 13 years and older. However, in 2000, the Royal College of Paediatrics and Child Health issued a policy statement on the use of unlicensed medicines, or the use of licensed medicines for unlicensed applications, in children and young people. This states that such use is necessary in paediatric

practice and that doctors are legally allowed to prescribe unlicensed medicines where there are no suitable alternatives and where the use is justified by a responsible body of professional opinion.[51]

Treatment of bipolar depression

Depression is the most common presentation of bipolar disorder in children and young people and it is associated with a risk of self-harm and suicide (Goldstein et al., 2012). Active treatment is, therefore, particularly important. The treatment of bipolar depression in children and young people, however, poses certain problems, not least of which is the recognition of bipolar depression, and its differentiation from unipolar depression. Early-onset bipolar disorder more often presents with depression than in adult-onset (Suominen et al., 2007). Hence, it is important to recognise children and young people at risk of bipolar disorder (see Chapter 5): those with recurrent depression, psychotic depression, treatment resistant depression and those with family histories of bipolar disorder or a hypomanic response to antidepressant treatment. Furthermore, antidepressant induced switching to mania is reported to occur more frequently in children and young people than adults (Lim et al., 2005).

NICE (NICE, 2005a) recommends as a first line the use of cognitive behavioural therapy (CBT) for the treatment of unipolar depression. It further recommends that when an antidepressant is prescribed to a child or young person with moderate to severe unipolar depression, it should be fluoxetine as this is the only antidepressant for which clinical trial evidence shows that the benefits outweigh the risks.

In children and young people empirical data on the treatment of bipolar depression are scarce. Open trials of lithium (Patel et al., 2006) and lamotrigine (Chang et al., 2006) show that these drugs may be effective in the treatment of depressive episodes; however, no trials of selective serotonin reuptake inhibitors (SSRIs) have been conducted in bipolar depression. The International Society for Bipolar Disorders recently reported on the use of antidepressants in bipolar disorder (Pacchiarotti et al., 2013), but was limited by the lack of evidence. In conclusion the report stated that that individual patients may benefit from antidepressants, however, for bipolar I disorder, antidepressants should be prescribed only as an adjunct to mood-stabilising medications.

Nutritional approaches

Fish oil supplements, either on their own or as a supplement to enhance pharmacological or psychological interventions, are used for a range of disorders, including early-onset bipolar disorder (Gracious et al., 2010). The mechanism is unclear but it suggested that omega 3 may act to stabilise neuronal signalling.

[51]Joint Royal College of Paediatrics and Child Health/Neonatal and Paediatric Pharmacists Group Standing Committee on Medicines (2000) The Use of Unlicensed Medicines or Licensed Medicines for Unlicensed Applications in Paediatric Practice–Policy Statement. London: Royal College of Paediatrics and Child Health.

Psychological interventions

There are a various psychological interventions for bipolar disorder in this age group, some adapted from adult models. These include: interpersonal and social rhythm therapy for adolescents (Hlastala et al., 2010), child- and family-focused cognitive behavioural therapy (Pavuluri et al., 2004) and dialectical behaviour therapy for adolescents (Fleischhaker et al., 2011). However, the number of RCTs of psychological interventions for children and young people with bipolar disorder is limited to two studies involving family psychoeducational approaches: multifamily psychoeducational psychotherapy (Cummings & Fristad, 2007; Fristad et al., 2009) and family-focused therapy (Miklowitz et al., 2008). In addition to psychoeducation, which includes information about the appropriate use of medication, and appropriate adaption of lifestyle, these approaches involve several components, mainly problem solving and communication enhancement with family members.

Services

There is very little research about services specifically for children and young people with bipolar disorder, but there is a growing body of research and good practice guidance about supporting young people during transition to adult services. This focuses on transition between inpatient and community child and adolescent mental health services (CAMHS) (Street & Svanberg, 2003), transition from CAMHS to adult inpatient services (Singh et al., 2008) and what young people say about their experiences of transition (Kane, 2008).

Young people with bipolar disorder often face problems when moving from mental health services for children and adolescents to adult mental health services. The result of poorly developed transition services is that sometimes young people are left with no help when they need it most and have no one to turn to in crisis. The gains made from contact with CAMHS are diminished or lost as a result of inadequate or failed transition to adult services. The negative impact of an unsuccessful mental health transition can also affect parents and carers, having implications for the whole family.

Young people aged 16 and 17 are making the transition to adulthood, and so may have a range of needs including those related to living independently and developing as young adults. Regardless of which service a young person may be moving to, professionals should get to know them before the transition, and plans should be in place to ensure that the transition is as smooth and as seamless as possible.

The negative impact of an unsuccessful mental health transition can also affect parents and carers, having implications for the whole family. Young people and their parents have been clear in saying that they want to be involved in transition planning (Kane, 2008), reflecting the Department of Health's guidance on transition support (Department of Health, 2006).

10.2 SERVICE-LEVEL INTERVENTIONS

10.2.1 Clinical review protocol

The review protocol summary, including the review question and eligibility criteria can be found in Table 36 (a complete list of review questions and protocols can be found in Appendix 7; further information about the search strategy can be found in Appendix 8).

Table 36: Review protocol summary for service-level interventions

Topic	Interventions
Review question	RQ5.6: 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? What amendments, if any, need to be made for (i) particular cultural or minority ethnic groups, (ii) gender
Objectives	To estimate the efficacy of services in treating bipolar disorder.
Criteria for considering studies for the review	
• Intervention	Lithium clinics Mood clinics Collaborative care
• Comparator	Treatment-as-usual Other services
• Types of participants	Children and young people (aged 18 years and younger) with suspected bipolar disorder. Special consideration will be given to the groups above.
• Outcomes	5) Relapse (all, mania/mixed, depression) 6) Hospitalisation (rate, duration) 7) Quality of life 8) Mortality
• Time	At least 1 year after initiating treatment.
• Study design	Randomised controlled trials (RCTs) and cluster RCTs with a parallel group design. We will exclude quasi-RCTs, such as trials in which allocation is determined by alternation or date of birth.
Note. RCT = Randomised controlled trial.	

10.2.2 Studies considered

No studies met the inclusion criteria for this review. An additional search for systematic reviews did not reveal additional evidence that addressed the review question.

10.3 PHARMACOLOGICAL AND NUTRITIONAL INTERVENTIONS FOR MANIA

10.3.1 Clinical review protocol

The review protocol summary, including the review question and eligibility criteria can be found in Table 37 (a complete list of review questions and protocols can be

found in Appendix 7; further information about the search strategy can be found in Appendix 8) .

