SAMPLE CHAPTER FROM:

Bipolar Disorder

Management of Bipolar Disorder in Adults, Children and Adolescents in Primary and Secondary Care

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4. BIPOLAR DISORDER AND ITS DIAGNOSIS

4.1 THE DISORDER

4.1.1 Overview

The concept of bipolar disorder grew out of Emil Kraepelin's classification of manic depressive insanity, which was postulated around the end of the 19th century. However, descriptions of frenetic activity associated with the manic state can be found in the writings of Hippocrates and as far back as the ancient Egyptians. In 1957 Leonhard coined the term 'bipolar' for those patients with depression who also experienced mania. 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 stood the test of time and 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 depression, which was tightly associated with psychosis. It became recognised that not all patients who experience mania and depression become psychotic and therefore psychosis should not be required for a diagnosis. In this modern conceptualisation, bipolar disorder is a cyclical mood disorder involving periods of profound disruption to mood and behaviour interspersed with periods of more or less full recovery. The key feature of bipolar disorder is the experience of hypomania or mania – grandiose and expansive 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 4.4 below). ICD-10 requires two discrete mood episodes, at least one of which must be manic. In DSM-IV a single episode of mania or a single episode of hypomania plus a single 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-IV a distinction is drawn between bipolar I disorder, in which the patient suffers full-blown manic episodes (most commonly interspersed with episodes of major depression), and bipolar II disorder, in which the

patient experiences depressive episodes and less severe manic symptoms, classed as hypomanic episodes (it must be noted that ICD-10 does not include bipolar II disorder). Cyclothymia is a condition in which the patient has 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 for the patient and interferes with everyday functioning. '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.

4.1.2 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. Patients with bipolar disorder spend a substantial proportion of time suffering from syndromal or sub-syndromal 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.*, 2002). 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.*, 2003). A similar study by the Stanley Foundation Bipolar Network monitored 258 bipolar patients (three quarters of whom had bipolar I disorder) for a 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%) suffered four or more mood episodes in a year (Post *et al.*, 2003). However, the proportion of time spent depressed did not differ between bipolar I and II patients. To date, such studies have all been conducted on adults and it is not clear whether these observations extend to children or adolescents with bipolar disorder.

Major depressive episodes in bipolar disorder are similar to those experienced in unipolar major depression. Patients suffer depressed mood and experience 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. For patients presenting with a first episode of depression, it may not be possible to distinguish between those who will go on to suffer recurrent unipolar depression and those who will develop bipolar disorder. However, evidence suggests there may be subtle differences between bipolar and unipolar depression. In particular, depression in the course of bipolar disorder may be more likely to show signs of psychomotor retardation, to have melancholic

features (such as feelings of worthlessness and marked anhedonia), to show features of atypical depression (such as hypersomnia and weight gain) (Mitchell & Mahli, 2004) and to show psychotic features – especially in young people (Strober & Carlson, 1982). Patients experiencing a first episode of depression who display these features and have a family history of bipolar disorder may be at increased risk of developing bipolar disorder.

Sub-syndromal depressive symptoms are common in patients with bipolar disorder (especially those with bipolar II disorder) and are often associated with significant interpersonal or occupational disability. The management of these chronic, low-grade depressive symptoms is therefore of major importance, but is also a substantial treatment challenge.

Vignette of a patient with sub-syndromal depression

Unfortunately, living with bipolar disorder isn't always simply a case of being either well or ill – there can be an awful lot of grey in between. It can be very difficult to work out what is 'normal' mood and what isn't.

Diagnosed with rapid-cycling bipolar I aged 19, by 23 I was on a combination of lithium and carbamazepine, which seemed to work for me. However, at some point the following year, in agreement with my psychiatrist, I cut back on my medication. I now know that this resulted in a slow and imperceptible slide into depression. At the time, I just thought I was going through a difficult patch because I was stuck at home convalescing with severe back pain.

It seems unbelievable now, but looking back it appears I remained in this mild to moderate depressed state for about 6 years. I wasn't going up and down because the drugs stopped the cycling, so I didn't realise I was ill. I assumed I was well because I was still taking what I thought was the best possible combination of medication for me.

I was desperately unhappy. Small things like going to the shops and talking to people – even my girlfriend – left me wracked with anxiety. I just came to think I was miserable by nature. I was regularly in contact with several general practitioners (GPs) and psychiatrists over this time, but none identified that I was experiencing sub-syndromal symptoms.

I think there were three reasons for this. My symptoms weren't full-blown major depression – mostly I wasn't suicidal – and I was able to hold down a job and a relationship, so on the surface I appeared to be functioning. Also, my psychiatrists seemed to rely on my judgement as to my health and perhaps would have made treatment recommendations if I'd complained bitterly about feeling depressed. Unfortunately, without having a recent benchmark of experiencing 'normal' mood to compare against, I didn't realise I was depressed. However, there were lots of things which in hindsight were tell-tale signs that I wasn't well.

Continued

Vignette of a patient with subsyndromal depression (*Continued*)

I developed lots of physical aches and pains. My back pain got steadily worse, and I developed neck pain and mysterious tingles in the arms and legs. It later became apparent that these physical problems resulted from muscular trigger points all over my body caused by the depression.

I was so anxious that I could barely speak to anyone without stuttering. My speech became such a problem, I even started seeing a psychologist, which didn't address the real problem.

As the years passed, I felt more and more unhappy. I felt hopeless about the future and decided that life was not worth living. My attempt to take my life finally prompted my psychiatrist into taking some action, and he prescribed mirtazapine. This was a revelation. It immediately sent me into psychotic rapid cycling, but at the same time it dawned on me that I had in fact been unknowingly depressed for ages. I could now tell that my mood, even though it was still up and down, was 'on average', much better than it had been.

I was put on lamotrigine instead of the carbamazepine and then, when that failed to lift my baseline mood, quetiapine. As my mood improved and stabilised over the following months, my physical symptoms of depression – the aches and pains – began to drop away. The easing of my physical symptoms was perhaps the best objective indicator for me that my mood was stabilising at a 'normal' level. Without those outward signs of improvement, it was hard to gauge what 'normal' mood was. I fear that many patients are in the same predicament I was. Psychiatrists must always be vigilant for sub-syndromal symptoms – they ruin lives.

The risk of suicide is greatly elevated during depressive episodes. Approximately 17% of patients with bipolar I disorder and 24% of patients with bipolar II disorder attempt suicide during the course of their illness (Rihmer & Kiss, 2002). Most suicide attempts and most completed suicides occur in the depressed phase of the illness and patients with bipolar II disorder are at especially high risk (Baldessarini *et al.*, 2003a). Annually around 0.4% of patients with bipolar disorder will die by suicide, which is vastly greater than the international population average of 0.017% (Baldessarini & Tondo, 2003). The standardised mortality ratio (SMR) for suicide in bipolar disorder is estimated to be 15 for men and 22.4 for women (Osby *et al.*, 2001).

