# 10 - 7 Bipolar illness

# 01 - 7 Bipolar illness

# 7 Bipolar illness



316 Chapter 7 Bipolar illness Introduction Bipolar affective disorder (previously known as manic depression) is one of the most common, severe, and persistent psychiatric illnesses. In the public mind, it is associated with notions of ‘creative madness’, and indeed it has affected many creative people—both past and present (see Box 7.1). Appealing as such notions are, most people who battle with the effects of the disorder would rather live a normal life, free from the unpredictability of mood swings, which most of us take for granted. Chameleon-like in its presentation, the symptoms may vary from one pa tient to the next, and from one episode to the next within the same patient. The variety of presentations make this one of the most difficult conditions to diagnose. More than other psychiatric disorders, the clinician needs to pay attention to the life history of the patient and to third-party information from family and friends. Classically, periods of prolonged and profound depression alternate with periods of excessively elevated and/or irritable mood, known as mania. The symptoms of mania characteristically include a d need for sleep, pressured speech, i libido, reckless behaviour without regard for consequences, and grandiosity (E Mania/manic episode, p. 320). In severe cases, there may be severe thought disturbances and even psychotic symptoms. Between these highs and lows, patients usually experience periods of full remission. This classic presentation appears, however, to be one pole of a spectrum of mood disorders (E Bipolar spectrum disorder, p. 324). A milder form of mania (hypomania), associated with episodes of depression, may also occur (E Hypomania/hypomanic episode, p. 322). There is also a sub clinical presentation—cyclothymia—in which an individual may experience oscillating high and low moods, without ever having a significant manic or depressive episode (E Cyclothymia, p. 348). Equally, it may be difficult to distinguish a manic episode with psychotic symptoms from schizoaffective disorder (E Disorders related to schizophrenia, p. 228) on the basis of a single episode. Full assessment should consider: the number of previous episodes (which may have been subclinical); the average length of previous episodes; the average time between episodes; the level of psychosocial functioning be tween episodes; previous responses to treatment (especially treatment of early depressive episodes); family history of psychiatric problems; and cur rent (and past) use of alcohol and drugs. Although, at the present time, there is no cure for bipolar disorder,

for most cases, effective treatment is possible and can substantially decrease the associated morbidity and mortality (the suicide rate is high). Some pa tients do develop severe or chronic impairments and may need specific rehabilitative services. In general, however, the specific aims of treatment are to decrease the frequency, severity, and psychosocial consequences of episodes and to improve psychosocial functioning between episodes.

Introduction Box 7.1 Famous people and bipolar disorder Famous people who have publicly stated they have bipolar disorder Buzz Aldrin, astronaut Tim Burton, artist and movie director Francis Ford Coppola, director Patricia Cornwell, writer Ray Davies, musician Robert Downey Jr, actor Larry Flynt, magazine publisher Connie Francis, actor and musician Stephen Fry, actor, author, and comedian Stuart Goddard (Adam Ant), musician Linda Hamilton, actor Kay Redfield Jamison, psychologist and writer Ilie Nastase, athlete (tennis) and politician Axl Rose, musician Ben Stiller, actor and comedian Gordon Sumner (Sting), musician and composer Jean-Claude Van Damme, athlete (martial arts) and actor Tom Waits, musician and composer Brian Wilson, musician, composer, and arranger Catherine Zeta Jones, actress Famous people (deceased) who had a confirmed diagnosis of bipolar disorder Louis Althusser, 1918–1990, philosopher and writer Clifford Beers, 1876–1943, humanitarian Neal Cassady, 1926–1968, writer Carrie Fisher, 1956–2016 writer and actor Graham Greene, 1904–1991, writer Frances Lear, 1923–1996, writer, editor, and women's rights activist Vivien Leigh, 1913–1967, actor Robert Lowell, 1917–1977, poet Burgess Meredith, 1908–1997, actor and director Spike Milligan, 1919–2002, comic actor and writer Theodore Roethke, 1908–1963, writer Don Simpson, 1944–1996, movie producer David Strickland, 1970–1999, actor Joseph Vasquez, 1963–1996, writer and movie director Mary Jane Ward, 1905–1981, writer Virginia Woolf, 1882–1941, writer Other famous people thought to have had bipolar disorder William Blake, Napoleon Bonaparte, Agatha Christie, Winston Churchill, TS Eliot, F Scott Fitzgerald, Cary Grant, Victor Hugo, Samuel Johnson, Robert E Lee, Abraham Lincoln, Marilyn Monroe, Mozart, Isaac Newton, Plato (according to Aristotle), Edgar Allan Poe, St Francis, St John, St Theresa, Rod Steiger, Robert Louis Stevenson, Lord Tennyson, Mark Twain, Van Gogh, Walt Whitman, Tennessee Williams.

318 Chapter 7 Bipolar illness Historical perspective Bipolar affective disorder has been known since ancient times. Hippocrates described patients as 'amic' and 'melancholic', and clear connections be tween melancholia and mania date back to the descriptions of the two syndromes by Aretaius of Cappadocia (c.150 BC) and Paul of Aegina (625– 690). Thinking at that time reflected 'humoral' theories, with melancholia believed to be caused by excess of 'black bile' and mania by excess of 'yellow bile'. Despite the view of some clinicians in the eighteenth century that mel ancholia and mania were interconnected (e.g. Robert James, 1705–1776), it was the middle of the nineteenth century before this was more widely accepted. In 1854, Jules Baillarger (1809–1890) published a paper in the Bulletin of the Imperial Academy of Medicine describing la folie à double forme, closely followed 2wks later by a paper in the same journal by Jean-Pierre Falret (1794–1870), who claimed that he had been teaching students at the Salpêtrière about la folie circulaire for 10yrs. Although the two men were to continue arguing about who originated the idea, they at least agreed that the illness was characterized by alternating periods of melancholia and mania, often separated by periods of normal mood. In 1899, Emil Kraepelin com prehensively described 'manic–depressive insanity' (MDI) in the sixth edi tion of his textbook Psychiatrie: Ein Lehrbuch für Studirende und Ärzte. In the fifth edition, he had already divided severe mental illnesses into those with a deteriorating course (i.e. schizophrenia and related psychoses) and those with a periodic course

(i.e. the mood disorders). It was his view that the mood disorders ‘represented manifestations of a single morbid process’. At the turn of the twentieth century, hopes were high that understanding of the pathophysiology of mental illness might be within reach. In 1906, the German microbiologist August Wassermann discovered a method of detecting syphilitic infection in the CNS, and in the same year, an effective treatment was developed by Paul Ehrlich using arsenic compounds. Syphilis was, at that time, one of the most common causes of severe (often mania- like) psychiatric symptoms—GPI. Reliably diagnosing and treating such a condition was a huge step forward. In cases of MDI, however, neuropath ologists failed to find any structural brain abnormalities. Although some still maintained it was a physical illness, caused by disruptions in biological functioning, the pervasive new psychodynamic theories regarded functional illnesses (i.e. schizophrenia and MDI) as illnesses of the mind, not the brain. In 1903, Carl Jung introduced a non-psychotic version of MDI, describing ‘a number of cases whose peculiarity consists in chronic hypomanic behav iour’, with associated episodes of depression and mixed mood states, in the context of personal and interpersonal difficulties. The idea that patients could be understood and treated only if the trau matic childhood events, repressed sexual feelings, or interpersonal conflicts were uncovered influenced psychiatric thinking for over half a century. Adolf Meyer’s (1866–1950) reframing of mental disease as biopsychosocial ‘reaction types’, in the context of an individual’s life, rather than biologically specifiable entities, led to the adoption of the terms ‘depressive reaction’ and ‘manic–depressive reaction’ in DSM-I (1952).

Historical perspective It was not until specific drug treatments for these functional illnesses were found that psychiatry came full circle again, and new life was breathed into the old search for biological mechanisms. In 1949, John Cade published a report on the use of lithium salts in manic patients, but it took nearly three decades, and the work of many psychiatrists, including Morgens Schou in Denmark and Ronald Fieve in the USA, before lithium would become the mainstay of treatment for MDI. Equally significant was the observation by Ronald Kuhn in 1958 that when patients with ‘manic–depressive psych osis’ were treated with imipramine, they could switch from depression to mania. That this did not occur in all patients with depression suggested that there was a different biological mechanism underlying depressive illness, compared to MDI. In 1957, Karl Leonhard introduced the terms ‘bipolar’ and ‘unipolar’. In 1968, both the newly revised classification systems ICD-8 and DSM-II acknowledged the shift in aetiological view by using the term ‘manic–depressive illness’, but it took another decade before Leonhard’s bipolar/unipolar dichotomy was adopted in the RDC in the 1970s, and ultimately integrated into ICD-9 (1975) and DSM-III (1980). This created a very narrow ‘bipolar disorder’ and reflected a turning away from the Kraepelinian MDI concept. Much of the subsequent controversy over ‘bipolar spectrum’ disorders (E Bipolar spectrum disorder, p. 324) reflected a clinical need to broaden the diagnosis to encompass less severe presentations such as type II bi polar disorder (hypomania + depression), which was included in DSM-III-R (1987), ICD-10 (1992), and DSM-IV (1994). Cyclothymia and dysthymia were also re-categorized as mood disorders, rather than personality dis orders. ICD-10 recognized ‘mixed affective’ presentations, but it was only in DSM-5 (2013) that the symptomology specifier ‘with mixed features’ could be applied to both bipolar I/II and depressive episodes. With the growth of biological research in the 1990s and 2000s, it be came clear that neurotransmitter theories about catecholamines had been overly simplistic. Second messengers and long-term neuroplastic changes in the brain were seen in both bipolar and unipolar disorders. Newer anti psychotics also showed efficacy in both acute mania and depressive epi sodes. Some anticonvulsants also appeared to be good in treating bipolar disorder and, in some cases (e.g. lamotrigine), more

effective in preventing depression, rather than mania. The remaining questions regarding the true nature of the mood disorders are likely to be settled only by future research utilizing neuroimaging, gen etic, and other biomarker data to help identify the underlying aetiology and pathophysiology, with the ultimate aim of developing early diagnostic tests and, perhaps through pharmacogenomics, better individualized treatments.

320 Chapter 7 Bipolar illness Mania/manic episode Essence A distinct period of abnormally and persistently elevated, expansive, or irritable mood, with three or more characteristic symptoms of mania (see Box 7.2). DSM-5, ICD-10, and ICD-11 specify the episode should last at least 1wk, or less if admission to hospital is necessary. By definition, the dis turbance is sufficiently severe to impair occupational and social functioning. Psychotic features may be present. Clinical features • Elevated mood (out of keeping with circumstances). • i energy, which may manifest as: • Over-activity. • Reduced need for sleep. • Formal thought disorder which may manifest as: • Pressured speech. Box 7.2 Medications that may induce symptoms of hypomania/mania • Antidepressants: drug-induced mania described with most antidepressants (or withdrawal; E Antidepressant discontinuation syndrome, p. 1024), less so with SSRIs and bupropion (also seen with ECT and light therapy). May be a particular problem with TCAs and SNRIs such as venlafaxine • Other psychotropic medications: • BDZs—may be confused with ‘paradoxical’ agitation reactions (E Paradoxical reactions to benzodiazepines, p. 999). • Antipsychotics (rare)—olanzapine, risperidone. • Lithium—toxicity and when combined with TCAs. • Anticonvulsants (rare)—carbamazepine (and withdrawal), valproate, gabapentin. • Psychostimulants—fenfluramine, amphetamine, dexamfetamine, methylphenidate. • Other—disulfiram. • Anti-Parkinsonian medication: amantadine, bromocriptine, levodopa, procyclidine. • Cardiovascular drugs: captopril, clonidine, digoxin, diltiazem, hydralazine, methyldopa withdrawal, procainamide, propranolol (and withdrawal), reserpine. • Respiratory drugs: aminophylline, ephedrine, salbutamol, terfenadine, pseudoephedrine. • Anti-infection: anti-TB medication, chloroquine, clarithromycin, dapsone, isoniazid, zidovudine. • Analgesics: buprenorphine, codeine, indometacin, nefopam (IM), pentazocine, tramadol. • GI drugs: cimetidine, metoclopramide, ranitidine. • Steroids: ACTH, beclometasone, corticosteroids, cortisone, dexamethasone, DHEA, hydrocortisone, prednisolone, testosterone. • Other: baclofen (and withdrawal), cyclizine, ciclosporin, interferon.

