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SECTION 26 Psychiatric and drug-related disorders 6498 FURTHER READING Archer J, et al. (2012). Collaborative care for depression and anxiety problems. Cochrane Database Syst Rev, 10, CD006525. Katon WJ (2011). Epidemiology and treatment of depression in pa- tients with chronic medical illness. Dialogues Clin Neurosci, 13, 7–23. Katon WJ, et al. (2010). Collaborative care for patients with depression and chronic illnesses. N Engl J Med, 363, 2611–20. National Institute for Health and Care Excellence (NICE) (2009). Depression in adults: recognition and management. Clinical guide- line [CG90]. Last updated: April 2016. https://www.nice.org.uk/ guidance/CG90 National Institute for Health and Care Excellence (NICE) (2009). Depression in adults with a chronic physical health problem: recogni- tion and management. Clinical guideline [CG91]. https://www.nice. org.uk/guidance/CG90 26.5.7 Bipolar disorder Kate E.A. Saunders and John Geddes ESSENTIALS Bipolar disorder is a highly heritable, lifelong, relapsing, and remitting chronic mental illness. While traditionally characterized as a disorder with distinct periods of elated and depressed mood, it is now clear that interepisode mood instability is common. Comorbid psychiatric and medical conditions are common. When occurring in medical settings mania can be both disruptive and hazardous, and may re- quire active psychiatric management. Pharmacological approaches are the mainstay of treatment, although adjunctive psychotherapies are helpful in preventing relapse. Compulsory detention in hospital using mental health law may sometimes be required for both manic and depressive states. Introduction Bipolar disorder is a chronic recurrent mood disorder, previously known as manic-depressive illness. It is characterized by un- stable mood with periods of both depressed and elevated mood. Bipolar disorder is classified into three subtypes: bipolar I which is characterized by the presence of mania (Box 26.5.7.1), bipolar II which is characterized by hypomania (Box 26.5.7.2), and bi- polar not otherwise specified (NOS) which is used to describe those who do not fulfil the duration criteria for hypomania/ mania or where there is little discernible effect on the individual’s functioning. Aetiology The main cause of bipolar

disorder is genetic, although environ- mental factors also play a role. The heritability (the extent to which the disorder can be accounted for by genetic factors) is estimated to be 85%. People with a first-degree relative with bipolar disorder have a 14-fold increased risk of developing the condition. Genome- wide association studies have identified association with several common genetic polymorphisms with considerable overlap in sus- ceptibility with other disorders, including schizophrenia, but as yet there are no valid biomarkers. Epidemiology Bipolar I and bipolar II disorders affect around 2% of the popula- tion, with subthreshold forms present in a further 2%. The mean age of onset in community studies is 17 years. However, delays in the initial diagnosis are common, hence it is possible that the age of onset has become earlier since the 1990s. This may reflect in- creased use of antidepressants and stimulants precipitating epi- sodes of mania, or simply be attributable to greater awareness of the diagnosis. The prevalence of bipolar disorder is similar in males and females. An early age of onset is heritable and associated with poorer prognosis. The diagnosis of bipolar disorder in children has increased in recent years, especially in the United States, but the persistence of this increased rate of diagnosis into adulthood remains unclear as no comparable increase in adults has been observed. Clinical features The key feature of bipolar disorder is the occurrence of manic or hypomanic episodes. There are usually also episodes of depression (Fig. 26.5.7.1). Box 26.5.7.2 Features of hypomania • Symptoms as described for mania • A minimum duration of four days • A change in functioning, but not one severe enough to severely impair functioning or to necessitate hospitalization Box 26.5.7.1 Features of mania

1. A period of abnormally and persistently elevated, expansive, or irrit- able mood, lasting at least one week (or any duration if hospitalization is necessary)
2. Additional symptoms that include • Inflated self-esteem or grandiosity • Decreased need for sleep • More talkative than usual or pressure to keep talking • Flight of ideas or a subjective experience that thoughts are racing • Distractibility • Increase in goal-directed activity (either socially, at work or school, or sexually) • Agitation • Risky behaviour (e.g. rash purchases and sexual indiscretion)