Table 37: Clinical review protocol summary for the review of pharmacological and nutritional interventions for mania

Topic	Interventions
Review question(s)	RQ 5.1: 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? 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).
Objectives	To estimate the efficacy of interventions to treat manic, hypomanic and mixed episodes.
Criteria for considering studies for the review	
• Intervention	All licensed oral medications (and their combinations). Nutritional interventions (for example, herbal supplements, fatty acid supplementation).
• Comparator	Waitlist, no intervention, placebo and other interventions.
• Types of participants	Children (younger than 13 years) and young people (13 to 18 years) with bipolar disorder. Special consideration will be given to the groups above.
• Outcomes	1) Change in symptoms of mania 2) Response (50% reduction or greater) 3) Discontinuation (because of side effects, other)
• Time •	The main analysis will include outcomes at the end of the acute treatment phase.
• Study design	Randomised controlled trials (RCTs) and cluster RCTs with a parallel group design in which providers and participants were blind to treatment. Quasi-RCTs, such as trials in which allocation is determined by alternation or date of birth, and single-blind studies, will be excluded.
• Dosage	Fixed or flexible doses within the therapeutic range (BNF recommended).
• Study setting	Primary, secondary, tertiary health and social care

10.3.2 Studies considered[52]

Fifteen RCTs (N = 1,543) met the eligibility criteria for this review: DELBELLO2002 (Delbello et al., 2002), DELBELLO2005 (Delbello et al., 2005), DELBELLO2006 (Barzman et al., 2006; DelBello et al., 2006), ELILILLY2011 (Lilly, (unpublished) 2011),FINDLING2009 (Findling et al., 2013; Findling et al., 2009; Findling et al., 2012b; Mankoski et al., 2011), , GRACIOUS2010 (Gracious et al., 2010), HAAS2009 (Haas et al., 2009), HEBRANI2009 (Hebrani et al., 2009), PATHAK2013 (Pathak et al., 2013), PAVULURI2010 (Pavuluri et al., 2010), PAVULURI2012 (Pavuluri et al., 2012a; Pavuluri et al., 2012b), PFIZER2011 (Pfizer, (unpublished) 2011), TOHEN2007 (Tohen et al., 2007b), TRAMONTINA2009 (Tramontina et al., 2009), WAGNER2009

[52]Here and elsewhere in the guideline, each study considered for review is referred to by a study ID in capital letters (primary author and date of study).

(Wagner et al., 2009; Waslick, 2006). Of these, two were unpublished and 12 were published in peer-reviewed journals between 2002 and 2013.

Three studies were excluded because the treatment was open-label: GELLER2012 (Geller et al., 2012), JOSHI2013 (Joshi et al., 2013), KOWATCH2000 (Kowatch et al., 2000). One trial of olanzapine plus topiramate in comparison with olanzapine monotherapy was excluded because the allocation of participants was quasi-random: WOZNIAK2009 (Wozniak et al., 2009). It was also not possible to include one trial because it was terminated early: WOZINAK2012 (Wozniak, (unpublished) 2012).

Of the 18 eligible trials, 17 (N = 1,732) included sufficient data to be included in the statistical analysis. Of these, there were ten RCTs (N = 1,452) involving a comparison of medication with placebo and four (N = 280) involving a comparison of medication with valproate. It was not possible to include in the analysis one trial (GRACIOUS2010, N = 51) comparing flax oil with placebo because participants were manic or depressed at randomisation and disaggregated data were not available.

Participants were on average 13 years old (mean of means), ranging from 6 to 18 years. Approximately half of the included participants were female (48%). Of the 11 trials that reported the percentage of participants with a comorbid diagnosis of ADHD, seven included 50% or more. The drugs included were: aripiprazole, quetiapine, olanzapine, risperidone, ziprasidone, topiramate and valproate. The length of treatment was 6 weeks on average, ranging from 2 to 12 weeks.

Further information about the included and excluded studies can be found in Appendix 27and Appendix 34, respectively.

10.3.3 Subgroup analysis

Meta-analyses were conducted for subgroups in each class of intervention. For each comparison, response/relapse, symptoms of mania/depression and discontinuation outcomes were analysed. To explore the possibility of a differential effect of treatment in children and young people, a sensitivity analysis was carried out by removing trials with a mean age under 12 years or data from participants aged 12 and under where disaggregated data were reported.

Three trials (FINDLING2009; HAAS2009; PATHAK2013) included different dosages of the same intervention; in the analysis each arm was considered in a separate subgroup and the control group was split to avoid double-counting. For studies including both children and young people, the authors were contacted for data disaggregated by age.

10.3.4 Risk of bias

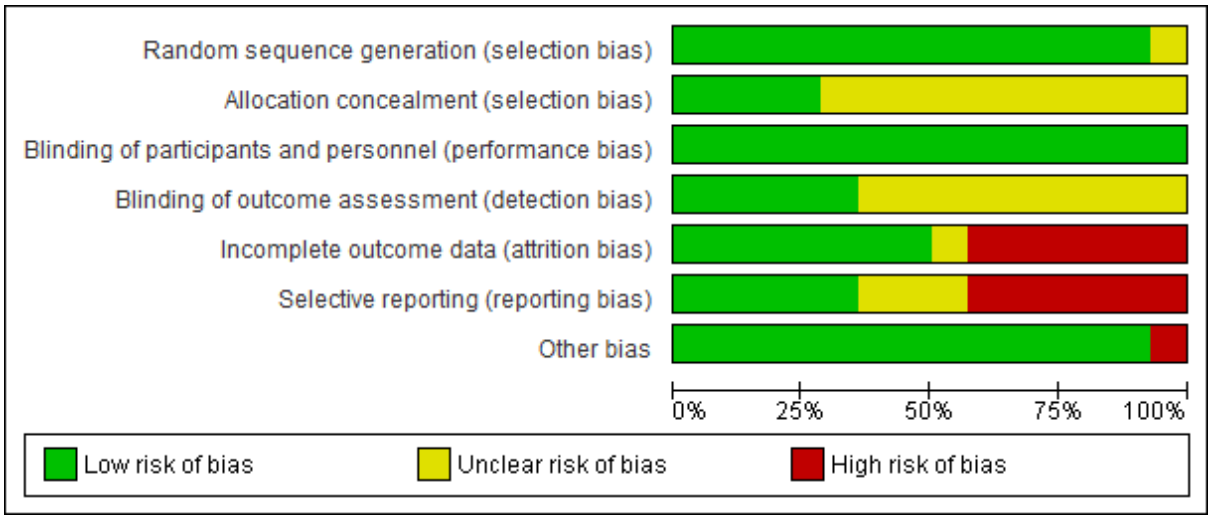
All included trials were assessed for risk of bias (see Appendix 28 and Figure 9). For sequence generation, 13 trials were at low risk of bias and of these, four were at low risk of bias for allocation concealment. Allocation concealment was unclear in 10

trials. For blinding of participants and providers all14 trials were at low risk of bias. Assessor blinding was considered separately for all trials and a low risk of bias was found in five trials. Ten trials had an unclear risk of bias for assessor blinding. For incomplete outcome data, nine trials were at low risk of bias and five trials were at high risk of bias (this was mainly owing to very large amounts of missing data and to differences in missing data between treatment groups).