Mania and hypomania

The longitudinal study of bipolar symptomatology mentioned above reported that patients with bipolar I disorder suffered syndromal or sub-syndromal manic or hypomanic symptoms approximately 9% of the time over 12 years (Judd *et al.*, 2002). For patients with bipolar II disorder, approximately 1% of weeks were spent hypomanic (Judd *et al.*, 2003). Similarly, the 1-year prospective follow-up study conducted by the Stanley Foundation Bipolar Network reported that on average patients experienced syndromal manic symptoms 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 patients with bipolar I or II disorder. In the majority of cases, individuals with bipolar disorder will experience both manic and depressive episodes throughout the course of their illness, although one epidemiological survey identified a sub-population 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 patients with mania often require hospitalisation to minimise harm to themselves or others.

Patients in the acute 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 patients with pure mania suggest dysphoric mood (such as depression, guilt and anxiety) can be prominent in some manic patients (Cassidy *et al.*, 1998; Cassidy & Carroll, 2001).

The clinical presentation of mania is marked by several features, which can lead to significant impairment to functioning (see also the vignette below). These may include inflated self-esteem and disinhibition, for example, over-familiar or fractious and outspoken behaviour. To the observer, an individual with mania may 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, flight of ideas can render speech incoherent and impossible to understand. The patient may find that racing thoughts or ideas can be difficult to piece together into a coherent whole. Patients often describe increased productivity and creativity during the early stages of mania which may feel satisfying and rewarding. However, as the episode worsens severe distractibility, restlessness, and difficulty concentrating can render the completion of tasks impossible. Patients often experience a decreased need for sleep and begin sleeping less without feeling tired. 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 with a high potential for negative consequences. Libido may rise, with increased interest in sexual activity, which may culminate in risky sexual practices. In severe cases individuals may develop psychotic symptoms such as grandiose delusions and mood-congruent hallucinations – for example, the voice of God sending messages of special purpose. 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. 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 patients 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 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 non-depressed and the change is noticed by others, but it is not associated with marked impairment in social or occupational function. According to the DSM-IV 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 4.4.2 below).

Vignette of a patient with mania

I first fell ill with rapid-cycling bipolar disorder at the age of 19. At first, when manic, I felt 'on top of the world', much more sociable than normal and very active and self-confident. I'd have an 'up' of about 9 days, followed by a 'down' for the same period. The same pattern would repeat itself with my mood swings becoming more and more extreme each time. Within a few months, I was experiencing full-blown psychosis. When manic, I was euphoric. Everything was in overdrive. I would only sleep for an hour or two a night. I craved stimulation, whether it was smoking, even though I'm a non-smoker, driving fast or listening to more and much louder music than was normal for me.

As I entered a manic cycle, my thoughts would start to race. I'd develop delusions of grandeur. Suddenly everything seemed to revolve around me and I was the most important thing in the world. The most extreme manifestation of this was the religious delusions I experienced when psychotic. Despite not having a Christian upbringing, I came to secretly believe I was some sort of manifestation of Jesus Christ on a God-given mission. Wherever I looked I saw 'the face of God' staring out at me. For a while, I was haunted by light switches turn with the screw either side of the switch representing the eyes and nose of a face.

And then, as sure as night follows day, everything would come crashing down after about 9 days and I would plunge into a deep depression, in bed 18 hours a day. My thoughts became painfully sluggish and grossly distorted in a negative way. I felt suicidal and haunted by irrational self-doubt such as the belief I was certain to end up homeless or that people thought I was a paedophile because I was standing outside a school.

Mixed states

In a full-blown mixed episode, criteria are met for a depressive episode and a manic episode nearly every day for at least 1 week (American Psychiatric Association, 1994). However, a mixture of manic and depressed symptoms may occur without reaching full diagnostic criteria. For example, a patient may have racing thoughts, agitation, overactivity and flight of ideas, but feel worthless, guilty and suicidal. The

patients with bipolar I disorder who took part in the 12-year longitudinal study mentioned previously spent an average 6% of weeks in a mixed or cycling state (where polarity of episode was changing and symptoms of both were present) (Judd *et al.*, 2002). For patients with bipolar II disorder the proportion was just over 2% (Judd *et al.*, 2003). It is estimated that approximately two thirds of patients will suffer a mixed episode at some point in their illness (Mackin & Young, 2005). A study of 441 patients with bipolar disorder reported that subclinical mixed episodes are common – with 70% of those in a depressed episode showing clinically significant signs of hypomania and 94% of those with mania or hypomania showing significant depressive symptoms (Bauer *et al.*, 2005). Sub-threshold mixed episodes were more than twice as prevalent as threshold mixed episodes. The combination of morbid, depressed affect with overactivity and racing thoughts makes mixed states a particularly dangerous time for people with bipolar disorder.

Cycle frequency

There is a large amount of variation in how often patients suffer mood episodes and no criteria exist to define 'normal' cycle frequency. Some patients 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 fail to fully recover between episodes. A subset of patients suffers from 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 review of the last 30 years of research on rapid versus non-rapid cycling indicated differences in illness course and prognosis (Mackin & Young, 2004) and reports suggest the distinction is of value as a course modifier (Maj *et al.*, 1994; Maj *et al.*, 1999). Patients with a rapid cycling illness course tend to be more treatment resistant, suffer a greater burden of depressive episodes and have a higher incidence of substance misuse. A recent study in a sample of 456 bipolar probands identified 91 (20%) patients with a rapid cycling illness who, in comparison to those without rapid cycling, suffered more severe mood symptoms and a greater degree of functional impairment (Schneck *et al.*, 2004). Further data from this cohort suggests rapid cycling is not more common in females than males (Baldassano *et al.*, 2005) as had been indicated by previous studies in smaller samples.

4.2 INCIDENCE AND PREVALENCE

Community-based epidemiological studies consistently report the lifetime prevalence of bipolar I disorder to be approximately 1% (based on DSM-III-R, or DSM-IV criteria). A review of epidemiological surveys in six non-European countries reported that the lifetime rate of bipolar I disorder ranged from 0.3% to 1.5% (Weissman *et al.*, 1996).

Rates reported in European studies have varied more widely from 0.1% to 2.4% (Faravelli *et al.*, 1990; Pini *et al.*, 2005; Szadoczky *et al.*, 1998; ten Have *et al.*, 2002; Regeer *et al.*, 2004). A recent study in Australia reported a lifetime prevalence of 2.5% (Goldney *et al.*, 2005). Estimates of the lifetime prevalence of bipolar II disorder vary more widely due to differences in diagnostic practices both over time and geography. One early American study estimated the lifetime risk of bipolar II disorder to be approximately 0.6% (Weissman & Myers, 1978), whereas more recent studies have suggested a lifetime prevalence of between 5.5%–10.9% for more broadly-defined bipolar II disorder (Angst, 1998; Angst *et al.*, 2003). European studies have produced more conservative prevalence estimates of between 0.2%–2.0% (Faravelli, *et al.*, 1990; Szadoczky, *et al.*, 1998).

