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180 Chapter 5 Schizophrenia and related psychoses Introduction Schizophrenia and the related psychotic illnesses belong to a group of dis orders traditionally called the ‘functional psychoses’. ‘Functional’ in this con text means a disorder of brain function with no corresponding structural abnormality. Despite improvements in our understanding of the pathology of these disorders, their aetiology is currently unknown and there is no de finitive diagnostic test available. For this reason, diagnosis is made clinically, using operationally defined criteria (characteristic symptoms and signs) and specific exclusion criteria (e.g. absence of primary organic disorder). The cardinal feature of schizophrenia and related psychotic illnesses is the presence of psychotic symptoms—hallucinations and/or delusions. These symptoms are qualitatively different from normal experiences, ra ther than the quantitatively abnormal responses of neurotic and affective disorders, and because of this, they are regarded—by patients and other health professionals—as more serious and needing immediate psychiatric attention. However, when an individual experiences hallucinations or be comes paranoid that people are talking about them, for example, it does not mean they necessarily have a severe and enduring mental disorder. They could be experiencing a reaction to drugs (prescribed or recreational), be experiencing severe anxiety, be

acutely confused, or have early signs of dementia. The differential diagnosis encompasses almost all psychiatric diag noses (E Differential diagnosis of schizophrenia, p. 186) as well as some ‘normal experiences’. Careful history-taking and appropriate investigations (E Investigations, p. 193) are essential. Of the psychoses, schizophrenia has received the greatest attention in terms of research. This is almost certainly because of the dramatic and devastating effects the disorder can have on an individual’s quality of life and their prospects for employment, marriage, and parenthood. Schizophrenia affects about 1 in 100 individuals, usually beginning in late adolescence or early adulthood. Untreated, it runs a chronic, deteriorating course. In addition to the personal tragedy, schizophrenia creates a substantial public health burden due to the cost of lifelong healthcare needs and lost productivity. The symptoms of schizophrenia are conventionally divided into positive symptoms (an excess or a distortion of normal functioning) and negative symptoms (a decrease or loss of functioning): • Positive symptoms Delusions (commonly persecutory, thought interference, or passivity delusions). Hallucinations (usually auditory hallucinations commenting on the subject or referring to them in the third person, e.g. ‘he looks like a fool’). Formal thought disorder (loss of the normal flow of thinking usually shown in the subject’s speech or writing). • Negative symptoms Impairment or loss of volition, motivation, and spontaneous behaviour. Loss of awareness of socially appropriate behaviour and social withdrawal. Flattening of mood, blunting of affect, and anhedonia. Poverty of thought and speech.

Introduction Fortunately, there are effective interventions that can benefit individuals and help them to lead more normal lives. Current research is directed to wards establishing the cause(s) of schizophrenia and investigating the pos sibility of early interventions in those identified at high risk for the disorder or with prodromal symptoms (possible early signs of the disorder). Other psychoses with more specific symptoms, e.g. delusional misidentification syndromes (E Delusional misidentification syndromes, p. 240), may even help us understand how we normally perceive the world and help solve the mystery of the true nature of conscious experience. Why are there so few famous people with schizophrenia? Often there is a history of declining social and educational function which precludes significant achievements (sometimes in spite of early promise). The chronic course of the condition and the major disruptions caused by periods of more severe symptoms also make it less likely that a person with schizophrenia will achieve as much as their peers. Until relatively recently, there have been few specific treatments for the disorder, and even today prognosis is at best guarded. Nonetheless, there are notable exceptions to the rule—people who have battled with the disorder and achieved greatness in their chosen fields: in the arts, Vaslov Fomich Nijinski (1891–1950), the God of the Dance, whose personal account is to be found in his autobiography The Diary of Vaslov Nijinksy (1999); in sport, Lionel Aldridge (1941–1998), a member of Vince Lombardi’s legendary Green Bay Packers of the 1960s, who played in two Super Bowls and, until his death, gave inspirational talks on his battle against paranoid schizophrenia; and, in popular music, Roger (Syd) Barrett (1946–2006) of Pink Floyd and Peter Green (1946–) of Fleetwood Mac. Perhaps the most famous, due to the Academy Award-winning dramatiza tion of his life, is the mathematician John Forbes Nash Jr (1928–2015), who was awarded (jointly with Harsanyi and Selten) the 1994 Nobel Prize in Economic Science for his work on game theory. His life story (upon which the film was based) is recorded by Sylvia Nasar in the book A Beautiful Mind (1998).

 Historical views of schizophrenia In 1856, Morel coined the term Démence Précoce to describe a once bright and active adolescent patient who had gradually become silent and with drawn. Other clinical descriptions included Kahlbaum’s

Katatonie (1868), Griesinger's primare Verrücktheit (1868), Hecker's Hebephrenie (1869), and Sommer's inclusion of deteriorating paranoid syndromes in the concept of dementia (1894). In 1896, Emil Kraepelin described and separated the two major forms of insanity on the basis of different symptoms, course, and outcome. The first, manic-depressive insanity, had a relapsing and remitting course, with full recovery after each episode. The second grouped together catatonia, hebephrenia, and the paranoid psychoses under the term de mentia praecox, which had a progressive, deteriorating course where any improvement was only partial. Over the next two decades (and further revisions of his textbook), Kraepelin's ideas were gradually accepted. Later the influence of Freud's psychoanalytical ideas shifted the focus from Kraepelin's 'disease of the brain' to a 'splitting of the mind' (schizophrenia), as proposed by Eugen Bleuler in his book Dementia Praecox or the Group of Schizophrenias (1911). He believed the disorder to be due to a 'loosening of associations' between psychic functions, with fundamental symptoms being thought disorder, blunting/incongruity of affect, autism, and ambivalence. He added 'simple schizophrenia' to Kraepelin's subtypes and did not consider hallucinations, delusions, and catatonic symptoms to be necessary for the diagnosis. This view of schizophrenia was to have a profound influence on clinical practice, particularly in the USA. European psychiatrists continued to regard schizophrenia as a disease of the brain. Detailed classification systems were developed based on symp tomatology, culminating in the teachings of Kurt Schneider, who described 'symptoms of first rank' in the acute phase of the illness (E Dictionary of psychiatric symptoms, p. 110) and 'second-rank symptoms' which, although highly suggestive of schizophrenia, could also occur in other psychoses (e.g. emotional blunting, perplexity, and other kinds of delusions and hallucinations). The differences in diagnostic practices were highlighted in the 1970s. In 1972, Cooper found identical symptomatology in psychiatric admissions in New York and London, but higher rates of schizophrenia diagnosed in New York. Similarly, in 1973, the WHO's International pilot study of schizo phrenia found the incidence of schizophrenia, using agreed diagnostic cri teria, to be 0.7–1.4 per 10 000 aged 15–54 across all countries studied, but with much higher rates of diagnosis evident in the USA and the USSR. This was explained by broader syndrome definition in the USA with milder ab normalities considered part of the schizophrenia spectrum, and in the USSR due to the political pressure to declare dissidents insane. This led to an international push towards operationally defined criteria (based on symptoms and course), with various systems proposed. The St Louis Criteria (Feighner et al. 1972) require the patient to have been con tinuously ill for 6mths, with no prominent affective symptoms, the presence of delusions, hallucinations, or thought disorder, and for personal and family history to be taken into account (marital status, age under 40, premorbid social adjustment). Other systems adopt the Schneiderian concept of

Historical views of schizophrenia schizophrenia, including Catego (Wing et al. 1974)—a computer program that uses the Present State Examination (PSE) to generate diagnoses; Spitzer et al.'s (1975) research diagnostic criteria (RDC)—requiring at least 2wks duration, lack of affective symptoms, presence of thought disorder, and hallucinations and delusions similar to Schneiderian first-rank symptoms; as well as the ICD-10 (WHO 1992). The American Psychiatric Association's DSM-5 (2013) has dispensed with Schneiderian first-rank auditory hallu cinations (2+ voices conversing) but requires the presence of at least one of delusions, hallucinations, or disorganised speech. (E The diagnosis of schizophrenia, p. 184). ICD-11 proposals (2018) consider persistent delu sions, hallucinations, thought disorder, and feelings of passivity, influence or control, as core symptoms. With the advent of neuroimaging, the biological substrate of schizo phrenia could be investigated in the living brain. In 1974 Ingvar and Franzén showed, with the aid of radiolabelled

xenon gas, that blood flow was re duced in the frontal lobes. In 1976 Johnstone et al. published the first con trolled CT brain study, which found enlarged ventricles associated with poorer cognitive performance. In the absence of an aetiological model of schizophrenia, pathophysiological models were developed to describe and explain the varieties of presentations found. In 1980 Crow described his ‘Two syndrome hypothesis’, dividing schizophrenia into type 1 (predom inant positive symptoms, acute onset, good premorbid adjustment, good treatment response, normal cognition and brain structure, reversible neurochemical disturbance) and type 2 (predominant negative symptoms, insidious onset, poor premorbid adjustment, poor treatment response, im paired cognition, structural brain abnormalities [ventricular enlargement] underlying irreversible neuronal loss). The first quantitative MRI study by Andreasen et al. in 1986 also demonstrated smaller frontal lobes, and re duced intracranial and cerebral volume: further evidence for schizophrenia as a neurodevelopmental disorder. Based upon examination of symptomatology and functional brain im aging Liddle (1992) proposed his ‘Three syndrome hypothesis of schizo phrenia’: (1) Psychomotor poverty syndrome—poverty of speech, flattened affect, and decreased spontaneous movement; hypoperfusion of left dorsal prefrontal cortex, extending to the medial prefrontal cortex and the cin gulate cortex and hypoperfusion in the head of caudate; reduced ability to generate action; (2) Disorganization syndrome—disorders of form of thought and inappropriate affect; - hypoperfusion of right ventral prefrontal cortex and increased activity in anterior cingulate and dorsomedial thal amic nuclei projecting to the prefrontal cortex; relative hypoperfusion of Broca’s area and bilateral hypoperfusion of parietal association cortex; reduced ability to inhibit inappropriate mental activity; and (3) Reality dis tortion syndrome—delusions and hallucinations; increased activity in left parahippocampal region and left striatum; disorder of internal monitoring. Schizophrenia research in the last two decades has focused more on finding fundamental neuronal, neurochemical, or cognitive mechanisms than on localizing specific symptoms (E Aetiological theories, p. 188). It is hoped that this approach may provide workable hypotheses that can fa cilitate the search for molecular mechanisms and lead to new treatment approaches.

184 Chapter 5 Schizophrenia and related psychoses The diagnosis of schizophrenia The diagnosis of schizophrenia is made on the basis of the patient’s symp toms, and currently no confirmatory test is available. DSM-IIIR, DSM-IV, DSM-5, and ICD-10 set out operational criteria against which a clinical diag nosis can be confirmed. Subtypes of schizophrenia (see Table 5.1) are no longer retained by DSM-5 or as currently proposed for ICD-11 (2018).1 ICD-10 schizophrenia

1. At least one of the following: • Thought echo, insertion, withdrawal, or broadcasting. • Delusions of control, influence, or passivity; clearly referred to body or limb movements or specific thoughts, actions, or sensations; and delusional perception. • Hallucinatory voices giving a running commentary on the patient’s behaviour or discussing him/her between themselves, or other types of hallucinatory voices coming from some part of the body. • Culturally inappropriate or implausible persistent delusions (e.g. religious/political identity, superhuman powers and ability). Table 5.1 ICD-10 subtypes Paranoid schizophrenia Delusions and hallucinations Hebephrenic schizophrenia Disorganized speech and behaviour (often silly/ shallow); flat or inappropriate affect Catatonic schizophrenia Psychomotor disturbance (E The catatonic patient, p. 1054) Undifferentiated schizophrenia Meeting general criteria, but no specific symptom subtype predominates Post-schizophrenic depression Some residual symptoms, but depressive picture predominates Residual schizophrenia Previous ‘positive symptoms’ less marked;

prominent ‘negative’ symptoms Simple schizophrenia No delusions or hallucinations—a ‘defect state’ (negative symptoms) gradually arises without an acute episode 1 ‘Schizophrenia’ in ICD-11 proposals is characterized by ‘disturbances in multiple mental modalities, including: thinking (e.g. delusions, disorganization in the form of thought), perception (e.g. hallucin ations), self-experience (e.g. the experience that one’s feelings, impulses, thoughts, or behaviour are under the control of an external force), cognition (e.g. impaired attention, verbal memory, and social cognition), volition (e.g. loss of motivation), affect (e.g. blunted emotional expression), and behaviour (e.g. behaviour that appears bizarre or purposeless, unpredictable or inappropriate emotional responses that interfere with the organization of behaviour)’. Symptoms present for 1+ months. Usual exclusions apply. No subtypes. New symptom specifiers: positive, negative, depres sion, mania, psychomotor, and cognitive symptoms. New course specifiers: first and subsequent epi sodes, chronic (non-episodic) course, acute episodes (with full-blown symptoms, partial remission, and complete remission).

The diagnosis of schizophrenia 2. Or, at least two of the following: • Persistent hallucinations in any modality, when accompanied by fleeting or half-formed delusions without clear affective content, persistent over-valued ideas, or occurring every day for weeks or months on end. • Breaks of interpolations in the train of thought, resulting in incoherence or irrelevant speech or neologisms. • Catatonic behaviour such as excitement, posturing, or waxy flexibility, negativism, mutism, and stupor. • Negative symptoms such as marked apathy, paucity of speech, and blunting or incongruity of emotional responses. • A significant and consistent change in the overall quality of some aspects of personal behaviour, manifest as loss of interest, aimlessness, idleness, a self-absorbed attitude, and social withdrawal. 3. Duration of ≥1mth. DSM-5 schizophrenia A. Characteristics of symptoms:2 two or more of the following, each present for a significant portion of time during a 1-mth period (or less if successfully treated). At least one of these must be (1), (2), or (3): (1) Delusions. (2) Hallucinations. (3) Disorganized speech (e.g. frequent derailment or incoherence). (4) Grossly disorganized or catatonic behaviour. (5) Negative symptoms (i.e. diminished emotional expression/ avolition). B. Social/occupational dysfunction: for a significant portion of the time since onset of the disturbance, the level of functioning in one or more major areas, such as work, interpersonal relations, or self-care, is markedly below the level achieved prior to onset (or when the onset is in childhood or adolescence, there is failure to achieve the expected level of interpersonal, academic, or occupational functioning). C. Duration: continuous signs of the disturbance persist for at least 6mths that must include at least 1mth of symptoms meeting criterion A. D–F. Exclusions: • Schizoaffective disorder and depressive or bipolar disorder with psychotic features have been ruled out. • Presentation is not attributable to the physiological effects of a substance (e.g. drug of abuse, medication) or other medical condition. • If there is a history of ASD or a communication disorder of childhood onset, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations, in addition to the other required symptoms of schizophrenia, are also present for at least 1mth (or less if successfully treated). 2 DSM-5 allows for course specifiers after 1-yr duration: first episode (currently in acute episode/in partial remission/in full remission); multiple episodes (currently in acute episode/in partial remission/ in full remission); continuous or unspecified pattern. Other specifiers include ‘with catatonia’ and a rating scale for psychosis symptom severity.

