SCHIZOPHRENIA, ANTIPSYCHOTICS AND RELATED DISORDERS-1

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Introduction

Schizophrenia can be a particularly disabling illness because its course, although variable, is frequently chronic and relapsing. The care of patients with schizophrenia places a considerable burden on all careers, from the patient's family through to the health and social services.

Definition of psychosis:

- A gross impairment in reality testing
- An inability to distinguish what is real from what is not real
- A loss of contact with reality

Epidemiology of schizophrenia

Incidence : 15-50 per 100,000 population per year

prevalence: 1%

Lifetime risk: 1%

Male : female 1:1

A etiology :

1-Genetic risk factors : The most important risk factor for schizophrenia is having a relative suffering from this disorder. The risk to develop schizophrenia for the general population is 0.5 - 1%, the first degree relatives of a schizophrenia patient is 10% and the offspring of two affected parents is 46%.

Neuregulin 1 gene on chromosome 8, dysbindin gene on chromosome 8 and chromosome 22q11 (Velo-cardio-facial syndrome) are implicated in the aetiology of schizophrenia.

2-Antenatal and perinatal risk factors

Second-trimester exposure to influenza infection may increase the risk of the foetus subsequently developing schizophrenia. Associations have also been found with maternal measles and rubella infections.

There is a significant association between schizophrenia and premature rupture ofmembranes, preterm labour, low birth weight and use of resuscitation during delivery.

Foetal hypoxia during delivery predicts reduced grey matter throughout the cortex in people with schizophrenia but not in controls.

3-Biological risk factors

Head injury: This may lead to paranoid schizophrenia.

Epilepsy and temporal lobe disease: The most common causative factor that results in both schizophrenia and epilepsy might have developed in the uterus.

Substance misuse: Cannabis may increase the risk of schizophrenia in people who are homozygous for VAL/VAL alleles in COMT genotypes.

Patients suffering from rheumatoid arthritis have lower risk to develop schizophrenia (One-third the risk of the general population).

4-Demographic risk factors

Age and gender: Male schizophrenia patients tend to have more severe disease, with earlier onset, more structural brain diseases and worse premorbid adjustment compared to the female patients.

Advanced paternal age at the time of birth is a risk factor for the offspring to develop schizophrenia.

Social class: It is still controversial whether low social class is caused by schizophrenia or is an effect of the course and the nature of the disease.

1. **Breeder hypothesis**: socio-economic adversity precipitates schizophrenia in genetically vulnerable individuals.

2. **Social drift explanation**: people who have an underlying predisposition to schizophrenia are more likely to drift down the social scale.

Rural/urban difference: The higher prevalence of schizophrenia in urban areas is due to interaction of genetic factors, migration, higher rates of social deprivation and more social problems in the inner city. There is more favourable outcome in non-industrialized countries as compared to industrialized countries.

Ethnicity: Afro-Caribbean immigrants to the UK have higher risk of schizophrenia even in the second generation

5-psychological risk factors

Stressful life events are a precipitant of the first episode psychosis.

High expressed emotion comprising over-involvement, critical comments and hostility from family members for more than 35 hours per week increase the risk of relapse of schizophrenia.

Neurobiology of schizophrenia

Gross pathological changes in schizophrenia:

1. Atrophy of the prefrontal cortex and temporal lobe (disturbed neural network in the prefrontal and medial temporal lobes is the core psychopathological feature).
2. Changes in the corpus callosum.
3. Increased ventricular size at commencement of disease (CT changes in the third and lateral ventricles and the temporal horns).
4. Reduction in the overall brain volume.
5. Smaller thalamus.
6. Morphological abnormalities in Corpus Collasum

Histological changes in schizophrenia:

1. Cellular loss in the hippocampus.

2. Reduction of the number of medio-dorsal thalamic neurons.

3. Reduced neuronal density in the prefrontal, cingulate and motor cortex

4. Abnormal patterns of myelination in the hippocampus and temporal lobes as a result of abnormal migration, abnormally sized neurons,

Neurochemical abnormalities

Dopamine: iccrease dopamine in mesolimbic pathway and the dopamine hypothesis proposes that increased levels of dopamine cause schizophrenia.

Serotonin (5 HT): There is an interesting relationship between serotonin and dopamine. The two serotonin pathways which are affected in schizophrenia include (1) the projections from dorsal raphe nuclei to the substantia nigra and (2) the projections from the rostral raphe nuclei ascending into the cerebral cortex, limbic regions and basal ganglia.