Age at onset

Bipolar disorder has a fairly early age of onset, with the first episode usually occurring before the age of 30. In the review of epidemiological surveys mentioned previously, the mean age at onset reported by each of the six studies ranged from 17.1–29 years, with a peak in onset rate occurring between the ages of 15 and 19 years (Weissman *et al.*, 1996). A large retrospective study of patients with bipolar disorder reported that there was an average 8 years' delay from a patient's first recollected mood episode to receiving a diagnosis of bipolar disorder (Mantere *et al.*, 2004). Affective or functional changes occurring prior to the development of bipolar disorder have not been studied systematically. One study provided some evidence of prodromal mood disturbance in patients who went on to develop bipolar disorder, but could not distinguish between patients who went on to develop a different psychiatric disorder (Thompson *et al.*, 2003). In a longitudinal study, the presence of an anxiety disorder in adolescence predicted an increased risk of bipolar disorder in early adulthood (Johnson *et al.*, 2000), suggesting early psychopathology other than mood disturbance may predict later bipolar disorder. While most episodes of bipolar disorder first present by 30 years of age, it can present later in life. Late onset bipolar disorder is characterised by a reduced family history of psychiatric disorder, greater medical comorbidities and a greater incidence of subsequent neurological problems. Late onset bipolar disorder may also show a greater latency between the initial depressive episode and subsequent manic episode.

Gender

Bipolar I disorder occurs approximately equally in both sexes (Lloyd *et al.*, 2005). The symptom profile may differ between men and women; there is some evidence that women tend to experience more episodes of mixed or dysphoric mania than men (Arnold *et al.*, 2000). There is disputed evidence that bipolar II disorder is more common in females than males. Recent data from a large sample of patients with bipolar disorder found a significantly higher incidence of bipolar II disorder in women (29.0%) than men (15.3%) (Baldassano *et al.*, 2005). 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). However, a population

study using broader criteria for bipolar II disorder not requiring this minimum duration found a 1-year prevalence rate for hypomania of 7.4% in females and only 2.7% in males (Angst *et al.*, 2003).

For some women, the experience of psychosis in the postnatal period may be the first indicator of bipolar illness. In one study of a well-characterised sample of mothers with bipolar affective puerperal psychosis, almost two thirds went on to experience a non-puerperal mood episode (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 recent Aesop Study (Lloyd *et al.*, 2005), which examined the incidence of bipolar disorder in three cities in the UK, reported a higher incidence amongst black and minority ethic groups than in a comparable white population and this finding is consistent with other UK-based studies (Leff *et al.*, 1976; Van Oss *et al.*, 1996). The evidence for the increased incidence of bipolar disorder in minority ethnic groups is similar to that for schizophrenia. In addition to the increased prevalence of bipolar disorder in black and minority ethnic groups 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 Afro-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 Afro-Caribbean groups were also more likely to present with severe psychotic symptoms when first presenting with mania. A study in the United States looking at the experience of African Americans with bipolar disorder (Kupfer *et al.*, 2005) reported that Afro-Caribbeans were more likely to be hospitalised than Caucasians (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 misuse. 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 amongst black and minority ethnic patients 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 suffering from 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. An important conclusion to be drawn from the evidence is that services ought to be more available and accessible. This may present a particular challenge for first-episode psychosis services currently being developed in the English healthcare system (Department of Health 2002). More immediately, the evidence suggests that clinicians responsible for the assessment and provision of services for people with serious mental illness should be aware of the increased incidence of bipolar disorder in black and minority ethnic groups and also that 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

Findings indicate that people with intellectual disability are at high risk of developing comorbid serious mental illness, including bipolar disorder. However, dual diagnosis is often overlooked due to difficulties associated with establishing a diagnosis of a mental disorder in people with an intellectual disability, a problem which is heightened when the individual's capacity to participate in a clinical assessment is limited (White *et al.*, 2005). For example, until relatively recently, it was considered that Down's syndrome precluded a diagnosis of mania, or gave rise to an atypical presentation (Cooper & Collacot, 1993). However, this has been shown not to be the case and the clinical features of mania are noted to be similar to those previously described in individuals with learning difficulties due to other causes. However, it has been suggested that rapid-cycling bipolar disorder in people with learning difficulties may differ from non-learning difficulty populations in terms of a relative preponderance of males and a potentially different response to medication (Vanstraelen & Tyrer, 1999). Given the uncertainty around treatment options, the most important point is that the disorder is appropriately recognised in the learning difficulty population and treated effectively.

Clinical practice recommendation

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

Rapid cycling

Estimates of the prevalence of rapid cycling within bipolar I and II disorders have ranged from 13–56% depending on the definition of rapid cycling used, but most studies suggest approximately 20% (Mackin & Young, 2004). Although previous studies suggested a strong association between rapid cycling and female gender, reporting that more than two thirds of those with a rapid cycling illness were women

(Bauer *et al.*, 1994; Schneck *et al.*, 2004), a more recent large study reported an equal prevalence in both sexes (Baldassano *et al.*, 2005). The index episode tends to be depression in those with a rapid cycling course and the clinical picture is dominated by depressive symptoms and episodes (Calabrese *et al.*, 2001). As such, several studies have documented that rapid cycling is more common in bipolar II disorder. However, recent investigations in large samples followed longitudinally for several years have suggested it is equally prevalent in bipolar I and II disorders (Kupka *et al.*, 2005; Schneck *et al.*, 2004). In general, rapid cycling is associated with an earlier age of onset, greater severity of symptoms and treatment resistance (Coryell *et al.*, 2003).

4.3 AETIOLOGY

Despite its long history, little is known about what causes bipolar disorder. Explanations in terms of psychosocial factors were mainstream in the 19th century, but recent research has concentrated on identifying possible biological underpinnings of the disorder including genetic components, neurohormonal abnormalities and structural brain differences. There has also been some recent but scanty revival of interest in psychosocial research, including life events and social rhythm (Malkoff-Schwartz *et al.*, 1998), and behavioural activation system (Depue *et al.*, 1987). However, currently there is no overarching explanation and the heterogeneous clinical presentation of bipolar disorder suggests that a number of different mechanisms are involved.

4.3.1 Genetics

Affective disorders often cluster in families, indicating that they may have a heritable basis. Evidence from a number of different sources has identified a high heritable component to bipolar disorder, suggesting a potentially large genetic contribution to the illness. However, the inheritance pattern is not simple and is not consistent with a single gene model of bipolar disorder. Instead it is likely that many genes are involved that convey susceptibility to a spectrum of psychiatric illnesses. There may also be genes that reduce the risk of developing bipolar disorder. No specific genes have been identified, but several areas of the genome are being investigated.

