Schizophrenia

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Schizophrenia is one of the most serious and frightening of all mental illnesses. No other disorder arouses as much anxiety in the general public, the media, and doctors. Effective treatments are available, yet patients and their families often find it hard to access good care. In the United Kingdom, as in many parts of the world, this is often due to poor service provision, but sometimes it is simply down to misinformation. In this review, we clarify the causes and presentation of schizophrenia, summarise the treatments that are available, and try to clear up a few myths.

Methods

We searched the online electronic databases Web of Knowledge, the Cochrane Library, and the current National Institute for Health and Clinical Excellence (NICE) guidelines for suitable evidence based material.

What is schizophrenia?

The name schizophrenia derives from the early observation that the illness is typified by “the disconnection or splitting of the psychic functions.”^{w1} Unfortunately, this has led to the misconception that the illness is characterised by a “split personality,” which it is not. Box 1 lists the common symptoms of schizophrenia.

People with schizophrenia typically hear voices (auditory hallucinations), which often criticise or abuse them. The voices may speak directly to the patient, comment on the patient's actions, or discuss the patient among themselves. Not surprisingly, people who hear voices often try to make some sense of these hallucinations, and this can lead to the development of strange beliefs or delusions.

Many patients also have thought disorder and negative symptoms. While negative symptoms may be less troubling to the patient, they can be very distressing to relatives.

While we often think of schizophrenia as a major departure from normal health, mild symptoms can occur in healthy people and are not associated with illness.¹ This has led to the conclusion that schizophrenia reflects a quantitative rather than qualitative deviation from normality, rather like hypertension or diabetes.

How common is schizophrenia?

Systematic reviews show that despite its relatively low incidence (15.2/100 000),² the prevalence of schizophrenia (7.2/1000)² is relatively high, because it often starts in early adult life and becomes chronic. The incidence of

schizophrenia varies; at present it is rising in some populations (such as South London^{w3}) but falling in others.³ A comprehensive global survey concluded that schizophrenia accounts for 1.1% of the total disability adjusted life years worldwide and 2.8% of the years lived with disability worldwide.^{w4}

Who gets schizophrenia?

Schizophrenia typically presents in early adulthood or late adolescence. Men have an earlier age of onset than women, and also tend to experience a more serious form of the illness with more negative symptoms, less chance of a full recovery, and a generally worse outcome.⁴ Systematic reviews show that it is more common in men than women (risk ratio 1.4:1²) and is more frequent in people born in cities—the larger the city and the longer the person has lived there the greater the risk.⁵ It is more common in migrants.⁶ A large and comprehensive study showed that rates of schizophrenia in African-Caribbean people living in the UK are six to eight times higher than those of the native white population.^{w5} Rates remain high in the children of migrants, but this is not reflected in increased rates in their home country.^{w6} Environmental and social factors have been implicated in this increased risk, and intriguingly the risk of schizophrenia in migrants is greatest when they form a small proportion of their local community.⁷

What causes schizophrenia?

Are genes important?

Schizophrenia is a multifactorial disorder, and the greatest risk factor is a positive family history. While the lifetime risk in the general population is just below 1%, it is 6.5% in first degree relatives of patients,⁸ and it rises to more than 40% in monozygotic twins of affected people.⁹ Extended family, adoption, and twin studies show that this risk reflects the genetic proximity between relative and proband.

It seems likely that many risk genes exist—each of small effect and each relatively common in the general population. Patients probably inherit several risk genes, which interact with each other and the environment to cause schizophrenia once a critical threshold is crossed.

What environmental factors are important?

A meta-analysis has shown that patients with schizophrenia are more likely to have experienced obstetric

Fig 1 | Physical care algorithm: adapted from NICE guidelines¹⁸

complications, in particular premature birth, low birth weight, and perinatal hypoxia.¹⁸ These early environmental hazards appear to have a subtle effect on brain development. In adulthood different environmental stressors act—including social isolation, migrant status, and urban life¹⁰—and this remains the case even when life events attributable to the incipient psychosis itself are excluded. The way parents raise their children does not seem to have a major impact on future vulnerability, but families do have an important part to play in the course of the illness; patients with supportive parents do much better than those with critical or hostile ones. Collectively, these risk factors point to an interaction between biological, psychological, and social risk factors that

drive increasingly deviant development and finally frank psychosis.^{11 w9}

Can drug abuse cause schizophrenia?

