NEUROLEPTICS = ANTIPSYCHOTIC DRUGS:

• agents show the ability to reduce positive psychotic symptoms after several weeks of treatment

• In long use nlps let patients to stabilise their mental state, preventing relapse.

• Withdrawal of neuroleptic agents causes relapse of psychosis in patients with schizophrenia, at the rate of approximately 10% per month,

• so that 50% or more have relapsed by 6 months after discontinuation of nlps.
NEUROLEPTICS = ANTIPSYCHOTIC DRUGS:

- 1947 – PROMETAZYNA used as anti-histaminic agent
- 1950 – synthesis of CHLORPROMAZINE – Charpentier
- 1953 – RESERPINE – used in USA to psychotic patients
- 1955-1960 evidences of action Chlorpromazine in Europe
- 1958- synthesis of HALOPERIDOL (Janssen) - more sedative, more eps
- 1958 – KLOZAPINE - Wander Labs (Switzerland)
- 1958 – SULPIRYDE – selective D2-antagonist
- 1984 – RISPERIDON – Janssen
- 1996 – OLANZAPINE
ANTIPSYCHOTIC DRUGS

ARE SIMPLY DIVIDED INTO TWO GROUPS:

1. **TYPICAL**— block mainly D2 receptors

2. **ATYPICAL** – affect 5-HT2A receptors, are more selective to dopamine receptor subtypes
Mechanism of NLPs action

the place of action:
There are four major dopamine pathways in the brain:

the **mesocortical system** - negative symptoms of psychosis or of antipsychotic agents

the **mesolimbic system** - mediate the positive symptoms of psychosis

the **nigrostriatal system** - extrapyramidal muscular reactions and tardive dyskinesia

the **tuberoinfundibular system** - the control of plasma prolactin levels.
THE ANATOMY OF THE BRAIN INCLUDING THE LIMBIV SYSTEM

Cerebral hemisphere
Lentiform nucleus
Head of caudate nucleus
Anterior horn of lateral ventricle
Tail of caudate nucleus
Inferior horn of lateral ventricle
Cerebellum
Hippocampus
Amygdala
Pons
Medulla
Spinal cord
Dopaminergic pathways in the brain

Arcuate nucleus of hypothalamus
Corpus striatum
Substantia nigra
Frontal cortex
Pituitary gland
Anterotegmental area
Typical neuroleptic mechanism of action
I. PHENOTHIAZINES DERIVATIVES
   the oldest group of NLPs
   • with aliphatic group—sedative property; anticholinergic effect
   • chlorpromazine (Fenactil, Thorazine)- can induce depression
   • levomepromazine (Tisercin)- also antidepressive
   • promazine (Promazin)- mild and safe in the old
TYPICAL NEUROLEPTICS

PHENOTHIAZINES DERIVATIVES

piperidine group—sedative and anti-depressive action, marked anticholinergic and low extrapyramidal side effects.

Thioridazine — can provoke cardiac dysrhythmia!
TYPICAL NEUROLEPTICS

Phenothiazines derivatives

- **piperazine group**—high potency of antipsychotic action, cause severe EPS
  - fluphenazine (Prolixin, Permitil, Mirenil)
  - perazine (Pernazinum)
  - perphenazine (Trilafon)
  - trifluoperazine (Stelazine)

- Depot form – fluphenazine, perphenazine
TYPICAL NEUROLEPTICS

- Thioxanthenes derivatives
  - chlorprothixene (Chlorprothixen) - antidepressive
  - flupentixol (Fluanxol) – activating, depot form
  - zuklopentixol (Clopixol, Sordinol) – strong inhibiting action, depot and „acuphase form”
  - tiotixene (Navane)
TYPICAL NEUROLEPTICS

- BUTYROPHENONES
  severe antipsychotic, sedative and inhibiting properties. Cause EPS

- Haloperidol (Haldol, Haloperidol) – many different forms and doses
- Droperidol (Droleptan, Dehydrobenzperidol)
Haloperidol – way of action
IV. DIPHENYLBUTYLPIPERIDINE DERIVATES

effective against a wide range of positive symptoms, antiautistic and stimulating to activity. They are used in treating severe chronic psychosis.