DSM-5 Diagnostic Criteria of Schizophrenia

Presence of 2 or more of the following symptoms over a 1 month period:

a. Delusions b. Hallucinations

c. Abnormal speech d. Disorganized behavior e. Negative symptom

(at least 1 of which must be a, b or c) Such that an individual's premorbid level of functioning is affected in several major domains of life. There must be continuous impairment over a period of at least 6 months, during which the individual might experience either active or residual symptoms. These symptoms must not be due to the effects of substance usage or an underlying medical condition

Types of schizophrenia

1. **Paranoid type** (best prognosis): Older patients (Onset is in their late twenties or thirties) .Presenting Symptoms: Preoccupation with delusions and/or hallucinations, usually Involving grandeur or persecution

2. **Disorganized type** :(worst prognosis) younger than 25, Disorganized speech and behavior. Flat or inappropriate affect. Marked regression to primitive disinhibited behavior (Bizarre Behavior). Severe thought disorder. Poor contact with reality

3. **Catatonic type** Psychomotor Disturbances, ranging from severe retardation to excitation. Extreme negativism. Peculiarities of voluntary movements. Mutism is very common Complications: Medical care may be necessary because of exhaustion, malnutrition, self- inflicted injury, or hyperpyrexia

4. **Undifferentiated type** Meet criteria for schizophrenia. Do not meet criteria for other schizophrenia types

5. **Residual type** (mainly the presence of negative symptoms) Absence of positive symptoms. Patients tend to have negative symptoms (Social Withdraw, Flat Affect, Occupational Dysfunction)

Differential diagnosis

1. Misuse of substances such as alcohol, stimulants, hallucinogens,or sympathomimetics
2. Medications include steroids, anticholinergics and antiparkinson drugs.
3. General medication condition including: CVA, CNS infection, CNS tumours, temporal lobe epilepsy, metabolic abnormalities (vitamin B12 deficiencies, thiamine deficiencies), head injury, SLE, acute intermittent porphyria, endocrine abnormalities related to thyroid and adrenal glands.
4. Severe depression or mania with psychotic features.
5. Delusional disorders.
6. Dementia and delirium.
7. Personality disorders – Paranoid / schizotypal personality disorders

Management of an acute episode of schizophrenia

When the diagnosis is sufficiently clear, antipsychotic medication is started. The antipsychotic effect may not occur immediately, but antipsychotics also have a calming effect which may reduce the need for a sedative agent.

Antipsychotic drug therapy

The most effective treatment for acute psychotic symptoms is antipsychotic drug therapy. Most antipsychotic drugs have an immediate sedative effect, followed by an effect on psychotic symptoms (especially hallucinations and delusions), which may take up to 2-4 weeks to develop fully.

Antipsychotics

Conventional		Atypical	
Haloperidol	2-30 mg	Risperidone	4-16 mg
Chlorpromazine	100-600 mg	Olanzapine	5-20 mg
Trifluoperazine	5-30mg	Quetiapine	150-800 mg
Sulpiride	400-800 mg	Clozapine	100-900 mg

Side effect of Conventional antipsychotics

- Sedation, 70–80%
- Anticholinergic and anti-adrenergic effects (includin dry mouth, constipation, blurred vision, urinary retention, tachycardia), 10–50%
- Extrapyramidal side effects (parkinsonism, dystonia, akathisia, neuroleptic malignant syndrome), 60%
- Tardive dyskinesia: 4% per year of antipsychotic medication
- Endocrine effects: galactorrhoea and oligomenorrhoea
- Weight gain
- Sexual dysfunction
- Allergy

Side effect of Atypical antipsychotics (e.g. risperidone, olanzapine)

- Sedation
- Weight gain
- Orthostatic hypotension
- Hyperglycaemia
- Sexual dysfunction

Side effect of Clozapine

- Sedation
- Weight gain
- Hypersalivation
- Tachycardia
- Orthostatic hypotension
- Seizures, 3%
- Agranulocytosis, < 1%

Prognosis of schizophrenia:

Good prognosis	Poor prognosis
Demographics: women, married	Men, single
Aetiology: precipitated by stressful life events, no past psychiatric history, family history of affective illness	Past psychiatric history, family history of schizophrenia
Nature of illness: late onset of symptoms, paranoid type, positive symptoms	Early onset, negative symptoms
Treatment: good response to treatment, short duration of untreated psychosis	Poor response to treatment, long duration of untreated psychosis.

