Chapter 15: Schizophrenia

Anthony Harris

Specialty of Psychiatry, Sydney Medical School, The University of Sydney, Australia, Westmead Institute for Medical Research, Australia, and Western Sydney Local Health District Mental Health Services, Australia.

Introduction

Schizophrenia is the most common of the group of psychotic illnesses that include schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, bipolar disorder and major depression with psychotic features. In most of our public hospitals people admitted with psychotic disorders form a significant proportion of the total number of admissions and the personal and societal cost of their care is high and increasing in both high and low income countries (Solmi et al., 2023). Schizophrenia is also a highly stigmatised illness, the effect of which has contributed to the under-resourcing of mental health services and the inadequacy of treatments available for people with schizophrenia when they present for the treatment of their physical illnesses.

Epidemiology

Schizophrenia is an uncommon but chronic disorder with a lifetime prevalence of 7.2/1000 (95% CI 3.1 – 27.1) (Saha et al., 2005). The risk of having the disorder is increased by being male, living in an urban environment or migrating into a community that is subject to discrimination. It is an illness with an onset mostly in young adulthood with 64.8% of people having the onset of the illness before the age of 25 years. As you can see from Figure 15.1 it is rare to see schizophrenia in people younger than 15 years, and in those people developing schizophrenia over the age of 30 there is a slight preponderance of women. The onset of the illness mostly occurs over a one to six month timespan. The period prior to presentation is usually marked by a decrease in functioning and withdrawal from family and friends. This period of time is known as the prodrome of the illness. Recent improvements in early intervention services have allowed for a proportion of these individuals to be identified before the clear onset of their full psychotic illness. These individuals are said to have an “at risk mental state”. Intervention at

this stage may contribute to a decrease in the number of people who transitioned to a full psychotic illness.

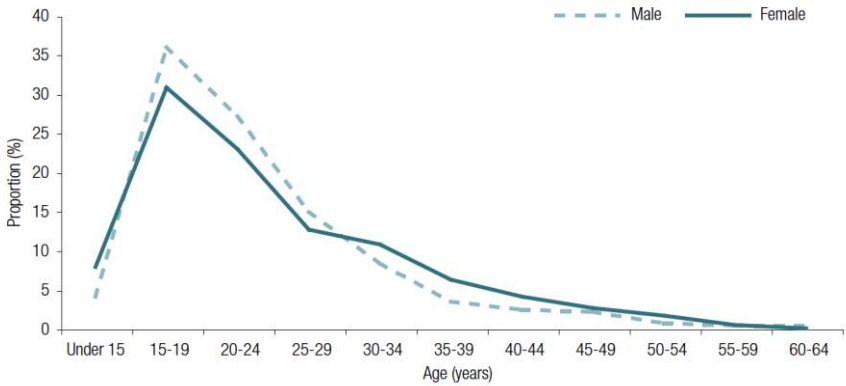

Figure 15.1. Age of onset of psychosis by sex (Morgan et al., 2012).

Aetiology

Although there is no clear pathophysiology for schizophrenia at present, we know much about the aetiology of the disease. It is genetically based. If your monozygotic twin has schizophrenia your morbid risk of also getting the disease ranges from 41-68%. If, on the other hand, your dizygotic twin has schizophrenia then that risk is decreased to between 0-28% (Cardno and Gottesman, 2000). This information underlines the importance of the genetic contribution to schizophrenia but also indicates a considerable environmental or non-inheritable contribution to the disorder.

Large scale Genome-Wide Association Studies (GWAS) have now identified 287 distinct genetic loci that are associated with schizophrenia (Trubetskoy et al., 2022). These genes, individually of low effect size, code for both presynaptic and postsynaptic functions, in a number of cell types, including interneurons, pyramidal and spiky neurons, and in multiple brain regions. A small proportion of schizophrenia is associated with *de novo* or rare copy number variants that have a large effect and are sometimes a part of other neurodevelopmental disorders such as velo-cardio-facial syndrome. These individuals have a higher incidence of other neurodevelopmental disorders such as developmental delay (Rees et al., 2015).

Schizophrenia was thought to be a disorder of excess dopaminergic activity on the basis that (1) all effective antipsychotic medications block or partially agonise dopamine D2 receptors, (2) the psychotogenic effect of dopamine agonists such as

amphetamines or dopamine precursors such as levodopa, and, (3) an increase in presynaptic dopamine synthesis and release in schizophrenia (Howes et al., 2017). However, other strands of evidence clearly implicate the glutamatergic system and in particular the N-methyl-D-aspartate (NMDA) receptor. This is strongly supported by the GWAS evidence that has identified numerous genes important to glutamatergic and NMDA function. Substances such as ketamine and phencyclidine are also potent glutamatergic agents acting at the NMDA receptor. Intoxication with these substances mimic the positive symptoms of psychosis. However, medications that act via the glutamatergic system have yet to effectively treat schizophrenia in randomised controlled trials.