Selective outcome reporting and publication bias

Several methods were employed to minimise risk of selective outcome reporting and publication bias. All authors were contacted to request trial registrations and unpublished outcomes, and all authors of included studies, all stakeholders and all pharmaceutical manufacturers were asked to provide unpublished trials. Only nine of the included studies were known to be registered and five were at low risk of selective outcome reporting bias; were at high risk and three were unclear.

Figure 9: Risk of bias table for pharmacological interventions for mania



10.3.5 Clinical evidence review

Evidence from each important outcome and overall quality of evidence are presented in Table 38. The full evidence profiles and associated forest plots can be found in Appendix 27 and Appendix 29, respectively.

Considering response, symptoms of mania and discontinuation, there was low to very low quality evidence that the benefits outweighed the harms for the following drugs when compared with placebo: aripiprazole (k = 2; N = 340), olanzapine (k = 1; N = 159), quetiapine (k = 2; N = 308), risperidone (k = 1; N = 169) and ziprasidone (k = 1; N = 238). In contrast, very low quality evidence found no evidence of benefit for valproate (k = 1; N = 144) or topiramate (k = 1; N = 56).

Very low quality evidence showed no difference between valproate and quetiapine (k = 1; N = 50). There was evidence of benefit in favour of risperidone (k = 3; N =

234) compared with valproate, whereas topiramate (k = 1; N = 120) was significantly less effective than valproate for symptoms of mania.

Disaggregated data were provided for PATHAK2013. One other trial (TRAMONTINA2009) reported some outcomes disaggregated by age. A sensitivity analysis indicated no differential effect of age on outcomes.

Table 38: Summary of results at post-treatment for mania

Comparison	Response (95% CI)	Symptoms of mania (95% CI)	Discontinuation for any reason (95% CI)	Study ID
Pharmacological interventions				
Medication compared with placebo				
Aripiprazole	RR = 1.97 (1.50, 2.61) k = 2; N = 340	SMD = -0.65 (-0.91, -0.40) k = 2; N = 340	RR = 0.77 (0.49, 1.22) k = 2 ; N = 340	FINDLING2009, TRAMONTINA2009
Olanzapine	RR = 2.19 (1.28, 3.74) k = 1; N = 159	SMD = -0.91 (-1.25, -0.57) k = 1; N = 159	RR = 0.58 (0.35, 0.98) k = 1; N = 161	TOHEN2007
Quetiapine	RR = 1.82 (1.36, 2.43) k = 2; N = 308	SMD = -0.41 (-0.76, -0.06) k = 1; N = 278	RR = 0.64 (0.38, 1.10) k = 1; N = 306	DELBELLO2002, PATHAK2013
Risperidone	RR = 2.18 (1.40, 3.40) k = 1; N = 169	SMD = -0.80 (-1.03, -0.47) k = 1; N = 167	RR = 0.81 (0.34, 1.95) k = 1; N = 169	HAAS2009
Topiramate	RR = 1.55 (0.65, 3.69) k = 1; N = 56	SMD = -0.51 (-1.03, 0.02) k = 1; N = 56	RR = 2.50 (0.80, 7.79) k = 2; N = 86	DELBELLO2005, ELILILLY2011
Valproate	RR = 1.06 (0.59, 1.92) k = 1; N = 144	SMD = -0.09 (-0.41, 0.24) k = 1; N = 144	RR = 1.46 (0.79, 2.70) k = 1; N = 144	WAGNER2009
Ziprasidone	Not reported	SMD = -0.49 (-0.76, -0.21) k = 1; N = 218	RR = 0.84 (0.61, 1.17) k = 1; N = 238	PFIZER2011
Medication compared with valproate				
Risperidone	RR = 2.03 (1.49, 2.76) k = 3; N = 234	SMD = -0.44 (-0.87, -0.01) k = 2; N = 86	RR = 0.50 (0.30, 0.83) k = 3; N = 233	GELLER2012, PAVULURI2010, PAVULURI2012
Quetiapine	RR = 2.14 (1.06, 4.34) k = 1; N = 50	SMD = -0.54 (-1.10, 0.03) k = 1; N = 50	RR = 1.00 (0.37, 2.68) k = 1; N = 50	DELBELLO2006
Topiramate	Not reported	SMD = 0.73 (-1.10, 0.03) k = 1; N = 120	Not reported	HEBRANI2009

Note. CI = Confidence interval; k = Number of studies; N = Sample size; RR = Relative risk; SMD = Standardised mean difference.

10.3.6 Health economics evidence

The systematic search of the economic literature undertaken for the guideline identified one eligible study on the cost effectiveness of pharmacological interventions for manic episodes in children and young people with bipolar disorder (Uttley et al., 2013). References to included studies and evidence tables for all economic evaluations included in the systematic literature review are provided in Appendix 32. Completed methodology checklists of the studies are provided in Appendix 31. Economic evidence profiles of studies considered during guideline development (that is, studies that fully or partly met the applicability and quality criteria) are presented in Appendix 33.

Uttley and colleagues (2013) reported the methods and the results of an economic assessment of aripiprazole for the treatment of mania in young people with bipolar I disorder. The economic analysis was submitted to NICE by the manufacturers of aripiprazole as part of the NICE Technology Appraisal (NICE, 2013a); this analysis was subsequently critically reviewed, replicated and expanded by an independent Evidence Review Group (ERG).

The analysis, which was based on decision-analytic modelling, evaluated four strategies consisting of different drug sequences, in which aripiprazole was either not used, or used as first-, second- or third-line treatment. The following strategies were evaluated:

a. risperidone, quetiapine, olanzapine, lithium
b. risperidone, aripiprazole, quetiapine, lithium
c. aripiprazole, risperidone, quetiapine, lithium
d. risperidone, quetiapine, aripiprazole, lithium.