- fluspirilene (Imap)
- pimozide (Orap)
| Antipsychotics with high potency („strong”) | A. with medium or low potency  
Sedative antipsychotics with anticholinergic effect |
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>haloperidol</td>
<td>chlorpromazine</td>
</tr>
<tr>
<td>flufenazine</td>
<td>lewomepromazine</td>
</tr>
<tr>
<td>perfenazine</td>
<td>perazine</td>
</tr>
<tr>
<td>stelazine</td>
<td>thioridazine</td>
</tr>
</tbody>
</table>
ATYPICAL NEUROLEPTICS

- dibenzodiazepine derived group

- clozapine (Leponex, Clozaril)-
  protoypical of atypical nlp, most effective
  and at least safe

- indicate for drug-resistant schizophrenia
  (30% benefited).

Side effects: excessive salivation, sedative, hypotension,
  dizziness, delirium, seizures

0.5 % agranulocytosis, leukopenia 1-1,5%, - required WBC
  monitoring, 1x/week – 1x/month.
Atypical antipsychotics – mechanism of action
Olanzapine—antagonist of 5-HT$_2$ and dopamine receptors (D$_1$-D$_4$). Doses: 15-30 mg/die. Side effects: 20-30% ↑↑↑ weight gain, diabetes.

• **Olanzapine**—antagonist of 5-HT$_2$ and dopamine receptors (D$_1$-D$_4$). Doses: 15-30 mg/die. Side effects: 20-30% ↑↑↑ weight gain, diabetes.

• **Quetiapine**—well tolerated, effective for positive and negative symptoms.
**BENZAMIDES** – especially in negative symptoms,

- sulpipyryde - antidepressant and activating action, ↑PRL.
- amisulpiryde– D₂, D₃ receptors

**Others:**

**Risperidone** – licensed for acute and chronic psychosis, it has D₂ and 5-HT blocking action which is effective both in positive symptoms and negative ones. Improves cognitive processes. Less EPS then haloperidol. ↑PRL.

**Ziprasidone** - combined dopamine and serotonin receptor antagonist activity, well tolerated, no weight gain
<table>
<thead>
<tr>
<th>Typical antipsychotics</th>
<th>New atypical antipsychotics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reduce positive symptoms (eg. hallucinations and delusions)</strong></td>
<td>To a large extent influence negative symptoms and dezorganization.</td>
</tr>
<tr>
<td>Effectivness connected with binding of dopamine receptors in all system of dopamine neurotransmission.</td>
<td>Extenden way of action (reduction of many different symptoms) connected with affecting also another neurotransmitters eg. serotonin.</td>
</tr>
<tr>
<td>cause typical side-effects = EPS</td>
<td>cause slight if any EPS</td>
</tr>
<tr>
<td>exhibit preference for mesolimbic over nigrostriatal dopamine receptors</td>
<td></td>
</tr>
<tr>
<td>Many forms of applying.</td>
<td>depot form – only risperidon</td>
</tr>
</tbody>
</table>
THE INDICATIONS FOR ADMISSION of NLP:

PSYCHOSES

1. Acute and chronic schizophrenia
2. Schizophrenic-like psychosis and atypical psychosis
3. Schizoaffective disorder
5. Depression with psychotic symptoms
6. Organic disorders: delirium
THE INDICATIONS FOR ADMISSION of NLP: NONPSYCHOTIC DISTURBANCES

1. agitation, anxiety, dysphoria in patients with organic changes in CNS

2. behavioural disturbances in mental retardation

3. psychosomatic disorders

4. personality disorders with anxiety and impulsiveness
Some indication to the schizophrenia treatment:

1. Atypical NLPs in the first episode of illness
2. One drug and the lowest effective dose
3. The time of therapy at least 6-10 weeks in the therapeutic dose.
4. The supporting therapeutic dose of drug shouldn’t be less than 2/3 of the reached effective dose and kept for several months -2 years after 1. episode.
Which nlp aply to treat the first epizode of psychosis?

• Earlier intervention produces better outcome, any delayed treatment delays remission and results in poorer compliance.

• Traditional treatment are only typical neuroleptics.

• The modern treatment programms consider or recommend atypical agent, because of safety of medicaton and comfort for patients

• These tips don’t aply to klozapine, which is recommended after two unsuccesful courses of treatment in most countries of the world.
When can you expect of successful effect with NLPs therapy?

