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242 Chapter 6 Depressive illness Introduction Depressive disorders are common, with a prevalence of 5–10% in primary care settings. They rank fourth as causes of disability worldwide, and it has been projected that they may rank second by the year 2020. The prevalence of depressive symptoms may be as high as 30% in the general population, with women being twice as likely to be affected as men. Although effective treatments are available, depression often goes undiag nosed and undertreated. Symptoms often are regarded by both patients and physicians as understandable, given current social circumstances and/or back ground. Although in many cases this may be true, people should not be denied interventions that may help relieve some of the disabling symptoms of the disorder, allowing them to cope better with any current social problems. It should be borne in mind that depressive disorder has significant poten tial morbidity and mortality. Suicide is the second leading cause of death in persons aged 20–35yrs, and depressive disorder is a major factor in around 50% of these deaths. Depressive disorder also contributes to higher mor bidity and mortality when associated with other physical disorders [e.g. myocardial infarction (MI)], and its successful diagnosis and treatment have been shown to improve both medical and surgical outcomes. It is also as sociated with high rates of comorbid alcohol and substance misuse, and has a considerable social impact on relationships, families, and productivity (through time off work). The majority of patients will present to primary care, often with problems other than low mood (E Diagnosis 3: other clin ical presentations and differential, p. 252). Physicians ought to remain alert to this possibility, as early interventions may be critical in the prevention of major morbidity and comorbidity. There remains an innate reluctance to consider pharmacological interven tions for emotional problems, despite overwhelming evidence of efficacy.

There is also widespread concern that drugs which improve mood must be addictive, despite evidence to the contrary. While medication is not the only possible treatment for mild to moderate depression, when antidepres sants are prescribed, the onus is on the physician to give a therapeutic dose for an adequate length of time. Treatment failure is often due to patient non-compliance, particularly when the patient feels that their problems have not been taken seriously and they have been ‘fobbed off’. In a group of patients who generally have feelings of low self-worth or guilt, it is critical that they understand the rationale behind any treatment and that their pro gress is regularly reviewed, at least in the early stages. Depression among the famous As depression is common, it is not surprising that many famous people have had a depressive illness (see Box 6.1). However, there still remains a stigma attached to psychiatric illness, and it is only recently that people have be come more willing to discuss their illnesses publicly. A study that examined the lives of almost 300 world-famous men found that over 40% had experi enced some type of depression during their lives.11 The highest rates (72%) were found in writers, but the incidence was also high in artists (42%), poli ticians (41%), intellectuals (36%), composers (35%), and scientists (33%). 1 Post F (1994) Creativity and psychopathology. A study of 291 world-famous men. Br J Psychiatry 165:22–34.

Introduction Box 6.1 Famous people and depressive illness Famous people who have publicly stated they have suffered from a depressive illness Roseanne Barr, actress, writer, comedienne Halle Berry, actress Barbara Bush, former First Lady (USA) Jim Carrey, actor, comedian John Cleese, comedian, actor, writer Sheryl Crow, musician Ellen DeGeneres, comedienne, actor Cara Delevingne, fashion model, actress Harrison Ford, actor Paul Gascoigne, professional footballer Germaine Greer, writer John Hamm, actor Anthony Hopkins, actor Janet Jackson, musician Billy Joel, musician, composer Elton John, musician, composer Jessica Lange, actress Courtney Love, musician, actor Paul Merton, comedian Alanis Morissette, musician, composer SP Morrissey, musician Sinead O’Connor, musician Ozzy Osbourne, musician Donny Osmond, musician Marie Osmond, musician Winona Ryder, actress Monica Seles, athlete (tennis) Paul Simon, composer, musician Bruce Springsteen, musician Famous people (deceased) known to have had a depressive illness Samuel Beckett, Menachem Begin, Marlon Brando, Kurt Cobain, Leonard Cohen, Michel Foucault, Judy Garland, Stephen Hawking, Ernest Hemingway, Audrey Hepburn, William James, Franz Kafka, Claude Monet, Richard M Nixon, Laurence Olivier, Wilfred Owen, George S Patton, Sylvia Plath, Jackson Pollock, Cole Porter, Lou Reed, Joan Rivers, Mark Rothko, Dmitri Shostakovich, Tennessee Williams, Yves Saint Laurent.

244 Chapter 6 Depressive illness Historical perspective The changing face of depression Current ideas of what constitutes depression date from the mid-eighteenth century.22 Earlier, the illness was understood in terms of ‘melancholia’, from classical humoural theories (melancholia derived from the Greek melaina kole—black bile), reflecting ‘intensity of idea’ (Haslam, 1809), i.e. the pres ence of few, rather than many, delusions. Sadness or low mood were not primary symptoms. The ‘melancholic’ symptoms we now regard as part of depressive disorder would have been called ‘vapours’, ‘hypochondria’, or ‘neuroses’. ‘Depression’, a term used to mean ‘reduced functioning’ in other medical disciplines, came to be associated with ‘mental depression’, adopted because it implied a physiological change, defined as ‘a condition characterized by a sinking of the spirits, lack of courage or initiative, and a tendency to gloomy thoughts’ (Jastrow, 1901). The concept was enlarged and legitimized by Kraepelin (1921), who used the term ‘depressive states’ in his description of the unitary concept of ‘manic–depressive illness’, encompassing melancholia simplex

and gravis, stupor, fantastical melancholia, delirious melancholia, and involutional mel ancholia. A number of assumptions surrounded the affective disorders; they involved the primary pathology of affect and had stable psychopath ology and brain pathology, were periodic in nature, had a genetic basis, occurred in persons with certain personality traits, and were ‘endogenous’ (unrelated to precipitants). In 1917, Freud published Mourning and Melancholia, influencing more than a generation of practitioners in emphasizing cognitive and psychic factors in the aetiology of depression and shifting clinical descriptions from objective behavioural signs to subjective symptoms. Over the intervening years, there has been much debate as to whether a ‘biological’ type of depression exists separate from a ‘neurotic’ type. Terminology has fluctuated around endogenous, vital, autonomous, endomorphic, and melancholic depression, characterized by distinctive symptoms and signs, a genetic basis, and running an independent course unrelated to psychosocial factors. In contrast, ‘neurotic’ or ‘reactive’ de pression could manifest in multiple forms, showed clear responsiveness to the environment, and ran a more variable course. ICD-10/11 and DSM-5 fudge the issue somewhat by using severity specifiers (i.e. mild, moderate, severe), as well as symptom specifiers (i.e. somatic symptoms, psychotic symptoms). The advent of antidepressant drugs in the 1950s introduced a further complication into the mix. Although ECT was widely accepted as a treat ment for ‘vital’ depression, the idea of a drug treatment for ‘reactive’ de pressive disorders ran counter to the received wisdom of the psychological basis to these conditions and the need for psychological treatment. 2 For an exhaustive critique of conceptual ideas, see: Jackson SW (1987) Melancholia and Depression: From Hippocratic Times to Modern Times. New Haven, CT: Yale University Press.

Historical perspective The antidepressants and beyond The antidepressant effects of isoniazid were first observed in 1952 by Lurie and Salzer in patients being treated for tuberculosis (TB). Similar effects were noted by Shepherd and Davies, who conducted the first randomized controlled trial (RCT) in psychiatry, clearly demonstrating the efficacy of reserpine in anxious depression in 1955. The psychiatric community was initially reluctant to accept the idea of chemical ‘cures’ for mental disorders. It was not until iproniazid was promoted by Kline in 1957 as a ‘psychic ener gizer’, capable of treating ‘nervous’ conditions, that the tide began to turn. In 1956, Kuhn demonstrated the antidepressant effects of imipramine, a tricyclic antidepressant (TCA) marketed worldwide in 1958, closely fol lowed by amitriptyline in 1960. At the same time, new anxiolytics were also emerging, with meprobamate in 1955, and the first benzodiazepine (BDZ)— chlordiazepoxide—in 1960. The search for greater dissociation of anxiolytic and sedative properties led to the introduction of diazepam in 1963. The downside of this new psychopharmacology was the over-prescription in the 1960s and 1970s of these drugs to help with ‘the problems of living’ and evidence of dependence, particularly in the case of BDZs. As a re sult, non-pharmacological treatments flourished in the form of ‘re-branded’ psychotherapies. Behind the scenes, biological psychiatrists and psychopharmacologists de veloped the monoamine theories of depression, based upon the discovery of the neuropharmacological action of the antidepressants. This led to the development of more selective antidepressants—in the first instance, the selective serotonin reuptake inhibitors (SSRIs), with zimelidine patented in 1971 and indalpine marketed in 1978. The emphasis on safety and side effect issues when comparing SSRIs with TCAs, and the decline of BDZs, opened the floodgates in the 1980s and 1990s for the promotion of SSRIs [e.g. fluoxetine (1989)] not only in the treatment of depression, but also for anxiety disorders. Advances in mono amine theories also allowed the development of ‘dual-action’ agents [e.g. serotonin noradrenaline reuptake inhibitors (SNRIs)—venlafaxine (1995); noradrenaline and specific serotonin antagonists

(NaSSAs)—nefazodone (1995)/mirtazapine (1997); dopamine–noradrenaline reuptake inhibitors (DNRIs)—bupropion (2000)] and other selective agents [e.g. noradrenaline reuptake inhibitors (NARIs)—reboxetine (1997)]. Current theories of depression attempt to integrate biological models of stress [involving the hypothalamic–pituitary–adrenal (HPA) axis] with evi dence from biological psychology, genetics, neuropharmacology, and func tional neuropathology. A multifactorial biopsychosocial model (see Fig. 6.1) emerged, which helped to unite the divergent ideas of depression. Clinical symptoms and signs are seen as the final common pathway in a complex interaction between genes and the environment in determining predisposition or biological vulnerability, which may subsequently lead to bio logical variations in functioning necessary for behavioural and emotional change. This may be due to further psychosocial stressors or genetically predetermined factors, which give rise to alterations in brain functioning. Research into these interdependent factors may well lead to a greater understanding of the aetiology of depressive disorder, as well as allow the development of diagnostic tests and individualized treatments.

246 Chapter 6 Depressive illness Diagnosis 1: symptoms Although the terminology is slightly different between ICD-10, DSM-5 (see Table 6.1), and ICD-11, the core symptoms are almost identical and, for a positive diagnosis, should fulfil the following criteria: • Present for at least 2wks and represent a change from normal. • Are not secondary to the effects of drug/alcohol misuse, medication, a medical disorder, or bereavement (E Normal and abnormal grief, p. 400). • May cause significant distress and/or impairment of social, occupational, or general functioning. Core symptoms • Depressed mood: present most of the day, nearly every day, with little variation, and often lack of responsiveness to changes in circumstances. There may be diurnal variation in mood, with mood being worse in the morning and improving as the day goes on. • Anhedonia: markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others). • Weight change: loss of weight when not dieting or weight gain (e.g. a change of >5% of body weight in a month), associated with d or i appetite. • Disturbed sleep: insomnia [with early morning wakening (EMW) 2–3hrs sooner than usual] or hypersomnia (especially in atypical depression; E Atypical depressive episode, p. 272). • Psychomotor agitation or retardation: observable by others, not just subjective feelings of restlessness or being slowed down. • Fatigue or loss of energy. • Reduced libido. • Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional): not just self-reproach or guilt about being ill. • Diminished ability to think or concentrate or indecisiveness. • Recurrent thoughts of death or suicide—(not ‘fear of dying’), which may or may not have been acted upon. Somatic symptoms Also called biological, melancholic (DSM-5), or vital. Include: • Loss of emotional reactivity. • Diurnal mood variation. • Anhedonia. • EMW. • Psychomotor agitation or retardation. • Loss of appetite and weight. • Loss of libido.

Diagnosis 1: symptoms Table 6.1 ICD-10 and DSM-5 terminology ICD-10 DSM-5 Depressive episode Major depressive disorder – single episode Mild without somatic symptoms Mild Mild with somatic symptoms Moderate without somatic symptoms Moderate Moderate with somatic symptoms Severe without psychotic symptoms Severe Severe with psychotic symptoms With psychotic features Other Other specified depressive disorder Recurrent depressive disorder – current episode Major depressive disorder – recurrent episode mild without somatic symptoms Mild mild with somatic symptoms moderate without somatic symptoms Moderate moderate with somatic symptoms severe without psychotic symptoms Severe severe with psychotic symptoms With psychotic features Currently in remission In full remission Persistent mood (affective) disorders

Cyclothymia Cyclothymic disorder (E Cyclothymia, p. 348) Dysthymia Persistent depressive disorder (dysthymia) (E Dysthymia (ICD- 10)/persistent depressive disorder (DSM-5), p. 274) Other persistent mood (affective) disorder Disruptive mood dysregulation disorder (E Diagnosis, p. 700) Premenstrual dysphoric disorder (E Premenstrual dysphoric disorder, p. 488) Other specified depressive disorder Persistent mood (affective) disorder, unspecified Unspecified depressive disorder Note: DSM-5 includes additional specifiers—with anxious distress, mixed features, melancholic features, atypical features, mood-congruent or mood-incongruent psychotic features, catatonia, peripartum onset, and seasonal pattern. ICD-11 codes 'Single episode', 'Recurrent', 'Dysthymic disorder', 'Mixed depressive and anxiety', 'Other', and 'Unspecified'. Depressive disorders can be mild, moderate (± psychotic symptoms), or severe (± psychotic symptoms), with unspecified severity, in partial remission, or in full remission.

248 Chapter 6 Depressive illness Psychotic symptoms/features • Delusions: e.g. poverty; personal inadequacy; guilt over presumed misdeeds; responsibility for world events—accidents, natural disasters, war; deserving of punishment; other nihilistic delusions. • Hallucinations: e.g. auditory—defamatory or accusatory voices, cries for help, or screaming; olfactory—bad smells such as rotting food, faeces, and decomposing flesh; visual—tormentors, demons, the Devil, dead bodies, scenes of death, or torture. Note: these examples are mood-congruent. Other mood-incongruent psych otic symptoms are also possible (i.e. persecutory delusions, thought in sertion/withdrawal, and delusions of control—not clearly depressive in nature). Other features • Significant anxious distress. • Catatonic symptoms. • Marked psychomotor retardation (depressive stupor).

Diagnosis 1: symptoms 249

250 Chapter 6 Depressive illness Diagnosis 2: caseness and subtypes Clinically significant depressive episode (minimum criteria) • ICD-10 specifies the presence of at least two typical symptoms (depressed mood, anhedonia, or fatigue) plus at least two others from the core symptoms list. • DSM-5 requires the presence of five or more symptoms from the core symptoms list (at least one of which must be depressed mood or anhedonia). Severity criteria • ICD-10 and DSM-5 distinguish mild, moderate, and severe episodes on the basis of symptomatology (see Table 6.2). Subtypes • Without somatic symptoms (ICD-10): essentially defined as absence of psychotic or marked somatic symptoms, this subtype captures the clinical picture historically described by 'neurotic depression' (in those with certain premorbid personality traits and/or high levels of anxiety) and 'reactive depression' (due to a severely stressful life event; E Acute stress disorder (DSM-5), p. 394). Counterintuitively, there is little need to subdivide on the basis of there being a clear precipitant. Life events appear to be provoking factors, but only in those with a predisposition to depression, and treatment should focus on the underlying disorder, as well as coming to terms with any significant provoking factors. Clinically, two different presentations are commonly seen: • Irritable/hostile depression—younger, anxiety expressed as irritability, history of 'acting out' behaviours in response to stress [e.g. yelling, smashing things up, recklessness, impulsiveness, deliberate self-harm (DSH)]. Poor response to antidepressants. Table 6.2 Severity criteria ICD-10 DSM-5 Mild 2 typical symptoms + 2 other core symptoms 5 core symptoms + manageable distress + minor social/occupational impairment Moderate 2 typical symptoms + 3+ other core symptoms 5+ core symptoms + variable degree of social/occupational impairment Severe 3 typical symptoms + 4+ other core symptoms 5+ core symptoms + significant social/

occupational impairment Note: in ICD-11, severity is more qualitative, i.e. ‘Mild’ is when none of the symptoms of a depressive episode are intense, there is some, but not considerable, difficulty in continuing normal activities, and no delusions or hallucinations. ‘Moderate’ is when several symptoms of a depressive episode are present to a marked degree or a large number of depressive symptoms of lesser severity are present overall and there is considerable difficulty in continuing with normal activities, but the individual is still able to function in at least some areas. ‘Severe’ is when many or most symptoms of a depressive episode are present to a marked degree or a smaller number of symptoms are present and manifest to an intense degree and the individual is unable to function, except to a very limited degree.

Diagnosis 2: caseness and subtypes • ‘Anxious’ depression—shy and withdrawn, highly anxious (‘always a worrier’), usually early-onset depression, with a recurrent and persistent course, i likelihood of drug/alcohol dependency, and frequent DSH/attempted suicide. Better response to antidepressants (e.g. SSRIs). • With somatic symptoms (ICD-10)/melancholic features (DSM-5): the presence of ‘somatic symptoms’ (E Diagnosis 1: symptoms, p. 246) defines what is regarded as a more ‘biological’ or ‘endogenous’ depressive episode, which is more severe (and more amenable to antidepressant treatment). DSM-5 also includes ‘excessive or inappropriate guilt’, although this may often be difficult to distinguish from delusional guilt. In clinical studies, the best distinguishing factor from ‘non-melancholic’ disorders is actually the presence of psychomotor disturbance (an objective sign manifest by motor retardation, periodic agitation, and reduced/slowed cognitive functioning). • With psychotic symptoms (ICD-10) or features (DSM-5): usually there is pervasive depressed mood (no reactivity) and marked psychomotor disturbance (sometimes to the point of depressive stupor/catatonia) accompanying delusions (commonly) and hallucinations (10–20%). Constipation is often a feature (730%), unrelated to medication, and may have a delusional interpretation (e.g. presence of cancer, bowels having been sewn up).

