**Dopaminergic Projections**

**Nigrostriatal**
- Substantia Nigra to Caudate-Putamen
- Extrapyramidal Motor System (Parkinsonian symptoms, dystonias, akathisia, tardive dyskinesias)

**Mesolimbic & Mesocortical**
- VTA to limbic and cortical regions (schizophrenic symptoms, also reward mechanisms)

**Tuberoinfundibular**
- Chemoreceptor Trigger Zone

**Chemoreceptor Trigger Zone:**
- Area Postrema (emesis)

**Management of Parkinson’s Disease**
Increase dopaminergic tone

Increase DA synthesis
Enhance DA release
Stimulate DA receptors
Inhibit catabolism of DA

Increase DA synthesis

\[
\text{L-Dopa} \xrightarrow{\text{Pyridoxine - PO$_4$}} \text{Dopamine}
\]

Nausea and vomiting
Dyskinesias
Psychiatric disturbances
“On-Off” response

Carbidopa + L-DOPA = Sinemet®

Stimulate DA receptors:
Ergot derivatives - D2 receptor agonists
bromocriptine, pergolide

Enhance DA release:
Amantadine
Stimulate DA receptors:

- Non-ergot D2 agonist: ropinirole
- D3 selective agonist: pramipexole

Inhibit DA catabolism:

- Inhibit COMT
  - tolcapone
  - entacapone
- Inhibit MAO
  - selegiline (aka deprenyl):
    - blocks catabolism of DA
    - may be neuroprotective

Inhibit COMT

Reduce cholinergic tone:

- trihexyphenidyl
- benztpine

Spasmolytic Agents

- centrally-acting with little sedation
  - benzodiazepines
  - baclofen
  - tizanidine
  - dantrolene
**Antipsychotic Drugs**

All antipsychotic drugs block at least one type of dopamine receptor (D2).

Drugs that increase DA in the limbic system can cause paranoid psychosis (e.g. amphetamine, cocaine).

Methylphenidate greatly exacerbates schizophrenic symptoms.

**Dopamine hypothesis of schizophrenia**

Conventional antipsychotics are only partially effective in most (70%) and ineffective for some (30%) patients.

Phencyclidine, an NMDA receptor antagonist, produces more schizophrenia-like symptoms in non-schizophrenic subjects than do DA agonists.

Atypical antipsychotics have low affinity for D2 receptors.

Focus is broader now and research is geared to produce drugs with less extrapyramidal effects.

**Evidence against the DA hypothesis:**

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**Other possible approaches:**

Serotonin receptor blockade (5-HT2A): clozapine

Increased glutamate (NMDA) receptor activity: Phencyclidine produces a better approximation of schizophrenic symptoms.

**Antipsychotic drugs are used**

To control symptoms of schizophrenia
To control mania
As anti-emetics
As a component in “neurolept anesthesia”

**Conventional Antipsychotics**

Used clinically from 1950's to mid 1990's
Primarily effective against positive symptoms

**Phenothiazines:** Chlorpromazine (Thorazine®), thioridazine (Mellaril®), prochlorperazine (Compazine®)

**Thioxanthines:** Chlorprothixene (Taractan®), Thiothixene (Navane®)

**Butyrophenones:** Haloperidol (Haldol®)
Aliphatic: chlorpromazine (Thorazine®)
Piperidine: thioridazine (Mellaril®)
Piperazine: prochlorperazine (Compazine®), trifluoperazine (Stelazine®), flufenazine (Prolixin®)

Conventional Antipsychotics: Phenothiazines

Conventional Antipsychotics: Thioxanthenes

Aliphatic: Chlorprothixene (Taractan®)
Piperazine: Thiothixene (Navane®)

Conventional Antipsychotics: Butyrophenones

haloperidol (Haldol®)
droperidol (Inapsine®)

Conventional Antipsychotics

Side effects vary according to the degree and type of receptor blockade
DA receptors: extrapyramidal side effects, gynecomastia, galactorrhea
NE receptors: orthostatic hypotension
Muscarinic receptors: blurred vision, constipation, BUT fewer extrapyramidal side effects
Histamine receptors: sedation

Conventional Antipsychotics

Other side effects (primarily phenothiazines)
Photosensitivity
Cardiac abnormalities (prolonged QTc interval, also torsade de pointes)
Thioridazine

Tardive dyskinesias are one of the primary drawbacks to conventional antipsychotic drugs.
Atypical Antipsychotics
Clinical use began around 1990
Usually do not produce extrapyramidal side effects
Have fewer problems with non-compliance
Are more efficacious against negative symptoms

Atypical Antipsychotics

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Generic name</th>
<th>Manufact.</th>
<th>Appr. Date</th>
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<td>Clozaril</td>
<td>Clozapine</td>
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<td>Janssen</td>
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<td>Abilify</td>
<td>Aripiprazole</td>
<td>Otsuka/BMS</td>
<td>2002*</td>
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HOWEVER ...
Clozapine can produce bone marrow suppression, including fatal agranulocytosis.

Atypical antipsychotics tend to produce weight gain and raise serum TGs.

Atypical antipsychotics have been associated with type II diabetes (severe).