Schizophrenia

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Schizophrenia is still one of the most mysterious and costliest mental disorders in terms of human suffering and societal expenditure. Here, we focus on the key developments in biology, epidemiology, and pharmacology of schizophrenia and provide a syndromal framework in which these aspects can be understood together. Symptoms typically emerge in adolescence and early adulthood. The incidence of the disorder varies greatly across places and migrant groups, as do symptoms, course, and treatment response across individuals. Genetic vulnerability is shared in part with bipolar disorder and recent molecular genetic findings also indicate an overlap with developmental disorders such as autism. The diagnosis of schizophrenia is associated with demonstrable alterations in brain structure and changes in dopamine neurotransmission, the latter being directly related to hallucinations and delusions. Pharmacological treatments, which block the dopamine system, are effective for delusions and hallucinations but less so for disabling cognitive and motivational impairments. Specific vocational and psychological interventions, in combination with antipsychotic medication in a context of community-case management, can improve functional outcome but are not widely available. 100 years after being so named, research is beginning to understand the biological mechanisms underlying the symptoms of schizophrenia and the psychosocial factors that moderate their expression. Although current treatments provide control rather than cure, long-term hospitalisation is not required and prognosis is better than traditionally assumed.

Lancet 2009; 374: 635–45

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Introduction

Although the precise societal burden of schizophrenia is difficult to estimate, because of the wide diversity of accumulated data and methods employed, cost-of-illness indications uniformly point to disquieting human and financial costs.[1] Schizophrenia does not just affect mental health; patients with a diagnosis of schizophrenia die 12–15 years before the average population, with this mortality difference increasing in recent decades.[2] Thus, schizophrenia causes more loss of lives than do most cancers and physical illnesses. Although some deaths are suicides, the main reason for increased mortality is related to physical causes, resulting from decreased access to medical care and increased frequency of routine risk factors (poor diet, little exercise, obesity, and smoking).[2]

Diagnosis

Identification of delusions and hallucinations in psychosis is not difficult, but their classification has not been simple. Psychosis is not exclusive to schizophrenia and occurs in various diagnostic categories of psychotic disorder (panel). The criteria used to distinguish between these different categories of psychotic disorder are based on duration, dysfunction, associated substance use, bizarreness of delusions, and presence of depression or mania. However, the resulting diagnostic categories show overlap in genetic liability among themselves[3] and with bipolar disorder,[4–6] suggesting common underlying aetiology.

Analysis of the psychopathological features in the various psychotic disorders suggests that symptoms can be clustered into five main categories: (i) psychosis (encompassing delusions and hallucinations—also called the positive-symptom dimension); (ii) alterations in drive and volition (lack of motivation, reduction in spontaneous speech, and social withdrawal—the negative-symptom dimension); (iii) alterations in neurocognition (difficulties in memory, attention, and executive functioning—the cognitive-symptom dimension); and (iv and v) affective dysregulation giving rise to depressive and manic (bipolar) symptoms. The negative dimension is associated with neurocognitive alterations, but the positive and affective dimensions of psychopathological changes are not,[7] and the positive and negative symptoms seem to follow independent courses over time.[8]

Within the cluster of diagnostic categories, the term schizophrenia is applied to a syndrome characterised by long duration, bizarre delusions, negative symptoms, and few affective symptoms (non-affective psychosis). Patients who present with a psychotic disorder with fewer negative symptoms, but whose psychosis is preceded by a high level of affective (depression and mania) symptoms, are usually diagnosed with psychotic depression or bipolar disorder (affective psychosis; figure 1).

The US-based 4th Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) and the 10th International Classification of Diseases (ICD-10) are currently used to diagnose schizophrenia. However, the various work groups who are developing the next generation of DSM and ICD (DSM-V and ICD-11; expected after 2012) have to find solutions for several

Search strategy and selection criteria

We searched publications in PubMed using the search terms "schizophr*[ti]" or "psychosis[ti]" or "psychotic[ti]". We used 1558 English language reviews and meta-analyses published in the past 5 years. These reports were downloaded into an Endnote library file and scanned for relevance with regard to the topics selected for this review. Further focused searches on PubMed were then done on the selected topics.

Panel: **DSM-IV main diagnostic categories of psychotic disorders**

Based on current principles of diagnosis taking into account duration, dysfunction, associated substance use, bizarreness of delusions, co-presence of depression or mania, presence of a somatic disorder, and other criteria.