252 Chapter 6 Depressive illness Diagnosis 3: other clinical presentations and differential There may be marked individual variation in the clinical presentation. Sometimes anxiety may also be prominent (mixed anxiety and depressive disorder—ICD-10; with anxious distress—DSM-5). Patients with a depressive disorder may not present complaining of low mood but may consult with other primary problems. The possibility of a depressive disorder should be borne in mind, particularly in the primary care setting where many of these patients first seek treatment. Indirect presentations may include • Insomnia, fatigue, or other somatic complaints (e.g. headache, GI upset, change in weight). On further questioning, patients may describe irritability or anhedonia but attribute this as secondary to what they regard as the primary problem (E Sleep-related breathing disorders 1, p. 444; E Assessment prior to organ transplantation, p. 878; E Dissociative (conversion) disorders, p. 868). • Elderly persons presenting with agitation, confusion, or a decline in normal functioning (pseudodementia) (E Other mental health problems in the elderly, p. 554). • Children presenting with symptoms such as irritability, decline in school performance, or social withdrawal (E Bipolar disorder in children and adolescents, p. 700). • Persons from a different cultural background presenting with culture- specific symptoms (E Culture-bound syndromes?, p. 988). Other symptoms that may hinder diagnosis • Presence of a physical disorder whose secondary symptoms (e.g. anorexia, fatigue, insomnia) may mask symptoms of depression. • Histrionic behaviour (making assessment of severity difficult). • Exacerbation of other underlying disorders (phobias, OCD—especially when there are depressive ruminations). • Hypochondriacal ideas (which may have been long-standing). • The presence of self-harming behaviours (e.g.

cutting, frequent overdose), which may represent underlying borderline traits (usually individuals will say they have never felt happy or describe chronic feelings of ‘emptiness’). • Cognitive impairment or ID (which may mask depressive symptoms or appear more severe because of depression, and hence improve with antidepressants). • Alcohol and drug misuse (primary or secondary). Other subtypes of depressive disorder These are formally recognized in DSM-5 but are subsumed under the rubric ‘Other depressive episodes’ in ICD-10. They include: • Atypical depression/DSM-5 ‘with atypical features’ (E Atypical depressive episode, p. 272). • Postnatal depression/DSM-5 ‘with peripartum inset’ (E Postnatal depression, p. 494).

253 DIAGNOSIS 3: OTHER CLINICAL PRESENTATIONS & DIFFERENTIAL • Seasonal affective disorder/DSM-5 ‘with seasonal pattern’ (E Seasonal affective disorder, p. 273). • Premenstrual dysphoric disorder/same in DSM-5 (E Premenstrual disorders, p. 490). As a description of the experience of symptoms of depression, the fol lowing has never been bettered: ‘I have of late but wherefore I know not lost all my mirth, forgone all custom of exercises; and indeed it goes so heavily with my disposition that this goodly frame, the earth, seems to me a sterile promontory, this most excellent canopy, the air, look you, this brave o’erhanging firmament, this majestical roof fretted with golden fire, why, it appears no other thing to me than a foul and pestilent congregation of vapours. What a piece of work is a man! how noble in reason! how infinite in faculty! in form and moving how express and admirable! in action how like an angel! in apprehension how like a god! the beauty of the world! the paragon of animals! And yet, to me, what is this quintessence of dust? man delights not me: no, nor woman neither.’ Shakespeare: Hamlet, Act II Scene 2.
Differential diagnosis • Other psychiatric disorders: dysthymia, stress-related disorders (adjustment disorders/bereavement, PTSD), bipolar disorder, anxiety disorders (OCD, panic disorder, phobias), eating disorders, schizoaffective disorders, schizophrenia (negative symptoms), personality disorders [especially borderline personality disorder (BPD)]. • Neurological disorders: dementia, Parkinson’s disease, Huntington’s disease, MS, stroke, epilepsy, tumours, head injury. • Endocrine disorders: Addison’s disease, Cushing’s disease, hyper-/ hypothyroidism, perimenstrual syndromes, menopausal symptoms, prolactinoma, hyperparathyroidism, hypopituitarism. • Metabolic disorders: hypoglycaemia, hypercalcaemia, porphyria. • Haematological disorders: anaemia. • Inflammatory conditions: systemic lupus erythematosus (SLE). • Infections: syphilis, Lyme disease, and HIV encephalopathy. • Sleep disorders: especially sleep apnoea. • Medication-related: antihypertensives (β-blockers, reserpine, methyldopa, and calcium channel blockers); steroids; H2 blockers (e.g. ranitidine, cimetidine); sedatives; muscle relaxants; chemotherapy agents (e.g. vincristine, procarbazine, L-asparaginase, interferon, amphotericin, vinblastine); medications that affect sex hormones [oestrogen, progesterone, testosterone, gonadotrophin-releasing hormone (GnRH) antagonists]; cholesterol-lowering agents; and psychiatric medication (especially antipsychotics). • Substance misuse: alcohol, BDZs, opiates, marijuana, cocaine, amphetamines, and derivatives.

254 Chapter 6 Depressive illness Epidemiology Prevalence 6-mth prevalence range: 2.2% (ECA), 5.3% (NCS), 6.7% (NCS- R; note 2% prevalence of severe episodes) in the general population. Lifetime rates Wide range: 4.4% (ECA), 16.5% (NCS-R), 30% (Virginia Twin Study); most authorities agree the true rate in the general population is probably 10–20%. There is also evidence that rates are increasing among younger adults. Sex ratio ♂:♀ = 1:2. Risk factors (See also E Aetiology 1, p. 256–257.) • Genetic (see Box 6.2): heritability estimates range from 17% to 75% (mean 37%), and families also have high rates of anxiety disorders and neuroticism, suggesting a shared

genetic basis. • Childhood experiences: loss of a parent (inconsistent across studies), lack of parental care, parental alcoholism/antisocial traits, childhood sexual abuse (CSA). Note: cumulative childhood disadvantage confers a greater risk than any single variable. High intelligence and one good adult relationship are protective and increase resilience. • Personality traits: anxiety, impulsivity, obsessionality (i.e. high neuroticism scores). • Social circumstances: • Marital status—men: low rates associated with marriage, high rates with separation or divorce; women: probably similar, but less clear-cut. • Brown and Harris3 found that, for women, having three or more children under the age of 11, lack of paid employment, and lack of a confiding relationship were associated with i risk of depression (recent studies support the lack of a confiding relationship, but not the other factors). • Adverse life events—particularly 'loss' events (i risk 2–3mths after event) in vulnerable individuals. • Physical illness: especially if chronic, severe, or painful. Neurological disorders (e.g. Parkinson's disease, MS, stroke, epilepsy) have higher risk (perhaps due to 'shared' pathology). Higher rates also noted in post-MI, diabetic, and cancer patients, although family or personal histories of depression are important determinants of occurrence. Comorbidity About two-thirds of patients will also meet criteria for an other psychiatric disorder (e.g. anxiety disorders, substance misuse, alcohol dependency, personality disorders). 3 Brown GW, Harris TO (1978) Social Origins of Depression: A Study of Psychiatric Disorders in Women. London: Tavistock Publications.

Epidemiology Box 6.2 Genetic factors While the existence of genetic vulnerability to depression is well es tablished in family and twin studies, progress in the identification of its molecular basis has been slow.1 Functional candidate gene studies have identified few replicable associations, and genome-wide linkage studies have yielded suggestive, rather than conclusive, results. Genome-wide as sociation studies (GWAS) have detected suggestive evidence for a role of genetic variants in the piccolo (PCLO) gene (which encodes a presynaptic cytomatrix protein that influences monoamine neurotransmitter release and regulation of the HPA axis) and neuroligin-1 (NLGN1) gene (which has a role in the formation and remodelling of CNS synapses). However, the general findings of these studies indicate that the genetic liability to depression is likely to involve multiple genetic variants of weak effects.2 Similarly, GWAS of antidepressant treatment outcome, which hope ultimately to help match medications with patients, have been disappointing. Polymorphisms in genes involved in antidepressant me tabolism (cytochrome P450 isoenzymes), antidepressant transport (ABCB1), glucocorticoid signalling (FKBP5), and serotonin neurotransmis sion (SLC6A4 and HTR2A) have shown initial promise. However, four in dependent samples—the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) sample (n = 1953), the Munich Antidepressant Response Signature (MARS) sample (n = 339), the Genome-based Therapeutic Drugs for Depression (GENDEP) sample (n = 706), and the GENetic and clinical Predictors Of treatment response in Depression (GENPOD) sample (n = 601)—have failed to report any results that achieved genome-wide significance or that could be replicated, suggesting that much larger samples and better outcome measures will be needed if we are to understand the complex interplay of biological factors involved in depression.3 1 Fabbri C, Hosak L, Mössner L, et al. (2017) Consensus paper of the WFSBP Task Force on Genetics: genetics, epigenetics and gene expression markers of major depressive disorder and antidepressant response. World J Biol Psychiatry 18:5–28. 2 Lewis CM, Ng MY, Butler AW, et al. (2010) Genome-wide association study of major recurrent depression in the UK population. Am J Psychiatry 167:949–57. 3 Laje G, McMahon FJ (2011) Genome-wide association studies of antidepressant outcome: a brief review. Progr Neuro-Psychopharmacol Biolog Psychiatry 35:1553–7.

256 Chapter 6 Depressive illness Aetiology 1 The aetiology of depression has yet to be fully understood; however, it is likely to be due to the interplay of biological, psychological, and social fac tors in the lifespan of an individual. Psychosocial stressors may play a role both as precipitants and perpetuating factors, increasing the risk of chronicity and recurrence, while individuals with established depression are at higher risk of further stressors of many kinds. One attempt to integrate these fac tors is the biopsychosocial model (see Fig. 6.1). Early adverse experience Developmental or social effects have previously been viewed as not being biological in nature. The modern view is that the fetal environment and later environmental stressors do have neurobiological consequences mediated through the HPA axis (possibly by epigenetic effects on genes that regu late glucocorticoid sensitivity, e.g. FKBP5, NF-κB). These changes in stress regulation may contribute to the expression of psychiatric disorder. More research is needed in this area, as data from human studies are limited. Personality/temperament factors These are enduring traits with a biological basis, influenced over the lifespan by inherited factors, experience, and maturation. They mediate the level and nature of response to sensory experience, regulated by context and manifest as subjective emotions and objective behaviours. Certain tempera ments (e.g. neuroticism or high ‘N’) may increase vulnerability to depres sion, perhaps due to the presence of autonomic hyperarousal (heightened responses to emotional stimuli), lability (unpredictable responses to emo tional stimuli), or negative biases in attention, processing, and memory for emotional material. Genetic predisposition Biological vulnerability Early adverse life experiences Personality/temperament Biological alterations in brain functioning Traumatic or adverse life events Social circumstances Alcohol/substance misuse Physical illness Symptoms of depressive illness Fig. 6.1 The biopsychosocial model of depression.

Aetiology 1 Psychological factors Disruption of normal social, marital, parental, or familial relationships is cor related with high rates of depression and is a risk factor for recurrence. An aetiological role has yet to be demonstrated, but adverse childhood experiences/chronic stressors may influence the sensitivity of individuals to later stressful events. Low self-esteem (negative view of self, the past, current events, and the future) is proposed as a vulnerability factor (either as a causal factor or as a symptom of depression). Gender Although the i prevalence of depression in women is a robust finding, explanations of why this may be so are various. These include: restricting social and occupational roles, being over- or under-occupied, ruminative response styles, and endocrine factors (suggested by i risk of depression in the premenstrual and post-partum periods). There is little supportive evidence for these theories. One popular hypothesis is that women are more likely to admit to depressive symptoms, whereas men are not and tend to express their symptoms differently (e.g. through alcohol abuse and antisocial behaviour).
Social factors There are two main arguments to explain why people of low socio- economic status (low levels of income, employment, and education) are at a higher risk of depression: social causation—stress associated with such problems leads to depression (an environmental argument); and social selection—predisposed individuals drift down to lower social positions or fail to rise from them (a genetic argument). There is stronger evidence for the social causation argument, as social isolation has been shown to be a key risk factor. Biology (See Box 6.3.) Box 6.3 Evolution, inflammation, and depression Complex interactions between inflammatory pathways (activated by psychosocial stressors) and brain function may explain how behaviours, such as avoidance and alarm that evolved to help deal with pathogens and predators, lead to the development of depression in modern hu mans, with altered motivation and motor activity (anhedonia, fatigue, and psychomotor impairment) and i threat sensitivity (anxiety, arousal, and alarm).1 Biomarkers of

inflammation in patients with depression include blood levels of IL-1β, IL-6, TNF, and CRP. Blockade of cytokines (e.g. TNF) or inflammatory signalling pathway components, such as cyclo- oxygenase 2, have been shown to reduce depressive symptoms in pa tients with medical illnesses, including rheumatoid arthritis, psoriasis, and cancer, as well as in patients with depression. Better understanding of these neuropsychoimmunological mechanisms is likely to lead to novel future therapeutic approaches to depression. 1 Miller AH, Raison CL (2016) The role of inflammation in depression: from evolutionary im perative to modern treatment target. Nat Rev Immunol 16:22–34.

258 Chapter 6 Depressive illness Aetiology 2 Brain pathology Structural brain changes Severe depression is associated with ventricular en largement and sulcal prominence. i rate of white matter lesions in older patients (perhaps related to vascular disease). Refractory cases associated with reduced grey matter in the left hippocampus (correlating with verbal memory), basal ganglia, and thalamus. Other studies find reduced cortical volumes in the left parietal and frontal association areas. Post-mortem findings Reduced GABA function, abnormal synaptic density or neuronal plasticity in the hippocampus; glial cell abnormalities; reduced expression of serotonin transporter (SERT) mRNA in the dorsal raphe nucleus. Functional imaging (see Box 6.4) Studies report hypoperfusion in frontal, temporal, and parietal areas (especially in older patients) and i perfusion in the frontal and cingulate cortex (in younger patients, associated with good treatment response). Activation, lesioning, and brain stimulation Box 6.4 Endophenotypes, imaging, and genetic correlates in the aetiology of depression Imaging studies identify traits, or 'endophenotypes', that are heritable, intermediate phenotypes associated with depression. These presumably have a simpler genetic basis than the full syndrome (or even individual symptoms), making them more amenable to genetic analysis and enabling the generation of testable hypotheses.1 Examples include: • Mood-congruent phenomenon of i activity of the amygdala in response to negative stimuli, which is likely moderated by the 5-HT transporter gene (SLC6A4) promoter polymorphism (5-HTTLPR). • Hippocampal volume loss, especially in elderly or chronically ill samples related to val66met brain-derived neurotrophic factor (BDNF) gene variant and 5-HTTLPR SLC6A4 polymorphism. • White matter pathology in elderly and more severely ill samples (allowing for complications of cerebrovascular disease). • i blood flow or metabolism of the subgenual anterior cingulate cortex (sgACC) and associated grey matter loss. • Attenuation of the usual pattern of fronto-limbic connectivity, particularly d temporal correlation in amygdala–anterior cingulate cortex (ACC) activity. • d 5-HT1A binding in the raphe, medial temporal lobe, and medial prefrontal cortex (mPFC) and a functional polymorphism in the promoter region of the 5-HT1A gene. • Alterations in the binding potential of the 5-HT transporter. Hopefully, it will not be long before we begin to see further advances in these areas, as epigenetic, copy number variant, gene–gene interaction, and GWAS (see Box 6.2) approaches are brought to bear on imaging data. 1 See review: Savitz JB, Drevets WC (2009) Imaging phenotypes of major depressive dis order: genetic correlates. Neuroscience 164:300–30.

Aetiology 2 studies in humans4 all point to two functionally segregated areas of the prefrontal cortex as being critical neural substrates for depression: the ventromedial prefrontal cortex (vmPFC)—associated with negative affect, physiological symptoms, self-awareness/insight; and the dorsolateral pre frontal cortex (dlPFC)—associated with cognitive/executive functioning, (re)-appraisal of affect states, suppression of emotional responses. Neurotransmitter abnormalities The discovery that all antidepressants increase monoamine (i.e. 5-HT, NA, DA) release and/or reduce their reuptake in the synaptic cleft led to devel opment of the monoamine theory of depression,

which suggests that reduced monoamine function may cause depression. Blunted neuroendocrine re sponses and symptom induction by tryptophan depletion (5-HT precursor) suggest an important role for 5-HT. Neuroendocrine challenge tests Blunted prolactin and growth hormone (GH) responses to tryptophan/ citalopram (5-HT system), blunted GH responses to clonidine (NA system) and apomorphine (DA system), and i GH response to physostigmine (ACh system) suggest reduced monoamine functioning and i cholinergic functioning in depression. i cortisol seen in 750% of patients (particularly 'endogenous' subtype), associated with adrenal hypertrophy, and dexa methasone non-suppression of cortisol (also in other psychiatric condi tions, hence not a sensitive test, despite an apparent specificity of 796%). Thyroid abnormalities Abnormalities in the thyroid-stimulating hormone (TSH) response to thyrotropin-releasing hormone (TRH) have been found—both blunting and enhancement—despite normal thyroid hormone levels, suggesting fur ther research is necessary, especially when T3 is shown to have utility in treatment-resistant cases (E An approach to treatment-resistant depres sion, p. 270). Changes in sleep pattern EMW is most typical in endogenous or melancholic depression; initial in somnia, frequent waking, and unsatisfactory sleep are also commonly seen in depression. Causal relationship of sleep to depression is currently unknown. In severe depression, there is reduced total SWS and short ened REM latency [secondary to i cholinergic (REM-on) and/or reduced serotonergic/noradrenergic (REM-off) drive]. Sleep changes resolve with recovery from depression, and sleep disturbance may be an early predictor of impending relapse. 4 Steele JD, Lawrie SM (2004) Segregation of cognitive and emotional function in the prefrontal cortex: a stereotactic meta-analysis. Neuroimage 21:868–75.

