

Dealing with schizophrenia in general practice

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Abstract

Schizophrenia is a psychiatric illness of unknown aetiology, and impairs cognition and social and occupational functioning. It is challenging in terms of the disability it causes, the unclear nature of what causes it, the complexity of diagnosis and treatment limitations. General practitioners can play a role in various phases of the illness, from early intervention to chronic care, in liaison with the psychiatrist.

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Introduction

Schizophrenia is a chronic psychiatric illness, with a relapsing and remitting course. It is a syndrome; namely a collection of signs and symptoms of unknown aetiology, and is commonly associated with social and occupational functioning impairment. Schizophrenia is ranked by the World Health Organization as one of the top 10 illnesses that contributes to the global burden of disease.

Schizophrenia has a prevalence of one per cent in the general population. Genetic and environmental factors have been implicated in the aetiology of the disease, and genetic factors contribute about 80% of the risk of developing schizophrenia. A number of chromosomal regions have been linked to the risk of developing the disease, and the predominant genetic view of schizophrenia is that it is a heterogeneous, polygenic disease. It is known that schizophrenia aggregates in families, and having an affected family member increases the risk of developing the disease substantially. However, two thirds of new cases of schizophrenia occur sporadically.

Numerous environmental exposures have also been implicated as risk factors for the development of schizophrenia, and include biological and psychosocial risk factors. Environmental factors linked to a higher likelihood of developing schizophrenia include a history of obstetric and perinatal complications, a history of a winter birth, as well as older paternal age at conception. Childhood trauma and abuse, and parental separation or death during childhood or adolescence, has been linked to an increased risk of developing schizophrenia. Other important risk factors

that have been associated with an increased liability for developing the disease include cannabis abuse, urbanicity and migration, social adversity, and stressful life events.

Neurochemical alterations that have been considered in the pathophysiology of schizophrenia include dopamine, glutamate, and gamma-aminobutyric acid dysregulation. Neuroanatomical and neuropathological structural changes that are seen in these patients include reduced grey matter volumes in a wide range of brain regions subserving cognitive, affective and thought processes, and these include the prefrontal, temporal, parietal, thalamic and striatal regions.

It appears that a range of environmental factors have been linked to the risk of developing schizophrenia, but how these factors interact with each other, and with genetic risk factors, to cause illness, and the extent to which neurobiological processes mediate these effects, remains a major gap in the understanding of the disease.

Clinical symptom domains of schizophrenia

Kraepelin used the term “dementia praecox”, or “premature dementia” to describe the cognitive impairments experienced by these patients. Bleuler was more impressed by the disorder of thought and feeling, and created

the term “schizophrenia”. Positive symptoms can be an exaggeration of a normal process, and include hallucinations which may be auditory, visual, tactile or olfactory, and delusions, which are fixed false beliefs that can be bizarre or non-bizarre, and are categorised according to the content,

for example, paranoid, grandiose and religious delusions. These symptoms are present in 80% of patients. Other symptoms include disorganised speech and behaviour, and negative symptoms that are considered to be either an absence of, or decrease in normal processing. They can be primary or secondary in nature. Primary negative symptoms represent core features of schizophrenia, and include apathy, anhedonia, alogia, affective flattening and avolition. Secondary negative symptoms can occur as a result of manifestations of the illness, or due to treatment with antipsychotic medication.

Deficits in cognitive and executive functioning are also observed in these patients. The most affected areas are processing speed, attention, working memory, verbal and visual learning and memory, executive functioning and social cognition. Neuromotor symptoms are also present, and include varying degrees of catatonia and stereotypic movements. Catatonia can present as extreme negativism,

mutism or excitement. Several neurological soft signs have been observed and encompasses impairments in integration, motor coordination and sequencing, but are unrelated to medication use.

Mood and anxiety symptoms are common in schizophrenia, and occur at a higher rate in these patients. Substance-use disorders also occur more frequently in these patients. It can be challenging to diagnose depressive disorders and anxiety disorders in patients with schizophrenia. A primary co-morbid disorder needs to be distinguished from symptoms of schizophrenia, antipsychotic drug side-effects, and other clinical presentations.

Diagnosis

The diagnosis of schizophrenia is one of exclusion, and no symptom or group of symptoms are pathognomonic of the disease. Psychosis is central to the diagnosis under the Diagnostic and Statistical Manual of Mental Disorders (DSM) IV text revision (TR) classification system, and requires the presence of characteristic symptoms of the disorder referred to as the A criteria, coupled with social and occupational dysfunction that has lasted for at least six months.

