

The management of bipolar disorder

Bipolar disorder is a common mental disorder which is relapsing and remitting in nature. Subsyndromal symptoms are common and associated with poorer outcomes. Management of the disorder can be challenging and depends on the polarity and severity of the mood episode.

Bipolar disorder is a mental illness which affects 1–4% of the population. It is associated with significant morbidity and mortality and has one of the highest mortality rates of any mental disorder. Suicide accounts for 15–19% of all deaths in those with bipolar disorder at long-term follow up (Abreu et al, 2009). Standardized suicide mortality rates between 120 and 200 per 100 000 (Osby et al, 2001) have been reported which equate to 15–20 times that of the general population. Between 25% and 50% of those with bipolar disorder will attempt suicide (Novick et al, 2010). Elevated cardiovascular and cerebrovascular mortality has also been reported in bipolar disorder although recent studies of community samples (as opposed to hospitalized cohorts) suggest that this may not be the case.

Around 25% of people with bipolar disorder have ever sought help from health services (ten Have et al, 2002). Of those who seek help, many experience long delays between the onset of symptoms and correct diagnosis.

The diagnosis of bipolar disorder is based entirely on the clinical history and mental state examination. The diagnostic criteria for bipolar disorder characterize bipolar disorder as consisting of periods of elated mood (mania) and low mood (depression) interspersed by periods of stability (euthymia). However, this description does not capture the full clinical picture, particularly the chronic mood instability revealed by prospective mood monitoring (Bonsall et al, 2012) and the cognitive impairment which persists in euthymia.

Even with treatment over one-third of patients will experience a relapse of depression or mania within a year and nearly two-thirds within 2 years. Depressive symptoms are common and bipolar patients will suffer residual depressive symptoms for about a third of their lives. Current management is focussed on the treatment and prevention of acute mood episodes although this can be complex because treatments for depression may exacerbate symptoms of mania, and vice versa.

Drug treatment is the main approach to the management of bipolar disorder although it remains limited because of our limited understanding of the underlying neurobiology of this complex phenotype and the consequent absence of any validated pharmacological targets. The majority of current treatments for bipolar

disorder have been re-purposed from other disorders such as epilepsy, schizophrenia and depression. The exception is lithium which is the best established treatment and appears to have a specific effect on mood instability although its mechanism of action remains unclear because it has multiple cellular and pharmacological effects (Alda, 2015).

Treatment of mania

Antipsychotic drugs are the first-line treatment for acute mania. In a network meta-analysis of over 16 000 patients, risperidone and olanzapine were found to have the best efficacy and tolerability (Cipriani et al, 2011). Haloperidol and quetiapine were also found to be highly efficacious although haloperidol in particular was less well tolerated. In instances where the first-line antipsychotic treatment has been ineffective or poorly tolerated switching to another of these four agents is recommended (Kendall et al, 2014). If patients are on antidepressant treatment, then this should be stopped. In those in whom longer-term treatment is planned the introduction of a mood stabilizer is recommended.

Treatment of acute depression

Historically the treatment of bipolar depression has been based upon strategies developed in unipolar depression but it is widely acknowledged that this is problematic (Frye et al, 2015b). The reason is that there is a relative paucity of evidence on the efficacy of treatments in acute bipolar depression and more uncertainty about the appropriate first-line treatment. Two meta-analyses have reached different conclusions. A network meta-analysis of over 8000 patients found quetiapine, olanzapine or the combination of olanzapine and fluoxetine to be most efficacious. In a further network meta-analysis of over 9000

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patients valproate, lamotrigine and lurasidone were also found to be efficacious (Kendall et al, 2014). The recently reported CEQUEL trial supported the use of lamotrigine in combination with quetiapine (Geddes et al, 2015). Other agents such as adjunctive armodafinil may also be helpful in bipolar-1 disorder (Frye et al, 2015a).

