Schizophrenia and associated disorders

Judit Tolna M.D., PhD
Semmelweis University,
Psychiatric and Psychotherapeutic Department
2006. 11. 15.
Possible manifestations of psychiatric disorders

Symptoms of experience
(hallucinations, delusions, anxiety)

Symptoms of behavior
Maladjustment of social adaptation
Decrease of productivity
Behavior suggest psychiatric disorder, if...

- It is not in accordance with social norms
- It is not in accordance with personal habits and motivations, and cannot be understood on the basis of previous personality traits
Persons to discover the illness in everyday life:

- parents
- spouse
- teachers
- colleagues
- GP (general practitioners)
- pharmacologists
- policemen
- lawyers
- priests
- etc.
Psychosis: loss of reality control
Psychoses according to etiology

• **Organic:** known somatic illness in the background

• **Exogenous:** known drug in the background

• **Reactive:** understood from special situations, psychic experiences

• **Endogenous**
„ENDOGENEOUS”:  
• Non organic/somatic  
• Non exogenous  
• Non psychic  
„inner” origin
Differential diagnosis of schizophrenia

„Functional”
- Schizotypal disorder
- Persistent delusional disorders
- Schizoaffective disorders
- Induced delusional disorder
- Mania
- Depression

„Organic”
- Drug/substance-induced psy
- Epilepsy
- Tumors
- Stroke
- Early dementia
- Endocrine causes
- Infections
- Multiple sclerosis
- Autoimmune disorder (SLE)
- Metabolic disorders
Schizophrenia

„The psychopathology of schizophrenia is one of the most intriguing, since it permits a many-sided insight into the workings of the diseased as well as the healthy psyche”

Eugen Bleuler
No two cases are ever exactly the same
Benedict-Augustin Morel (1809-1873)

First use „premature dementia“ (in the nineteenth century meaning of incoherence rather than low intelligence)

The first psychiatrist to classify psychotic illnesses on the basis of outcome rather than clinical presentation at a given moment
Diagnoses considered different, yet with similar courses of illness

- Mendel: Paranoia (1884)
- Kahlbaum: Catatonia (1868-1874)
- Hecker: Hebephrenia (1871)
Emil Kraepelin (1856-1926)

dementia praecox (1893)
onset at a relatively early age
chronic and deteriorating course

- to differentiate sch as an independent illness
- to establish disease on the basis of outcome/course
- separating from manic-depressive illness
Eugen Bleuler (1857-1939)

schizophrenia 1911

the reason of the cognitive impairment is the splitting of the psychic processes (behavior, emotion, thinking)

fundamental (basic) symptoms: four A’s
- affective blunting
- disturbance of association
- autism
- ambivalence

accessory (additional) symptoms: delusions, hallucinations

Dementia Praecox or the Group of Schizophrenias 1911
Bleuler shifted the emphasis in schizophrenia from course and outcome to the **cross-sectional study of symptoms**, essentially broadening the concept of the disease and give a more generous prognosis.
Kurt Schneider (1887-1967)  
not a separate disease, but a type of illness

**first-rank psychotic symptoms**

- Audible thoughts  
- Voices heard arguing  
- Voices heard commenting on one’s actions  
- The experience of influences playing on the body  
- Thought withdrawal and other interferences with thought  
- Delusional perception  
- Feelings, impulses and volitional acts experienced as the work or influence of others

**second-rank psychotic symptoms**

- Hallutinations  
- Flight of ideas  
- Distractedness  
- Perplexity  
- Out-of-body experiences  
- Emotional blunting  
- Compulsive behavior
Definition (DSM-IV-TR)

• characteristic positive and/or negative symptoms
• deterioration in social, occupational, and/or interpersonal relationship
• continuous signs of the disturbance for at least 6 months
• the disturbance is not due schizoaffective disorder, mood disorder with psychotic features, substance abuse and/or general medical condition
Subtypes of schizophrenia

