Classification of antipsychotic drugs

- **PHARMACOLOGICAL CLASSIFICATION**
  - **FIRST-GENERATION ANTIPSYCHOTIC (low potency)**
    - ***Chlorpromazine***
    - *Prochlorperazine*
    - *Thioridazine*
  - **FIRST-GENERATION ANTIPSYCHOTIC (high potency)**
    - ***Fluphenazine***
    - ***Haloperidol***
    - *Pimozide*
    - *Thiothixene*
  - **SECOND GENERATION ANTIPSYCHOTIC**
    - *Aripiprazole*
    - *Asenapine*
    - ***Clozapine***
    - *Iloperidone*
    - *Lurasidone*
    - ***Olanzapine***
    - ***Quetiapine***
    - *Paliperidone*
    - ***Risperidone***
    - *Ziprasidone*

Classification of antipsychotic drugs

- **CHEMICAL CLASSIFICATION**
  - **Phenothiazines**
    - **Aliphatic side chain:** Chlorpromazine, triflupromazine
    - **Piperidine side chain:** Thioridazine
    - **Piperazine side chain:** Trifluoperazine, fluphenazine
  - **Butyrophenones:** Haloperidol, Trifluperidol, Penfluridol
  - **Thioxanthenes:** Flupenthixol
  - **Other heterocyclics:** Pimozide, Loxapine
  - **Atypical antipsychotics:** Clozapine, risperidone, olanzapine, quetiapine, aripiprazole, ziprasidone

Pharmacotherapy of metal illness

- Pathophysiology of mental illness is not clear, it maybe dopaminergic over activity in the limbic system (schizophrenia and mania), deficit in monoamines [NA, 5-HT] (depression).
- Treatment is empirical, symptom oriented and not disease specific. Depending on the primary use, the psychotropic drugs may be grouped into:
  - Anti-psychotic
  - Anti manic
  - Antidepressants
  - Antianxiety
  - Psychotomimetic