Familial inheritance 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 co-twins of bipolar probands face a 40–70% risk of developing bipolar disorder and the concordance rate of approximately 60% is markedly higher than that for dizygotic

twins (Craddock & Jones, 1999). The difference in concordance rates between monozygotic and dizygotic twins can be used to estimate the size of the genetic contribution to the illness. The largest twin study investigating heritability to date 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.

Linkage studies

Attempts to identify candidate genes using families with multiple cases of bipolar disorder have suggested several potential areas of interest including 4p16, 12q23–q24, 16p13, 21q22 and Xq24–q26 (Craddock & Jones, 2001). More recently McQueen and colleagues (2005) reported on the combined analysis of 11 linkage studies (comprising 5179 individuals from 1067 families) and established significant linkage on chromosomes 6q and 8q. Using a sibling pair genome-wide scan approach, Lambert and colleagues (2005) have confirmed evidence of linkage between bipolar disorder and the chromosomal region 6q16–q21 but also showed linkage at 4q12–q21, an area of interest on the genome reported by Craddock and Jones (2001). As can be seen, studies to date have identified broad areas of the genome rather than specific genes; therefore much work remains before this research can have clinical utility.

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. This method has identified the gene for catechol-O-methyl transferase (COMT), an enzyme involved in the breakdown of catecholamines, as a potential course-modifier in bipolar disorder (Craddock & Jones, 2001). In patients with bipolar disorder, those with the low-activity version of the gene are significantly more likely to have rapid-cycling bipolar disorder. However, the gene itself occurs equally often in people with and without bipolar disorder, therefore it is not a candidate susceptibility gene.

Increasing evidence suggests an overlap in genetic susceptibility across the classification systems that separated psychotic disorders into schizophrenia and bipolar disorder with association findings at several loci (Craddock *et al.*, 2005). Identification of susceptibility genes may have a major impact on our understanding of pathophysiology and lead to changes in classification and perhaps management.

4.3.2 Neurohormonal abnormalities

Much attention recently has focussed 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 which blocks the corticosteroid receptors in the hypothalamus. A number of studies have reported abnormalities in this system in patients 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. Interestingly, signs of HPA axis dysfunction have been observed in all stages of bipolar illness, including during remission. Such dysfunction could underlie susceptibility to future episodes and account for the often chronic course of bipolar disorder.

HPT axis and rapid cycling
The HPT axis is also of interest in bipolar disorder, particularly in the genesis of rapid cycling. Abnormalities of thyroid function are noted in patients with depression and mania. Subclinical hypothyroidism is seen in a significant proportion of patients with treatment-resistant depression. Along with evidence of mild hypothyroidism, patients 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 patients with rapid-cycling bipolar disorder have evidence of hypothyroidism, which contrasts with only 2–5% of depressed patients in general (Muller, 2002). Since thyroid hormones have profound effects on mood and behaviour, dysfunction in the HPT axis could explain some of the presenting symptoms of patients with bipolar disorder.

4.3.3 Structural brain differences

In comparison with work on schizophrenia, there have been relatively few studies investigating structural brain differences in patients with bipolar disorder and findings have been contradictory. A major review of neuroanatomical studies in bipolar disorder reported some evidence of enlarged ventricles and abnormalities in the frontal and

temporal lobes in at least a sub-population of patients (Bearden *et al.*, 2005). An excess of white matter lesions has also been reported (Altshuler, 1995) and one study reported that the number of white matter lesions correlated negatively with functional outcome (Moore *et al.*, 2001). Although the hope in identifying a neuroanatomical profile of bipolar disorder is to develop an understanding of neurodevelopmental or genetic contributions to the illness, it is currently unknown whether differences are the cause or consequence of affective disorder. Interestingly, neuroimaging in the unaffected first-degree relatives of bipolar probands has identified grey matter deficits that correlated with the degree of genetic risk of developing the disorder (McDonald *et al.*, 2004). This suggests that structural brain differences are present before illness onset. However, it is yet to be understood how or whether these differences contribute to observed symptoms.

4.3.4 Psychosocial influences

Although much recent research has focussed 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 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 age at 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 patients with bipolar disorder (Yan *et al.*, 2004) and levels of depressive and manic symptoms (Kim & Miklowitz, 2004; Miklowitz *et al.*, 2005). The high prevalence of bipolar disorder in ethnic minority groups, as demonstrated in recent studies in the UK (Lloyd *et al.*, 2005), may relate to the psychosocial stressors of social isolation and lack of social support often experienced by these groups (Bentall, 2004; Leff, 2001).

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 misuse disorders, increased axis I and II

comorbidities, and a rapid cycling course (Leverich *et al.*, 2002; Garno *et al.*, 2005). It is estimated that 16% of patients with bipolar disorder also have PTSD, the development of which is associated with greater exposure to trauma, higher levels of neuroticism, lower social support and lower social class (Otto *et al.*, 2004). A study of the impact of childhood abuse on the illness course of adult male patients with bipolar disorder found that those who reported both sexual and physical abuse had higher rates of current PTSD and lifetime alcohol misuse disorders, a poorer level of social functioning, a greater number of lifetime depressive episodes and an increased likelihood of at least one suicide attempt (Brown *et al.*, in press).

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. This formulation suggests there is a degree of fragility to the manic state and evidence of negative self-concept or thinking styles should be evident in both patients with mania and remitted patients. There is evidence that patients with bipolar disorder have a negative self-concept, highly variable self-esteem and increased drive even during the remitted state (Winters & Neale, 1985; Lyon *et al.*, 1999; Bentall *et al.*, in press). Studies using implicit or disguised measures of explanatory style have found that remitted patients tend to attribute negative outcomes to themselves, but positive outcomes to others – a thinking style typical of patients with depression (Winters & Neale, 1985; Lyon *et al.*, 1999). However, this may be better understood as chronic low-grade depression due either to the debilitating aspects of the illness or due to the physiological processes outlined above rather than as the underlying fuel for mania. Nonetheless, psychological theories of bipolar disorder may help observers understand some of the ideas and beliefs held by those suffering from mania.

4.4 DIAGNOSIS OF ADULTS

4.4.1 Criteria for diagnosis

Both the DSM-IV 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-IV

Full criteria for manic, hypomanic, depressed and mixed episodes are outlined in Box 1.

DSM-IV recognises a spectrum of bipolar disorders consisting of bipolar I disorder, bipolar II disorder and cyclothymia. A diagnosis of bipolar I disorder requires the

Box 1: DSM-IV criteria for a manic episode
(American Psychiatric Association, 1994, p. 332)

A. A distinct period of abnormally and persistently elevated, expansive or irritable mood, lasting at least 1 week (or any duration if hospitalisation is necessary).