260 Chapter 6 Depressive illness Diagnosis and investigations Diagnosis • The diagnosis of depression is primarily based on a good psychiatric history and physical examination (E Why do psychiatrists not look at the brain?, p. 14). • In addition to focused questioning on mood (E Speech, p. 62; E Abnormal mood, p. 63; E Asking about depressed mood, p. 64; E Diagnosis 1: symptoms, p. 246), it is useful to administer a standardized rating scale, such as the Hamilton Rating Scale for Depression (HAM-D), the Beck Depression Inventory (BDI), or the Zung Self-Rating Depression Scale,5 as a baseline measure prior to any change to management plans. • Given the significant comorbidity with anxiety, some clinicians will also rate anxiety symptoms separately, e.g. the Hamilton Anxiety Rating Scale (HAM-A), the Beck Anxiety Inventory (BAI), or the Zung Self- Rating Anxiety Scale.6 • Patients with depression often complain of poor memory or concentration. In these cases, it is also worth administering the MMSE (E Assessing cognitive function 2, p. 86). If cognitive impairment is significant, further more detailed neuropsychological testing may be indicated (e.g. ACE-R). Investigations There are no specific tests for depression. Investigations focus on the ex clusion of treatable causes (E Differential diagnosis, p. 253) or other sec ondary problems (e.g. loss of appetite, alcohol misuse). • Standard tests: FBC, ESR, B12/folate, U&Es, LFTs, TFTs, glucose, Ca^{2+}. • Focused investigations: only if indicated by history and/or physical signs: • Urine or blood toxicology. • Breath or blood alcohol. • Arterial blood gas (ABG). • Thyroid antibodies. • Antinuclear antibody. • Syphilis serology. • Additional electrolytes, e.g. phosphate, magnesium, zinc. • Dexamethasone suppression test (Cushing's disease). • Cosyntropin stimulation test (Addison's disease). • Lumbar puncture (VDRL, Lyme antibody, cell count, chemistry, protein electrophoresis). • CT/MRI, EEG. 5 The Zung Self-Rating Depression Scale is copyright © free, and one version can be found at: M http://www.mentalhealthministries.net/resources/flyers/zung_scale/zung_scale.pdf [ac cessed 13 June 2018]. 6 The Zung Self-Rating Anxiety Scale is also copyright © free and can be found at: M https://www. mnsu.edu/comdis/isad16/papers/therapy16/sugarmanzunganxiety.pdf [accessed 13

June 2018].

Course and prognosis Course and prognosis Points to note • Depression may occur at any age, although late-onset depression may be milder, more chronic, more likely to be associated with life events, and more likely to have a subclinical prodrome. • Depressive episodes vary from 4 to 30wks for mild to moderate cases, to an average of about 6mths for severe cases (25% will last up to 1yr). • Episodes of recurrent depression tend to be shorter (4–16wks). • 10–20% of patients will have a chronic course, with persistent symptoms lasting over 2yrs. • The majority of patients experiencing a depressive episode will have further episodes later in life (risk of recurrence is 730% at 10yrs, 760% at 20yrs), but inter-individual variation makes it impossible to predict the likely period of time before future episodes, although, as with bipolar disorder, the greater the number of recurrences, the shorter the time between episodes. • Risk of recurrence is greater when there are residual symptoms after remission (about a third of cases), e.g. low mood, anxiety, sleep disturbance, reduced libido, and physical symptoms (headache, fatigue, GI upset). • There is good evidence that modern antidepressant treatments impact significantly upon all these quoted figures, reducing the length of depressive episodes; and if treatment is given long term, the incidence of residual symptoms is less, there are fewer recurrent episodes, and chronicity may be as low as 4%. Mortality • Suicide rates for severe depressive episodes vary but may be up to 13% (i.e. up to 20 times more likely than the general population), with a slightly higher rate for those who have required hospital admission (12– 19%). For less severe episodes, rates are much lower. • The overall death rate for patients with depression is higher than the general population [standardized mortality ratio (SMR) 1.37–2.49], with the cause of death usually due to suicide, drug and alcohol problems, accidents, cardiovascular disease, respiratory infections, and thyroid disorders. Prognostic factors • Good outcome: acute onset, endogenous depression, earlier age of onset. • Poor outcome: insidious onset, neurotic depression, elderly, residual symptoms, neuroticism, low self-confidence, comorbidity (alcohol or drug problems, personality disorders, physical illness), lack of social supports.

262 Chapter 6 Depressive illness Management principles and outpatient treatment
Initial assessment • History: key areas of enquiry include: • Any clear psychosocial precipitants. • Current social situation. • Use of drugs/alcohol. • Past history of previous mood symptoms (including ‘subclinical’ periods of low or elevated mood, previous DSH/suicide attempts). • Previous effective treatments. • Premorbid personality. • Family history of mood disorder. • Physical illnesses. • Current medication. • MSE (E Diagnosis and investigations, p. 260): focused enquiry about subjective mood symptoms, somatic symptoms, psychotic symptoms, symptoms of anxiety, thoughts of suicide. Objective assessment of psychomotor retardation/agitation, evidence of DSH, cognitive functioning (MMSE). • Physical examination: focused on possible differential diagnoses (E Differential diagnosis, p. 253). • Baseline investigations (E Diagnosis and investigations, p. 260). Questions of severity and initial treatment options7 • When depressive symptoms are mild and of recent onset and there is no previous history of a more severe mood disorder, most guidelines suggest refraining from use of antidepressants. Close active monitoring is advised and, depending on patient preference, use of individual guided self-help (based on CBT principles), computerized cognitive behavioural therapy (CCBT), or structured group physical activity programmes. • Antidepressants may be considered where there is: • A past history of moderate or severe depression. • An initial presentation of subthreshold depressive symptoms that have been present for a long period (typically at least 2yrs). • Subthreshold depressive

symptoms or mild depression that persist(s) after other interventions. • Treatment for moderate or severe depression combines antidepressant medication (E Treating depressive illness (without psychotic features), p. 266; E Treating depressive illness (with psychotic features), p. 268) and a high-intensity psychological intervention [e.g. CBT or interpersonal therapy (IPT); E Treating depressive illness (without psychotic features), p. 266]. 7 See National Institute for Health and Care Excellence (2009) Depression in adults: recognition and management. Clinical guideline [CG90] (this is a partial update of NICE clinical guideline CG23). M https://www.nice.org.uk/guidance/cg90 [accessed 13 June 2018].

Management principles and outpatient treatment • Usually pharmacological treatment can be initiated on an outpatient basis (severe cases may require admission; E Hospital admission, p. 264). • Choice of antidepressant is guided by anticipated safety and tolerability, physician familiarity (which allows for better patient education in anticipation of adverse effects), presenting symptoms, and history of prior treatments (E Antidepressants, p. 276). • Initially, follow-up will usually be fairly frequent (1–4wks) to monitor treatment response and assess for any unwanted side effects. • Once treatment is established (and is effective), the time between appointments may be i (see E Aftercare following discharge, p. 265; E Treating depressive illness (without psychotic features), p. 266; and E Treating depressive illness (with psychotic features), p. 268 for further guidance).

264 Chapter 6 Depressive illness Hospital admission Sometimes acute episodes of depressive disorder are severe enough to require hospital admission (which may be on a compulsory basis). As for all psychiatric disorders, issues of safety and the provision of effective treat ment will govern the decisions about whether a patient can remain in the community. Points to note • Due to symptoms of low self-esteem or guilt, some patients may refuse admission to hospital because they feel unworthy or they are ‘using up a valuable bed’. Sympathetic reassurance that this is not the case and that the clinician believes they are sufficiently ill to benefit from hospital admission may avoid unnecessary detention. • Some patients (or relatives) may demand admission to hospital. Although this usually is due to personality factors, it may also be due to (sometimes erroneous) ideas of what may be reasonably achieved in a hospital setting (e.g. intensive psychotherapy for one specific issue) or may reflect undisclosed factors that have created a social crisis. A non- confrontational approach in eliciting the reasons behind such demands may reveal other important issues that may help the decision-making process (including those which may be dealt with by other agencies, e.g. emergency accommodation/refuge). Common reasons for hospital admission • Serious risk of suicide (E Asking about depressed mood, p. 64). • Serious risk of harm to others (especially children; E Child maltreatment 2: the duty of care, p. 714). • Significant self-neglect (especially weight loss). • Severe depressive symptoms. • Severe psychotic symptoms. • Lack or breakdown of social supports. • Initiation of ECT. • Treatment-resistant depression (where inpatient monitoring may be helpful). • A need to address comorbid conditions (e.g. physical problems, other psychiatric conditions, inpatient detoxification). Suitable environment? Where there is significant risk of harm to self (or others), admission should be to a ward where close observation and monitoring are possible. Observation levels ought to be regularly reviewed. The ward environment is often not the quiet sanctuary patients hope for, and this may lead to dif ficult decisions in balancing the risk of self-harm against the use of compul sory admission. Careful assessment of a patient’s insight into their illness, issues of comorbid substance misuse, and clear evidence of their ability to seek additional support when symptoms are worse

may allow for a more flexible approach in permitting time out from the ward environment (per haps in the company of a responsible relative or friend).

Hospital admission Aftercare following discharge Following hospital discharge or for outpatients started on antidepressant treatment, initial follow-up should be regular (2–4wks) to monitor progress, ensure treatment response is maintained, and allow time for other supports (e.g. CPN services, crisis/home treatment services, day hospitals, specific psychotherapies) to become established. 0 Risk of suicide is i at this time, as energy and motivation improve and the patient struggles with the consequences of being unwell. Key aims for follow-up • Establishing and maintaining a therapeutic alliance. • Monitoring the patient's psychiatric status. • Providing education regarding depressive disorder and the treatment options. • Enhancing treatment compliance. • Monitoring side effects of medication. • Identifying and addressing any significant comorbidity. • Promoting regular patterns of activity and rest. • Identifying unmet needs for specific (practical) support, counselling, (bereavement, stress management), or psychotherapy. • Promoting understanding of, and adaptation to, the psychosocial effects of symptoms. • Identifying new episodes early. • Reducing the morbidity and sequelae of depressive disorder. The ultimate aim is return to normal activities (academic, employment, home life, social activities), usually in a graded way as the resolution of symptoms allows, using a collaborative approach. Maintenance treatment (E Treating depressing illness (without psych otic features), p. 266; E Treating depressing illness (with psychotic fea tures), p. 268) will usually be monitored in the primary care setting, with specific advice about continuation of medication and what to do should symptoms recur.

266 Chapter 6 Depressive illness Treating depressive illness (without psychotic features) First-line treatment • Antidepressant drugs are effective in 65–75% of patients. • For mild to moderate episodes or where antidepressants are contraindicated (e.g. recent MI), CBT or other psychotherapies may have a role (E Management principles and outpatient treatment, p. 262 for NICE recommendations CG90). • The combination of psychological approaches and pharmacotherapy may be synergistic, but in severe cases, treatment—at least initially—is almost exclusively pharmacological or physical (e.g. ECT). Choosing an antidepressant The decision about which antidepressant to choose will depend upon: • Patient factors: age, sex, comorbid physical illness (cardiac, renal, liver, neurological) (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), previous response to antidepressants. • Issues of tolerability (E Antidepressants, p. 276). • Symptomatology: sleep problems (more sedative agent), lack of energy/ hypersomnia (more adrenergic/stimulatory agent), mixed (e.g. with anxiety/panic—SSRI/imipramine), OCD symptoms (clomipramine/ SSRI), risk of suicide (avoid TCAs). Adequate trial Generally, an adequate trial of an antidepressant is defined as at least 4wks of the highest tolerated dose (up to BNF maximum). 0 Suicide risk The risk of suicide may actually be i in the early stages of antidepressant treatment. Often patients with previous marked psychomotor retardation have been unable to act upon their thoughts of self-harm. Partial treatment response may 'free' them to do this, hence careful monitoring is critical (and admission to hospital may be indicated). Treatment failure—second-line treatment Failure of an adequate trial of an antidepressant may occur in 725% of cases. A similar number of patients will experience unacceptable side ef fects, leading to withdrawal of the agent without completing an adequate trial. For these patients, second-line treatment is with an alternative agent, usually from a different

class of antidepressant or from the same class but with a different side effect profile.
Partial responders (E An approach to treatment-resistant depression, p. 270.) 750% of patients who have only partially responded to a TCA, an SSRI, or an MAOI may benefit from the addition of lithium (usual dose 600–900mg/ day). Treatment response is generally observed within 2wks. Alternative ‘aug mentative’ strategies include the use of tri-iodothyronine (T3) or tryptophan.

Treating depressive illness (without psychotic features) Electroconvulsive therapy (E ECT 2: indications, contraindications, and considerations, p. 296.) • ECT may be considered as a first-line therapy when there are severe biological features (e.g. significant weight loss/reduced appetite) or marked psychomotor retardation.8 • It is sometimes used when the patient is at high risk of harming themselves or others (where there is clear evidence of repeated suicide attempts or significantly aggressive behaviour) or where psychotic features are prominent (E Treating depressive illness (with psychotic features), p. 268). Under these circumstances, issues of consent to treatment must be considered (E ECT 2: indications, contraindications, and considerations, p. 296). • It may also be considered as a second- or third-line treatment for non- responders to pharmacotherapy. Maintenance therapy First episode • A collaborative approach with the patient should emphasize compliance (even when feeling ‘better’), with advice to continue the effective treatment for 6mths to 1yr after remission (particularly if there are residual symptoms). • Discontinuation should be gradual, and if there is recurrence of symptoms, revert to the effective dose, with further attempt at withdrawal after at least a further 4–6mths. • Often patients wish to continue medication indefinitely (particularly after a severe episode), and reassurance should be given that there is no evidence of any specific long-term problems with such a course of action. Recurrent episodes • If the period between episodes is <3yrs, or with severe episodes (especially with marked suicidal thought/actions), prophylactic treatment should be maintained for at least 5yrs (often indefinitely—risk of relapse if medication stopped is 70–90% within 5yrs). • Otherwise treat as for first episode. Electroconvulsive therapy • If ECT has been used as a first-line therapy and remission is maintained with medication, treat as for first episode. • If ECT has been used successfully as second- or third-line treatment, consider maintenance ECT as an option. [Note: not recommended in recent NICE guidelines (E ECT 5: further notes on treatment, p. 304) where there is evidence that ECT effectively treats relapse of symptoms. There is some evidence that ECT every 2wks may be an effective prophylactic (this does not preclude further trials of pharmacotherapy).] 8 Recently published NICE guidelines (E Box 6.11, p. 296) do not allow for some of these uses of ECT. However, NICE guidance does not override the individual responsibility of health professionals to make decisions appropriate to the circumstances of a specific patient (such action should be dis cussed, documented in the notes, and, where appropriate, validated by a second opinion).

268 Chapter 6 Depressive illness Treating depressive illness (with psychotic features) Electroconvulsive therapy (E ECT 2: indications, contraindications, and considerations, p. 296.) • For depression with psychotic features, ECT should be considered as first-line therapy, as evidence supports the superior efficacy of ECT to pharmacotherapy in this patient group, with significant benefit in 80–90% of cases. (Note: current NICE guidelines do not support this practice; E Box 6.11, p. 296). • Often issues of consent or relative contraindications may preclude the immediate use of ECT, and its role is often that of a second-line treatment after partial response or failure of pharmacotherapy. Combination treatment (antidepressant plus antipsychotic) • It is usual to commence treatment with an antipsychotic agent (as for an acute psychotic episode; E Initial treatment of acute psychosis, p. 200) for a few days before commencing an antidepressant. This

allows for a period of assessment (to exclude a primary psychotic disorder), may improve compliance (when psychotic symptoms clearly improve with medication), avoids potential worsening of psychotic symptoms with an antidepressant (in some predisposed individuals), and may help identify the 30–50% of patients who do respond to an antipsychotic alone. This approach is effective in 70–80% of patients. • There is no clear evidence for any particular combination of medication being more efficacious, but the available evidence indicates that combination therapy with an antidepressant plus an antipsychotic is more effective than either treatment alone or placebo.9 It is not unusual for low doses of antipsychotics to be added to an antidepressant, e.g. chlorpromazine or quetiapine (25–50mg at night). The most studied is the olanzapine–fluoxetine combination (OFC), mainly due to the fact that it is available as a single capsule (OFC—Symbyax®) in the USA.10 • Starting an antidepressant first and adding an antipsychotic, if necessary, may be a better strategy as far as cost–benefit to the patient.11 9 Wijkstra J, Lijmer J, Burger H, Cipriani A, Geddes J, Nolen WA (2015) Pharmacological treatment for psychotic depression. Cochrane Database Syst Rev 30:CD004044. 10 RCT evidence actually suggests a combination approach is superior to an antipsychotic alone for olanzapine vs olanzapine/fluoxetine [Rothschild AJ, Williamson DJ, Tohen MF, et al. (2004) A double- blind, randomized study of olanzapine and olanzapine/fluoxetine combination for major depression with psychotic features. J Clin Psychopharmacol 24:365–73]; olanzapine/sertraline vs olanzapine/ placebo [Meyers BS, Flint AJ, Rothschild AJ, et al. (2009) A double-blind randomized controlled trial of olanzapine plus sertraline vs. olanzapine plus placebo for psychotic depression: the study of pharmacotherapy of psychotic depression (STOP-PD). Arch Gen Psychiatry 66:838–47]; and for OFC (olanzapine–fluoxetine) vs olanzapine or fluoxetine alone [Trivedi MH, Thase ME, Osuntokun O, et al. (2009) An integrated analysis of olanzapine/fluoxetine combination in clinical trials of treatment resistant depression. J Clin Psychiatry 70:387–96). In the USA, the FDA has approved four SGAs as adjunctive therapies for MDD: aripiprazole, quetiapine, brexpiprazole, and olanzapine (specifically with fluoxetine). In the UK, only quetiapine is licensed. 11 Wijkstra J, Lijmer J, Balk FJ, et al. (2006) Pharmacological treatment for unipolar psychotic depres sion: systematic review and meta-analysis. Br J Psychiatry 188:410–15.