- Non-affective psychotic disorders:
  - Schizophrenia
  - Schizoaffective disorder
  - Schizophreniform disorder
  - Delusional disorder
  - Brief psychotic disorder
  - Psychotic disorder not otherwise specified
- Affective psychoses:
  - Bipolar disorder with psychotic features
  - Major depressive disorder with psychotic features
- Substance-induced psychotic disorder:
  - Alcohol-induced
  - Other substance-induced
- Psychotic disorder due to a general medical condition

difficult diagnostic issues. First, how many disorders ought to be carved out of the current cluster of categories (panel)? And how should a specific category of schizophrenia be defined among them? Second, does diagnosis of schizophrenia refer to a categorical illness (such as Huntington's disease that one either has or has not) or is it a continuous or dimensional concept (such as the regularly reviewed boundaries of arterial blood pressure above which hypertension is diagnosed)? Finally, is the 19th-century expression referring to a state of so-called split mind a suitable term to diagnose patients in the 21st century?

The current diagnoses (panel) are unlikely to represent discrete nosological entities.[9] For example, schizophrenia-like psychopathological changes are also expressed, in an attenuated form, in individuals with schizotypal or schizoid personality traits. A systematic review of general-population surveys indicated that the experiences associated with schizophrenia and related categories—such as paranoid delusional thinking and auditory hallucinations—are observed in an attenuated form in 5–8% of healthy people.[10] These attenuated expressions could be regarded as the behavioural marker of the underlying liability for schizophrenia and related disorders, just as high blood pressure indicates high susceptibility for cardiovascular disease in a dose–response fashion.

Because of evidence for shared genetic causes underlying diagnoses of psychotic disorders, including bipolar disorder, and evidence for continuity with mental activity in healthy individuals, a major probable change in DSM-V and ICD-11 is the addition of dimensional indicators that can be applied across diagnostic categories of affective and non-affective psychotic disorder (figure 2). Research suggests that the use of a combination of dimensional and categorical representations of psychopathology for the purpose of diagnosis in psychotic disorders conveys more information about treatment needs and prognosis.[11]

A debate exists as to whether the term schizophrenia, which refers to a state of so-called split mind, should be retained in DSM-V and ICD-11.[12–15] Japan was the first country to abandon the term schizophrenia, and modified the name of the illness from Seishin Bunretsu Byo (mind-split disease) into Togo Shitcho Sho (integration-dysregulation syndrome). The change of name had an instant response. Most psychiatrists started using it in the first year, bringing about an improved communication of diagnosis to patients and better perception of the disorder.[16] Thus, the term schizophrenia will continue to evolve; however, the underlying mechanisms and the effect on the person will not change.

Epidemiology

A systematic review of epidemiological data indicates that, if the diagnostic category of schizophrenia is considered in isolation, the lifetime prevalence and incidence are 0·30–0·66% and 10·2–22·0 per 100 000 person-years, respectively.[17] Rates vary three-fold depending on the diagnostic definition of schizophrenia that is used: a narrow definition, including patients with illness duration of at least 6 months, age below 45 years, and negative symptoms has lower rates than a broad definition with less specific criteria.[18] A recent landmark study—allowing for a broad definition of psychotic disorder, including diagnostic categories such as delusional disorder, brief psychotic disorder, and the catch-all diagnostic category of psychotic disorder not otherwise specified—revealed a lifetime rate of schizophrenia and related categories of 2·3%,[19] rising to 3·5% if other psychotic disorders, such as bipolar disorder and substance-induced psychotic disorder, were included.

Diagnostic categories that are biased towards negative symptoms and long duration of illness (both associated with poor outcome) produce diagnostic categories with higher incidence rates for men than for women,[20] whereas those including more affective symptoms and brief presentations (associated with better outcome) show similar rates in men and women.[18,21] These data suggest that the symptomatic expression of schizophrenia and related diagnoses is more severe in men than in women. The finding of an earlier onset in men than in women supports this notion.[17,18]

Perinatal and early childhood factors

Prospective studies have shown that some factors in fetal life—including hypoxia, maternal infection, maternal stress, and maternal malnutrition—might account for a small proportion of incidence of schizophrenia.[22–25] Birth

cohort and high-risk studies have yielded consistent evidence that, as a group, children who as adults will be diagnosed with schizophrenia have, compared with their peers, a higher incidence of non-specific emotional and behavioural disturbances and psychopathological changes, intellectual and language alterations, and subtle motor delays.[26–28] Some of these developmental indicators could be relevant for differential diagnosis within the cluster of diagnostic categories because motor and cognitive alterations seem to be specific for the diagnosis of schizophrenia (ie, have not been observed in bipolar disorder).[29–31]