B. During the period of mood disturbance, three (or more) of the following symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree:

1. inflated self-esteem or grandiosity
2. decreased need for sleep (e.g., feels rested after only 3 hours of sleep)
3. more talkative than usual or pressure to keep talking
4. flight of ideas or subjective experience that thoughts are racing
5. distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli)
6. increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation
7. excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)

experience of at least one manic or mixed episode. Frequently, people with bipolar disorder will have experienced one or more depressed 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, severe without psychotic features, severe with psychotic features, in partial remission, in full remission, with catatonic features or with postnatal onset.

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 manic or mixed episodes rules out a diagnosis of bipolar II disorder. Mood specifiers are the same as for bipolar I disorder.

Cyclothymia describes a chronic disturbance of mood consisting of a number of periods of depression and hypomania. Depressive symptoms must not meet full severity or duration criteria for a major depressive episode: however, hypomanic symptoms may meet full criteria for a hypomanic episode. The fluctuating mood should have lasted at least 2 years (1 year in children and adolescents) and must be the source of significant functional impairment.

ICD-10

Full criteria for manic, hypomanic, depressed and mixed episodes are outlined in Box 2.

A diagnosis of bipolar affective disorder requires the experience of at least two mood episodes, one of which must be manic or hypomanic. Unlike DSM-IV, a single

Box 2: ICD-10 criteria for a manic episode
(World Health Organization, 1992)

F30. Manic episode

All the subdivisions of this category should be used only for a single episode. Hypomanic or manic episodes in individuals who have had one or more previous affective episodes (depressive, hypomanic, manic, or mixed) should be coded as bipolar affective disorder (F31.-)

Includes: bipolar disorder, single manic episode

F30.0 Hypomania

A disorder characterised by a persistent mild elevation of mood, increases energy and activity and usually marked feelings of well being and both physical and mental efficiency. Increase sociability, talkativeness. Over familiarity, increases sexual energy, and a decreased need for sleep are often present but not to the extent that they lead to severe disruption of work or result in social rejection. Irritability, conceit and boorish behaviour may take the place of the more usual euphoric sociability. The disturbances of mood and behaviour are not accompanied by hallucinations or delusions.

F30.1 Mania without psychotic symptoms

Mood is elevated out of keeping with the patient's circumstances and may vary from carefree joviality to almost uncontrollable excitement. Elation is accompanied by increased energy, resulting in overactivity, pressure of speech and a decreased need for sleep. Attention cannot be sustained, and there is often marked distractibility. Self-esteem is often inflated with grandiose ideas and overconfidence. Loss of normal social inhibitions may result in behaviour that is reckless, foolhardy or inappropriate to the circumstances, and out of character.

F30.2 Mania with psychotic symptoms

In addition to the clinical picture described in F30.1, delusions (usually grandiose) or hallucinations (usually of voices speaking directly to the patient) are present, or the excitement, excessive motor activity and flight of ideas are so extreme that the subject is incomprehensible or inaccessible to ordinary communication.

Mania with:
- mood-congruent psychotic symptoms
- mood-incongruent psychotic symptoms

Manic stupor

F30.8 Other manic episodes

F30.9 Manic episode, unspecified

Includes: Mania NOS [not otherwise specified]

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 include bipolar II disorder as a separate diagnostic entity.

4.4.2 Diagnostic issues

Hypomania

A matter of considerable and ongoing debate in bipolar disorder is the definition of hypomania. In both DSM-IV 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. 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. 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 overactivity 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 patients with subtle signs of bipolarity. 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.

Clinical practice recommendations

Assessment in primary care

4.4.2.1 Primary care clinicians should ask about hypomanic symptoms when assessing a patient with depression and overactive, disinhibited behaviour.

4.4.2.2 Primary care clinicians should normally refer patients with suspected bipolar disorder for a specialist mental health assessment and development of a care plan, if either of the following are present:

- periods of overactive, disinhibited behaviour lasting at least 4 days with or without periods of depression, or
- three or more recurrent depressive episodes in the context of a history of overactive, disinhibited behaviour.

4.4.2.3 Primary care clinicians should urgently refer patients with mania or severe depression who are a danger to themselves or other people, to specialist mental health services.

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

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

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

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

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

Assessment in secondary care

4.4.2.7 When assessing suspected bipolar disorder healthcare professionals should:

- take a full history including family history, a review of all previous episodes and any symptoms between episodes
- assess the patient's symptom profile, triggers to previous episodes, social and personal functioning, comorbidities including substance misuse and anxiety, risk, physical health, and current psychosocial stressors
- obtain where possible, and within the bounds of confidentiality, a corroborative history from a family member or carer
- consider using formal criteria, including self-rating scales such as the Mood Disorder Questionnaire (MDQ).[10]

[10]Hirschfeld, R.M., Williams, J.B., Spitzer, R.L., *et al*. (2001) Development and validation of a screening instrument for bipolar spectrum disorder: the Mood Disorder Questionnaire. *American Journal of Psychiatry, 158*. 1743–1744.

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

Special considerations for older people in secondary care

4.4.2.9 Local services should have a robust protocol for transferring patients from services for adults of working age to those for older people (usually those older than 65 years). This should include agreement about the clinical parameters to take into account (for example, medical comorbidity or cognitive deterioration) and what to do if the patient is no longer in contact with services for adults of working age. Referral or re-referral should be based on the needs of the patient first, rather than simply their chronological age.

4.4.3 Distinguishing bipolar disorder from other diagnoses

The manic stage 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
In the acute stages mania resembles schizophrenia. Between one tenth and one fifth of manic patients 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 patient 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. Individuals with predominately psychotic symptoms who also suffer affective

disturbance may be more appropriately diagnosed with schizoaffective disorder, although this may be difficult to distinguish from a severe form 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

Manic-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 manic symptoms last much longer. Since substance misuse is a common comorbidity in bipolar disorder (see Section 4.4.5), 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 manic episode and the effects of substance use. A clear history of stimulant drug use preceding any manic symptoms with no previous history of manic, hypomanic or mixed 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 and be aware of the possibility that this episode may be the first presentation of bipolar disorder triggered by use of drugs. Urine screening may be necessary to rule out the use of illicit substances.

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 patients 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 patients who have developed the illness only after suffering 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 of the effective 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 patients 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.

Clinical practice recommendation

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

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

4.4.4 Assessment methods

Screening
The Mood Disorder Questionnaire (MDQ) is a brief, easy-to-use, self-report form, which has been validated against the structured clinical interview for DSM-IV (SCID) – see below (Hirschfeld *et al.*, 2000). It has shown good sensitivity and specificity in a clinical population but in a general population sample, while the specificity remained high, the sensitivity was low (Hirschfeld *et al.*, 2003a).