Treating depressive illness (with psychotic features) Additional practice points • Symptoms ought to be carefully monitored, as antipsychotic side effects may mask improvement in depressive symptoms—hence use of the lowest effective dose is advocated (e.g. around 2–4mg haloperidol or equivalent). • Combinations of antidepressant/antipsychotic may worsen side effects common to both (e.g. sedation, anticholinergic effects), and careful dose titration is necessary. • Once acute psychotic symptoms have resolved, a lower dose of antipsychotic (or withdrawal) may be indicated, particularly when patients begin to manifest side effects (which were not seen in the acute stages, even with higher doses)—with careful monitoring for recurrence of psychotic symptoms. Dual-action agents There is some evidence that single agents with dual actions, such as amoxapine (a tetracyclic antidepressant with significant D2 antagonism), or antipsychotics, such as aripiprazole, clozapine, olanzapine, quetiapine, or risperidone, may be effective in treating both aspects of depression with psychotic symptoms. To date, evidence does not exist to support use of these agents for long-term treatment—where there are issues of compli ance/tolerability, the utility of using a single agent is attractive but should be considered carefully.9 Maintenance therapy • When ECT has been used, maintenance usually involves treatment of the underlying depressive symptoms with an antidepressant (as in episodes without psychotic symptoms; E Treating depressive illness (without psychotic features), p. 266). • When combination treatment has been

successful, maintenance often involves a clinically effective antidepressant with the lowest effective antipsychotic dose. As for dual-action agents, evidence is lacking with regard to long-term treatment, and this tends to be pragmatic, on the basis of continued symptomatology. • In view of the severity of the disorder, prophylactic use of an antidepressant and/or antipsychotic is prudent (often indefinitely, as for recurrent depressive episodes; E Recurrent episodes, p. 267).

270 Chapter 6 Depressive illness An approach to treatment-resistant depression Commonly defined as ‘failure to respond to adequate (dose and duration— i.e. max BNF dose for at least 4wks) courses of two antidepressants, or one antidepressant and ECT’. The consequences of resistant depression include reduced quality of life, excessive strain on relationships (which may lead to break-up of families), significant personal economic impact, i phys ical comorbidity (e.g. malignancy, cardiovascular disease, even premature death), i risk of suicide, therapeutic alienation (making further interven tions difficult due to difficulties forming a therapeutic alliance), and high use of psychiatric services (without clear benefit). Differentiating treatment resistance It is important to distinguish actual treatment resistance from chronicity of symptoms. Apparent treatment failure may also occur due to: incorrect initial diagnosis (i.e. not depressive disorder in the first place), inadequate initial treatment, poor compliance, incomplete formulation (especially role of maintaining factors), and issues of comorbidity (both physical and other psychiatric disorders). Risk factors for treatment resistance Concurrent physical illness, drug/alcohol abuse, personality disorder, high premorbid neuroticism, long period of illness prior to treatment. Management (See references.)12,13 • Review diagnostic formulation: is the diagnosis correct? Are there any unaddressed maintaining factors (e.g. social, physical, psychological)? Note: a proportion of individuals with chronic, refractory depression will have unrecognized bipolar disorder. • Check patient understanding/compliance: serum levels may help. • Continue monotherapy at maximum tolerable dose: may mean exceeding BNF guidelines (especially if there has been partial benefit). • Consider change in antidepressant: try a different class of antidepressant. • Consider augmentation with an antipsychotic: e.g. quetiapine, aripiprazole, risperidone, olanzapine. • Consider mood stabilizer augmentation: e.g. lithium, lamotrigine. • Consider additional augmentative agents: e.g. T3, tryptophan (since February 2013 no longer available in the UK). • Consider combining antidepressants from different classes: caution is advised, due to possible serious adverse reactions (E Serotonin syndrome, p. 1022), e.g. mirtazapine, bupropion (E Combining antidepressants, p. 279). 12 Cleare A, Pariante CM, Young AH, et al. (2015) Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 2008 British Association for Psychopharmacology guidelines. J Psychopharmacol 29:459–25. 13 Useful guidance and assessment tools for treatment-resistant depression, including advice re garding criteria for ‘adequate treatment’, can be found on the Dundee Advanced Interventions Service website: M http://www.advancedinterventions.org.uk [accessed 16 June 2018].

An approach to treatment-resistant depression • Other pharmacological possibilities: buspirone, modafinil, stimulants, oestrogen in perimenopausal women, testosterone in men with low testosterone levels. • Consider use of ECT (E ECT 2: indications, contraindications, and considerations, p. 296): especially if severe biological features or psychotic symptoms. • Consider possibility of psychosurgery or other advanced intervention: E Neurosurgery for mental disorder, p. 310; E Other physical treatments, p. 312. Points to note • There is little definitive evidence to support any specific augmentative regime (see Box 6.5). • Spontaneous remission is possible—‘regression to the mean’ suggests that symptoms will improve; bear in mind that the

natural life of depression is 6–18mths, even when untreated. • Psychological and social interventions, particularly when psychosocial factors appear paramount, may be important (often overlooked or undisclosed) aspects of management. Box 6.5 STAR*D trial The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial is one of the largest independent studies undertaken by the NIMH to examine the effectiveness of a variety of treatments for non-psychotic major depression. The initial report was published in the American Journal of Psychiatry in November 2006.1 • A fairly representative outpatient sample (n = 3671) underwent four steps: • Level 1—citalopram. • Level 2—switch (to bupropion, sertraline, venlafaxine XR, or cognitive therapy) or combine (bupropion, buspirone, cognitive therapy). • Level 2a—if cognitive therapy alone or plus citalopram, add or switch to bupropion or venlafaxine XR. • Level 3—switch (to nortriptyline or mirtazapine) or augment (with lithium or T3). • Level 4—switch (to tranylcypromine) or combine (venlafaxine XR plus mirtazapine). • Remission rates were 37%, 31%, 14%, and 13%, respectively, for each level, with an overall cumulative remission rate of 67%. • The trial highlighted patient preference for combinations/ augmentations and provided some evidence to support certain strategies, e.g. lithium or T3 augmentation; combining citalopram plus bupropion, buspirone, or venlafaxine plus mirtazapine. 1 Rush AJ, Trivedi MH, Wisniewski SR, et al. (2006) Acute and longer-term outcomes in de pressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry 163:1905–17.

272 Chapter 6 Depressive illness Atypical depressive episode Regarded as a subtype of depressive disorder, rather than a separate entity. Atypical features coded in DSM-5 as an ‘episode specifier’. May be coded under ‘Other (specified) depressive episodes’ in ICD-10 (/ICD-11). Clinical features • Mood is depressed but remains reactive (able to enjoy certain experiences, but not to ‘normal’ levels). • Hypersomnia (sleeping >10hrs/day, at least 3 days/wk, for at least 3mths). • Hyperphagia (excessive eating, with weight gain of over 3kg in 3mths). • ‘Leaden paralysis’ (feeling of heaviness in the limbs, present for at least 1hr/day, 3 days/wk, for at least 3mths). • Oversensitivity to perceived rejection.14 • Other infrequent symptoms may include: initial insomnia, rather than EMW; reversed diurnal mood variation (better in the morning); severe motor retardation; and absence of feelings of guilt. Epidemiology Onset usually in late teens and early 20s, often (up to 30%) family history of affective disorders. Comorbidity Higher rates of anxiety (especially panic disorder and social phobia), soma tization disorder (E Somatization disorder, p. 864), alcohol and drug misuse than in other depressive disorders. Management (See Reference.)15 • Best evidence is for the use of phenelzine (15mg/day, i gradually to 60– 90mg/day in divided doses—continue for 8–12wks to assess benefit) or another MAOI (E Monoamine oxidase inhibitors and reversible monoamine oxidase inhibitors, p. 282 for guidance on prescribing/ dietary advice). Reversible monoamine oxidase inhibitors (RIMAs) theoretically ought to be as effective and safer (but evidence is lacking). • Alternatives include SSRIs (e.g. fluoxetine or sertraline) or possibly a NARI (e.g. reboxetine). • TCAs have traditionally been regarded as less effective. However, some individuals may respond well, and the best evidence is for the use of imipramine. • Where there is failure to respond to an adequate trial of an antidepressant, follow management principles outlined in E Treating depressive illness (without psychotic features), p. 266; E Treating depressive illness (with psychotic features), p. 268; E An approach to treatment-resistant depression, p. 270). 14 ‘Rejection sensitivity’ (to both real and imagined rejection) adds to the difficulty of managing atypical depression, as the patient may have had adverse experiences with doctors in the past, may have been labelled as ‘personality-disordered’, and may find the idea of a therapeutic alliance alien. 15 Henkel V, Mergl R, Allgaier AK, Kohnen R, Möller HJ, Hegerl U (2006) Treatment of

depression with atypical features: a meta-analytic approach. Psychiatry Res 141:89–101.

Seasonal affective disorder Seasonal affective disorder A somewhat controversial concept, both in terms of diagnosis (E Clinical features, see below) and treatment (using bright light therapy; E Other physical treatments, p. 312). In DSM-5, ‘with seasonal pattern’ is included in specifiers describing the course of recurrent depressive episodes of both depressive and bipolar disorder. Included under ‘Recurrent depressive dis order’ in ICD-10/11. Clinical features There must be a clear seasonal pattern to recurrent depressive episodes (i.e. they have occurred at the same time of year each time and fully remit once the season is over). In the northern hemisphere, this is said to be usually around January/February (‘winter depression’). Symptoms are generally mild to moderate, with low self-esteem, hypersomnia, fatigue, i appetite (including carbohydrate craving), weight gain, and d social and oc cupational functioning. Aetiology It is unclear whether this constitutes a separate subtype of depressive disorder or whether it is simply a manifestation of atypical depression (E Atypical depressive episode, p. 272). The speculated mechanism involving melatonin synthesis has not been confirmed in controlled studies, and some authors suggest that seasonal psychosocial factors may be more important in determining the timing of recurrent depressive episodes (e.g. i work demands over the Christmas and New Year periods for shopworkers). Epidemiology In the USA, prevalence of seasonal affective disorder (SAD) is estimated at 75%; ♂:♀ = 1:5. Management • Bright light therapy (E Other physical treatments, p. 312): initially, 2hrs of 2500lx (or equivalent) on waking (response seen within 5 days and full response in 1–2wks). Maintenance therapy should be given all winter (30min of 2500lx every 1–2 days). Patients should avoid exposure to bright light during night-time. Good prognostic factors—patients with clear hypersomnia, carbohydrate craving, reduced energy in the afternoon. • Pharmacological: best evidence for bupropion XL (licensed in the USA, not the UK16) and SSRIs (fluoxetine, sertraline, citalopram, escitalopram). Alternatives include pre-sunrise propranolol (60mg/ day) to suppress morning melatonin; melatonin/agomelatine at night; or other antidepressants (e.g. mirtazapine, reboxetine, duloxetine, moclobemide). • Psychological: standard cognitive-based interventions are often used (as for depression), but the evidence base for effectiveness is lacking. 16 Gartlehner G, Nussbaumer B, Gaynes BN, et al. (2015) Second-generation antidepressants for preventing seasonal affective disorder in adults. Cochrane Database Syst Rev 8:CD011268..

274 Chapter 6 Depressive illness Dysthymia (ICD-10)/persistent depressive disorder (DSM-5) Previously considered a subtype of personality disorder (see Box 6.6). Essentially, the presence of chronic depressive symptoms. These may be long-standing, but careful history-taking reveals a time when the person did feel ‘well’. It is possible to have superimposed depressive episodes (double depression), when care is needed in assessing treatment response, as base line may be dysthymic, rather than euthymic. Clinical features • Depressed mood (>2yrs). • Reduced/i appetite. • Insomnia/hypersomnia. • Reduced energy/fatigue. • Low self-esteem. • Poor concentration. • Difficulties making decisions. • Thoughts of hopelessness. Aetiology Findings suggest dysthymia is biologically related to depressive disorder, e.g. family history suggesting shared genetics; shortened REM latencies in sleep studies; diurnality of symptoms; TRH/TSH challenge test abnormalities; low testosterone and adrenal–gonadal steroid levels; lowered interleukin (IL)-1β; small genual corpus callosum volume; enlarged amygdala; s-allele polymorphism of 5-HT transporter gene. Epidemiology Prevalence 3–5%, ♂:♀ = 1:2, usually early onset (<20yrs), but late-onset subtype seen (>50yrs). Course Less severe. More chronic than

depression. Community studies show low spontaneous remission rate (2–20yrs, median 5yrs). Management • Pharmacological: SSRIs are probably the treatment of choice, with the best evidence for citalopram (40mg/day) and fluoxetine (20–40mg/ day). Alternatives include moclobemide, TCAs (e.g. amitriptyline, desipramine, imipramine), MAOIs, or low-dose amisulpride (25–50mg/ day). Drug therapy may take several months to show benefit17 and should be regarded as a long-term treatment. • Psychological: although evidence is lacking, CBT may be useful (usually in combination with an antidepressant). Alternatives include psychodynamic, insight-orientated or interpersonal psychotherapy, or cognitive–behavioural analysis system of psychotherapy (CBASP) (E Cognitive–behavioural analysis system of psychotherapy, p. 928). Prognosis
Variable: spontaneous recovery reported as 13% over 1yr in community samples; outpatient studies suggest 10–20% of treated patients achieve re mission within 1yr; 725% suffer chronic symptoms. 17 Silva de Lima M, Hotopf M (2003) A comparison of active drugs for the treatment of dysthymia. Cochrane Database Syst Rev 3:CD004047.

Dysthymia (ICD-10)/persistent depressive disorder (DSM-5) Box 6.6 Dysthymia—an brief history ‘Dysthymia’, meaning ‘bad mood’ in Greek, was originally considered part of the Hippocratic concept of melancholia (E Historical perspective, p. 244). The term disappeared from use until the nineteenth century when, in 1838, the German pathologist Karl Wilhelm Stark (1787–1845) used it to differentiate disorders of mood from those of the will (dysbulias) and intellect (dysnoesias). Carl Friedrich Flemming (1799–1880) is attributed as the first psychiatrist to use the term in 1844. Flemming, who founded the Allgemeine Zeitschrift für Psychiatrie, distinguished between disorders of intellect (anoesia), disorders of mood (dysthymia), and disorder of both intellect and mood (mania). He was one of the first psychiatrists to draw a distinction between affective disorders, which he termed ‘dysthymias’, and non-affective disorders. Influenced by the writings of Kahlbaum (1863), he later changed his views to a system based more on clinical observation and course than theoretical concepts, distinguishing disorders of mood (dysthymia), disorders of intelligence (paranoia), and disorders of will (diastrephia). Kraepelin, in his textbooks (1909–1915), did not keep the term ‘dys thymia’, although, regarding the ‘depressive constitution’, he wrote: ‘ . . . they show a certain sensitivity for life’s sorrows, grieves and disappointments. Everything is burdensome for them . . . Their whole course of life is strongly influenced by their suffering. . . . They feel weak, without energy. . . . Sleep is normally insufficient; these patients have a great urge for sleep, but they fall asleep very late . . . , in the morning they do not feel refreshed but tired . . . The illness described here normally first manifests during adolescence and may persist without major changes throughout life.’ Due to the influence of psychodynamic thinking in the mid-twentieth century, dysthymia was overshadowed by ‘neurotic (psychogenic) de pression’. Eugen Kahn (1928) and Karl Leonhard (1968) did utilize the term to describe persons with ‘psychopathic personalities’ who had chronically disturbed or irritable mood. However, the antidepressant era—from the 1960s onward—brought with it a revolution in thinking about affective disorders, culminating in the sidelining of ‘neurotic de pression’ in DSM-III with a compromise diagnosis of ‘dysthymic disorder (neurotic depression)’. There was a growing consensus that dysthymia described a disabling chronic mood disorder that was treatable pharma cologically (ergo: not a personality disorder). While DSM-IV maintained ‘dysthymic disorder’ within the depressive disorders, ICD-10 placed it in a subcategory of ‘persistent mood disorders’, along with cyclothymia (E Cyclothymia, p. 348), with the emphasis on chronic, low-grade symptoms. More recently, DSM-5 uses the term ‘persistent depressive disorder’ to consolidate DSM-IV-defined ‘chronic major depressive dis order’ and ‘dysthymic disorder’, with the emphasis on chronicity. It looks like ICD-11 will put ‘dysthymic

disorder’ back into the depressive dis orders but keep it as a less severe form of depressive disorder.

