3 Psychosis and Schizophrenia

3.1 What is ‘psychosis’ and how does this relate to schizophrenia?

The term psychosis refers to a set of symptoms that impair the ability of a person experiencing psychosis to distinguish reality from fiction. It is characterised by the following signs and symptoms:

- delusions—beliefs that are not consensually validated or demonstrably true;
- hallucinations—perceptions that cannot be verified by others; and
- communication and behaviour that are partly or completely unintelligible.

Psychosis is usually thought of in association with schizophrenia, but is also present to varying degrees in a number of other mental health disorders. It should be noted that discrete psychotic symptoms (e.g. seeing something that is not there, as can occur in delirium associated with fever, for example) can be experienced without necessarily being part of a psychotic disorder. If the symptoms are severe enough, or there are multiple symptoms co-occurring for a sufficient time, then a psychotic disorder, such as schizophrenia, may be diagnosed (see Box 3.1).

Box 3.1: How is schizophrenia diagnosed?

To diagnose schizophrenia the following criteria need to be met:

(a) Experience of two or more* characteristic symptoms for a significant part of a one-month period:
   - delusions (e.g., believing that someone is stealing thoughts from your mind or controlling your actions)
   - hallucinations (e.g., hearing a voice commenting on your actions)
   - disorganised speech (e.g., incoherent speech, or frequently going off topic in a conversation)
   - grossly disorganised or catatonic behaviour (e.g., unpredictable agitation, or strange postures)
   - ‘negative symptoms’, which refer to a set of symptoms such as a lack of emotional expression, lack of speech, and lack of motivation

(b) Social or occupational dysfunction; and

(c) Continuous signs of disturbance for at least six months.

* If the delusion is bizarre, or the hallucination consists of a voice commenting on the person’s behaviour or two voices conversing with each other, then only one characteristic symptom is required to fulfil criterion (a).

From the Diagnostic and Statistical Manual of Mental Disorders, fourth edition

Schizophrenia is a psychiatric disorder that can be severely disabling; poor social and occupational functioning is characteristic of the disorder. Schizophrenia can exert a
distressing effect both on the person experiencing this disorder and on their family. It usually emerges in late adolescence or early adulthood and can often persist throughout the person’s lifetime, making schizophrenia a significant contributor to the global burden of disease [64]. Approximately one in ten people with schizophrenia will take their own life [30]. It was estimated that $1.85 billion was spent on the direct and indirect costs of schizophrenia in Australia in 2001 [65]. Annual costs have been estimated to be over $46,000 per patient in Australia, with lost productivity accounting for $27,500, inpatient costs accounting for $13,800 and $4,900 in other service costs [66]. In terms of impact on the lives of people experiencing schizophrenia and their family, care, and cost, schizophrenia represents a substantial burden on the community.

3.2 How common is schizophrenia?

There are two main ways to describe the number of people in the population that experience a disorder: prevalence and incidence. Prevalence describes the proportion of people at any one time with the disorder, whereas incidence refers to rate at which new cases of the disorder emerge, e.g. cases per million per year.

Most literature states that the prevalence of schizophrenia is around 1% of the adult population [30]. Males usually have a slightly higher prevalence of schizophrenia than females, as do people born in urban rather than rural areas, and migrant groups versus non-migrants [67][68]. Two recent systematic reviews have found that the median incidence of schizophrenia is 15.2 per 100,000 persons per year [68] and the median lifetime risk of developing the disorder is 0.72% [64]. In Australia, it has been estimated that about 2,000 people are newly diagnosed with schizophrenia every year [69].

It should be noted that the prevalence of schizophrenia is likely to be different among different populations simply because the cause of the disorder is so complex, as will be discussed below [64]. For example, although genes do play a part in the development of schizophrenia, there is also a significant environmental component, which suggests that varying environments would lead to varying levels of psychosis. Indeed, the incidences of schizophrenia in the review mentioned above varied quite widely [70]. It is increasingly acknowledged that the incidence of schizophrenia varies across time and populations [71][70].

3.3 What causes schizophrenia?

The causes, or aetiology, of schizophrenia are elusive. It is likely that a number of risk factors, through a variety of mechanisms, contribute to the development of psychotic disorders [72]. Some examples of risk factors include genes, birth complications, and substance use.