186 Chapter 5 Schizophrenia and related psychoses Differential diagnosis of schizophrenia The differential diagnosis of schizophrenia is wide. Early in the course of the illness, there may be significant uncertainty as to the true diagnosis. In general, compared to other disorders with psychotic symptoms, in schizo phrenia, there is a broader range of psychotic symptoms (e.g. other than relatively circumscribed delusions) and greater functional impairment. Substance-induced psychotic disorder (For example, alcohol, stimulants, hallucinogens, steroids, antihistamines, and sympathomimetics.) Careful history-taking may reveal onset, persist ence, and cessation of symptoms to be related to drug use or withdrawal. Psychotic disorder due to a general medical condition Focused history, examination, and investigations should help exclude other disorders, including brain disease (e.g. head injury, CNS infection, CNS tu mour, TLE, post-epileptic states, vCJD), and metabolic (hypernatraemia, hypocalcaemia) or endocrine disturbance (hyperthyroidism, Cushing's syndrome). Mood disorders with psychotic features Mood and related biological symptoms are usually more severe and pre cede psychosis. The psychotic features will usually be mood-congruent (E Diagnosis 1: symptoms, p. 246). There may be a personal or family history of affective disorder. Acute/transient (brief) psychotic disorder and schizophreniform disorder Diagnosed only after the psychotic symptoms have resolved, based on the time course (E Acute and transient psychotic disorders, p. 236). Sleep-related disorders When symptoms characteristically only occur while falling asleep or on waking up (hypnagogic/hypnopompic hallucinations; E Abnormal percep tions, p. 72). If there is excessive daytime tiredness due to lack of sleep or side effects of medication, symptoms may occur at any time of the day. Delusional disorder Presence of at least one non-bizarre delusion with lack of thought dis order, prominent hallucinations, mood disorder, and flattening of affect (E Delusional disorder 1: clinical features, p. 230). Dementia and delirium Evidence of cognitive impairment or altered/fluctuating LOC, respectively. Delirium characteristically has a waxing and waning course. Note: also con sider 'late paraphrenia', which has an extensive literature and is thought to be distinct from delusional disorder and schizophrenia, associated with social isolation, ageing, medical problems/treatments, and sensory loss (E Specific aspects of psychiatric illnesses in the elderly 3: mood disorders, p. 552).

Differential diagnosis of schizophrenia Body dysmorphic disorder Significant overlap with delusional disorder; few significant differentiating factors exist (E Body dysmorphic disorder, p. 872). Post-traumatic stress disorder Evidence of a past life-threatening trauma (E Post-traumatic stress dis order 1: diagnosis, p. 402). Pervasive developmental disorder Evidence of impairment in functioning from the pre-school years. Obsessive–compulsive disorder Significant overlap with delusional disorder and, if reality testing regarding obsessions or compulsions is lost, delusional disorder is often diagnosed (E Obsessive–compulsive disorder 1: clinical features, p. 384). Hypochondriasis Health concerns generally are more amenable to reality testing and are less fixed than in delusional disorder. Paranoid personality disorder Absence of clearly circumscribed delusions, presence of a pervasive, stable pattern of suspiciousness or distrust (E Table 12.1, p. 523). Schizotypal personality disorder Odd or eccentric behaviour, absence of clearly circumscribed delusions (E Table 12.1, p. 523). Misidentification syndromes Easily confused with delusional disorder; may be associated with other CNS abnormalities (E Delusional misidentification syndromes, p. 240). Induced/shared psychotic disorder Evidence that relatives or close friends share similar delusional beliefs (E Induced delusional disorder, p. 238). Anxiety disorder Sometimes patients use 'paranoia' or 'feeling paranoid' to describe over-concern, hypersensitivity, anxiety, agoraphobia, or social phobia— clarification is all that is required when terminology has acquired

common parlance. Factitious disorder Rarely, psychotic symptoms may be feigned, usually to avoid responsibilities and/or to maintain a sick role (E Factitious disorder (Munchausen’s syn drome), p. 876).

188 Chapter 5 Schizophrenia and related psychoses Aetiological theories Neurochemical abnormality hypotheses It seems unlikely that the aetiology of schizophrenia can be fully attributed to a single neurotransmitter abnormality (although there are precedents, not ably Parkinson’s disease). In the study of models for psychosis, particularly with the psychotomimetic (psychosis-mimicking) effects of certain drugs, there is evidence for the involvement of multiple neurotransmitters in the genesis of psychotic symptoms. Some of the evidence implicating different neurotransmitters is outlined here (E Other theories, see opposite):
Dopaminergic overactivity • The fact that all known effective antipsychotics are DA antagonists. • Positive correlation between the antipsychotic efficacy of a drug and its potency as a DA receptor antagonist. • Induction of psychotic symptoms by dopaminergic agents [e.g. amphetamine, cocaine, phencyclidine [PCP], levodopa, bromocriptine]. • Imaging studies showing that amphetamine induces greater displacement of radiolabelled-ligands bound to D2 receptors in the striatum in never- treated schizophrenia patients (suggesting a predisposition to i DA release). • Evidence of a correlation between DA metabolite homovanillic acid (HVA) plasma levels and both the severity of psychotic symptoms and the treatment response to antipsychotics.
Glutaminergic hypoactivity • NMDA receptor antagonists, (e.g. ketamine, PCP) have been shown to induce both positive and negative symptoms of schizophrenia in healthy volunteers (possibly via modulation of the DA system) and exacerbate symptoms of patients with schizophrenia. • The effects of ketamine (in both animals and humans) are attenuated by antipsychotic medication (notably clozapine). • Facilitation of NMDA receptor function by glycine (which binds to a modulatory site on NMDA receptors) and D-cycloserine (a selective partial agonist at the glycine modulatory site) may lead to symptomatic improvement. Serotonergic (5-HT) overactivity • The primary mode of action of LSD is through partial 5-HT agonism, associated with sensory distortions and hallucinations. • The efficacy of clozapine in treatment-resistant schizophrenia is thought to be due to its combined dopaminergic and serotonergic antagonism. Alpha-adrenergic overactivity • Some antipsychotics also have clear adrenergic antagonism. • i levels of noradrenaline (NA) have been found in the CSF of patients with acute psychotic symptoms. • Chronic treatment with antipsychotic drugs leads to d firing rates in the locus coeruleus (the origin of the noradrenergic system).

Aetiological theories Gamma-aminobutyric acid hypoactivity • Loss of GABA inhibition has been shown to lead to overactivity in other neurotransmitter systems (e.g. DA, 5-HT, NA). • There is some evidence to support the loss of GABAergic neurons in the hippocampus of patients with schizophrenia. • Use of BZDs may augment the therapeutic effects of antipsychotics by their GABA facilitation. The neurodevelopmental hypothesis Some authors hypothesize that schizophrenia may be a disorder of neurodevelopment, based on the following: • Excess of obstetric complications in those who develop the disorder. • Affected subjects have motor and cognitive problems which precede the onset of illness. • Schizophrenic subjects have abnormalities of the cerebral structure at first presentation. • Schizophrenic subjects have dermatoglyphic and dysmorphic features. • Although the brain is abnormal, gliosis is absent—suggesting that differences are possibly acquired in utero. • Evidence of excessive synaptic pruning during adolescence/early adulthood. The disconnection hypothesis Neuropsychological, neuroanatomical, and functional investigations

(SPECT, PET, fMRI) have revealed: • Widespread reductions in grey matter in schizophrenia (particularly the temporal lobe). • Disorders of memory and frontal lobe function occurring on a background of widespread cognitive abnormalities. • Reduced correlation between frontal and temporal blood flow on specific cognitive tasks. • A reduction in white matter integrity in tracts connecting the frontal and temporal lobes. These findings have led to speculation that frontal–temporal/parietal connectivity may be the final common pathway for the development of schizophrenia. Other theories In the 1960s, social theories of schizophrenia (e.g. schizophrenogenic mother, marital skew, and schism) were common. They are now of his torical interest only, not having withstood scientific scrutiny. A number of other theories exist, including those which postulate that schizophrenia is an abnormality of information processing (Braff, 1993), a problem of working memory (Goldman-Rakic, 1994), caused by cognitive dysmetria (Andreasen et al., 1999), an inability to think in 'meta-representations' or grasp 'theory of mind' (Pickup & Frith, 2001), a neurodegenerative disorder (Weiberger and McClure, 2002), a disorder of language (Berlim and Crow, 2003), due to abnormal neuronal migration and the DISC1 gene (Johnstone et al., 2011), and due to excessive synaptic pruning and the C4 (comple ment) gene (Sekar et al., 2016).

190 Chapter 5 Schizophrenia and related psychoses Epidemiology of schizophrenia Incidence The incidence of schizophrenia worldwide is relatively similar when re stricted, operational diagnostic criteria are used to establish the diagnosis. The incidence in the UK and USA is around 15 new cases per 100,000 population. ♂ = ♀, although ♂ tend to have an earlier onset than ♀ (23 vs 26yrs) and develop more severe illnesses. A few studies have reported a falling incidence over time, although this may be due to changing diagnostic practices/criteria. Prevalence The lifetime risk of schizophrenia is between 15 and 19 per 1000 popula tion. The point prevalence is between 2 and 7 per 1000. There are some differences between countries, although these differences are minimized when a restrictive definition of schizophrenia, based on first-rank symp toms, is used. Fertility Early studies reported low fertility in both men and women with schizo phrenia. More recent studies suggest that although men are reproductively disadvantaged, the fertility of women with schizophrenia has i probably due to deinstitutionalization. Mortality The diagnosis of schizophrenia carries around a 20% reduction in life expectancy. Suicide is the most common cause of premature death in schizophrenia. It accounts for 10–38% of all deaths in schizophrenia. Risk is probably highest in the year after the first presentation and is greater in men. Morbidity There is significant comorbidity in patients with schizophrenia: • Common medical problems that occur more frequently, e.g. communicable diseases (HIV, hepatitis C, TB), epilepsy, diabetes, arteriosclerosis, ischaemic heart disease. • Rare conditions that co-occur with schizophrenia, e.g. metachromic leukodystrophy, acute intermittent porphyria, coeliac disease, dysmorphic features (high-arched palate, low-set ears, minor physical abnormalities). • Substance misuse—cannabis, stimulants, and nicotine, in particular. Inheritance Genetic factors account for the majority of liability to schizophrenia. Heritability estimates range from 60% to 80%. The risk of developing schizophrenia when one has an affected relative is shown in Table 5.2. It is likely that an individual needs to have several genes 'of small effect' that interact with each other and with time-specific exposure to other environ mental risk factors.

Epidemiology of schizophrenia Recent molecular genetic studies in large populations have found >100 loci in the human genome containing single nucleotide polymorphism (SNP) haplotypes that associate with a risk of schizophrenia.3 The functional alleles and mechanisms at these loci remain to be discovered. The strongest gen etic relationship is schizophrenia's association with genetic

markers across the major histocompatibility complex (MHC) locus, which spans several megabases of chromosome 6. Other notable associations relevant to major hypotheses of the aetiology and treatment of schizophrenia include DRD2 (the target of all effective antipsychotic drugs), multiple genes involved in glutamatergic transmission and synaptic plasticity (e.g. GRM3, GRIN2A, SRR, GRIA1), and voltage-gated calcium channel subunits (e.g. CACNA1C, CACNB2, CACNA1I). The involvement of the immune system and other genes encoding synaptic proteins has added evidence to the theory that schizophrenia arises due to diverse synaptic abnormalities interacting with the complement system and other pathways to cause excessive stimula tion of microglia and elimination of synapses during adolescence and early adulthood. Genes involved in neurodevelopment have also been associated with schizophrenia, including DISC1, NRG1, DTNBP1, KCNH2, AKT1, and RGS4 genes. Environmental factors The following have been associated with an i risk of schizophrenia: • Complications of pregnancy, delivery, and the neonatal period. • Delayed walking and neurodevelopmental difficulties. • Early social services contact and disturbed childhood behaviour. • Severe maternal malnutrition. • Maternal influenza in pregnancy and winter births. • Degree of urbanization at birth. • Use of cannabis, especially during adolescence. Table 5.2 Schizophrenia liability based on affected relatives Family member(s) affected Risk (approximate) (%) Identical twin One sibling/fraternal twin 12–15 Both parents One parent 12–15 One grandparent No relatives affected 0.5–1 3 Schizophrenia Working Group of the Psychiatric Genomics Consortium (2014) Biological insights from 108 schizophrenia-associated genetic loci. Nature 511:421–7.

192 Chapter 5 Schizophrenia and related psychoses Examination of the patient with psychotic symptoms A thorough medical history, including a systematic review and thorough physical examination, is important is the assessment of all patients pre senting with psychotic symptoms. It is all too easy to focus on the psychiatric aspects of the assessment to the exclusion of medical aspects, which may inform the diagnosis and aid treatment planning. Key features in systematic review • Neurological—headache, head injury, abnormal movements of the mouth or tongue, diplopia, hearing or visual impairment (delusional disorder is more common when there is sensory impairment), fits/ faints/blackouts/dizzy spells, altered consciousness or memory problems, stroke, coordination problems, marked tremor, or muscle stiffness. • Respiratory—dyspnoea, orthopnoea. • Cardiovascular—chest pain, palpitations. • GI—constipation (can be a side effect of anticholinergic psychotropic drugs), nausea, vomiting. • Genitourinary—urinary hesitancy (retention related to anticholinergic drugs); in women, a menstrual history; for both: sexual problems (which may be secondary to medication). Mental state examination • Aside from the more obvious psychotic features, a comprehensive assessment includes asking about mood, sleep, symptoms of anxiety, and cognitive function. • Be sure to check orientation, attention, concentration, and anterograde/retrograde memory at a minimum—always consider the underlying neurological condition when disorientation is present or if memory problems are severe or persistent in spite of adequate treatment. Diagnostic formulation Even in the absence of a specific cause, the aetiology of schizophrenia is predominantly influenced by factors affecting the brain. However, the fol lowing areas might be considered as a guide to the assessment of predis posing, precipitating, and perpetuating factors: • Biological—consider family history of psychiatric illness, recent substance misuse, drug non-compliance, history of obstetric complications, brain injury, and comorbid medical illness. • Psychosocial—consider recent stressful life events, family cohesion/ friction, living conditions, attitude, and knowledge of illness.

Examination of the patient with psychotic symptoms Physical examination • Full physical examination is essential for all inpatients. • The need for a complete physical examination in an outpatient setting tends to be based on presenting complaints and/or the availability of adequate facilities/time constraints. • There really can be no excuse for overlooking systemic comorbidities—at the very least, arrange for the primary care physician to review the patient or reschedule a longer appointment somewhere where facilities are available. • A full neurological examination may be the most important investigation and should focus on gait inspection; examination of the extremities for weakness and/or altered sensation; examination of hand–eye coordination; examination of smooth ocular pursuit; and examination of the cranial nerves. Scales, such as AIMS, may be useful to record and monitor potential movement side effects of medication. Investigations Blood tests • Routine—U&Es, LFT, calcium, FBC, glucose. • When suggested by history/examination—VDRL (Venereal Disease Research Laboratory), TFTs, parathyroid hormone (PTH), cortisol, tumour markers. Radiological • CT or MRI in the presence of suggested neurological abnormality or persistent cognitive impairment. • CXR only where examination/history suggests comorbid respiratory/ cardiovascular condition. Urine • Urinary drug screen (particularly stimulants and cannabis). • Microscopy and culture (where history suggestive). Other • EEG rarely necessary unless history of seizure or symptoms suggest TLE. Special investigations • 24-hr collection for cortisol (if Cushing's disease suggested from history/examination). • 24-hr catecholamine/5-hydroxyindoleacetic acid (5-HIAA) collection for suspected phaeochromocytoma/carcinoid syndrome, respectively.