26.5.7 Bipolar disorder 6499 Mania and hypomania A manic episode is a distinct period of abnormality of mood of at least a week’s duration that is severe enough to cause social or occu- pational difficulty or to lead to hospital admission. Mood is persist- ently elevated, expansive, or sometimes irritable. Other symptoms include persistently increased activity or energy and commonly a reduced need for sleep. The patient may appear unusually talkative, with rapid speech, and be unusually distractible. They may express inflated or grandiose ideas about their ability or status, and may be- have in an unwise or risky way such as spending excessively. If the mania is severe, there may also be delusions and hallucinations, the context of which is typically grandiose and in keeping with the ele- vated mood. There is no reduction of conscious level as with organic brain states. A hypomanic episode is a noticeable but less disruptive period of elevated mood. Depression The core symptoms of depression are low mood and/or anhedonia (loss of interest or pleasure in activities). In contrast to mania, with- drawal and reduced energy are common. Speech may be slow and ideas of low self-worth, pessimism, and even suicide expressed. Sleep is commonly disturbed and in bipolar depression may take the form of increased rather than reduced or disrupted sleep. A period of depressed mood typically occurs after an episode of elevated mood. Differential diagnosis The diagnosis of bipolar disorder requires a history of (hypo) manic symptoms. The main medical differential diagnosis for mania or hypomania is intoxication

with stimulant drugs such as cocaine or amphetamines and from other organic brain states. These include delirium from any cause, where there is typically clouding of con- sciousness, and occasionally head injuries, brain tumours, or epi- lepsy. The psychiatric differential includes cyclothymic and other personality disorders, and the main alterative diagnosis is schizo- phrenia if there are persistent hallucinations or delusions in a clear consciousness. For presentations with symptoms of depression, the main dif- ferential diagnosis is from unipolar depression. Bipolar disorder is commonly initially misdiagnosed as unipolar depression. Psychiatric comorbidity Other psychiatric disorders commonly co-occur with bipolar dis- order, particularly with bipolar II. Sixty-five per cent (65%) of people with bipolar disorders have at least one comorbid psychiatric dis- order, with many having two or more. Anxiety disorders are the most common and are associated with higher rates of suicide, al- cohol misuse, and a poorer response to lithium. Alcohol misuse is common. Personality disorders are present in between 25% and 50% of patients, although these estimates are imprecise as most studies 20 10 5 0 20 10 5 0 20 30 40 Weeks Mood scores Mood scores 50 10 0 20 30 40 Weeks 50 10 0 20 10 5 0 Mood scores 20 30 40 Weeks 50 10 0 20 10 5 0 20 10 5 0 20 30 40 Weeks Mood scores Mood scores 50 10 0 20 30 40 Weeks 50 10 0 20 10 5 0 Mood scores 20 30 40 Weeks 50 10 0 Fig. 26.5.7.1 Examples of mood instability in six patients with bipolar disorder in the OXTEXT cohort (data anonymized), as captured by prospective mood monitoring using the True Colours system (http://oxtext.psych.ox.ac.uk/). Blue line: scores for depressive symptoms as rated with the Quick Inventory of Depressive Symptoms (http://www.ids-qids.org/). Red line: scores for manic symptoms as rated with the Altman Self-Rating Mania Scale (http://www.cqaimh.org/pdf/tool_asrm.pdf).