276 Chapter 6 Depressive illness Antidepressants Assumed mode of action All currently available antidepressants appear to exert antidepressant action by increasing the availability of monoamines (5-HT, NA, and DA) via one or more of the following: • Presynaptic inhibition of reuptake of 5-HT, NA, or DA. • Antagonist activity at presynaptic inhibitory 5-HT or NA receptor sites, which enhances neurotransmitter release. • Inhibition of monoamine oxidase, reducing neurotransmitter breakdown. • Increasing the availability of neurotransmitter precursors. Although this net increase happens almost immediately following administration, initial resolution of depressive symptoms generally takes 10–20 days, implying therapeutic effect involves mechanisms possibly re lated to receptor regulation over time/changes in intracellular signalling. Selectivity vs specificity Although the newer antidepressants are more selective than TCAs and MAOIs in their pharmacological effects, this should not be confused with them being more specific for any particular type of depressive symptoms. All antidepressants have unwanted and often unpleasant side effects. A balance needs to be struck between efficacy in treating psychiatric symp toms and the possibility of iatrogenic problems. Patients may not be able to tolerate the anticholinergic side effects of TCAs or will be unable to achieve a therapeutic level because of side effects. Similarly, nausea or GI upset may limit the usefulness of SSRIs in some individuals. Sometimes side effects may even be useful (e.g. sedation for patients with insomnia). Cautionary notes Particular caution is necessary in prescribing for certain patient groups (E Prescribing in pregnancy, p. 1028; E Prescribing in lactation, p. 1030; 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; E Prescribing for patients with epilepsy, p. 1038) such as those with renal or hepatic impairment, car diac problems, and epilepsy; pregnant or breastfeeding women; the eld erly; children; and those on other medications which may interact with antidepressants. There are also well-recognized problems such as weight gain (E Weight gain with psychiatric medication, p. 1000), hyponatraemia (E Hyponatraemia and antidepressants, p. 1026), sexual dysfunction (E Sexual dysfunction and psychiatric medication, p. 1006), and discontinu ation syndromes (E Antidepressant discontinuation syndrome, p. 1024). Swapping and stopping antidepressants (See also Table 6.3.) An adequate ‘washout’ period is required when switching to or from the MAOIs, whereas it is usual to cross-taper between other antidepres sants (i.e. gradually reducing the dose of one, while slowly increasing the dose of the other). During this process, side effects may be enhanced (due to pharmacokinetic effects) and it is possible to induce the serotonin syn drome (SS) (E Serotonin syndrome, p. 1022).

TCAs* XXX HDWS W2w W2w W7d CCT HDWS CCT HDWS HDWS CCT CCT CCT HDWS CCT CCT HDWS CCT HDWS RG4w Clomipramine CCT XXX W3w W3w W7d W3w W3w W3w W3w W3w W3w W3w W3w CCT CCT CCT W3w CCT W3w RG4w Hydrazines W3w W3w XXX W2w W2w W2w W2w W2w W2w W2w W2w W2w W2w W2w W2w W2w W2w CCT W2w RG4w Tranylcypromine W3w W3w W2w XXX W2w W2w W2w W2w W2w W2w W2w W2w W2w W2w W2w W2w W2w W2w CCT W2w RG4w Moclobemide W1d W1d W1d W1d XXX W1d W1d W1d W1d W1d W1d W1d W1d W1d W1d W1d W1d CCT W1d RG4w Just stopping Vortioxetine Agomelatine Bupropion Reboxetine Mirtazapine Trazodone Mianserin Duloxetine Venlafaxine Sertraline Paroxetine Fluvoxamine Fluoxetine Citalopram/ escitalopram Table 6.3 Swapping or stopping antidepressants Moclobemide Tranylcypromine Hydrazines Clomipramine TCAs* TO FROM (Continued.) escitalopram CCT WSLD

W7d W7d W7d XXX WSLD WSLD CCT CCT CCT CCT CCT CCT CCT CCT CCT CCT CCT RG4w+ Paroxetine CCT WSLD W7d W7d W7d CCT WSLD WSLD XXX CCT CCT CCT CCT CCT CCT CCT CCT CCT CCT CCT RG4w+ Sertraline CCT WSLD W7d W7d W7d CCT WSLD WSLD CCT XXX CCT CCT CCT CCT CCT CCT CCT CCT CCT RG4w+ Venlafaxine CCT WSLD W7d W7d W7d CCT WSLD WSLD CCT CCT XXX CCT CCT CCT CCT CCT CCT CCT CCT RG4w+ Fluoxetine W1w W2w W6w W6w W6w W1w XXX W2w W1w W1w WSLD WSLD CCT CCT CCT CCT CCT CCT W1w ≤20mg

> 20mg RG2w Fluvoxamine CCT WSLD W7d W7d W7d WSLD WSLD XXX WSLD WSLD WSLD WSLD CCT CCT CCT CCT CCT W1w WSLD RG4w STOP Citalopram/

Duloxetine CCT WSLD W7d W7d W7d CCT WSLD WSLD CCT CCT CCT XXX CCT CCT CCT CCT CCT CCT CCT CCT RG4w+ Mianserin CCT CCT W7d W7d W7d CCT CCT CCT CCT CCT CCT CCT CCT XXX CCT CCT CCT CCT CCT CCT CCT RG4w Trazodone CCT CCT W7d W7d W7d CCT CCT CCT CCT CCT CCT CCT CCT CCT XXX CCT CCT CCT CCT CCT RG4w Mirtazapine CCT CCT W2w W2w W7d CCT CCT CCT CCT CCT CCT CCT CCT CCT CCT XXX CCT CCT CCT CCT RG4w Reboxetine CCT CCT W7d W7d W7d CCT CCT CCT CCT CCT CCT CCT CCT CCT CCT CCT CCT XXX CCT CCT CCT RG4w Just stopping Vortioxetine Agomelatine Bupropion Reboxetine Mirtazapine Trazodone Mianserin Duloxetine Venlafaxine Sertraline Paroxetine Fluvoxamine Fluoxetine Citalopram/ escitalopram Moclobemide Tranylcypromine Hydrazines Clomipramine Table 6.3 (Contd.) TCAs* TO FROM Bupropion CCT CCT W2w W2w W1d CCT CCT CCT CCT CCT CCT CCT CCT CCT CCT CCT CCT XXX CCT CCT RG4w Vortioxetine CCT WSLD W3w W3w W7d CCT WSLD WSLD CCT CCT CCT CCT CCT CCT CCT CCT CCT CCT CCT XXX RG1w Agomelatine W1d W1d W1d W1d W1d W1d W1d W1d W1d W1d W1d W1d W1d W1d W1d W1d W1d XXX W1d STOP W2w = withdraw and wait 2wks; W3w = withdraw and wait 3wks; W6w = withdraw and wait 6wks; RG4w(+) = reduce gradually over 4wks (or longer); RG1w = reduce gradually over 1wk; Key: TCAs* = all TCAs, except clomipramine; CCT = cautious cross-taper; W1d = withdraw and wait 1 day; W7d = withdraw and wait 7 days; WSLD = withdraw and start at low dose; Source: data from from MIMS online: M https://www.mims.co.uk/antidepressants-guide-switching-withdrawing/mental-health/article/882430 [accessed: 12 July 2018]. STOP = no dose tapering required; HDWS = half dose, add new agent, and then withdraw slowly.

Antidepressants Combining antidepressants Combinations of antidepressants may be more efficacious than one alone. In clinical practice, combinations are not reserved solely for treatment-resistant cases (E An approach to treatment-resistant depression, p. 270), but may also help to treat residual symptoms or offset side effects. When combining antidepressants, safety is the main priority (even before effi cacy)—there is little point in using theoretically effective (heroic) combin ations if the patient cannot tolerate the side effects. Common problems • Combining other antidepressants with MAOIs is especially likely to result in SS (E Serotonin syndrome, p. 1022). • Combining TCAs and SSRIs may lead to more severe TCA side effects due to elevated blood levels secondary to SSRI effects on the P450 2D6 liver enzyme system, resulting in a blockade of the metabolism of TCAs. Low doses of both agents are to be preferred if used together. • Combining SSRIs or SSRIs + SNRIs risks SS and should be done only with great caution (and explicit informed patient consent). Common combinations (generally well tolerated) • SSRI + trazodone or mirtazapine for those troubled by insomnia but who have responded well to the antidepressant effects of the SSRI. • Venlafaxine + mirtazapine (as in the STAR*D study; E Box 6.5, p. 271) for

treatment resistance. • Bupropion or mirtazapine + SSRIs or SNRIs to combat sexual dysfunction, which can be a consequence of SSRI or SNRI treatment. The following topics outline the main groups of antidepressants. This in formation should be used as a guide, and the clinician is always advised to consult manufacturers' data sheets or more detailed formularies for less common problems or specific details of administration.

280 Chapter 6 Depressive illness Tricyclic antidepressants (See Table 6.4.) • Common mode of action and effects/side effects: • Serotonin/NA (and DA) reuptake inhibition—antidepressant effects. • Anticholinergic (antimuscarinic—M1)—dry mouth, blurred vision, constipation, urinary retention, drowsiness, confusion/memory problems (particularly in the elderly), palpitations/tachycardia. • Adrenergic antagonism (α1)—drowsiness, postural hypotension (occasionally syncope), tachycardia, sexual dysfunction. • 5-HT2 antagonism—anxiolytic, reduced sexual dysfunction, sedation. • Antihistaminergic (H1)—drowsiness, weight gain. • Advantages: well-established efficacy and large literature (in all varieties of patient groups); possibly more effective in severe depression; low cost. • Disadvantages: toxicity in OD; may be less well tolerated than SSRIs; all TCAs may slow cardiac conduction and lower seizure threshold. • Contraindications: acute MI, heart block, arrhythmias, IHD, severe liver disease, pregnancy, and lactation (E Prescribing in pregnancy, p. 1028; E Prescribing in lactation, p. 1030; 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; E Prescribing for patients with epilepsy, p. 1038). • Cautions (E Antidepressants, p. 276): cardiovascular, liver, renal disease; endocrine disorders (hyperthyroidism, adrenal tumours, diabetes); urinary retention/prostatic hypertrophy; constipation; glaucoma; epilepsy; psychotic disorders; patients with thoughts of suicide; elderly (use lower doses). • Significant interactions (variable for different agents—always check data sheets): alcohol, anticoagulants, anticonvulsants, antihypertensives, antipsychotics, barbiturates, BDZs (rare), cimetidine, digoxin, MAOIs (rare), methylphenidate, morphine, SSRIs, smoking. • Monitoring: it is good practice to monitor cardiac and liver function, U&Es, FBC, and weight during long-term therapy.

phobic disorders, adjunctive treatment of catalepsy (in (hospital) Depression (with anxiety) 300mg Depression (especially if given IV/IM Depression, OCD, and 100–150mg 150mg Metabolized to nortriptyline Depression, nocturnal enuresis, chronic pain, migraine, insomnia dose Notes

Indications

narcolepsy) 250mg Most SSRI-like of the TCAs. Can be maintenance dose Max daily (Prothiaden®) 14–40 C/T 25mg 75–150mg/day 75–150mg/day 225mg (divided or just at 10mg/day 30–150mg/day Doxepin 8–24 C 10/25/50/75mg 75mg/day Up to 300mg/ dose Usual night) Drug

Half-life (hr) Formulations

Usual starting just at night) (divided or 75mg/day Table 6.4 Tricyclic antidepressants (TCAs) S 25 or 50mg/5mL Amitriptyline 8–24 T 10/25/50mg;

Clomipramine 17–28 C 10/25/50mg; SR 75mg; Inj

C 25/50mg;

12.5mg/mL Dosulepin Tricyclic antidepressants C 50mg 75mg/day 150–300mg/day 300mg May be very sedating Depression (with anxiety) S 25mg/5mL 25mg up to tds 50–100mg/day 200mg Metabolized to desipramine Depression, nocturnal Depression, nocturnal sedation needed) Depression enuresis enuresis (‘therapeutic window’ 50–150ng/mL) Nortriptyline 18–96 T 10/25mg 25mg tds 75–100mg 150mg Manufacturer recommends plasma monitoring in doses <100mg/day S 70mg/5mL 70mg/day 70–210mg/day 210mg May be safer in overdose. Least pro-convulsant. Metabolized to desipramine Key: T = tablets; C = capsules; S = oral suspension/solution; SR = modified-release capsules; Inj = injectable form. day (divided if <100mg/day) Imipramine 4–18 T 10/25mg;

Trimipramine 7–23 T 10/25mg;

Lofepramine 1.6–5 T 70mg;

282 Chapter 6 Depressive illness Monoamine oxidase inhibitors and reversible monoamine oxidase inhibitors • Mode of action: • MAOIs: irreversible inhibition of MAO-A (acts on NA, DA, 5-HT, and tyramine) and MAO-B (acts on DA, tyramine, phenylethylamine, and benzylamine), leading to accumulation of monoamines in the synaptic cleft (see Table 6.5). • RIMAs: act by reversible inhibition of MAO-A (Table 6.5). • Side effects: • Risk of hypertensive crisis due to inhibition of intestinal monoamine oxidase, allowing pressor amines to enter the bloodstream (hence foods high in tyramine and certain medications should be avoided). • Sources of dietary tyramine: cheese (except cottage and cream cheese), meat extracts and yeast extracts (including Bovril®, Marmite®, Oxo®, and other fermented soya bean extracts), alcohol—including low- alcohol drinks (especially chianti and fortified wines and beers), non- fresh fish, non-fresh poultry, offal, avocado, banana skins, broad bean pods, caviar, herring (pickled or smoked). • Medications: indirect sympathomimetics (amphetamine, fenfluramine, ephedrine, phenylephrine, phenylpropanolamine), cough mixtures containing sympathomimetics, nasal decongestants with sympathomimetics, levodopa, pethidine, antidepressants [TCAs, SSRIs/SNRIs, mirtazapine, bupropion, St John’s wort (see Box 6.7)]. These effects may be less with RIMAs. However, large amounts of tyramine-rich food should be avoided. • Other side effects: antimuscarinic actions, hepatotoxicity, insomnia, anxiety, appetite suppression, weight gain, postural hypotension, ankle oedema, sexual dysfunction, possible dependency. • Indications: usually used as second-line therapy for treatment-resistant depression (particularly atypical symptoms)/anxiety disorders (with or without panic attacks). • Cautions: cardiovascular disease, hepatic failure, poorly controlled hypertension, hyperthyroidism, porphyria, phaeochromocytoma. • Advantages: well-established efficacy in a broad range of affective and anxiety disorders. • Disadvantages: dietary restrictions and drug interactions (less so with RIMAs). • Other significant drug interactions (variable for MAOIs vs RIMAs—always check data sheets): antidiabetics, antiepileptics, antihypertensives, antipsychotics, barbiturates, BDZs, β-blockers, buspirone, cimetidine, dopaminergics (selegiline), dextromethorphan, mazindol, pethidine, morphine, 5-HT1 agonists (rizatriptan, sumatriptan), tetrabenazine.

Possible hyponatraemia. ‘Cheese (Manerix®) RIMA 1–2 T 150mg 150mg bd 150–600mg/day 600mg/day May be used for social phobia. 10–40mg/day 60mg/day Hydrazine derivative—less 90mg/day) Hydrazine derivative—less reaction’ least likely Most stimulant of stimulating stimulating dose Max daily dose

Notes

day to 15mg qds 60mg/day (hospital Tranylcypromine MAOI 2.5 T 10mg 10mg bd 10mg/day 30mg/day dose Usual maintenance Phenelzine (Nardil®) MAOI 1.5 T 15mg 15mg tds 15mg every other (divided or single (hr) Formulations Usual starting Isocarboxazid MAOI T 10mg 30mg/day daily dose) Drug

Class Half-life Table 6.5 MAOIs and RIMAs Moclobemide MAOI AND RIMA Do not give after 3 p.m. i risk of MAOIs (amphetamine-related). significant interactions (or greater if supervised)
Key: T = tablets.

284 Chapter 6 Depressive illness Box 6.7 St John's wort (SJW, Hypericum perforatum) Considered a first-line antidepressant in many European countries (and recently becoming popular in the USA); not yet in the UK. May be ef fective for mild to moderate depressive symptoms.1 • Mode of action: recent research suggests it may act as a weak SSRI (and/or NARI/MAOI). • Usual dose: 300mg tds (with food to prevent GI upset). • Notable interactions: anticoagulants (especially warfarin), antidepressants (risk of serotonin syndrome; E Serotonin syndrome, p. 1022), antiepileptics, antivirals, barbiturates, ciclosporin, digoxin, 5-HT1 agonists (rizatriptan, sumatriptan), oral contraceptives, theophylline. 1 Linde K, Berner MM, Kriston L (2008) St John's wort for major depression. Cochrane Database Syst Rev 4:CD000448.

285 MAOI AND RIMA

286 Chapter 6 Depressive illness Selective serotonin reuptake inhibitors • Common mode of action and effects/side effects: serotonin reuptake inhibition (leads to i 5-HT in synaptic cleft; see Table 6.6). • 5-HT1A agonism—antidepressant, anxiolytic, anti-obsessive, anti- bulimic effects. • 5-HT2 agonism—agitation, akathisia, anxiety/panic, insomnia, sexual dysfunction. • 5-HT3 agonism—nausea, GI upset, diarrhoea, headache. • Advantages: ease of dosing; may be better tolerated than TCAs—less cardiotoxic; fewer anticholinergic side effects; low toxicity in OD. • Disadvantages: commonly cause nausea and GI upset, headache, restlessness, and insomnia; may be less effective for severe depressive episodes; problems on discontinuation (E Antidepressant discontinuation syndrome, p. 1024). • Contraindications: manic episode, concomitant use of MAOIs. • Cautions (E Antidepressants, p. 276): variable and significant inhibitory effects on hepatic P450 (particularly CYP2D6) enzymes. Hence, take care when co-prescribing with drugs that undergo extensive liver metabolism and have a narrow therapeutic range. • Significant interactions (variable for different agents—always check data sheets): alcohol, anticoagulants, anticonvulsants, antipsychotics, BDZs, β-blockers, bupropion, buspirone, cimetidine, cyproheptadine, hypoglycaemics, lithium, methadone, MAOIs, morphine, smoking, TCAs, theophylline, warfarin.