• Catatonic type
• Disorganized type
• Paranoid type
• Residual type
• Undifferentiated type
Catatonic schizophrenia

- Catalepsy
- Stupor
- Hyperkinesiae
- Stereotypies
- Mannerisms
- Negativism
- Automatisms
- Impulsivity
Hebephrenic/ Disorganized schizophrenia

• Incoherence
• Sever emotional disturbance
• Wild excitement alternating with tearfulness
• Vivid hallutinations
• Absurd, bizarr delusions, that are prolific, fleeting, and frequently concerned with ideas of omnipotence, sex change, cosmic identity and rebirth
Paranoid schizophrenia

• Feeling, that external reality has changed and somehow become different
• Suspiciousness and ideas of dedication
• Ideas of references
• Hallucinations, especially of body sensations
• Delusions of persecutions or of grandiosity
Residual schizophrenia

• Interepisodic form

• The condition of being without gross psychotic symptoms following a psychotic schizophrenic episode
Syndromes of schizophrenia

- Positive thought disorder
- Social withdrawal
- Apathy
- Self-neglect
- Negative thought disorder

- Reality distortion

- Delusions
- Hallucinations
- Passivity phenomena

Disorganization
Negative
Positive symptoms

- Formal thought disorder
- Disorganised behavior
- Inappropriate affect
- Delusions
- Hallucinations
Negative symptoms

• Poverty of speech
• Flattening of affect
• Anhedonia-asociality
• Avolition-apathy
• Attentional impairment
Affective symptoms

• anxiety

• dysthymia
Catatonic symptoms

These motor symptoms may occur in any form of schizophrenia, but are particularly associated with the catatonic subtype

- Ambitendence
- Echopraxia
- Stereotypies
- Negativism
- Posturing
- Waxy flexibility
# The most frequent symptoms of acute phase

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of insight</td>
<td>97</td>
</tr>
<tr>
<td>Auditory hallucinations</td>
<td>74</td>
</tr>
<tr>
<td>Ideas of reference</td>
<td>70</td>
</tr>
<tr>
<td>Suspiciousness</td>
<td>66</td>
</tr>
<tr>
<td>Flatness of affect</td>
<td>66</td>
</tr>
<tr>
<td>Second person hallucinations</td>
<td>65</td>
</tr>
<tr>
<td>Delusional mood</td>
<td>64</td>
</tr>
<tr>
<td>Delusion of persecution</td>
<td>64</td>
</tr>
<tr>
<td>Thought alienation</td>
<td>52</td>
</tr>
<tr>
<td>Thoughts spoken aloud</td>
<td>50</td>
</tr>
</tbody>
</table>

International Pilot Study of Schizophrenia 1970
Hallucinations

• False perceptions in the absence of a real external stimulus
• May involve any of the sensory modalities
• The most common are auditory hallucinations in the form of voices (60-70%)
• Visual hallucinations occur 10% (but: organic disorder!!!)
• Olfactory hallucinations are more common in temporal lobe epilepsy
• Tactile hallucinations are more frequently than is reported by patients
Figure 1.12  Grey self-portrait, by Bryan Charnley. This painting illustrates aspects of Charnley’s psychotic symptoms, including that of hearing voices. Reproduced with kind permission of the Bethlem Royal Hospital Archives and Museum, Beckenham, Kent, UK
Epidemiology

• Schizophrenia occurs in all cultures

• Incidence is about 2-4 cases per 10 000 population per year

• Lifetime risk is 0.85-1%
Age and sex

The peak incidence of onset is

15-25 years in men

and

25-35 years in women
THE DEVELOPMENTAL RISK FACTOR MODEL

Childhood vulnerability

Early causes (genetic, obstetric complications)

Birth

Late causes (life events, drug abuse)

Adolescence

Dysplastic networks
Cognitive impairment
Social difficulties

Psychosis
Environmental influences

• Concordance in MZ twins is only about 50% !!!