- Usually after 4-6 weeks.

- If the effect is poor the doctor change NLP to another.

- When you apply clozapine, distinct effect appears usually later – even after 2 – 3 months.
Depot formulations of antipsychotics

• Group of typical neuroleptics with specially created forms of long-acting injections, which given intramuscularly are slowly released in a body.
• Owing to that, the patient has the permanent concentration of nlp in a body and become the same dose of the drug every day.
• Drug „depot” is administered every 2-4 weeks (period of permanent concentration of
• It also the way of therapy-supervising for doctor, patient and family..
• Side-effect are the same as with tablets or drops.
• The risk of relapse is reduced twice in compare with oral antipsychotics.
Antipsychotics in depot form

- zuclopentixol
- flupentixol
- haloperidol
- perphenazine
- flufenazine
- pipothiazine
- risperidon
ADVERSE EFFECTS OF NLP DRUGS THERAPY:

Extrapyramidal syndromes = EPS

<table>
<thead>
<tr>
<th>symptom</th>
<th>features</th>
<th>time of occurring</th>
<th>treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>acute dystonic reactions</td>
<td>young men, sudden tonic contractions of the muscles: facial, neck, back</td>
<td>1-7 days</td>
<td>anti-cholinergic drugs, BZD</td>
</tr>
</tbody>
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ADVERSE EFFECTS OF NLP DRUGS THERAPY:

Extrapyramidal syndromes = EPS

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<td>parkinsonism</td>
<td>in elderly; cogwheel rigidity, bradykinesia, tremor, mask – like face</td>
<td>in the first weeks</td>
<td>NLP’s dosage reducing, antiparkinsonian agents, atypical NLP</td>
</tr>
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### ADVERSE EFFECTS OF NLP DRUGS THERAPY:

Extrapyramidal syndromes = EPS

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<td>acathisia</td>
<td>motor restlessness “in legs and feet”</td>
<td>1-30 days</td>
<td>as above + propranolol, BZD, vit. E</td>
</tr>
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ADVERSE EFFECTS OF NLP DRUGS THERAPY:

Extrapyramidal syndromes = EPS

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<td>tardive dyskinesia</td>
<td>lingual-facial hyperkinesias, choreoathetotic movements of the extremities and trunk</td>
<td>months, years</td>
<td>diminution of NLP, calcium-blockers may be useful</td>
</tr>
</tbody>
</table>
Neuroleptic Malignant Syndrome – is connected with the complete block of dopaminergic receptors

Potentially life-threatening event

- changes of consciousness
- severe muscular rigidity
- fever
- autonomic instability
- leucocytosis, creatine kinaze > 400 j./l, myoglobinuria

Treatment: stop NLP, bromocriptine (Parlodel), dantrolen, forced diuresis, ECT, benzodiazepines.
Anticholinergic effects
Occur with low-potency neuroleptics
At risk: clozapine or combinations with tricyclics, anti-parkinsonian agents.

Symptoms:
blurred vision (impaired accommodation)
dry mouth, urinary retention, constipation

Central anticholinergic delirium (anticholinergic poisoning) - life-threatening event!!
disorientation, confusion, visual hallucinations, delusions, tachycardia, flushed dry skin
Other adverse effects

• Orthostatic hypotension
• ECG abnormalities (T-wave changes, prolonged QT intervals)
• Serious ventricular arrhythmias
• Hyperprolactinemia
• Jaundice and ↑ liver enzyme
• Allergic rashes, photosensitivity
• Pigmenary rethinopathy
CONTRAINDICATIONS to NLPS

- severe toxic central nervous system depression
- comatose states from any cause
- Parkinson's disease
- Neuroleptic Malignant Syndrome
Why the patients with schizophrenia relapses?

- Doctor’s ambivalence to continue maintenance therapy after first episode
- Poor insight in patients
- Ambivalence of families about treatment in general
- Public reluctance to psychotropic drugs

*Angermayera et al. 1993*
*Kane 1996*
Kane: "one out of every three compliant patients become noncompliant within twelve months"

- Patient’s doubts about taking drugs if they feel well.
- "unrealistic" aspiration to complete recovery
- Patients take drugs like under constraint: "Drugs remember me my illness."
- No consensus of professionals about period of maintenance treatment.