Substance abuse is frequently implicated in the onset or relapse of psychosis (see Chapter 29). There is a complex association of substances such as cannabis or amphetamines with psychotic symptoms during the phase of intoxication, but also during withdrawal and subsequently with persistent psychotic syndromes. Chronic abuse of substances such as amphetamines or cannabis can result in a chronic psychotic state that is phenomenologically identical to schizophrenia. However, this is by no means inevitable and the majority of people who abuse these substances do not develop schizophrenia. A gene x environment relationship has been identified for cannabis use and an increased risk of the development of schizophrenia in individuals with a specific single nucleotide polymorphism (SNP) – either in the catechol-O-methyltransferase (COMT) gene or the AKT1 gene (Caspi et al., 2005; Di Forti et al., 2012).

Early life stress (ELS) is a significant risk for most psychiatric illnesses and schizophrenia is no exception. These early life stressors can be biological factors that interfere with the normal neurodevelopment of the foetus such as maternal infection, malnutrition such as experienced in the Dutch hunger winter of 1944 or obstetric complications. ELS caused by physical abuse, sexual abuse or neglect during childhood is also associated with schizophrenia and other psychotic disorders (Bailey et al., 2018). The effect of interpersonal stress is probably one of the factors contributing to the increased rate of schizophrenia seen in migrant populations from marginalised communities such as the Afro-Caribbean community in Britain.

These biological, psychological and social factors have a measurable effect upon the brain. Neuroimaging studies have identified widespread reductions in cortical grey and white matter and increases in lateral and 3rd ventricle size in people with schizophrenia (Brugger and Howes, 2017). On a microscopic scale, the cortical grey matter is thinner, with a loss of volume particularly in laminae 2 and 3. There is no decrease in the number of pyramidal cells, but a loss of the neurophil between the cells caused by a decrease in cell arborization – a reduction in cell dendrites and axons. Aberrant cell migration is also seen. There may be a reduction in

oligodendrocytes and in white matter volume. Unfortunately, none of these changes are pathognomonic of schizophrenia (Harrison, 1999).

The effect of all this is to disrupt the normal network of connectivity in the brain. This subtle disruption to cortical connectivity is thought to be at the heart of the typical symptoms of schizophrenia such as hallucinations and delusions as well as the loss of function seen with the negative and cognitive symptoms. A useful model of schizophrenia is that of a genetically based neurodevelopmental disorder which requires multiple additional triggers before the actual disorder is manifest. These triggers are diverse and may be an obstetric problem at birth or maternal infection during the first or second trimester. These individuals are then further compromised (or protected) by the quality of their early childhood upbringing and their history of substance use. This model makes sense of the multiple aetiological strands of the illness and, importantly, provides avenues for intervention.

Symptomatology

The signs and symptoms of schizophrenia are diverse, and it is possible for two individuals to both be diagnosed with this illness but share few symptoms. A five-domain model (see Table 15.1) of the signs and symptoms of schizophrenia helps with understanding the management of the disorder and will be used here.

Table 15.1. Five domain model of the signs and symptoms of schizophrenia.

Positive	Negative	Disorganisation	Mood	Cognitive
Hallucinations (e.g., hearing voices)	Lack of motivation	Disorganised thinking and speech	Depression	Impaired attention and concentration
Delusions (e.g., persecutory, bizarre, grandiose)	Anhedonia	Disorganised behaviour	Anxiety	Reduced mental flexibility
	Blunted affect	Aggression		Impaired Memory
	Reduced speech content and output	Hostility		Impaired Social cognition
	Social withdrawal			

The positive symptoms are hallucinations and delusions. A hallucination is a perception in the absence of any external stimulus. They may be perceived in any one of our senses (auditory, visual, olfactory, gustatory, somatosensory e.g., feeling

something touch their skin, as well as interoception e.g., feeling something living inside of the person). Although auditory hallucinations are typical of schizophrenia - experienced in approximately 80% of people with schizophrenia - they are not pathognomonic as they also occur in other pathological states such as dementia, mania or alcoholic hallucinosis. The voices are commonly experienced as originating outside of the person, frequently derogatory or critical and often male. The volume can vary from the softest whisper to shouts and the content can vary from conversation or a voice describing what the person is doing ("She is now lifting a cup") to voices talking about, criticising or commanding the patient. They can echo or speak the person's thoughts out loud. They can persist all day or only occur fleetingly.

Delusions are false unshakeable beliefs out of keeping with the person's cultural and educational background. These beliefs are very varied but commonly include delusions of persecution (that someone is trying to harm them, e.g., the CIA or KGB), of reference – that experiences or sensations in the outside world pertain to the individual (the TV is talking about them); of passivity – that their own thoughts, feeling and actions are taken over by an external agency; of thought alienation – that their own thoughts are being controlled or broadcast out loud, or are being inserted into their mind; of misidentification – that familiar people have been replaced by others (Capgras syndrome). Many other delusional beliefs are possible.

The negative symptoms of schizophrenia describe a loss of function. These include blunted affect in which the emotional expressivity of the person is lost; anhedonia, when the ability to experience emotions, both good or bad, is lost; amotivation, when personal drive or motivation is diminished or lost; asociality, when the wish to be with others is decreased or lost; and alogia where there is a loss of the richness, complexity and/or quantity of thought, leading to a poverty of expression or content of thought.