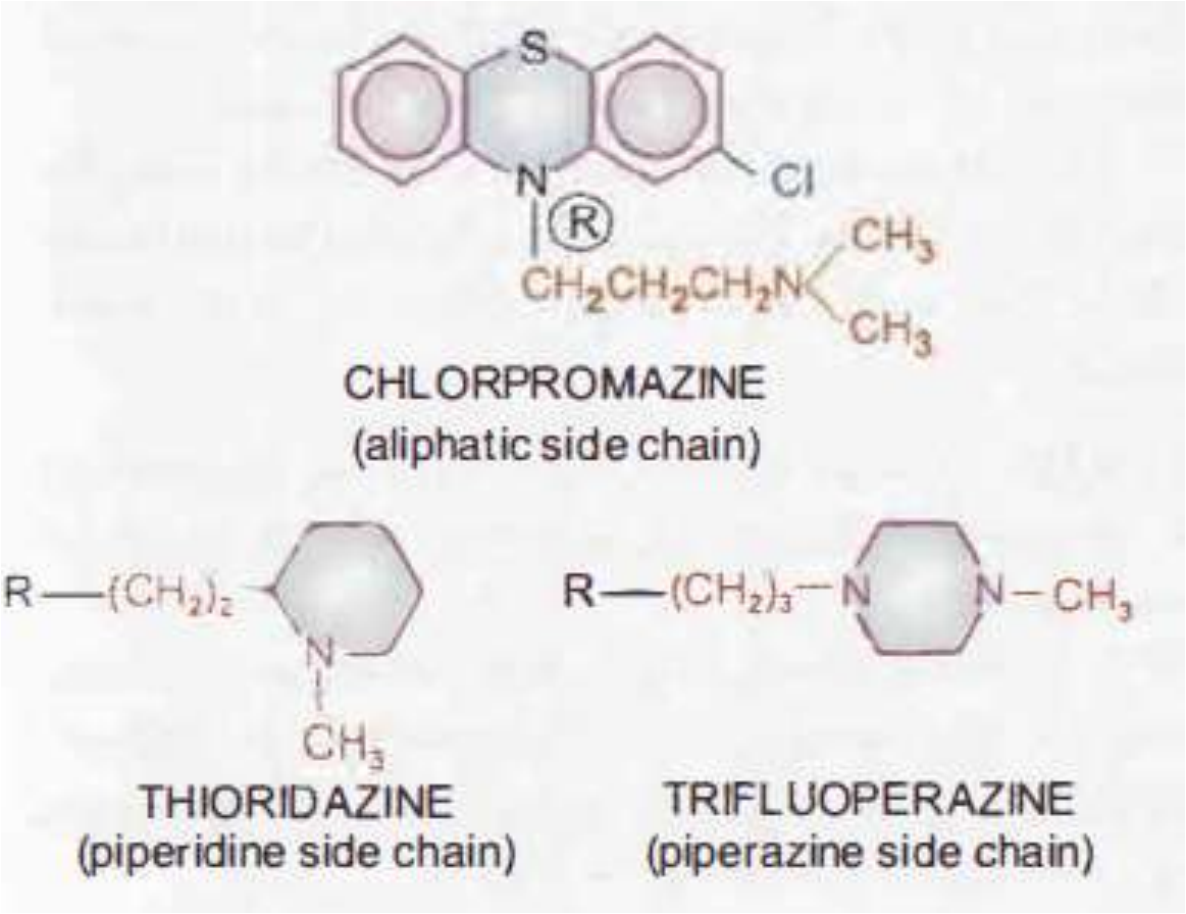
Pharmacotherapy of metal illness

- **First-generation antipsychotics**
- The first-generation antipsychotic drugs (also called conventional, typical, or traditional antipsychotics) are competitive inhibitors at a variety of receptors, but their antipsychotic effects reflect competitive blocking of D2 dopamine receptors.
- First-generation antipsychotics are more likely to be **associated with movement disorders**, particularly for drugs that bind tightly to dopaminergic neuroreceptors, such as *haloperidol*.

Pharmacotherapy of metal illness

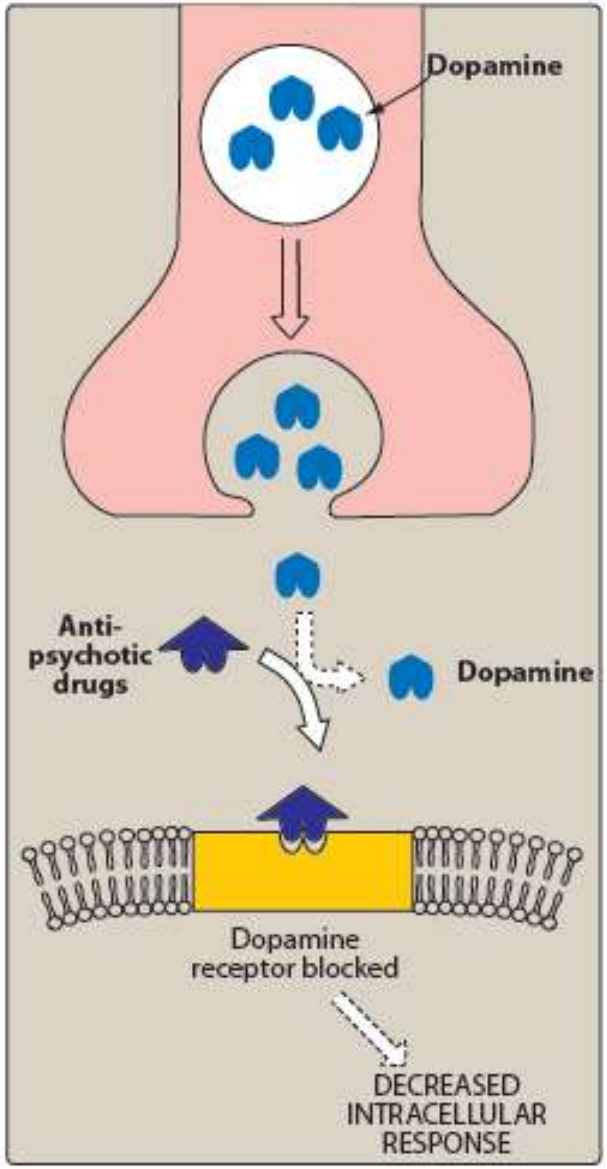
- **Second-generation antipsychotic drugs**
- The second generation antipsychotic drugs (also referred to as “atypical” antipsychotics) have fewer extrapyramidal symptoms (EPS) than the first-generation agents, but are **associated with a higher risk of metabolic side effects, such as diabetes, hypercholesterolemia, and weight gain**.
- The second-generation drugs appear to owe their unique activity to blockade of both serotonin and dopamine receptors.