194 Chapter 5 Schizophrenia and related psychoses Presentations of psychosis 1 When discussing the management of schizophrenia and related psychoses, it is helpful to consider three distinct, but related, phases: the prodromal phase, the acute psychotic episode, and the maintenance phase. Before an individual fulfils DSM-5/ICD-10/11 criteria for schizophrenia, there may be a pro dromal period of disturbed behaviour and partial psychotic symptoms that suggest, especially in the presence of other risk factors, that schizophrenia is imminent and inevitable (see further text). Acute psychotic episodes may represent a first episode/relapse of schizophrenia or another illness within the differential diagnosis (E Differential diagnosis of schizophrenia, p. 186). Treatment in an acute episode is to abolish psychotic symptoms while min imizing distress and ensuring patient safety (E Initial treatment of acute psychosis, p. 200). Once psychotic symptoms have been abolished (or im proved as far as possible), one enters the maintenance phase. Here the concern shifts to prophylaxis (which often includes maintenance medica tion), rehabilitation, and maximization of function (E Maintenance phase, p. 202). Unfortunately acute psychotic relapse is possible in schizophrenia despite optimum maintenance treatment. Prodromal schizophrenia (See Box 5.1.) 'Prodrome' is a retrospective concept relating to evidence of premorbid change in an individual who later develops a condition. In schizophrenia, there is evidence of prodromal symptoms in 80–90% of cases (10–20% have acute onset). The typical presentation is of non-specific or negative symptoms (early prodrome), followed by attenuated, mild, positive symp toms (late prodrome).4 The main problem in detecting attenuated or subthreshold symptoms is that the rate of conversion to schizophrenia is low. Use of specific screening tools, such as the PACE (Personal Assessment and Crisis Evaluation Clinic), COPS (Criteria of Prodromal Syndromes), or SIPS (Structured Interview for Prodromal Syndromes), raises detection rates to 20–40%.5 These populations are perhaps better termed as having an 'at-risk' mental state (ARMS) for psychosis or being at 'ultra high risk' (UHR) for psychosis. Preliminary evidence suggests that low-dose anti psychotics, CBT, and antidepressants can improve presenting symptoms.6 However, there is no

convincing evidence yet that any intervention can delay, prevent, or reduce the severity of the psychotic illness. Neither is there evidence that the mean duration of untreated psychosis (DUP) in pa tients who develop psychosis improves the long-term outcome. Whether treatment is indicated at this stage remains controversial, but assessment and monitoring may be prognostically useful. 4 Yung AR, Phillips LJ, McGorry PD, et al. (1998) Prediction of psychosis: a step towards indicated prevention of schizophrenia. Br J Psychiatry (Suppl) 172:14–20. 5 Miller TJ, McGlashan TH, Rosen JL, et al. (2002) Prospective diagnosis of the initial prodrome for schizophrenia based on the Structured Interview for Prodromal Syndromes: preliminary evidence of interrater reliability and predictive validity. Am J Psychiatry 159:863–5. 6 Ruhrmann S, Bechdolf A, Kühn KU, et al. (2007) Acute effects of treatment for prodromal symptoms for people putatively in a late initial prodromal state of psychosis. Br J Psychiatry 191(Suppl. 51):88–95.

Presentations of psychosis 1 Risk of transition to psychosis Transition risks from pooled data estimate the risk of someone with clinical high-risk status of developing psychosis after initial presentation to services to be 18% at 6mths, 22% at 1yr, 29% at 2yrs, and 36% after 3yrs.7 This means that, after 2-yr follow-up, over 70% of those at high risk will not have converted to psychosis. There is also a small proportion who will convert after the 2-yr period—one of the reasons why at least 3yrs follow-up is recommended. Box 5.1 Guidance and advice on preventing psychosis • If a person is distressed, has a decline in social functioning and has (1) transient/attenuated psychotic symptoms, or (2) other experiences or behaviour suggestive of possible psychosis, or (3) a first-degree relative with psychosis or schizophrenia, then they ought to be referred without delay to a specialist mental health service or an early intervention in psychosis service for assessment by a consultant psychiatrist or a trained specialist with experience in at-risk mental states.* • Treatments that may be considered include: individual CBT with or without family intervention; management of anxiety, depression, emergent personality disorders, or substance misuse, but not antipsychotic medication as there is little evidence that this will decrease the risk of, or prevent, psychosis.** • If a clear diagnosis cannot be made, but there are continued symptoms, impaired functioning, or distress, then further monitoring for a period of up to 3yrs is recommended. • If the person wishes to be discharged from the service, offer follow- up appointments and the option to self-refer in the future, and communicate this need for continued monitoring to their GP.

- M https://www.nice.org.uk/guidance/cg178/chapter/1-Recommendations#preventing-psychosis-2 [accessed 30 May 2018]. ** M https://www.bap.org.uk/pdfs/BAP_Guidelines-Schizophrenia.pdf [accessed: 30 May 2018]. 7 Fusar-Poli P, Bonoldi I, Yung AR, et al, (2012) Predicting psychosis: meta-analysis of transition out comes in individuals at high clinical risk. Arch Gen Psychiatry 69:220–9.

196 Chapter 5 Schizophrenia and related psychoses Presentations of psychosis 2 The first schizophrenic episode The first episode of schizophrenia in an individual generally occurs in late adolescence or early adult life. Many people experiencing their first episode will have no personal or family experience of mental ill health, and some will lack insight that their symptoms are a result of mental illness. As a result, many patients will present in crisis and not directly complaining of psychotic symptoms. The range of possible presentations is very wide; however, the following presentations (or their variants) are commonly seen: • A spouse or relative noticing withdrawn or bizarre behaviour. • Failure to achieve educational potential with referral by school or student

health services. • Onset of personality change, social withdrawal, and ‘odd’ behaviour. • Presentation via the criminal justice system (see section on schizophrenia and offending, E Mental disorder and offending 2: specific disorders and offending, p. 746). • Presentation following deliberate self-harm or suicide attempt. • Complaining to the council/police, etc. on the basis of delusional symptoms (e.g. hearing voices of neighbours throughout the night). • Occasionally, the first sign may be symptoms more typically characteristic of another disorder (e.g. depression, mania, OCD, panic disorder). The first episode of schizophrenia is often a time of diagnostic uncertainty (and occasionally the diagnosis may take months/years to become clear). Frequently, the clinical picture includes comorbid substance misuse, person ality difficulties, recent stressful life events, or a combination of all three. It is usually necessary to admit people suspected of first schizophrenic episodes in order to assess the extent of their psychopathology, to provide a time for education of both the patient and their family, and to provide pharma cological and psychological treatments in an environment where compliance can be carefully assessed. If local early intervention (see Box 5.2) or crisis intervention and home treatment services are sufficiently well developed, it may be possible to provide a viable less restrictive option to admission. Inpatient admission is always necessary where the patient poses a significant danger to themselves or others. Subsequent episodes Subsequent presentations may be due to relapse of psychotic symptoms after remission, a deterioration or a change in the quality of partially treated psychotic symptoms, or a crisis relating to life events in a patient who, as a result of their illness, has an impaired ability to manage stress. Relapses can occur spontaneously in the absence of causative factors and in spite of good compliance with antipsychotic treatment. However, very often, relapses relate to medication non-compliance, drug or alcohol misuse, or life stresses (or a combination of these). Often in an individual patient, the time course, prodromal features, and symptomatology of a relapse are characteristic—the so-called ‘relapse sig nature’. Educating the patient and carers about these warning signs and awareness and documentation of these features within the treating team are important parts of relapse prevention.

Presentations of psychosis 2 Box 5.2 Early intervention for psychosis (EIP) In the NICE guideline (CG178) Psychosis and schizophrenia in adults: pre vention and management (2014), there are specific recommendations: • EIP services should be accessible to all people with a first episode or first presentation of psychosis, irrespective of the person’s age or the duration of untreated psychosis. • People should be assessed without delay, and if the service cannot provide urgent intervention, then the person should be referred to a crisis resolution and home treatment team (with support from EIP services). • Services may be accessed from primary or secondary care (including other community services) or a self- or carer referral. • EIP services should aim to provide a full range of pharmacological, psychological, social, occupational, and educational interventions for people with psychosis and be available beyond 3yrs if the person has not made a stable recovery from psychosis or schizophrenia. The resource implications of having a specific EIP service are significant, and the guidance for implementation suggests that these standards should apply to all psychoses—including acute psychotic episodes in the context of trauma and substance misuse.1 It is likely that evidence of whether EIP services improve outcome in psychosis will emerge in the next few years, as they are now a priority for the NHS and beyond.2,3 1 M https://www.england.nhs.uk/mentalhealth/wp-content/uploads/sites/29/2016/04/eip- guidance.pdf [accessed 30 May 2018]. 2 Mcdaid D, Park A, Iemmi V, Adelaja B (2016) Growth in the use of early intervention for psychosis services: An opportunity to promote recovery amid concerns on health care sustainability. M https://

www.researchgate.net/publication/296822046_Growth_in_the_Use_of_Early_Intervention_for_Psychosis_Services_An_Opportunity_to_Promote_Recovery_Amid_Concerns_on_Health_Care_Sustainability [accessed 5 January 2019]. 3 The Early Intervention in Psychosis IRIS Network brings together elected early intervention (EI) regional leads to share issues and solutions. M http://www.iris-initiative.org.uk/silo/files/ iris-guidelines-update--september-2012.pdf [accessed 30 May 2018].

198 Chapter 5 Schizophrenia and related psychoses Initial assessment of acute psychosis Issues affecting initial management decisions In view of the range and variety of presentations and the broad differential (E Differential diagnosis of schizophrenia, p. 186), it is difficult to be pre scriptive in dealing with a patient who presents with psychotic symptoms. Symptoms may range from mild paranoid ideas to elaborate and firmly held delusions with associated auditory hallucinations urging the patient to vio lence. Often it is difficult to establish a clear history initially, and assessment is focused on the immediate concerns: • The risk they currently pose to themselves—not just the possibility of acts of self-harm or suicide, but also because of other aspects of their behaviour (e.g. police becoming involved, family relationships, work, continued driving, etc.). • Risk of violence—the nature of risk (E Assessing risk of violence, p. 748) and any association with current symptoms (e.g. delusions about a specific person or group of individuals; what the 'voices' are telling them to do). • The degree of insight retained by the patient and the likelihood of them cooperating with medical management. • Whether hospital admission or transfer to a psychiatric ward is warranted to assess and manage the acute symptoms [with or without use of the Mental Health Act (MHA)]. • Whether their current behaviour is so disturbed as to require urgent treatment (E Severe behavioural disturbance, p. 1048) to allow further assessment, including physical examination and other routine investigations (E Investigations, p. 193). • The person's current social circumstances and the level of support available to them [partner, relatives, friends, community psychiatric nurse (CPN), etc.] that may allow some flexibility in management (as well as being a source of third-party information). The greatest influence on your course of action will often be the reason why the person has been referred in the first place (e.g. brought up by a concerned relative, no longer able to be managed at home, breach of the peace, self-referral because of own concerns, attempted suicide). When there is a good account of the history of the presenting complaint(s), it may be possible to establish the most likely diagnosis and proceed accordingly, e.g. a drug- or alcohol-related disorder, acute confusional state (E Acute confusional state (delirium), p. 854), first epi sode of schizophrenia (E The first schizophrenic episode, p. 196), relapse of known schizophrenia (E Subsequent episodes, p. 196), delusional dis order (E Delusional disorder 1: clinical features, p. 230), and acute psych otic disorder (E Acute and transient psychotic disorders, p. 236). During initial assessment, particularly with unmedicated patients, record (verbatim, if possible) specific aspects of the patient's psychopathology (nature and content of delusions and hallucinations), before they become modified by the necessary use of medication. This information is important, as it will influence later decisions regarding, for example, assessment of treatment response and the need for continued use of the MHA.

Initial assessment of acute psychosis Many patients with a psychotic presentation will have comorbid drug and/or alcohol problems. The fact that the psychotic episode is suspected to be wholly or partially attributable to comorbid substance use should not be allowed to affect the treatment offered acutely, which should be planned on the basis of the nature and severity of the psychotic symptoms and the associated risk. On recovery from the acute episode, the comorbid

sub stance use should become a focus for clinical attention. The need for hospital admission As noted previously (E Issues affecting initial management decisions, p. 198), certain clinical features and situations will determine whether hos pital admission (or transfer to a psychiatric ward) is necessary: • High risk of suicide or homicide. • Other illness-related behaviour that endangers relationships, reputation, or assets. • Severe psychotic, depressive, or catatonic symptoms. • Lack of capacity to cooperate with treatment. • Lack or loss of appropriate psychosocial supports. • Failure of outpatient treatment. • Non-compliance with treatment plan (e.g. depot medication) for patients detained under the MHA. • Significant changes in medication for patient at high risk of relapse (including clozapine 'red' result; E Clozapine 2: starting and stopping, 'Traffic light' notification, p. 220). • Need to address comorbid conditions (e.g. inpatient detoxication, physical problems, serious medication side effects). Suitability of the ward environment A busy psychiatric ward may not be an ideal environment for a patient ex periencing acute psychotic symptoms. As far as possible, the person should be nursed in calm surroundings (a single room, if possible), with minimal stimulation (e.g. unfamiliar people, TV, radio). A balance should be struck between the need for regular observation and the likelihood that this may reinforce persecutory delusions. If behaviour becomes unmanageable, des pite regular medication, it may be necessary to consider referral of the pa tient to a more secure environment, e.g. an intensive psychiatric care unit (IPCU). Early review Regular review is critical in the first 72hrs to assess any improvement in mental state, response to medication, level of observation needed, and carry out statutory duties under the MHA (including the need for continued detention, if emergency powers have been used). This is also a time for information gathering from friends, family, GP, other agencies, etc. and or ganizing any investigations, including physical examination and routine blood tests that may not have been possible initially.

200 Chapter 5 Schizophrenia and related psychoses Initial treatment of acute psychosis The management of psychotic patients should include, wherever possible, the usual features of good medical practice: undertaking a comprehensive assessment of medical, social, and psychological needs; involving patients and their relatives in decisions about medical care; and providing patients and carers with clear verbal and, if necessary, written information (for NICE guidelines, see Box 5.3). Emergency treatment of behavioural disturbance Follow guidance as detailed for the management of acute behavioural dis turbance (E Severe behavioural disturbance, p. 1048). Points to note • Attempts to defuse the situation should be made, whenever possible. • Reassurance and the offer of voluntary oral/intramuscular medication are often successful. • The content of delusions and hallucinations is of poor diagnostic value but may better predict violence/behavioural disturbance. Box 5.3 Updated NICE guidelines (CG178) on choice of antipsychotic medication Although previous guidelines (2002) had advocated the use of 'atypical' drugs as first-line choice, this is no longer the case. Instead, for people with newly diagnosed schizophrenia, NICE advises:1 • The choice of antipsychotic medication should be made by the service user and healthcare professional together, taking into account the views of the carer if the service user agrees. • Providing information and discussing the likely benefits and possible side effects of each drug, including: • Metabolic (including weight gain and diabetes). • Extra-pyramidal (including akathisia, dyskinesia, and dystonia). • Cardiovascular (including prolonging the QT interval). • Hormonal (including increasing plasma PL). • Other (including unpleasant subjective experiences). • Not initiating regular combined antipsychotic medication, except for short periods (e.g. when changing medication). • To consider offering depot/long-acting injectable antipsychotic medication to people with psychosis or schizophrenia: • Who would prefer such treatment after an acute

episode. • Where avoiding covert non-adherence (either intentional or unintentional) to antipsychotic medication is a clinical priority within the treatment plan. • Offering clozapine to people with schizophrenia whose illness has not responded adequately to treatment despite the sequential use of adequate doses of at least two different antipsychotic drugs. At least one of the drugs should be a non-clozapine SGA. 1 NICE clinical guideline 178 (Feb 2014) Psychosis and schizophrenia in adults: prevention and management. M https://www.nice.org.uk/guidance/cg178/chapter/recommendations#choice- of-antipsychotic-medication [accessed 30 May 2018].