Disorganisation describes how an individual's behaviour and thought process can be fractured and disorganised. This can be seen in the increasingly chaotic behaviour of people with psychosis which can put them on the streets or renders their homes filthy. It also is associated with an increase in aggression and hostility. Schizophrenia is associated with an increased rate of aggression towards other people particularly in the early stages of the illness. This is exacerbated by substance use. The disorganisation seen in behaviour is also seen in thought processes. Formal thought disorder describes the fragmentation of the coherence of thought as expressed in speech or writing. This can range from minor changes, such as unusual syntax, to the complete breakdown in the expression of thought in word salad, where words are jumbled together in a seemingly meaningless combination.

Schizophrenia is also associated with cognitive problems in both the neurocognitive (attention, concentration, speed of processing, memory and executive functioning) and social cognitive domains (emotion recognition, social knowledge and perception, theory of mind and attributional bias) (Heinrichs and Zakzanis, 1998; Savla et al., 2013). These deficits become apparent during the prodrome when there is frequently a deterioration in the level of cognitive functioning prior to the onset of the first psychotic episode. Cognitive functioning thereafter tends to remain stable despite increasing chronicity. The negative symptoms and the cognitive symptoms of schizophrenia are responsible for the bulk of the loss of function in individuals in our community.

People with schizophrenia have high rates of both anxiety and depression. The anxiety that people with schizophrenia suffer from may arise independently of the psychotic illness causing the full array of anxiety disorders, for example social anxiety disorder, or it can arise secondary to psychotic symptoms. For example, someone with persecutory delusions can feel intensely anxious and under scrutiny as part of their delusional thoughts. Treatment will differ according to if the anxiety is primary or secondary to other psychotic symptoms. People with schizophrenia also have a high rate of post-traumatic stress disorder.

Depression is also common in people with schizophrenia. It can occur as part of the prodrome of schizophrenia, or in response to the stress of having a psychotic illness, or independently as a comorbid condition. Suicide unfortunately ends the lives of approximately 5.6% (95% CI 3.7 – 8.5%) of people with schizophrenia (Palmer et al., 2005) and this tends to occur most frequently in the first one to two years after the diagnosis of the disorder.

A loss of insight, into the idea that the signs and symptoms of schizophrenia are part of an illness is frequent, with between 30-55% of people with schizophrenia having a decrease or lack of awareness of certain symptoms or their level of functioning (Sevy et al., 2004). Finally, schizophrenia is associated with a wide range of movement disorders. Some, such as catatonia, cause changes in the control of movement with people displaying mutism, posturing, negativism, staring, rigidity, and echophenomena (Taylor and Fink, 2003). People with schizophrenia not uncommonly have other movement disorders e.g. tardive dyskinesia, most frequently as an adverse effect of treatment but also sometimes developing prior to the start of treatment.

Diagnosis

Diagnosis requires the clinician to consider symptom profile, duration of symptoms and effect upon function. It requires a full assessment and history including mental state examination and physical examination (see Table 15.2). There is a considerable differential diagnosis that needs to be considered. Schizophrenia usually presents after a prodrome of between one to six months with a clinical picture of positive, negative and disorganisation symptoms in the context of a deterioration in the level of functioning. The presentation to services is usually precipitated by an exacerbation of the positive symptoms. Occasionally, the negative symptoms of the disease predominate, and the person presents with a picture of social withdrawal, amotivation and severe functional decline.

Table 15.2. Differential diagnosis for psychotic disorders in adults.

Disorder	Typical Symptoms	Duration	Context	Function
At risk mental state (ARMS)	Positive	Attenuated or Fleeting		some
Brief Psychotic Disorder	Positive	< 4 weeks		some
Schizophreniform	Positive, negative	< 6 months		some
Schizoaffective	Positive, negative & mood	> 2 weeks		
Schizophrenia	Positive, negative & cognitive	> 6 months		marked
Substance Induced Psychotic Disorder	Positive	> 2 weeks	Substance Use	varied
Bipolar Disorder	Mood	> 1 week	History of moods symptoms	varied
MDD with psychotic features	Mood	> 2 weeks	History of moods symptoms	
Autoimmune encephalitis	Positive	Rapid onset	Neurological symptoms.	marked
Autistic Spectrum Disorder	Social and communicative	Lifelong	Childhood onset	yes
Schizoid Personality Disorder	Social	Lifelong	Adolescence	

Investigations

Investigations play a two-fold role in the assessment of people with schizophrenia. Firstly, to exclude possible neurological or other organic causes of psychotic illness such as autoimmune encephalitis, complex partial seizures, or thyroid disease. These are relatively rare. Secondly, they serve to provide a baseline for subsequent pharmacological treatment which can cause significant physical morbidity. This includes basic anthropometric information such as cardiovascular parameters and body mass index as well as a range of investigations (see Table 15.3).

Table 15.3. Adapted from the RANZCP Clinical Guidelines for the management of Schizophrenia (Galletly et al., 2016).