Environmental factors

Systematic reviews of epidemiological studies have indicated that the rate of schizophrenia and related disorders is affected by some environmental factors.[17,32] First, the risk of schizophrenia and related categories increases linearly with the extent to which the environment in which children grow up is urbanised (odds ratio [OR] ~2).[33] Second, evidence exists that some immigrant ethnic groups have a higher risk of developing psychotic disorders than have native-born individuals,[34] particularly if they live in a low ethnic density area, or an area where there are fewer people of the same migrant group (OR 2–5).[35,36] Third, randomised experimental studies have shown that exposure to dronabinol, the main psychotropic component of cannabis, causes mild and transient psychotic states[37,38] to which individuals with pre-existing liability to psychosis are more susceptible than are healthy controls.[39,40]

Systematic reviews of prospective studies have suggested that cannabis use is associated with increased risk for psychotic disorder and symptoms (OR 1·5–2·0).[41] Although establishment of causality on the basis of epidemiological data is difficult,[42] the acute psychotic states induced by dronabinol provide an important model of psychotic symptoms, especially as national register follow-up studies have suggested that cannabis-induced acute psychotic states treated in psychiatric services are the early signs of schizophrenia and related disorders.[43,44]

The large effect sizes, in terms of relative risk (≤5) and high fraction (≤30%) of overall incidence attributable to environmental factors in urbanised areas, migrant and ethnic group, and cannabis, assuming causality, raise a number of important issues. First, the association with urbanisation and migration might indicate a common environmental influence linked to chronic experience of social disadvantage and isolation,[45] suggesting that public health policies targeting these factors might also affect rates of schizophrenia. Further work is needed focusing on the identification of specific environmental influences and mechanisms underlying the proxy risk factors of migration and extent of urbanisation. Some studies are attempting this aim using virtual reality[46] or momentary assessment designs.[47]

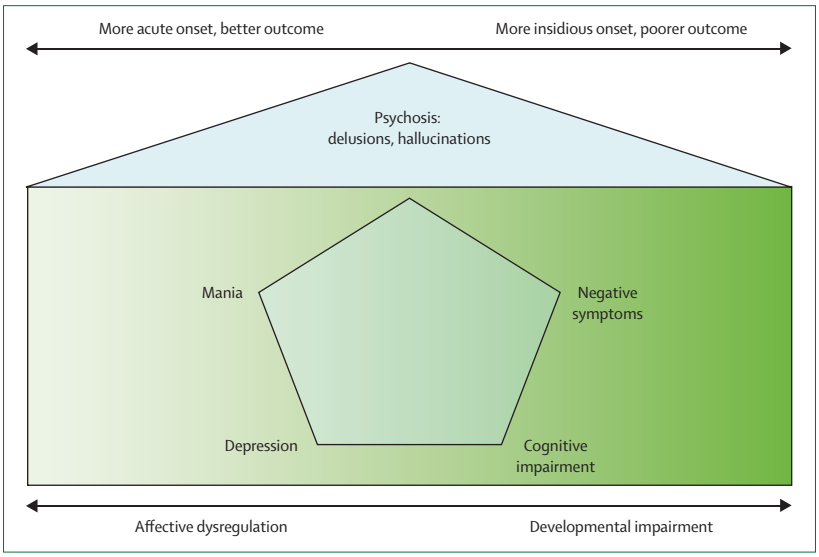

Figure 1: **Principles underlying the main distinction between affective psychosis (eg, bipolar disorder and psychotic depression) and non-affective psychosis (eg, schizophrenia and schizophreniform disorder)**