Initial treatment of acute psychosis • Act decisively and with sufficient support to ensure restraint and forcible administration of medication proceed without unnecessary delay or undue risk to the patient or staff. • Do not attempt to manage severe violence on an open ward when secure facilities with appropriately trained staff are available elsewhere. Instigation of antipsychotic treatment In the treatment of psychotic symptoms, antipsychotic medication has the strongest evidence base. Although little evidence exists to support the choice of one drug over the other, the following may be used as a guide to treatment. It is good practice to establish baseline measures of phys ical health prior to commencing antipsychotic treatment (E Physical health monitoring and antipsychotics, p. 1040). Option 1 • Commence a second-generation antipsychotic (SGA) [e.g. olanzapine, amisulpride, risperidone, quetiapine; see E Second-generation antipsychotics 1 & 2, pp. 201–213)] at an effective dose [see the British National Formulary (BNF)]. • Use long-acting BDZ (e.g. diazepam) to control non-acute anxiety/ behavioural disturbance. Option 2 • Prescribe a low-potency first-generation antipsychotic (FGA) (such as chlorpromazine, initially in the range of 75–200mg/d in divided doses) for a first episode. • Increase the dose according to clinical effect and the need for sedation. • Previous episodes and the response/side effects experienced should inform the management of subsequent episodes. • No additional antipsychotic benefit is likely when doses of 400–600mg chlorpromazine (or equivalent) are exceeded; however, sedation may be a useful effect of increasing the dose above this level. Extra-pyramidal side effects EPSEs, including dystonias, Parkinsonism, and akathisia, are common side effects of treatment with antipsychotic medication and are a frequent cause of non-compliance. • EPSEs are less likely with option 1, although the tolerability of both options overall is approximately equal. • Prescribe procyclidine (or alternative) orally, as required, for Parkinsonian side effects. • Review regularly, since requirement for procyclidine may diminish over time and the drug may contribute to non-response and tardive dyskinesia.

202 Chapter 5 Schizophrenia and related psychoses Maintenance phase Post-acute phase With the emergence of ‘stability’ (i.e. less active psychotic symptoms and less behavioural disturbance), treatment shifts towards the gradual simplifi cation of medication regimes and maximization of tolerability. The patient may be more able to engage actively with other therapeutic modalities available in the hospital environment. Time to remission of symptoms is very variable and may take 3–9mths or more. It is important the patient and their family/friends have realistic expectations. Continuing treatment A more considered view of management may be taken once maximal im provements are considered to have occurred. This is the time to estab lish the minimal effective dose of medication, and maintenance regimes can often be significantly lower than those needed for management of the acute phase of the illness. A secondary goal is the minimization of side effects, with the aim of establishing compliance with medication. Finally, there is the more complex goal of rehabilitation—returning the patient to their highest possible level of social and

occupational functioning. The final steps in this process may require input, where available, of better resourced multidis ciplinary rehabilitation units or community teams over many months, with the ultimate aims of successful discharge (E Discharge planning, p. 204) and outpatient follow-up (E Outpatient treatment and follow-up, p. 206). Comorbid depression Depression can affect up to 70% of patients in the acute phase but tends to remit along with the psychosis. In the maintenance phase, post-psychotic or post-schizophrenic depression occurs in up to one-third of patients and there is some evidence that tricyclic antidepressants (TCAs) (e.g. imipra mine) may be effective. Surprisingly, despite it being common clinical prac tice, there are few studies supporting other interventions such as SSRIs. Managing negative symptoms Specific interventions may help to mitigate the impact of persistent negative symptoms: • Ensure EPSEs (especially bradykinesia) are detected and treated with anticholinergics, with amantadine, by reducing antipsychotics, or by switching to lower-potency/SGA agents. • If there is evidence of dysphoric mood, consider treating with antidepressants, with anxiolytics, by reducing the antipsychotic dose, with supportive management, or by switching to an SGA. • Address the contribution of the environment (e.g. institutionalization, lack of stimulation) by resocialization and/or rehabilitation. • If the patient is on long-term medication, consider reduction to minimal reasonable maintenance dose or switching to an SGA or clozapine. • If clozapine is prescribed, consider augmentation with an antidepressant, lamotrigine, or a suitable second antipsychotic (E An approach to treatment-resistant schizophrenia (TRS), p. 216).

Maintenance phase Addressing comorbid substance use As previously noted, there is significant comorbidity of substance abuse in patients with schizophrenia. While this may complicate and exacerbate positive and negative symptoms, sometimes patients believe they are self- medicating and may be reluctant to give up a ‘useful’ treatment. Elements of a pragmatic approach include: • A comprehensive assessment, including why and how substances are taken, as well as routine testing for substance misuse. • Optimization of antipsychotic medication and consideration of clozapine for patients with persisting substance misuse. • The offer of specific treatment for substance misuse and possibly referral to local drug and alcohol services—while psychosocial approaches will be the mainstay (including relapse prevention), the possible benefits of pharmacotherapy should not be ignored, e.g. nicotine substitution/withdrawal, alcohol detoxification, and opiate substitution.

204 Chapter 5 Schizophrenia and related psychoses Discharge planning Good communication between members of the multidisciplinary team (MDT) (psychiatry, community nurse, GP, social worker, etc.) is essential for good overall care. This may be formalized using the care programme approach (CPA) (E Aftercare following detention, p. 954), but when this is not mandatory, components of this approach may be useful in everyday practice. Pre-discharge meetings Prior to leaving hospital, a meeting should be arranged with all those in volved in a person’s care, including informal carers and key clinical staff. In some areas, Crisis Teams/Community Teams with Crisis Services will work intensively with people to facilitate early discharge and should be alerted of plans for discharge well in advance. Discharge plans Discharge plans should include information on everyone involved in a person’s care and should be clear about who is coordinating the care (e.g. key nurse, formal care coordinator, responsible medic). Plans should in clude explicit outcomes or expectations and follow-up arrangements, and it must be clear how help will be available in a crisis (e.g. contact numbers or formal relapse management/safety plan). All discharge plans should include a risk assessment and information on how risks will be managed. Medication Continue

antipsychotic medication at the minimum necessary dose. Possible regimens include: • An SGA (e.g. amisulpride, olanzapine, risperidone, quetiapine). • Preferably a non-sedating FGA (e.g. trifluoperazine, flupentixol, haloperidol). • Depot antipsychotic medication, particularly where use of oral medication has resulted in relapse due to non-compliance—there is good evidence that, in these circumstances, depot medication is slightly more effective and may improve adherence, with a lower risk of relapse, suicide, and rehospitalization (or incarceration).8 • High-potency FGAs (trifluoperazine, haloperidol) and olanzapine may be given once daily. This may be an advantage in non-compliant, institutionalized, or cognitively impaired patients. • In patients with complicated drug regimes, cognitive impairment, or dubious compliance, consider a compliance aid such as a multicompartment compliance aid (e.g. Dosette® box). 8 Khan AY, Salaria S, Ovais M, Ide GD (2016) Depot antipsychotics: where do we stand? Ann Clin Psychiatry 28:289–98.

Discharge planning Psychological9 • Family therapy and psychoeducation are effective in reducing relapse and should: • If possible, include the person with psychosis or schizophrenia and take account of the family's preference for single- or multi-family group intervention. • Usually last for 3–12mths and include at least ten sessions. • Incorporate specific supportive, educational, treatment-related, problem-solving, and crisis management elements. • Individual CBT approaches: • Manualized—aimed at establishing links between thoughts, feelings, or actions and current or past symptoms and/or functioning; re- evaluation of perceptions, beliefs, or reasoning related to symptoms. • Promoting alternative ways of coping with the target symptom, reducing distress, and improving functioning. • Compliance therapy may also be helpful. • Art therapies may be useful to promote recovery, especially where negative symptoms are prominent. Social/community/service provision • Functional assessment by OT in hospital and at home may help identify any specific needs that ought to be addressed before or after discharge home. • Social work and housing involvement are often necessary too, as illness may have led to a period of neglect or significant social upset, which may delay discharge until rectified. • Education or employment may also have been disrupted by illness, and support should be offered to negotiate a phased return to normal activities as soon as possible. • CPNs may help to provide information/education and monitor for early signs of relapse. Some areas may have specific teams for first-episode psychosis or home treatment following discharge from hospital— assertive approaches may be more beneficial. • For patients on depot, non-attendance at the GP surgery/CPN appointment may act as an early warning system. • Where day hospitals exist, they may provide an alternative means of supporting discharge and preventing the need for readmission. 9 M https://www.nice.org.uk/guidance/cg178/chapter/1-Recommendations#how-to-deliver- psychological-interventions [accessed 30 May 2018].

206 Chapter 5 Schizophrenia and related psychoses Outpatient treatment and follow-up When reviewing patients in clinic, after discharge and the acute episode has settled, the following areas should be considered. Medical • Conduct an MSE at every appointment. • Enquire about side effects and attitude to medication. • Record any recent life events or current stresses. • Enquire about suicidal ideas and, if appropriate, homicidal ideas. • When symptoms appear unresponsive to treatment, review the history and provide additional investigations/interventions, as appropriate (e.g. clozapine). • Be aware that following an acute episode, post-psychotic depression (E Maintenance phase, p. 202) is particularly common and should be properly assessed and treated.10 • Conduct appropriate investigations where complications of illness or its treatment arise (e.g. LFTs, FBC, U&Es, glucose) or where monitoring is indicated (e.g. high-dose guidelines; E

Box 5.7, p. 216), and physical health monitoring and antipsychotics (E Physical health monitoring and antipsychotics, p. 1040). Psychological • Above all, try to provide supportive and collaborative treatment, wherever possible. • Provide education about schizophrenia and its treatment. • Do not dismiss concerns, even if apparently based on delusional content. • Offer to meet family members or carers where appropriate. • Discuss additional specific psychological therapies intervention if this has not been previously tried (E Psychological, p. 205). Social • Remember statutory obligations (e.g. review of compulsory powers). • Consider referral to social work where there are housing, benefit, employment, education, or other problems. • Drop-in community centres and other support provided by non- statutory or voluntary organizations are often helpful. • Consider interventions offered by other professions (e.g. OT, physiotherapy) when particular problems arise (e.g. poor sleep, hygiene, anxiety management, etc.). • Some patients and their carers find user organizations helpful (e.g. SANE or Rethink—see useful addresses, E Resources for patients, p. 1072). There is usually a large degree of uncertainty regarding the course and prognosis in first-episode patients, regardless of their presenting symptoms or demographic/personal history. 10 Mao YM, Zhang MD (2015) Augmentation with antidepressants in schizophrenia treat ment: benefit or risk. Neuropsychiatr Dis Treat 11:701–13.

Outpatient treatment and follow-up Outcomes (See Box 5.4.) Box 5.4 Outcome in schizophrenia Approximate guide to course and prognosis at 13yrs' follow-up:1 • 715–20% of first episodes will not recur. • Few people will remain in employment. • 52% are without psychotic symptoms in the last 2yrs. • 52% are without negative symptoms. • 55% show good/fair social functioning. Prognostic factors Poor prognostic factors: • Poor premorbid adjustment. • Insidious onset. • Onset in childhood or adolescence. • Cognitive impairment. • Enlarged ventricles. • Symptoms fulfil more restrictive criteria. Good prognostic factors: • Marked mood disturbance, especially elation, during initial presentation. • Family history of affective disorder. • ♀ sex. • Living in a developing country. 1 Mason P, Harrison G, Glazebrook C, et al. (1995) Characteristics of outcome in schizophrenia at 13 years. Br J Psychiatry 167:596–603.

208 Chapter 5 Schizophrenia and related psychoses First-generation antipsychotics Phenothiazine derivatives Group 1—aliphatic phenothiazines Chlorpromazine-like drugs with mainly anti-adrenergic and antihistaminergic side effects, including pronounced sedation, moderate antimuscarinic ef fects, and moderate EPSEs (for drug doses equivalent to 100mg chlorpro mazine, see Table 6.3). Chlorpromazine (non-proprietary and Largactil®) • 75–300mg daily in divided doses (or at night)—max 1g daily. • Available as intramuscular (IM) injection (25–50mg every 6–8hrs). • Also available as 25mg or 100mg suppositories. Levomepromazine (methotrimeprazine, Levinan®, Nozinan®) • 100–200mg daily in divided doses—max 1g daily. • Available as IM or IV injection (25–50mg every 6–8hrs). Promazine • 400–800mg daily in divided doses. • Rarely causes haemolytic anaemia. • Usually used for agitation and restlessness, e.g. 100mg four times daily (qds) (25–50mg for elderly). Group 2—piperidine phenothiazines Thioridazine-like drugs with mainly antimuscarinic side effects and fewer EPSEs than groups 1 and 3. Pericyazine • 75–300mg daily in divided doses. • In behavioural management: 15–30mg daily in divided doses.
Group 3—piperazine phenothiazines Trifluoperazine-like drugs with mainly anti-dopaminergic side effects. These drugs are potent antipsychotics but tend to produce troublesome EPSEs, particularly at higher doses. They have limited sedative properties. Trifluoperazine (non-proprietary and Stelazine®) • No stated maximum dose. • For psychosis or behavioural management—5mg bd, i by 5mg after 1wk, then every 3 days, according to response. Fluphenazine Modecate®) • Available in

decanoate (long-acting) form. Perphenazine • 12–24mg daily. • For behavioural management, usually 4mg three times daily (tds). • Rarely causes SLE.

First-generation antipsychotics Thioxanthines Have moderate sedative, antimuscarinic, and extra-pyramidal effects. Flupentixol (Depixol®, Fluanxol®) • 3–9mg bd (max 18mg daily). • Also available as depot (E Antipsychotic depot injections, p. 224). Zuclopenthixol (Clopixol®, Ciatyl-Z®) • 20–30mg daily in divided doses (max 150mg daily). • Available in injectable forms as acetate—for management of acute behavioural disturbance (Clopixol acuphase®) and decanoate—for depot injection (Clopixol Conc®) (E Antipsychotic depot injections, p. 224). Butyrophenones Similar to group 3 phenothiazines—high potency, troublesome EPSEs. Haloperidol (non-proprietary and Haldol®, Halkid®, Serenace®) • 1.5–5mg bd to tds in divided doses (max 30mg daily). • Available as IM injection (2–10mg every 4–8hrs, max 18mg daily). Benperidol (non-proprietary and Anquil®) • 0.25–1.5mg daily in divided doses. • Used to treat deviant antisocial sexual behaviour (E Management, p. 741). Diphenybutylpiperidines Reduced sedative, antimuscarinic and extrapyramidal effects. Pimozide (Orap®) • 2–20mg daily. • Increase slowly by 2–4mg at intervals not less than 1wk. • May be more effective for monodelusional states, e.g. hypochondriasis, delusional jealousy. Substituted benzamides Sedative, antimuscarinic, and extrapyramidal effects less likely. Sulpiride (non-proprietary and Dolmatil®) • 200–400mg bd. • Lower max dose for negative symptoms (800mg daily) than for positive symptoms (2.4g daily).