Investigation	Baseline	6 monthly	Indication
Physical examination	✓	✓	Monitor physical health, movement disorders
BP, weight, BMI, waist circumference	✓	✓	Monitor weight, metabolic syndrome
Full Blood Count	✓	✓	Blood dyscrasias
Electrolytes, Liver Function Tests	✓	✓	Renal/hepatic dysfunction
Fasting glucose, blood lipids, HbA_{1c}	✓	✓	Metabolic state
Prolactin	✓	✓	Hyperprolactinaemia
Thyroid Function Test	✓	-	Thyroid disease
Anti-NMDA, GAD	✓	-	Autoimmune encephalitis
Urine drug screen	✓	If indicated	Substance abuse
Electrocardiogram	✓	✓	Cardiac arrhythmias, QTc
Electroencephalogram	If indicated	-	Seizure activity
MRI/CT - head	✓	-	Brain pathology
Psychometric testing	✓	-	Cognitive deficits
Blood borne virus	If indicated	-	HIV, liver pathology
Sexually transmitted disease	If indicated		Syphilis, other STD
Pregnancy test	If indicated		Teratogenetic risk

Note: BP = Blood Pressure; BMI = Body Mass Index; HbA1c = Hemoglobin A1c; NMDA = N-Methyl-D-Aspartate (receptor); GAD = Glutamic Acid Decarboxylase; MRI = Magnetic Resonance Imaging; CT = Computed Tomography; STD = Sexually Transmitted Disease; HIV = Human Immunodeficiency Virus.

Management

The biopsychosocial aetiology and broad impact of schizophrenia needs to be managed in a way that addresses the complexity of the disorder. This requires both a pharmacological and psychosocial approach to treatment. Guidelines for the

management of schizophrenia (Galletly et al., 2016) and first episode psychosis (Early Psychosis Guidelines Writing Group and EPPIC National Support Program, 2016) are available and are both excellent resources. Early intervention in psychosis, an approach developed in Australia, reduces the number of hospitalisations and improves functioning and quality of life of young people with psychosis (Correll et al., 2018). Nonetheless, chronicity and disability remain a significant problem and the basic course of the disorder has not been altered.

Pharmacological Management

At initial presentation, it is reasonable to use a benzodiazepine such as diazepam or lorazepam to provide sedation and anxiolysis. However, if the key symptoms of psychosis continue then initiating an antipsychotic medication with a low adverse effect profile and an evidence base in first episode psychosis is recommended (see Figure 15.2) (Galletly et al., 2016). If the clinical situation allows, a slow but steady increase in medication dose over a 2-4 week period is done until there is a significant reduction in symptoms. Continued use of benzodiazepines, to be tapered and discontinued later, can assist in calming the person and helping with sleep. Non-response should prompt a review of other possible aetiological causes and treatment adherence, as around 80% of first episode schizophrenia will respond (Zhu et al., 2017).

Unfortunately, the majority of people with a first episode of schizophrenia will relapse, though this is usually due to ceasing antipsychotic medication. With each relapse, treatment response decreases (Bowtell et al., 2018). Changing to another antipsychotic with a different receptor activity profile is reasonable, along with the use of a long-acting injectable form of medication if available. If three trials of medication have failed to help the person with schizophrenia, or if significant problems with movement disorder or aggression occurs, a trial of clozapine is recommended.

Antipsychotic Adverse Effects

There are many antipsychotic medications available, all with differing profiles of adverse effects (see Table 15.4). As schizophrenia usually warrants long term treatment, it is important to anticipate possible problems and promote the long-term health of the individual from the time of first treatment with education, exercise and diet. Common adverse effects (Huhn et al., 2019) of medication include weight gain (particularly chlorpromazine, olanzapine, clozapine and quetiapine), movement disorders such as dystonia, parkinsonism, akathisia and tardive dyskinesia (chlorpromazine, haloperidol, zuclopenthixol), raised prolactin (haloperidol, amisulpride, risperidone, paliperidone), sedation (clozapine,

olanzapine, chlorpromazine, quetiapine) and QTc changes (amisulpride and ziprasidone).

Rarer or unusual adverse effects such as blood dyscrasias, neuroleptic malignant syndrome, phototoxicity or the propensity to water intoxication need to be checked for. However, the use of antipsychotics with a heavier burden of adverse effects, may be required because of a poor response to first-line medications.

Clozapine is a highly effective medication that has been relegated to the third line because of the range and severity of adverse effects. Of most concern is its propensity to cause agranulocytosis in approximately 1 to 2% of people taking it. Because of this, a compulsory monitoring system has been developed to ensure that all people on clozapine have regular full blood counts. In addition, clozapine can cause myocarditis and cardiomyopathy requiring close cardiac monitoring (initially cardiac enzymes and ECG, followed by regular ECG and echocardiogram). Clozapine's other adverse effects are numerous and can be dangerous as well as inconvenient, for example severe constipation.