SCHIZOPHRENIA, ANTIPSYCHOTICS AND RELATED DISORDERS- II

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Other psychiatric disorders

- Prodromal symptoms of Schizophrenia
- Catatonia
- Schizoaffective disorder
- Acute\transient psychotic disorder
- Delusional disorders

Prodromal symptoms of Schizophrenia

Prodromal symptoms refers to a range of subjective experiences that occurs prior to the onset of schizophrenia.

Overview of Positive Symptoms:

- Unusual perception
- Odd beliefs
- Vague and circumstanital speech
- Preoccupation with religion, occult and philosophy
- Suspiciousness
- Pre-psychotic anxiety
- Praecox feeling: feeling by the clinician that the patient is odd.

Overview of negative symptoms:

- Blunted affect

- A motivation

- Isolation and social withdrawal

Cognitive symptoms

- Worsened academic, work or social functioning, and self care

- Reduced attention and concentration

General symptoms:

- Sleep disturbances such as initial insomnia

- Depressed mood

- Irritable mood

- Poor hygiene

Interventions:

- Careful observation

- Consideration of differential diagnosis including organic causes

- Consideration of comorbidity such as substance abuse

- Aim to minimize risk of relapse

- Aim to eliminate exposure to cannabis and psychostimulants via psychoeducation, enhance stress management and consideration for maintenance antipsychotic treatment

- Discussion of treatment options such as commencement of antipsychotics and CBT

For **prodromal schizophrenia**, the conversion to schizophrenia is 35%.

70% of the individuals are able to achieve full remission within 3-4 months

80% achieve stable remission in 1 year.

Catatonia

Causes of catatonia: schizophrenia, severe depressive disorder, bipolar disorder, organic disorders e.g. CNS

infections, CNS tumour, cerebrovascular accident, severe intoxication of recreational drugs and lethal catatonia.

Clinical features: Ambitendency, automatic obedience (mitgehen,mitmachen), waxy flexibility / catalepsy, negativism, stereotypy, mannerism, echolalia and echopraxia.

Investigations: FBC, RFT, LFT, TFT, blood glucose, CK, urine drug screen, ECG, CT, MRI,EEG, urine and blood culture, syphilis screeen, HIV, heavy metal screen, auto-antibody screen and lumbar puncture.

Management strategies (non-pharmacological):

Hydration, early mobilization, close monitoring, transferal to ICU if patient deteriorates.

Medications:

1. Benzodiazepines (e.g. IM lorazepam up to 4mg per day).

2. If benzodiazepine does not work and symptoms are severe, ECT is an option.

Prognosis: Two-third of patients improve after treatment.

Schizoaffective disorder

Epidemiology

Lifetime prevalence: 0.05% - 0.08% -M:F Women > men

Diagnostic criteria:

The DSM-5 specified that for an individual to fulfill

the diagnostic criteria, there must be the presence of solely hallucinations or delusions for at least 2 weeks in the absence of an affective episode, throughout the whole duration of the psychiatric illness.

There must also have an uninterrupted period where there are prominent affective symptoms concurrent with symptoms of schizophrenia (Criterion A).

Individuals should have symptoms fulfilling the diagnosis of an affective disorder for most of the duration of the illness.

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DSM-5 has specified 2 subtypes of schizoaffective

disorder, which are: a. Bipolar type - Whereby a manic episode is part of the entire course of the illness.

b. Depressive type - Whereby a major depressive episode is part of the entire course of the illness

Investigations: same as schizophrenia.

Treatment:

- Psychotic symptoms: antipsychotics (e.g. olanzapine has good mood stabilising effects).
- **Manic subtype:** Mood stabiliser e.g. **lithium** or **carbamazepine.**
- **Depressive subtype:** Antidepressant, usually a SSRI.
- **Poor response to pharmacological treatments:** ECT.

- **Psychosocial treatments:** similar to schizophrenia.

Prognosis:

- The outcome for schizoaffective disorder is intermediate between schizophrenia and affective disorders.

- Manic subtype has a better prognosis than depressive subtype.

Brief or acute/transient psychotic disorder

Age of Onset: 20-30 years.

Gender: More common in women.

Aetiology:

1) Acute stressful life event e.g. disaster, bereavement or severe psychological trauma.

2) Underlying personality disorders: borderline, histrionic, paranoid and schizotypal.