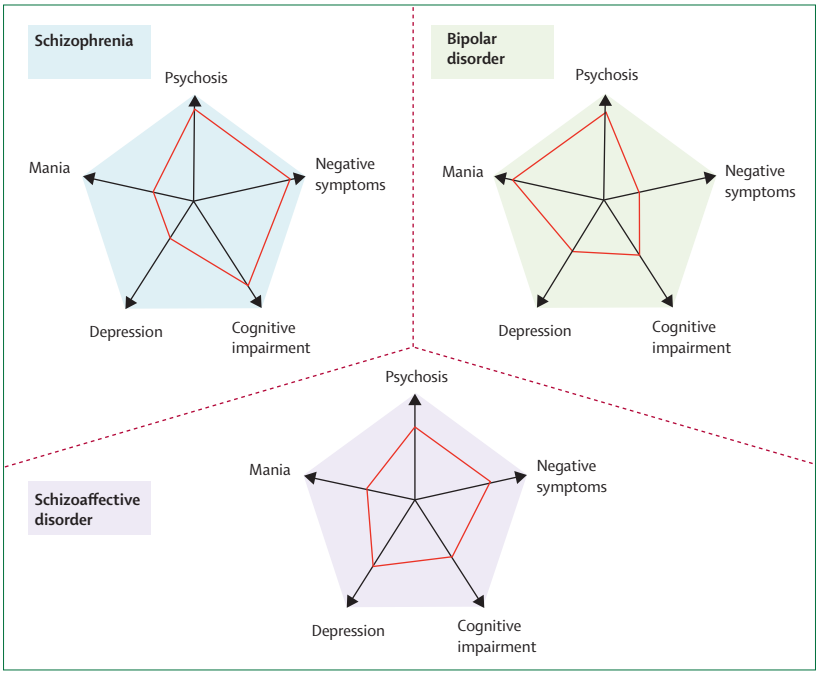

Figure 2: **Three hypothetical typical patients diagnosed with a combination of categorical and dimensional representations of psychopathology**

Categorical diagnoses of schizophrenia (blue), bipolar disorder (green), and schizoaffective disorder (violet) are accompanied by a patient's quantitative scores (connected by red lines) on five main dimensions of psychopathology.

Second, since the incidence and expression of schizophrenia varies in different social contexts, a level of explanation focusing on the effect of the environment on cognitive schemata as well as on brain neurobiological mechanisms is necessary. For example, exposure to trauma during childhood could predispose to a paranoid way of thinking[48,49] and, when this is paired with a sensitised dopamine system,[50] it could predispose the individual to psychotic disorder.

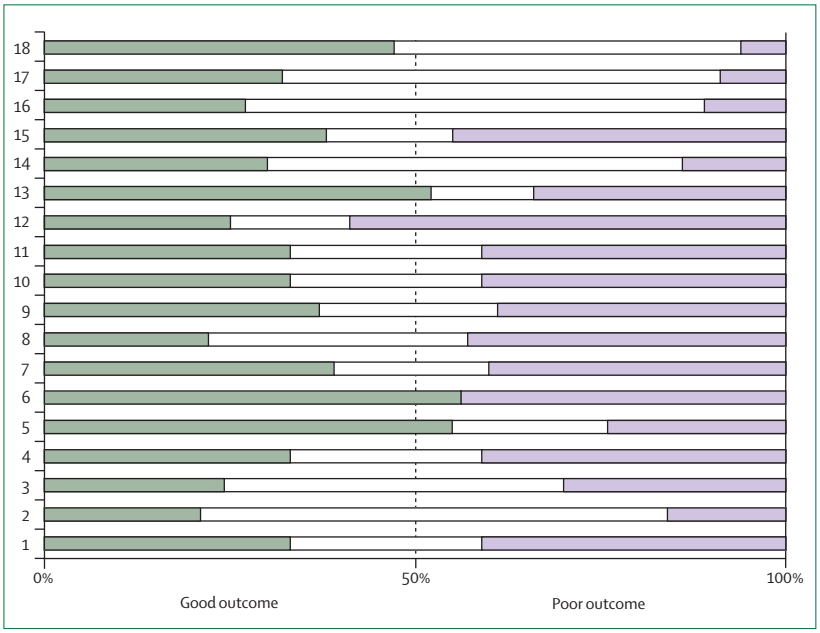

Figure 3: **Outcome heterogeneity in schizophrenia**
Summary of 18 prospectively designed outcome studies of first admission and first diagnosis of schizophrenia with follow-up of more than 1 year with variably defined good and poor outcomes, showing balanced proportions of good and poor outcomes across studies. Studies 1 to 18 are references 76–93. Examples of good outcomes: symptomatic recovery with no social or intellectual deficit throughout follow-up (study 2, reference 77); full recovery over follow-up (study 12, reference 87); complete remission and never readmitted (study 16, reference 91). Examples of poor outcome definition: severe chronic social or intellectual deficit (study 2, reference 77); moderate-to-severe symptoms at time of follow-up (study 12, reference 87); chronic continuous psychotic symptoms over full follow up time (study 16, reference 91). For full description of all outcome definitions see reference 94.

Third, although migration and cannabis use do not seem to be specific for a particular diagnostic category among the different psychotic disorders, urbanisation exposure is associated with the diagnostic category of schizophrenia and not with bipolar disorder,[51] suggesting that some environmental exposures affect different causal pathways resulting in specific psychopathological outcomes.

Finally, the fact that only a minority of those exposed to urban environments, migration, and cannabis develop schizophrenia indicates that some are resilient to these risk factors. The basis for this resilience could help devise public health strategies.