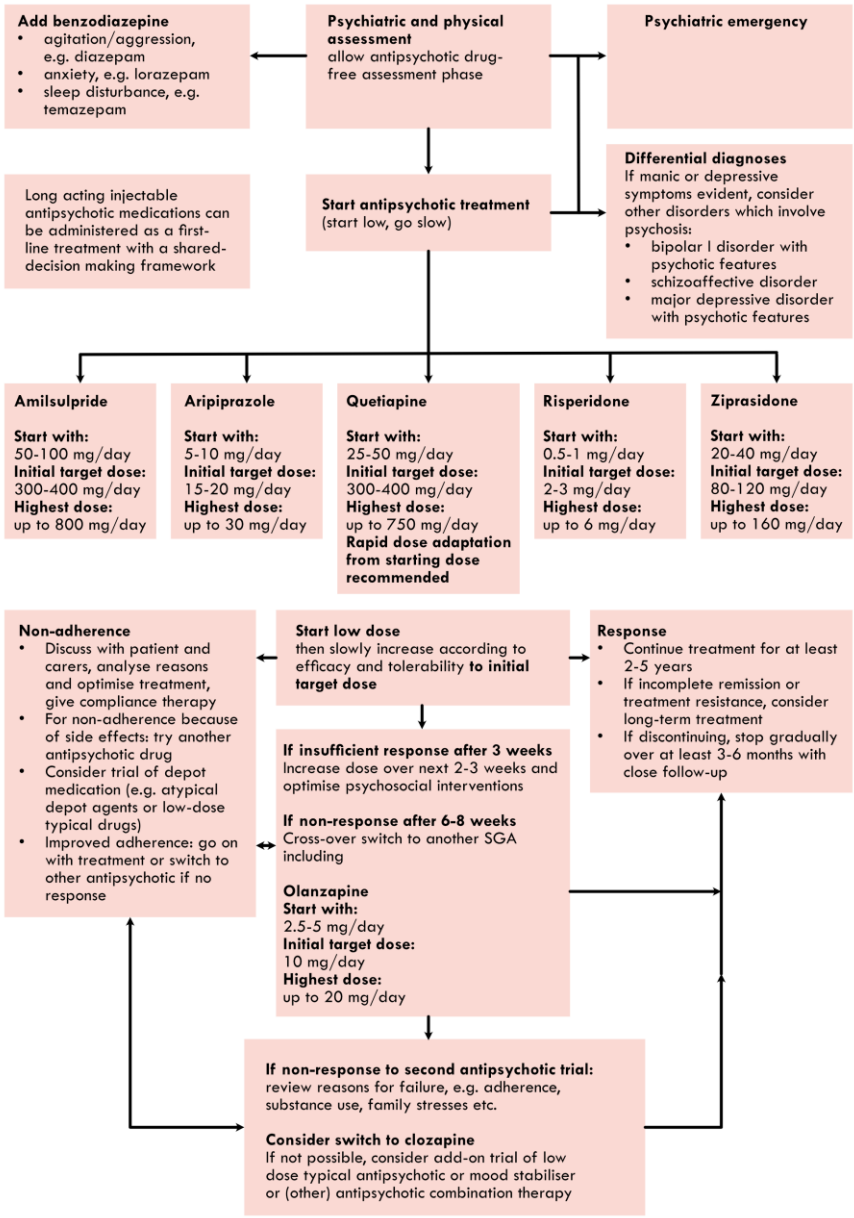

Figure 15.2. From Galletly et al. (2016). Treatment algorithm for first episode schizophrenia.

Psychosocial Management

Psychosocial management describes a range of interventions that aim to engage people in treatment, educate them about the symptoms and problems caused by the disorder, provide them with the cognitive and behavioural tools to tackle their disabilities, and monitor their progress. These treatments are best provided by a multidisciplinary team, including peer workers.

Treatment is built around a case manager whose role it is to remain in close contact with the person with schizophrenia and help coordinate the many aspects of care. This can be provided assertively for people with a record of multiple hospitalisations and difficulty in engagement so as to reduce readmission rates (Burns et al., 2007). Accurate information is essential in an area such as mental health and psychoeducation provides information about aetiology, treatment and the mental health care system. This lowers hospitalisation and improves satisfaction (Xia et al., 2011). Schizophrenia is corrosive of family ties. Many families benefit from family therapy that aims to educate, provide problems solving skills and reduce miscommunication and the resultant arguments or family dysfunction (Bighelli et al., 2021). Cognitive behavioural therapy (see Chapter 33) can be used to challenge pathological thoughts and perceptions such as hallucinations and delusions. It has also been used to improve medication adherence (Bighelli et al., 2021; Gray et al., 2016).

Table 15.4. Antipsychotic Medication Adverse effects.

