Schizophrenia
- Part 2 -

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Agenda for Today’s Meeting
1. Lecture: SCZ aetiology and treatment
2. Clinical vignette
   • Mike, Eddie, Jerry? => analysis of symptoms observed approx. 30 – 45 min.
   • Q&A
3. Homework: Psychotic disorders in brief
Homework
(a) Psychotic disorders in brief

Plan of the lecture

- SCZ aetiology
- SCZ treatment
Schizophrenia – Aetiology

- A group of schizophrenia disorders probably with heterogeneous causes
- **Stress Vulnerability Model** - stress of biological, environmental or psychological origin – allows schizophrenic symptoms to develop (head traumas, infections, death of parents, sexual abuse, substance abuse, genetic factors)

Schizophrenia – Aetiology

- **Gentic factors**: chromosomes 5,11,18,19,X.. 6,8,22
- **Neuropathology**: loss of brain volume, reduced density of axons, enlargement of brain ventricles, decrease in hippocampus – excessive pruning of synapses that starts from foetus stage to adolescence
- **Neurotransmission**: ↑DA in mesolimbic system, ↓DA in mesocortical system (hypofrontality), ↓GABA, ↓GLUT, ↑SER (r. 5HT2)
- **Psychosocial theories**: ↑EE correlates with more frequent active episodes, “double bind thieries”, fixation on symbiotic phase of development.
- **Cognitive dysmetria** – different structure of left and right brain in schizophrenic patients
- “schizophrenia is the price of language specialization” T. Crow
Aetiology – Neurodevelopmental Model of Schizophrenia (R. Murray, D. Wainberger, T. Crow)

The Role of Genes

<table>
<thead>
<tr>
<th>Relationship</th>
<th>Percentage schizophrenia</th>
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<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>
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<tr>
<td>Children of one affected parent</td>
<td>12.8</td>
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<tr>
<td>Children of two affected parents</td>
<td>46.3</td>
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<tr>
<td>Uncle/aunt/stepbrother/sister</td>
<td>2.8</td>
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<tr>
<td>Grandchild</td>
<td>3.7</td>
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<tr>
<td>Unrelated</td>
<td>0.9</td>
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</table>

Table 1. Lifetime expectancy of broadly defined schizophrenia in relatives of schizophrenics. Table reproduced with permission from Kendell RE, Zalesky AC. Comparison of Psychiatric Studies. Edinburgh: Churchill.
Aetiology – evidence from adoption studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Schizophrenia spectrum disorders (%)</th>
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</thead>
<tbody>
<tr>
<td>Ketty et al. 11: Biological parents of schizophrenic adoptees</td>
<td>12.1</td>
</tr>
<tr>
<td>Biological parents of control (normal) adoptees</td>
<td>6.2</td>
</tr>
<tr>
<td>Adoptive parents of schizophrenic adoptees</td>
<td>4.4</td>
</tr>
<tr>
<td>Adoptive parents of control adoptees</td>
<td>18.5</td>
</tr>
<tr>
<td>Rosenthal et al. 12: Children of schizophrenics adopted away</td>
<td>10.1</td>
</tr>
</tbody>
</table>

Susceptibility genes for SCZ

- Dysbindin (dystrobovin binding protein 1 or DTNBP1)
- Neuregulin (NRG1)
- DISC1 (disrupted in SCZ1)
- DAOA (d-amino acid oxidase activator; G72/G30)
- DAO (d-amino acid oxidase)
- RGS4 (regulator of G protein signalling 4)
- COMT (Catechol-O-methyl transferase)
- CHRNA7 (alpha-7 nicotinic cholinergic receptor)
- GAD1 (glutaminic acid decarboxylase 1)
- GRM3 (mGluR3)
- PPP3C, BDNF (brain derived neurotrophic factor), MAO-A
- And ... many more

Stahl’s Essentials of Psychopharmacology, 2010
Aetiology – obstetric complications

Aetiology – obstetric complications - cont.
Aetiology - environmental risk factors:
Severe famine in wartime Holland

Figure 2.11: Exposure to nutritional deficiency during fetal development may be a risk factor for schizophrenia, as demonstrated by this study where the incidence of schizophrenia rose twofold in the group whose early fetal development occurred between February and April 1945 – a period of severe famine in wartime Holland. Figure reproduced with permission from Sutker PB, Neugroschel K, Hold HH, et al. Schizophrenia after prenatal famine: further evidence. Arch Gen Psychiatry 1986; 43: 343–351.

Aetiology – role of cannabis consumption

Figure 2.12: Substance misuse can contribute to later development of schizophrenia. This study following army recruits found that those who admitted taking cannabis on more than 50 occasions had a twofold risk of schizophrenia compared with non-users. Figure reproduced with permission from Andersen S, Allebeck P, Ericsson A, Rydberg U. Cannabis use and schizophrenia: A longitudinal study of Swedish conscripts. Lancet 1987; 2: 1483–6.
Aetiology – role of life events

Figure 2.13 The rate of life events is increased in schizophrenia, although the effect is not as great as in depression. Figure reproduced with permission from Bebbington P, Welhns S, Jones P. et al. Life events and psychosis: Initial results from the Camberwell Collaborative Psychosis Study. Br J Psychiatry 199;162:72-9.