Gene and environment interplay

Vulnerability for schizophrenia is partly genetic. Twin studies suggest that the syndrome has heritability estimates of around 80% (compared with ~60% for osteoarthritis of the hip and 30–50% for hypertension). Despite this genetic association, the identification of specific molecular genetic variation has not been easy. Modification of diagnostic criteria and uncertainty about the natural phenotype of psychosis are likely to have hampered progress in this regard.

Recent findings have suggested that a small proportion of schizophrenia incidence could be explained by rare structural variations (copy number variants occasioned by small duplications or deletions, or inversions). These genomic variants are usually rare individually, but have now been observed at a higher rate in autism[52] and schizophrenia compared with controls,[53–58] suggesting a possible shared neurodevelopmental pathway for these disorders.[59] Similarly, new genome-wide association studies have yielded the first genome-wide results replicated across multiple samples for bipolar disorder and schizophrenia on the one hand, and evidence suggestive for association across disorders on the other hand.[60,61]

The high heritability (80%) of schizophrenia is not only due to genetic influences but also due to environmental effects that are moderated by genes (gene–environment interaction). Epigenetic factors susceptible to environmental influence might also affect twin heritability estimates.[62] Meta-analytic work suggests that paternal age above 40 years is associated with schizophrenia, indicating that epigenetic mechanisms might have a role.[63] Genetic epidemiological studies have proposed that gene–environment interaction in schizophrenia and related diagnostic categories is common.[64] Therefore, the worldwide challenge is to bring together the various disciplines that are needed to examine models of disease causation based on various aspects of gene–environment interplay.[65]

Research in twins and first-degree relatives of patients has shown that the genes predisposing to schizophrenia and related disorders affect some heritable traits[66–68] that underlie the illness: neurocognitive functioning, structural MRI brain volume measures, neurophysiological information processing traits and sensitivity to stress.[69–72] These so-called intermediary phenotypes (because they are between the predisposing genes and the disease phenotype) might be closer to alterations in gene function than the diagnostic category of schizophrenia and related disorders, and for this reason could be useful targets for molecular genetic studies. Some of these intermediary phenotypes could be diagnostically relevant; for example, the intermediary phenotype of cognitive impairment could have high specificity for the diagnostic category of schizophrenia. Indeed, meta-analytic work has indicated that relatives of patients with bipolar disorder have only minimal cognitive alterations.[73]

Prognosis

The traditional clinical and societal view of schizophrenia is of a debilitating and deteriorating disorder with poor outcome. However, most patients now live independently outside the hospital and the typical duration of admission is short (a few weeks). Although most patients need some degree of formal or informal financial and daily-living support, the perspective now is one of recovery, where the patient takes an active role in the development of new meaning and purpose while growing beyond the misfortune of mental illness.[74,75]

Prospectively designed outcome studies of first admission and first diagnosis of schizophrenia with follow-up time of more than 1 year have suggested that heterogeneity is common with poor outcome in less than 50% of patients and, similarly, with good outcome in less than 50% of patients (figure 3). Therefore, the course and outcome of schizophrenia is characterised by mainly unexplained[94] heterogeneity rather than uniform poor outcome.[95] Understanding of these data and communication to patients and their families at the time of diagnosis are crucial steps, because patients and families often suffer for the common assumption of a negative outcome.

Pathophysiology

Since the advent of modern neuroimaging techniques, the number of studies of the pathophysiological changes of schizophrenia has dramatically increased, with more than 1000 reports published in the past 10 years. Structural brain imaging studies have shown a subtle, almost universal, decrease in grey matter, enlargement of ventricles, and focal alteration of white matter tracts.[96–98]

Neurochemical imaging studies to test the dopamine hypothesis of schizophrenia with ^{18}F-dopa and ^{11}C-raclopride are consistent in showing that schizophrenia, in its acute psychotic state, is associated with an increase in dopamine synthesis, dopamine release, and resting-state synaptic dopamine concentrations.[99,100] These neurochemical findings provide a logical link to the fact that all current pharmacological treatments of schizophrenia block dopamine receptors.[101] Abnormal brain structure and neurochemical composition lead to abnormal function that is shown by functional MRI (fMRI) and electrophysiological techniques. fMRI studies show abnormalities in the brain response to cognitive tasks, with an abnormal network response characterised by both hyperactivity and hypoactivity in different brain regions (compared with the response in healthy volunteers), depending on the specific tasks.[102] Event-related potential studies have looked at the response of patients to novel stimuli (P300) and to repeated stimuli (P50), showing that patients have a diminished brain response to new stimuli and a decreased ability to suppress brain activation in response to repeated stimuli.[70,103] In conclusion, diagnosis of schizophrenia is associated with altered brain function; however, these results raise the question of why a change in dopamine concentrations leads a person to become convinced that their colleagues are conspiring and the police are out to get them.