Mania/manic episode • Flight of ideas. • Racing thoughts. • i self-esteem, evident as: • Over-optimistic ideation. • Grandiosity. • Reduced social inhibitions. • Over-familiarity (which may be overly amorous). • Facetiousness. • Reduced attention/i distractibility. • Tendency to engage in behaviour that may have serious consequences: • Preoccupation with extravagant, impracticable schemes. • Spending recklessly. • Inappropriate sexual encounters. • Other behavioural manifestations, including excitement, irritability, aggressiveness, and suspiciousness. • Marked disruption of work, usual social activities, and family life. Psychotic symptoms In its more severe form, mania may be associated with psychotic symptoms (usually mood-congruent but may also be incongruent): • Grandiose ideas may be delusional, related to identity or role (with special powers or religious content). • Suspiciousness may develop into well-formed persecutory delusions. • Pressured speech may become so great that there is significant difficulty in communicating with, and understanding, the individual affected. • Flight of ideas, prolixity, and pressured thoughts can result in the loss of clear associations. • Irritability and aggression may lead to violent behaviour. • Preoccupation with thoughts and schemes may lead to self-neglect, to the point of not eating or drinking, and poor living conditions. • Catatonic features—also termed manic stupor. • Total or

partial loss of insight. Differential diagnosis • Schizophrenia, schizoaffective disorder, delusional disorder, other psychotic disorders. • Anxiety disorders/PTSD. • Circadian rhythm sleep–wake disorders (E Circadian rhythm sleep– wake disorders (CRSD) 1: overview, p. 454). • ADHD/conduct disorder. • Alcohol or drug misuse, e.g. stimulants, hallucinogens, opiates. • Physical illness, e.g. hyper-/hypothyroidism, Cushing's syndrome, SLE, MS, head injury, brain tumour, epilepsy, HIV, other encephalopathies, neurosyphilis, Fahr's disease, WD, and pseudobulbar palsy. • Other antidepressant treatment or drug-related causes (see Box 7.2). Management • Risk assessment and ensure safety. • Exclusion of other causes and appropriate investigations (E Bipolar (affective) disorder 2: clinical notes, p. 330). • Address any specific psychosocial stressors. • For specific management, see E Treatment of acute manic episodes, p. 340.

322 Chapter 7 Bipolar illness Hypomania/hypomanic episode Essence Three or more characteristic symptoms (E Clinical features, see below) lasting at least 4 days (DSM-5/ICD-10) or 'several' days (ICD-11) and are clearly different from 'normal' mood (third-party corroboration). By defin ition, not severe enough to interfere with social or occupational functioning, require admission to hospital, or include psychotic features. Clinical features Hypomania shares symptoms with mania, but these are evident to a lesser degree and do not significantly disrupt work or lead to social rejection: • Mildly elevated, expansive, or irritable mood. • i energy and activity. • Marked feelings of well-being, physical, and mental efficiency. • i self-esteem. • Sociability. • Talkativeness. • Over-familiarity. • i sex drive. • Reduced need for sleep. • Difficulty in focusing on one task alone (tasks often started, but not finished). Differential diagnosis (See Box 7.3.) • Agitated depression. • OCD/other anxiety disorders. • Circadian rhythm sleep–wake disorders (E Circadian rhythm sleep–wake disorders (CRSD) 1: overview, p. 454). • Substance misuse/physical illness/medication-related (see Box 7.2). Management • Exclusion of other possible causes with appropriate investigations (E Bipolar (affective) disorder 2: clinical notes, p. 330). • Address any specific psychosocial stressors. • Ensure safety of the patient and others is maintained. • If sleep disturbance is a problem, consider use of a hypnotic. • If agitation is prominent, judicious use of BDZs may be appropriate. • If the episode is prolonged, discuss medication possibilities (E Treatment of acute manic episodes, p. 340) and the possibility of prophylaxis (E Prophylaxis, p. 344).

Hypomania/hypomanic episode 323

324 Chapter 7 Bipolar illness Bipolar spectrum disorder In the early 1980s, Gerald Klerman proposed a 'spectrum of mania', which included 'bipolar subtypes' and Hagop Akiskal originally suggested a similar 'bipolar spectrum' that broadened the very narrow DSM-III bipolar concept (see Table 7.1). Type II would become accepted officially a decade later and included in ICD-10 in 1992 and DSM-IV in 1994. Type III finally made it into DSM-5 in 2013 as 'Substance/medication-induced bipolar and related disorder'. Also in the 1980s, Athanasios Koukopoulos challenged the prevailing di chotomous view by showing that mood episodes were usually not purely depressive or manic, but 'mixed'. 'Mixed depression' was the opposite of 'melancholia'. It was not characterized by marked psychomotor retardation, but rather excitation, including 'manic' symptoms (e.g. flight of ideas or pres sured speech), agitation, irritability, rage, marked anxiety, and suicidal impul sivity. Much like bipolar disorder, mixed depression often got worse with antidepressants and responded to antipsychotics, whereas in melancholia, antidepressants sometimes worked, ECT was very effective, and lithium reduced recurrence rates. High rates of mixed depression symptoms were seen in both bipolar illness and major depressive disorder (MDD).1 Table 7.1 Subtypes of bipolar

disorder Klerman (1981)1 Akiskal (1999)2 Description—‘Depression plus . . . ’ Bipolar ½ Schizobipolar Bipolar I Bipolar I Mania Bipolar I ½ Protracted hypomania Bipolar II Bipolar II Hypomania Bipolar II ½ Cyclothymia Bipolar III Bipolar III Hypomania or mania precipitated by tricyclic (antidepressant) drugs Bipolar III ½ Bipolarity masked and unmasked by stimulant abuse Bipolar IV Cyclothymia Bipolar IV Hyperthymia Bipolar V Familial history of bipolar disorder Bipolar VI Mania alone (i.e. without depression) 1 Klerman GL (1981) The spectrum of mania. Compr Psychiatry 22:11–20. 2 Akiskal HS, Pinto O (1999) The evolving bipolar spectrum. Prototypes I, II, III, and IV. Psychiatr Clin North Am 22:517–34. 1 Benazzi F (2007) Mixed depression and the dimensional view of mood disorders. Psychopathology 40:431–9.

Bipolar spectrum disorder Box 7.3 ‘I think I’m a little bit bipolar . . . ’ A worrying trend in outpatient clinics is the ‘expert’ patient who has self-diagnosed bipolar disorder. One of the unexpected consequences of anti-stigma campaigns is the identification of individuals with celeb rities who claim to have a psychiatric disorder (usually of a ‘softer’ var iety—like bipolar II). While acceptance and more positive attitudes to psychiatric disorders are to be welcomed, it is still the provenance of the psychiatrist to legitimize such presumptive diagnoses. Good history- taking is of paramount importance. It is essential that differentials and comorbidity are considered (e.g. personality traits, anxiety, alcohol and substance misuse). As far as possible, collateral information may help with possible recall bias, and evidence of secondary gain prohibits the medicalization of difficult or imprudent behaviour. Clinicians must try and remain objective, and not collude with the patient, professional col leagues, fashionable labelling (e.g. ‘bipolar spectrum’; E Bipolar spec trum disorder, see opposite), or unsubstantiated claims of Big Pharma. Diagnosis carries not only far-reaching psychosocial consequences, but also will often suggest a need for specific interventions which are not without risk. The main differentials not to miss include: • Thyroid disorders: may resemble depression or mania/hypomania; can be caused by lithium; may present subclinically as mixed states; and are treatable! • Substance abuse: can mimic affective states; may unmask pre-existing illness/predisposition; may be a form of self-medication; should always be treated first. • ADHD: overlapping symptoms—restlessness, hyperactivity, distractibility, impulsiveness, poor concentration/attention, temper dyscontrol; lifelong, pervasive, not episodic; may respond to antidepressants and mood stabilizers. • Borderline personality disorder: stormy, unstable lifestyles; overly dramatic; intense unstable relationships; acutely sensitive to abandonment; unrealistically demanding of families and physicians; exhibiting self-defeating and self-destructive behaviours; heightened sense of personal rights (repeated vexatious complaints); frequently associated with dissociative symptoms, substance abuse, self-harm (mutilation), and repeated suicidal acts. • Other personality disorders: traits often seen in bipolar disorder: dependency, passive aggression, histrionics, paranoia, narcissism, hypochondriasis, manipulative antisocial traits. When these are secondary to bipolar disorder, they tend to disappear between episodes and with treatment, and the patient is more likely to be embarrassed and remorseful. Patients with fixed personality disorders are often demanding, defiant, manipulative, self-defeating, actively undermine efforts to address needs, are non-compliant with medication, abuse alcohol or substances, and end up in prison.

326 Chapter 7 Bipolar illness Jules Angst, whose work had previously been central to the move to a dichotomous view of the mood disorders in the 1960s, become an advo cate for the bipolar spectrum concept (‘bipolarity’) when, in later studies, he found many intermediate forms between the original bipolar and uni polar ideal types, with mixed states (three or more mania symptoms of

any duration) occurring in up to 50% of all depressive conditions.2 These findings brought into question the whole idea of ‘polarity’ as a useful dis tinction. Perhaps it might be better to base any nosology on something like recurrence, in much the same way that Emil Kraepelin originally framed ‘manic depressive insanity’? (E Box 7.3, p. 325). DSM-5 maintained the dichotomy but allowed the specifier ‘with mixed features’ to be applied to both bipolar I/II and depressive episodes. Researchers also voiced concerns about the possible underdiagnosis of bipolar disorder and the potential problems of mis-prescribing antidepres sants to patients for whom mood stabilizers might be of greater benefit. To help identify patients with ‘bipolar spectrum illness’, Nassir Ghaemi3 pro posed operational criteria that included a history of recurrent severe de pression, no spontaneous hypomanic/manic episodes, and some additional features, e.g. first-degree relative with bipolar disorder, antidepressant- induced mania/hypomania, hyperthymic4 or cyclothymic personality, re current major depressive episodes (>3), brief major depressive episodes (on average <3mths), atypical depressive symptoms, psychotic major de pressive episodes, early age of onset of major depressive episode (age <25), postpartum depression, antidepressant ‘wear-off’ (acute, but not prophylactic, response), or lack of response to up to three antidepressant trials. These features were already part of screening questionnaires, e.g. the MDQ (M http://www.integration.samhsa.gov/images/res/MDQ.pdf [accessed 20 June 2018]). The term ‘bipolar spectrum’ is often erroneously used to denote a clin ical presentation with mood instability or lability and a history of impul sive, foolish, excessive, or risky behaviour. Without other significant mood symptoms, it is highly unlikely that this is a bipolar presentation (E Box 7.3, p. 325). DSM-5 does use the category ‘Other specified bipolar and related disorder’ to capture ‘subsyndromal’ disorders that do not meet the duration criteria for hypomania (<4+ consecutive days), have too few symptoms for bipolar II syndrome (despite lasting 4+ days) in the context of a history of MDD, and have hypomania without prior depressive epi sode or short-duration cyclothymia (<24mths). Patients with these features may represent a subset of patients who do not respond well to antidepres sants (often precipitating a switch to a hypomanic or manic episode) and for whom a mood stabilizer may be a better choice if a treatment trial is proposed. 2 Angst J (2007) The bipolar spectrum. Br J Psychiatry 190:189–91. 3 Ghaemi SN, Ko JY, Goodwin FK (2002) ‘Cade’s disease’ and beyond: misdiagnosis, antidepressant use, and a proposed definition for bipolar spectrum disorder. Can J Psychiatry 47:125–34. 4 Characterized by cheerful, optimistic personality style, a tendency to become easily irritated, ex troverted, and sociable, and requiring little sleep (<6hrs/night)—a lifelong disposition, unlike short- lived hypomania. Neither in ICD-10 nor DSM-5, but significant overlap with narcissistic or antisocial personality.