We know that stimulants like cocaine and amphetamines can induce a picture clinically identical to paranoid schizophrenia, and recent reports have also implicated cannabis. The evidence that patients with established schizophrenia smoke more cannabis than the general population is overwhelming. Well conducted and comprehensive cohort studies, like that from Dunedin in New Zealand,¹² show that early cannabis use—long before psychotic symptoms appear—increases the future risk of schizophrenia fourfold, while a meta-analysis of prospective studies reported a doubling of the risk.¹³ This effect is robust, even after controlling for any effect of self medication,¹³ undermining the suggestion that early cannabis use is an attempt to alleviate distress caused by the developing illness. Only a small proportion of people who use cannabis develop schizophrenia, just as only a few of those who misuse alcohol develop cirrhosis. This probably reflects a genetically determined vulnerability to the environmental stressor, a gene-environment interaction. Indeed, variations in the dopamine metabolising COMT (catechol-O-methyltransferase) gene affect the propensity to develop psychosis in people who use cannabis.¹⁴

Early diagnosis and management in primary care

Box 2 lists the most common positive symptoms of schizophrenia, and box 3 shows the ICD-10 (international classification of diseases, 10th revision) diagnostic criteria. However, few patients initially present with such florid symptoms. Patients are more likely to have more nebulous symptoms such as anxiety and depression, social problems, or changes in behaviour, particularly difficulties in concentrating or becoming withdrawn from their normal social life. Box 4 outlines useful screening questions for patients presenting in this manner.

If the onset of psychosis is suspected, the patient should be rapidly referred to secondary care. This will be the local early intervention or home treatment team in many parts of the UK, or the generic catchment area community mental health team. The risk that patients pose to themselves and others must be assessed at this

Box 1 | Definitions of symptoms of schizophrenia

Positive symptoms

Lack of insight
Failure to appreciate that symptoms are not real or caused by illness

Hallucination

A perception without a stimulus

Hallucinations can occur in any sense—touch, smell, taste, or vision—but auditory hallucinations are the most common (usually “hearing voices”)

Delusions

A fixedly held false belief that is not shared by others from the patient’s community

Delusions often develop along personal themes; for example:

- Persecution—patients think they are victims of some form of threat or are central to a conspiracy
- Passivity—patients think that their thoughts or actions are being controlled by an external force or person
- Other—delusions can develop along any theme; for instance grandiose, sexual, or religious

Thought disorder

Manifests as distorted or illogical speech—a failure to use language in a logical and coherent way

Typified by “knight’s move” thinking—thoughts proceed in one direction but suddenly go off at right angles, like the knight in chess, with no logical chain of thought

Negative symptoms

These include social withdrawal, self neglect, loss of motivation and initiative, emotional blunting, and paucity of speech

Box 2 | Most common positive symptoms of schizophrenia¹⁷

- Lack of insight (97%)
- Auditory hallucinations (74%)
- Ideas of reference (70%)
- Delusions of reference (67%)
- Suspiciousness (66%)
- Flatness of affect (66%)
- Delusional mood (64%)
- Delusions of persecution (64%)
- Thought alienation (52%)
- Thoughts spoken aloud (50%)

first assessment and this information included in the referral. If the presence of psychotic symptoms is confirmed by a psychiatrist, then after discussion it may be appropriate for the general practitioner to prescribe an antipsychotic. Current NICE guidelines¹⁵ recommend considering and offering an oral atypical antipsychotic such as amisulpiride, risperidone, quetiapine, or olanzapine in low doses. The need for hospital admission and even the use of the Mental Health Act will depend mainly on the patient's presentation, the risk assessment, and the availability of good community support. General practitioners can contribute greatly to this decision because of their long term relationship with the patient and family.

Is early recognition important?

Most general practitioners with a couple of thousand patients on their list will see one or two new cases of psychosis each year. The mean duration of untreated psychosis—the time between full symptoms emerging and starting continuous antipsychotic treatment—is currently around one to two years in the UK.^{w10} A systematic review and meta-analysis have shown that the longer this period, the worse the outcome.^{16 w11} The idea that reducing the duration of untreated psychosis will be reflected in improved outcome has led to a recent expansion in first episode services in the UK and other countries. Whether or not this proves to be the case,¹⁷ patients with psychotic symptoms should be identified and treated as quickly as possible.