210 Chapter 5 Schizophrenia and related psychoses Second-generation antipsychotics 1 In deference to the BNF and in light of recent controversies over classifica tion of antipsychotics, we have adopted the abbreviations FGA and SGA for consistency only. It may, in fact, be better to simply call them all ‘anti psychotics’.11 Although not strictly a separate class of antipsychotics, the newer ‘atypical’ drugs do have a slightly different pharmacokinetic profile. They have a wider therapeutic range and are generally less likely to cause EPSEs and raise serum prolactin levels (for completeness, additional SGAs are listed in Box 5.5). Olanzapine (Zyprexa®, Zalasta®) • Receptor antagonism: 5-HT2A = H1 = M1 > 5-HT2C > D2 > α1 > D1. • Optimum dose 5–20mg daily. • Available as an orodispersible tablet, a short-acting IM injection, and depot (olanzapine embonate/olanzapine pamoate or ZypAdhera®) (E Table 5.7, p. 225). • EPSEs similar to placebo in clinical doses, with less increase in prolactin (PL) than with haloperidol or risperidone. • Side effects of sedation, weight gain, dizziness, dry mouth, constipation, and possible glucose dysregulation. Risperidone (Risperdal®) • Receptor antagonism: 5-HT2 > D2 = α1 = α2; little histamine H1 affinity; minimal D1 and 5-HT1 affinity. • Available as orodispersible tablet and depot preparation (Risperdal Consta®; E Table 5.7, p. 225). • Dosage 4–6mg daily, given in 1–2 doses (max 16mg daily). • Less EPSEs than with conventional antipsychotics at lower doses, but dystonias and akathisia can occur (especially if dose >6mg or in the elderly) and can raise PL and cause weight gain. Paliperidone (Invega®) • Paliperidone (9-OH risperidone) is the major active metabolite of risperidone. • Receptor antagonism: as for risperidone. • Available as modified-release tablet or depot preparation (Xeplion®, Trivecta®; E Table 5.7, p. 225). • Dosage 6mg in the morning, adjusted in increments of 3mg over at least 5 days; usual range 3–12mg daily. • Low potential for EPSEs and, due to limited hepatic metabolism, reduced drug interactions. Quetiapine (Seroquel®, Atrolak®, Biquelle®, Brancico®, Mintreleq®, Sondate®, Zaluron®) • Receptor antagonism: H1 > α1 > 5-HT2 > α2 > D2. • Usual dose 300–450mg daily in two divided doses (max 750mg daily). • EPSEs = placebo, with no increase in PL. • Can cause sedation, dizziness (postural hypotension), constipation, dry mouth, weight gain, and alterations in triglycerides and cholesterol.

11 Kendall T (2011) The rise and fall of the atypical antipsychotics. Br J Psychiatry 199:266–8.

Second-generation antipsychotics 1 Box 5.5 Other SGAs (not currently listed in BNF for schizophrenia or withdrawn) Asenapine (Sycrest®) Not licensed for use in schizophrenia or related psychoses but is licensed as monotherapy or combination therapy for treatment of moderate to severe manic episodes in bipolar. • D2 and 5-HT2A antagonist, with additional D1, D3, D4, 5-HT1A, 5- HT1B, 5-HT2B, 5-HT2C, 5-HT5, 5-HT6, and 5-HT7, α1, α2, and H1/2 antagonism. No affinity for mACh. • Available as a sublingual tablet (need to avoid food and liquids for at least 10mins post-administration)—low bioavailability if swallowed. • Usual dose 5mg bd (max 20mg daily as a divided dose). • Common side-effects: akathisia (and other EPSEs), oral hypoesthesia, dizziness, somnolence, and weight gain. • Other side effects (related to sublingual administration): dysphagia, glossodynia, hypersalivation, speech disturbance, taste disturbance, tongue swelling. Zotepine (Zoleptil®) Discontinued by Healthcare Logistics from the UK market from January 2011 for commercial reasons. • High affinity for D1 and D2 receptors, also 5-HT2, 5-HT6, and 5-HT7 receptors, 25–100mg tds. • Inhibits NA reuptake. • Effective against positive and negative symptoms of schizophrenia, but controlled trial data limited. • EPSEs less than with FGAs. • i risk of seizures at higher doses (above 300mg). • Weight gain, sedation, constipation, asthenia, dry mouth, akathisia. • Raised hepatic enzymes. Sertindole (Serdolect®) Voluntarily withdrawn by Lundbeck in December 1998 due to concerns about arrhythmias associated with an increase in QTc. Limited reintro duction in June 2002 in Europe under strict monitoring for patients in clinical trials and who are intolerant of at least one other antipsychotic. • D2, 5-HT2, and α1 antagonist with D2 limbic selectivity. • Effective against positive and negative symptoms of schizophrenia. • 12–20mg single daily dose (max 24mg daily). • EPSEs = placebo. • Increase in QTc—needs ECG monitoring. • Other side effects include: nasal congestion, d ejaculatory volume, postural hypotension, dry mouth, and raised liver enzymes.

212 Chapter 5 Schizophrenia and related psychoses Second-generation antipsychotics 2 Clozapine (Clozaril®, Denzapine®, Zaponex®) (E Clozapine 1: general guidelines, p. 218; E Clozapine 2: starting and stopping, p. 220; E Clozapine 3: side effects, p. 222.) Amisulpride (non-proprietary and Solian®) • Selective and equipotent antagonism for D2 and D3, with negligible affinity for other receptors. • Similar efficacy to haloperidol for acute and chronic schizophrenia. • Optimum dose 400–800mg (max 1.2g) daily in two divided doses. • Lower doses (50–300mg) may be more effective for patients with mainly negative symptoms. • EPSEs similar to placebo at lower doses, but dose-dependent EPSEs and prolactinaemia at higher doses. • Less weight gain, compared with risperidone or olanzapine. Aripiprazole (Abilify®) • D2 receptor partial agonist; partial agonist at 5-HT1A receptors; high-affinity antagonist at 5-HT2A receptors; low-/moderate-affinity antagonist at H1 and α1 receptors; no anticholinergic effect. • Dosage 10–30mg od, optimum dose 10–20mg od. • Available as tablet, orodispersible tablet, oral solution (1mg/mL), solution for injection (9.75mg/1.3mL), and depot preparation (Abilify Maintena®; E Table 5.7, p. 225). • Low EPSEs similar to placebo at all doses (akathisia-like symptoms can occur in the first 2–3wks of treatment, with associated insomnia—use of additional hypnotic may be clinically necessary). • Does not increase plasma PL levels (and may decrease levels), and weight gain is less likely. Lurasidone (Latuda®) • Receptor antagonism: 5HT2C > D1 > α1 > α2C > 5HT2A > D2 > α2 > 5HT7; partial agonist: 5-HT1A; weak effects: H1 and mACh. • Dosage: initially 37mg od, i if necessary to max 148mg od. • Low propensity for QTc interval changes, weight- and lipid-related adverse effects. • Absorption i when taken with food.

Table 5.3 Estimated antipsychotic dose equivalents Oral Amisulpride 150mg/day Aripiprazole 7mg/day Asenapine 5mg/day Benperidol 2mg/day Chlorpromazine 150mg/day Clozapine 150mg/day Flupentixol 2mg/day Haloperidol 2.5mg/day Lurasidone 18.5mg/day Olanzapine 5mg/day Paliperidone 3mg/day Perphenazine 8mg/day Pimozide 2mg/day Promazine 100mg/day Quetiapine 100mg/day Risperidone 1.5mg/day Sulpiride 200mg/day Trifluoperazine 2-5mg/day Zuclopenthixol 25mg/day Depot Aripiprazole LAI 75–100mg/wk Flupentixol decanoate 10–20mg/wk Fluphenazine decanoate 5–10mg/wk Haloperiol decanoate 10–15mg/wk Olanzapine embonate 37.5mg/wk Paliperidone palmitate 7.5mg/wk Risperidone LAI 12.5mg/wk Second-generation antipsychotics 2 213

214 Chapter 5 Schizophrenia and related psychoses Antipsychotic side effects Tolerability No single antipsychotic is substantially better tolerated than another at daily doses of <12mg haloperidol or equivalent. However, FGAs prescribed above this range are less well tolerated and probably also less effective than SGA drugs (see Box 5.6). The choice of antipsychotic therefore depends substantially on the profile of side effects and which ones are more im portant to avoid. • Sedation Avoid chlorpromazine/promazine. Prescribe high-potency antipsychotics (e.g. haloperidol) or non-sedating SGA (risperidone, amisulpride, aripiprazole). • Weight gain Avoid phenothiazines, olanzapine, and clozapine. Prescribe haloperidol or fluphenazine. • EPSEs Avoid high-dose FGAs. Prescribe SGAs. • Postural hypotension Avoid phenothiazines. Prescribe haloperidol, amisulpride, or trifluoperazine. Box 5.6 SGAs vs FGAs? Effectiveness studies, such as the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE),1 the Cost Utility of the Latest Antipsychotic drugs in Schizophrenia Study (CUtLASS),2 and the European First-Episode Schizophrenia Trial (EUFEST),3 have been inter preted as showing no differences between FGAs and SGAs (with the pos sible exception of clozapine and perhaps olanzapine). Although this may be true in terms of overall effectiveness, most clinicians (and patients) would agree there are many real differences among drugs, particularly when it comes to side effects. While guidelines from NICE, SIGN, or the British Association for Psychopharmacology (BAP) may provide helpful frameworks for rational prescribing, treatment ought to be individualized through a shared decision-making process. Tolerability is a huge factor in adherence (E Medication adherence, p. 994), and it ought to be remem bered that the best antipsychotic in the world will not work if the patient does not actually take it. 1 Lieberman JA, Stroup TS, McEvoy JP, et al. (2005) Effectiveness of antipsychotic drugs in pa tients with chronic schizophrenia. N Engl J Med 353:1209–23. 2 Jones PB, Barnes TRE, Davies L, et al. (2006) Randomized controlled trial of the effect on quality of life of second- vs. first-generation antipsychotic drugs in schizophrenia: Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1). Arch Gen Psychiatry 63:1079–87. 3 Kahn RS, Fleischhacker WW, Boter H, et al. (2008) Effectiveness of antipsychotic drugs in first- episode schizophrenia and schizophreniform disorder: an open randomised clinical trial. Lancet 371:1085–97.

Antipsychotic side effects Extra-pyramidal side effects • Acute dystonia Contraction of muscle group to maximal limit, typically sternocleidomastoid and tongue, although can be widespread (e.g. opisthoclonus); eye muscle involvement (e.g. oculogyric crisis) may occur. Virtually always distressing and preceded by increasing agitation. Parenteral antimuscarinic (e.g. procyclidine 10mg iv) (for more detail, see E Dystonic reactions, p. 1016). • Parkinsonism Tremor, rigidity, and bradykinesia occurring >1wk after administration. Treatment Consider dose reduction/use of oral antimuscarinic (e.g. procyclidine 5mg tds) (for more detail, see E Antipsychotic-induced Parkinsonism, p. 1010). • Akathisia Restlessness, usually of lower limbs, and a drive to move.

Occurs usually >1mth after initiation of antipsychotic drug. Treatment Propranolol and BDZs may be helpful. Symptoms can be notoriously difficult to treat (for more detail, see E Akathisia, p. 1012). • Tardive dyskinesia (TD) Continuous, slow writhing movements (i.e. athetosis) and sudden involuntary movements, typically of the oral–lingual region (chorea). Symptoms of TD tend to be irreversible. Treatment12 Although a consequence of antipsychotic treatment, there is little evidence that a reduction in the dose of antipsychotic improves symptoms in the short or long term. Vitamin E may prevent deterioration but does not improve established symptoms (E Tardive dyskinesia, p. 1014). Anticholinergic side effects Dry mouth, blurred vision, difficulty passing urine, urinary retention, consti pation, and rarely ileus and glaucoma. Anti-adrenergic side effects Postural hypotension, tachycardia (sometimes bradycardia), sexual dysfunc tion (particularly erectile dysfunction; E Sexual dysfunction and psychiatric medication, p. 1006). Antihistaminic side effects Sedation, weight gain (although precise mechanism unclear; E Weight gain with psychiatric medication, p. 1000). Idiosyncratic Cholestatic jaundice, altered glucose tolerance, hypersensitivity reactions, skin photosensitivity (sun block important in sunny weather), yellow pig mentation to skin (chlorpromazine), NMS (rigidity, fluctuating conscious ness, and pyrexia)—may be fatal, requires immediate transfer to general medical care, and usually intensive care unit (ICU)/anaesthetic support/ dantrolene may be helpful (for more detail, see E Neuroleptic malignant syndrome, p. 1018). 12 Soares-Weiser KV, Joy C (2003) Miscellaneous treatments for neuroleptic-induced tardive dys kinesia. Cochrane Database Syst Rev 3:CD000208.

216 Chapter 5 Schizophrenia and related psychoses An approach to treatment-resistant schizophrenia (TRS) Definition Treatment resistance is the failure to respond to two or more antipsychotic medications given in therapeutic doses for 6wks or more. Patients with re fractory symptoms generally have more severe functional impairments and are more likely to have abnormalities of the cerebral structure and neuro psychology. See Box 5.7 for guidelines. Prevalence 730% of patients respond poorly to antipsychotic medication, and the number of people who show ‘total non-response’ is 77%. Box 5.7 Guidelines for the use of high-dose antipsychotics Where a patient has failed to respond to, or has only partially responded to, antipsychotic medication, some practitioners advocate high-dose prescribing. High-dose prescribing refers either to the prescription of a single antipsychotic at doses greater than the BNF maximum or the pre scription of two or more antipsychotics with a combined chlorpromazine equivalent dose of >1g daily (see Table 5.3). Although there may be a therapeutic response to this approach in some individual patients, there is no evidence that high-dose prescribing confers any therapeutic advantage in first-episode psychosis, acute psychotic episodes, relapse prevention, emergency tranquillization, persistent aggression, or treatment resist ance. There is clear evidence for greater side effect burden and the need for appropriate safety monitoring. The Royal College of Psychiatrists’ most recent guidance1 suggests that: • Any prescription of high-dose antipsychotic medication should be seen as an explicit, time-limited, individual trial, with a distinct treatment target. • There should be a clear plan for regular clinical review, including safety monitoring (E Physical health monitoring and antipsychotics, p. 1040). • The trial of high-dose treatment should only be continued if there is clear evidence that the benefits outweigh any tolerability or safety problems. • In most areas, local protocols will exist for the purpose of ensuring good medical practice. 1 Royal College of Psychiatrists London, Council Report CR190 (Nov 2014) Consensus state ment on high-dose antipsychotic medication. M https://www.rcpsych.ac.uk/docs/default-source/ improving-care/better-mh-policy/college-reports/college-report-cr190.pdf?sfvrsn=54f5d9a2_ 2 [accessed 30 May 2018].