328 Chapter 7 Bipolar illness Bipolar (affective) disorder 1: classification Diagnostic classification (See Box 7.4.) ICD-10 Requires at least two episodes, one of which must be hypomanic, manic, or mixed, with recovery usually complete between episodes. Criteria for depressive episodes are the same as unipolar depression (E Diagnosis 1: symptoms, p. 246). Separate category (manic episode) for hypomania or mania (with or without psychotic symptoms) without a history of depres sive episodes. Cyclothymia included with dysthymia in the persistent mood disorders section. DSM-5 Allows a single manic episode and cyclothymic disorder to be considered as part of bipolar disorder, and defines two subtypes (with additional specifiers): • Bipolar I disorder: the occurrence of one or more manic episodes with or without a history of one or more depressive episodes or hypomanic episodes. • Bipolar II disorder: the occurrence of one or more depressive episodes

accompanied by at least one hypomanic episode. • Severity specifiers: mild, moderate, severe. • Special syndrome specifiers: with anxious distress, mixed features, rapid cycling, catatonia, melancholic features, atypical features, peripartum onset, seasonal pattern, mood-congruent or mood-incongruent psychotic features. • Longitudinal course specifiers: in partial or full remission. Mixed episodes (ICD-10)/with mixed features (DSM-5) • The occurrence of both manic/hypomanic and depressive symptoms in a single episode, present every day for 2wks (ICD-10) or the majority of days during the episode of hypomania or mania (DSM-5). • Typical presentations include: • depression plus over-activity/pressure of speech. • mania plus agitation and reduced energy/libido. • dysphoria plus manic symptoms (with the exception of elevated mood). • rapid cycling (fluctuating between mania and depression—four or more episodes/year)—DSM-5 uses the specifier 'with rapid cycling' for bipolar I or II disorder. Note: 'ultra-rapid' cycling refers to an illness where fluctuations in mood are over days or even hours. 'The clinical reality of manic-depressive illness is far more lethal and infinitely more complex than the current psychiatric nomenclature, bipolar disorder, would suggest. Cycles of fluctuating moods and energy levels serve as a background to constantly changing thoughts, behaviors,

Bipolar (affective) disorder 1: classification and feelings. The illness encompasses the extremes of human experience. Thinking can range from florid psychosis, or "madness", to patterns of unusually clear, fast and creative associations, to retardation so profound that no meaningful mental activity can occur. Behavior can be frenzied, expansive, bizarre, and seductive, or it can be seclusive, sluggish, and dangerously suicidal. Moods may swing erratically between euphoria and despair or irritability and desperation. The rapid oscillations and combinations of such extremes result in an intricately textured clinical picture. Manic patients, for example, are depressed and irritable as often as they are euphoric; the highs associated with mania are generally only pleasant and productive during the earlier, milder stages.' Dr Kay Redfield Jamison (1993) Touched with fire: manic-depressive illness and the artistic temperament, pp. 47–8. New York: Free Press, Macmillan. Box 7.4 Classification of bipolar disorder ICD-10: bipolar affective disorder • Current episode, hypomanic. • Current episode, manic without psychotic symptoms. • Current episode, manic with psychotic symptoms. • Current episode, mild or moderate depression. • Current episode, severe depression without psychotic symptoms. • Current episode, severe depression with psychotic symptoms. • Current episode, mixed. • Currently in remission. • Other bipolar affective disorders/unspecified. DSM-5: bipolar and related disorders • Bipolar I disorder: • Current or most recent episode manic. • Current or most recent episode hypomanic. • Current or most recent episode depressed. • Current or most recent episode mixed. • Bipolar II disorder: • Current or most recent episode hypomanic. • Current or most recent episode depressed. • Cyclothymic disorder. • Substance/medication-induced bipolar and related disorder. • Bipolar and related disorder due to another medical condition. • Other specified/unspecified bipolar and related disorder. Note: ICD-11 is very similar to DSM-5 with bipolar I, bipolar II, cyclothymic disorder, other, and unspecified. Bipolar I and II include current episode manic (± psychotic symptoms), hypomanic, depressive [mild, moderate, severe (± psychotic symptoms), in partial or complete remission]. Bipolar I may also have mixed symptoms.

330 Chapter 7 Bipolar illness Bipolar (affective) disorder 2: clinical notes Epidemiology Lifetime prevalence 0.3–1.5% (0.8% bipolar I; 0.5% bipolar II); ♂ = ♀ (bi polar II and rapid cycling more common in ♀; first episodes: ♂ tend to be manic, ♀ depressive); no significant racial differences; age range 15–50+ yrs (peaks at 15–19yrs and 20–24yrs; mean 21yrs). Course Extremely variable.

First episodes may be hypomanic, manic, mixed, or de pressive. This may be followed by many years (5 or more) without a further episode, but the length of time between subsequent episodes may begin to narrow. There is often a 5- to 10-yr interval between the age at onset of illness and age at first treatment or first admission to hospital. Often patients with recurrent depression have a first manic episode in later life (>50yrs). Presentation in later life increases the suspicion of an underlying organic cause. It is known that untreated patients may have >10 episodes in a lifetime and that the duration and period of time between episodes sta bilize after the fourth or fifth episode. Although the prognosis is better for treated patients, there still remains a high degree of unpredictability. Morbidity/mortality Morbidity and mortality rates are high, in terms of lost work, lost prod uctivity, and effects on marriage (i divorce rates) and the family, with at tempted suicide in 25–50% and completed suicide in 10% (♂ > ♀, usually during a depressive episode). Often significant comorbidity—especially drug/alcohol misuse and anxiety disorders (both increase the risk of suicide). Differential diagnosis Depends upon the nature of the presenting episode (E Mania/manic epi sode, p. 320; E Hypomania/hypomanic episode, p. 322, and E Diagnosis 1: symptoms, p. 246). Investigations As for depression; full physical and routine blood tests to exclude any treat able cause, including FBC, ESR/CRP, glucose, U&Es, Ca2+, TFTs, LFTs, and drug screen. Less routine tests: urinary copper [to exclude WD (rare)], ANF (SLE), infection screen (VDRL, syphilis serology, HIV test). CT/ MRI brain (to exclude tumour, infarction, haemorrhage, MS)—may show hyperintense subcortical structures (esp. temporal lobes), ventricular en largement, and sulcal prominence; EEG (baseline and to rule out epilepsy). Other baseline tests prior to treatment should include ECG and creatinine clearance.

Bipolar (affective) disorder 2: clinical notes Management See specific sections (E Bipolar affective disorder 4: management prin ciples, p. 336) for management principles, other issues, treatment of acute manic episodes, depressive episodes, prophylaxis, and psychotherapeutic interventions. Prognosis Within the first 2yrs of first episode, 40–50% of patients experience an other manic episode. Fifty to 60% of patients on lithium gain control of their symptoms (7% no recurrence; 45% some future episodes; 40% persistent recurrence). Often, the cycling between depression and mania accelerates with age. Poor prognostic factors: poor employment history; alcohol abuse; psychotic features; depressive features between periods of mania and de pression; evidence of depression; ♂ sex; treatment non-compliance. Good prognostic factors: manic episodes of short duration; later age of onset; few thoughts of suicide; few psychotic symptoms; few comorbid physical prob lems; good treatment response and compliance.

332 Chapter 7 Bipolar illness Bipolar affective disorder 3: aetiology (See Box 7.5.) Despite significant research efforts, the definitive pathophysiology of bi polar disorder remains elusive. There are many similarities with gene ex pression and neuroimaging studies of persons with schizophrenia and major depression, suggesting that mood disorders and schizophrenia may share a biological basis. Genetic Twin, family, and adoption studies point to a significant genetic contribu tion. First-degree relatives are 7 times more likely to develop the condition than the general population (i.e. 10–15% risk). Children of a parent with Box 7.5 Aetiological theories Abnormal programmed cell death Animal studies have shown that antidepressants, lithium, and valproate indirectly regulate a number of factors involved in cell survival path ways (e.g. CREB, BDNF, Bcl-2, and MAP kinases), perhaps explaining their delayed long-term beneficial effects (via under-appreciated neuro trophic effects, especially in the frontal cortex and the hippocampus1). Neuroimaging studies also indicate cell loss in these same brain regions, suggesting that bipolar

disorder may result from abnormal programmed cell death (apoptosis) in critical neural networks involved in emotional regulation. Treatments may stimulate cell survival pathways, increase neurotrophic factors, and improve cellular resilience. Kindling Through a mechanism of electrophysiological kindling, this older hy pothesis2 draws on animal models to suggests a role for neuronal injury. A genetically predisposed individual experiences an increasing number of minor neurological insults (e.g. due to drugs of abuse, excessive gluco corticoid stimulation, acute or chronic stress, or other factors), which eventually result in mania. After the first episode, neuronal damage may persist, allowing for recurrence with or without minor environmental or behavioural stressors (like epilepsy), which may result in further injury. This could explain why later episodes become more frequent, anticon vulsants may be useful in preventing recurrent episodes, and treatment should be as early as possible and long term. It may be that the balance between primary pathological, secondary adaptive alterations in gene ex pression in the illness, and pharmacological enhancement or dampening determines the typical episodic course of relapses and remissions of mood symptoms.3 1 Manji HK, Duman RS (2001) Impairments of neuroplasticity and cellular resilience in severe mood disorders: implications for the development of novel therapeutics. Psychopharmacol Bull 35:5–49. 2 Post RM, Weiss SR (1989) Sensitization, kindling, and anticonvulsants in mania. J Clin Psychiatry 50(Suppl):23–30. 3 Post RM, Speer AM, Hough CJ, Xing G (2003) Neurobiology of bipolar illness: implications for future study and therapeutics. Ann Clin Psychiatry 15:85–94.

Bipolar affective disorder 3: aetiology bipolar disorder have a 50% chance of developing a psychiatric disorder (genetic liability appears shared for schizophrenia and schizoaffective and bi polar affective disorders). Monozygotic (MZ) twins: 33–90% concordance; dizygotic (DZ) twins: 723%. Recent evidence indicates an overall heritability of 770%. Candidate genes Results from four genome-wide association studies (GWAS) of large samples of subjects with bipolar disorder give combined support for two particular genes ANK3 (ankyrin G) and CACNA1C (α1C subunit of the L-type voltage-gated calcium channel).5 Other candidates are genes as sociated with biochemical pathways that lithium regulates, e.g. the phos phatidyl inositol pathway [diacylglycerol kinase eta (DGKH) gene); cell death/neuroprotection mechanisms [e.g. glycogen synthase kinase 3-beta (GSK3β)]; circadian periodicity (e.g. CLOCK gene); neuronal migration (NCAN); and oestrogen receptor binding site variations in women associ ated with the transglutaminase 2 (TGM2) gene. There are indications that large copy number variants (>100kb—both deletions and duplications) increase the risk of bipolar disorder. Post-mortem studies have found d levels of expression of oligodendrocyte-myelin-related genes, implicating abnormal myelination in the illness. Shared genetics with schizophrenia As well as overlapping family susceptibility, there are reports of shared genes, e.g. G72 on 13q34, which encodes d-amino acid oxidase activator (DAOA) and DISC1 (Disrupted in Schizophrenia 1) on 1q42. A large meta-analysis by the NIH on recent GWAS found evidence for a shared suscep tibility locus around 6p22.1 known to harbour genes involved in immunity and turning other genes on and off.6 Neuroimaging A recent meta-analysis of structural and functional brain imaging found d activation and reduced grey matter in areas associated with emotional regu lation, and i activation in ventral limbic brain regions that mediate and gen erate emotional responses.77 A post-mortem study88 has shown evidence of loss of hippocampal interneurons in patients with bipolar disorder. Biochemical factors There is increasing evidence of the importance of glutamate in bipolar disorder and major depression; the cathecholamine hypothesis study sug gests that an increase in adrenaline and noradrenaline causes mania, while 5 Ferreira MA, O’Donovan MC, Meng YA, et al.