Other conditions or psychotic mood disorders must be excluded. Table I refers to the diagnostic criteria for schizophrenia. There are no laboratory or physical examination findings or biomarkers that are useful in making the diagnosis, but the diagnostic criteria may be useful in excluding other medical causes of psychosis. The assessment is based on diagnostic interview and collateral information which can be provided by family members and caregivers.

The clinical symptom domains of schizophrenia are grouped in the following clusters (Table II).

The course of schizophrenia is deteriorative in 80% of patients. Recovery occurs in about 20% of patients, but mortality is high, with 5-10% of patients dying from suicide, while a large percentage of patients die due to co-morbid illnesses.

Table I: Diagnostic criteria for schizophrenia

<p>A. <i>Characteristic symptoms of the active phase:</i> Two or more of the following, that are present for a significant portion of time during a one-month period (or less if successfully treated):</p> <ul style="list-style-type: none"> • Delusions • Hallucinations • Disorganised speech • Grossly disorganised or catatonic behaviour • Negative symptoms.
<p>B. <i>Social and occupational dysfunction:</i> Social and occupational dysfunction needs to be present for a significant portion of time since the onset of disturbance, in one or more areas of functioning.</p>
<p>C. <i>Duration:</i> Continuous signs of the disturbance must have persisted for at least six months. This six-month period must include at least one month of symptoms, or less, if successfully treated that meet criterion A, and may include periods of prodromal or residual periods. During these prodromal or residual periods, the signs of the disturbance may be manifested by negative symptoms, or two or more symptoms listed in criterion A in attenuated form.</p>
<p>D. Schizoaffective and mood disorder exclusion.</p>
<p>E. Substance abuse or general medical condition exclusion.</p>

Table II: Clinical symptom domains of schizophrenia

Positive symptoms	Negative symptoms	Cognitive deficits	Mood symptoms	Neuromotor
Delusions	Affective blunting	Attention	Depression	Catatonia
Hallucinations	Alogia	Memory	Hopelessness	Stereotypic movements
Disorganised speech	Avolition	Executive function	Suicidality	Dystonia
Disorganised behaviour	Anhedonia		Anxiety	Hypokinesia
	Social withdrawal		Agitation	Dyskinesia
			Hostility	

Management

Managing patients who are suffering from schizophrenia can be challenging. It is a chronic remitting and relapsing disorder, associated with significant impairments in social and occupational functioning. Comprehensive treatment entails a multimodal approach, including medication and psychosocial interventions. Treatment objectives are to reduce the morbidity and mortality of the disorder by decreasing the frequency and severity of the psychotic episodes, and also to improve the functional capacity and quality of life of the individuals.

Antipsychotic medication is the cornerstone in the pharmacological treatment of schizophrenia, and is classified into groups of first- and second-generation antipsychotics (Table III). One pharmacological property that is shared by all antipsychotic agents is their ability to block the dopamine 2 receptor to a varying degree. The potency of the antipsychotic is found to correlate with its affinity for the receptor. Treatment needs to be individualised, and current symptoms, co-morbid conditions, past therapeutic responses, adverse effects, and patient choice, as well as expectations, must be taken into consideration. Acute and long-term treatment goals and side-effect profiles also need to be balanced.

First-generation antipsychotic agents are fairly effective in reducing the positive symptoms of hallucinations and delusions. However, these medications are minimally effective in reducing the negative and cognitive symptoms that contribute to illness-related disability. They also cause side-effects such as acute extra-pyramidal symptoms (EPS) and tardive dyskinesia, following long-term use.

Common side-effects of second-generation antipsychotics include weight gain, dyslipidaemias, hypertension,

insulin resistance, and the metabolic syndrome. Cardiac rhythm disturbances can occur, especially prolongation of the QT interval. Important investigations that need to be conducted prior to commencing second-generation antipsychotics include measurements of body mass index, waist circumference, haemoglobin A1c, serum lipids, and blood pressure, as well as undergoing an electrocardiogram (ECG).

Results of large-scale studies comparing the effectiveness of first- and second-generation antipsychotics agents in schizophrenia appear to indicate that the latter are no more effective than the former, and are not associated with better cognitive or social outcomes.