Long term management in primary care

An average general practitioner in the UK will look after about 12 patients with schizophrenia^{w12} and exclusively manage the care of about six. Once a patient has recovered from an acute episode of schizophrenia, current NICE guidelines recommend that they remain on prophylactic doses of antipsychotic for one to two years and continue to be supervised by specialist services. After that time, if they are well and symptom free, the drug dose can gradually be reduced and the patient carefully monitored to detect any signs of relapse; if such signs occur, then the dose must be increased until they disappear. Such a programme of

Fig 2 | Pharmacological treatment algorithm. Adapted from the Maudsley prescribing guidelines¹⁹

careful monitoring may best be achieved by collaboration between primary and secondary care.

General practitioners are central to ensuring that patients with schizophrenia receive good quality physical health care (fig 1).¹⁸ Current NICE guidelines encourage all practices to establish a mental health register and offer regular physical health checks tailored to the needs of the patient. Special attention should be paid to screening for endocrine disorders; hyperglycaemia and hyperprolactinaemia; cardiovascular risk factors such as smoking, hypertension, and hyperlipidaemia; and side effects of medication, particularly neurological, cardiovascular, and sexual ones (box 5).

Some patients will inevitably need to be referred back to secondary care. Guideline criteria for this decision include:

- Poor treatment compliance
- Poor treatment response
- Ongoing substance misuse
- Increase in risk profile.

What treatment can a patient expect in secondary care? Pharmacological

The first line drug for a patient with a first episode of psychosis is an oral atypical antipsychotic, such as risperidone or olanzapine (fig 2). Drug companies have emphasised the superior side effect profile of these drugs, but in reality the atypicals have different side effects from typical antipsychotics, and they can be just as debilitating. Well conducted randomised controlled trials have shown that, except for clozapine, they are no more effective than the older typical drugs.^{20 21} Thus, patients with established illness who already take

Box 3 | ICD-10 diagnostic criteria for schizophrenia

At least one present most of the time for a month

- Thought echo, insertion or withdrawal, or thought broadcast
- Delusions of control referred to body parts, actions, or sensations
- Delusional perception
- Hallucinatory voices giving a running commentary, discussing the patient, or coming from some part of the patient's body
- Persistent bizarre or culturally inappropriate delusions

Or at least two present most of the time for a month

- Persistent daily hallucinations accompanied by delusions
- Incoherent or irrelevant speech
- Catatonic behaviour such as stupor or posturing
- Negative symptoms such as marked apathy, blunted or incongruous mood

Ongoing research questions

Might there be better ways to define schizophrenia than by the presence of hallucinations and delusions?

What are the biological underpinnings of schizophrenia? Can we gain a better understanding of the site of any pathophysiological lesions and their impact on cerebral function?

What other factors in the environment increase vulnerability to schizophrenia?

How does early substance misuse increase vulnerability to schizophrenia?

Can we tailor treatment—especially drug treatment—to individual patients, to improve outcome and reduce the risk of side effects?

a typical antipsychotic, who are clinically well, and who have no troublesome side effects should not change to an atypical.¹⁵ Clinicians should consider changing patients who take typical antipsychotics and have extrapyramidal side effects to an atypical drug. Intermittent dosing regimens and drug holidays to reduce side effects are not recommended because of the increased risk of relapse. Depot preparations are usually offered to prevent covert non-concordance with treatment and to facilitate dosing regimens. The lowest effective dose of antipsychotic should be used, and the concurrent use of two or more antipsychotics should be limited to specialist services. Anticholinergic drugs should not be routinely prescribed to prevent side effects because of their adverse effects on cognition and memory.

Meta-analysis has shown that clozapine is the best drug for 20-30% of patients who are resistant to treatment.²² Treatment resistance is defined as failure to respond to two or more antipsychotics (one of which should be an atypical) when given at an adequate dose for at least six to eight weeks, and once confounding factors such as concordance failure or substance misuse have been excluded. To prevent agranulocytosis, which occurs in less than 1% of patients taking clozapine, a full blood count must be done regularly. Clozapine is the only antipsychotic that can reduce positive and negative symptoms in patients with treatment resistance, and it should be prescribed as soon as treatment resistance is confirmed.