(2008) Collaborative genome-wide association ana lysis supports a role for ANK3 and CACNA1C in bipolar disorder. Nat Genet 40:1056–8. 6 National Institutes of Health (2009) Schizophrenia and bipolar disorder share genetic roots. M https://www.nih.gov/news-events/news-releases/schizophrenia-bipolar-disorder-share-genetic- roots [accessed 20 June 2018]. 7 Houenou J, Frommberger J, Carde S, et al. (2011) Neuroimaging-based markers of bipolar dis order: evidence from two meta-analyses. J Affect Disord 132:344–55. 8 Konradi C, Zimmerman EI, Yang CK, et al. (2011) Hippocampal interneurons in bipolar disorder. Arch Gen Psychiatry 68:340–50.

334 Chapter 7 Bipolar illness a decrease causes depression; drugs that may cause mania (e.g. cocaine, levodopa, amphetamines, antidepressants) suggest a role for DA and 5- HT; disruption of Ca2+ regulation may be caused by neurological insults such as excessive glutaminergic transmission or ischaemia; hormonal imbal ances and disruptions of the hypothalamic–pituitary–adrenal axis involved in homeostasis and stress response are also important. Environmental factors Stressful life events may precipitate episodes, particularly in vulnerable indi viduals. Pregnancy especially carries a high risk of a mixed affective presen tation or puerperal psychosis (E Post-partum psychosis, p. 494). Pharmacological risk factors Concerns about the possibility of antidepressant treatment precipitating mania have been investigated recently in over 21,000 patients presenting with unipolar depression. Conversion to mania/bipolar disorder was 10.9 per 1000 person-years, with a peak incidence between 26 and 35 years (12.3 per 1000 person-years). Prior antidepressant treatment i the likeli hood of conversion by about 30%.99 9 Patel R, Reiss P, Shetty H, et al. (2015) Do antidepressants increase the risk of mania and bipolar disorder in people with depression? A retrospective electronic case register cohort study. BMJ Open 5:e008341.

Bipolar affective disorder 3: aetiology

336 Chapter 7 Bipolar illness Bipolar affective disorder 4: management principles Acute episodes This will depend upon the nature of the presenting episode (E Mania/ manic episode, p. 320; E Hypomania/hypomanic episode, p. 322; E Bipolar spectrum disorder, p. 324). Often the episode may require hospital admission (E Hospital admission, see opposite). Special consid eration should also be given to certain specific issues related to the clinical presentation, the presence of concurrent medical problems, and particular patient groups, both in terms of setting and choice of treatment (E Other issues affecting management decisions, p. 338). Issues of prophylaxis (E Prophylaxis, p. 344) should be considered, and this may sometimes involve not only pharmacological, but also psychotherapeutic interventions (E Psychotherapeutic interventions, p. 346). Outpatient follow-up Once the diagnosis has been clearly established, possible physical causes excluded, and the presenting episode effectively treated, follow-up has a number of key aims: • Establishing and maintaining a therapeutic alliance. • Monitoring the patient's mental state. • Providing education regarding bipolar disorder. • Enhancing treatment compliance. • Monitoring side effects of medication and ensuring therapeutic levels of any mood stabilizer. • Identifying and addressing any significant comorbid conditions (E Other issues affecting management decisions, p. 338). • Promoting regular patterns of activity and wakefulness. • Promoting understanding of, and adaption to, the psychosocial effects of bipolar disorder. • Identifying new episodes early. • Reducing the morbidity and sequelae of bipolar disorder. • Maintaining a pragmatic view of how interventions will help—to reduce the frequency and severity of episodes, but perhaps not to eliminate them completely—bipolar disorder is a chronic condition.

• Providing an opportunity to discuss any new treatment developments in a balanced and evidence-informed manner. Relapse prevention A key part of psychiatric management is helping patients to identify precipi tants or early manifestations of illness, so that treatment can be initiated early. This may be done as part of the usual psychiatric follow-up or form part of a specific psychotherapeutic intervention (E Psychotherapeutic interventions, p. 346), e.g. insomnia may often be either a precipitant or an early indicator of mania or depression—education about the importance of regular sleep habits and occasional use of a hypnotic (E Insomnia 2: gen eral management strategies, p. 442) to promote normal sleep patterns may be useful in preventing the development of a manic episode. Other early or subtle signs of mania may be treated with the short-term use of BDZs or

Bipolar affective disorder 4: management principles antipsychotics. A good therapeutic alliance is critical, and the patient, who often has good insight, ought to feel that they can contact their clinician as soon as they are aware of these early warning signs. Use of a Mood Diary or Life Chart can help in this regard (see M http://bipolarnews.org; select the 'Mood Charting' tab).
Hospital admission Frequently acute episodes of bipolar disorder are severe enough to require hospital admission (often on a compulsory basis). Issues of safety and the provision of effective treatment will govern decisions about whether a pa tient can remain in the community. Points to note • Patients with symptoms of mania/hypomania or depression often have impaired judgement (sometimes related to psychotic symptoms), which may interfere with their ability to make reasoned decisions about the need for treatment. • Risk assessment includes not only behaviours that may cause direct harm (e.g. suicide attempts or homicidal behaviour), but also those that may be indirectly harmful (e.g. overspending, sexual promiscuity, excessive use of drugs/alcohol, driving while unwell). • The relapsing/remitting nature of the disorder makes it possible to work with the patient (when well) and their family/carers to anticipate future acute episodes—agree a treatment plan. Clinical features and situations where admission may be necessary • High risk of suicide or homicide. • Illness behaviour endangering relationships, reputation, or assets. • Lack of capacity to cooperate with treatment (e.g. directly due to illness or secondary to availability of social supports/outpatient resources). • Lack (or loss) of psychosocial supports. • Severe psychotic symptoms. • Severe depressive symptoms. • Severe mixed states or rapid cycling (days/hours). • Catatonic symptoms. • Failure of outpatient treatment. • Address comorbid conditions (e.g. physical problems, other psychiatric conditions, inpatient detoxification).
Suitable environment During an acute manic episode, maintain a routine, calm environment (not always possible). A balance should be struck between avoiding over- stimulation (e.g. from outside events, TV, radio, lively conversation) and provision of space to walk or exercise to use up excess energy. Where possible, restrict access to alcohol and drugs. Regular observations by staff may be overly intrusive and feel uncomfortable on a busy ward. Patients may make requests that may be reasonable, but not practical. Psychiatrists should adopt a pragmatic approach, listen to concerns, and balance risks. This may result in a difficult decision about whether to detain a patient to a hospital environment, which, although far from ideal, is the 'least worst' option.

 Other issues affecting management decisions Specific clinical features Certain clinical features will strongly influence the choice of treatment. For issues of substance misuse or other psychiatric morbidity, these should be addressed directly (see specific sections). • Psychotic symptoms: not uncommon for patients to experience delusions and/or hallucinations during episodes of mania or depression. Management—an antipsychotic with mood-stabilizing

properties (e.g. olanzapine or quetiapine) is the first-line choice. A mood stabilizer (semisodium valproate or lithium typically) may also be appropriate for prophylaxis; consider ECT; if severe, consider admission to hospital. • Catatonic symptoms: during a manic episode (manic stupor). Management—admit to hospital; exclude medical problem; clarify psychiatric diagnosis; if clear, treat with ECT and/or BDZ, alongside mood-stabilizing antipsychotic medication. • Risk of suicide: assess nature of risk (E Asking about depressed mood, p. 64); note association with rapid cycling mood. If significant risk, or unacceptable uncertainty, admit to hospital (or if in hospital, increase the level of observation). • Risk of violence: assess nature of risk (E Assessing risk of violence, p. 748). Note i risk with rapid mood cycling, paranoid delusions, agitation, and dysphoria. Admit to hospital; consider the need for secure setting. • Substance-related disorders: comorbidity is high, often confusing the clinical picture. Substance misuse may lead to relapse both directly and indirectly (by reducing compliance and precipitating difficult social circumstances). Equally, alcohol consumption may increase when on lithium. Management—address issues of misuse; if detoxification considered, admit to hospital as risk of suicide may be i. • Other comorbidities: personality difficulty/disorder, anxiety or conduct disorder, ADHD. Concurrent medical problems The presence of other medical problems may affect management either by exacerbating the course or severity of the disorder or by complicating drug treatment (i.e. issues of tolerability and drug interactions). • Cardiovascular/renal/hepatic disorders: may restrict the choice of drug therapy or increase the need for closer monitoring (E Prescribing for patients with cardiovascular disease, p. 1032; E Prescribing for patients with liver disease, p. 1034; E Prescribing for patients with renal impairment, p. 1036). • Endocrine disorders: e.g. hypo-/hyperthyoidism. • Infectious diseases: e.g. HIV-infected patients may be more sensitive to CNS side effects of mood stabilizers. • Use of steroids: e.g. for treatment of asthma/irritable bowel syndrome (IBS).

Other issues affecting management decisions Special patient groups • Children and adolescents (E Management, p. 701) Lithium has been shown to be effective, but long-term effects on development have not been fully studied. Lithium may be excreted more quickly, allowing more rapid dose adjustments, but therapeutic levels are the same as for adults. Risks associated with other adjunctive agents (e.g. antipsychotics, antidepressants, BDZs) should be considered separately. ECT is rarely used but may be effective. Education, support, and other specific psychosocial interventions should be considered (usually involving family, teachers, etc.). • The elderly (E Management, p. 553) When a first manic episode occurs in a patient after age 60, there is usually evidence of previous depressive episodes in their 40s and 50s. Full physical examination is necessary to exclude medical causes (especially CNS disorders). Older patients may be more sensitive to the side effects of lithium (particularly neurological and renal) and may require lower therapeutic levels (i.e. below 0.7mmol/L). • Pregnancy and lactation (E Prescribing in pregnancy, p. 1028; E Prescribing in lactation, p. 1030). Consider ECT earlier than in other situations of significant manic, depressed, or psychotically depressed episodes. Published guidelines There are now a number of guidelines that can help inform practice, including the slightly ageing APA guideline (2002)1010 and the more up-to- date UK NICE guideline (2014)1111 and the BAP guideline (2016)1212. Many UK hospitals are also developing integrated care pathways (ICPs), which will include treatment guidelines based on these, as well as reflecting local custom and practice. 10 American Psychiatric Association (2002) Practice guideline for the treatment of patients with bi polar disorder. Am J Psychiatry 159(Suppl 4): 1–50. M https://psychiatryonline.org/pb/assets/raw/ sitewide/practice_guidelines/guidelines/bipolar.pdf [accessed 20 June 2018]. 11 National Institute for Health and Care Excellence (2014) Bipolar

disorder: assessment and man agement. Clinical guideline [CG185]. M http://www.nice.org.uk/guidance/cg185 [accessed 20 June 2018]. 12 Goodwin GM; Consensus Group of the British Association for Psychopharmacology (2016) Evidence-based guidelines for treating bipolar disorder:  revised third edition—recommendations from the British Association for Psychopharmacology. J Psychopharmacol 30:495–553. M http://www.bap.org.uk/pdfs/BAP_Guidelines-Bipolar.pdf [accessed 20 June 2018].