Acute-phase treatment

The goal of treatment is to reduce the severity of psychotic symptoms and behaviours. Randomised trials have shown that antipsychotics reduce positive symptoms to a tolerable level in 70% of patients. Antipsychotics should be used at the lowest dose that is effective for the individual as the adverse effects of medication may outweigh the benefit of dosage increases.

Psychotic symptoms of schizophrenia, such as frightening delusions, suspiciousness, and command hallucinations, can cause patients to become agitated. Agitation caused by substance use or withdrawal must be excluded, and can be diagnosed by a history, physical exam, and toxicology. EPS, such as akathisia, can also be difficult to distinguish from psychotic agitation, and this can be treated with a benzodiazepine, for example, lorazepam, started at 0.5 mg orally twice daily, and gradually increased to a maximum of 6-10 mg/day.

The selection of a drug, and the route of administration, depends on the urgency of calming the patient, as well as the mental state and cooperation of the patient. The goal is to induce a calmer state, which can be accomplished without inducing sedation. This can be achieved by an oral formulation, rapid dissolving, or intramuscularly injected antipsychotic formulations. Intramuscular antipsychotics have two potential advantages over oral antipsychotics, namely they can be administered safely to uncooperative individuals, and patients reach an effective plasma concentration sooner than that achieved with oral formulations.

Clinicians tend to favour sedating antipsychotics for agitated patients, but non-sedating agents can also be effective in reducing agitation. Haloperidol 2.5-5mg, risperidone 1-2 mg, or olanzapine 5-10 mg, and ziprasidone 10-20 mg, can be used.

Table III: Classification of antipsychotic medication

Antipsychotics: equivalent doses	mg/day
First generation	
Haloperidol	0.5-5
Trifluoperazine	5-30
Chlorpromazine	100-400
Second generation	
Risperidone	2-6
Olanzapine	5-20
Quetiapine	150-750
Aripiprazole	15-30
Ziprasidone	80-160

Oral rapidly dissolving formulations are helpful in poorly compliant patients.

Short-acting intramuscular injectable formulations are available, for example, haloperidol, olanzapine, aripiprazole and ziprasidone. Olanzapine 5-10 mg administered intramuscularly is a good choice, but cannot be administered with a benzodiazepine concurrently, due to the risk of respiratory suppression. Haloperidol is effective in treating severe agitation, but should be given with an anticholinergic to reduce the risk of severe EPS, including dystonias. A combination of haloperidol 5 mg, lorazepam 2mg and benzotropine 5mg, can be given intramuscularly.

Repeat administration of an oral or intramuscular antipsychotic is common if the prior dose does not reduce the agitation, but the overall antipsychotic dose should be limited, as significant side-effects, such as hypotension, EPS and sedation can occur, particularly at high doses, over a brief period of time. When patients fail to respond to one or two doses of an antipsychotic, to limit the amount of antipsychotic used, it is recommended that either a combination of an antipsychotic and a benzodiazepine, or use of a benzodiazepine, is started.

Patients experiencing a first psychotic episode tend to have higher response rates than those who have experienced multiple psychotic episodes. Younger patients and first-episode patients have a greater vulnerability to side-effects, such as weight gain and EPS. The Schizophrenia Patient Outcomes Research Team study recommended that first-episode patients receive antipsychotic doses in the lower half of the recommended dose range, and also advocated treating first-episode psychosis with antipsychotics other than olanzapine and clozapine, due to the side-effect profile.

Maintenance treatment

Usually, patients who have recovered from an acute psychotic episode will reach a stable or maintenance phase, in which psychotic symptoms are reasonably controlled. The goal of maintenance treatment is to minimise symptoms and functional impairments, avoid relapses, and promote recovery, as well as reintegration into the community. Patients and their clinicians should make a joint decision about treatment duration. However, it is recommended that antipsychotic treatment should be continued indefinitely, even for patients who have achieved remission from a first psychotic episode. A review of randomised controlled studies suggests that the rate of relapse over one year is much higher for patients on placebo treatment, compared to those treated with antipsychotics.

Refractory symptoms

Switching antipsychotics can be helpful when a poor response relates to side-effects. Switching antipsychotics is less clearly beneficial when the initial medication lacks effectiveness. Studies have shown that poor responders to one antipsychotic are likely to be poor responders to another antipsychotic, with the exception of clozapine. Clinicians often add a second antipsychotic when there is a suboptimal response, but there is little empirical evidence to support this use. Poor compliance to oral antipsychotic treatment is another problem that is encountered during the maintenance phase. Long-acting injectable antipsychotics may be useful for these patients.