Diagnosis
The most widely used and validated instrument for generating a DSM-IV Axis I diagnosis is the SCID which also generates diagnoses on the other DSM-IV axes. The structured interview includes six modules, which cover a wide range of possible different disorders, and the SCID is thus comprehensive and its validity in clinical samples is high. The reliability is lowest in patients whose symptoms are less well defined (Baldassano, 2005). 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 patients and can be very useful as a therapeutic tool (Denicoff *et al.*, 2000). Another instrument suitable for bipolar disorder is the Altman Self-Rating Mania Scale (Altman *et al.*, 1997). However, most self-report scales are not very specific and are less sensitive to detecting problems with cognition and functional impairment.

4.4.5 Comorbidity

Comorbidity is the norm rather than the exception in bipolar disorder. A study of 288 patients with bipolar disorder found 65% had suffered from 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). However, 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.

Anxiety and substance misuse disorders
The most common comorbid axis I disorders are anxiety and substance misuse disorders, both of which occur in approximately 30–50% of patients with bipolar disorder. Those who have comorbidities tend to have had an earlier age at onset and are more likely to experience cycle acceleration and suffer a more severe illness and self-harm than those without. In those with concurrent substance misuse, 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. In general, substance misuse is approximately twice as common in men with bipolar disorder as women. However, rates of substance misuse disorders are four to seven times higher in women with bipolar disorder than rates derived from community samples (Krishnan, 2005).

Personality disorders
Personality disorders are sometimes diagnosed alongside bipolar disorder, although the comorbidity rate varies drastically depending on which measurement instrument is used. Based on strict DSM-IV criteria for axis II disorders, one study reported a comorbidity rate of 38% in euthymic patients with bipolar disorder (Kay *et al.*, 1999). However, previous studies have reported rates as high as 89% using other assessment instruments and assessing patients while they are acutely affectively ill (Turley *et al.*, 1992). 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 patient when they have not had affective symptoms, preferably since the patient was an

adolescent or younger. Cluster B (dramatic and emotional) and C (anxious and fearful) disorders are the most common personality disorder comorbidities in patients with bipolar disorder. Borderline personality disorder, the hallmark of which is affective instability due to markedly reactive mood, shares some features in common with bipolar disorder, particularly with the ultra-rapid cycling variant. 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).

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

Clinical practice recommendation

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

- during initial assessment, consider a diagnosis of bipolar disorder before a diagnosis of personality disorder in a person with mood swings and functional impairment
- during treatment, ensure the patient has had adequate treatment to stabilise symptoms before considering a diagnosis of comorbid personality disorder.

4.4.6 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 suicides occur when depression is underdiagnosed and undertreated, especially in bipolar II disorder, and when there is no long-term maintenance treatment. Suicide may occur with little warning, especially in patients with bipolar disorder comorbid with other impulse control disorders such as substance misuse, borderline personality disorder and eating disorder. 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 patient groups but healthcare professionals should be aware that mental state and suicide risk can change quickly. Immediate action is required if a patient with bipolar disorder is assessed to be at high or immediate risk of suicide, such as those with a definite plan or persistent suicidal ideation. 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 through violent or reckless behaviour.

Clinical practice recommendations

Assessment of risk in primary and secondary care

4.4.6.1 A risk assessment should be undertaken when:

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

Crisis and risk management plans

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

- a list of identified or potential personal, social or environmental triggers, and early warning symptoms of relapse
- a protocol for increasing the dose of medication or taking additional medication (which may be given to the patient in advance) for patients who are at risk of rapid onset of mania and for whom clear early warning signs can be identified – protocols should be monitored regularly, and are not a substitute for an urgent review
- how primary and secondary healthcare services have agreed to respond to any identified increase in risk, for example by increased contact
- how the patient (and where appropriate their carer) can access help, and the names of healthcare professionals in primary and secondary care who have responsibilities in the crisis plan.

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

4.5 DIAGNOSIS OF CHILDREN AND ADOLESCENTS

The diagnosis for bipolar disorder in children and adolescents is an area of considerable difficulty and some controversy (Biederman *et al.*, 2000). In light of this, the GDG convened a consensus conference to draw on the experience of national and international experts in the area. A fuller account of the outcome of the consensus conference is provided in Appendix 19. What follows is a brief summary of the issues and the outcomes and recommendations of the consensus conference.

The peak age for onset of bipolar disorder is in later adolescence and early adult life. However, a significant number of adults with bipolar disorder, perhaps up to 20%, have experienced initial symptoms before the age of 19 (Harrington, 1994). Lewinsohn and colleagues (1995) estimated a point prevalence figure for adolescence of around 1%. However, the number of pre-pubertal children presenting with bipolar disorder is very small. In a large study in Oregon in the United States (Lewinsohn *et al.*, 1993, 2003) researchers were able to identify only three cases of pre-pubertal bipolar disorder. The

typical presentation of bipolar disorder in children and adolescents, particularly those with earlier onset, is that depressive disorder presents first. Children and adolescents with bipolar disorder tend to have a disorder with longer duration of episode, increased mixed presentation and a higher incidence of rapid cycling than in late-onset bipolar disorder.

One considerable problem that the consensus conference faced was the different presentations of symptoms in children, adolescents and adults. Features such as grandiosity and involvement in pleasure and activities vary considerably as a function of age and developmental level, therefore what is pathological in an adult might not be appropriately described as such in a child. A further complication is that for many children with serious mental disorder there is also considerable evidence of comorbidity and co-presentation with symptoms such as those with attention deficit hyperactivity disorder (ADHD), and indeed their subsequent management and medication, can make the diagnostic challenge even more difficult.

After a careful consideration of the current evidence for the diagnosis of bipolar I and bipolar II disorder in children and adolescents, the consensus conference concluded that it was possible and appropriate to diagnose bipolar I disorder in both children and adolescents, although accepted it was a very rare disorder in the former group. However, the consensus conference did not feel, given the present level of evidence, that it was appropriate at this stage to reach a diagnosis of bipolar II disorder in a child or adolescent. A possible exception to this is in older and developmentally well-advanced adolescents where the use of the standard adult diagnostic criteria may be appropriate.

However, in accepting that the diagnosis of bipolar I disorder can be present in children and adolescents, the consensus conference made a number of suggestions for the refinement of the diagnosis. Specifically, the conference took the view that for a diagnosis of bipolar I disorder to be established in a pre-pubescent child mania must be present, euphoria must be present for most days most of the time for 7 days and, although irritability may be a symptom, it should not be a core diagnostic criterion. For adolescents, the conference took the view that in order to establish a diagnosis of bipolar I disorder mania must be present, as must euphoria over a 7-day period. Irritability should not be a core diagnostic criterion, but its presentation if episodic in nature and if it results could be important in helping establishing a diagnosis of bipolar I disorder.

The consensus conference also felt that the diagnosis of bipolar disorder in a young person presenting solely with a depressive episode, but in the context of a family history of bipolar, should not itself warrant a diagnosis of bipolar I disorder. The conference also commented on common comorbidities and important differential diagnoses, appropriate assessment methods and the management of special groups (see Appendix 19).