Aetiology – structural brain abnormalities

Prof. Eve Johnstone
Univ. Edinburgh
Brain CT Studies
1976
Aetiology – structural brain abnormalities

Figure 3. Ventricular size in monozygotic twins discordant for schizophrenia. Structural magnetic resonance images obtained discordant for schizophrenia show lateral ventricular enlargement in the affected twin (Figure reproduced with permission from Siddiqui RL, Chitnis G, Wu, Toney EF, et al. Anatomical abnormalities in the brains of monozygotic twins discordant for schizophrenia. N Engl J Med 1998;339:789–94).

COMPARATIVE MEAN VOLUMES OF BRAIN REGIONS IN SCHIZOPHRENIA

Ventricle volume
- Left lateral ventricle
- Right lateral ventricle
- Left frontal horn
- Right frontal horn
- Left parietal horn
- Right parietal horn
- Left occipital horn
- Right occipital horn
- Third ventricle
- Fourth ventricle
- Temporal horn
- Cerebellar volume
- Left hemisphere
- Right hemisphere
- Left hemisphere volume
- Right hemisphere volume
- Left hippocampus
- Right hippocampus
- Left parahippocampal gyrus
- Right parahippocampal gyrus
- Left anterior temporal gyrus
- Right anterior temporal gyrus
- Left posterior temporal gyrus
- Right posterior temporal gyrus
- Whole brain

Comparative mean volumes of subjects with schizophrenia (%)

60 70 80 90 100 110 120 130 140 150 160 170 180

Grey matter
White matter

60 70 80 90 100 110 120 130 140 150 160 170 180

Comparative mean volumes of subjects with schizophrenia (%)

Grey matter
White matter
Figure 3.5 Some structural brain abnormalities possibly implicated in the pathogenesis of schizophrenia. Structural abnormalities have been described in many brain areas, and at a variety of anatomical levels, from gross macroscopic changes in whole brain volume, through to subtle cellular displacement or disorganization in the cortex. Increasingly interest has focused on the distribution of abnormalities, and their structural connectivity, other, white matter myelinization, as well as cortical abnormalities, are targets of investigation.

Structural brain abnormalities - cont.
What’s wrong with that image?
Aetiology – Annual gray matter loss

Image acquisition:
- 2 scans \(t_0, ..., t_1\)
- \(\ldots\) - 1 year interval between scans
- Image = scan \(t_1\) – scan \(t_0\)
- Averaging technique used

Aetiology – 5 years’ gray matter loss

DLPFC – dorso-lateral prefrontal cortex
STG – superior temporal gyrus
Aetiology of SCZ - **White matter (neuronal fibres) loss**  
- diffusion tensor MRI imaging (DT-MRI) => **Tractography, dysconnectivity hypothesis**  
a consequence of neurodevelopmental abnormalities

The stages of schizophrenia are shown here over a lifetime. The patient has full functioning (100%) early in life and is virtually asymptomatic (stage I). However, during a prodromal phase (stage II) starting in the teens, there may be odd behaviors and subtle negative symptoms. The acute phase of the illness usually announces itself fairly dramatically in the twenties (stage III), with positive symptoms, remissions, and relapses but never a complete return to previous levels of functioning. This is often a chaotic stage of the illness, with a progressive downhill course. The final phase of the illness (stage IV) may begin in the forties or later, with prominent negative and cognitive symptoms and some waxing and waning during its course, but often more of a burnout stage of continuing disability. There may not necessarily be a continuing and relentless downhill course, but the patient may become progressively resistant to treatment with antipsychotic medications during this stage.
**Aetiology – loss of neurons**

![Diagram of a neuron with labels: Genetic Programming of Axon, Positive Synaptic Closing, Neuron Loss of Dendrites.](image)

Neurodegenerative causes of schizophrenia may lead to a final common pathway rather than neuronal death or possible destruction of synapses and the axons and dendrites of such neurons. The causes can range from predetermined genetic programming of neuronal or synaptic destruction in fetal neurons, such as trauma, infection, toxins, or maternal immunization, to perhaps a distortion of the positive synapses themselves on synapses and neurons via glutamate-mediated mechanisms.