Clozapine is recommended for treatment-resistant cases in which patients experience persistent and significant positive symptoms after trials of two other antipsychotics. Clozapine should be started at a dose of 12.5 mg, and titrated very slowly upwards. In trials, clozapine has also been shown to reduce suicide attempts in patients with schizophrenia.

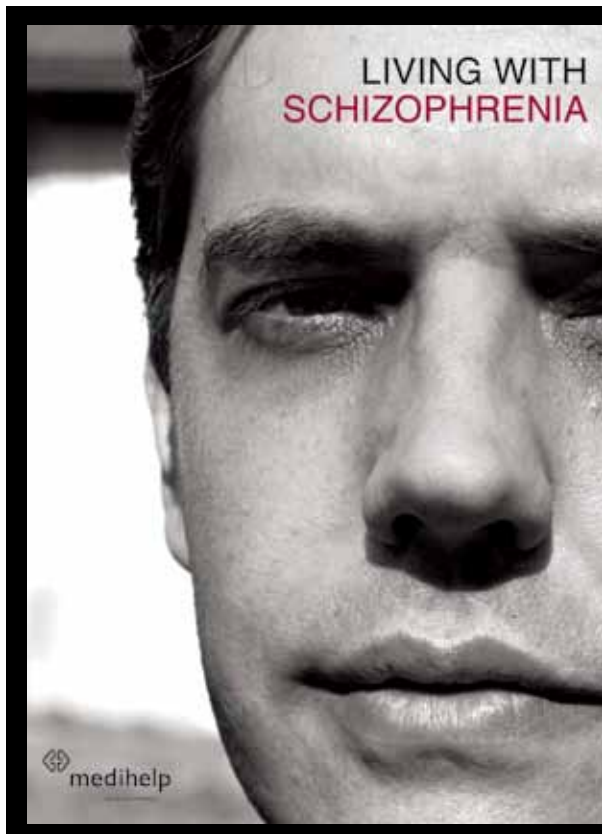
Side-effects of clozapine include life-threatening agranulocytosis in two per cent of patients. Initially, it is important to monitor the patients' weekly creatinine clearance (WCC) during the first six months, then bi-weekly for the next six months, and monthly thereafter. Other side-effects of clozapine include sedation, orthostatic hypotension weight gain, constipation and hypersalivation. Clozapine can also decrease the threshold for seizures and cause myocarditis.

Improving cognitive impairment has increasingly become an objective of schizophrenia treatment. Studies suggest that antipsychotic medication may improve cognition when received early in the course of schizophrenia, as generally, studies of patients with chronic schizophrenia have found less improvement in cognition during antipsychotic treatment.

Finally, schizophrenia is a syndrome that continues to pose significant challenges in all aspects of the disease. Therefore, diagnosis and early intervention in the disease process may limit the cognitive, social and functional impairments caused by the disorder.

References

1. Nasrallah HA, Tandon R, Keshavan M. Beyond the facts in schizophrenia: closing the gaps in diagnosis, pathophysiology and treatment. *Epidemiol Psychiatric Sci.* 2011;20(4):317-27.
2. Diagnostic and statistical manual of mental disorders: text revision (DSM- IV- TR). American Psychiatric Association. 4th ed. Washington DC: American Psychiatric Association; 2000.
3. Fischer BA, Buchanan RW. Schizophrenia: clinical manifestations, course, assessment and diagnosis. UpToDate [homepage on the Internet]. c2012. Available from: <http://www.uptodate.com/contents/schizophrenia-clinical-manifestations-course-assessment-and-diagnosis>
4. Brissos S, Dias VV, Balanza-Martinez V, et al. Symptomatic remission in schizophrenia patients: relationship with social functioning, quality of life and neurocognitive performance. *Schizophrenia Res.* 2011;129(2-3):133-136.
5. Buckley P, Citrome L, Nichita C, Vitacco M. Psychopharmacology of aggression in schizophrenia. *Schizophrenia Bull.* 2011; 37(5):930-936.



In the documentary “Living with Schizophrenia”, Steven Swart bravely shares his experience of living with probably the most serious mental illness, often referred to as the “cancer of the soul”. Visit www.medihelplivingwith.co.za or phone 0800 203 048 to order a copy of the DVD.