	Sedation	Weight Gain	EPSE	Anti - cholinergic	Prolactin	QTc
Older D2 antagonists						
Chlorpromazine	+++	+++	++	+++	+++	++
Flupentixol	+	++	++	++	+++	+
Haloperidol	+	++	++ +	+	+++	++
Zuclopenthixol	+++	++	++	++	+++	?
D2 -5HT2a antagonists						
Asenapine	++	++	+	-	+/-	+
Clozapine	++++	+++	0	XXX	0	+
Lurasidone	++	+	+	-	+	-
Olanzapine	+++	+++	+	++	+	+
Paliperidone	+	++	+	-	+++	+
Quetiapine	++	++	+	-	+	++
Risperidone	+	++	++	-	+++	+
Ziprasidone	+	+/-	+	-	0	++
Benzamide antipsychotic						
Amisulpride	+	+	++	-	+++	++
D2 partial agonists						
Aripiprazole	+/-	+/-	+	-	0	+
Brexpiprazole	+/-	+/-	+	-	+/-	-
Cariprazine	+	+	+	-	-	-

Note: EPSE – extrapyramidal side effects, for example parkinsonism, rigidity, tremor, dystonia and propensity to tardive dyskinesia; anticholinergic – dry mouth, blurry eyes, dilated pupils, constipation, urinary hesitancy or retention, decreased sweating; prolactin – hyperprolactinaemia causing breast tenderness or enlargement, galactorrhoea and menstrual irregularity, long term risk of osteoporosis; QTc – corrected QT interval, indication of risk of torsades de pointes cardiac rhythm; XXX – hypersalivation despite high anticholinergic effects.

An important goal for many is to return to work (Morgan et al., 2011). The most successful approach for this in people with schizophrenia is supported employment – more specifically known as the Individual Placement and Support model - that places people directly in employment and supports them in the workplace (Modini et al., 2016). Cognitive Remediation Therapy, a therapy that

targets the significant cognitive dysfunction that is part of psychotic illnesses, improves both neurocognition and social cognition. This flows on to an improvement in community functioning, especially when combined with other psychosocial interventions e.g. supported employment (Vita et al., 2021).

Anxiety and Depression

Anxiety and depression form one of the domains of symptomatology and there are increased rates of both major depression (see Chapter 16) and anxiety disorders (see Chapter 18) in people with schizophrenia compared to the rest of the community (Buckley et al., 2009). Suicide ends the life of approximately 5% of people with schizophrenia (Palmer et al., 2005). Diagnosis of these disorders is frequently overshadowed by psychotic symptoms. Treatment with CBT (Chapter 33), pharmacotherapy (Chapter 35) or both is appropriate and effective.

Physical Health

People with schizophrenia die on average 14.5 years earlier than the rest of the community (Hjorthøj et al., 2017). This decrease in life expectancy is not just due to suicide and accident, rather it relates to a broad range of chronic medical conditions including infections, cardiovascular, respiratory, endocrine and substance use (Laursen et al., 2019). There are a number of reasons for this. Adverse effects of psychotropic drugs contribute to an increase weight and the frequency of metabolic syndrome, though overall treatment adherence is associated with a lower morbidity and mortality rate (Taipale et al., 2020). There is a higher rate of substance abuse including nicotine in people with schizophrenia (Firth et al., 2019). Lifestyles are less heathy with less sleep, exercise and a poorer diet (Morgan et al., 2011; Firth et al., 2019). However, despite coming into contact with medical practitioners more often than the rest of the community, they are less likely to have routine investigations, diagnostic procedures or interventions for illnesses such as cardiovascular disease when in care, which reflects physician behaviour and stigma (Mitchell et al., 2012; Solmi et al., 2021). Ironically, lifestyle interventions such as diet and exercise are effective for people with schizophrenia (Teasdale et al., 2017) and they adhere to treatments for their physical illnesses just as well as the rest of the community (Owen-Smith et al., 2016), they are just not tried.

Outcome

The majority of people with schizophrenia have a reasonable outcome with symptomatic improvement but a less certain functional recovery. Recent work suggests that multimodal treatment and early intervention improves outcome (Lally et al., 2017). However this is yet to change long term outcome which has remained

stubbornly poor with only 13.5% of people with schizophrenia recovering when recovery is defined as a remission of symptoms and a return of function in social, occupational and educational domains (Jääskeläinen et al., 2012). This is almost certainly contributed to by the demands of our developed world as outcome is better in developing countries. Poor treatment adherence and substance use often leads to relapse and the development of chronicity. Also, around 20% of people with schizophrenia never respond to treatment even at their first presentation to services (Siskind et al., 2022). These individuals are more likely to be male, with poor education and a long duration of undiagnosed psychosis (Morgan et al., 2021). This clinical picture, along with strong consumer advocacy, has led to the adoption of recovery-led practice models of care that focus less on symptomatic remission and more on the development of a meaningful and contributing life (Australian Health Ministers' Advisory Council, 2013).

Conclusion

Schizophrenia is the most common of the psychotic illnesses. It develops early in adult life disabling the majority who have it, isolating them from family and friends and interrupting relationships, education and employment. We have discovered much about its underlying causes, however this has not significantly altered outcome. Management requires a multidisciplinary team with both pharmacological and psychosocial interventions. Finally, schizophrenia contributes to an early death due to physical illness and poor care. Neglect based upon stigma and marginalisation continue to affect those who have the disorder.

Further Reading

Galletly, C., Castle, D., Dark, F., Humberstone, V., Jablensky, A., Killackey, E., … & Tran, N. (2016). Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the management of schizophrenia and related disorders. *Australian & New Zealand Journal of Psychiatry*, *50*(5), 410-472.