4.5.1 Clinical practice recommendations

Diagnosing bipolar disorder 1 in prepubescent children

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

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

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

Diagnosing bipolar I disorder in adolescents

4.5.1.3 When diagnosing bipolar I disorder in adolescents the same criteria should be used as for adults except that:

- mania must be present
- euphoria must be present most days, most of the time (for at least 7 days)
- irritability can be helpful in making a diagnosis if it is episodic, severe, results in impaired function and is out of keeping or not in character; however, it should not be a core diagnostic criterion.

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

Diagnosing bipolar I disorder in older or developmentally advanced adolescents

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

Bipolar II disorder in both children and adolescents

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

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

Differential diagnosis for both children and adolescents

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

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

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

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

Children and adolescents with learning difficulties

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

Children and adolescents with sub-threshold symptoms of bipolar disorder

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

Assessment methods for children and adolescents

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

4.5.1.14 Assessment should include:

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

4.5.1.15 A specialist diagnostic instrument such as the WASH-U-KSADS may be used; scales completed by parents or carers such as the Child Behaviour Checklist, Conners' Abbreviated Rating Scale, Parent Young Mania Rating

Scale and Parent General Behaviour Inventory may also be used. These should not replace a full clinical interview.

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

4.6 COURSE AND PROGNOSIS

For most patients 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 patients 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. 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.*, 2004b). 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 patients 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). 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.

4.6.1 Early warning signs

Early detection in bipolar disorder is important for instigating an appropriate management regime with the aim of improving ultimate outcome and minimising harm caused by repeated episodes. 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. 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.

4.6.2 Neuropsychological function

A number of recent studies have demonstrated that many patients 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 can occur when the patient is depressed or manic 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 4.3.3) or to some other unknown psychological or biological process. The impairments worsen as the illness progresses and are particularly associated with the number of manic episodes (Robinson & Ferrier, 2006). The impact of these impairments on rehabilitation, engagement in therapy, compliance and quality of life is uncertain but likely to be significant.

4.6.3 Drug/alcohol outcomes

As mentioned above, substance misuse is common in patients with bipolar disorder and impacts negatively on illness outcome. Mixed episodes and rapid cycling mania are more common in patients with comorbid substance misuse, as are medical disorders, suicide and suicide attempts (Krishnan, 2005; Potash *et al.*, 2000). Generally, substance misuse destabilises the illness, increases the time taken to recover and/or triggers relapse.

4.6.4 Switching

Longitudinal studies suggest somewhere between 0–46% of people presenting with major depressive disorder will experience a manic or hypomanic episode and merit rediagnosis with bipolar disorder. One study followed 74 patients prospectively for 15 years from their first episode of depression and documented subsequent episodes of mania or hypomania. It was found that 19% of patients went on to experience a full-blown manic episode and a further 27% had at least one hypomanic episode (Goldberg *et al.*, 2001). Those who presented with psychotic depression were significantly more likely to go on to develop bipolar disorder.

4.6.5 Late-onset bipolar disorder

Mania or hypomania that first appears in later life (after 40 years of age) 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 cases of 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. The majority of the increased mortality rate is accounted for by a greater burden of physical illness, especially cardiovascular and cerebrovascular disease, rather than suicide. The SMR for cardiovascular death may be twice that of the general population but appears to be reduced if patients adhere to long-term medication.

4.7 THE TREATMENT AND MANAGEMENT OF BIPOLAR DISORDER IN THE NHS

4.7.1 History of service provision for adults

Bipolar disorder has struggled to establish itself as a separate diagnostic entity from both unipolar depressive disorder (Angst, 1966; Perris, 1966) and schizophrenia. Traditionally, provision of services for people with bipolar disorder has been through general outpatient and inpatient services of secondary mental health services. The only special service provision for service users with bipolar disorder has been the lithium clinic (Fieve, 1975), typically run by a psychiatrist and a nurse in hospital outpatient departments. Although lithium can be effective, it can also be toxic (Cookson *et al.*, 2002) (the side-effects are discussed in Chapter 8), so lithium clinics were seen as a way of ensuring safe regular monitoring and review of people with bipolar disorder who take lithium as a maintenance treatment. In the 1980s and 1990s lithium clinics were almost universal in British mental health services but they became less popular as mental health services developed a more community, rather than hospital, focus and alternatives to lithium became available.

By the late 1990s, the care of people with bipolar disorder in contact with secondary care services was largely provided by psychiatric outpatient and inpatient services. Only 50% of people with bipolar disorder who had an acute episode of mania or depression were in contact with a community mental health team (CMHT) (Perry *et al.*, 1999). The dominant model of care in England was the care programme approach (CPA) from mental health services or care management from social services, models that addressed the needs of service users with more severe mental illness. Sometimes people with bipolar disorder who had been admitted involuntarily under the 1983 Mental Health Act were soon discharged from the caseloads of CMHTs and the CPA because they seemed to be less needy of continuing support than other patients. The high risk of recurrence of bipolar episodes within 12 months of a manic episode (Tohen *et al.*, 1990) was not recognised. Once discharged from the CPA,

people with bipolar disorder would receive only outpatient appointments with a psychiatrist no longer working in a lithium clinic. Apart from via the psychiatrist, general practitioner or emergency department, there was limited access to crisis support and, once a patient was discharged from a CMHT, arrangements to be seen again by the CMHT might take weeks. Few patients with bipolar disorder were treated in day hospitals or lived in supported accommodation. There was little provision of psychoeducation.

As a result of the paucity of care from secondary mental health services, service users accessed self-help, support and education about bipolar disorder from service user groups, particularly MDF The BiPolar Organisation (Shepherd & Hill, 1996). Since the publication of the National Service Framework for Mental Health, a raft of new service developments have been introduced to mental health services in England (Department of Health, 1999b). None of these is specifically targeted at bipolar disorder but may have had an impact on provision of services to service users with bipolar disorder in England. The same service changes have not been implemented in Wales, where services are only now implementing the CPA.

4.7.2 Service needs of adults with bipolar disorder

Recent 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 Britain, the needs of people with bipolar disorder have largely been regarded as similar to the needs of other service users with serious mental illness (Department of Health, 1999a). 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 (Simon & Unutzer, 1999; Ogilvie *et al.*, 2005).
- 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.*, 2002) and suicide attempts (Jamison, 2000).
- 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).

There have been few models of service provision specifically for bipolar disorder in the United Kingdom or anywhere else in the world. If such service provision were to be developed, then it should 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 patient 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).

4.7.3 Service needs of children and adolescents

The process of care and provision of treatment for children and adolescents should take account of the four-tier model of child and adolescent mental health services (CAMHS) organisation and delivery (NHS Health Advisory Service, 1995). This is consistent both with the current organisation of CAMHS in England and Wales and with the National Service Framework (NSF) for children and adolescents across both jurisdictions.