• The rest of the variance must depend on the person’s environment
### Lifetime expectancy of broadly defined schizophrenia in the relatives of schizophrenics

<table>
<thead>
<tr>
<th>Relationship</th>
<th>Percentage schizophrenic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parent</td>
<td>5,6</td>
</tr>
<tr>
<td>Sibling</td>
<td>10,1</td>
</tr>
<tr>
<td>Sibling and one parent affected</td>
<td>16,7</td>
</tr>
<tr>
<td>Children of one affected parents</td>
<td>12,8</td>
</tr>
<tr>
<td>Children of two affected parents</td>
<td>46,3</td>
</tr>
<tr>
<td>Uncles/aunts/nephews/nieces</td>
<td>2,8</td>
</tr>
<tr>
<td>Grandchildren</td>
<td>3,7</td>
</tr>
<tr>
<td>Unrelated</td>
<td>0,86</td>
</tr>
</tbody>
</table>
Dopaminergic pathways

The four major dopamine tracts:
1) nigrostriatal  
2) mesolimbic  
3) mesocortical  
4) tuberohypophyseal

mRNA Localization
- $D_1$ and $D_2$: caudate/putamen
- $D_3$: n. accumbens
- $D_4$: cortex/hippocampus
Mesocortical DA (decreased)

Weinberger 1987

Mesocortical DA

Mesolimbic DA

Current DA hypothesis

Negative symptoms

Schizophrenia

Positive symptoms

Mesolimbic DA (increased)

Mesolimbic DA

Current DA hypothesis

Negative symptoms

Schizophrenia

Positive symptoms

Mesolimbic DA (increased)

Mesolimbic DA
Outcome

After a first episode, all outcomes are possible

• Recover completely
• Relapsing and remitting course
• Severe progressive, disabling disorder with premature death (either from suicide or from a range of physical causes)
COURSE OF SCHIZOPHRENIA (THEORETICAL MODEL)

Course

Years

Deteriorating  Stable  Improving
### Table 1.1 Summary of long-term clinical outcome studies in schizophrenia.

Table reproduced with permission from Frangou S, Murray RM. *Schizophrenia*. London: Martin Dunitz, 1997

<table>
<thead>
<tr>
<th>Study</th>
<th>Years of follow-up</th>
<th>Number of patients</th>
<th>Good clinical outcome (%)</th>
<th>Poor clinical outcome (%)</th>
<th>Social recovery (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciompi 1980(^{11,12})</td>
<td>37</td>
<td>289</td>
<td>27</td>
<td>42</td>
<td>39</td>
</tr>
<tr>
<td>Bleuler 1978(^{13})</td>
<td>23</td>
<td>208</td>
<td>20</td>
<td>24</td>
<td>51</td>
</tr>
<tr>
<td>Bland &amp; Orne 1978(^{14})</td>
<td>14</td>
<td>90</td>
<td>26</td>
<td>37</td>
<td>65</td>
</tr>
<tr>
<td>Salokangas 1983(^{15})</td>
<td>8</td>
<td>161</td>
<td>26</td>
<td>24</td>
<td>69</td>
</tr>
<tr>
<td>Shepherd et al., 1989(^{16})</td>
<td>5</td>
<td>49</td>
<td>22</td>
<td>35</td>
<td>45</td>
</tr>
</tbody>
</table>
Treatment
Drug treatment strategy

- Acute treatment
- Maintenance treatment
Assessment of patient

• Diagnosis

• Evaluate risk of potential suicidal or antisocial behavior

• Evaluate possible consequences of delaying treatment
  • Poor treatment response and overall outcome
  • Rejection; difficult acceptance or reintegration into the community
Aims of treatment of acute psychosis

• to prevent harm and worsening of the pt’s state
• control disturbed behavior
• suppress symptoms
• rapid return to the best level of functioning
• develop an alliance with the patient and a close collaboration with the patient’s family
• short- and long-term treatment plans
• connect the patient with appropriate maintenance and follow-up care in the community
• adjust aims of treatment within a context of the community in which it takes place
Choice of treatment setting