An approach to treatment-resistant schizophrenia (TRS) Aetiology The aetiology is uncertain. However, the following factors may be important: • Neurodevelopmental factors: soft signs, history of obstetric complications, cognitive impairment. • Drug non-compliance. • Lack of adequate treatment: poor drug administration/absorption. However, over-treatment (>12mg haloperidol or equivalent) may also lead to poor tolerability/response. • Aggravating factors despite adequate treatment: concurrent drug or alcohol misuse, anticholinergic effects of anti-Parkinsonian medication or antidepressants. Management • Clarify diagnosis The clinical history and presentation should always be re-inspected to ensure the correct diagnosis has been reached. • Address comorbidity Comorbid substance misuse is common in schizophrenia and worsens outcome. • Non-compliance Consider interventions such as psychoeducation, compliance therapy, or family therapy to improve compliance with prescribed medication. • Pharmacological interventions Clozapine is the intervention most strongly supported by the evidence,13 and there is evidence that depot antipsychotic medication may convey a small advantage over oral equivalents. • Clozapine resistance Switching from clozapine to a previously untried SGA (e.g. olanzapine, risperidone, quetiapine) might be of benefit in partial treatment resistance. In more difficult cases, augmentation of clozapine with benzamides (sulpiride, amisulpride) and antiepileptics (lamotrigine) shows some success.14 ECT may be another option.15 • Rehabilitation Consider the role of NHS/non-NHS rehabiliation facilities in maximizing function, maintaining quality of life, and supporting those who remain symptomatic despite treatment—best evidence supports a combination of medication with psychosocial treatments. 13 Kane JM (2012) Addressing nonresponse in schizophrenia. J Clin Psychiatry 73:e07. 14 Kerwin RW, Bolonna A (2005) Management of clozapine-resistant schizophrenia. Adv Psychiat Treat 11:101–6. 15 Miyamoto S, Jarskog LF, Fleischhacker WW (2015) Schizophrenia: when clozapine fails. Curr Opin Psychiatry 28:243–8.

218 Chapter 5 Schizophrenia and related psychoses Clozapine 1: general guidelines Clozapine, an SGA, is a dibenzodiazepine derivative. Shortly after its intro duction to clinical practice in the mid-1970s, it was withdrawn because of several episodes of fatal agranulocytosis in patients on treatment. It was thought to have special efficacy in treatment-resistant schizophrenia, and this clinical belief was supported by an important trial by Kane et al. (1988), leading to its reintroduction in psychiatric practice, albeit with strict limita tions to its prescription. Patients on clozapine and doctors prescribing the drug must be registered with a monitoring agency and have regular, initially weekly, FBCs to monitor for neutropenia. In the CATIE trial,16 clozapine was shown to be superior in both treat ment response (positive and negative symptoms) and compliance for pa tients who failed to improve on an SGA, randomized to receive either another SGA or clozapine. Recent evidence from a meta-analysis found it to be superior for treatment-refractory disorder but recommended that if there is no response by 6mths, medications with lower adverse reactions should be considered.17 NICE guideline NICE (2014)18 recommends offering clozapine ‘to people with schizo phrenia whose illness has not responded adequately to treatment despite the sequential use of adequate doses of at least 2 different antipsychotic drugs’ (at least one of which was a non-clozapine SGA). Mode of action Clozapine mainly blocks D1 and D4 receptors; with less effect on D2 re ceptors than traditional FGAs (which may partially explain its lack of EPSEs and hyperprolactinaemia). Clozapine does have significant anticholin ergic, antihistaminergic, and anti-adrenergic activity, which accounts for its common side effects (E Clozapine 3: side effects, p. 222). The superior ef ficacy of clozapine in treating resistant schizophrenic patients may be due to its additional blockade of 5HT2 receptors or it causing i turnover of GABA in the nucleus accumbens,

which inhibits dopaminergic neurons. Pharmacokinetics Rapidly absorbed when taken orally (unaffected by food). Extensive first- pass metabolism (only 27–50% of a dose reaches the systemic circulation unchanged). Wide interindividual variations in the resulting plasma concen trations (influenced by factors such as smoking, hepatic metabolism, gastric absorption, age, and possibly gender). Steady-state plasma concentrations 16 McEvoy JP, Lieberman JA, Stroup TS, et al.; CATIE Investigators (2006) Effectiveness of clozapine versus olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia who did not respond to prior atypical antipsychotic treatment. Am J Psychiatry 163:600–10. 17 Siskind D, McCartney L, Goldschlager R, Kisely S (2016) Clozapine v. first- and second-generation antipsychotics in treatment-refractory schizophrenia: systematic review and meta-analysis. Br J Psychiatry 209:385–92. 18 National Institute for Health and Care Excellence (2014) Psychosis and schizophrenia in adults: pre vention and management. Clinical guideline [CG178]. M https://www.nice.org.uk/guidance/cg178/chapter/recommendations#choice-of-antipsychotic-medication [accessed 30 May 2018].

Clozapine 1: general guidelines take 7–10 days of treatment. Mean terminal elimination half-life ranges from 6 to 33hrs. Onset of antipsychotic effect may take several weeks, but max imal effects can require several months (and improvement may continue for up to 2yrs). Interactions (See Table 5.4 for summary.) • Lithium can increase the risk of developing seizures, confusion, dyskinesia, and possibly NMS. • May interfere with the action of AChEIs (e.g. donepezil and tacrine). • Smoking cigarettes increases the clearance of clozapine and may result in a substantial reduction in clozapine plasma concentrations. • Plasma concentrations of clozapine are i by caffeine (caffeinism is surprisingly common in this population), hence dose changes will be necessary when there is a change in caffeine-drinking habits. Contraindications Previous/current neutropenia or other blood dyscrasias; previous myo carditis, pericarditis, and cardiomyopathy; severe renal or cardiac dis orders; active or progressive liver disease/hepatic failure (see BNF for a complete list). Table 5.4 Clozapine interactions Effect Examples i drowsiness, sedation, dizziness, and possibility of respiratory depression Ethanol, H1-blockers, opiate agonists, anxiolytics, sedatives/hypnotics, tramadol, and TCAs i possibility of developing myelosuppressive effects Use of clozapine with other drugs known to cause bone marrow depression (e.g. chemotherapy agents) Drugs known to induce CYP1A2 activity may reduce efficacy Carbamazepine, phenobarbital, phenytoin, rifabutin, and rifampicin Drugs known to inhibit the activity of CYP1A2 may increase clozapine serum levels Cimetidine, clarithromycin, ciprofloxacin, diltiazem, enoxacin, erythromycin, or fluvoxamine Drugs known to inhibit the activity of CYP2D6 may increase clozapine serum levels Amiodarone, cimetidine, clomipramine, desipramine, fluoxetine, fluphenazine, haloperidol, paroxetine, quinidine, ritonavir, sertraline, and thioridazine Highly protein-bound drugs (may increase serum concentrations) Digoxin, heparin, phenytoin, or warfarin Worsening of anticholinergic effects H1-blockers, phenothiazines, TCAs, and antimuscarinic drugs i risk of hypotension Antihypertensive agents

220 Chapter 5 Schizophrenia and related psychoses Clozapine 2: starting and stopping Initiation of treatment and monitoring This is best done either as an inpatient or where appropriate facilities exist for monitoring (e.g. a day-patient facility). All patients must be registered with a monitoring service (see Table 5.5). A normal leucocyte count [white cell count (WCC) >3500/mm3, neutrophils >2000/mm3) must precede treatment initiation. FBCs must be repeated (and sent to monitoring ser vice) at weekly intervals for 18wks and then fortnightly until 1yr. Blood monitoring should continue monthly indefinitely thereafter. If there are concerns about compliance, serum blood

levels may also be checked (for reference range, see E Plasma level monitoring, p. 998). Dosing • Starting regime: 12.5mg once or twice on first day, then 25–50mg on second day, then i gradually (if well tolerated) in steps of 25–50mg daily over 14–21 days, up to 300mg daily in divided doses (larger dose at night; up to 200mg daily may be taken as a single dose at bedtime). • May be further i in steps of 50–100mg once or twice weekly. • Usual dose 200–450mg daily (max 900mg daily). • Increase in seizure frequency occurs above 600mg/day. • Routine blood level monitoring is not recommended; however, increasing the dose until a plasma level of 350mcg/L is achieved is sometimes recommended. If adverse effects are noted, reduce the dose until side effects settle, then increase again more slowly. • Lower doses may be required for the elderly, ♀, or non-smoking patients, and if the patient is on other medication that may affect the metabolism of clozapine. • Where there has been a break in treatment of >48hrs, treatment should be re-initiated with 12.5mg once or twice on the first day, and re-escalated. Table 5.5 Clozapine monitoring services Brand (manufacturer) Formulation Monitoring Clozaril® (Novartis) T: 25mg (scored), 100mg Clozaril Patient Monitoring Service (CPMS) Login: M https://www.clozaril.co.uk/ (accessed 30 May 2018) Denzapine® (Merz) T: 25mg (scored), 50mg, 100mg S: 50mg/mL Denzapine Monitoring Service (DMS) Login: M https://www.denzapine.co.uk/ (accessed 30 May 2018) Zaponex® (TEVA UK) T: 25mg (scored), 100mg Zaponex Treatment Access System (ZTAS) Login: M http://www.ztas.co.uk/ (accessed 30 May 2018) Key: T = tablets; S = suspension.

Clozapine 2: starting and stopping ‘Traffic light’ notification Telephone (urgent action) • No sample received Send another sample to the Clozapine Patient Monitoring Service (CPMS)/Denzapine Monitoring System (DMS)/ Zaponex Treatment Access System (ZTAS) and the local haematology laboratory, so that the next supply of medication may be dispensed. • Sample non-suitable for analysis As for ‘no sample received’. • Abnormal haematological results (e.g. neutrophil count) Either repeat the blood count or STOP clozapine, with advice regarding further monitoring (i.e. red light situation—see E ‘Written reports’ below). Written reports • Green light Normal—clozapine may be administered to the patient. • Amber light Caution—further sampling advised. If either WCC falls to 3000–3500/mm3 or the absolute neutrophil count falls to 1500–2000/ mm3, blood monitoring must be performed at least twice weekly until the WCC and absolute neutrophil count stabilize within the range of 3000–3500/mm3 and 1500–2000/mm3, respectively, or higher. • Red light STOP clozapine immediately. If the WCC is <3000/mm3 or the absolute neutrophil count is <1500/mm3, discontinue treatment with clozapine. Take blood samples daily until abnormality is resolved. Seek specialist advice from a haematologist. Monitor patients closely for symptoms suggestive of infection. Do not administer other antipsychotic drugs. Discontinuation Abrupt discontinuation of clozapine is not recommended, unless required by the patient’s medical condition (e.g. leucopenia). Gradually discontinue over 1–2wks (like the initiation schedule in reverse). Patients should be carefully observed for the recurrence of psychotic symptoms during drug discontinu ation. Symptoms related to cholinergic rebound, such as profuse sweating, headache, nausea, vomiting, and diarrhoea, may also occur.

 Clozapine 3: side effects (See Table 5.6 for management.) Common side effects • Anticholinergic Constipation, dry mouth, blurred vision, difficulty passing urine. • Anti-adrenergic Hypotension, sexual dysfunction. • Other Sedation, weight gain, nausea, vomiting, ECG changes, headache, fatigue, hypersalivation, tachycardia, hypertension, drowsiness, dizziness. Less common • Fainting spells. • Gastric discomfort. • Small involuntary muscle contractions. • Periodic catalepsy (reduced responsiveness and prolonged lack

of movement). • Enuresis. Rarer or potentially life-threatening • Impaired temperature regulation, fever, hepatitis, cholestatic jaundice, pancreatitis. • Agranulocytosis: leucopenia, eosinophilia, leucocytosis. (Note: the risk of fatal agranulocytosis19 is estimated to be 1:4250 patients treated.) • Thrombocytopenia (discontinuation of clozapine is recommended if the platelet count falls below 50,000/mm3). • Dysphagia. • Circulatory collapse, arrhythmias, myocarditis, cardiomyopathy, pericarditis, pericardial effusion, thromboembolism. Discontinue if persistent tachycardia occurs in the first 2mths of treatment. Note: the risk of fatal myocarditis or cardiomyopathy is estimated to be up to 1:1300 patients treated, although there is wide variation in the data (e.g. USA: 1:67,000 patients treated). • Pulmonary embolism. Note: the risk of fatal pulmonary embolism is estimated to be 1:4500 patients treated. • Confusion, delirium, restlessness, agitation. • Diabetes mellitus, hypertriglyceridaemia, intestinal obstruction, paralytic ileus, enlarged parotid gland, fulminant hepatic necrosis. • Interstitial nephritis, priapism, skin reactions. • NMS. Note: clozapine actually reduces mortality in schizophrenia, mainly due to a lower risk of suicide. 19 A report of data from the Clozaril® National Registry revealed that agranulocytosis occurred in 400 (0.6%) of 67,600 patients during the period of 1990–1995. Twelve of these 400 patients died; 340 of these 400 developed agranulocytosis in the first 6mths of therapy. The incidence rate of 0.6% is similar to earlier data published in 1993. The risk of developing agranulocytosis i with age and was higher in women.

Clozapine 3: side effects Table 5.6 Dealing with clozapine side effects Problem Possible solution Constipation Encourage high-fibre diet, adequate fluid intake, use of aperients if persistent Fever Symptomatic relief, check FBC, and look for sources of infection Hypersalivation Consider use of hyoscine hydrobromide (up to 300mcg tds) Hypertension Monitor closely, slow rate, or halt dose increase; if persistent, consider use of hypotensive agent (e.g. atenolol) Hypotension Advise caution when getting up quickly, monitor closely, slow or halt dose increase Nausea Consider use of anti-emetic (avoid metoclopramide and prochlorperazine if previous problems with EPSEs) Neutropenia/ agranulocytosis Stop clozapine; if outpatient, admit to hospital Nocturnal enuresis Avoid fluids in the evening, alter dose scheduling; if severe, consider use of desmopressin Sedation Reschedule dosing to give smaller morning or total dose Seizures Withhold clozapine for 24hrs, recommence at lower dose, consider prophylactic anticonvulsant (e.g. valproate) Weight gain Dietary and exercise counselling (E Weight gain with psychiatric medication, p. 1000)

224 Chapter 5 Schizophrenia and related psychoses Antipsychotic depot injections Antipsychotics may be given as a long-acting depot injection (the active drug in an oily suspension) injected into a large muscle (usually gluteus maximus), allowing for sustained release over 1–4wks. Previously, only FGAs were available, but now a number of SGA preparations have been developed and are finding their place in clinical practice. Dose for dose, the efficacy of these preparations is not greater than oral medication, but they do increase the likelihood of compliance. Indications Poor compliance with oral treatment, failure to respond to oral medica tion, memory problems or other factors interfering with the ability to take medication regularly, clinical need to ensure patient compliance (e.g. due to treatment order for patients detained under the MHA). Administration (See Table 5.7 and Box 5.8.) Test the dose, as undesirable side effects can be prolonged. Not more than 2–3mL of oily injection should be admin istered at any one site. Correct injection technique (including the use of z-track technique) and rotation of injection sites are essential. If the dose needs to be reduced to alleviate side effects, remember the plasma drug concentration may not fall for some time after reducing the dose and it may be many weeks before side effects subside.