**Aetiology – cytoarchitecture abnormalities**

Neurodevelopmental abnormalities in schizophrenia may include:
- toxic or genetic insults to neurons, either killing them or rendering their functioning inadequate;
- poor neuronal migration during fetal brain development;
- inadequate and improper selection of synaptic targets during synaptogenesis, especially before the age of 6;
- and/or inadequate innervation received from inputs of other neurons.
Abnormal synaptogenesis – wrong synaptic connections

Synaptogenesis abnormalities shown schematically => dysconnectivity

Aetiology - Cytoarchitecture abnormalities

(a) Anterior

(b) Anterior Middle Posterior

Fornix Hippocampus

(c) Dentate gyrus
Aetiology - Cytoarchitecture abnormalities

(d) CA2

(e) Organized

Disorganized

(f) Normal control

(g) A patient with schizophrenia
Aetiology – Functional imaging studies

Figure 3.13 This study investigated the hypothesis that a predisposition to verbal hallucinations is associated with a failure to activate areas concerned with the monitoring of inner speech. Subjects, who included patients with schizophrenia both with and without a significant history of hallucinations, as well as normal controls, were asked to imagine sentences being spoken in another person’s voice. The figure illustrates positron emission tomography data superimposed on a normal magnetic resonance imaging scan, and shows reduced activation in the left middle temporal gyrus and the rostral part of the supplementary motor area in hallucinators compared to non-hallucinators. Similar findings were found in the comparison between schizophrenic patients and controls. Figure reproduced with permission from McGuire PK, Silbersweig DA, Wright I. Speech: a physiological basis for auditory hallucinations. Lancet 1995; 346: 596–599.

Aetiology – Electrophysiological abnormalities

Figure 3.16 Abnormalities in evoked potentials have consistently shown abnormalities in schizophrenia. The P300 auditory event-related potential (ERP), seen here as one of several components of the auditory ERP, is seen as a response to ‘oddball’ or unexpected stimuli, and shows robust changes in both amplitude and latency in schizophrenic patients and their relatives.
Aetiology – Electrophysiological abnormalities

Figure 3.17 These data suggest an increased P300 latency in patients with schizophrenia and their relatives when there is a strong family history of schizophrenia (+FH), but not in sporadic cases (-FH). P300 latency may be an important trait marker for the genetic vulnerability to schizophrenia. Figure reproduced with permission from Frangou S, Sharma T, Airecon G, et al. The Maudeley Family Study, II: Endogenous event-related potentials in familial schizophrenia. Schizophr Res 1997;23:45–53.

Aetiology – Abnormal Electrooculography (EOG)

Eye movement recording
Smooth-pursuit response of eyes to moving target
Tracking of a patient with schizophrenia
Aetiology – Premorbid Cognitive deficit

Figure 3.18 Deficits in premorbid IQ (as measured by the National Adult Reading Test) are seen in people with schizophrenia, but not in their first-degree relatives, or patients or relatives of patients with affective psychoses. The zero line is that of normal controls. Figure reproduced with permission from Gilvarry C, Takei N, Russell A, et al. Premorbid IQ in patients with functional psychosis and their first-degree relatives. *Schizophrenia Res* 2000;41:417–29

Aetiology – Cognitive dysfunction in SCZ

Figure 3.19 Profile of neuropsychological performance of patients with schizophrenia. The deficits seen in schizophrenia are not uniform, but they encompass both executive function and memory. The zero line is the score of normal controls. Figure reproduced with permission from Bilder RM, Goldman RS, Robinson DJ, et al. Neuropsychology of first-episode schizophrenia: initial characterization and clinical correlates. *Am J Psychiatry* 2000;157:549–59
Aetiology – Dopamine Overstimulation

→ A. Carlson - Dopamine Hypothesis of SCZ (1960-70)
→ Chlorpromazine 1952 (Delay, Denniker)

Chlorpromazine was the first effective neuroleptic drug

Phenothiazines block dopamine D2 receptor
Aetiology – Dopamine hypothesis cont.
Positive correlation between D2 rec. affinity and antipsychotic dose

Figure 4.1 Plot of the affinity of a wide variety of antipsychotic medications for the dopamine D2 receptor (y-axis), plotted against the average clinical daily dose used for controlling schizophrenia (x-axis), as an estimate of clinical potency. As can be seen, there is a direct relationship between these two indices. This replicated finding contributed to the use of high dose antipsychotics on the assumption that higher dosages would make an antipsychotic more potent by ‘blocking’ more receptors.

Dopamine hypothesis – evidence from PET scans

Figure 4.2 Three single photon emission tomography (SPECT) scans of striatal D2-like receptor availability at the level of the basal ganglia. In the scan on the left from a healthy volunteer, there is no receptor occupancy and therefore 100% receptor availability for the binding of the D2 receptor tracer [11C]N-FBZM. The scan on the right is from a patient with schizophrenia receiving a typical antipsychotic. The bright area from the left hand scan indicating high receptor density are not evident on the right hand scan as the antipsychotic is occupying the majority of the receptors and preventing the tracer from binding. Unfortunately despite this high level of occupancy this patient has failed to respond to treatment. The central scan is from a patient receiving clozapine, although the striatum are not as bright as in the healthy volunteer they are visible. This scan indicates intermediate occupancy of the receptors by clozapine. Importantly the patient with the intermediate occupancy has responded to treatment. Studies such as this one, when performed in larger groups, indicate that the simple dopamine hypothesis suggested by the data in Figure 4.1 would not hold. Figure reprinted with permission from Piovella V, Costa DC, El F, et al. Clozapine, single photon emission tomography, and the D2 dopamine receptor blockade hypothesis of schizophrenia. (Lancet 1992;340:1096-107)
Dopamine hypothesis
evidence from dopamine release
induced by amphetamine

Amphetamine and cocaine block dopamine transporter (DAT) hence increase synaptic DA concentration.