The study population consisted of young people aged 15 years experiencing a manic or mixed episode. Effectiveness data for aripiprazole were taken from a double-blind, phase III, placebo-controlled trial of aripiprazole in children and young people with bipolar disorder aged 10 to 17 years, in a manic or mixed episode. Effectiveness data for the other antipsychotic drugs considered in the analyses were taken from published RCTs and were synthesised in a network meta-analysis. The measure of outcome was the QALY. The perspective of the analysis was that of the NHS and PSS; costs included hospitalisation and out-of-hospital costs, medication and management of side effects. The time horizon of the analysis was 3 years.

The manufacturer analysis showed that strategy 'b' dominated all other strategies. The strategy that did not include aripiprazole (strategy 'a') was dominated by all other strategies that contained aripiprazole. A number of sensitivity analyses were undertaken, including a change in the dose of aripiprazole, use of a larger number of trials in the network meta-analysis, swapping the position of quetiapine and olanzapine in strategy 'a', use of a different set of utility values, change in the starting age of participants, reduction in the treatment efficacy between lines 1 and 2 and between lines 2 and 3, inclusion of the cost of drug-related adverse events, and an extension of the acute and euthymic treated phases of the model. These sensitivity analyses demonstrated the uncertainty of the results, although in the majority of analyses the strategies containing aripiprazole were shown to remain cost-effective compared with the strategy not containing aripiprazole.

On the other hand, the ERG demonstrated that small changes in costs and QALYs (1 to 2%) resulted in different conclusions, indicating that the results were very sensitive to consideration of personalised medicine (that is, clinical practice tailored to the individual person's needs, taking into account factors such as the severity of symptoms and the potential side-effect profile), which could potentially lead to such small changes in costs and QALYs. The ERG thus argued that the optimal (cost-

effective) strategy was likely to depend on the individual's characteristics. The ERG also noted that aripiprazole had received approval by the European Medicines Agency Committee for Medicinal Products for Human Use for only up to 12 weeks of treatment. However, the manufacturer's economic analysis allowed use of aripiprazole to exceed this licensed period of 12 weeks. On the other hand, expert opinion suggested that the average duration of antipsychotic treatment in young people could reach 12 months. Hence, the ERG argued that the treatment duration used in the economic analysis did not reflect either the licensed duration of treatment for aripiprazole or the real-world prescribing of antipsychotics.

The ERG also expressed concerns about the comparability between the study population in the RCT that provided the efficacy data for aripiprazole and the typical UK paediatric population with bipolar I disorder. The trial population consisted of children and young people of low mean age with high prevalence of comorbid ADHD and suicidal children and young people were excluded from the trial. Moreover, some of the participants were not hospitalised but instead they were being treated in the community. Finally, the ERG noted that the model structure may not reflect routine clinical practice because the economic analysis considered only three lines of atypical antipsychotics, whereas four may be used in clinical practice.

The Appraisal Committee considered the evidence presented by the manufacturer and the ERG comments (NICE, 2013a). The Committee expressed the opinion that the structure of the economic model was appropriate, and concluded that the RCT that provided the efficacy data for aripiprazole considered in the economic analysis was relevant to the UK clinical practice. The Committee reviewed the economic results, including the findings of the sensitivity analyses, and acknowledged that the base-case results suggested that a treatment strategy that includes aripiprazole is a cost-effective option when compared with a treatment strategy without it. Nevertheless, the Committee agreed that the results were not sufficiently robust to make a recommendation on the position of aripiprazole in the treatment pathway. The Committee concluded that aripiprazole should be recommended as an option for the treatment of moderate to severe manic episodes in bipolar I disorder in adolescents.

The economic analysis described by Uttley and colleagues (2013) is directly applicable to the UK context but it is characterised by potentially serious methodological limitations and very high uncertainty in the results.

Economic evidence statement

There is limited evidence that pharmacological treatment strategies that include aripiprazole may be cost-effective options for the treatment of mania in young people with bipolar I disorder. This evidence is directly applicable to the guideline context but is characterised by potentially serious limitations and high uncertainty.

10.4 PHARMACOLOGICAL AND NUTRITIONAL INTERVENTIONS FOR ACUTE EPISODES OF BIPOLAR DEPRESSION

10.4.1 Clinical review protocol

The review protocol summary, including the review question and eligibility criteria can be found in Table 39 (a complete list of review questions and protocols can be found in Appendix 7; further information about the search strategy can be found in Appendix 8).

Table 39: Clinical review protocol for the review of pharmacological and nutritional interventions for bipolar depression

Topic	Interventions
Review question(s)	RQ 5.2: 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? 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).
Objectives	To estimate the efficacy of interventions to treat episodes of bipolar depression.
Criteria for considering studies for the review	
• Intervention	All licensed oral medications (and their combinations). Nutritional interventions (for example, herbal supplements, fatty acid supplementation).
• Comparator	Waitlist, no intervention, placebo and other interventions.
• Types of participants	Children (younger than 13 years) and young people (13 to 18 years) with bipolar disorder. Special consideration will be given to the groups above.
• Outcomes	1) Change in symptoms of depression 2) Response (50% reduction or greater) 3) Discontinuation (due to side effect, other)
• Time •	The main analysis will include outcomes at the end of the acute treatment phase.
• Study design	Randomised controlled trials (RCTs) and cluster RCTs with a parallel group design in which providers and participants were blind to treatment. Quasi-RCTs, such as trials in which allocation is determined by alternation or date of birth, and single-blind studies, will be excluded.
• Dosage	Fixed or flexible doses within the therapeutic range (BNF recommended).
• Study setting	Primary, secondary, tertiary health and social care
Note. BNF = British National Formulary.	

10.4.2 Studies considered

Four RCTs (N = 567) met the eligibility criteria for this review: ASTRAZENECA2011B (Astrazeneca, (unpublished) 2011a), DELBELLO2009 (Chang et al., 2012; DelBello et al., 2009), ELILILLY2013 (Lilly, (unpublsihed) 2013; Wozniak & Biederman, 1997) and GRACIOUS2010. Of these, two were unpublished and two

were published in peer-reviewed journals between 2009 and 2010. No studies were excluded,

Of the four eligible trials, three (N = 516) included sufficient data to be included in the statistical analysis. Of these, one involved a comparison of quetiapine with placebo (N = 225) and one involved a comparison of olanzapine and fluoxetine combination therapy with placebo (N = 291). It was not possible to include one trial (GRACIOUS2010, N = 51) comparing flax oil with placebo because participants were manic or depressed at randomisation and disaggregated data were not available.

Participants were, on average 15 years old (mean of means), ranging from 10 to 18 years. Approximately half of the included participants were female (58%).Only one trial reported the percentage of participants with a comorbid diagnosis of ADHD, which was low (13%). The length of treatment was 8 weeks for all three included trials.