Selective serotonin reuptake inhibitors Table 6.6 Selective serotonin reuptake inhibitors (SSRIs) Drug Half-life (hr) Formulations Usual starting dose Usual maintenance dose Max daily dose Notes Indications Citalopram (Cipramil®) T 10/20/40mg; S 40mg/mL 20mg od (10mg for panic, increase slowly) 20–60mg od 60mg Least likely to interact with other drugs. Less likely to reduce seizure threshold (caution) Depression, panic disorder (with or without agoraphobia) Escitalopram (Cipralex®) T 5/10/20mg; S 10mg/mL 10mg od (5mg for panic, increase slowly) 5–20mg od 20mg Active enantiomer of citalopram Depression, panic disorder (with or without agoraphobia), social

anxiety Fluoxetine (Prozac®, Oxactin®, Olena®, Prozep®) 24–140 C 20/60mg; S 20mg/5mL 20mg od 20–60mg od 60mg Most alerting. May cause weight loss Depression (with or without anxiety symptoms), OCD, bulimia nervosa, PMDD Fluvoxamine (Faverin®) 13–22 T 50/100mg 50–100mg od 100–300mg (if <150mg, in divided doses) 300mg Moderately sedating Depression, OCD Paroxetine (Seroxat®) 10–24 T 20/30mg; S 20mg/10mL 20mg od (10mg for panic, increase slowly) 20–50mg od 50mg Most anticholinergic. Withdrawal syndrome may be more frequent. May be sedating Depression (with or without anxiety), OCD, panic disorder (with or without agoraphobia), social phobia, PTSD, GAD Sertraline (Lustral®) 25–36 T 50/100mg 50mg (25mg for PTSD, increase slowly) 50–200mg od 200mg Moderately alerting. Fewer drug interactions, but caution still necessary Depression (with or without anxiety), OCD, PTSD Key: T = tablets; C = capsules; S = oral suspension/solution.

288 Chapter 6 Depressive illness Other antidepressants 1 Serotonin/noradrenaline reuptake inhibitors • Mode of action: 5-HT and NA reuptake inhibition. • Common adverse effects: nausea, GI upset, constipation, loss of appetite, dry mouth, dizziness, agitation, insomnia, sexual dysfunction, headache, nervousness, sweating, weakness. Venlafaxine (Efexor®, Alventa®, Depeflex®, Politid®, Sunveniz®, Tonpular®, Venaxx®, Vencarm®, Venlablue®, Venladex®, Venlalic®, Venlasov®, Vensir®,Venzip®, Viepax®) • Half-life: 1–2hrs; peak plasma concentration 5hrs [10hrs for metabolite: desmethylvenlafaxine (Pristiqs®—licence in the USA for depression, anxiety, and menopausal symptoms, 2008; not licensed in the UK yet)]. • Formulations: 37.5/75mg tablets (MR 75/150mg capsules; 75/150/ 225mg tablets). • Indications: depression, GAD, social anxiety. • Usual dose: depression—37.5mg bd (or 75mg od of MR form), i if necessary after at least 2wks to max 375mg/day. Severe depression— begin at 150mg/day, increasing by 75mg every few days to max dose 375mg/day. GAD and social anxiety—75mg od (i 2-weekly to max 225mg/day). • Advantages: variable pharmacological profile over dose range; possibly more rapid onset of action than other antidepressants; available in controlled-release form, allowing od administration. • Disadvantages: moderate to high doses less well tolerated; need to monitor BP at doses over 200mg; troublesome side effects; discontinuation effects common. Duloxetine (Cymbalta®, Yentreve®, Depalta®, Duciltia®) • Half-life: 8–17hrs; peak plasma concentration 6hrs. • Formulations: 30/60mg capsules. • Cautions: potential hepatotoxicity (i.e. cases of severe elevations of liver enzymes or liver injury with a hepatocellular, cholestatic, or mixed pattern have been reported); also caution in glaucoma secondary to mydriasis. • Indications: depression, GAD, diabetic neuropathy, stress urinary incontinence. • Usual dose: depression 60mg od; GAD start with 30mg od, increasing, as necessary, to max 120mg/day; diabetic neuropathy 60–120mg/day (divided doses); stress urinary incontinence 20–40mg bd. • Advantages: as for venlafaxine, but no controlled-release form available. May have utility in treating chronic pain and urinary incontinence. • Disadvantages: dose-dependent elevations in BP require monitoring; discontinuation effects common. (Note: little evidence that doses

> “ 60mg/day confer any additional benefit in depression.)

Other antidepressants 1 Tetracyclic antidepressants Mianserin • Mode of action: similar to TCAs, but with fewer anticholinergic side effects. • Half-life: 12–29hrs; peak plasma concentration 1–3hrs. • Formulations: 10/30mg tablets. • Indications: depression, particularly if sedation required. •

Common adverse effects: as for TCAs, but fewer cardiovascular problems, blood dyscrasias more common (especially elderly—FBC recommended 4-weekly for first 3mths of treatment, thereafter 3- to 6- monthly; stop treatment and check FBC if fever, sore throat, stomatitis, or other signs of infection develop), jaundice, arthritis, arthralgia. • Usual dose: 30–40mg (elderly 30mg) daily in divided doses or as a single night-time dose, i gradually as necessary; usual range 30–90mg/day. • Advantages: better side effect profile than some TCAs (e.g. cardiotoxicity), sedating (which may be a desirable effect). • Disadvantages: idiosyncratic adverse effects. Serotonin antagonists/reuptake inhibitors Trazodone (Molipaxin®) • Mode of action: • 5-HT1A/1C/2A antagonism—sedating/anxiolytic, less sexual dysfunction. • 5-HT agonism through the active metabolite (m-chlorophenylpiperazine)— antidepressant effect. • α1 antagonism—orthostatic hypotension. • H1 antagonism—sedation and weight gain. • Common adverse effects: sedation; orthostatic hypotension; otherwise similar to TCAs (but less anticholinergic and cardiotoxic); rarely priapism (discontinue immediately; see E Priapism, p. 1008). • Half-life: 3–7hrs; peak plasma concentration 0.5–2hrs. • Formulations: 50/100mg caps; 150mg tablets; liquid 50mg/5mL. • Indications: depression (especially with insomnia), anxiety disorders. • Usual dose: 150mg/day (as divided dose or just at night), i to 300mg/ day (max dose 600mg/day in divided doses—in hospital). For anxiety, start at 75mg/day—max 300mg/day. • Advantages: sedation (may be used in low doses as an adjunct to other less sedating antidepressants or to counter sexual dysfunction), safer than TCAs in epilepsy. • Disadvantages: higher doses necessary for antidepressant effects may not be tolerated.

290 Chapter 6 Depressive illness Other antidepressants 2 Noradrenergic and specific serotonergic antidepressants Mirtazapine (Zispin SolTab®) • Mode of action: • α2 antagonism—increases 5-HT and NA release (antidepressant). • α1 antagonism—orthostatic hypotension. • M1 antagonism—anticholinergic side effects. • 5-HT2A/C antagonism—sedating/anxiolytic, less sexual dysfunction. • 5-HT3 antagonism—reduced nausea/GI upset. • H1 antagonism—sedation and weight gain. • Common adverse effects: sedation (greater at lower doses), i appetite, weight gain. Less common: transaminase elevation, jaundice, oedema, orthostatic hypotension, tremor, myoclonus, blood dyscrasias (rare agranulocytosis—if a patient develops sore throat, fever, stomatitis, or signs of infection accompanied by neutropenia, discontinue medication and closely monitor the patient). • Half-life: 20–40hrs; peak plasma concentration 1–3hrs. • Formulations: 15/30/45mg tablets/orodispersible tablets; oral solution 15mg/mL. • Indications: depression (with anxiety, agitation, insomnia, weight loss). • Usual dose: 15–30mg nocte, i if necessary to max 45mg/day (divided dose or just at night). • Advantages: low toxicity in OD, less sexual dysfunction and GI upset. • Disadvantages: weight gain, sedating effects may be lost at higher doses (may be used to advantage). Noradrenergic and dopaminergic reuptake inhibitors Bupropion (Zyban®) • Mode of action: NA and DA reuptake inhibition. • Common adverse effects: agitation/insomnia, dry mouth, GI upset (nausea, vomiting, abdominal pain, constipation), hypertension (especially if also using nicotine patches), risk of seizures (0.4%), taste disturbance. • Half-life: 3–16hrs (12–38hrs active metabolite hydroxybupropion); peak plasma concentration 4hrs. • Formulations: 150mg MR. • Indications: depression (with marked psychomotor retardation or hypersomnia; SAD), but only licensed in the UK for treatment of nicotine dependence (and possibly withdrawal from other stimulants); may be useful in adult/child ADHD (unlicensed). • Usual dose: 150mg od; i after 6 days to 150mg bd (max 300mg/day), max single dose 150mg, minimum of 8hrs between doses (maximum duration of treatment for nicotine dependence 7–9 wks). • Advantages: unusual mode of action; alerting effects may be useful for

patients with symptoms of fatigue or hypersomnia; may help treat impulse disorders/addictions when used primarily as an antidepressant. • Disadvantages: possible seizure induction, hypersensitivity reactions (rare but may be severe).

Other antidepressants 2 Noradrenaline reuptake inhibitors Reboxetine (Edronax®) • Mode of action: NA reuptake inhibition. • Common adverse effects: insomnia, sweating, postural hypotension/ dizziness, tachycardia, sexual dysfunction, dysuria, urinary retention, dry mouth, constipation, hypokalaemia if used long term in the elderly. • Half-life: 13hrs; peak plasma concentration 2hrs. • Formulations: 4mg tablets (scored). • Indications: depression (particularly with atypical features). • Usual dose: 4mg bd, i after 3–4wks to 10mg/day in divided doses (max 12mg/day). • Advantages: novel mode of action; alerting effects may be useful for patients with symptoms of fatigue or hypersomnia; may improve social functioning; relatively safe in OD. • Disadvantages: mainly due to adverse effects. Psychedelics (See Box 6.8.) Box 6.8 Psychedelics for mood disorders? Psychedelic drugs, such as LSD and psilocybin, were extensively used in the treatment of mood disorders and other psychiatric conditions before their prohibition in the late 1960s. A recent systematic review of pub lished clinical treatment studies for mood disorders, while highlighting the methodological shortcomings of such other publications, did find clear evidence of clinician-judged improvement after treatment with psyche delics in 79.2% of participants.1 At the very least, there are reasonable grounds for further investigations using more robust methodologies. In one recently completed pilot study in the UK,2 psilocybin was tested with psychological support for treatment-resistant depressive disorder. After a single 25mg dose of psilocybin, depressive symptoms were markedly reduced at 1wk and 3mths, with marked and sustained improvements in anxiety and anhedonia. Another study giving psilocybin to cancer pa tients3 found marked improvements in both clinician- and self-rated meas ures of depressed mood and anxiety, along with increases in quality of life, life meaning, and optimism and decreases in death anxiety that were sus tained at 6-mth follow-up. The degree of mystical-type psilocybin experi ence on the session day correlated with positive therapeutic outcomes. 1 Rucker JJ, Jelen LA, Flynn S, Frowde KD, Young AH (2016) Psychedelics in the treatment of unipolar mood disorders: a systematic review. J Psychopharmacol 30:1220–9. 2 Carhart-Harris RL, Bolstridge M, Day CMJ, et al. (2016) Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study. Lancet Psychiatry 3:619–27. 3 Griffiths RR, Johnson MW, Carducci MA, et al. (2016) Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: a randomized double-blind trial. J Psychopharmacol 30:1181–97.

292 Chapter 6 Depressive illness Other antidepressants 3 Melatonin agonist and specific serotonin antagonists (MaSSAs) Agomelatine (Valdoxan®) • Mode of action: • MT1/MT2 melatonin agonism—may promote sleep; • 5-HT2C antagonism—may increase NA and DA in the frontal cortex. • Common adverse effects: nausea, dizziness, headache, somnolence, insomnia, migraine, diarrhoea, constipation, upper abdominal pain, sweating, back pain, fatigue, anxiety, raised serum transaminases. Less common: paraesthesiae, blurred vision, eczema. Rare: hepatitis, rash, suicidal behaviour. • Half-life: 1–2hrs (no major active metabolites); peak plasma concentration 1–2hrs. • Formulations: 25mg coated tablet. • Indications: depression (with initial insomnia). • Usual dose: 25mg nocte, i if necessary after 2wks to 50mg nocte. • Advantages: unusual mode of action, possibly useful if there is significant sleep–wake disturbance, well tolerated—no known discontinuation symptoms, sexual side effects, weight gain, or cardiac effects. • Disadvantages: need to check liver function before starting and afterwards (recommended: 6, 12, 24wks).

Serotonin modulator and stimulators (SMS) Vortioxetine (Brintellex®) • Mode of action: • Inhibition of serotonin reuptake transporter. • 5-HT1A agonist. • 5-HT3, 5-HT1D, 5-HT7 antagonist. • 5-HT1B partial agonist. • Common adverse effects: nausea, vomiting, constipation, headache, dry mouth. • Half-life: 766hrs (no major active metabolites); peak plasma concentration 7–11hrs. • Formulations: 5mg, 10mg, 20mg tablets. • Indications: depression. • Usual dose: 10mg mane, i if necessary to 20mg mane; maintenance 5–20mg daily. • Advantages: similar efficacy to other antidepressants, well tolerated, reduced risk of weight gain and sexual dysfunction. Possibly cognitive enhancing. • Disadvantages: high rates of nausea. Therapeutic role remains to be established, as just launched in the UK in 2015 (in the USA and European Union in 2013); M https://www.nice.org.uk/guidance/ta367/chapter/1-Guidance [accessed 20 June 2018].

Other antidepressants 3 The future (See Box 6.9.) Box 6.9 Antidepressants of the future While there are a number of SNDRIs ('triple reuptake inhibitors') in development [e.g. tedatioxetine (Lu AA24530) (Lundbeck/Takeda), ansofaxine (LY03005) (Luye America Pharmaceuticals), amitifadine (DOV-21,947 or EB-1010) (Euthymics Bioscience)], there is a lot of an ticipation around a new class of antidepressants—the NMDA receptor modulators (NRMs). Early work with ketamine1 has suggested that these drugs may be neuroprotective, have minimal side effects, and even treat depression within 24hrs of administration. Not surprisingly, many drug companies have an NRM in development [e.g. AV-101 (VistaGen Therapeutics), AVP-786 (Avanir Pharmaceuticals), AZD-6423 (AstraZeneca), CERC-301 (Cerecor), esketamine (intra-nasal ketamine) (Janssen Pharmaceuticals), NRX-1074 and rapastinel (GLYX- 13) (Naurex)]. Other non-monoaminergic drugs in the pipeline include: mifepristone (RU-486) (Corcept Therapeutics) for psychotic depression which acts by modulating activity within the HPA axis of the brain; LY2940094 (Eli Lilly) that acts as nociception (NOC) antagonist; ALKS-5461 (Alkermes) that targets opioid receptors; strada (MSI-195 or ademetionine) (MSI Methylation Sciences) which is a form of the amino acid methionine and acts by modulating cytokines through promoting methylation; and NSI- 189 (NeuralStem) that stimulates neurogenesis within the hippocampus. 1 Malhi GS, Byrow Y, Cassidy F, et al. (2016) Ketamine: stimulating antidepressant treatment? BJPsych Open 2:e5–9.

294 Chapter 6 Depressive illness ECT 1: background Electroconvulsive therapy A highly effective (if controversial) treatment for depression (particularly with psychotic symptoms). May act more rapidly than antidepressant medi cation. Advances in brief anaesthesia and neuromuscular paralysis, intro duction of brief-pulse ECT machines, and use of EEG monitoring have led to improved safety and tolerability. Decline in the use of ECT reflects the in fluence of non-evidence-based factors, rather than being an indicator of its efficacy (see Box 6.10). Over the last 20yrs, there have been active efforts to improve standards of delivery, education, and training. These are set out clearly in recent APA and Royal College of Psychiatrists publications.18,19 ECT clinics in England and Wales, Northern Ireland, and the Republic of Ireland are accredited by Electroconvulsive Therapy Accreditation Service (ECTAS) and in Scotland by Scottish ECT Accreditation Network (SEAN).20 Does ECT actually work? A comprehensive meta-analysis of all ECT studies in depression21 found: • ECT vs all placebo (n = 523): odds ratio (OR) 4.77 [95% confidence interval (CI): 2.39–9.49]. • ECT vs sham ECT (n = 245): OR 2.83 (95% CI: 1.30–6.17). • ECT vs pill placebo (n = 266): OR 11.08 (95% CI 3.10–39.65). • ECT vs antidepressants (n = 892): OR 3.72 (95% CI 2.60–5.32). Mode of action Controversial therapy needs a sound evidence base. Presuming ignorance ('we don't really know how it works, but it does . . . ') ignores real progress in our understanding of ECT. • Rejected theories: psychoanalytical views of ECT

efficacy as due to ‘fear’, ‘regression’, or ‘punishment’; brain injury theory (E Box 6.12, p. 309); amnestic theory—ECT has some effects on cognitive function (E ECT 6: side effects and other specific problems, p. 308), but it is not the primary mode of action. • Anticonvulsant/altered functional activity theory: ECT acts as a powerful anticonvulsant (increases seizure threshold, delta activity, and inhibitory transmitters, e.g. GABA and opioids), causing a reduction in functional activity within, and in connectivity between, specific brain regions related to the therapeutic response (regional cerebral blood flow/ glucose metabolism show reduction in anterior frontal regions post- ictally and for weeks to months after, associated with better outcomes and correlating with raised seizure threshold). 18 American Psychiatric Association (2001) The Practice of Electroconvulsive Therapy: Recommendations For Treatment, Training and Privileging, 2nd edn. Washington, DC: American Psychiatric Association. 19 Royal College of Psychiatrists (2005) The ECT Handbook, 2nd edn. The third report of the Royal College of Psychiatrists’ Special Committee on ECT (Council Report CR128). London: Royal College of Psychiatrists. 20 ECTAS is the Royal College of Psychiatrists’ ECT Accreditation Service, M https://www.rcpsych. ac.uk/improving-care/ccqi/quality-networks-accreditation/ectas [accessed 24 January 2019]; SEAN is the Scottish ECT Accreditation Network, M http://www.sean.org.uk/ [accessed 20 June 2018]. 21 Pagnin D, de Queiroz V, Pini S, et al. (2004) Efficacy of ECT in depression: a meta-analytic review. J ECT 20:13–20.