Figure 4.4. The effect of amphetamine (0.3 mg/kg) on \(^{123}I\)IBZM binding in healthy control subjects and untreated patients with schizophrenia. \(^{123}I\)IBZM is a tracer for D₂ receptors which allows in vivo measurement of D₂ receptor availability (or binding potential) in humans using single photon emission tomography (SPECT). The y-axis shows the percentage decrease in \(^{123}I\)IBZM binding potential induced by amphetamine, which is a measure of the increased occupancy of D₂ receptors by dopamine following the challenge. Thus, these results indicate that, when challenged with amphetamine, patients with schizophrenia release more dopamine than do healthy controls. Figure reproduced with permission from Lancelle M, Abi-Dargham A, Gil R, et al. Increased dopamine transmission in schizophrenia: relationship to illness phases [Review]. Biol Psychiatry. 1999; 46:56–72.
Dopamine hypothesis – D receptors

**CLASSIFICATION OF DOPAMINE RECEPTORS**

- **D_1**
  - Caudate-putamen
  - N. accumbens
  - Orbitofrontal cortex

- **D_2**
  - Hypothalamus
  - N. accumbens
  - Amygdala

- **D_3**
  - Caudate-putamen
  - N. accumbens
  - Orbitofrontal cortex

- **D_4**
  - Hypothalamus
  - N. accumbens
  - Cerebellum

- **D_5**
  - Fronto-cortical
  - Medulla
  - N. accumbens

Figure 4.5 There are currently five types of dopamine receptor identified in the human nervous system. D_1 to D_5 receptors are similar in that they both stimulate the formation of cAMP by activation of a stimulatory G-coupled protein. D_1 and D_2 are therefore known as D1-like receptors. D_3 to D_5 receptors activate an inhibitory G-coupled protein, thereby inhibiting the formation of cAMP. They are collectively known as D2-like receptors. D_2 receptors are more abundant than D_1 or D_3 receptors. D_3 receptors are differentially situated in the various acerbrum (one of the septal nuclei in the limbic system) and D_4 receptors are especially concentrated in the frontal cortex.

**THE DOPAMINERGIC PATHWAYS**

- A: Substantia nigra
- B: Ventral tegmental area
- C: Thalamus
- D: Hypothalamus
- E: N. accumbens
- F: Cerebellum
- G: Frontal cortex

Figure 4.6 Representation of the primary dopamine-containing tracts in the human brain. The nigrostriatal tract is primarily involved in motor control, but also involved in goal-directed behavior. Blockade of D_1 receptors has been shown to have effects on the mesolimbic pathway, with high levels of blockade (left) producing parkinsonism-like side effects. Blockade of D_2 receptors in the mesolimbic pathway increases drug addiction. It is thought that it is the blockade of D_1 and D_2-like receptors in the motor and mesocortical circuits that underlies the primary antipsychotic effects of all currently available antipsychotics.
Dopamine Hypothesis

**Overactivation of mesolimbic dopamine pathway**

=> **Positive symptoms**

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**FIGURE 10—9. The dopamine hypothesis of psychosis.** Hyperactivity of dopamine neurons in the mesolimbic dopamine pathway theoretically mediates the positive symptoms of psychosis, such as delusions and hallucinations. This pathway is also involved in pleasure, reward, and reinforcing behavior, and many drugs of abuse interact here.
Several different causes of dopamine deficiency may result in negative and cognitive symptoms. In schizophrenia itself, there may be a primary dopamine (DA) deficiency or a DA deficiency secondary to blockade of postsynaptic D2 dopamine receptor by an antipsychotic drug. If serotonin is hyperactive, this may also cause a relative DA deficiency by inhibiting DA release. Either primary or secondary DA deficiency in this pathway may cause cognitive blunting, social isolation, indifference, apathy, and anhedonia.
5HT Hypothesis of schizophrenia

- LSD (5HT agonist) $\rightarrow$ psychosis
- Atypical antipsychotics $\rightarrow$ block 5HT2A receptors
Is early recognition important?

- Yes!!!!
- Mean duration of untreated psychosis in the UK is 1-2 years
- The longer this period the worse the outcome

Schizophrenia - treatment

- **Classic neuroleptics** – block rec. D2, **atypical neuroleptics** – blocks rec. D2, D4 more selectively in mesolimbic system, also blocks rec. 5HT2
- Pharmacotherapy should be continued 1-2 years after the first episode, 5 years after next episodes (maintenance therapy)
- ECT is applied in drug-resistant schizophrenia also in catatonic subtype of schizophrenia
- Psychosocial interventions
Treatment strategies of SCZ

- Medication treatment
- Individual supportive therapy
- Cognitive and psychosocial therapies
- Family psychoeducation and support
- Social support
- Case management
- Housing
- Financial support
- Vocational support

SCZ treatment: medication

- The acute psychotic schizophrenic patients will respond usually to antipsychotic medication.
- According to current consensus we use in the first line therapy the newer atypical antipsychotics, because their use is not complicated by appearance of extrapyramidal side-effects, or these are much lower than with classical antipsychotics.