Further information about the included studies can be found in Appendix 27.

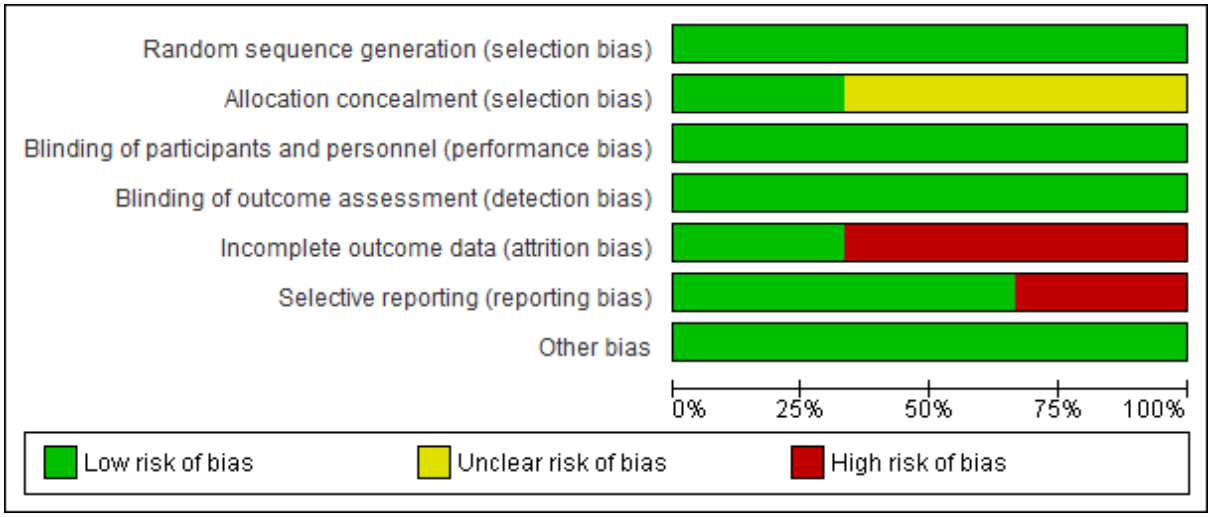
10.4.3 Risk of bias

All included trials were assessed for risk of bias (see Appendix 28 and Figure 10). For sequence generation, all trials were at low risk of bias and of these one was at low risk of bias for allocation concealment. Allocation concealment was unclear in two trials. For blinding of participants and providers all trials were at low risk of bias. Assessor blinding was considered separately for all trials and a low risk of bias was found in all three trials. For incomplete outcome data, one trial was at low risk of bias and two were at high risk of bias (this was mainly because of very large amounts of missing data).

Selective outcome reporting and publication bias

Several methods were employed to minimise risk of selective outcome reporting and publication bias. All authors were contacted to request trial registrations and unpublished outcomes, and all authors of included studies, all stakeholders and all pharmaceutical manufacturers were asked to provide unpublished trials. All three trials were registered and two were at low risk of selective outcome reporting bias; one trial was at high risk.

Figure 10: Risk of bias table for pharmacological interventions for acute episodes of bipolar depression



10.4.4 Clinical evidence review

There was very low quality evidence from up to three trials (N = 516) of some benefit for quetiapine or fluoxetine in combination with olanzapine (see Table 40). Authors were asked for data disaggregated by age but these were not provided. The full evidence profiles and associated forest plots can be found in Appendix 27 and Appendix 29, respectively.

Table 40: Summary of results at post-treatment for bipolar depression

Comparison	Response (95% CI)	Symptoms of depression (95% CI)	Discontinuation for any reason (95% CI)	Study ID
Pharmacological interventions				
Medication compared with placebo				
Quetiapine	RR = 1.13 (0.91, 1.39) k = 2; N = 224	SMD = -0.11 (-0.38, 0.15) k = 2; N = 224	RR = 0.93 (0.37, 2.34) k = 2; N = 225	ASTRAZENECA2011B, DELBELLO2009
Fluoxetine and olanzapine	Not reported	SMD = -0.35 (-0.61, -0.09) k = 1; N = 254	RR = 1.05 (0.78, 1.43) k = 1; N = 291	ELILILLY2013
Note. CI = Confidence interval; k = Number of studies; N = Sample size; RR = Relative risk; SMD = Standardised mean difference.				

10.4.5 Health economics evidence

No studies assessing the cost effectiveness of pharmacological and nutritional interventions for acute episodes of bipolar depression in children and young people were identified by the systematic search of the economic literature undertaken for this guideline.

10.5 PHARMACOLOGICAL AND NUTRITIONAL INTERVENTIONS FOR LONG-TERM MANAGEMENT

10.5.1 Clinical review protocol

The review protocol summary, including the review question and eligibility criteria can be found in Table 41 (a complete list of review questions and protocols can be found in Appendix 7; further information about the search strategy can be found in Appendix 8).

Table 41: Clinical review protocol for the review of pharmacological and nutritional interventions for long-term management

Topic	Interventions
Review question(s)	RQ 5.3: For children and young people with bipolar disorder, what are the relative benefits and harms of pharmacological and nutritional interventions for long-term management? 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).
Objectives	To estimate the efficacy of interventions for the long-term management of bipolar disorder.
Criteria for considering studies for the review	
• Intervention	All licensed oral medications (and their combinations) or nutritional intervention delivered for 1 year or more.
• Comparator	Pill placebo Other pharmacological or nutritional interventions
• Types of participants	Children (younger than 13 years) and young people (13 to 18 years) with bipolar disorder. Special consideration will be given to the groups above.
• Outcomes	1) Relapse (all, mania/mixed, depression) 2) Discontinuation (due to side effect, other) 3) Hospitalisation (rate) 4) Quality of life 5) Mortality (all cause, suicides completed) 6) Weight
• Time	At least 1 year after initiating treatment.
• Study design	Randomised controlled trials (RCTs) and cluster RCTs with a parallel group design. Quasi-RCTs, such as trials in which allocation is determined by alternation or date of birth, will be excluded.
• Study setting	Primary, secondary, tertiary health and social care

10.5.2 Studies considered

Two RCTs (N = 120) met the eligibility criteria for this review: FINDLING2005 (Carlson, 2005; Findling et al., 2000; Findling et al., 2005; Townsend et al., 2007) and FINDLING2012 (Findling et al., 2012a). These were published in peer reviewed journals between 2005 and 2012. One study comparing aripiprazole with placebo was excluded because participants were randomised during an acute episode and were followed up for less than 12 months: FINDLING2013 (Findling et al., 2013). No long-term trials of nutritional interventions were located.