340 Chapter 7 Bipolar illness Treatment of acute manic episodes For severe behavioural disorder Follow local protocols for management (E Severe behavioural disturbance, p. 1048). Pharmacological interventions should be regarded as separate from specific management of acute mania, although there is a degree of overlap. Cautious treatment with BDZs (e.g. lorazepam) and low-dose antipsychotics (e.g. haloperidol) are recommended. Local guidelines should be followed. For severe/life-threatening manic episode ECT has been shown to be a valid treatment option in acute mania13 and should be offered, especially if the patient has had a previous good re sponse or there is an advance statement/directive of preference. Current practice reserves ECT for clinical situations where pharmacological treat ments may not be possible, such as pregnancy or severe cardiac disease, or when the patient's illness is refractory to drug treatments. If currently on antidepressant medication Give consideration to reducing, stopping, or swapping to an alternative medication if manic episode related to commencement or recent dose change (or possible compliance issues). Not currently on any treatment Most guidelines recommend the use of one of the licensed SGAs first line in view of ease of use, rapidity of action, and tolerability (see Table 7.2)—with most evidence for olanzapine, risperidone, and quetiapine. Haloperidol is also one of the best options for the treatment of manic epi sodes.14 Valproic acid or lithium are usually second line, unless there is clear evidence of previous benefit. 13 Mukherjee S, Sackeim HA, Schnur DB (1994) Electroconvulsive therapy of acute manic epi sodes: a review of 50 years' experience. Am J Psychol 151:169–76. 14 Cipriani A, Barbui C, Salanti G, et al. (2011) Comparative efficacy and acceptability of antimanic drugs in acute mania: a multiple-treatments meta-analysis. Lancet 378:1306–15. Table 7.2 Licensed antipsychotics (UK): starting doses and therapeutic ranges (see BNF for further details) Drug Starting dose Therapeutic range Olanzapine 15mg/day 5–20mg/day Quetiapine 50mg bd 400–800mg/day Risperidone 2mg/day 1–6mg/day Aripiprazole 15mg/day 15–30mg/day Asenapine 10mg bd 10–20mg/day

Treatment of acute manic episodes If already on semisodium valproate or lithium • Ensure compliance and therapeutic dose. • Consider combining lithium with semisodium valproate. • Consider adding antipsychotic treatment. If already on antipsychotic medication • Ensure compliance and therapeutic dose. • Consider adding lithium or semisodium valproate. Treatment notes • Lithium (E Lithium, p. 350) Up to 3wks of treatment may be necessary to reach maximal effectiveness for manic patients. Due to this delayed effect, especially for severe mania or psychotic symptoms, with associated acute behavioural disturbance, an antipsychotic and/or BDZ is often used first line (see 'Benzodiazepines' further below). Predictors of good response include—previous response to lithium, compliance with medication, >3 previous episodes, family history of mood disorder, euphoria (not dysphoria), lack of psychotic symptoms or suicidal behaviour. • Semisodium valproate (E Valproate/valproic acid, p. 354) Well tolerated and has very few drug interactions, making it more suitable for combined treatment regimes. May also work faster than lithium, but not suitable for women of childbearing age due to the risk of neural tube defects. Predictors of good response include—rapid cycling, dysphoric mania, mixed

episodes/features, stable or decreasing frequency of manic episodes, less severe bipolar spectrum disorders. • Benzodiazepines May reduce the need for using high antipsychotic doses in order to achieve sufficient sedation. Clonazepam and lorazepam are most widely studied, alone or in combination with lithium. • Carbamazepine (E Carbamazepine, p. 356) Or its derivative oxcarbazepine, may be effective, either alone or in combination with lithium or antipsychotics.15 May be better tolerated in patients with comorbid drug or alcohol problems, in obesity, or in women of childbearing age. Predictors of good response include—previous response to carbamazepine, poor compliance (due to wide therapeutic window), absence of psychotic symptoms, secondary mania (e.g. drug-induced, neurological disorder, brain injury), dysphoria, mixed episodes/features, rapid cycling, episode part of schizoaffective disorder. • Other anticonvulsants Meta-analysis does not support the use of lamotrigine, gabapentin, or topiramate for acute mania.14 • Clozapine (E Clozapine 1: general guidelines, p. 218 May be considered for refractory illness where symptoms are inadequately controlled with optimized doses of the first-line medicine and/or mania is very severe. 15 McElroy SL, Keck PE Jr (2000) Pharmacologic agents for the treatment of acute bipolar mania. Biol Psychiatry 48:539–57.

342 Chapter 7 Bipolar illness Treatment of depressive episodes Bipolar depression occurs more frequently, lasts longer, is more disruptive, and may be associated with a greater risk of suicide than mania. Until re cently, research has focused more on treatment of mania and prophylaxis. The pharmacological treatment of depressive episodes in bipolar disorder represents a particular challenge.16 Although almost all of the antidepres sants used in the treatment of unipolar depression are used in the treatment of bipolar depression, the response rates are lower and it is not confirmed that they have a significant effect at all. Despite this, many clinicians choose to prescribe them pragmatically, given the risks of depressive episodes in the context of bipolar disorder. Furthermore, antidepressants can increase the risk of precipitating a manic episode or inducing/accelerating rapid cyc ling.17 When symptoms are mild to moderate, consider combining pharma cological and psychological interventions (as for unipolar depression; E Management principles and outpatient treatment, p. 262). If the patient is already on prophylaxis • Optimize (ensure compliance), check serum levels. • Exclude/treat associated problems (e.g. hypothyroidism). • Review the need for other medications that may lower the mood. Consider other conditions that may mimic or cause depression (E Differential diagnosis, p. 253). • Consider adding SSRI (along with mood-stabilizing prophylaxis). • If not on antipsychotic, then consider the addition of quetiapine instead of SSRI (E Treatment notes, see opposite). If evidence of recent mood instability (manic/hypomanic episodes and depression) • First line: increase or (re)commence antimanic agent. • Second line: consider using lamotrigine. If no response to SSRI • Consider alternative antidepressant, e.g. mirtazapine, venlafaxine; or augmentation strategies (E Treatment notes, see opposite). • Consider the addition of quetiapine or olanzapine if not currently on an antipsychotic (E Treatment notes, see opposite). For severe/life-threatening depressive episode (or previous good response/advance statement of preference) • ECT should be strongly considered as first-line treatment. • Although well established for treatment of unipolar depressive disorder, ECT in bipolar disorder has not been fully researched but should not be overlooked (especially severe cases). • Take care if the patient is on prophylaxis (E Table 6.7, p. 298). 16 Hirschfeld RM (2004) Bipolar depression: the real challenge. Eur Neuropsychopharmacol 14(Suppl 2): S83–8. 17 Compton MT, Nemeroff CB (2000) The treatment of bipolar depression. J Clin Psychiatry 61(Suppl):57–67.

Treatment of depressive episodes Following remission of depressive symptoms • Taper antidepressants after 8–12wks of maintenance treatment. • Continue a mood stabilizer to prevent relapse. Treatment notes • Choice of antidepressant: although evidence is scarce, recent studies have suggested that SSRIs may be better tolerated, work more quickly, and have a lower associated risk of inducing mania or rapid cycling, compared to TCAs. In general, choice will depend on issues of previous response, side effects (both desired and undesired), and tolerability issues (E Antidepressants, p. 276). • Role of antipsychotics: quetiapine is licensed to treat depression in bipolar disorder (50mg nocte day 1, 100mg day 2, 200mg day 3, 300mg day 4; adjust according to response, usual dose 300mg nocte; max 600mg daily). Efficacy has been demonstrated in two RCTs (BOLDER 1 and 2) and the EMBOLDEN I and II replication trials.18 Olanzapine, as an olanzapine–fluoxetine combination (OFC), is licensed for bipolar depression in the USA as Symbyax® (6/25, 6/50, or 12/50mg/day). Not licensed for bipolar depression in the UK, but licensed for mania and propylaxis. Recommended as first line either on its own or with fluoxetine in NICE (CG185, 2014) and BAP (2016) guidelines (E Published guidelines, p. 339). Similarly, lurasidone is unlicensed in the UK but recommended for use first line in BAP (2016) guidelines. • Other anticonvulsants: a recent meta-analysis supports monotherapy with lamotrigine (licensed in the USA, but not in the UK; E Lamotrigine, p. 358), particularly for treatment-refractory bipolar depression.19 Gabapentin appears much less effective. Controlled clinical trials comparing standard treatments for depression in patients with bipolar disorder are lacking. It is a widely accepted practice to add a second mood stabilizer to the treatment regimens of patients with bipolar disorder (e.g. carbamazepine or valproate). Be alert for evidence of lithium toxicity, even at ‘normal’ serum levels (E Toxicity, p. 353). • Alternative strategies/treatment resistance: other suggested strategies include the use of adjunctive tri-iodothyronine (T3)—even if there is no evidence of clinical hypothyroidism20—and the novel use of inositol.21 Evidence for omega-3 fatty acids is equivocal at best. For treatment- resistant depressive episodes, the principles of management are as for unipolar depression (E An approach to treatment-resistant depression, p. 270). 18 For a review of the studies, see: Bogart GT, Chavez B (2009) Safety and efficacy of quetiapine in bipolar depression. Ann Pharmacother 43:1848–56. 19 Geddes JR, Calabrese JR, Goodwin GM (2009) Lamotrigine for treatment of bipolar depres sion: independent meta-analysis and meta-regression of individual patient data from five randomised trials. Br J Psychiatry 194:4–9. 20 Bauer M, Berghofer A, Bschor T, et al. (2002) Supraphysiological doses of L-thyroxine in the maintenance treatment of prophylaxis-resistant affective disorders. Neuropsychopharmacol 27:620–8. 21 Chengappa KN, Levine J, Gershon S, et al. (2000) Inositol as an add-on treatment for bipolar depression. Bipolar Disord 2:47–55.

344 Chapter 7 Bipolar illness Prophylaxis Primary aim Prevention of recurrent episodes (mania, hypomania, or depression). Suicide prevention Patients with bipolar disorder represent a group at high risk of suicide. Retrospective and prospective studies do suggest that long-term lithium therapy reduces the risk of suicide. There are still little data available on the anti-suicidal effects of other prophylactic treatments. Indications Following effective remission of acute symptoms of mania or bipolar de pression; also recommended in bipolar II disorder. Procedure following remission of acute symptoms of mania or depression • Ensure therapeutic dose of mood stabilizer/optimal balance of risk– benefit for any antipsychotic medication. • Withdraw gradually any additional antipsychotic or BDZ used to manage acute symptoms. • When euthymia achieved following depressive episode, consider tapering antidepressant after 8–12wks. • Continue monitoring of side effects, blood levels, and physical checks as per protocols for individual agents

(E Lithium, p. 350; E Lithium: adverse effects, p. 352; E Valproate/valproic acid, p. 354; E Carbamazepine, p. 356; E Lamotrigine, p. 358). Guiding principles • Manage with the lowest dose necessary of any maintenance medication. • Aim for a single agent, if possible; most will require mood stabilizer + low-dose antipsychotic or mood stabilizer + antidepressant. • Off-licence use of valproate or antipsychotic may be justified in the maintenance phase if there is good evidence of benefit in acute phase management (i.e. continuation is not unreasonable, perhaps at a lower dose, and few medications are licensed). • 'Wait and see' policy for possible bipolar II disorder where use of mood stabilizer may prevent more serious later episodes should be discussed with the patient in light of a detailed clinical interview (especially high genetic risk), since treatments themselves are not without risks (evidence supports possible use of quetiapine or lamotrigine in this regard, but these are off-licence indications). Licensed treatments • Lithium (E Lithium, p. 350): to date, remains the gold standard choice for maintenance treatment in patients,22 especially with a 'classical' course of illness. • Carbamazepine (E Carbamazepine, p. 356): appears to be effective in the long-term treatment of bipolar disorder, with an overall response 22 Kessing LV, Hellmund G, Geddes JR, et al. (2011) Valproate v. lithium in the treatment of bipolar disorder in clinical practice:  observational nationwide register-based cohort study. Br J Psychiatry 199:57–63.