<table>
<thead>
<tr>
<th>conventional antipsychotics (classical neuroleptics)</th>
<th>chlorpromazine, chlorprothixene, clopenthixole, levopromazine, pericizine, thioridazine</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>droperidol, flupentixol, fluphenazine, fluspirilene, haloperidol, melperone, oxyprothepine, penfluridol, perphenazine, pimozide, prochlorperazine, trifluoperazine</td>
</tr>
<tr>
<td>atypical antipsychotics</td>
<td>amisulpride, clozapine, olanzapine, quetiapine, risperidone, sertindole, sulpiride</td>
</tr>
</tbody>
</table>
Antipsychotic action – D2 blockade in mesolimbic pathway

Figure 11 — 1. The dopamine receptor antagonistic hypothesis of antipsychotic drug action for positive symptoms of psychosis in the mesolimbic dopaminergic pathway is shown here. Blockade of postsynaptic dopamine D2 receptors by a dopamine 2 antagonist acting in the mesolimbic dopaminergic pathway is hypothesized to mediate the antipsychotic efficacy of the antipsychotic drugs and their ability to diminish or block positive symptoms.

Antipsychotic efficacy ≈ D2 rec. Affinity

Figure 4.1 Plot of the affinity of a wide variety of antipsychotic medications for the dopamine D2 receptor (y-axis), plotted against the average daily clinical dose used for controlling schizophrenia (x-axis), as an estimate of clinical potency. As can be seen, there is a direct relationship between these two indices. This replicated finding contributed to the use of high-dose antipsychotics on the assumption that giving higher doses would make an antipsychotic more potent by blocking more receptors.
Conventional Antipsychotics – D2 blockade in mesocortical pathway
=> secondary negative symptoms

Conventional Antipsychotics – D2 blockade in nigrostriatal pathway
=> extrapyramidal symptoms (EPS)
D2 blockade (striatum) => Extrapyramidal symptoms (EPS)

Long-term D2 blockade => postsynaptic D2 rec. up-regulation => tardive dyskinesia
D2 blockade in tubero-infundibular pathway => Hyperprolactinaemia
**Other DA pathways → adverse reactions**

D2 receptor blockade in nigrostriatal pathway

=> Extrapyramidal symptoms (EPS)

D2 receptor blockade in tubero-infundibular pathway

(DA = Prolactin Inhibiting Factor)

=> Hyperprolactinaemia

**Conventional antipsychotics vs atypicals**

<table>
<thead>
<tr>
<th></th>
<th>Typical</th>
<th>Atypical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extrapyramidal side-effects</td>
<td>+++</td>
<td>+/-</td>
</tr>
<tr>
<td>Hyperprolactinaemia</td>
<td>+++</td>
<td>+/-</td>
</tr>
<tr>
<td>Binding to mesolimbic D2 dopamine receptors</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Efficacy for negative symptoms</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Efficacy for cognitive symptoms</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Effect on broader domains of outcome (e.g. depression, suicide)</td>
<td>+/-</td>
<td>+</td>
</tr>
</tbody>
</table>
FIGURE 11—17. Serotonin–dopamine interactions in the nigrostriatal dopamine pathway. Serotonin inhibits dopamine release, both at the level of dopamine cell bodies in the brainstem substantia nigra and at the level of the axon terminals in the basal ganglia–neostriatum (see also Figs. 11—18 through 11—20). In both cases, the release of serotonin acts as a "brake" on dopamine release.
FIGURE II — 10. Serotonin regulation of dopamine release from nigrostriatal dopamine neuron, part 1. Here, dopamine is being first released from its axon terminal in the striatum because there is no serotonin causing any inhibition of dopamine release.
5HT2A blockade in nigrostriatal pathway => lower risk of EPS

5HT2A blockade in mesocortical pathway => improvement of cognitive and negative symptoms
Serotonin Dopamine Antagonists vs Atypical Antipsychotics

FIGURE 11.1. Beyond the SDA concept. Atypical antipsychotics are not merely simple serotonin-dopamine antagonists (SDAs). In truth, they have some of the most complex networks of pharmacologic properties in psychopharmacology. Shown here is an icon with all these properties. Beyond antagonism of serotonin 2A and dopamine 2 receptors, some agents in this class interact with multiple other receptor subtypes for both dopamine and serotonin, including 5HT1A, 5HT1D, 5HT2C, 5HT3, 5HT5, 5HT7, and D1, D3, and D4. Other neurotransmitter systems are involved as well, including both noradrenergic and serotonergic receptor blockade, as well as dopamine, adrenergic, and alpha 1 adrenergic plus alpha 2 adrenergic blockade. No two atypical antipsychotics, however, have identical binding properties, which probably helps to explain why they all have distinctive clinical properties.