Of the two eligible trials, one (N = 60) compared lithium with valproate and one (N = 60) compared aripiprazole with placebo.

Participants were on average 9 years old (mean of means), ranging from 4 to 17 years. A third of the included participants were female (33%). The proportion of participants with a comorbid diagnosis of ADHD was 75%. The average length of treatment was 74 weeks, ranging from 72 to 76 weeks.

Further information about the included and excluded studies can be found in Appendix 27 and Appendix 34, respectively.

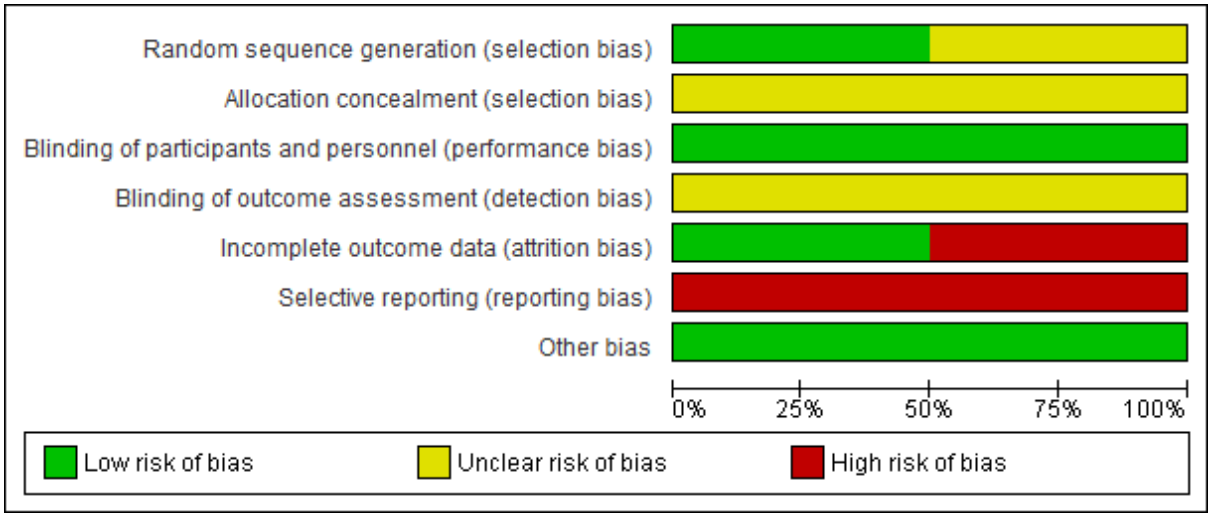
10.5.3 Risk of bias

All included trials were assessed for risk of bias (see Appendix 28 and Figure 11). For sequence generation, one trial was at low risk and one was unclear. Allocation concealment was unclear in both trials. For blinding of participants and providers both trials were at low risk of bias. Assessor blinding was considered separately for all trials and an unclear risk of bias was found for both trials. For incomplete outcome data, one trial was at low risk of bias and one was at high risk (this was mainly because of very large amounts of missing data).

Selective outcome reporting and publication bias

Several methods were employed to minimise risk of selective outcome reporting and publication bias. All authors were contacted to request trial registrations and unpublished outcomes, and all authors of included studies, all stakeholders and all pharmaceutical manufacturers were asked to provide unpublished trials. One trial was known to be registered and both were at high risk of selective outcome reporting bias.

Figure 11: **Risk of bias table for pharmacological interventions for long-term management**



10.5.4 Clinical evidence for review

One trial (FINDLING2005) compared lithium with valproate for up to 76 weeks and one (FINDLING2012) compared aripiprazole with placebo for 72 weeks. Both trials only randomised participants who responded to open-label treatment. There was no evidence of benefit on relapse or discontinuation and in both trials only 10% of the sample completed the study (see Table 42). Authors were asked for data disaggregated by age but these were not provided. The full evidence profiles and associated forest plots can be found in Appendix 27 and Appendix 29, respectively.

Table 42: Summary of results at post-treatment for pharmacological interventions for long-term management

Comparison	Relapse: (hypo)mania/mixed (95% CI)	Relapse: depression (95% CI)	Discontinuation for any reason (95% CI)	Study ID
Pharmacological interventions				
Long-term management				
Aripiprazole compared with placebo	RR = 0.74 (0.51, 1.07) k = 1; N = 60	Not reported	RR = 1.00 (0.40, 2.50) k = 1; N = 60	FINDLING2012
Lithium compared with valproate	RR = 0.79 (0.50, 1.24) k = 1; N = 60	RR = 3.00 (0.33, 27.23) k = 1; N = 60	RR = 1.29 (0.55, 3.00) k = 1; N = 60	FINDLING2005
Note. CI = Confidence interval; k = Number of studies; N = Sample size; RR = Relative risk.				

10.5.5 Health economics evidence

No studies assessing the cost effectiveness of pharmacological and nutritional interventions for long-term management of bipolar disorder in children and young people were identified by the systematic search of the economic literature undertaken for this guideline.

10.6 PSYCHOLOGICAL INTERVENTIONS FOR ACUTE EPISODES OF BIPOLAR DEPRESSION AND/OR LONG-TERM MANAGEMENT

10.6.1 Clinical review protocol

The review protocol summary, including the review question and eligibility criteria can be found in Table 43 (a complete list of review questions and protocols can be found in Appendix 7; further information about the search strategy can be found in Appendix 8).

Table 43: Clinical review protocol for the review of psychological interventions for acute episodes of bipolar depression and/or long-term management

Topic	Interventions
Review question(s)	RQ 5.4: 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? RQ 5.5: For children and young people with bipolar disorder, what are the relative benefits and harms of psychological and psychosocial interventions for long-term management? 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).
Objectives	To estimate the efficacy of psychological interventions to manage bipolar disorder in children and young people.
Criteria for considering studies for the review	
• Intervention	All psychological and psychosocial interventions (for example, cognitive behavioural therapy) with or without pharmacological interventions.
• Comparator	Waitlist, no intervention and other interventions.
• Types of participants	Children (younger than 13 years) and young people (13 to 18 years) with bipolar disorder. Special consideration will be given to the groups above.
• Outcomes	1) Change in symptoms of depression 2) Response (50% reduction or greater) 3) Relapse (all, mania/mixed, depression) 4) Discontinuation (due to side effect, other)
• Time •	For treatments, the main analysis will include outcomes at the end of the intervention. For long-term management, the main analysis will include outcomes after at least 1 year.
• Study design	Randomised controlled trials (RCTs) and cluster RCTs with a parallel group design. Quasi-RCTs, such as trials in which allocation is determined by alternation or date of birth, will be excluded.
• Study setting	Primary, secondary, tertiary health and social care

10.6.2 Studies considered

Two RCTs (N = 223) met the eligibility criteria for this review: CUMMINGS2007 (Cummings & Fristad, 2007; Cummings & Fristad, 2012; Fristad et al., 2009; Mendenhall et al., 2009) and MIKLOWITZ2008 (Miklowitz et al., 2008; Sullivan et al.,

2012).Both studies were published in peer-reviewed journals between 2007 and 2008.One study of family-focused therapy (MIKLOWITZ2013 (Miklowitz et al., 2013)) was excluded because participants had a diagnosis of bipolar disorder not otherwise specified.