Prophylaxis rate of 63%. Although it does not have worldwide approval as yet, carbamazepine may be more effective in the treatment of bipolar spectrum than classical bipolar disorder. • Lamotrigine (E Lamotrigine, p. 358): licensed as monotherapy or adjunctive therapy (200–400mg/day); efficacy established in a pair of controlled studies for the prevention of depression and, to a lesser extent, mania following discontinuation of other psychotropic medications.23 • Olanzapine: licensed for prevention of recurrence in bipolar disorder (5–20mg/day); appears to be effective either alone or in combination with lithium or valproate. • Aripiprazole: licensed for treatment and recurrence prevention of mania (15–30mg/day). • Quetiapine: licensed for prevention of mania and depression in bipolar disorder (300–800mg/day in two divided doses). Unlicensed treatments • Semisodium valproate/valproate/valproic acid (E Valproate/valproic acid, p. 354): licensed for treatment of mania, but not specifically as prophylaxis. Caution required in women of childbearing age. Evidence of efficacy in rapid-cycling bipolar disorder and the most widely prescribed therapy for bipolar depression (unequivocal evidence of successful prophylaxis has not yet emerged). Indeed, the recent BALANCE study showed that both combination therapy (lithium plus valproate) and lithium monotherapy are more likely to prevent relapse than valproate monotherapy.24 • Other antipsychotics: risperidone may have an adjunctive or maintenance role orally and as depot. Asenapine is licensed for use in mania and may be continued as prophylaxis. FGAs, including depots (usually low dose), are anecdotally effective, but evidence is lacking. • Other anticonvulsants: there have been promising reports on the efficacy of oxcarbazepine, topiramate, gabapentin, and tiagabine, but the evidence is relatively weak. • Alternative/augmentative agents: a number of other compounds that may have clinical utility include: Ca2+ channel antagonists such as verapamil, nifedipine, and nimodipine; thyroid hormones; tamoxifen; omega-3 fatty acids; and even vitamin/mineral supplements. These agents should only be considered following attempts to treat with more conventional approaches. Risks of discontinuation Substantial evidence exists that abrupt discontinuation of lithium is associ ated with an i risk of relapse. The risk, particularly of mania, may be min imized by gradually reducing the lithium dose. Although comparable studies are not available for the anticonvulsants or antipsychotics, a similarly cau tious approach would seem advisable. 23 Goodwin GM, Bowden CL, Calabrese JR, et al. (2004) A pooled analysis of 2 placebo-controlled 18-month trials of lamotrigine

and lithium maintenance in bipolar I disorder. J Clin Psychiatry 65:432–41. 24 BALANCE investigators and collaborators (2010) Lithium plus valproate combination therapy versus monotherapy for relapse prevention in bipolar I disorder (BALANCE): a randomised open- label trial. Lancet 375:385–95.

346 Chapter 7 Bipolar illness Psychotherapeutic interventions Most patients will struggle with some of the following issues: • Emotional consequences of significant periods of illness and receiving the diagnosis of a chronic psychiatric disorder. • Developmental deviations and delays caused by past episodes. • Problems associated with stigmatization. • Problems related to self-esteem. • Fear of recurrence and the consequent inhibition of normal psychosocial functioning. • Interpersonal difficulties. • Issues related to marriage, family, childbearing, and parenting. • Academic and occupational problems. • Other legal, social, and emotional problems that arise from illness-related behaviours. For some patients, a specific psychotherapeutic intervention (in addition to usual psychiatric management and social support) will be needed to address these issues. Approaches include: psychodynamic, interpersonal, behavioural, and cognitive therapies. In addition, couple, family, and group therapy may be indicated for some patients. The selection of appropriate interventions is influenced by the local availability of such treatments, as well as the patient's needs and preferences. Key elements of selected interventions • Psychoeducation:25,26 key component to most therapies, psychoeducation goes further than simply delivering information and does appear to reduce recurrence and relapse. Patients are given a theoretical and practical approach to understanding their illness and the medication they are prescribed. Through understanding, patients can attain improved adherence to medication, recognize symptoms that might lead to decompensation, and recover occupational and social function. • CBT:27 time-limited, with specific aims—educating the patient about bipolar disorder and its treatment, teaching cognitive behavioural skills for coping with psychosocial stressors and associated problems, facilitating compliance with treatment, and monitoring the occurrence and severity of symptoms. • Interpersonal and social rhythm therapy (IPT/SRT):28 to reduce lability of mood by maintaining a regular pattern of daily activities, e.g. sleeping, eating, physical activity, and emotional stimulation. Evidence suggests IPT/SRT should be initiated immediately following an acute episode 25 Vieta E, Pacchiarotti I, Scott J, et al. (2005) Evidence-based research on the efficacy of psychologic interventions in bipolar disorders: a critical review. Curr Psychiatry Rep 7:449–55. 26 Colom F, Vieta E, Martinez-Aran A, et al. (2003) A randomized trial on the efficacy of group psychoeducation in the prophylaxis of recurrences in bipolar patients whose disease is in remission. Arch Gen Psychiatry 60:402–7. 27 Lam DH, Watkins ER, Hayward P, et al. (2003) A randomized controlled study of cognitive therapy for relapse prevention for bipolar affective disorder: outcome of the first year. Arch Gen Psychiatry 60:145–52. 28 Frank E, Kupfer DJ, Thase ME, et al. (2005) Two-year outcomes for interpersonal and social rhythm therapy in individuals with bipolar I disorder. Arch Gen Psychiatry 62:996–1004.

Psychotherapeutic interventions when individuals are most likely to make the lifestyle changes required to achieve social rhythm stability. • Family-focused therapy (FFT):29 usually brief, includes psychoeducation (of patient and family members) with specific aims—accepting the reality of the illness, identifying precipitating stresses and likely future stresses inside and outside the family, elucidating family interactions that produce stress on the patient, planning strategies for managing and/ or minimizing future stresses, and bringing about acceptance of the patient's family of the need for continued treatment. Benefits more pronounced in depressed patients and in those

living in a high-expressed emotional environment. • Support groups: may provide useful information about bipolar disorder and its treatment. Patients may benefit from hearing the experiences of others, struggling with similar issues. This may help them to see their problems as not being unique, understand the need for medication, and access advice and assistance with other practical issues. In the UK, groups such as the Manic Depression Fellowship, MIND, and SANE provide both support and educational material to patients and their families (E Resources for patients, p. 1072). ‘At this point in my existence, I cannot imagine leading a normal life without both taking lithium and having had the benefits of psychotherapy. Lithium prevents my seductive but disastrous highs, diminishes my depressions, clears out the wool and webbing from my disordered thinking, slows me down, gentles me out, keeps me out of a hospital, alive, and makes psychotherapy possible. But, ineffably, psychotherapy heals. It makes some sense of the confusion, reins in the terrifying thoughts and feelings, returns some control and hope and possibility of learning from it all. Pills cannot, do not, ease one back into reality; they only bring one back headlong, careening, and faster than can be endured at times. Psychotherapy is a sanctuary; it is a battleground; it is a place I have been psychotic, neurotic, elated, confused, and despairing beyond belief. But, always, it is where I have believed or have learned to believe—that I might someday be able to contend with all of this. No pill can help me deal with the problem of not wanting to take pills; likewise, no amount of psychotherapy alone can prevent my manias and depressions. I need both. It is an odd thing, owing life to pills, one’s own quirks and tenacities, and this unique, strange, and ultimately profound relationship called psychotherapy.’ Dr Kay Redfield Jamison (1996) An unquiet mind: a memoir of moods and madness, pp. 88–9. London: Picador. 29 Miklowitz DJ, George EL, Richards JA, et  al. (2003) A randomized study of family-focused psychoeducation and pharmacotherapy in the outpatient management of bipolar disorder. Arch Gen Psychiatry 60:904–12.

348 Chapter 7 Bipolar illness Cyclothymia Previously regarded as a disorder of personality (‘cyclothymic tempera ment’; see Boxes 7.6 and 7.7), mainly because of its early age of onset and relative stability throughout adult life, cyclothymia is now considered to be a mood disorder.30 Clinical features • Persistent instability of mood, numerous periods of mild depression and mild elation, not sufficiently severe or prolonged to fulfil the criteria for bipolar affective disorder or recurrent depressive disorder. • The mood swings are usually perceived by the individual as being unrelated to life events. The diagnosis is difficult to establish without a prolonged period of obser vation or an unusually good account of the individual’s past behaviour. In DSM-5, the symptoms must have been present for at least 2yrs (or 1yr in children and adolescents), with no period lasting longer than 2mths, during which they have been at a normal state, and an additional specifier ‘with anxious distress’ may be used. Epidemiology • Prevalence: 3–6% of general population. • Age of onset: usually early adulthood (i.e. teens or 20s), but sometimes may present later in life. • More common in relatives of patients with bipolar affective disorder. Differential diagnosis Bipolar affective disorder, recurrent depressive disorder, drug or alcohol misuse, ADHD, conduct disorder, personality disorder (emotionally un stable), medical conditions (E Differential diagnosis, p. 321). Course Onset often gradual, making it difficult to pinpoint when symptoms began. Alternating ups and downs may fluctuate in hours, weeks, or months. Because mood swings are relatively mild and periods of mood elevation may be enjoyable (with i activity and productivity, self-confidence, and so ciability), cyclothymia frequently fails to come to medical attention. The person may often present either because of the impact of the depressive episodes on social and work situations or because of problems related to comorbid drug or alcohol misuse. Usually runs a chronic course,

persisting throughout adult life. In some cases, symptoms may cease temporarily or permanently or develop into more severe mood swings meeting the criteria for bipolar affective disorder or recurrent depressive disorder. 30 When Kahlbaum (1863) introduced the term ‘cyclothymia’ into modern psychiatry, he described it as the mildest form of manic–depressive disease. Kraepelin (1896) treated it the same way (see Box 7.6), but Schneider (1958) used the term cyclothymia synonymously with manic–depressive dis ease. He described and conceptualized the ‘labile psychopath’ as a personality disorder (see Box 7.7) as distinct from manic–depressive illness. Classification systems no longer reflect Schneider’s view, and DSM-5, ICD-10, and ICD-11 include cyclothymia (or cyclothymic disorder) within the affective (mood) disorders. Debate continues regarding the interface between such subthreshold affective conditions, personality, and temperament (E Bipolar spectrum disorder, p. 324; E Box 7.3, p. 325).

Cyclothymia Management • If pharmacological treatment is contemplated, this usually consists of a trial of a mood stabilizer (e.g. lithium, low dose 600–900mg/day). • Recently, there has been a tendency to use anticonvulsants, such as valproate (500–750mg/day), carbamazepine, or lamotrigine, as these may be better tolerated. As yet, there is no clear evidence to suggest any of these approaches is superior. • At times of ‘crisis’ due to temperamental excesses, a short course of a low-dose sedating antipsychotic (e.g. chlorpromazine 50mg nocte; risperidone 1mg nocte; olanzapine 2.5mg nocte; quetiapine 25–50mg nocte) may be helpful. • Psychoeducation and insight-orientated psychotherapy may help the person to understand the condition and allow them to develop better ways of coping. • There is often a reluctance to continue to take medication, as this not only treats the depressive episodes, but also may be perceived as ‘blunting’ creativity, productivity, or intellectual capacity. Box 7.6 Kraepelin’s ‘cyclothymic temperament’ These are the people who constantly oscillate hither and thither between the two opposite poles of mood, sometimes ‘rejoicing to the skies’, sometimes ‘sad as death’. Today lively, sparkling, beaming, full of the joy of life, the pleasure of enterprise, and the pressure of activity, after some time they meet us depressed, enervated, ill-humored, in need of rest, and again a few months later they display the old freshness and elasticity. Kraepelin E (1896) Manic-depressive insanity and paranoia. (Extract from translation of the 8th edn of Kraepelin’s textbook Psychiatrie). Box 7.7 Schneider 1958 ‘(Kurt) Schneider (1958, in Psychopathic Personalities) admonished the kin of labile individuals (who might approximate what we might diagnose today as cyclothymia with borderline personality features) “on their bad days . . . to keep out of their way as far as possible” (p. 121). Cyclothymes, with some insight into their own temperament, would give the same ad vice to their loved ones. Cautious trial of anticonvulsants will often prove effective in those distressed enough by their behavior as to comply with such treatment.’ Extract from Akiskal HS (2001) Review article: dysthymia and cyclothymia in psychiatric practice a century after Kraepelin. J Affect Disord 62: 17–31 with permission from Elsevier.