FIGURE 11.2. Clozapine's pharmacologic icon. The most prominent binding properties of clozapine are represented here. It has perhaps one of the most complex binding profiles in psychopharmacology. Its binding properties vary greatly with technique and species and from one laboratory to another. This icon portrays a qualitative consensus of current thinking about the binding properties of clozapine, which are constantly being revised and updated.
SCZ Treatment - efficacy

Atypical antipsychotics => different pharmacological properties
Side effects of antipsychotic drugs

First generation antipsychotics *(conventional 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)
Figure 4.14. Graphical representation of the point prevalence of extrapyramidal side-effects in 86% of all known schizophrenics living in Nithsdale,西南 Scotland (n=146), treated with conventional antipsychotics. There was no relationship between antipsychotic plasma levels and akathisia, parkinsonism or tardive dyskinesia. Figure reproduced with permission from McCready RG, Robertson LJ, Wiles DH. The Nithsdale schizophrenia surveys. IX: Akathisia, parkinsonism, tardive dyskinesia and plasma neuroleptic levels. Br J Psychiatry 1992;160:793–9.

Figure 4.15. Side-effects of antipsychotics. Side-effects will vary between drugs depending on their receptor profile. In general, all antipsychotics produce some degree of dopaminergic D2 receptor blockade: they are all likely to produce neurological side-effects above a certain dose with the exception of olanzapine and quetiapine.
Second generation antipsychotics

Side effects

Olanzapine (Zyprexa):
- Weight gain sedation
- Glucose intolerance and frank diabetes mellitus
- Hypotension

Risperidone (Risperidal):
- Hyperprolactinaemia
- Hypotension
- Extrapyramidal side effects at higher doses
- Sexual dysfunction

Amisulpride (Solian):
- Hyperprolactinaemia
- Insomnia
- Extrapyramidal effects

Quetiapine (Seroquel):
- Hypotension
- Dyspepsia
- Drowsiness
Clozapine – side effects

- 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

Antipsychotics’ side effects

Table 4.4 Qualitative comparison of the relative side-effects of the newer medications. These will be subject to change over time, as new tolerability data are published and report forms returned. Adapted from reference 85

<table>
<thead>
<tr>
<th></th>
<th>Typical</th>
<th>Clozapine</th>
<th>Risperidone</th>
<th>Olanzapine</th>
<th>Quetiapine</th>
<th>Aripiprazole</th>
<th>Ziprasidone</th>
</tr>
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<tbody>
<tr>
<td>Anticholinergic</td>
<td>±</td>
<td>+++</td>
<td>±</td>
<td>+</td>
<td>±</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td>± to +++</td>
<td>+++</td>
<td>+</td>
<td>±</td>
<td>+</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>Prolactin elevation</td>
<td>++ to +++</td>
<td>0</td>
<td>++</td>
<td>±</td>
<td>±</td>
<td>+</td>
<td>±</td>
</tr>
<tr>
<td>QT prolongation</td>
<td>± to +</td>
<td>+</td>
<td>± to +</td>
<td>± to +</td>
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<td>Sedation</td>
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<td>+</td>
<td>++</td>
<td>++</td>
<td>±</td>
<td>+</td>
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<tr>
<td>Seizures</td>
<td>±</td>
<td>± to +++</td>
<td>+</td>
<td>±</td>
<td>±</td>
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<td>±</td>
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<tr>
<td>Weight gain</td>
<td>± to ++</td>
<td>+++</td>
<td>± to ++</td>
<td>+++</td>
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Near future: possible drug targets in SCZ

Schizophrenia – indication for hospitalization

- high risk of suicide ("voices made me do this")
- high risk of active aggression towards other people (majority to family members)
- electroconvulsive therapy
- change of pharmacotherapy i.e. owing to noncompliance - change to Depot forms of neuroleptics
- first episode of disorder (?)
- Acute agitation
- Catatonic state
Long term management

- Once acute episode has passed recommendation of 1-2 years of prophylactic treatment
- Then titrate down with careful monitoring
- Patients need high level physical care
  - General follow up and screening with identifying drug side effects
Psychological Treatment

- CBT can reduce persistent symptoms and improve insight
- Family therapy – reduces relapse rates, admission rates, symptoms, and the burden on carers, and improves compliance
- Psychodynamic psychotherapy may increase the risk of relapse

SCZ Treatment – Psychotherapy → Cognitive Behavioural Therapy (CBT)

![Figure 6.2](#)
Compliance/Adherence - 6 months

Figure 5.3 Over half of a group of 615 patients admitted to having stopped their medication. Figure reproduced with kind permission from Hellewell, JSE. Antipsychotic tolerability: the attitudes and perceptions of medical professionals, patients and caregivers towards the side effects of antipsychotic therapy. *Euro Neuropsychopharmacol* 1998;8:5248

Figure 5.4 The views of psychiatrists and nurses on the main reasons for patients' non-compliance with medication. Both groups underestimate the importance of sexual side-effects, the psychiatrists more so than the nurses. Figure reproduced with kind permission from Hellewell, JSE. Antipsychotic tolerability: the attitudes and perceptions of medical professionals, patients and caregivers towards the side effects of antipsychotic therapy. *Euro Neuropsychopharmacol* 1998;8:5248
Long term treatment – is it really needed?