The use of antidepressants in bipolar disorder remains controversial although they are commonly prescribed in clinical practice. Antidepressant monotherapy is not endorsed by current guidelines because of concerns about inducing mania or mood instability. Data from the STEP-BD study found that the addition of paroxetine or bupropion to a mood stabilizer conveyed no additional benefit to mood stabilizer monotherapy in the treatment of bipolar depression (Sachs et al, 2007). However, post-hoc analysis of these data suggests that higher doses of adjunctive antidepressant were associated with greater clinical improvement with no evidence of increased mood switching (Tada et al, 2015). Other data from STEP-BD indicate that the risk of switching is likely to be higher in those with concomitant manic symptoms during depressive episodes (Goldberg et al, 2007). Overall antidepressants may be a helpful adjunctive treatment in bipolar depression in those individuals deemed at low risk of emergent mania.

The use of electroconvulsive therapy in bipolar disorder has not been widely studied but is widely proposed as a treatment for those who have failed to respond to first-line medications (Yatham et al, 2009; Goodwin et al, 2016). In the only randomized control trial in patients with treatment-resistant bipolar depression, electroconvulsive therapy was significantly more effective than algorithm-based pharmacological treatment although remission rates did not differ between the two groups (Schoeyen et al, 2015). There is very little evidence for the treatment of treatment-resistant bipolar depression and guidelines are largely based on evidence extrapolated from treatment-resistant unipolar depression.

Long-term maintenance treatment

Lithium continues to have a central role in the long-term treatment of bipolar disorder. Despite having been used in clinical practice for more than 50 years the majority of the evidence for its efficacy has been derived from trials of newer agents where lithium has been used as the comparator. In a meta-analysis of all randomized controlled trials comparing lithium with placebo and other treatments (1580 participants) lithium was more effective than placebo in preventing new mood episodes in bipolar disorder (relative risk 0.61). Fewer manic relapses were observed in those on lithium compared to those on anticonvulsants (relative risk 0.66) but no significant difference in depressive relapse was found (Severus et al, 2014).

Lithium is the only known treatment which reduces suicidal behaviour by over 50% (Cipriani et al, 2013). However, the benefits of lithium have to be balanced against its narrow therapeutic index, side effects and the risk of long-term adverse effects. Lithium is associated with an increased risk of renal impairment, hypothyroidism, hyperparathyroidism and weight gain, although few patients experience clinically significant renal impairment or end stage renal failure (McKnight et al, 2012; Shine et al, 2015). A network meta-analysis of all maintenance treatments in bipolar disorder (6846 patients) (Miura et al, 2014) evaluated the evidence for long-term drug treatments in bipolar disorder. Olanzapine, risperidone and lithium plus valproate were more protective against manic relapse than placebo. Lamotrigine was better than placebo for depressive relapse. Only quetiapine and lithium prevented relapse in both polarities. Given the consistency of the evidence for lithium it remains the first choice long-term treatment despite its limitations.

Treatment of rapid cycling

Rapid cycling is (arbitrarily) defined as four or more distinct mood episodes in a year. It affects a significant number of patients and although it may be a transitory phenomenon it is associated with high rates of substance misuse and suicidality. There is a paucity of evidence and uncertainty about how best to manage rapid cycling bipolar disorder. At present treatment broadly follows the same guidelines for the management of acute episodes and maintenance although antidepressants should be avoided as they may exacerbate the clinical presentation (Fountoulakis et al, 2013).

Treatment of mixed states

Mixed states are defined as the concurrent presence of both depressive and manic symptoms. Patients with mixed affective features often have more severe symptoms, higher rates of comorbidity and a worse prognosis. The general consensus is that second generation antipsychotics are the treatment of choice although most of the evidence comes from subgroup analyses of acute mania treatment trials. Antidepressants tend to worsen the manic symptoms while having minimal impact on depressive symptoms and are not recommended.