350 Chapter 7 Bipolar illness Lithium Despite problems with tolerability, lithium31 still remains the gold standard in the prophylactic treatment of bipolar affective disorder. The effectiveness of long-term treatment with lithium is supported by at least nine controlled, double-blind studies,32 far exceeding the available support for other alterna tives such as anticonvulsants or antipsychotics. Mode of action Uncertain—numerous effects on biological systems (particularly at high concentrations). Lithium can substitute for sodium ($Na^+$), potassium ($K^+$), $Ca^{2+}$, magnesium ($Mg^{2+}$) and may have effects on cell membrane electro physiology. Lithium interacts with systems involving other cations, including the release of neurotransmitters and second messenger systems

(e.g. adenylyl cyclase, inositol-1,4,5-triphosphate, arachidonate, protein kinase C, G proteins, and Ca2+), effectively blocking the actions of transmit ters and hormones. It may also reduce receptor upregulation and have a neuroprotective action through glycogen synthase-3 (GSK-3) gene expres sion and upregulation of the neuroprotective protein Bcl-2. Interactions • E plasma concentration (risk of toxicity, even at therapeutic serum levels): angiotensin-converting enzyme (ACE) inhibitors/angiotensin II receptor antagonists, analgesics (especially NSAIDs), antidepressants (especially SSRIs), antiepileptics, antihypertensives (e.g. methyldopa), antipsychotics (especially haloperidol), calcium channel blockers, diuretics, metronidazole. • d plasma concentration (risk of d efficacy): antacids, theophylline. • Other interactions: anti-arrhythmics (e.g. amiodarone: i risk of hypothyroidism), antidiabetics (may impair glucose tolerance), antipsychotics (i risk of EPSEs), muscle relaxants (enhanced effect), parasympathomimetics (antagonizes neostigmine and pyridostigmine). Guidelines on lithium therapy (See Box 7.8.)33 • Prior to commencing lithium therapy: physical examination, FBC, U&Es, TFTs, renal function, baseline weight and height [body mass index (BMI)], if clinically indicated—ECG, pregnancy test. • Starting dose: usually 400–600mg given at night; i weekly, depending on serum monitoring, to max 2g (usual dose 800mg–1.2g)—actual dose depends upon preparation used (molar availability varies: 200mg carbonate is equivalent to 509mg citrate; see Table 7.3). 31 The use of lithium salts in the treatment of ‘psychotic excitement’ is usually credited to John Cade in 1949 (Med J Aust 2:349–52). However, this was a ‘rediscovery’ of the use of lithium to treat ‘in sanity’ first described by WA Hammond WA in 1871 (in A Treatise on Diseases of the Nervous System. Appleton, New York, NY, pp. 325–84). 32 Burgess S, Geddes J, Hawton K, et al. (2001) Lithium for maintenance treatment of mood dis orders. Cochrane Database System Rev 3:CD003013. 33 National Institute for Health and Care Excellence (2014) Bipolar disorder: assessment and man agement. Clinical guideline [CG185]. M https://www.nice.org.uk/guidance/CG185 [accessed 20 June 2018].

Lithium • Monitoring: check lithium level 5 days after starting and 5 days after each change of dose. Take blood samples 12hr post-dose. • Once a therapeutic serum level has been established:34 continue to check lithium level/estimated glomerular filtration rate (eGFR) every 3mths, TFTs every 6mths, monitor weight (BMI), and check for side effects (E Lithium: adverse events, p. 352). • Stopping: reduce gradually over 1–3mths, particularly if the patient has a history of manic relapse (even if started on other antimanic agent). Box 7.8 Safer lithium therapy The UK National Patient Safety Agency (NPSA) issued a Patient Safety Alert (NPSA/2009/PSA005) on safer lithium therapy, following re ports of harm caused to patients, including fatalities, by lithium therapy. In collaboration with the Prescribing Observatory for Mental Health (POMH-UK) of the Royal College of Psychiatrists, the National Pharmacy Association (NPA), other organizations, clinicians, and patients, it was de signed to help NHS organizations to take steps to minimize the risks asso ciated with lithium therapy. The following recommendations were made: • Patients should be monitored in accordance with NICE guidelines. • There are reliable systems to ensure blood test results are communicated between laboratories and prescribers. • Throughout their treatment, patients receive appropriate ongoing verbal and written information and complete a record book.* • Prescribers and pharmacists check that blood tests are monitored regularly and that it is safe to prescribe and/or dispense lithium. • Systems are in place to identify and deal with medicines that might adversely interact with lithium therapy.

- NPSA patient information booklet, lithium alert card, and record book can be found at: M https://www.sps.nhs.uk/articles/npsa-alert-safer-lithium-therapy-2009/ [accessed 20

June 2018]. Table 7.3 Lithium preparations (UK) Preparation Active component Available strengths Camcolit® (tablets) Lithium carbonate 250/400mg (scored) Li-liquid® (oral solution) Lithium citrate 509mg/5mL Liskonum® (tablets) Lithium carbonate 450mg (scored) Priadel® (tablets) Lithium carbonate 200/400mg (scored) Priadel® (liquid) Lithium citrate 520mg/5mL 34 NICE suggests lithium levels of between 0.6 and 0.8mmol/L when prescribed for the first time. Those who have relapsed on lithium or who still have subthreshold symptoms with functional im pairment while on lithium may warrant a trial of at least 6mths with levels of between 0.8 and 1.0mmol/L.

352 Chapter 7 Bipolar illness Lithium: adverse effects As lithium is a highly toxic ion, safe and effective therapy requires moni toring of serum levels. Up to 75% of patients treated with lithium will ex perience some side effects.35 Dose-related side effects Polyuria/polydipsia [reduced ability to concentrate urine due to antidiuretic hormone (ADH) antagonism], weight gain (effects on carbohydrate metab olism and/or oedema), cognitive problems (e.g. dulling, impaired memory, poor concentration, confusion, mental slowness), tremor, sedation or leth argy, impaired coordination, GI distress (e.g. nausea, vomiting, dyspepsia, diarrhoea), hair loss, benign leucocytosis, acne, and oedema. Management Usually dealt with by lowering the dose of lithium, splitting the total daily dose, or changing the formulation. If side effects persist, additional medica tions may be necessary, e.g. β-blockers (tremor), thiazide or loop diuretics (polyuria, polydipsia, or oedema), and topical antibiotics or retinoic acid (acne). GI problems can be managed by administering lithium with meals or switching from carbonate to citrate. Cardiac conduction problems Usually benign ECG changes (e.g. T-wave changes, widening of QRS). Rarely, exacerbation of existing arrhythmias or new arrhythmias due to conduction deficits at the sinoatrial (SA) or atrioventricular (AV) nodes (contraindicated in heart failure and sick sinus syndrome). Long-term effects Renal function Ten to 20% of patients on long-term therapy demonstrate morphological kidney changes (interstitial fibrosis, tubular atrophy, and sometimes glom erular sclerosis). Over 1% may develop irreversible renal failure (rising serum creatinine levels) after 10yrs or more of treatment. If urea and creatinine levels become elevated, assess the rate of deterioration (E Prescribing for patients with renal impairment, p. 1036); the decision whether to continue lithium depends on clinical efficacy and the degree of renal impairment; seek advice from a renal specialist and a clinician with expertise in the man agement of bipolar disorder. Subclinical/clinical hypothyroidism Five to 35%, more frequent in women, tends to appear after 6–18mths of treatment, and may be associated with rapid-cycling bipolar disorder. Although hypothyroidism is generally reversible on discontinuation of lithium, it is not an absolute contraindication for continuing lithium treat ment, as the hypothyroidism is readily treated with levothyroxine.36 In add ition to the classic signs and symptoms of hypothyroidism, patients with bipolar disorder are also at risk of developing depression and/or rapid cyc ling as a consequence of suboptimal thyroid functioning. Should this occur 35 Goodwin FK, Jamison KR (1990) Manic-Depressive Illness. Oxford: Oxford University Press. 36 Bocchetta A, Bernardi F, Pedditzi M, et al. (1991) Thyroid abnormalities during lithium treatment. Acta Psychiatr Scand 83:193–8.

Lithium: adverse effects and suboptimal thyroid functioning confirmed, supplementation with or without lithium discontinuation is the treatment of choice. 0 Teratogenicity (E Prescribing in pregnancy, p. 1028.) The much-quoted 400-fold i risk of Ebstein’s anomaly (a congenital mal formation of the tricuspid valve) due to first trimester lithium exposure now appears to be substantially less than first reported—at most an 8-fold relative risk.37 Other reported second and

third trimester problems include polyhydramnios, premature delivery, thyroid abnormalities, nephrogenic diabetes insipidus, and floppy baby syndrome. The estimated risk of major congenital anomalies for lithium-exposed babies is 4–12%, compared with 2–4% in untreated control groups. Management A balance needs to be struck between the risks of teratogenicity and the risks of relapse following discontinuation: • Mild, stable forms of bipolar disorder: lithium may be tapered down and stopped pre-pregnancy. • Moderate risk of relapse: lithium should be tapered and discontinued either before pregnancy or during the first trimester (following discussion with the patient and with a clear multidisciplinary care plan). • Severe forms of bipolar disorder, at high risk of relapse: lithium should be maintained during pregnancy (with informed consent, appropriate counselling, prenatal diagnosis, detailed ultrasound and echocardiography at 16–18wks' gestation, and lithium monitoring). 0 Toxicity The usual upper therapeutic limit for 12-hr post-dose serum lithium level is 1.2mmol/L. With levels of >1.5mmol/L, most patients will experience some symptoms of toxicity; >2.0mmol/L definite, often life-threatening, toxic effects occur. There is often a narrow therapeutic window where the beneficial effects outweigh the toxic effects (especially in older patients). Early signs and symptoms Marked tremor, anorexia, nausea/vomiting, diarrhoea (sometimes bloody), dehydration, and lethargy. As lithium levels rise Severe neurological complications:  restlessness, muscle fasciculation, myoclonic jerks, choreoathetoid movements, marked hypertonicity. This may progress to ataxia, dysarthria, i lethargy, drowsi ness, and confusion/delirium. Hypotension and cardiac arrhythmias pre cede circulatory collapse, with emerging seizures, stupor, and coma (high risk of permanent neurological impairment or death). Management • Education of patients (methods of avoiding toxicity, e.g. maintaining hydration and salt intake, and being alert to early signs and symptoms). • Careful adjustment of dosage may be all that is required. • In severe toxicity [e.g. following overdose (OD)], rapid steps to reduce serum lithium level are urgently necessary (e.g. forced diuresis with IV isotonic saline) and, if accompanied by renal failure, haemodialysis. • Review the need for prophylaxis (E Prophylaxis, p. 344). 37 Cohen LS, Friedman JM, Jefferson JW, et al. (1994) A reevaluation of risk of in utero exposure to lithium. JAMA 271:146–50.

354 Chapter 7 Bipolar illness Valproate/valproic acid 2 From April 2018 in the UK: valproate medicines must not be used in women or girls of childbearing potential, unless a Pregnancy Prevention Programme is in place.38 Valproate [valproic acid (as the semisodium salt—Depakote®) and so dium valproate (Episenta®)] is licensed for the treatment of acute mania. Although not specifically licensed, other preparations are also used as prophylaxis for bipolar disorder (see Table 7.4). Note: the equivalent amount of valproic acid available from Depakote® 500mg, Epilim® 500mg, and Epilim Chrono® 500mg are 500mg, 433mg, and 433mg, respectively. Psychiatric indications • Acute mania (up to 56% effective) (E Treatment of acute manic episodes, p. 340). • Acute depressive episode (in bipolar affective disorder), in combination with an antidepressant. Data limited (E Treatment of depressive episodes, p. 342). • Prophylaxis of bipolar affective disorder—possibly more effective in rapid cycling (E Prophylaxis, p. 344). Mode of action Uncertain. Modulates voltage-sensitive Na+ channels, acts on second mes senger systems, and increases the bioavailability of GABA (or mimics action at post-synaptic receptor sites) in the CNS. Pharmacokinetics Sodium valproate is available in multiple forms. Semisodium valproate (Depakote®)comes as enteric-coated tablets containing valproic acid and sodium valproate. Both are rapidly absorbed orally (peak serum level: so dium valproate 72hr; semisodium valproate 3–8hr), with a plasma half-life of 6–16hr) (see Box 7.9 and Table 7.4). Interactions • Raised serum levels with phenobarbital, phenytoin, and antidepressants (TCAs, fluoxetine). d serum levels with

carbamazepine. • Toxicity may be precipitated by other highly protein-bound drugs (e.g. aspirin), which can displace valproate from its protein-binding sites. Side effects and toxicity • Dose-related side effects: GI upset (anorexia, nausea, dyspepsia, vomiting, diarrhoea), raised LFTs, tremor, and sedation—if persistent, may require dose reduction, change in preparation, or treatment of specific symptoms (e.g. β-blocker for tremor; H2-blocker for dyspepsia). • Unpredictable side effects: mild, asymptomatic leucopenia and thrombocytopenia (reversible upon drug reduction/discontinuation), hair loss (usually transient), i appetite, and weight gain. 38 Details and materials are available at: M https://www.gov.uk/drug-safety-update/valproate- medicines-epilim-depakote-pregnancy-prevention-programme-materials-online? [accessed June 2018].