For missed doses, refer to the specific product information. Box 5.8 Specific depot dosing for SGAs dependent on original oral dose Olanzapine • Olanzapine 10mg/day (oral): start 210mg/2wks or 405mg/4wks, maintenance after 2mths treatment, 150mg/2wks or 300mg/4wks. • Olanzapine 15mg/day (oral): start 300mg/2wks, maintenance after 2mths, 210mg every 2wks or 405mg every 4wks. • Olanzapine 20mg/day (oral): start 300mg/2wks, maintenance after 2mths, 300mg/2wks. • Adjust dose according to response; max 300mg every 2wks. Risperidone • Risperidone up to 4mg/day (oral), start 25mg/2wks. • Over 4mg/day risperidone (oral), start 37.5mg/2wks. • Dose adjusted at intervals of at least 4wks in steps of 12.5mg to max 50mg/2wks. • During initiation, oral risperidone should be continued for 4–6wks; oral dosing may also be used during dose adjustment of depot.

decanoate Haldol® 18–21d 3–9d 10–12wks 50mg 4wks 50mg 4wks 300mg/4wks interval Starting dose Dose interval Max dose

(md) 3–7d 10–12wks 20mg 7d 20–40mg 2–4wks 400mg/wk Maintena® 30–46d 7d 20wks No test dose—start 400mg and continue monthly; maintain oral dose for 14d 14–100d (md) 6–48hrs 6–12wks 12.5mg 4–7d 12.5–100mg 14–35d

Test to treatment steady state Test dose

dose Time to Table 5.7 Dosing schedules for depot antipsychotics

Peak decanoate Depixol® 8d (sd); 17d decanoate Modecate® 6–10d (sd); Generic name

Brand name t½

Aripiprazole Abilify Fluphenazine Haloperidol Olanzapine Flupentixol Antipsychotic depot injections embonate/pamoate ZypAdhera® 23–42d 2–4d 12wks E Antipsychotic depot injections, p. 224 For patients taking oral olanzapine; risk palmitate Piportil® 14–21d 9–10d 8–12wks 25mg 4–7d 25–50mg 4wks 200mg/4wks Paliperidone Xeplion® 25–49d 13d 10–16wks 150mg 8d 100mg 4wks 150mg/4wks decanoate Clopixol® 17–21d 4–9d 10–12wks 100mg 7d 200–500mg 1–4wks 600mg/wk paliperidone – consult product literature 3mths 525mg/ Consta® 3–6d 4–6wks 6–8wks E Antipsychotic depot injections, p. 224. Release of drug starts 3wks after 3mths Trivecta® 84-139d 30-33d Dosage is based upon previous once monthly dose of IM t½ = elimination half-life; d = days; hr(s) = hour(s); wk(s) = week(s); sd = single dose; md = multiple dose; supp = supplementation. injection and subsides by 7wk of post-injection syndrome Risperidone Risperdal Zuclopenthixol Pipotiazine

226 Chapter 5 Schizophrenia and related psychoses Specific side effects Pain/swelling at injection site, rarely abscesses, nerve palsies. Side effects as for oral medication but may take 2–3 days to emerge and persist for weeks after discontinuation. May be more likely to cause EPSEs than oral prepar ations (good evidence is lacking). 0 Post-injection syndrome Depot olanzapine embonate carries an unpredictable risk (1.4% of patients or 1:1500 injections) of idiosyncratic excessive sedative akin to olanzapine overdose between 1 and 6hrs postinjection. It is recommended that, after injection, the patient should be observed for at least 3hrs for any signs of this syndrome (e.g. sedation, acute confusion/aggression, EPSEs, dys arthria/ataxia, or seizure).

228 Chapter 5 Schizophrenia and related psychoses Disorders related to schizophrenia ICD-10/11 and DSM-5 describe a number of disorders that show sig nificant symptomatic overlap with schizophrenia. It is currently unclear whether these disorders represent distinct disorders or (as seems more likely) they share some degree of common aetiology with schizophrenia. Schizoaffective disorder This disorder has features of both affective disorder and schizophrenia which are present in approximately equal proportion. Its nosological status is uncertain, since some believe it to be a variant of schizophrenia; others, bipolar disorder; and some believe it represents a point on a continuum of 'unitary psychosis', lying between schizophrenia and mood disorders.20 Lifetime prevalence is 0.5–0.8%, with limited data available on gender and age differences. ICD-10/11 criteria • Schizophrenic and affective symptoms simultaneously present for at least 2wks (ICD-10) or 1mth (ICD-11), and both are equally prominent. • Excludes patients with separate episodes of schizophrenia and affective disorders and episodes due to substance use or medical disorders. DSM-5 criteria • An uninterrupted period of illness during which there is a major depressive, manic, or mixed episode, concurrent with symptoms that meet criterion A for schizophrenia. • ≥2wks of delusions and/or hallucinations without prominent mood symptoms during the lifetime of the illness. • Symptoms meeting criteria for a mood episode are present for the majority of the total duration of the active and residual periods. • The disturbance is not due to the direct physiological effects of a drug of abuse or medication or a general medical condition. Treatment As for schizophrenia, but treat manic or depressive symptoms as outlined in bipolar disorder (E Treatment of acute manic episodes, p. 340; E Treatment of depressive episodes, p. 342; E Prophylaxis, p. 344). Prognosis Depressive symptoms are more likely to signal a chronic course than manic symptoms. Good/poor prognostic factors are the same as schizophrenia, but outcomes are better than schizophrenia, due to the non- deteriorating course, and worse than primary mood disorder. Schizotypal disorder Schizotypal disorder is classified along with schizophrenia and related dis orders, in ICD-10/11, but along with cluster A/'odd-eccentric' personality disorders in DSM-5. It shares some of the clinical features of schizophrenia, but not the delusions or hallucinations. It is seen in 73% of the general population and 74.1% of psychiatric inpatients. The disorder tends to run a stable course. It is currently viewed as representing 'partial expression' of 20 Mellor C (2007) Schizoaffective, paranoid and other psychoses. In: Stein G, Wilkinson G (eds). Seminars in General Adult Psychiatry, 2nd rev edn, pp. 187–201. London: RCPsych Publications.

Disorders related to schizophrenia the schizophrenia phenotype—schizophrenia twin studies show an i risk of schizotypy in the unaffected twin; schizotypy is more common in first- degree relatives of schizophrenic subjects than the general population, and relatives of schizotypal subjects show an i risk of schizophrenia. Symptoms (DSM-5 criteria) Ideas of reference. Excessive social anx iety. Odd beliefs or magical thinking. Unusual perceptions (e.g. illusions). Odd/eccentric behaviour or appearance. No close friends/confidants. Odd speech. Inappropriate or constricted affect. Suspiciousness or paranoid ideas. Differential diagnosis Autism/Asperger syndrome, expressive/mixed receptive–expressive language disorder, chronic substance misuse, other personality disorders (especially borderline, schizoid, and paranoid). Treatment Risperidone (≤2mg/day)21 has some support from an RCT. Other antipsychotics may also be helpful. There is little evidence for other interventions, but highly structured supportive CBT may be best. Schizophreniform disorder (DSM-5) (May be coded under 'Other schizophrenia' in ICD-10 and 'Other specified schizophrenia' in ICD-11) The original term referred to patients with schizophrenic

symptoms with a good prognosis22 and now refers to a schizophrenia-like psychosis that fails to fulfil the duration criterion for schizophrenia in DSM-5. The treatment is the same as for an acute episode of schizophrenia. Most common in adoles cence and young adults and is much less common than schizophrenia, with a lifetime prevalence of 0.2%. DSM-5 • Criteria A, D, and E of schizophrenia are met. • An episode of the disorder (including prodromal, active, and residual phases) lasts at least 1mth, but <6mths. • Specified as with good prognostic features (as evidenced by 2+ of: onset of prominent psychotic symptoms within 4wks of the first noticeable change in usual behaviour or functioning, confusion or perplexity at the height of the psychotic episode, good premorbid social and occupational functioning, absence of blunted or flat affect); or without good prognostic features (applied when two or more of the above features have not been present). Course and prognosis By definition, episodes last for >1mth, but <6mths. Patients return to baseline functioning once the disorder has resolved. Progression to schizophrenia is estimated to be between 60% and 80%. Some patients have two or three recurrent episodes. Treatment Antipsychotics ± a mood stabilizer and psychotherapy. 21 Koenigsberg HW, Reynolds D, Goodman M, et al. (2003) Risperidone in the treatment of schizo typal personality disorder. J Clin Psychiatry 64:628–34v. 22 Langfeldt G (1982) Definition of ‘schizophreniform psychoses’. Am J Psychol 139:703.

230 Chapter 5 Schizophrenia and related psychoses Delusional disorder 1: clinical features Essence Delusional disorder is an uncommon condition in which patients present with circumscribed symptoms of non-bizarre delusions (DSM-5 now allows ‘with bizarre content’; ICD-11 does not specify), but with ab sence of prominent hallucinations and no thought disorder, mood disorder, or significant flattening of affect. Symptoms should have been present for at least 1mth (DSM-5). ICD-10/11 specify at least 3mths for delusional disorder but, if it is less than this, allow diagnosis under other persistent delusional disorder (ICD-10) or delusional disorder, unspecified (ICD-11). DSM-5 has par ticular subtypes (see Box 5.9). Box 5.9 DSM-5 subtypes1 • Erotomanic (De Clérambault syndrome) Patients present with the belief that some important person is secretly in love with them and may make efforts to contact that person. Clinical samples are often ♀ and forensic samples more likely to be ♂. Some cases are associated with dangerous or assaultive behaviour. • Grandiose Patients believe they fill some special role, have some special relationship, or possess some special ability(ies).They may be involved with social or religious organizations. • Jealous2 (Othello syndrome) Patients possess the fixed belief that their spouse or partner has been unfaithful. Often patients try to collect evidence and/or attempt to restrict their partner’s activities. May be associated with forensic cases involving murder. • Persecutory This is the most common presentation of delusional disorder. Patients are convinced that others are attempting to do them harm. Often they attempt to obtain legal recourse (litigious or ‘querulous paranoia’), and they sometimes may resort to violence. • Somatic Varying presentation, from those who have repeat contact with physicians requesting various forms of medical or surgical treatment to patients who are delusionally concerned with bodily infestation, deformity (E Body dysmorphic disorder, p. 872), or odour (E Olfactory reference disorder (ORD), p. 388). • Mixed Presence of 2+ themes; no single theme predominating. • Unspecified The theme cannot be determined or does not fit the listed categories.1 1 ICD-10 subtypes are similar: Erotomanic, Grandiose, Jealous, Persecutory, Litigious, Hypochondriacal, and Self-referential. ICD-11 delusional subtypes are differentiated in a section ‘Mental or behavioural symptoms, signs or clinical findings’ and include: bizarre, being controlled, guilt, reference, erotomanic, grandiose, jealous, persecutory, religious, somatic, nihilistic, misiden tification, impoverishment, other, and unspecified. 2 Shepherd M (1961) Morbid jealousy: some

clinical and social aspects of a psychiatric symptom. J Mental Sci 107:607–753 (the ‘classic’ paper).

Delusional disorder 1: clinical features Points to note • Patients rarely present to psychiatrists. More often, other physicians (due to somatic complaints), lawyers (due to paranoid ideas), or the police (when they act on, or complain about, their delusions) see them. • Careful assessment and diagnosis are vital, because delusions are the final common pathway of many illnesses (E Delusional disorder 2: differential diagnosis and aetiology, p. 232). When delusional disorder is discovered, treatment can be fraught with difficulty because of the reticent nature of such patients. With persistence, a combination of biopsychosocial treatments can be effective. Diagnosing pathological delusions—key points Judgement is necessary to distinguish delusions from over-valued ideas, par ticularly when the ideas expressed are not necessarily bizarre or culturally abnormal23 (and may have some basis in reality). Assess: • The degree of plausibility. • Evidence of systemization, complexity, and persistence. • The impact of the beliefs on behaviour. • The possibility that they might be culturally sanctioned beliefs different from one’s own (E Cultural context and the presentation of psychiatric disorders, p. 984). • Observation of associated characteristics, including hallucinations. • History of ‘morbid change’. • Evidence of other risk factors (E Risk factors, see below). Clinical features Level of consciousness is unimpaired; observed behaviour, speech, and mood may be affected by the emotional tone of delusional content (e.g. hyperalertness with persecutory delusions); thought process is generally unimpaired; thought content reflects preoccupation with circum scribed (usually single theme), (non-)bizarre delusions; hallucinations may occur but generally are not prominent and reflect delusional ideas (more commonly olfactory/tactile than visual/auditory); cognition and memory generally intact; insight and judgement impaired to the degree that the delu sions influence thought and behaviour; formally assess risk (e.g. violence to self and others and history of previous behaviour influenced by delusions). Note: persistent anger and fear are risk factors for aggressive ‘acting-out’ behaviours. Epidemiology Relatively uncommon. Prevalence 0.025–0.03% (1–2% of hospital admissions); age range 18–90yrs (mean 40–49yrs); ♂ = ♀, but de lusional jealousy more common in men and erotomania more common in women; 50% of patients are in employment; 80% are married. Risk factors Advanced age, social isolation, group delusions, low socio- economic status, premorbid personality disorder, sensory impairment (par ticularly deafness), recent immigration, family history, and history of head injury or substance abuse disorders. Course and prognosis Onset may be acute or insidious. Treatment out comes: remission (33–50%), improvement (10%), persisting symptoms (33–50%). Better prognosis: acute subtypes, where stress is a factor, jealous or persecutory subtypes, symptoms persisting <6mths. 23 Manschreck T (1996) Delusional disorder: the recognition and management of paranoia. J Clin Psychiatry 57(Suppl 3):8.

232 Chapter 5 Schizophrenia and related psychoses Delusional disorder 2: differential diagnosis and aetiology Differential diagnoses • Substance-induced delusional disorders (e.g. alcohol, cannabis, stimulants, hallucinogens, anabolic steroids, corticosteroids, antihistamines, sympathomimetics, antibiotics, disulfiram, dopamine agonists, anticholinergics, over-the-counter medications, herbal remedies). Careful history-taking focusing on temporal relationships may reveal onset, persistence, and cessation of symptoms to be related to drug use. • Other physical disorders Focused history, examination, and investigations should help exclude other disorders [e.g. head injury, CNS infection, vascular disease, epilepsy, neurodegenerative disorders, metabolic disorders, endocrine disorders, vitamin deficiencies (B12, folate, niacin, thiamine), toxins (mercury, arsenic, manganese, thallium)]. • Mood disorders with delusions (manic and depressive types)

Mood and related biological symptoms are usually more severe and precede delusions. • Schizophrenia Presence of psychotic symptoms other than relatively circumscribed delusions; thematically associated hallucinations; disorganized thought processes, speech, or behaviours; negative symptoms; cognitive deficits; and greater functional impairment. • Delirium Evidence of cognitive impairment, altered/fluctuating level of consciousness, altered sleep/wake cycle, and hallucinations. • Dementia Cognitive impairment which may be subtle and only found on formal testing. • Elderly patients (late paraphrenia) Thought to be distinct from delusional disorder (E Specific aspects of psychiatric illnesses in the elderly 3: mood disorders, p. 552) and schizophrenia, associated with social isolation, ageing, medical problems/treatments, and sensory loss. • Dysmorphophobia/body dysmorphic disorder (E Body dysmorphic disorder, p. 872) Significant overlap with delusional disorder, few significant differentiating factors exist. • OCD (E Obsessive–compulsive disorder, p. 690) Significant overlap with delusional disorder, and if reality testing regarding obsessions or compulsions is lost, delusional disorder often is diagnosed. • Hypochondriasis (E Hypochondriasis, p. 870) Health concerns generally are more amenable to reality testing and are less fixed than in delusional disorder. • Paranoid personality disorder (E Table 12.1, p. 523) Absence of clearly circumscribed delusions, presence of a pervasive, stable pattern of suspiciousness or distrust. • Misidentification syndromes (E Delusional misidentification syndromes, p. 240) Easily confused with delusional disorder; may be associated with other CNS abnormalities. • Induced/shared psychotic disorder (E Induced delusional disorder, pp. 238–239) Evidence that relatives/close friends share similar delusional beliefs.