Several recent theories attempt to fill the gap between biological alterations and actual experiences reported by patients.[104,105] One such theory is based on the fact that neurons in the dopamine system fire in response to novel rewards in the environment, and that the released dopamine leads to a switch in attention and behaviour towards the rewarding situation, thus imbuing the stimulus with motivational salience.[106,107] Aberrant firing of the dopamine system might lead to the aberrant assignment of motivational salience to objects, people, and actions.[105,108,109] The patient then makes an effort to interpret these aberrant experiences and constructs a seemingly plausible (to them) account to understand the changing situation.

Thus, a mixture of dopamine dysregulation and aberrant assignment of salience to stimuli, together with a cognitive scheme that attempts to grapple with these experiences to give them meaning, might lead to the development of psychotic symptoms.[110] Alterations in affective state (depression or mania) and some ways of thinking, such as a tendency to jump to conclusions, might combine with the dopamine dysfunction to increase the risk of delusion formation.[111]

Clinical management

Diagnosis of schizophrenia is made by reference to the criteria in DSM-IV and ICD-10. Even though these are clinical criteria, diagnosis can be achieved with acceptably high inter-rater reliability and compares well with diagnostic reliability in the rest of medicine. Unfortunately, no objective test exists for this diagnosis. Although several biological abnormalities have been reproduced (eg, abnormally large ventricles, abnormal dopamine concentration, and altered P300), they are not sensitive enough (usually seen only in 40–50% of patients) or not specific enough (seen in 30% of first degree relatives and 10% of otherwise normal controls) to be of diagnostic usefulness.[112] Thus, diagnosis is based on confirmation of the key symptoms and elimination of the most probable differentials (drug abuse, contributory neurological conditions, or metabolic illness).

Once the diagnosis is made, antipsychotic drugs, which block dopamine D2 receptors,[113] are the main treatment of schizophrenia. First-generation agents—discovered in the 1950s, also called first-generation antipsychotics (eg, haloperidol and chlorpromazine)—are effective in the treatment of psychotic symptoms, but often lead to motor side-effects.

In the past 10 years, new agents, known as the second-generation antipsychotics—risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole—that less frequently cause motor side-effects have been introduced for treatment. Initially, there was optimism that they would improve not only the positive psychotic symptoms but also the negative and cognitive aspects of the syndrome. Although the new second-generation antipsychotic drugs are effective in treating positive symptoms with a reduced burden of motor side-effects, the promise of efficacy against negative and cognitive symptoms has not been borne out.[114,115] Additionally, the new antipsychotics tend to induce a high incidence of metabolic side-effects (weight gain, increased triglycerides and cholesterol).

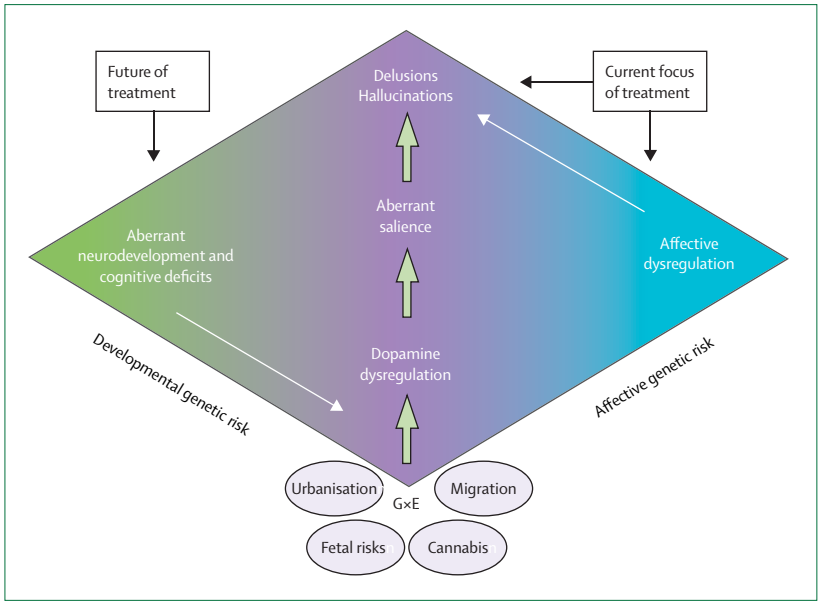

Figure 4: **A model of schizophrenia and related psychotic disorders**
The model brings together affective and non-affective dimensions of psychopathological changes and their overlapping genetic liabilities. Aberrant neurodevelopment contributes to biological alterations, whereas affective dysregulation contributes to cognitive explanations of aberrant salience. GxE=gene–environment interaction.