3.3.1 Genes and schizophrenia

With its roots in research conducted in the first half of the 20th century, the genetic influence on the aetiology of schizophrenia is well supported [73]. In the 1930s, it was discovered that the incidence of schizophrenia was about 14% higher within families of someone experiencing schizophrenia than in the general population [74].
One way to estimate the genetic influence of any condition is to compare the concordance of monozygotic (identical) twins, who share 100% of their genes, with that of dizygotic (fraternal) twins, who share 50% of each other’s genes on average. That concordance is much higher in identical twins (33% to 78%) than in fraternal twins (8% to 28%) [75]. Adoption studies have revealed that schizophrenia occurs more often in the biological relatives of adoptees experiencing schizophrenia than in the adopted relatives [76]. Having a first-degree relative (i.e., sibling or parent) with schizophrenia is the greatest risk factor for developing the disorder. The particular combination of genes involved in the aetiology of schizophrenia remains unknown, although recent advances have been made [77]. There is clearly a genetic component to schizophrenia, but it is not the only factor contributing to this disorder. If it was, then concordance rates of identical twins would be close to 100%, rather than the most commonly cited rate of 45% [73]. Other factors must also play a role in the development of schizophrenia.

3.3.2 Abnormal brain development and schizophrenia

It has been suggested that schizophrenia may arise from problems that occur around the time of birth, causing the brain to develop abnormally. This is known as the neurodevelopmental theory of schizophrenia [72][78]. For example, maternal malnutrition is recognised as a significant risk factor for schizophrenia [79]. At the onset of schizophrenia, diffuse structural brain abnormalities have been detected, and because this damage does not progress with the disease, it is thought to have occurred prior to the first symptoms of schizophrenia [73]. The particular areas of the brain that usually show abnormalities tend to be slowly developing areas [80]. This could help explain the gap between the damage to the brain and the subsequent symptoms (usually occurring in late adolescence or early adulthood), as abnormalities may not present themselves until the structure to which they relate is fully developed. It has often been noted that certain developmental abnormalities in children, such as social isolation [81], are related to the later emergence of schizophrenia.

Obstetric complications—such as low birth weight and maternal diabetes during pregnancy—have been identified as risk factors for later development of schizophrenia, although the effect sizes are small [82][80]. Other evidence in favour of the neurodevelopmental theory is the observation of childhood developmental abnormalities (such as developmental delays in cognitive and physical abilities)—indicative of abnormal brain development—in children who go on to develop schizophrenia [80]. Other developmental abnormalities in children, such as social isolation [81], may be related to the later emergence of schizophrenia. Although the mechanism of the relationship between brain development and schizophrenia is not fully elucidated, it is well accepted that schizophrenia has a developmental component [80].

3.3.3 Abnormalities in neurotransmitters and schizophrenia

Neurotransmitters are chemicals that transmit signals between neurons, and are a fundamental part of the operation of the brain. The first medications used to treat psychotic symptoms acted principally upon a neurotransmitter known as dopamine. Dopamine is one of many such substances in the brain that mediate communication between its cells [84]. Traditional antipsychotics reduced the activity of dopamine, and also reduced symptoms such as delusions and hallucinations [76]. In contrast, substances that strongly increase
activity of the dopamine system, such as amphetamines, cocaine and L-dopa (used to treat Parkinson’s disease), have been shown to worsen symptoms of psychosis or induce them in people who had not experienced psychosis previously \[85\]. These two pieces of evidence have led to the suggestion that schizophrenia and psychosis arise from a hyperactive dopamine system.

Further research has shown that the relationship between dopamine and schizophrenia is complex; increased dopamine activity has been found in some parts of the brain of people experiencing psychotic disorders, but decreased activity has been found in other parts \[86\]. It has been argued that the increased dopamine activity is responsible for the so-called ‘positive’ symptoms of schizophrenia, namely, delusions and hallucinations, while the decreased activity is implicated in the deficits in memory and attention and the ‘negative’ symptoms such as lack of motivation \[87\].

The role that other neurotransmitters, such as serotonin or glutamate, play in psychosis and schizophrenia has also received attention over the last few years \[76\]. It is likely that the relationship between neurotransmitter activity and the psychotic symptoms of schizophrenia is complex \[74\]. Further research into the biochemistry of schizophrenia, as well as further research into whether the areas of the brain affected in psychosis correspond to the areas of the brain where the neurotransmitter abnormalities are found, will help with the development of antipsychotic medication \[76\].

The three main hypotheses concerning the aetiology of schizophrenia described so far all have some support. It is likely that all three contribute to the cause of schizophrenia, which may indeed be an interaction between genetics, early brain disturbance, and aberrant neurotransmitter activity \[77\]. In the last two decades, the importance of environmental or social risk factors, such as substance use, has been clarified \[80\].

A recent review identifies numerous environmental risk factors related to the incidence of schizophrenia. Included are obstetric complications (discussed in section 3.3.2 above), substance use, stress, immigration, season of birth, urban residence, head injury, viral infection and history of trauma \[77\]. These risk factors vary in both their influence on schizophrenia and the available evidence for that influence.