Interventions for children and adolescents with bipolar disorder will usually be provided by specialist CAMHS (tiers 2/3 and 4), but children and adolescents also require help from non-specialist health, social work and education services (referred to as tier 1). Services may have tiers that are structural, functional or both, that is, some specialist CAMHS have a combined tier 2 and 3 service with single referral point, others may provide tier 2 as a stand-alone service.

Tier 1 services include those that have direct contact with children and adolescents for primary reasons other than mental health. These include general practitioners, health visitors, paediatricians, social workers, teachers, youth workers and juvenile justice workers. They are the first point of contact with the child/adolescent presenting with mental health problems. 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.

Tier 2 CAMHS are provided by specialist trained mental health professionals, working primarily in a community-based setting alongside tier 1 workers. This facilitates consultation to tier 1 workers, prompt assessment of children within the tier 1 setting and the identification of young people requiring referral to more specialist services. Tier 2 professionals are usually closely linked or embedded in tier 3 services, thereby facilitating timely access to the specialist CAMHS.

Tier 3 services comprise multidisciplinary teams of specialist CAMHS professionals working in (secondary care) specialist CAMHS facilities. They should

provide specialist co-ordinated assessments and treatments, including a full range of appropriate psychological and pharmacological interventions. Children and adolescents presenting with mania, mixed affective states or moderate to severe depression should be assessed by tier 3 specialist CAMHS. Outreach services should 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. There may also be a role for early intervention services (EIS) for first-episode psychosis, which is described in Chapter 6.

Tier 4 services are highly specialised tertiary CAMHS in inpatient, day patient or outpatient settings for children and adolescents with severe and/or complex problems requiring a combination or intensity of interventions that cannot be provided by tier 3 CAMHS. In general, referral to tier 4 comes only from tier 3 CAMHS professionals.

A child or adolescent presenting with possible bipolar disorder will usually require assessment and treatment by tier 4 services. Following tier 4 intervention, young people are discharged back to tier 3 CAMHS or outreach services.

4.7.4 Issues of consent for children and adolescents

When admitting a child or adolescent to inpatient care, it is desirable to do so with the informed consent of both the patient and his or her parents, not least because the success of any treatment approach significantly depends on the development of a positive therapeutic alliance involving the child or adolescent, the family and the inpatient team. However, there will be times when the professionals consider admission to be necessary, but either the child or adolescent, or the family, do not consent.

If a person under 18 years of age refuses treatment, but the parent (or guardian) believes strongly that treatment is desirable, then the child or adolescent's wishes may be overruled. However, an adolescent has the right to consent to treatment without involving the consent of parents after his or her 16th birthday, or younger, if deemed 'Gillick competent'. Clinicians need to be mindful of whether a child or adolescent is subject to an order under the Children Act (1989). In most cases, the use of the Mental Health Act (1983) should be considered as it includes safeguards such as involvement of other professionals, a time limit and a straightforward procedure for appeals and regular reviews.

Those professionals involved in assessing children or young people for possible inpatient admission (tier 4 CAMHS staff) should be specifically trained in issues of consent and capacity, the use of current mental health legislation and the use of child care legislation as it applies to this group of patients.

4.8 THE ECONOMIC COST OF BIPOLAR DISORDER

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, bipolar disorder was ranked by the World Health Organization (WHO)

as the 22nd leading cause of worldwide burden among all diseases in 1990, expressed in disability adjusted life years (DALYs), and the sixth leading cause of DALYs at ages 15–44 years. When separate estimates were made for years of life lost and years lived with disability among all diseases, bipolar disorder was ranked as the sixth leading cause of disability worldwide (Murray & Lopez, 1996).

A recent study estimated the annual cost of bipolar disorder in the UK (Das Gupta & Guest, 2002). 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 due 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 heath 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.

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) and the US (Begley *et al.*, 2001; Wyatt & Henter, 1995). Runge & Grunze 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.

In the US, Wyatt & Henter 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 disease 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 affected by the disease in 1998. The study took into account the fact that only a small number of cases (assumed at 20% per year) would be diagnosed and treated for the disease, whereas the remaining undiagnosed cases 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 misuse, as well as indirect costs associated with excess unemployment, reduced earnings due to disability and suicide. The lifetime cost of new cases affected by the disease in the US 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.

In addition to studies adopting a societal perspective, other studies aimed at estimating direct healthcare costs only. An Australian study (Sanderson *et al.*, 2003) estimated the total annual cost of routine treatment for bipolar disorder in Australia at AUS$60.9 million, in 1997/98 prices, based on the results of a national mental health survey. By applying optimal treatment (as achieved by operationalising detailed clinical practice guidelines and expert reviews), the total annual direct medical cost was expected to rise up to AUS$108.4 million.

In France, de Zelicourt and colleagues (2003) estimated the total annual inpatient cost of treating manic episodes at FRF8.8 billion, converted to €1.3 billion (1999 values), reflecting an annual number of 265,000 manic episodes, 63% of which led to hospitalisation. Estimation of cost was based on a prevalence-based top-down approach, using a number of assumptions combined with data from various sources. Using a different methodology, Olié & Lévy (2002) reported a 3-month cost following hospitalisation for a manic episode at €22,297 per case admitted (1999 prices), of which 98.6% accounted for inpatient care. In this case, the analysis was based on case record data derived from 137 patient files.

A significant number of studies undertaken in the US analysed the financial burden of bipolar disorder from the perspective of a third-party payer, such as Medicaid (a public insurance plan for the poor and disabled), or a private insurer, practically paid by the employer. Bipolar disorder was found to be among the most costly mental diseases from an employer's point of view (Goetzel *et al.*, 2000 & 2003; Peele *et al.*, 1998 & 2003). Employees with bipolar disorder were found to incur significantly 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). Comorbidity of bipolar disorder with other mental disorders and medical conditions was an additional factor contributing to high treatment costs associated with the disease (Peele *et al.*, 2003). Moreover, management of unrecognised/misdiagnosed cases of bipolar disorder characterised by overuse of antidepressants and underuse of potentially effective medications was frequently observed in the US, adding to the total cost of treatment (Birnbaum *et al.*, 2003; Li *et al.*, 2002; Matza *et al.*, 2005; Shi *et al.*, 2004).

Goetzel and colleagues (2000, 2003) found that bipolar disorder was associated with a lower cost per case 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 compared with costs incurred by employees with schizophrenia. Furthermore, the costs to the employers associated with management of patients with bipolar disorder were almost four times higher than the respective costs incurred by patients with unipolar depression, despite the similar numbers of employees affected by the two disorders, as the cost of a case with bipolar disorder was higher than that of a case 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 under employment, and a significant financial burden to the payers of health services and absenteeism/disability compensations (such as private insurance plans in the US and the public sector in the UK).

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