A recent study of first-episode patients reported that more than 50% of the patients gained significant (ie, >7%) weight, with an average weight gain of 4–7 kg, leading one in ten patients to develop a treatment-emergent metabolic syndrome.[116] Thus, the choice between antipsychotic drugs requires an analysis of the potential benefits, risks, and costs.[114]

However, medications alone are not the solution. Antipsychotic drugs are best administered in the context of other psychological and social supports, as indicated by case-management models of treatment delivery.[117,118] Community-case management (ie, a multidisciplinary team of mental health professionals, who engage with the patient and their carers inside and outside the hospital, and ensure a combination of health and social care[119,120]) is available in some countries (eg, the UK) but often remains the exception for most patients worldwide. The low availability of these services is lamentable, because teams and personnel can be easily trained, the model can be adapted to different settings, and, when properly implemented, it reduces hospital stay and hospital cost, increases patient retention in treatment, and improves satisfaction of patients and carers.[121]

With a combination of new medications and community-case management, remission of about 80% of patients can be achieved, especially if treatment is initiated early during the first episode of the illness.[122] The main challenges are to make sure that patients continue to take medication when required and to improve functional outcomes. Many patients with a diagnosis of schizophrenia stop their medication, increasing the risk of relapse.[122] The reasons for patients discontinuing antipsychotic treatment are not dissimilar from those in other chronic illnesses, although two issues may be specific to schizophrenia: the stigma[123,124] of being labelled as psychotic and the fact that dopamine-blocking medications dampen motivational drives.[125,126]

Although some experimental approaches to improve treatment adherence have been attempted (special pill bottles, reminders, economic incentives, and individual, family, and group therapy) and show some efficacy in experimental situations,[127] none is widely available or used. Even in patients with good control of positive symptoms, return to function could remain a challenge. Few patients currently resume employment, the major challenges being lack of effective interventions such as supported employment,[128] as well as neurocognitive alterations and impaired motivational drive.

Although some pharmacological approaches to improve negative symptoms have been tried (eg, antidepressants and glutamate modification), none have been successful.[129] Thus, the emphasis has been on vocational and occupational rehabilitation techniques to restore function. These interventions show good efficacy in increasing the chances of functional improvement in small experimental studies,[130,131] but, although some specialised centres offer these interventions, they are neither standardised nor available in routine care.

Despite some advances—new medications, and better psychological and vocational interventions—a substantial proportion of people with schizophrenia, about a third, remain symptomatic. With these patients, doctors often attempt different antipsychotic drugs or increase therapy with anxiolytic, antidepressant, and anticonvulsant medications, or experimental agents. A number of systematic reviews show that these additions are of low proven value and might result in unnecessary polypharmacy.[132] One intervention that most reliably improves symptoms is the use of clozapine, a unique antipsychotic drug that often works in patients in whom other antipsychotics have failed. It is used only in those who are refractory to other treatments and only given in combination with weekly blood monitoring because of the risk (1–4%) of agranulocytosis.[114]

For patients with drug-resistant symptoms, cognitive-behavioural therapy can improve coping and reduce distress and negative affect associated with psychotic symptoms;[133] however, such specialised psychological therapies are not routinely available. Comorbid substance misuse is common: more than half of patients with schizophrenia smoke (3–4 times the local population average) and a significantly higher number (than the local population) abuse cannabis and alcohol. Comorbid substance abuse is often undetected; even when noted, few therapeutic options exist, with scarce

evidence of benefit for pharmacological[134] or psychosocial interventions.[135]

Prevention

Because psychotic disorders occur in young people and disrupt educational and social development, early intervention is crucial and could favourably affect long-term prognosis. A few studies have assessed the use of specialised early interventions for first-episode psychotic disorder patients with encouraging results in the first year;[136] follow-up, however, suggests that the benefits of early intervention might be lost after 5 years.[137]