![RELAPSE AFTER STOPPING ANTIPSYCHOTICS](image)

### Prognosis

- More than 80% of patients with their first episode of psychosis will recover, 20% will never have another episode
- A large proportion will have few relapses and make a good functional recovery
- Worse prognosis - Poor premorbid adjustment, a slow insidious onset, and a long duration of untreated psychosis with prominent negative
- Better prognosis - An acute onset, an obvious psychosocial precipitant, and good premorbid adjustment
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!
Cases discussion – cont.

- Medical/Psychiatric History?
- Presenting signs and symptoms?
- Diagnosis?
- What subtype of illness?
- Differential diagnosis?
- Management?

FAQ about SCZ

1. A 62-year-old female with a chronic psychiatric disorder claims that the comments of a well-known news anchorman have a special meaning that only she understands. She is convinced that when he reports on local events he is really trying to persuade her to start a “sinful relationship.” This is an example of
   a. A visual hallucination
   b. An illusion
   c. A delusion of persecution
   d. A delusion of reference
   e. Concrete thinking
FAQ about SCZ

2. A medical student finds it hard to follow a patient’s train of thought because he gives very long, complicated explanations and many unnecessary details before finally answering the original questions. In his report, the medical student writes that the patient displayed
   a. Loose associations
   b. Circumstantiality
   c. Goal-oriented thought processes
   d. Perseveration
   e. Flight of ideas

3. A delusion can best be defined as
   a. A false belief that meets specific psychological needs
   b. A perceptual misrepresentation of a sensory image
   c. A perceptual representation of a sound or an image not actually present
   d. A viewpoint able to be changed when convincing evidence to the contrary is presented
   e. A dissociative reaction

5. A 7-year-old girl hospitalized for tonsillectomy awakens in the middle of the night and cries out that a “big bear” is in her room. She is relieved when a nurse turns on the light revealing that the bear was an armchair covered with a coat. This experience is an example of
   a. A delusion
   b. A hallucination
   c. An illusion
   d. A projection
   e. A dissociative reaction

21. A person is sitting alone and behaving as if listening intently, then suddenly begins to nod and mutter aloud. This person most likely is experiencing
   a. A delusion
   b. A depersonalization episode
   c. An hallucination
   d. An idea of reference
   e. Flight of ideas
Items 12–13
A 25-year-old man’s teaching career has been abruptly terminated by a psychiatric illness. During a psychiatric evaluation he is asked the meaning of the proverb “People in glass houses should not throw stones.” The patient replies, “They will break the windows.”

12. This response is an example of
a. Idiosyncratic thinking
b. Concrete thinking
c. Formal operation
d. Loose associations
e. Autistic thinking

13. This patient diagnosis is likely to be
a. Dysthymia
b. Conversion disorder
c. Communication disorder
d. Passive-aggressive personality disorder
e. Schizophrenia

22. The capacity to formulate concepts and generalize them is called
a. Concrete thinking
b. Abstract thinking
c. Delusional thinking
d. Intellectualization
e. Rationalization

FAQ about SCZ

23. A 28-year-old man is brought to the ER of a local hospital by the police, who found him wandering without a coat in subzero weather, muttering about being persecuted by a secret organization. During the evaluation he is disorganized, distractible, and from time to time dozes off in the middle of a sentence. Family members deny previous psychiatric or substance abuse history, but they add that lately the patient had complained of fatigue and increased thirst. The toxic screen is negative and glucose level is 450 mg/dL.

Choose the most likely diagnosis:

a. Delirium
b. Psychotic depression
c. Brief psychotic episode
d. Paranoid schizophrenia
e. Dementia

Items 18–19
A patient has been standing, immobile, for several hours. One of his arms is stretched upward, the other is wrapped around the patient’s neck. The patient does not appear aware of his surroundings and actively resists any attempt to make him change position.

18. This is an example of
a. Apraxia
b. Dystonia
c. Synesthesia
d. Catatonia
e. Trance

19. This symptom is usually seen in patients with
a. Schizophrenia
b. Parkinson’s disease
c. Delirium
d. Neuroleptic malignant syndrome
e. Huntington’s disease
205. A 38-year-old patient with paranoid schizophrenia is discovered by his Department of Mental Health caseworker during a routine home visit lying in his bed with a temperature of 103 degrees. The patient is disoriented and so rigid the caseworker is unable to stand him up. Which of the following is the most likely cause of such a presentation?
   a. An increase in the dose of haloperidol decanoate, received three days earlier
   b. Minor surgery two days earlier
   c. Patient stopped taking his medications for two weeks
   d. Patient has been drinking four to five beers every night
   e. Patient has been in close contact with a friend who has pneumococcal meningitis

206. A 45-year-old woman with a chronic mental illness seems to be constantly chewing. Her tongue darts in and out of her mouth and occasionally she smacks her lips. She also grimaces, frowns, and blinks excessively.