Valproate/valproic acid • Rare, idiosyncratic side effects: irreversible hepatic failure, pancreatitis, agranulocytosis, polycystic ovaries/hyperandrogenism. • Toxicity/OD: wide therapeutic window; hence, unintentional OD is uncommon. Signs of OD include somnolence, heart block, eventually coma, and even death (haemodialysis may be needed). Table 7.4 Valproate/valproic acid preparations (UK) Preparation Active agent Available strengths Convulex® Valproic acid C 150/300/500mg Depakote® Valproic acid T 250/500mg Epilim® (IV) Sodium valproate T 100/200/500mg L 200mg/5mL IV 400mg powder with 4mL water ampoule Epilim Chrono® (MR) Sodium valproate 200/300/500mg Epilim Chronosphere® (MR granules) Sodium valproate 50/100/250/500 750/1000mg sachets Episenta® (MR) (IV) Sodium valproate C 150/300mg Granules 500mg/1g IV 100mg/mL 3mL ampoule Epival® (MR) Sodium valproate T 300/500mg Sodium valproate (generic) Sodium valproate T 100/200/500mg L 200mg/5mL Key: T = tablet; C = capsule; L = liquid. Box 7.9 Guidelines for sodium valproate use • Full medical history (particularly liver disease, haematological problems, and bleeding disorders)/full physical examination; pregnancy test; check FBC, LFTs, baseline ECG, weight/height (BMI). • Sodium valproate: start with a low, divided dose (e.g. 200mg bd or tds), increase every few days/week by 200–400mg/day, according to response and side effects, up to a maximum of 2500mg/day, or until serum levels are 50–125mmol/L. Usual maintenance dose 1–2g/day. • Valproic acid as semisodium valproate: start with 250mg tds (or up to 20mg/kg for acute manic episode), increase every few days/every week by 250–500mg/day to a maximum of 2000mg/day, or until serum levels are 50–125mmol/L. Usual maintenance dose 1–2g/day. • Once the patient is stable, simplify the regimen and consider use of a slow-release preparation to enhance compliance/reduce side effects. Points to note • Once established, check 6-monthly FBC, LFTs, valproate level, and BMI. • Use doses and serum levels considered therapeutic for epilepsy. • Closer clinical monitoring for side effects may be necessary for patients who cannot reliably report early signs.

356 Chapter 7 Bipolar illness Carbamazepine Psychiatric indications • Acute mania (less effective than lithium/equivalent efficacy to antipsychotics)—alone or in combination with lithium (E Treatment of acute manic episodes, p. 340). • Acute depressive episode (in bipolar affective disorder)—alone or in combination with lithium (E Treatment of depressive episodes, p. 342). • Prophylaxis of bipolar affective disorder—data limited (E Prophylaxis, p. 344). Mode of action Uncertain. Modulates Na+ and Ca2+ ion channels, receptor mediation of GABA and glutamine, and various intracellular signalling pathways. Pharmacokinetics Available in a variety of forms (solutions, suspensions, syrups, and chewable or slow-release formulations), all with similar bioavailability. Peak plasma concentrations 4–8hrs (usually), may be as late as 26hrs. Plasma half-life 18–55hrs. With long-term use, carbamazepine induces its own metabolism, decreasing the half-life to 5–26hrs (see Box 7.10 and Table 7.5). Interactions • Carbamazepine decreases the plasma

levels of many drugs metabolized by the liver, e.g. antipsychotics, BDZs (except clonazepam), TCAs, other anticonvulsants, hormonal contraceptives, and thyroid hormones. • Carbamazepine serum concentrations can be i by certain drugs, e.g. erythromycin, calcium channel blockers (diltiazem and verapamil, but not nifedipine or nimodipine), and SSRIs. Side effects and toxicity • Unpredictable side effects: antidiuretic effects leading to hyponatraemia (6–31%), more common in the elderly, sometimes many months after starting treatment; decrease in total and free thyroxine levels/increase in free cortisol levels (rarely clinically significant). • Idiosyncratic side effects: agranulocytosis, aplastic anaemia, hepatic failure, exfoliative dermatitis (e.g. Stevens–Johnson syndrome), and pancreatitis (usually occur within the first 3–6mths of treatment, rarely after longer periods). Note: routine blood monitoring does not reliably predict blood dyscrasias, hepatic failure, or exfoliative dermatitis— patient education about early symptoms and signs is essential. • Other rare side effects: systemic hypersensitivity reactions, cardiac conduction problems, psychiatric symptoms (including occasional cases of mania and psychosis), and, extremely rarely, renal problems (failure, oliguria, haematuria, and proteinuria). • Toxicity/OD: early signs—dizziness, ataxia, sedation, and diplopia. Acute intoxication may present as marked irritability, stupor, or even coma. May be fatal in OD (if >6g ingested). Symptoms of OD—nystagmus, ophthalmoplegia, cerebellar/extra-pyramidal signs, impairment of

Carbamazepine consciousness, convulsions, respiratory depression, cardiac problems (tachycardia, hypotension, arrhythmias/conduction disturbances), GI upset, and other anticholinergic symptoms. Significant OD requires emergency medical management (i.e. close monitoring, symptomatic treatment, gastric lavage, and possible haemodialysis). Box 7.10 Guidelines for carbamazepine use • Full medical history (particularly liver disease, haematological problems, and bleeding disorders); physical examination; check FBC, LFTs, U&Es, baseline ECG, and weight/height (BMI). • Start with a low, divided dose (e.g. 200–600mg/day in 2–4 divided doses), increase every few days or every week by 200mg/day, according to response and side effects, up to 800–1200mg/day, with slower increases thereafter as indicated, to a maximum of 2000mg/day or until serum levels are 4–15g/mL (trough level—taken immediately prior to morning dose, and 5 days after dose change) (see Table 7.5). • Maintenance doses are usually around 1000mg/day (range 200– 1600mg/day). Doses higher than 1600mg/day are not recommended. • Check FBC, LFTs, and serum carbamazepine level every 2wks during first 2mths of treatment, then reduce monitoring to every 3mths, then every 6mths once well established (and monitor BMI). • Once the patient is stable, simplify the regimen and consider use of a slow-release preparation, to enhance compliance/reduce side effects. Points to note • Closer clinical monitoring for side effects may be necessary for patients who cannot reliably report early signs. • If carbamazepine is combined with lithium, there may be an i risk of developing acute confusional state. • Closer monitoring is advisable and minimization of the use or dose of other medications (e.g. antipsychotics, anticholinergics, BDZs) that may contribute to confusion. Table 7.5 Carbamazepine preparations Preparation Formulation Available strengths Tegretol® Tablet (also Chewtabs®) 100/200/400mg Liquid 100mg/5mL Suppositories 125/250mg Tegretol® prolonged release MR tablet 200/400mg Carbagen® SR MR capsule 200/400mg Carbamazepine (generic) Tablet 100/200/400mg

358 Chapter 7 Bipolar illness Lamotrigine Psychiatric indications • Maintenance treatment of bipolar disorder to delay relapse (depression, mania, hypomania, mixed episodes) (E Prophylaxis, p. 344). • May be more effective than other mood stabilizers in preventing depressive episodes in bipolar disorder. Mode of action Unknown. Inhibits voltage-gated Na+ channels and glutamate

release. Also has weak inhibitory effect on 5-HT3 receptors. Pharmacokinetics Rapidly and completely absorbed after oral administration, with negligible first-pass metabolism (absolute bioavailability 98%). Bioavailability is not af fected by food/drug administration. Peak plasma concentrations occur any where from 1 to 5hrs, half-life 24hrs, time to steady state 5–8 days. Drug is 55% protein-bound (see Box 7.11 and Table 7.6). Interactions • Certain medications have been shown to increase clearance of lamotrigine: carbamazepine (40%), oxcarbazepine (30%), phenobarbital (40%), phenytoin (50%), ritonavir, mesuximide, rifampicin, primidone, and certain oestrogen-containing oral contraceptives. • Valproate decreases the clearance of lamotrigine (i.e. more than doubles the elimination half-life of lamotrigine), so reduced doses (no greater than 50% of the usual dose) of lamotrigine should be given. Side effects and toxicity • Most common side effects: dizziness, headache, blurred/double vision, lack of coordination, sleepiness, nausea, vomiting, insomnia, and rash. • Rare side effects: rare incidence of multi-organ failure, various degrees of hepatic failure, aseptic meningitis, movement disorders. • Risk of rash: 10–14% of patients receiving lamotrigine will develop a rash. Most are benign. A minority may be serious/life-threatening skin reactions requiring hospitalization, e.g. Stevens–Johnson syndrome, toxic epidermal necrolysis, angio-oedema, and a rash associated with a number of systemic manifestations (i.e. fever, lymphadenopathy, facial swelling, and haematological and hepatological abnormalities). Rash is most likely to occur within first 2–8wks of treatment and more likely when combined with valproate, exceeding the recommended initial dose or rapid dose escalation. Although most rashes resolve even with continuation of treatment, it is not possible to predict which rashes will prove to be serious or life-threatening. Lamotrigine should be discontinued at first sign of rash, unless the rash is clearly not drug-related, and even this may not prevent a rash from becoming life-threatening or permanently disabling/disfiguring. Lamotrigine should not be restarted in patients who discontinued due to rash associated with prior treatment (unless the potential benefits clearly outweigh the risks).

Lamotrigine • Other rare side effects: serious hypersensitivity reactions, blood dyscrasias (neutropenia, leucopenia, anaemia, thrombocytopenia, pancytopenia and, rarely, aplastic anaemia and pure red cell aplasia), withdrawal seizures. Box 7.11 Guidelines for lamotrigine use • Prior to starting: pregnancy test (in women of childbearing age). • As monotherapy: start 25mg/day for wks 1 and 2. Increase to 50mg/ day for wks 3 and 4. Increase by max 50–100mg/day every 1–2wks thereafter. Usual dose 100–200mg/day in 1–2 divided doses (max 500mg/day) (see Table 7.6). • With valproate: start 25mg every other day for wks 1 and 2. Increase to 25mg/day for wks 3 and 4. Increase by 25–50mg/day every 1– 2wks. Usual dose 100–200mg/day in 1–2 divided doses. • With carbamazepine and NOT taking valproate: start 50mg/day for wks 1 and 2. Then 50mg bd for wks 3 and 4. Increase by max 100mg/ day every 1–2wks. Usual dose 200–400mg/day in two divided doses (up to 700mg/day sometimes needed). • If a patient has discontinued lamotrigine for a period of >5 half-lives (i.e. 5 days), it is recommended that initial dosing recommendations and guidelines be followed. • Although there is no well-established correlation between serum concentrations and mood-stabilizing effects, antiepileptic therapeutic serum levels are 8–10mg/mL. Monitoring • The value of monitoring plasma concentrations has not been established; however, due to drug interactions, monitoring of concomitant drugs may be indicated, particularly during dosage adjustments. • Prior to treatment, the patient should be warned that a rash or other signs or symptoms of hypersensitivity (e.g. fever, lymphadenopathy, hives, painful sores in the mouth or around the eyes, or swelling of the lips or tongue) warrant urgent medical assessment to determine if lamotrigine should be discontinued (E Risk of rash, see opposite). Table 7.6 Lamotrigine preparations Preparation Formulation Available strengths Lamictal® Tablet 25/50/100/200mg

Dispersible tablet 2/5/25/100mg Lamotrigine (generic) Tablet 25/50/100/200mg Dispersible tablet 5/25/100mg