Of the two eligible trials one (CUMMINGS2007) involved a comparison of multifamily psychoeducational psychotherapy with waitlist control and one (MIKLOWITZ2008) compared family-focused therapy with enhanced care.

Participants were on average 12 years old (mean of means), ranging from 8 to 17 years. Approximately half of the included participants were female (42%). The proportion of participants with a comorbid diagnosis of ADHD was 93%. The average length of treatment was 33 weeks, ranging from 26 to 39 weeks.

Further information about the included and excluded studies can be found in Appendix 27 and Appendix 34, respectively.

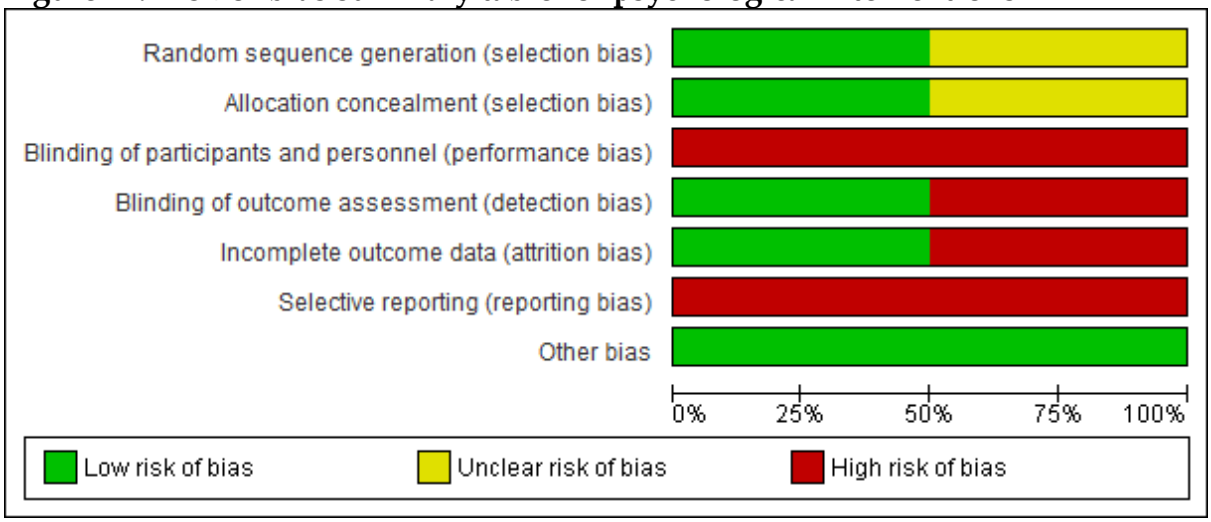
10.6.3 Risk of bias

All included trials were assessed for risk of bias (see Appendix 28 and Figure 12). Both trials were at low risk of bias for sequence generation and allocation concealment. As both trials were of psychological interventions, blinding of participants and providers to the participants' allocation was not possible. Assessor blinding was considered separately for all trials and a low risk of bias was found in one trial. One trial had a high risk of bias for assessor blinding. For incomplete outcome data, one trial was at high risk of bias and one was at low risk of bias.

Selective outcome reporting and publication bias

Several methods were employed to minimise risk of selective outcome reporting and publication bias. All authors were contacted to request trial registrations and unpublished outcomes, and all authors of included studies, all stakeholders and all pharmaceutical manufacturers were asked to provide unpublished trials. Both trials were registered and both were at high risk of selective outcome reporting bias.

Figure 12: Risk of bias summary table for psychological interventions



10.6.4 Clinical evidence review

One trial (CUMMINGS2007, N = 166) involved a comparison of multifamily psychoeducational psychotherapy with waitlist control and one (MIKLOWITZ2008, N = 58) compared family-focused therapy with enhanced care. There was very low quality evidence of no difference between the intervention and comparison group for discontinuation (see Table 44). Both studies reported outcomes using combined measures of manic and depressive symptoms that did not meet the inclusion criteria for this review. Authors were asked for data disaggregated by age but these were not provided. The full evidence profiles and associated forest plots can be found in Appendix 27 and Appendix 29, respectively.

Table 44: Summary of results at post-treatment for psychological interventions

Comparison	Discontinuation for any reason (95% CI)	Study ID
Family-focused therapy compared with (active) control	RR = 0.49 (0.17, 1.39) k = 2; N = 224	CUMMINGS2007, MIKLOWITZ2008
Note. CI = Confidence interval; k = Number of studies; N = Sample size; RR = Relative risk.		

10.6.5 Health economics evidence

No studies assessing the cost effectiveness of psychological interventions for acute episodes of bipolar depression and long-term management of bipolar disorder in children and young people were identified by the systematic search of the economic literature undertaken for this guideline.

10.7 LINKING EVIDENCE TO RECOMMENDATIONS

10.7.1 Relative value placed on the outcomes considered

The GDG determined that the critical outcomes for acute episodes were response to treatment, symptoms and treatment discontinuation. The GDG noted that long-term

management of bipolar disorder in adults focuses on the prevention of new episodes, and they determined that critical outcomes should include relapse and hospitalisation.

The GDG wished to emphasise the critical importance of side effects in this age group, including potential long-term consequences for physical health and cognitive functioning. They identified discontinuation for any reason as a measure of tolerability, and they determined that healthcare professionals, children and young people and their families and carers would need to consider possible short-term and long-term harms before initiating any intervention for an acute episode or for long-term management.

10.7.2 Trade-off between clinical benefits and harms

The GDG expressed concerns about the use of antipsychotics in children and young people but noted that manic episodes may themselves be associated with serious harm. The GDG found that evidence for the treatment of mania in children and young people is broadly consistent with the evidence for adults. On balance, they determined that the trade-off between benefits and harms would be similar to the trade-off for adults, although harms in young people could be greater than in adults. For this reason, pharmacological interventions should be used for no longer than 12 weeks and should be modified in line with the BNF for Children. The GDG wished to emphasise that valproate should not be offered to girls of child-bearing potential because of the risk of polycystic ovary syndrome and risks to the unborn child.