3.4 Drug use and psychotic symptoms

Many psychoactive drugs, including alcohol, amphetamine, cocaine and cannabis, stimulate the release of the neurotransmitter dopamine, and increase the risk of experiencing psychotic symptoms, or exacerbate existing symptoms of psychosis \[72\].

3.4.1 Alcohol

Psychotic symptoms such as delusions or hallucinations can occur either during severe alcohol intoxication or withdrawal from severe alcohol dependence \[30\]. Individuals who have been diagnosed with schizophrenia are more likely to be dependent on alcohol and to use it in a harmful manner than those without schizophrenia \[88\], but the reliability of this observation is debated. A cross-sectional survey of the Australian population found that, although alcohol dependence was associated with psychosis, once demographic and other substance use (cannabis use and tobacco use) were controlled for, alcohol dependence
was no longer significantly associated with psychosis [89]. In the British Psychiatric Morbidity Study, alcohol dependence predicted psychotic symptoms in a cross-sectional analysis, even after confounders were taken into account [90], but a follow-up longitudinal study found that heavy alcohol use did not predict psychotic symptoms once confounders were taken into account [91]. In a prospective epidemiological study from the United States, having an alcohol use disorder led to an eight-fold increase in the risk of psychotic experiences among men, regardless of cocaine and cannabis use [92].

It has been found that alcohol can exacerbate some of the symptoms of schizophrenia, such as hallucinations and delusions for a short period of time, but individuals experiencing schizophrenia also report greater euphoria and other positive effects of alcohol than those without schizophrenia [50]. Whether the known disinhibitory effects of alcohol account for this is not clear.

Overall, while transient psychotic signs associated with heavy and prolonged alcohol use are commonly reported, contradictory reports e.g. [93][55] indicate that our understanding of the influence of alcohol on schizophrenia is limited.

3.4.2 Amphetamines

The term ‘amphetamines’ refers to the substances methamphetamine and amphetamine sulphate. The former is currently much more common on the Australian street market [94]. Amphetamines have a variety of street names including base, speed, crystal and ice. Almost 40 years ago, experimental studies showed that the administration of amphetamine to otherwise healthy adults could induce symptoms of psychosis [95][96]. It is now well known that use of amphetamines can induce a psychotic episode that involves experiencing some of the symptoms of schizophrenia, such as persecutory delusions and hallucinations [97]. The psychotic symptoms usually disappear soon after drug use and intoxication cease, although there have been some cases reported where the psychotic episode lasts for longer than one month [98]. Individuals with pre-morbid personality characteristics that are related to schizophrenia (e.g. schizotypal personality traits) have been found to be more likely to develop amphetamine-related psychosis than those who did not have such characteristics [98]. Some argue that abuse of amphetamines sensitises the brain to amphetamine-related psychosis, making it more likely that use of amphetamines will lead to further episodes [99][100]. There is evidence that levels of dopamine—the major neurotransmitter involved in psychotic symptoms—are elevated in users of amphetamines [101]. This elevated dopamine was associated with more psychotic symptoms, even in the absence of intoxication with amphetamines or other substance use.

It has been suggested that in a small number of cases, amphetamines may have a causal relationship to the development of a chronic psychotic disorder, such as schizophrenia [102]. The relatively low use of amphetamines in the general population may prevent cohort studies from detecting such a relationship. If amphetamines became more widely used, the incidence and prevalence of psychosis would be expected to rise.
3.4.3 Cocaine

Cocaine use has been found to be related to psychotic experiences [103], and a specific cocaine-induced psychosis has been identified, with some studies reporting that about half of dependent cocaine users have experienced this disorder [104]. In an epidemiological study conducted in the United States, daily cocaine use was found to be highly predictive of psychotic experiences [92]. However, once cannabis use and the presence of alcohol disorder was controlled for, the association was no longer significant. This could have been because cannabis or alcohol disorder accounted for the association between cocaine and psychosis, or it could be because there was not enough power to detect the association, since the number of daily cocaine users was very small. The contribution of cocaine to the development of chronic psychotic disorders has received less attention than cannabis, yet there are consistent associations between its use and acute psychosis [105], subsequent psychosis [106][107] and the exacerbation of symptoms in users with psychosis [108].