Whether early intervention can be extended to at-risk mental states before the onset of full-blown psychotic illness is not clear.[138] Evidence exists from two birth cohorts,[139,140] three representative general population cohorts,[141–143] and other longitudinal studies[144] that mild psychotic experiences, such as delusional thinking and mild hallucinations, might precede the diagnosis of a psychotic disorder and hospital admission for schizophrenia by many years. Unfortunately, positive predictive values of such precursors are too low to be useful for ethical and cost-effective preventive interventions.[145] Nevertheless, dedicated early intervention clinics might be able to select groups of help-seeking individuals at high risk of making a transition to a clinical psychotic disorder.[146] Several small trials have suggested that cognitive-behavioural therapy or pharmacological interventions could reduce rate of transition from an at-risk mental state to full-blown psychotic disorder. More definitive conclusions about efficacy, and whether and how these programmes should be available for help-seeking individuals with an at-risk mental state, require more evidence.[136]

Cognition

Almost 100 years ago when schizophrenia was first defined in its current form, it was called dementia praecox, the focus being on the intellectual deterioration that accompanied the syndrome. In the following years, the focus shifted to the psychosis, the delusions, and the hallucinations as the cardinal features of the illness, perhaps because they are easy to identify and greatly affect functioning and society. However, during the past 10 years, there has been a resurgence of interest in the cognitive alterations of schizophrenia and it is now accepted that patients with a diagnosis of schizophrenia have a broad-based cognitive impairment of, on average, about 1 SD below the norm across a range of cognitive abilities (attention, speed of processing, working and long-term memory, executive function, and social cognition).[147]

These alterations are well established by the time of the first episode, show scarce relation to psychotic symptoms,[7] are not much influenced by the currently available medications, and often show no improvement despite complete resolution of psychotic symptoms.[148,149] Although these symptoms have received not much clinical attention, they are important contributors to the patients' inability to regain function and vocation,[150] possibly by affecting an area of cognition called social cognition, or the ability to understand and interact with the social world around. Consequently, development of new medications and cognitive remediation approaches[131] as add-ons to ongoing antipsychotic treatment is becoming increasingly topical. Several mechanisms are being exploited for new medication development (nicotinic drugs, glutamate system potentiation, treatments that increase dopamine D1 receptor stimulation, and drugs normalising GABA interneuron function[151]), new scales to measure and document cognitive impairments are being standardised,[152] and hope exists that use of these medications, with or without cognitive remediation, might provide the next major advance in the treatment of patients with schizophrenia.

Conclusions

In the 100 years that we have known the diagnosis of schizophrenia, its definition has swung between a biological illness, a psychological dysfunction, and a social construct. The advances of genetics, epidemiology, imaging, and pharmacology now allow us to put these perspectives together (figure 4). A clear genetic susceptibility exists in schizophrenia; however, what one inherits is not the illness, but altered brain development, shared partly with developmental disorders, such as autism, and partly with affective disorders such as bipolar disorder.

The behavioural expression of this vulnerability usually remains restricted to subtle alterations in cognition, some suspiciousness, or affective dysregulation, which generally leads only to subtle functional effect. In a minority of those who inherit these vulnerabilities, perhaps when genetic vulnerability is combined with environmental insults, a state of abnormal dopamine release might result, which gives rise to an aberrant assignment of salience, which in turn causes psychotic symptoms, bringing the patients to medical attention. The main treatments for psychosis are antipsychotic drugs, which do not address the vulnerability or the environmental insult but merely block the effects of an abnormal dopamine system. As long as the patient takes the antipsychotic medication, symptoms usually are dampened. However, if the medication is discontinued, the primary vulnerability might re-express itself, leading to relapse. During the past 50 years, advances have helped to deal with the symptomatic expression of the syndrome. In the next few decades, treatments that address the underlying neurobiological vulnerability and protect against environmental risks might be developed. Until then, we hope that society will treat those who suffer with psychosis with respect, hope, and dignity—rather than stigma, pessimism, and exclusion.

Contributors
JvO conceived the idea. Both JvO and SK were involved in the development of the structure of the review, literature search, summary of the results, writing of the article and constructing the graphics; and in responding to the referees' suggestions.

Conflicts of interest
JvO is or has been an unrestricted research grant holder with, or has received financial compensation as an independent symposium speaker from, Eli Lilly, BMS, Lundbeck, Organon, Janssen-Cilag, GlaxoSmithKline, AstraZeneca, Pfizer, and Servier. SK has been a research grant holder or has received financial compensation as an independent symposium speaker from AstraZeneca, Bristol Meyers Squibb, Eli Lilly, Janssen (Johnson and Johnson), Lundbeck, Otsuka, Organon, Pfizer , Sanofi-Synthelabo, Servier, Solvay Wyeth, and Theragenetics, which have an interest in the treatment of psychosis.

Acknowledgments
We thank Judith Allardyce for sharing data on course and outcome studies in schizophrenia.

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