Psychosocial treatments

Psychosocial treatments are an important adjunct to medication in the management of bipolar disorder. Psychoeducation reduces recurrence of mood episodes but this effect is limited to individuals who are in the early stages of a bipolar illness and have achieved near remission following an acute episode (Miziou et al, 2015). Cognitive behavioural therapy and interpersonal social rhythm therapy may have some beneficial effect during acute episodes but data are relatively limited. Family-focused therapy which involves both the patient and his/her caregivers may be helpful in relapse prevention and

recovery from acute episodes. Two randomized controlled trials of family-focused therapy found that patients who received therapy had 30–35% lower relapse rates than those who received intensive individual treatment (Rea et al, 2003) or case management (Miklowitz et al, 2007). In paediatric populations family-focused therapy in addition to medication was associated with a more rapid resolution of depressive symptoms than medication combined with psychoeducation (Miklowitz et al, 2008).

Treatment of comorbidity

Comorbid conditions are common in bipolar disorder. Two-thirds of patients with bipolar disorder will have at least one comorbid psychiatric disorder and many will have two or more. Anxiety disorders are found in around 70% of patients while a lifetime history of alcohol misuse is reported in over 40% of people with bipolar-1 disorder. Obsessive compulsive disorder is found in around 20%, attention deficit hyperactivity disorder in 9%, and eating disorders in 9% (Merikangas et al, 2007). Comorbid personality disorder is present in around 50% if measured during euthymia (Rosso et al, 2009). These comorbidities worsen prognosis in terms of suicide risk, quality of life and functioning. There are very few studies specifically exploring the treatment of comorbid psychiatric disorders in bipolar disorder and treatment options can be limited because of the risk of precipitating an acute mood episode.

Comorbid medical illness

Rates of comorbid medical illness are high in bipolar disorder although a similar pattern of comorbidities is found in unipolar depression. Migraine headache, asthma, elevated lipids, hypertension, thyroid disease and osteoarthritis are among the most prevalent comorbid conditions in bipolar disorder (Forty et al, 2014). Early diagnosis and treatment of these conditions is important in terms of reducing mortality and improving outcomes, both in terms of physical but also mental wellbeing.

Pregnancy and the perinatal period

Pregnancy should be considered in the management of all women with bipolar disorder. The risks and benefits of all medications should be discussed with women in advance of them conceiving. Sodium valproate is not advised in women of reproductive age. There are limited data on the safety of medications in pregnancy. To date there is little evidence to suggest that teratogenicity is associated with use of atypical antipsychotics (Gentile, 2010) and while a systematic review suggested that the risk of cardiac malformations associated with lithium are lower than has previously been reported, there remains relatively few reproductive safety data (McKnight et al, 2012). The perinatal period and especially the postnatal period is a high risk time for women with bipolar disorder with relapse rates of around 35%. Relapse rates are higher in women who are medication free during pregnancy compared to those on prophylaxis (66% *vs* 23%) (Wesseloo et al, 2015).

Children and adolescents

The diagnosis of bipolar disorder in pre-pubescent children remains controversial. When diagnosis is confirmed management should take into account the cognitive ability, emotional maturity and developmental level. Aripiprazole is recommended in acute mania in bipolar-1 in children and adolescents, but overall pharmacological management largely follows the recommendations for adults although dose adjustments may be necessary (National Institute for Health and Care Excellence, 2014).

Older adults

Older adults with bipolar disorder should be offered the same range of support and treatment as other age groups. Care will need to be taken to ensure that adverse effects (especially on cognitive function), the risk of drug interactions and medical comorbidities are minimized.

Management of suicide risk

Bipolar disorder is associated with one of the highest suicide rates of any mental disorder. Suicides are most likely to occur in depressive or mixed affective states. All individuals with bipolar disorder should have a management plan which includes provisions for the emergence of suicidal behaviour. Timely clinical assessment is necessary to ensure those at risk are identified. At present there are no validated tools for the assessment of suicide risk in patients with bipolar disorder. Management requires active treatment of any mood symptoms, intensifying clinical support, restricting access to means, and ongoing re-assessment (Saunders and Hawton, 2013).

Service delivery models

The relapsing and remitting nature of bipolar disorder means that patients often move between different parts of the health system and management in this context can be challenging. Very few models of specific service provision for bipolar disorder have been developed and, in the UK, the majority of organizations provide generic care for people with bipolar disorder. Treatment in a specialized mood disorder clinic for those who have had fewer than four admissions to a psychiatric hospital reduced readmissions by 40% compared to treatment as usual (Kessing et al, 2013). Specialist care involved close adherence to treatment guidelines (Goodwin and Consensus Group of the British Association for Psychopharmacology, 2009) and 12 sessions of group psychoeducation.