The GDG expressed concern that few studies investigated the management of acute episodes of bipolar depression in children and young people. They noted that many young people with bipolar disorder are incorrectly diagnosed and that recommending pharmacological interventions that are contraindicated in unipolar depression could cause harm. Although there was also little evidence for psychological interventions, the GDG determined that unipolar and bipolar depressive episodes share common psychological features, and they determined that the balance of benefits and harms favours a structured, manualised psychological intervention (CBT or IPT) as first-line treatment. Before any other treatment is offered for bipolar depression in children and young people, the GDG agreed that a multidisciplinary review needs to take place if it is clear that there is no response to CBT or IPT after four to six sessions of therapy. As in unipolar depression, the GDG judged that usually more than one psychological intervention should be tried before embarking on a pharmacological intervention, particularly if there are coexisting factors such as comorbid mental health problems, persisting psychosocial risk factors such as family discord, or parental mental ill health.

Because of possible risks associated with SSRIs in children and young people with bipolar disorder, the GDG decided that the evidence for pharmacological interventions commonly used in unipolar depression would not be applicable to this population. There was also some evidence of benefit for the combination of fluoxetine and olanzapine for bipolar depression, therefore the GDG agreed that

young people with moderate to severe bipolar depression who have not benefited from a psychological intervention might benefit from the pharmacological interventions used to treat acute episodes of bipolar depression in adults. Because the risks associated with antipsychotics and other medications may be greater in young people than in adults, the GDG agreed that pharmacological interventions should be used for no longer than 12 weeks and should be modified in line with the BNF for Children. As in unipolar depression, the GDG considered that pharmacological interventions should only be offered in conjunction with continued psychological intervention.

The GDG acknowledged that children and young people with bipolar disorder and their families experience significant distress as a consequence of their illness and that diagnosis and early management of bipolar disorder is particularly difficult. The GDG determined that many service users and their families could benefit from professional support, and that continued contact with professionals could minimise risk of harm. For these reasons, the GDG recommended a structured individual or family psychological interventions for long-term management. Because there was no evidence that pharmacological interventions are associated with long-term benefit, and because the diagnosis of bipolar disorder in children and young people may not be stable over time, the GDG determined that the long-term use of medication was more likely to cause harm than do good for most children and young people. They therefore determined that pharmacological interventions should not be used for the long-term management of bipolar disorder in children and young people.

10.7.3 Trade-off between net health benefits and resource use

The existing economic evidence in children and young people with bipolar disorder is very sparse; existing limited evidence is characterised by potentially serious limitations and high uncertainty in the results. The GDG considered the relevant economic evidence in adults with bipolar disorder, which indicated that psychological interventions offer clinical benefits at no additional cost compared with standard care. Moreover, the GDG took into account the economic evidence relating to pharmacological treatment of adults with bipolar disorder experiencing a manic episode. The GDG took into account the psychological and financial burden associated with bipolar disorder both for children and young people and for their families, as well as the clinical benefits associated with treatment. The GDG estimated that interventions that are effective in children and young people with bipolar disorder and cost effective in adults with bipolar disorder are likely to be cost-effective in children and young people with bipolar disorder as well.

10.7.4 Quality of the evidence

The reviews of acute and long-term treatments included few studies, and these had serious limitations. There was no evidence of differences across cultural or minority ethnic groups or people of different genders. Evidence for all analyses was very low to low quality and the expert consensus of the GDG was necessary to provide comprehensive guidance for the management of bipolar disorder in this population.

10.7.5 Other considerations

The NICE Technology Appraisal 292 (NICE, 2013a), *Aripiprazole for Treating Moderate to Severe Manic Episodes in Adolescents with Bipolar I disorder,* recommends aripiprazole 'as an option for treating moderate to severe manic episodes in adolescents with bipolar I disorder, within its marketing authorisation (that is, up to 12 weeks of treatment for moderate to severe manic episodes in bipolar I disorder in adolescents aged 13 and older)'. Aripiprazole is therefore included as an option to consider for the treatment of mania in young people alongside the drugs recommended for mania in adults in this guideline.

The GDG also considered the NICE clinical guideline on *Psychosis and Schizophrenia in Children and Young People (NICE, 2013c)* and judged that the same general principles of care applied across both populations, in the following areas: working safely and effectively with children and young people (as this applied to capacity, competence and current legislation); establishing relationships with children/young people and their parents/carers; communication and information; culture, ethnicity and social inclusion; and transfer and discharge from services. Therefore the GDG saw the benefit of referring to these general principles of care in *Psychosis and Schizophrenia in Children and Young People* to improve the experience of care of children and young people with bipolar disorder.

10.8 RECOMMENDATIONS

10.8.1 Clinical practice recommendations

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

10.8.1.1 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.

Management in young people

10.8.1.2 When offering treatment to young people with bipolar disorder, take into account their cognitive capacity, emotional maturity and developmental level.

Mania

10.8.1.3 For the treatment of mania or hypomania in young people consider following the recommendations for adults in section 6.6.1[53]. Aripiprazole is also a treatment option in line with NICE technology appraisal guidance on aripiprazole for treating moderate to severe manic episodes in adolescents with bipolar I disorder. 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 continue antipsychotic treatment for longer than 12 weeks.

10.8.1.4 Do not offer valproate to girls of childbearing potential.

Bipolar depression

10.8.1.5 Offer a structured, manualised 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.

10.8.1.6 If after 4 to 6 sessions there is no response to cognitive behavioural therapy or interpersonal therapy, carry out a multidisciplinary review.

10.8.1.7 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.

10.8.1.8 After the multidisciplinary review, if the young person's bipolar depression is moderate to severe, cautiously consider a pharmacological intervention in addition to a psychological intervention. Follow the recommendations for pharmacological interventions for adults in recommendations 6.6.1.14-6.6.1.18[54] but refer to the BNF for children to modify drug treatments, and do not continue antipsychotic treatment for longer than 12 weeks.

Long-term management

10.8.1.9 Consider a structured individual or family psychological intervention for managing bipolar disorder in young people in the longer term.

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[53] 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.

[54] 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.

10.8.2 Research recommendations

10.8.2.1 What is the clinical and cost effectiveness of structured psychological interventions for young people with bipolar depression?

10.8.2.2 What is the prevalence over a 12 month period of bipolar I disorder in children and young people presenting to secondary care mental health services with depression?

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