Depends on:

• severity of symptoms
• cooperation
• patient’s social situation and support
• need for specific therapy
• availability of various treatment options
• patient’s preferences
Management of acutely psychotic patients

ACUTELY PSYCHOTIC PATIENT

PERORAL ADMINISTRATION OF MEDICATION

PHYSICAL CONTROL OF BEHAVIORAL DISTURBANCES

PARENTERAL ADMINISTRATION OF MEDICATION
Relationship between the dose and $D_2$ receptor occupancy

Farde et al., 1992
Olanzapine: In Vivo Receptor Binding Affinity - 5-HT vs D₂

PET Study

D₂ Binding
[¹¹C]raclopride

5HT Binding
[¹¹C]NMSP

Baseline  10 mg olanzapine

• Single 10 mg Olanzapine dose given
• Greater 5HT (84%) than D₂ (61%) occupancy approximates clozapine and suggests a low EPSE profile in contrast to other antipsychotic drugs

Nyberg et al 1996
Conventional antipsychotics

- Effective in control of positive symptoms and agitation
- Shorten duration of psychotic episode
- Reduce number of relapses
- Available in various drug forms (liquid, inject, depot inject.)
Conventional antipsychotics:
Side effects I.

• Extrapyramidal side effects

  acut dystonia
  akathisia
  rigidity
  tardiv dyskinesia
Conventional antipsychotics: Side effects II.

- **Anticholinergic effects:**
  - dry mouth, blurred vision, constipation, tachycardia, urinary retention, cognitive impairments, confusion, delirium

- **Antihistaminic effects:**
  - sedation, weight gain

- **Antiadrenergic effects:**
  - orthostatic hypotension
Conventional antipsychotics: Side effects III.

- Allergy
- Photosensitivity
- Hepatic impairments (elevation of liver enzymes, jaundice)
- Pigmentary retinopathies; corneal opacities
- Leucopenia and agranulocytosis
- Pulmonary embolism
- QT prolongation
- Sudden death
- Seizures
- Neuroleptic-induced deficit syndrome?
Conventional antipsychotics: Limitations

- Less efficient in treatment of negative, affective, and cognitive symptoms
- Less effective in prophylaxis and control of relapses
- High number of non-responders and residual states
- High incidence of side effects
- High non-compliance rate
Second generation antipsychotics

- Amisulpirid (Amitrex)
- Aripiprazol (Abilify)
- Clozapine („gold standard”) (Leponex)
- Olanzapine (Zyprexa)
- Quetiapine (Seroquel)
- Risperidone (Risperdal)
- Ziprasidone (Zeldox)
Receptor selectivity vs multineurotransmitter activity

- **Haloperidol**
- **Clozapine**
- **Risperidone**
- **Quetiapine**
- **Olanzapine**
- **Sertindole**
- **Ziprasidone**
- **Zotepine**

Data From Bymaster et al., 1996 & Schotte et al., 1996
2nd generation antipsychotics: most frequent side effects

- Sedation (H1, alpha1)
- Orthostatic hypotension (alpha2)
- Anticholinergic effects (M)
- Weight gain (H1)
- ECG abnormalities - prolongation QTc
- Seizures
- EPS and hyperprolactinaemia
- Agranulocytosis
- Hypersalivation
Summary

• Second generation antipsychotics (SA) improve positive and negative symptoms in acute psychosis; they may also affect affective symptoms and cognitive impairment

• SA are better tolerated with less problematic side effects than conventional antipsychotics (CA)

• Second generation antipsychotics should be among the first-line options in treatment of acute psychotic disorders
Treatments are most effective when they are used in combination:

- pharmacotherapy
- psychotherapy
- psychosocial treatment/ family and social support
Psychosocial treatments

• Cognitive behavioural therapy

• Family interventions

• Psychoeducation

• Social skills training