Self-management

Mood monitoring has been used by patients for many years, but the emergence of smartphones and the ubiquity of mobile networks has transformed data capture in bipolar disorder. Large numbers of apps have been developed for mood monitoring, medication alerts, sleep and sleep tracking although very few have been independently validated. Early studies suggest that using such technologies to monitor mood and other related variables such as

KEY POINTS

- Bipolar disorder is a lifelong relapsing and remitting condition.
- Chronic mood instability is common.
- Lithium remains the most specific and efficacious treatment.
- Suicide risk should be assessed regularly.
- Prospective mood monitoring enhances clinical care and promotes self-management.

activity is widely accepted by patients. The integration of self-monitoring with clinical care has the potential to enhance collaborative clinical decision making and earlier identification of and intervention for relapse.

Future directions

Management of bipolar disorder is challenging. Earlier diagnosis is imperative if we are to minimize morbidity and mortality. The absence of a clearly defined prodrome in bipolar disorder makes this challenging and the future identification of high-risk phenotypes or relevant biological markers may allow earlier intervention. The pharmacological management of bipolar disorder has progressed little over the past few decades and lithium remains the only medication specific to bipolar disorder. There is an urgent need for a neurocognitive experimental medicine model in bipolar disorder to allow novel compounds to be investigated efficiently and early in the drug development pathway. The full potential of new technologies in promoting self and remote management has yet to be realized. If early findings regarding the association between mood and geolocation, mobile phone use and vocal prosody are replicated then current mood monitoring approaches could be replaced by low-friction passive data collection. In combination with emerging mathematical techniques such as machine learning and signal detection, individualized relapse recognition and management may become feasible. **BJHM**

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Conference Preview

Treating Depression 2016

This month brings our annual Treating Depression conference at the Hallam Conference Centre, London on Thursday 24 March.

The last decade has seen increasing recognition of mental health as an essential part of health care which needs to be improved in the UK. This meeting will bring together key decision makers in the field of depression to provide updates, so that this information can be translated directly into clinical practice.

There has been growing coverage of celebrities with depression in the media, with both the stigma associated with the condition and the risk of suicide being highlighted as factors which need to be tackled. Charity campaigns like Mind's 'Time to Change' campaign have demonstrated positive improvements in public attitudes

towards mental health. While this is a major achievement, there is still more to be done. These important areas will be highlighted at *Treating Depression 2016* with Dr Claire Henderson speaking on the topic of stigma, and Dr Roger Webb presenting on the risk of suicide and self-harm among primary care patients.

Another aspect of depression which has been under scrutiny is perinatal depression. In the UK approximately 40 000 women a year suffer from perinatal depression, which has led to David Cameron declaring that the NHS will give specialist help to tackle the mental strain of childbirth in pregnant woman and new mothers. This topic will be covered by Professor Susan Ayers, City University London.

The treatment options for depression are vast, but one of the main reasons that people stop taking antidepressants is the side effects they cause. Professor David Healy from Cardiff University will discuss the management of these side effects which include cardiac rhythms, sexual side effects

and compulsive behaviours, including alcoholism.

With an increased ageing population in the UK, depression linked to conditions related to old age is rising. Professor Janet M Lord from the University of Birmingham will outline the consequences of depression in older people with hip fractures. She will discuss the link between new onset depression after a hip fracture and compromised immune function, and will discuss the role that the hypothalamic–pituitary–adrenal axis may play in this correlation. The complex relationship between dementia and depression is another comorbidity associated with old age, which will be reviewed by Professor Klaus Ebmeier, University of Oxford.

For more information and the conference programme please go to: www.mahealthcarevents.co.uk/depression2016. On the day, you can follow the conference on Twitter at #treatingdepression16

To book your place, please call +44 (0)207 501 6762. **BJHM**

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