McCutcheon, R. A., Abi-Dargham, A., & Howes, O. D. (2019). Schizophrenia, dopamine and the striatum: from biology to symptoms. *Trends in Neurosciences*, *42*(3), 205-220.

Cite as:

Harris, A. (2024). Schizophrenia. In Boyce, P., Harris, A., and Malhi, G.S. (Eds.), *The Sydney textbook of psychiatry* (pp. 184–199). The University of Sydney.

References

Australian Health Ministers' Advisory Council (2013) A national framework for recovery-oriented mental health services: Guide for practitioners and providers. Reportno. Report Number|, Date. Place Published|: Institution|.

Bailey T, Alvarez-Jimenez M, Garcia-Sanchez AM, et al. (2018) Childhood Trauma Is Associated With Severity of Hallucinations and Delusions in Psychotic Disorders: A Systematic Review and Meta-Analysis. *Schizophrenia bulletin* 44(5): 1111-1122.

Bighelli I, Rodolico A, García-Mieres H, et al. (2021) Psychosocial and psychological interventions for relapse prevention in schizophrenia: a systematic review and network meta-analysis. *The Lancet Psychiatry* 8(11): 969-980.

Bowtell M, McGorry P and O'Donoghue B (2018) Is a higher dose of antipsychotic medication required to treat a relapse following discontinuation in first episode psychosis? *Schizophrenia research*. DOI: 10.1016/j.schres.2018.07.032.

Brugger SP and Howes OD (2017) Heterogeneity and Homogeneity of Regional Brain Structure in Schizophrenia: A Meta-analysis. *JAMA Psychiatry* 74(11): 1104-1111.

Buckley PF, Miller BJ, Lehrer DS, et al. (2009) Psychiatric comorbidities and schizophrenia. *Schizophrenia bulletin* 35: 383-402.

Burns T, Catty J, Dash M, et al. (2007) Use of intensive case management to reduce time in hospital in people with severe mental illness: systematic review and meta-regression. *Bmj* 335(7615): 336.

Cardno AG and Gottesman II (2000) Twin studies of schizophrenia: From bow-and-arrow concordances to Star Wars Mx and functional genomics. *American Journal of Medical Genetics* 97(1): 12-17.

Caspi A, Moffit TE, Cannon M, et al. (2005) Moderation of the effect of adolescent-onset cannabis use on adult psychosis by a functional polymorphism in the catechol-O-methyltransferase gene: Longitudinal evidence of a gene x environment interaction. *Biological Psychiatry* 57: 1117-1127.

Correll CU, Galling B, Pawar A, et al. (2018) Comparison of Early Intervention Services vs Treatment as Usual for Early-Phase Psychosis: A Systematic Review, Meta-analysis, and Meta-regression. *JAMA Psychiatry* 75(6): 555-565.

Di Forti M, Iyegbe C, Sallis H, et al. (2012) Confirmation that the AKT1 (rs2494732) Genotype Influences the Risk of Psychosis in Cannabis Users. *Biological Psychiatry* 72: 811-816.

Early Psychosis Guidelines Writing Group and EPPIC National Support Program (2016) Australian Clinical Guidleines for Early Psychosis. 2nd ed. Melbourne: Orygen, The National Centre of Excellence in Youth Mental Health,.

Firth J, Siddiqi N, Koyanagi A, et al. (2019) The Lancet Psychiatry Commission: a blueprint for protecting physical health in people with mental illness. *The Lancet Psychiatry* 6(8): 675-712.

Galletly C, Castle D, Dark F, et al. (2016) Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the management of schizophrenia and related disorders. *Australian and New Zealand Journal of Psychiatry* 50(5): 410-472.

Gray R, Bressington D, Ivanecka A, et al. (2016) Is adherence therapy an effective adjunct treatment for patients with schizophrenia spectrum disorders? A systematic review and meta-analysis. *BMC Psychiatry* 16(1): 90.

Harrison P (1999) The neuropathology of schizophrenia. A critical review of the data and their interpretation. *Brain* 122: 593-624.

Heinrichs RW and Zakzanis KK (1998) Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. *Neuropsychology* 12: 426-445.

Hjorthøj CD, Stürup AEMD, McGrath JJP, et al. (2017) Years of potential life lost and life expectancy in schizophrenia: a systematic review and meta-analysis. *The Lancet Psychiatry* 4(4): 295-301.

Howes OD, McCutcheon R, Owen MJ, et al. (2017) The Role of Genes, Stress, and Dopamine in the Development of Schizophrenia. *Biological Psychiatry* 81(1): 9-20.

Huhn M, Nikolakopoulou A, Schneider-Thoma J, et al. (2019) Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. *Lancet*. Epub ahead of print 2019/07/16. DOI: 10.1016/s0140-6736(19)31135-3.

Jääskeläinen E, Juola P, Hirvonen N, et al. (2012) A Systematic Review and Meta-Analysis of Recovery in Schizophrenia. *Schizophrenia bulletin*. DOI: 10.1093/schbul/sbs130.