3.4.4 Hallucinogens

The terms hallucinogenic and psychotomimetic have been used to describe a number of natural and synthetic substances that produce transient hallucinations and delusions. Individuals who have used hallucinogens typically report awareness of the artificial nature of the drug effects (“insight”), in contrast to psychotic hallucinations which are interpreted as real [109]. However, a small minority of users may fail to do this, and experience psychological and bodily injury as a result [110]. It is generally acknowledged that only heavy use in psychologically unstable individuals is likely to produce chronic psychosis [109].

3.4.5 Nicotine

Tobacco use is widespread among those with schizophrenia. The National Survey of Mental Health and Wellbeing showed that 60% of those who screened positively for psychosis were current tobacco users, compared with 23% of the general population [279]. Nicotine appears to have little or no adverse effects upon psychotic symptoms. It is perceived as having positive effects by those with mental health disorders [111], which may account for it being so commonly used.

It is commonly reported that smoking cigarettes helps those living with schizophrenia alleviate the symptoms of the disorder and the side effects of medication. Experimental studies have supported this by showing that some of the symptoms of schizophrenia (e.g. attentional deficits) are improved with cigarette smoking [112][113]. However, most people with schizophrenia started smoking before their disorder was diagnosed [114] lending some weight to the conjecture that drug use prior to schizophrenia is in part to deal with negative mental states [46]. A cohort study assessed the association between smoking in adolescence and subsequent hospitalisation for schizophrenia, and found a decreased risk of schizophrenia associated with heavy smoking [115]. However, the harms of smoking counter any potential benefits, thus the widespread use of tobacco among those experiencing schizophrenia is of concern.
3.5 Life events and schizophrenia

3.5.1 Stress
Animal studies have shown that stress can increase dopamine activity, and stressful adverse life events have been found to precede the onset of psychotic episodes in schizophrenia, although the mechanism of this relationship is not clear [116]. For those with a pre-existing vulnerability to schizophrenia, uncontrollable events and concern about social evaluation may be associated with the initiation or exacerbation of symptoms of schizophrenia [117]. This fits well with the social dysfunction typically observed in individuals diagnosed with schizophrenia, and often in those who eventually develop the disorder [80].

3.5.2 Migrant status
In Europe, increased rates of psychosis and schizophrenia among migrants have been reported [118]. The reason for this is unknown; increased stress associated with moving to another country has been put forward as a possible explanation [119]. Another explanation is the increased stress and disadvantage associated with being a minority group. Recently, Boydell and colleagues [119] found that the incidence of schizophrenia was greater among ethnic minorities in the United Kingdom when they form a smaller proportion of the population. However, Australian studies have not consistently found an association between migrant status and psychosis, with one study reporting decreased rates of psychotic disorders among migrants [120], and another finding that migrants were more likely to endorse psychotic symptoms than individuals born in Australia [121].

3.5.3 Season of birth
Studies from the northern hemisphere have found fairly consistently that individuals with schizophrenia are more likely to have been born in the winter months than at other times of the year, e.g. [122]. The reason for the effect is not clear; some of the possible explanations are viral infections and nutrition, which both vary with the seasons and may lead to pre or neonatal complications, which in turn could lead to the development of schizophrenia [123]. Studies of the effect in the southern hemisphere countries have been less consistent [124]. This season of birth effect has not been as strong in countries closer to the equator with less seasonal variation, which may explain why the effect is weaker in the southern hemisphere countries studied, which tend to have milder winters [124].

3.5.4 Place of birth (urban versus rural)
European studies have shown that those born in urban areas have a higher risk of schizophrenia and psychotic disorders than those born in rural areas [125]. Like the findings on migrant status and schizophrenia, Australian studies have produced conflicting results [120][121]. Reasons for the urban effect could be greater exposure to risk factors such as infections and stress.
3.5.5 Head injury

A history of head injury has long been proposed as a potential risk factor for schizophrenia [77]. Until recently, the studies assessing this link have suffered from methodological problems. Recent studies have produced conflicting findings, with some finding increased risk of schizophrenia in those with a history of head injury [126] and others finding no increased risk [127]. A recent review concluded that, based on current literature, it cannot be stated that head injury plays a causal role in schizophrenia [128].

3.5.6 Trauma

The association between the experience of traumatic events and subsequent development of psychosis has been gaining some attention in the literature lately [77]. A recent longitudinal study found that reporting a lifetime history of trauma (e.g. experiencing physical threats, being in a serious accident, or being sexually abused as a child) at baseline (i.e. the first point of assessment) was associated with reporting psychotic symptoms three years later. This association remained significant once possible confounding factors were taken into account and the effect was stronger for those who were vulnerable to psychosis.

It is clear that a variety of life events are associated with the development of schizophrenia. This review will now examine the evidence that cannabis is an independent risk factor for schizophrenia and, if so, the magnitude of that risk.