Psychological

Several psychological treatments can help ameliorate symptoms, improve functioning, and prevent relapse, although their availability is often limited by a lack of trained therapists. Systematic reviews show that cognitive behaviour therapy can reduce persistent symptoms and improve insight^{18,23}; NICE guidelines recommend that it should be provided for at least 10 sessions over three months. Family therapy provides support and

Box 5 | Common side effects of antipsychotic drugs¹⁹**First generation antipsychotics**

Extrapyramidal effects:

- Dystonia
- Pseudoparkinsonism
- Akathisia
- Tardive dyskinesia

Sedation

Hyperprolactinaemia

Reduced seizure threshold

Postural hypotension

Anticholinergic effects:

- Blurred vision
- Dry mouth
- Urinary retention

Neuroleptic malignant syndrome

Weight gain

Sexual dysfunction

Cardiotoxicity (including prolonged QTc)

Second generation antipsychotics

Olanzapine:

- Weight gain
- Sedation
- Glucose intolerance and frank diabetes mellitus
- Hypotension

Risperidone:

- Hyperprolactinaemia
- Hypotension
- Extrapyramidal side effects at higher doses
- Sexual dysfunction

Amisulpiride:

- Hyperprolactinaemia
- Insomnia
- Extrapyramidal effects

Quetiapine:

- Hypotension
- Dyspepsia
- Drowsiness

Clozapine

Sedation

Hypersalivation

Constipation

Reduced seizure threshold

Hypotension and hypertension

Tachycardia

Pyrexia

Weight gain

Glucose intolerance and diabetes mellitus

Nocturnal enuresis

Rare serious side effects:

- Neutropenia (93%)
- Agranulocytosis (0.8%)
- Thromboembolism
- Cardiomyopathy
- Myocarditis
- Aspiration pneumonia

Box 4 | Suggested screening questions for patient presenting with possible psychosis

- Do you hear voices when no one is around? What do they say?
- Do you ever think that people are talking or gossiping about you, maybe even thinking about trying to get you?
- Do you ever think that somehow people can pick up on what you are thinking or can manipulate what you are thinking?

SUMMARY POINTS

Schizophrenia usually starts in late adolescence or early adulthood
 Genetic risk and environmental factors interact to cause the disorder
 The most common symptoms are lack of insight, auditory hallucinations, and delusions
 Clinicians should suspect the disorder in a young adult presenting with unusual symptoms and altered behaviour
 Treatments can alleviate symptoms, reduce distress, and improve functioning
 Delayed treatment worsens the prognosis

education for families. It aims to improve communication between family members, raise awareness in all people involved, and reduce distress. It can help reduce relapse rates, admission rates, symptoms, and the burden on carers, as well as improve compliance with treatment. Systematic reviews have shown that psychoeducation can reduce relapse and readmission rates and is potentially cost efficient. Other treatments with less robustly established evidence include cognitive remediation therapy and social skills training. Psychodynamic psychotherapy may increase the risk of relapse.^{w15}

What is the prognosis?

The common perception that schizophrenia has a poor prognosis is not true. More than 80% of patients with their first episode of psychosis will recover, although less than 20% will never have another episode.²⁴ While many patients with schizophrenia have a lifelong vulnerability to recurrent episodes of illness, a large proportion will have few relapses and make a good functional recovery. Poor premorbid adjustment, a slow insidious onset, and a long duration of untreated psychosis—together with prominent negative symptoms—tend to be associated with a worse prognosis.^{16 w16} An acute onset, an obvious psychosocial precipitant, and good premorbid adjustment all improve the prognosis.

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Additional educational resources

Information for healthcare professionals

Mental Health Care (www.mentalhealthcare.org.uk/)—A collaboration between the Institute of Psychiatry and Rethink providing clinical and up to the minute research evidence on a wide range of mental health matters

EPPIC (www.eppic.org.au/index.asp)—Website produced by the EPPIC service in Melbourne with helpful advice and information sheets about the nature of first episode psychosis

Taylor D, Paton C, Kerwin R, eds. *The 2005 South London and Maudsley Hospital prescribing guidelines*. London: Martin Dunitz, 2005. This covers all aspects of psychiatric prescribing

Frith C, Johnson EC. *Schizophrenia: a very short introduction*. Oxford: Oxford University Press, 2003

Information for patients and carers

Mental Health Care (www.mentalhealthcare.org.uk/)—A collaboration between the Institute of Psychiatry and Rethink providing clinical and up to the minute research evidence on a wide range of mental health matters

Rethink (www.rethink.org/)—One of the major UK mental health charities that focus on psychotic illnesses

Royal College of Psychiatrists (www.rcpsych.ac.uk/mentalhealthinformation.aspx)—A series of articles aimed at professionals, carers, and patients that provides comprehensive information on a variety of mental health problems

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