206. These abnormal movements are seen, characteristically, in
   a. Tourette’s syndrome
   b. Akathisia
   c. Tardive dyskinesia
   d. Parkinson’s disease
   e. Wilson’s disease

207. What medication has she received for the past 25 years?
   a. Diazepam
   b. Phenytoin
   c. Clozapine
   d. Perphenazine
   e. Amitriptyline
208. A 17-year-old boy has just been diagnosed with schizophrenia. His distraught parents ask the psychiatrist if their two younger children are likely to develop the same disorder. Prevalence of schizophrenia in siblings is  
   a. 2.5%  
   b. 5%  
   c. 10%  
   d. 20%  
   e. 30%  

209. In the absence of other symptoms, episodic automatisms and olfactory hallucinations are suggestive of  
   a. Schizophrenia  
   b. Hysterical personality disorder  
   c. Schizophreniform psychosis  
   d. Nondominant parietal lobe lesion  
   e. Temporal lobe lesion  

215. A 25-year-old college student is admitted to a psychiatric ward with a six-month history of “personality change, strange behavior, and weird ideas.” Approximately six weeks before the admission, the patient became convinced that he was not able to remember his lessons because his thoughts were being “stolen” by other students. A male voice has been advising him to be suspicious of everyone. The patient’s parents report that for several weeks their son has been talking in a disorganized and obscure way. He has also been very depressed, he lost weight, cannot sleep, and has been barely able to take care of his basic needs. The most likely diagnosis is  
   a. Schizophrenia  
   b. Schizoaffective disorder  
   c. Delusional disorder  
   d. Bipolar I disorder  
   e. Schizoid personality disorder
217. A patient with schizophrenia has had a poor response to several trials of typical antipsychotic medications, risperidone and olanzepine. His psychiatrist recommends a trial of clozapine. What factor can represent a relative contraindication to the use of this medication?

a. A history of severe extrapyramidal symptoms while on haloperidol
b. A history of galactorrhea while on perphenazine
c. A history of recurrent depressive symptoms
d. A seizure disorder
e. The presence of mild tardive dyskinesia

218. A 47-year-old homeless woman attempts suicide by jumping off an overpass and she is admitted for the treatment of several fractures. Tearfully, she reports to the physicians that devil worshippers have tormented her for many years. She is convinced that her persecutors have managed to infiltrate the ward, masquerading as nurses and maintenance workers. She is treated with risperidone and sertraline. After three weeks, her mood has greatly improved and she is not suicidal but her beliefs about being persecuted have not changed. This patient has had three similar episodes in the past 10 years. Choose the most appropriate diagnosis:

a. Major depression, recurrent with psychotic features
b. Schizoaffective disorder
c. Chronic schizophrenia, paranoid type
d. Delusional disorder, paranoid type
e. Schizophreniform disorder

224. Which of the following statements regarding delusions is true?

a. Delusions are almost exclusively found in schizophrenia
b. Delusions of grandiosity are rarely encountered except in mania
c. Delusions involve a disturbance of thought content
d. Delusions involve a disturbance of perception
e. Delusions are a type of hallucination

225. The percentage of schizophrenic patients who ultimately commit suicide is approximately

a. 1%
b. 5%
c. 10%
d. 20%
e. 30%

226. A young mother is involved in a car accident that claims the life of her two sons. When she is told that her two children have died from the injuries they suffered in the crash, she becomes agitated and combative. Her speech is disorganized and incoherent, but the observers understand that she hears the voices of her children screaming to her to help them and that she believes that the hospital nurses are prison guards. These symptoms remit spontaneously in one week. What is the most likely diagnosis?

a. Delirium secondary to brain injury
b. Schizophreniform disorder
c. Major depression with psychotic features
d. Brief psychotic disorder
e. Post-traumatic stress disorder
### 228. The lifetime prevalence of schizophrenia is approximately

- a. 1%
- b. 3%
- c. 5%
- d. 10%
- e. 15%

### 230. Which of the following drugs may induce a psychosis that is easily confused with, or misdiagnosed as, paranoid schizophrenia?

- a. Barbiturates
- b. Heroin
- c. Benzodiazepines
- d. Amphetamines
- e. Chlorpromazine

### 231. Studies of the relationship between gender and schizophrenia have generally demonstrated that

- a. The usual age of onset is earlier for females than males
- b. Males tend to have a better prognosis than females
- c. The lifetime risk of developing schizophrenia is approximately the same in males and females
- d. Males tend to respond better to neuroleptic medication
- e. There is a higher concordance rate in male monozygotic twins as compared with female monozygotic twins

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Thank You for Your Attention 😊