Lally J, Ajnakina O, Stubbs B, et al. (2017) Remission and recovery from first-episode psychosis in adults: systematic review and meta-analysis of long-term outcome studies. *British journal of psychiatry* 211(6): 350-358.

Laursen TM, Plana-Ripoll O, Andersen PK, et al. (2019) Cause-specific life years lost among persons diagnosed with schizophrenia: Is it getting better or worse? *Schizophrenia research* 206: 284-290.

Mitchell AJ, Lord O and Malone D (2012) Differences in the prescribing of medication for physical disorders in individuals with v. without mental illness: meta-analysis. *British journal of psychiatry* 201(6): 435-443.

Modini M, Tan L, Brinchmann B, et al. (2016) Supported employment for people with severe mental illness: Systematic review and meta-analysis of the international evidence. *British journal of psychiatry* 209(1): 14-22.

Morgan C, Dazzan P, Lappin J, et al. (2021) Rethinking the course of psychotic disorders: modelling long-term symptom trajectories. *Psychological medicine*. Epub ahead of print 2021/02/04. DOI: 10.1017/S0033291720004705. 1-10.

Morgan VA, Waterreus A, Jablensky A, et al. (2012) People living with psychotic illness in 2010: The second Australian national survey of psychosis. *Australian and New Zealand Journal of Psychiatry* 46.

Morgan VA, Waterreus A, Jablensky A, et al. (2011) People living with psychotic illness 2010. In: Department of Health and Ageing (ed). Canberra ACT 2601: Commonwealth of Australia,.

Owen-Smith A, Stewart C, Green C, et al. (2016) Adherence to common cardiovascular medications in patients with schizophrenia vs. patients without psychiatric illness. *General hospital psychiatry* 38: 9-14.

Palmer BA, Pankratz VS and Bostwick JM (2005) The Lifetime Risk of Suicide in Schizophrenia: A Reexamination. *Archives of general psychiatry* 62(3): 247-253.

Rees E, O'Donovan MC and Owen MJ (2015) Genetics of schizophrenia. *Current Opinion in Behavioral Sciences* 2: 8-14.

Saha S, Chant D, Welham J, et al. (2005) A systematic review of the prevalence of schizophrenia. *PLoS Medicine* 2(5): e141.

Savla GN, Vella L, Armstrong CC, et al. (2013) Deficits in domains of social cognition in schizophrenia: a meta-analysis of the empirical evidence. *Schizophrenia bulletin* 39(5): 979-992.

Sevy S, Nathanson K, Visweswaraiah H, et al. (2004) The relationship between insight and symptoms in schizophrenia. *Comprehensive Psychiatry* 45(1): 16-19.

Siskind D, Orr S, Sinha S, et al. (2022) Rates of treatment-resistant schizophrenia from first-episode cohorts: systematic review and meta-analysis. *The British Journal of Psychiatry* 220(3): 115-120.

Solmi M, Fiedorowicz J, Poddighe L, et al. (2021) Disparities in Screening and Treatment of Cardiovascular Diseases in Patients With Mental Disorders Across the World: Systematic Review and Meta-Analysis of 47 Observational Studies. *American Journal of Psychiatry* 178(9): 793-803.

Solmi M, Seitidis G, Mavridis D, et al. (2023) Incidence, prevalence, and global burden of schizophrenia-data, with critical appraisal, from the Global Burden of Disease (GBD) 2019. *Molecular psychiatry* 28(12): 5319-5327.

Taipale H, Tanskanen A, Mehtälä J, et al. (2020) 20-year follow-up study of physical morbidity and mortality in relationship to antipsychotic

treatment in a nationwide cohort of 62,250 patients with schizophrenia (FIN20). *World Psychiatry* 19(1): 61-68.

Taylor MA and Fink M (2003) Catatonia in Psychiatric Classification: A Home of Its Own. *American Journal of Psychiatry* 160(7): 1233-1241.

Teasdale SB, Ward PB, Rosenbaum S, et al. (2017) Solving a weighty problem: Systematic review and meta-analysis of nutrition interventions in severe mental illness. *British journal of psychiatry* 210(2): 110-118.

Trubetskoy V, Pardiñas AF, Qi T, et al. (2022) Mapping genomic loci implicates genes and synaptic biology in schizophrenia. *Nature* 604(7906): 502-508.

Vita A, Barlati S, Ceraso A, et al. (2021) Effectiveness, Core Elements, and Moderators of Response of Cognitive Remediation for Schizophrenia: A Systematic Review and Meta-analysis of Randomized Clinical Trials. *JAMA Psychiatry* 78(8): 848-858.

Xia J, Merinder LB and Belgamwar MR (2011) Psychoeducation for Schizophrenia. *Cochrane Database of Systematic Reviews*. DOI: DOI: 10.1002/14651858.CD002831.pub2. (accessed 5/3/2012).

Zhu Y, Li C, Huhn M, et al. (2017) How well do patients with a first episode of schizophrenia respond to antipsychotics: A systematic review and meta-analysis. *European Neuropsychopharmacology* 27(9): 835-844.