ECT 1: background • Anti-delirium/restorative sleep theory: ECT does lead to EEG changes (e.g. i delta activity with greater amplitude and reduced frequency) similar to those seen in normal sleep and correlated with clinical improvement. Whether this is a therapeutic action or an (albeit important) epiphenomenon is not certain. • Neurochemical theories: despite the fact that neurochemical explanations have been advocated for explaining how ECT works, supporting evidence comes from pre-clinical and animal work. Preliminary human studies support a role for DA and GABA/glutamate. • Neuroendocrine theory: it is proposed that ECT works by correcting a dysregulation of neuropeptides through diencephalic stimulation. Studies have found ECT enhances the production and release of several neuropeptides (e.g. TRH, prolactin, corticotropin, cortisol, oxytocin, vasopressin, β-endorphin, and, less consistently, GH). However, these changes could be non-specific effects of stress/seizure, and not necessarily the therapeutic effect of ECT. • Other (speculative): neurogenesis—the animal model of ECT has been shown to promote neurogenesis in non-human primates; gene transcription—the likelihood of remission with ECT in patients with treatment-resistant depression has been associated with two polymorphisms related to DA metabolism in the prefrontal cortex; brain-derived neurotrophic factor (BDNF)—preliminary evidence suggests serum BDNF concentrations increase after ECT. Box 6.10 ECT: an historical perspective The use of convulsive treatments for psychiatric disorders originated with the clinical observation of apparent antagonism between schizophrenia (then dementia praecox) and epilepsy. Patients who had a seizure were relieved of their psychotic symptoms, and Meduna noted i glial cells in the brains of patients with epilepsy, compared with reduced numbers in those with schizophrenia. In 1934, he induced a seizure with an injec tion of camphor-in-oil in a patient with catatonic schizophrenia and con tinued this treatment every 3 days. After the fifth seizure, the patient was able to talk spontaneously and began to eat and care for himself for the first time in 4yrs, making a full recovery with three further treatments. Chemically induced convulsive treatments using camphor or metrazol (pentylenetetrazol) became accepted for the treatment of schizophrenia but had problems. Cerletti and Bini introduced the use of ‘electric shock’ to induce seizures in 1938, a method that became the standard. Initially, ECT was unmodified (i.e. without

anaesthetic or muscle relaxant), but because of frequent injury, curare was first used as a muscle relaxant in the 1940s, followed by succinylcholine in the 1950s. Advances in brief anaesthesia mean the current procedure is much safer and recovery more rapid. Indications have also changed, with the majority of patients receiving ECT for severe depressive illness, although it is also effective in other conditions (E ECT 2: indications, contraindication, and consider ations, p. 296). Further reading: Shorter E, Healy D (2007) Shock Therapy: A History of Electroconvulsive Treatment in Mental Illness. Piscataway Township: Rutgers University Press.

296 Chapter 6 Depressive illness ECT 2: indications, contraindications, and considerations Indications (See Box 6.11.) • Depressive episode: severe episodes, need for rapid antidepressant response (e.g. due to failure to eat or drink in depressive stupor; high suicide risk), failure of drug treatments, inability to tolerate side effects of drug treatment (e.g. puerperal depressive disorder, E Disorders related to childbirth, p. 494), previous history of good response to ECT, patient preference. • Other indications: treatment-resistant psychosis and mania (50–60% effective), schizoaffective disorder (E Disorders related to schizophrenia, p. 228), catatonia (E The catatonic patient, p. 1054), neuroleptic malignant syndrome (NMS) (E Neuroleptic malignant syndrome, p. 1018), neurological crises (e.g. extreme Parkinsonian symptoms: on–off phenomena), intractable seizure disorders (acts to raise seizure threshold). Contraindications There are no absolute contraindications. Where possible, use of ECT should be limited for patients with cerebral aneurysm, recent MI, car diac arrhythmias, intracerebral haemorrhage, acute/impending retinal detachment, phaeochromocytoma, high anaesthetic risk, and unstable vascular aneurysm/malformation (E ECT 5: further notes on treat ment, p. 304). Box 6.11 NICE Technology Appraisal 59 for ECT Guidance on the use of electroconvulsive therapy (May 2003) ECT is used only to achieve rapid and short-term improvement of se vere symptoms after an adequate trial of other treatment options has proven ineffective and/or when the condition is considered to be life-threatening in individuals with severe depressive illness, catatonia, or pro longed or severe manic episode . . . The current state of the evidence did not allow general use of ECT in the management of schizophrenia to be recommended . . . ECT is not recommended as a maintenance therapy in depressive illness because the longer-term benefits and risks of ECT have not been clearly established . . . The decision as to whether ECT is clinic ally indicated should be based on a documented assessment of the risks and potential benefits to the individual, including: risks associated with the anaesthetic, contemporaneous comorbidities, anticipated adverse events, particularly cognitive impairment, and risks of not having the treatment. Source: data from M https://www.nice.org.uk/Guidance/ta59 [accessed 20 June 2018].

297 INDICATIONS, CONTRAINDICATIONS, AND CONSIDERATIONS Other considerations • Time-limited action: benefit from ECT tends to dissipate after a couple of weeks. There is a need for a clear maintenance plan to be in place before the course of ECT finishes. ECT should not be considered the only treatment—except in very rare cases when continution/ maintenance treatment is indicated (E ECT 5: further notes on treatment, p. 304). • Consent (E Capacity and consent, p. 856): guidelines on ECT vary between legislatures concerning the use of capacity legislation/Mental Health Act (MHA). Decisions rest on assessment of capacity, informal/ formal status, active (or advance statement) refusal, and the potential as a lifesaving intervention. • Side effects: ECT does cause potential side effects (E ECT 6: side effects and other specific problems, p. 308), and administration of ECT will always be a balance of risk and benefit. Of particular note is the potential to cause cognitive problems (E ECT 6: side effects and other specific problems,

p. 308), and this may dictate electrode positioning (see Fig. 6.2). (See Table 6.7 for the effects of psychiatric drugs on ECT.)

298 Chapter 6 Depressive illness immediately before ECT (rule of thumb at addition of antidepressant towards end of Do not suddenly stop—safely reduce to minimum dose. Prophylaxis may require Lowest dose possible. Do not give least 3hrs pre-ECT for last dose) methods) Not contraindicated during ECT ECT course (inform ECT team) Drug class Notes Considerations Recommendations methods). Problems reported more for hypnotics. Do not suddenly stop if well ECT. Make seizures less likely Avoid, if possible. Consider non-BDZ Use low initial stimulus (dose titration Use low initial stimulus (dose titration established SSRIs Lithium Reduces seizure threshold. May prolong ECT. Reported prolongation of seizures Benzodiazepines May reduce antidepressant efficacy of Antidepressants May augment antidepressant effect of seizures. May increase post-ictal confusion (case reports only) Table 6.7 Psychiatric drugs and ECT and tardive seizures stop. If a mood stabilizer, continue initially and only reduce if seizure induction is problematic If prescribed for epilepsy, continue—do not methods) Clozapine should be withheld 12hrs before any anaesthetic and restarted once fully recovered Anticonvulsants Raise seizure threshold Clarify if drug is for treatment of epilepsy or as a mood stabilizer. Higher doses of Use low initial stimulus (dose titration ECT may be necessary Note: ensure the anaesthetist is fully informed of all medications the patient is currently taking. Concerns about clozapine (case reports of prolonged and tardive seizures) may Antipsychotics All tend to reduce seizure threshold. be overstated

299 INDICATIONS, CONTRAINDICATIONS, AND CONSIDERATIONS

300 Chapter 6 Depressive illness ECT 3: work-up and administration ECT work-up • Ensure full medical history and current medication are noted on the ECT recording sheet. • Also note any relevant findings from the physical examination. • Ensure recent routine blood results are available (FBC, U&Es, any other relevant investigations). • If indicated, arrange a pre-ECT CXR and/or ECG. • Ensure ECT is prescribed correctly. • Inform the anaesthetic team of the proposed ECT. • Inform the ECT service of the proposed ECT. • Ensure the patient is aware of the usual procedure and when treatment is scheduled. • Ensure the consent form has been signed. Pre-ECT checks • Check the patient's identity. • Check the patient is fasted (for 8hrs) and has emptied their bowels and bladder prior to coming to the treatment room. • Check the patient is not wearing restrictive clothing and jewellery/ dentures have been removed. • Consult the ECT record of previous treatments (including anaesthetic problems). • Ensure the consent form is signed appropriately. • Check no medication that might increase or reduce the seizure threshold has been recently given. • Check the ECT machine is functioning correctly. • Ensure dose settings are correct for the specific patient. Administration of anaesthetic • Establish IV access. • Attach monitoring (pulse oximetry, BP, EEG, EMG). • Ventilate the patient with pure O2 via a face mask. • Give a short-acting anaesthetic, followed by a muscle relaxant. • Hyperventilation with O2 is sometimes used to augment seizure activity. • Insert a bite-block between the patient's teeth to protect the tongue and teeth from jaw clenching (due to direct stimulation of masseter muscles). Administration of ECT • Apply electrodes to the scalp (see Fig. 6.2 for positioning). • Test for adequate contact between the electrodes and the scalp prior to treatment ('self-test' function on the ECT machine). • Administer the dose. • Monitor the length of seizure (E ECT 4: notes on treatment, p. 302). • Record the dose, seizure duration, and any problems on the ECT record (and ensure the anaesthetic administration is also

recorded). • Transfer the patient to recovery. Recovery • Ensure that there is an adequate airway. • Monitor the patient's pulse and BP until stable.

ECT 3: work-up and administration • There should be continuous recovery nurse presence and observation until the patient is fully orientated. • Maintain IV access until able to leave recovery. Bilateral ECT (BECT): one electrode is applied to each side of the head. This positioning is also referred to as bitemporal ECT or bi-frontotemporal ECT. The centre of the electrode on the left (L) and the right (R1) should be 4cm above, and perpendicular to, the midpoint of a line between the lateral angle of the eye and the external auditory meatus. Unilateral ECT (UECT): the electrodes are applied to the same 'non- dominant' hemisphere (which is usually the right-hand side). The first elec trode (R1) is in the same position as before, but the second electrode (R2) is applied over the parietal surface of the scalp. The exact position on the parietal arc is not crucial; the aims are to maximize the distance between the electrodes to reduce shunting of electrical current and to choose a site on the arc where the electrode can be applied firmly and flat against the scalp. The position illus trated in Fig. 6.2 is also known as the 'temporo-parietal' or 'd'Elia' positioning. Bilateral or unilateral electrode placement? Local ECT policy may vary, but the usual reasons for using unilateral/bilat eral electrode placement are:22 • BECT: speed of response is a priority, previous failure of UECT, previous good response without significant memory problems to BECT. • UECT: speed of response less important, previous good response to UECT, minimizing memory problems is a priority, e.g. cognitive impairment already present. Electrodes positioned on the same point on both sides Bilateral or bitemporal placement Unilateral placement 4cm Non-dominant hemisphere Midpoint Fig. 6.2 ECT: electrode placement. 22 Kellner CH, Knapp R, Husain MM, et al. (2010) Bifrontal, bitemperal and right unilateral electrode placement in ECT: randomised trial. Br J Psychiatry 196:226–34.

302 Chapter 6 Depressive illness ECT 4: notes on treatment 2 Ensure you have had adequate training and supervision before independ ently administering ECT.23 Energy dosing Because the higher the stimulus used, the greater the likelihood of transient cognitive disturbance, and because once the current is above the seizure threshold, further increases only contribute to post-ECT confusion, there are a number of dosing strategies used. Local policy and the type of ECT ma chine used will dictate which method is preferred. For example: • Dose titration: the most accurate method, delivering the minimum stimulus necessary to produce an adequate seizure, and therefore to be preferred. Treatment begins with a low stimulus, with the dose i gradually until an adequate seizure is induced. Once the approximate seizure threshold is known, the next treatment dose is i to about 50–100% (for BECT) or 100–200% (for UECT—some protocols 500–800%) above the threshold. The dose is only i further if later treatments are sub-therapeutic, and the amount of dose increase will be governed by local policy. • Age dosing: selection of a predetermined dose calculated on the basis of the patient's age (and the ECT machine used). The main advantage is that this is a less complex regime. However, there is the possibility of 'overdosing' (i.e. inducing excessive cognitive side effects) because the seizure threshold is not determined. As ECT itself raises the seizure threshold, the dose is likely to rise by an average of 80% over the length of a treatment course. Higher (or lower) doses will also be needed when the patient is taking drugs that raise (or lower) the seizure threshold (see Table 6.7). Effective treatment When a sub-therapeutic treatment is judged to have occurred, the treat ment is repeated at different energy settings (E Energy dosing, see above). • EEG monitoring: the gold standard, with an ictal EEG having typical phases (see Fig. 6.3). The presence of these features [Royal College of Psychiatrists' ECT Handbook

‘new’ (2005/13) criteria), no matter how short the seizure activity, is deemed to constitute a therapeutic treatment. Usually the ictal EEG activity lasts 25–130s (motor seizure 720% less). • Timing of convulsion: where EEG monitoring is not used, the less reliable measure of length of observable motor seizure is used, with an effective treatment defined as a motor seizure lasting at least 15s from the end of the ECT dose to the end of observable motor activity [Royal College of Psychiatrists’ ECT Handbook ‘old’ (1995) criteria]. • Cuff technique: often an under-used technique, involving the isolation of a forearm or leg from the effects of muscle relaxant, by inflation of a BP cuff to above the systolic pressure. As the isolated limb does not become paralysed, the motor seizure can be more easily observed. 23 Royal College of Psychiatrists (2017) ECT competencies 2017. M https://www.rcpsych.ac.uk/ docs/default-source/improving-care/ccqi/quality-networks/electro-convulsive-therapy-clinics- (ectas)/ect-competencies-for-psychiatrists-sep17.pdf?sfvrsn=f62e329_4 [accessed 24 January 2019].

ECT 4: notes on treatment 303

304 Chapter 6 Depressive illness ECT 5: further notes on treatment Other physiological effects of ECT • Musculoskeletal—direct stimulation: tonic contraction—opisthotonus, supraphysiological bite (not blocked by relaxants; may cause dental injury; bite-block essential); generalized (tonic–clonic) seizure—risk of fractures (vertebral, long bone, avulsion). • Cardiovascular (E ECT 2: indications, contraindications, and considerations, p. 296): cerebrovascular—i metabolic requirements due to seizure (i cerebral blood flow; i cerebral blood volume; raised ICP); autonomic effects—i vagal tone (bradycardia, risk of asystole/ AF, salivation); adrenaline release—peaks during seizure, resolves over 10–20mins (tachycardia, hypertension—post-ECT monitoring essential). • Neuroendocrine (E ECT 1: background, p. 294): increase in adrenocorticotrophic hormone (ACTH), cortisol, and glucagon may lead to insulin resistance (closely monitor diabetic patients). • Other: i intra-gastric pressure—possible risk of aspiration (appropriate pre-ECT fasting/pre-med); raised intraocular pressure (risk in narrow-angle glaucoma, recent ophthalmic surgery). A course of ECT • Rarely will a single treatment be effective to relieve the underlying disorder (but this does occasionally occur). • ECT is usually given twice a week, sometimes reducing to once a week once symptoms begin to respond. This limits cognitive problems, and there is no evidence that treatments of greater frequency enhance treatment response. • Treatment of depression usually consists of 6–12 treatments; treatment-resistant psychosis and mania of up to (or sometimes more than) 20 treatments; and catatonia usually resolves in 3–5 treatments. Continuation or maintenance ECT Continuation ECT (C-ECT): the provision of additional treatments during the 6-mth period after remission for the primary purpose of preventing relapse. Maintenance ECT (M-ECT): prophylactic use of ECT for periods longer than 6mths past the index episode for the purposes of mitigating recurrence.24 • Although not recommended in NICE guidelines in 2003 (see Box 6.11), the most recent update of NICE depression guidelines (October 2009) is neutral on the issue. • The Royal College of Psychiatrists’ ECT Handbook (2013) suggests that C-ECT ‘should be considered for patients with a relapsing or refractory depression that has previously responded well to ECT, but for whom standard pharmacological and psychological continuation treatment is ineffective or inappropriate’. 24 Trevino BA, McClintock SM, Husain MM (2010) A review of continuation electroconvulsive therapy: application, safety, and efficacy. J ECT 26:186–95.