233 DELUSIONAL DISORDER 2: DIAGNOSIS AND AETIOLOGY Aetiology Delusional disorders represent a heterogenous group of conditions that appear distinct from mood disorders and schizophrenia, although there is significant diagnostic (and genetic) overlap with paranoid personality traits/ disorder and schizophrenia. Data suggest that among patients diagnosed with delusional disorder, 3–22% are later reclassified as schizophrenic and fewer than 10% are later diagnosed with a mood disorder. Biological • Delusions can be a feature of a number of biological conditions, suggesting possible biologic underpinnings for the disorder. • Most commonly, neurological lesions associated with the temporal lobe, limbic system, and basal ganglia are implicated in delusional syndromes. • Neurological observations indicate that delusional content is influenced by the extent and location of brain injury. • Prominent cortical damage often leads to simple, poorly formed, persecutory delusions. • Lesions of the basal ganglia elicit less cognitive disturbance and more complex delusional content. • Excessive dopaminergic and reduced acetylcholinergic activity has been linked to the formation of delusional symptoms. Psychological/psychodynamic • Freud proposed that delusions served a defensive function, protecting the patient from intrapsychically unacceptable impulses through reaction formation, projection, and denial. • Cognitive psychology regards delusions as the result of cognitive defects where patients accept ideas with too little evidence for their conclusions; delusions as a result of attempting to find a rational basis for abnormal perceptual experiences. • Neuropsychological models:24 • Cognitive bias model (CBM): proposes paranoia is a defence against thoughts that threaten the ‘idealized self’, protecting a fragile self- esteem—positive events are attributed to the self, whereas negative events are ascribed to outside influences. • Cognitive deficit model (CDM): cognitive impairments and distortions of threat-evaluating mechanisms lead to delusion formation. Social/individual factors The chances of developing delusional disorder are i with: • Marked distrust and suspicion. • Social isolation. • Heightened feelings of jealousy. • Fragile self-esteem. • A tendency to see their own defects in others. • Habitual rumination over the meaning of

events and motivation of others. 24 Abdel-Hamid M, Brüne M (2008) Neuropsychological aspects of delusional disorder. Curr Psychiatry Rep 10:229–34.

234 Chapter 5 Schizophrenia and related psychoses Delusional disorder 3: assessment and management Assessment Patients with delusional disorder are exceptionally difficult to assess. At interview, they may be evasive, guarded, and suspicious. Often they be come irritated, angry, or hostile. They may be overly sensitive to some lines of questioning, even to the point of threatening legal action. Assessment should include: • A thorough history and MSE. • Information gathering (third party and other sources). • Exclusion of underlying causation (including physical investigations) to rule out other conditions that commonly present with delusions (E Differential diagnosis, p. 232). • Clearly documented risk assessment (especially aggression/self-harm). Where there is significant risk to another person/partner, duty of care may over ride patient confidentiality and allow warning of that individual and/or informing the police (E Breaking confidentiality, p. 970). Management Typical obstacles to the treatment of delusional disorder: • The patient's denial of the illness which causes difficulties in establishing a therapeutic alliance. • The patient's experiences of significant social and interpersonal problems (which may confirm their firmly held beliefs). • The fact that antipsychotic medication is often of limited efficacy. Admission to hospital ought to be considered if there is a clear risk of harm to self or violence towards others. Otherwise, outpatient treatment is pre ferred. Approaches to management include: • Separation From the source or focus of delusional ideas (if possible). • Pharmacological25,26 • Data forpharmacotherapy are limited to case reports or small open- label interventions. • Given the symptomatic overlap with psychotic disorders, antipsychotics have some utility (the most commonly reported SGAs used are risperidone and olanzapine). • There was a widely held anecdotal view supporting the preferential use of pimozide. However, although there are no full-scale clinical trials, what evidence there is suggests that no antipsychotic is preferentially effective, that response rates are around 50%, with 90% of patients seeing some improvement, and that somatic delusions are the most likely to respond. 25 Manschreck TC (2006) Recent advances in the treatment of delusional disorder. Can J Psychiatry 51:114–19. 26 Skelton M, Khokhar WA, Thacker SP (2015) Treatments for delusional disorder. Cochrane Database Syst Rev 5:CD009785.

Delusional disorder 3: assessment and management • The evidence also favours the use of SSRIs, given the overlap with OCD, body dysmorphic disorder, and mood disorder. • BDZs may be useful when there are marked anxiety symptoms. • Data for the use of anticonvulsant agents and mood stabilizers are even more limited. • Psychological/psychotherapeutic • Minimizing risk factors, e.g. sensory impairment, isolation, stress, and precipitants of violence. • Educational and social interventions Social skills training (e.g. not discussing delusional beliefs in social settings; promoting interpersonal competence; and increasing comfort in interacting with those who the individual feels are judging or having harmful intent towards them). Taking control and initiative can dissipate the feeling of loss of control that feeds into, and reinforces, the delusions. • Individual therapy Requires persistence in establishing a therapeutic alliance without validating or overtly confronting the patient's delusional system. • Supportive therapy May help with isolation and distress stemming from the delusional beliefs (reframing problems due to delusional beliefs as symptoms). • Cognitive techniques (best studied in persecutory subtype) Reality testing and reframing. Insight-orientated therapy to develop a sense of 'creative doubt' in the internal perception of the world through empathy with the patient's defensive position. • Post-psychotic depression • Ten per cent or more of delusional disorder patients who respond to antipsychotics

may develop severe depression with a risk of suicide. • Withdrawal of antipsychotic may improve mood but worsen delusions; hence, the addition of an antidepressant may be indicated, while maintaining the lowest effective dose of antipsychotic. Later the antidepressant may be gradually withdrawn.

236 Chapter 5 Schizophrenia and related psychoses Acute and transient psychotic disorders (Referred to as ‘Brief psychotic disorder’ in DSM-5; see Box 5.10.) Box 5.10 ICD-10 subtypes ICD-10 allows for these disorders to occur with or without the presence of an acute stressor, and outlines the following subtypes: • Acute polymorphic psychotic disorder with or without symptoms of schizophrenia • Variable and changeable psychotic symptoms (day to day or hour to hour), with frequent intense emotional turmoil. • Includes Perris’s (1974) ‘cycloid psychosis’ after Karl Leonard’s description—the treatment of choice is lithium (Perris, 1978). • Also ‘bouffée délirante’ (Magnan, 1895), reviewed by Allodi (1982) who stressed the avoidance of long-term medication, highlighting sociocultural factors, especially migration and language. • Acute schizophrenia-like psychotic disorder Also referred to as ‘brief schizophreniform psychosis’ or ‘schizophrenic reaction’ where the psychotic symptoms are relatively stable but have not lasted more than a month (ICD-10, DSM-5 brief psychotic disorder) or have lasted 1–6mths (DSM-5 schizophreniform disorder). • Other acute predominantly delusional psychotic disorder • Onset is acute (2wks or less), delusions or hallucinations present most of the time. If delusions persist longer than 3mths, then the diagnosis is that of persistent delusional disorder (E Delusional disorder 1: clinical features, p. 230). • Includes the Scandinavian concept of ‘psychogenic/reactive psychosis’ for which the prognosis is good, and the treatment of choice is supportive psychotherapy and short-term use of medication (Stromgren, 1989). • ‘Hysterical psychosis’ (Hirsch and Hollander, 1969), which includes three subtypes: culturally sanctioned behaviour (like culture-specific disorders); appropriation of psychotic behaviour (conversion process); and true psychosis (‘failure of repression when faced with acute stress in a vulnerable ego’, in, for example, histrionic personality)––in the USA, this is used as a diagnostic label for ‘reactive psychosis’. • ‘Ganser syndrome’—characterized by approximate answers, disorientation, clouding of consciousness, hallucinations, motor disturbance, anxiety or apathy, normal ADLs, sudden resolution with amnesia for the period of illness. Proposed mechanisms read much like the differential diagnosis for acute and transient psychotic disorders (E Acute and transient psychotic disorders, p. 236): hysterical conversion, organic confusion, psychosis, or malingering. In ICD-11, additional codes may be used for ‘symptomatic manifest ations’—including positive, negative, depressive, manic, psychomotor, and cognitive symptoms—and severity: mild, moderate, and severe.

Acute and transient psychotic disorders Clinical features Sudden onset, variable presentation (including per plexity, inattention, formal thought disorder/disorganized speech, delusions or hallucinations, disorganized or catatonic behaviour), usually resolving within <1mth (DSM-5) or 3mths (ICD-10/11). Aetiology Sometimes these disorders occur in the context of an acute stressor (both ICD-10 and DSM-5 allow for specifying ‘with or without’ marked stressor(s)/acute stress), e.g. life events such as bereavement, marriage, unemployment, imprisonment, accident, childbirth (DSM-5 ‘with post-partum onset’), or migration and social isolation (with language and cultural factors). ICD-11 has separate categories for ‘first episode’ and ‘mul tiple episodes’. Epidemiology Associated with certain personality types (e.g. paranoid, borderline, histrionic); more prevalent in developing nations where there is a strong emphasis on traditional values (may demonstrate culture-specific features; E Cultural context and the presentation of psychiatric disorders, p. 984).

Age of onset is later in industrialized nations. More common in women. Differential diagnosis • Organic disorders—dementia/delirium. • Bipolar affective disorder/depression—delusions of guilt/persecution. • Drug and alcohol disorders. • Personality disorder—paranoid/borderline/histrionic. • Culture-specific disorders (E Cultural context and the presentation of psychiatric disorders, p. 984). • Factitious disorder/malingering. • Schizophrenia (if it persists for >1mth). Management • Assessment is vital to make the appropriate diagnosis. • Short-term admission may help with any suicidal/aggressive tendencies, provide care, support, and address specific psychosocial stressors. • Where medication is considered, short-term use of antipsychotics/ BDZs may be helpful (E Severe behavioural disturbance, p. 1048). • Antidepressants/mood stabilizers may be useful to prevent relapse/ further episodes. • Address specific social issues, and consider reality-orientated, adaptive, supportive psychotherapy. Course and prognosis • By definition, these disorders are brief, lasting days, weeks, or months. • Prognosis better if short interval between onset and full-blown symptoms. Also better if there is confusion/perplexity, good premorbid social/occupational functioning, and absence of blunted/flat affect. • Outcome is better than schizophrenia (socially and symptomatically). • Relapse is common, with i mortality and suicide rates, compared with the general population. • The chances of recurrence are high, and follow-up/low-dose pharmacotherapy is recommended to continue for at least 1–2yrs (and withdrawn cautiously with close clinical review).

238 Chapter 5 Schizophrenia and related psychoses Induced delusional disorder (DSM-5: ‘Delusional symptoms in partner of individual with delusional dis order’ within ‘Other specified schizophrenia spectrum and other psychotic disorder’ (see Box 5.11); ICD-10 has the specific diagnosis ‘Induced delu sional disorder’, but ICD-11 codes under ‘Delusional disorder, unspecified’. Also known as ‘folie à deux’ (or even ‘folie à trois’ or ‘folie à famille’!), this disorder was recognized and described by Harvey as early as 1651 and reviewed as a concept by Howard in 1994. Silveira and Seeman (1995) also reviewed the literature and found equal sex ratio; broad range of ages; 90% of couples, siblings, or parent/child; comorbidity with depression, de mentia, and mental retardation; two-thirds socially isolated; and a common association with hallucinations. Without intervention, the course is usually chronic. The content of the shared belief depends upon the delusions of the individual with the primary illness. Examples may include: persecutory beliefs (‘them’: the paranoid pseudocommunity27), delusional parasitosis, delusional belief in a place being haunted, belief in having a child who does not exist, other misidentification delusions, or apocalyptical beliefs in cults and quasi-religions (with the serious risk of altruistic mass suicide). Subtypes • Folie imposée—the delusions of an individual with a primary psychotic illness are adopted by another healthy individual (separation alone usually cures the normally healthy individual). • Folie simultanée—when two persons with primary psychotic illness develop the same delusions at the same time. • Folie communiqué—after a period of resistance, a healthy individual adopts the delusions of a person with primary psychotic illness (separation is less successful without other interventions). • Folie induite—pre-existing primary psychosis in both patients, but one patient has adopted their fellow patient’s delusions. 27 Cameron N (1949) The paranoid pseudo-community. Am J Sociol 49:32–8. Box 5.11 DSM-5 Other specified schizophrenia spectrum and other psychotic disorder DSM-5 applies this category to a number of specific presentations that do not meet the full criteria for any of the other disorders in the schizo phrenia spectrum diagnostic class. For example: • Persistent auditory hallucinations Occurring in the absence of any other features. • Delusions with significantly overlapping mood episodes Persistent delusions with periods of overlapping mood episodes longer than just brief mood episodes allowed in delusional

disorder. • Attenuated psychosis syndrome Psychotic-like symptoms below the threshold for full psychosis (e.g. less severe, more transient, insight relatively maintained). • Delusional symptoms in partner of individual with delusional disorder (see opposite).

Induced delusional disorder Aetiology Psychodynamic theories These include the fear of losing an important relationship in an otherwise isolated individual with little scope for reality testing; or the passive acceptor has repressed oedipal fantasies that are released by the psychotic partner, causing identification of the dominant partner with a parent. Learning theory Psychotic thinking is learnt through ‘observational learning’. Social isolation Isolation due to language, geographical barriers, and per sonality may also play a part in the development of the illness. Management • Separation—may lead to complete remission in up to 40% of cases. • Psychological—aimed at giving up delusional beliefs (equivalent to rejecting a close relationship). • Pharmacological—for the active, not the passive, partner (except in the case of folie simultanée when both patients require treatment).

240 Chapter 5 Schizophrenia and related psychoses Delusional misidentification syndromes Usually manifest as symptoms of an underlying disorder (e.g. schizophrenia, mood disorder, delusional disorder, organic disorder), these syndromes rarely occur in isolation and hence are not included separately in ICD-10/11 or DSM-5. Recently, interest has been focused on these rare (and bizarre) symptoms because of the insight they may give into the normal functioning of the brain (a ‘lesion’ paradigm). Examples Capgras delusion (l’illusion des sosies) The patient believes others have been replaced by identical/near-identical imposters. Can apply to animals and other objects, and often associated with aggressive behaviour. Frégoli delusion (l’illusion de Frégoli) An individual, most often unknown to the patient, is actually someone they know ‘in disguise’. The individual is often thought to be pursuing or persecuting the patient. Intermetamorphosis delusion The patient believes they can see others change (usually temporarily) into someone else (both external appearance and internal personality). Subjective doubles delusion The patient believes there is a double (‘doppelgänger’) who exists and functions independently. Autoscopic syndrome The patient sees a double of themselves projected onto other people or objects nearby. Reverse subjective double syndrome The patient believes they are an imposter, in the process of being physically and psychologically replaced. Reverse Frégoli syndrome The patient believes others have completely misidentified them. Aetiology Psychodynamic These syndromes are viewed as the extremes of normal misidentification due to intense focusing on particular details; the effects of beliefs/emotions on perception; the effects of vivid imagination in a person experiencing a disorder of mood, judgement, and coenesthesia; and mani festations of the defence mechanisms of projection, splitting, or regression with loss of identity and flawed reconstruction. Biological There may be evidence of underlying right hemisphere dys function, anterior cortical atrophy, temporal lobe pathology, bifrontal disconnectivity—with resultant impaired facial recognition, dissociation of sensory information from normal affect, and failure to suppress inappro priate, repetitive behaviour. Management • Full physical and psychiatric assessment. • Interventions should be directed towards any underlying problem. • Antipsychotics/anticonvulsants may also treat clearly organic cases.