 have sought to establish the presence of personality disorder in the presence of ongoing mood symptoms. Comorbid personality dis- order is associated with poorer treatment response, greater sub- stance misuse, and a worse prognosis. Medical comorbidity Bipolar disorder is associated with coexisting medical illness. The most prevalent are migraine, asthma, elevated lipids, hyperten- sion, thyroid disease, and osteoarthritis. Genome-wide association studies suggest that the bipolar disorder and metabolic disorders such as type II diabetes have common genetic links and may share pathophysiological pathways. Treatment The treatment of bipolar disorder is done in two stages: first, treat- ment of acute affective episodes, and second, maintenance treat- ment. See Table 26.5.7.1. Acute mania Current evidence favours the use of antipsychotic medication in the initial treatment of mania. For this purpose, antipsychotic drugs are superior to lithium or carbamazepine. Risperidone, olanzapine, and haloperidol have the best efficacy and tolerability. If a patient is al- ready taking a mood stabilizing agent such as lithium, the dose of this should be optimized. Acute depression The treatment of bipolar depression is a challenge with few ef- ficacious treatments. A recent meta-analysis of the efficacy of antidepressants found no efficacy. However, antidepressants are heterogeneous in terms of mechanism of action, tolerability and efficacy, and it may be premature to conclude that none is of any use. There is also a risk that antidepressant monotherapy in the absence of an antimanic treatment may precipitate mania or greater mood instability. This risk can be reduced by only using antidepressants in combination with a mood stabilizer or antimanic agent. Some atypical antipsychotics, such as quetiapine and olanzapine (in combination with fluoxetine), and lurasidone are effective in bi- polar depression, as well as having an antimanic effect. Lamotrigine, an antiepileptic drug, also appears to be effective in bipolar depres- sion. Drugs used solely for acute treatment should be tapered over several weeks once the patient is in remission. Maintenance treatment Drug treatment Lithium is the mainstay of maintenance

treatment in bipolar dis- order. It has been in use ever since its discovery by John Cade in 1949. Most of the evidence for its efficacy comes from randomized controlled trials of atypical antipsychotics in which lithium was an active comparator. Its use is limited by its narrow therapeutic window, adverse effects, and toxicity in overdose. Lithium is as- sociated with renal impairment in a small but significant number of people, although the relationship with end stage renal failure is not established. The risk of decline in renal function is greatest in younger women and in those with higher serum lithium concen- trations. Thyroid, parathyroid, and calcium metabolism can all be affected and must be monitored, both before and during treatment. In pregnancy, there is a possible risk of fetal cardiac malformations. A decision to withdraw lithium during pregnancy needs to consider both the risk to the fetus and the risk of relapse in the mother. The use of sodium valproate has dramatically increased in recent years despite the paucity of evidence from randomized controlled trials. The BALANCE trial found that lithium monotherapy was better than valproate monotherapy in preventing mood episodes, and combined treatment with lithium and valproate is better than valproate monotherapy. Valproate is associated with neural tube de- fects so is not recommended for use in women of childbearing age. Lamotrigine appears more effective than placebo in preventing depressive or manic episodes and has comparable efficacy to lithium, although adverse events are more common with lithium. There is only weak evidence that antipsychotic drugs are ef- fective in prevention, although quetiapine appears to be effective in preventing the recurrence of depressive episodes. Most patients will require maintenance treatment for many years; discontinuing stable treatment often leads to the emergence of a new episode of mood disturbance. Of those taking lithium more than half experience a recurrence within 10 weeks of discontinuation and approximately 90% within a year. Slow withdrawal of medication is associated with a lower rate of recurrence. One of the challenges in the treatment of bipolar disorder is the gap between the evidence, which mostly concerns single treatments, and clinical practice where polypharmacy is common. Almost all patients are taking more than one agent. Adherence is often poor and those with comorbid personality disorders, substance misuse, and greater illness severity are more likely to stop medication. Psychological treatment Although pharmacotherapy is the mainstay of treatment, psy- chotherapy has a role in improving adherence to drug treatment and in preventing relapses. The main goals of this adjunctive psy- chotherapy are to educate patients and caregivers and improve adherence to pharmacotherapy. There is also a role for stress management, the identification of triggers, and signs of relapse and strategies to maintain regular patterns of sleep and activity (see Box 26.5.7.2). Cognitive behavioural therapy, family fo- cused therapy, interpersonal and social rhythm therapy, group psychoeducation, and systematic care management all have evi- dence to support their use in bipolar disorder, although which specific ingredients of these complex treatments is effective re- mains unclear (Box 26.5.7.3). Table 26.5.7.1 Treatment of bipolar disorder Acute mania

1. Stop antidepressant (if currently taking one)
2. Offer an antipsychotic drug
3. Optimize lithium/mood stabilizer if already taking this Acute depression
4. Offer quetiapine OR olanzapine and fluoxetine
5. Offer lamotrigine alone or in combination with quetiapine Maintenance
6. Lithium
7. Consider adding valproate to lithium
8. If previous response in an acute episode consider quetiapine

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