(a) (b) ECT 5: further notes on treatment convulsion); 4. classic 3Hz ‘spike and wave’ (delta) activity; 5. gradual loss of 3Hz pattern; 6. endpoint with lower amplitude and frequency than baseline subthreshold ‘non-therapeutic’ stimulation. In example (A), typical features are seen: 1. end of electrical stimulation; 2. latent phase—low-voltage polyspike activity (no visible convulsion); 3. increasing amplitude of polyspike activity and slowing of frequency (associated with clonic phase of Fig 6.3 EEG monitoring of ECT. ‘Real world’ examples of EEG traces for: (A) a short ‘therapeutic’ seizure (20s visual and 22s EEG) and (B) a (‘post-ictal suppression’).

306 Chapter 6 Depressive illness • APA (2001) ECT guidelines identify a similar patient group but additionally require: (1) the patient is able to provide informed consent; (2) evidence that the patient’s cognitive function and physical condition do not preclude the ongoing administration of ECT; and (3) the patient’s attitude, circumstances, and level of social support are conducive to ensuring treatment compliance and safety after treatment. • There is no specific or universally supported treatment schedule for C-ECT; however, after completing a course of conventional bi-weekly ECT, a common strategy is: weekly for 1mth; fortnightly for 1mth; and monthly for up to 6mths after remission. • Only in exceptional circumstances should M-ECT (i.e. >6mths after remission) be considered as a treatment option, in close consultation with the patient and with a formal review by another consultant, preferably with specific ECT experience. • Usually patients are aware of how effective ECT has been for them, and a collaborative approach can be established (balancing the frequency of ECT against the return of symptoms and side effects, especially memory problems). Outpatient ECT ECT should be given to outpatients in exceptional circumstances only if: • Mild to moderate illness, as defined by a psychiatrist (e.g. CGI 2–4). • Availability of 24hr supervision to ensure safety and observation. • The patient should not have active thoughts of suicide. • Regular (weekly) assessment by the consultant (or deputy). ECT in pregnancy • ECT may be the preferred treatment choice due to its rapid action. • ECT in the second or third trimester may present more technical difficulties for the anaesthetist, as the risk of aspiration of stomach contents increases. • The patient’s obstetrician and the anaesthetist should be involved before a decision is taken to proceed to treatment. • Preparation for ECT should be as per routine, with the addition of any instructions from the anaesthetist, e.g. administration of antacids on the morning of treatment. • Any concerns should be reported urgently to the obstetrician. ECT in children and adolescents An exceptionally rare circumstance—hence, special provisions apply: • The Royal College of Psychiatrists recommends that for those under 16yrs, two further opinions are sought, in addition to the treating consultant—one from a child and adolescent psychiatrist and one from another psychiatrist from a different clinical unit. • Adolescents aged 16–18yrs are able to consent and refuse treatment in the same way as an adult, but parental approval is advised. In Scotland, those under 16yrs can consent if they understand the process, but again parental approval is advised. • For compulsory treatment, it should be noted that provisions of legislation governing ECT have no lower age limit.

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308 Chapter 6 Depressive illness ECT 6: side effects and other specific problems Side effects • Early: some loss of short-term memory (STM) (E ECT and memory loss, see below), retrograde amnesia—usually resolves completely (64%), headache (48%—if recurrent, use simple analgesia), temporary confusion (10–27%), nausea/vomiting (9%), clumsiness (5%), muscular aches. • Late: loss of long-term memory (rare; E ECT and memory loss, see below). • Mortality: no greater than

for general anaesthesia in minor surgery (2:100,000)—usually due to cardiac complications in patients with known cardiac disease (hence the need for close monitoring). Specific problems • Persistent ineffective seizures: check the use of drugs that may raise the seizure threshold; consider use of IV caffeine or theophylline. • Prolonged seizures (i.e. over 150–180s): administer IV Diazemuls® (5mg), repeated every 30s until seizure stops (alternative: midazolam). Lower energy dosing for next treatment. • Post-seizure confusion: reassurance; nurse in a calm environment; ensure safety of patient; if necessary, consider sedation (e.g. Diazemuls®/ midazolam). If a recurrent problem, use a low dose of a BDZ prophylactically during recovery, immediately after ECT. ECT and memory loss • Research has focused on retrograde amnesia because of (highly publicized) claims that ECT causes more enduring deficits in past memories (especially autobiographical) than new memories. • These studies show that the period closest to receiving ECT is least well remembered and can be permanently lost. • Recent systematic reviews of evidence for loss of past memories25 highlight the difficulties in interpreting the literature, e.g. unknown sensitivity of autobiographical memory measures, need for premorbid measures of cognitive status. Nevertheless, they find: • Autobiographical memory loss does occur. • It is related to how ECT is administered. • Specific recommendations to minimize memory loss include: use of right UECT; brief pulse, rather than sine wave, ECT; dose titration; and limited number and frequency of ECT sessions. Does ECT damage the brain? • Psychiatrists—such as Peter Breggin, author of Toxic Psychiatry (1993) and Brain-Disabling Treatments in Psychiatry (2007)—have been very vocal opponents of ECT, believing official reports have deliberately ignored evidence of negative effects. 25 Fraser LM, O'Carroll RE, Ebmeier KP (2008) The effect of electroconvulsive therapy on autobio graphical memory: a systematic review. J ECT 24:10–17.

ECT 6: side effects and other specific problems • Even proponents of ECT in early writings suggested they believed that a degree of cerebral damage (akin to a concussion) was necessary for ECT to work—the rejected brain injury theory. • Strong evidence against ECT causing damage comes from a primate study comparing ECT, magneto-convulsive therapy (MCT), or anaesthesia alone, which reports no histological lesions after 6wks of daily treatment.26 • There are few post-mortem reports, but one study found no histopathological evidence of brain injury in the brain of a 92-yr-old lady with major depression who had received 91 sessions of ECT during the last 22yrs of her life.27 • Most mental health associations and colleges, including the APA and the Royal College of Psychiatrists, have concluded there is no evidence that ECT causes structural brain damage (see Box 6.12). Box 6.12 Structural brain damage from ECT Devanand, Dwork, Hutchinson, et al. (1994)1 stated that, 'prospective CT and MRI studies show no evidence of ECT-induced structural changes', commenting that early autopsy case reports from the unmodified ECT period had cerebrovascular lesions due to undiagnosed disease or agonal changes. Furthermore, animal studies using human-comparable inten sity and frequency of stimulus showed no neuronal loss, even after long courses of ECT, when appropriate controls were in place. 'It is more dangerous to drive to the hospital than to have the treatment. The unfair stigma against ECT is denying a remarkably effective medical treatment to patients who need it.' 1 Devanand DP, Dwork AJ, Hutchinson ER, et al. (1994) Does ECT alter brain structure? Am J Psychiatry 151:957–70. Charles Kellner, Professor of Psychiatry, Mount Sinai Hospital, New York City quoted in USA Today (6 December, 1995) while editor of Convulsive Therapy (now Journal of ECT). 26 Dwork AJ, Arango V, Underwood M, et al. (2004) Absence of histological lesions in primate models of ECT and magnetic seizure therapy. Am J Psychiatry 161:576–8. 27 Scalia J, Lisanby SH, Dwork AJ, et al. (2007) Neuropathological examination after 91 ECT treat ments in a 92-year-old woman with late-onset

depression. J ECT 23:96–8.

310 Chapter 6 Depressive illness Neurosurgery for mental disorders Despite the controversial nature of irreversible neurosurgery for mental disorders (NMD), it is surprising that patients—rather than psychiatrists— often raise the issue, particularly when they retain insight into the chronic, intractable nature of their illness.28 Neurosurgery is only performed in ex ceptional cases (see Box 6.13) when all other treatments have failed, and its use is governed by specific mental health legislation. It is still possible, how ever, to encounter patients who have had surgical procedures performed in the past, and this may complicate the diagnosis of current problems (e.g. depression, OCD, dementia, especially frontal lobe symptoms) when there is demonstrable damage to key brain structures on CT/MRI. Current criteria for NMD • Severe mood disorders, OCD, severe anxiety disorders. • The patient must want the operation. • All other reasonable treatments have repeatedly failed (i.e. pharmacological, ECT, psychological). • The patient remains ill but has capacity to provide informed consent.29 Current surgical techniques These employ stereotactic methods using preoperative MRI to establish target coordinates and a fixed stereotactic frame (or new ‘frameless’ stereo tactic instruments utilizing infrared positioning). Lesioning may be effected by implantation of yttrium rods or radiofrequency lesioning. Lesions are localized to the orbitofrontal and anterior cingulate loop (the ‘limbic’ loop), which is strongly implicated in the regulation of emotion and mood,,30 e.g.: • Stereotactic subcaudate tractotomy (SST). • Anterior cingulotomy (ACING). • Stereotactic limbic leucotomy (SLL) (combining subcaudate tractotomy and ACING). • Anterior capsulotomy (ACAPS). Adverse effects Older techniques were associated with severe amotivational syndromes (up to 24%), marked personality change (up to 60%), and epilepsy (up to 15%). Stereotactic techniques report minimal post-operative problems with confusion (3–10%), incontinence (1–9%), apathy, weight gain, and seizures (dependent on the type of surgery). More significant personality change and impaired social or cognitive functioning are infrequent, and there is more likely to be improvement. 28 Christmas D, Morrison C, Eljamel MS, Matthews K (2004) Neurosurgery for mental disorder. Adv Psychiatr Treat 10:189–99. 29 For current criteria in the UK, see Dundee Advanced Interventions Service website at M http://www.advancedinterventions.org.uk/index.php/the-service/referral-information/professionals.html [accessed 20 June 2018]. 30 Alexander GE, Crutcher MD, DeLong MR (1990) Basal ganglia-thalamocortical circuits: parallel substrates for motor, oculomotor, ‘prefrontal’ and ‘limbic’ functions. Progr Brain Res 85:119–46.

Neurosurgery for mental disorders Outcome Given the treatment-resistant nature of the patients receiving surgery, reports of good outcome are surprisingly high (e.g. depression 34–68%; OCD 27–67%), although results should be interpreted cautiously in view of the obvious lack of any control data. ACAPS and SLL appear better for OCD, and ACING and SST better for severe mood disorder. Box 6.13 Psychosurgery—a historical perspective In 1935, Egas Moniz and Almeida Lima carried out the first ‘prefrontal leucotomy’ (based on the work of Fulton and Jacobsen in bilateral ab lation of prefrontal cortices in chimpanzees in 1934). At the time, this was viewed with great enthusiasm (culminating in Moniz being awarded a Nobel Prize for his work in 1949), and other practitioners adapted the early procedures, with Freeman and Watts introducing the standard ‘prefrontal leucotomy’ (the notorious lobotomy) in 1936, publishing a standard textbook Psychosurgery in 1942, and Freeman pioneering ‘trans orbital leucotomy’ in 1946. The impact of surgical treatment at a time when there were few other physical treatments should not be underestimated, and around 12,000 procedures were performed between 1936 and 1961 in the UK

alone (over 40,000 in the USA). Techniques were refined (e.g. open cingulotomy, bimedial leucotomy, orbital undercut) from earlier blind, free-hand procedures. However, the advent of effective psychophar macological treatments and changes in the social climate led to a marked decline in practice from the 1960s onwards. Nowadays, the term ‘psychosurgery’ has been abandoned and re placed with the more accurate ‘neurosurgery for mental disorder’. Modern techniques could not be further removed from older procedures and utilize neuroimaging and neurosurgical techniques to lesion clearly defined neuroanatomical targets (E Current surgical techniques, see op posite). Between 1984 and 1994, there were a total of only 20 operations per year performed in the UK,1 and since then, the number has dimin ished further. Available data for England and Wales report four proced ures in 2015/2016 and only one in 2016/2017.2 In Scotland, the Dundee Advanced Interventions Service similarly reported just four procedures for 2015/2016 and none in 2016/2017.3 1 CRAG Working Group (1996) Neurosurgery for Mental Disorder. Scotland: HMSO (J2318 7/ 96). 2 Care Quality Commission (2019) Monitoring the Mental Health Act in 2016/17 report. M
https://www.cqc.org.uk/sites/default/files/20190108_mhareport2017_amend_1.pdf [accessed 24 January 2019]. 3 Advanced Interventions Service (2018) AIS annual report 2018. M http://www.advancedinterventions.org.uk/index.php/most-recent-reports.html [accessed 20 June 2018].

312 Chapter 6 Depressive illness Other physical treatments Bright light therapy (phototherapy) First introduced for the treatment of SAD (a proposed new syndrome at the time) by Rosenthal,31 on the basis that bright light therapy might ameli orate symptoms of winter depression, due to effects on circadian and sea sonal rhythms mediated by melatonin. Recent research has suggested that the effects of phototherapy may be independent of melatonin and produce a ‘phase advance’ in circadian rhythms (hence, treatment may be best given first thing in the morning). It is usually administered by use of a light box (alternatives include light visors) producing 2500–10,000lx. Treatment dur ation is for 2hrs (with 2500lx) or 30min (with 10,000lx) a day, with a course lasting 1–3wks (treatment response is usually noticeable within 5 days). If no response within 3wks, discontinue. When effective, continue until time of natural remission to prevent relapse (usually 2–5wks). Dawn-stimulating alarm clocks that gradually illuminate the bedroom over 2hrs to around 250lx at the point of waking may also be effective. Adverse effects Particularly with 10,000lx: headache, visual problems (e.g. eye strain, blurred vision)—usually settle; if persistent, reduce the duration or intensity of exposure; i irritability; rarely: manic episodes, i thoughts of suicide (possibly due to alerting effect and i energy). Indications SAD (E Seasonal affective disorder, p. 273), circadian rhythm disorders (E Circadian rhythm sleep–wake disorders (CRSD) 1: overview, p. 454), possibly other depressive disorders and dysthymia. Contraindications Agitation, insomnia, history of hypomania/mania. Repetitive transcranial magnetic stimulation Currently being researched. However, the difference in stimulation param eters used across reported studies makes comparisons difficult. The ra tionale for treatment is either to increase activity in the left dorsolateral prefrontal cortex (using high-frequency stimulation, e.g. 20Hz) or to re duce activity in the right dorsolateral prefrontal cortex (using lowfrequency stimulation, e.g. 1Hz). Initial results in treatment-resistant depression ought to be viewed with caution (see Cochrane review),32 although this mode of therapy presents an attractive alternative to ECT, without the accompanying risks and adverse effects. The 2015 NICE recommendations found the evi dence of efficacy for repetitive transcranial magnetic stimulation (rTMS) to be adequate in the short term and encouraged further research.33 Adverse effects Minimal, but patients often report headache or facial dis comfort; rarely, seizure induction. Indications Experimental treatment for

treatment-resistant depression; possible use in treatment of treatment-resistant auditory hallucinations; negative symptoms of schizophrenia; OCD; panic disorder. Contraindications History of stroke, brain tumour, or epilepsy. 31 Rosenthal NE, Sack DA, Gillin JC, et al. (1984) Seasonal affective disorder. A description of the syndrome and preliminary findings with light therapy. Arch Gen Psychiatry 41:72–80. 32 Rodriguez-Martin JL, Barbanoj JM, Schlaepfer T, et al. (2002) Transcranial magnetic stimulation for treating depression. Cochrane Database System Rev 2:CD00393. 33 National Institute for Health and Care Excellence (2015) Repetitive transcranial magnetic stimula tion for depression. Interventional procedure guidance [IPG542]. M https://www.nice.org.uk/guid ance/ipg542/chapter/1-Recommendations [accessed 20 June 2018].

Other physical treatments Magneto-convulsive therapy Another experimental treatment that utilizes the potential problem of seizure induction by rTMS. A varying magnetic field is used to induce seiz ures in a more controlled way than is possible with ECT. The potential advantages include targeting of brain structures essential for treatment re sponse and a reduction in side effects (particularly memory impairment).34 Vagus nerve stimulation (VNS) Vagus stimulation by an implanted pacemaker (first used as a treatment for epilepsy) has been tested as a treatment of depression since 1998. Stimulation is of the left cervical vagus nerve using bipolar electrodes, at tached below the cardiac branch (usually 0.5ms pulse-width, at 20–30Hz, with 30s stimulation periods alternating with 5min breaks). Response rates of 31–40% (short-term)35 and 27–58% (long-term) have been quoted for treatment-resistant depressive disorder, but the quality of this evidence is low and further research is required. NICE recommends special arrange ments for clinical governance, consent, and audit or research.36 Adverse effects May include voice alteration (e.g. hoarseness), pain, coughing, and dysphagia. Deep brain stimulation (DBS) Best regarded as an experimental treatment for OCD and depression. Has been used in the treatment of neurological disorders, including: Parkinson’s disease, tremor, dystonia, refractory pain syndromes, and epilepsy. Involves implantation of bilateral electrodes under stereotactic guidance and MRI confirmation. Targets for DBS in OCD include the anterior limb of the in ternal capsule (like ACAPS NMD) and, for depression, the subgenual cin gulate gyrus (like ACING NMD). Initial reports of long-term outcomes are promising.37 Adverse effects Reported problems include throbbing/buzzing sensations, nausea, jaw tingling, and unexpected battery failure resulting in rebound depression with marked suicidal ideation. 34 Alice Engel A, Kayser S (2016) An overview on clinical aspects in magnetic seizure therapy. J Neural Transm 123:1139–46. 35 George MS, Sackeim HA, Rush AJ, et al. (2000) Vagus nerve stimulation: a new tool for brain research and therapy. Biol Psychiatry 47:287–95. 36 National Institute for Health and Care Excellence (2009) Vagal nerve stimulation for treatment- resistant depression. Interventional procedures guidance [IPG330]. M https://www.nice.org.uk/guid ance/ipg330 [accessed 20 June 2018]. 37 Naesström M, Blomstedt P, Bodlund O (2016) A systematic review of psychiatric indications for deep brain stimulation, with focus on major depressive and obsessive-compulsive disorder. Nord J Psychiatry 70:483–91.