3) Family history of mood disorders or schizophrenia.

Diagnostic criteria:

The DSM-5 specified that for an individual to fulfill this diagnosis, he/she must have, for aduration of between 1 day to 1 month the following symptoms:

a. Delusions. b. Hallucinations

c. Disorganized speech. d. Grossly disorganized or catatonic behaviour

Clinicians need to exclude differentials like major depression or bipolar depression with psychotic features, schizophrenia and exclude the possibility of the symptoms being due to underlying substance use or medical conditions.

Precipitant: With or without stressful life event, and with postpartum onset

Symptoms: Present with delusions, hallucinations, disorganized speech, disorganized or

Catatonic behavior.

Return to premorbid function.

Sub classified into:

1) Brief reactive psychosis with marked stressor.

2) Without marked stressor.

3) With postpartum onset.

Treatment:

1) Short-term use of low dose antipsychotic e.g. risperidone 1 to 2mg daily to control psychotic symptoms.

2) Short-term use of low dose benzodiazepine e.g. lorazepam 0.5mg for sleep.

3) Problem solving or supportive psychotherapy.

Prognosis:

Complete recovery usually occurs within 2-3 months. Relapse is common.
The more acute/abrupt the onset, the better the long term outcome.

Delusional disorders

Incidence: 1-3 per 100,000

Mean Age of onset: 35 years for men

45 years for women

Gender ratio: More common in women. Eratomania is more common in women.

Aetiology:

1) Genetic risk factors such as family history of schizophrenia. Delusional disorder and paranoid personality disorder.

2) The main neurotransmitter involved is excessive dopamine.

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3) The key neuroanatomical areas involved are the basal ganglia and the limbic system.
4) The cognitive theory proposes that delusions are caused by cognitive deficits, resulting in misinterpretation of external reality.
5) Organic diseases such as CNS disorders (e.g. Parkinson's disease, Huntington's disease, sub-arachnoid haemorrhage, brain tumour), degenerative disorders (e.g. Alzheimer's disease), infectious diseases (e.g. AIDS, neurosyphilis, encephalitis), metabolic diseases (e.g. hyper calcaemia, hyponatraemia, hypoglycaemia, uraemia, hepatic encephalopathy), endocrine diseases (e.g. syndrome, hypothyroidism, hyperthyroidism, pan hypopituitarism) and vitamin deficiencies (e.g. vitamin B12, folate)
6) Other factors: sensory impairment, isolation, migration with cultural barrier

Diagnostic criteria (DSM-5):

At least 1 month's duration.

individuals need to have fixed, firmed and unshakeable beliefs (delusions) for a minimum duration of at least 1month. These delusional beliefs must not have a marked impairment on an individual's level of functioning.

Individuals might experience hallucinations at times, but the content of the hallucinations are usually in relation to the delusional beliefs.

Clinicians need to distinguish between delusional disorder and schizophrenia

DSM-5 specified several subtypes of delusional disorder, which are as follows:

a. Erotomanic type - characterized as individuals believing that others are in love with them

b. Grandiose type - characterized as individuals believing that they possess unique abilities

c. Jealous type - characterized as individuals believing that their loved ones are not faithful

d. Persecutory type - characterized as individuals believing that others are out there to harm, cheat or even poison them

e. Somatic type - characterized as individuals believing that there are some abnormalities pertaining to bodily functions.

f. Mixed type - when no major delusional theme could be identified

g. Unspecified type

Delusions can be also be sub-classified into those with or without bizarre content (previously in DSM IV-TR, delusions were deemed only as non-bizarre).

Management : 1) Hospitalization may be appropriate if the patient has high risk of suicide or self-harm (e.g. high risk for self-operation in delusion of dysmorphophobia); high risk of violence or aggression (e.g. a patient with morbid jealousy is using violence to interrogate the spouse) and there is a need to apply Mental Disorder and

Treatment Act to treat the patient during compulsory admission.

2) Pharmacological treatment: similar to schizophrenia, antipsychotics and benzodiazepine. Patient may require covert antipsychotics (e.g. administering liquid antipsychotics through patient's food in patient with very poor insight and refuses oral treatment). The decision of covert medication is determined by a consultant psychiatrist with detailed discussion with family members and after analysis of risks and benefits.

3) Psychosocial interventions include cognitive therapy targeting at delusions, family therapy and provide shelter or alternative accommodation to the spouse of a patient with morbid jealousy.