FIRST-GENERATION ANTIPSYCHOTIC AGENTS/ TYPICAL ANTIPSYCHOTICS



Pharmacology of chlorpromazine (CPZ)

- Mechanism of action
  - **Dopamine receptor–blocking activity in the brain:** All of the first generation and most of the second-generation antipsychotic drugs block dopamine receptors in the brain and the periphery (**except clozapine-like atypical**).
  - The clinical efficacy of the typical antipsychotic drugs correlates closely with their relative ability to block D2 receptors in the mesolimbic system of the brain.



Pharmacology of chlorpromazine (CPZ)

- Mechanism of action
  - The actions of the antipsychotic drugs are antagonized by agents that raise synaptic dopamine concentrations (for example, ***levodopa*** **and amphetamines, bromocriptine**) or mimic dopamine at post-synaptic binding sites.
  - Dopaminergic blockade pituitary locatotropes cause the hyperprolactinemia, while that in CTZ is responsible for antiemetic action.

Pharmacology of chlorpromazine (CPZ)

- Chlorpromazine is a prototype agent for typical antipsychotic agent.
- **CNS:** Effects differ in normal and psychotic individuals

- In normal individual CPZ indifference to surroundings, paucity of thought, **psychomotor slowing, emotional quietening, reduction in initiative and tendency to go off to sleep**. Spontaneous movements are minimized but slurring of speech, ataxia or motor incoordination does not occur.
- In normal individuals CPZ produces neuroleptic syndrome, and is quite different from the sedative action of barbiturates.

- In CPZ reduces irrational behaviour, agitation and aggressiveness and controls psychotic symptomatology. Disturbed thought and behaviour are gradually normalized, anxiety is relieved.
- Hyperactivity, hallucinations and delusions are suppressed.
- All phenothiazines, thioxanthenes and butyrophenones have the same antipsychotic efficacy, but potency differs in terms of equieffective doses.

Pharmacology of chlorpromazine (CPZ)

- CNS (in psychotic individuals):
  - The sedative effect is produced promptly, while antipsychotic effect takes weeks to develop. Moreover, tolerance develops to the sedative but not to the antipsychotic effect.
  - Extrapyramidal motor disturbances are intimately linked to the antipsychotic effect, but are more prominent in the high potency compounds and least in thioridazine, clozapine and other atypical antipsychotics.
  - Chlorpromazine lowers seizure threshold and can precipitate fits in untreated epileptics.
  - Temperature control is knocked off at relatively higher doses rendering the individual poikilothermic-body temperature falls if surroundings are cold.

Pharmacology of chlorpromazine (CPZ)

- ***ANS:***
  - ANS effect of antipsychotic agents are complex and unpredictable. Neuroleptics have varying degree of alpha adrenergic blocking activity. Chlorpromazine, clozapine, and thioridazine have particularly significant alpha adrenergic antagonistic activity.
  - phenothiazines have weak H1-antihistaminic and anti-5-HT action.
- ***Effects on Sleep:*** Antipsychotic drugs have inconsistent effects on sleep patterns but tend to normalize sleep disturbances characteristic of many psychoses and mania.

Pharmacology of chlorpromazine (CPZ)

- ***Local anaesthetic:*** Chlorpromazine is as potent a local anaesthetic as procaine. Because of its irritation action CPZ is not used for this purposes and also its having weaker/ no membrane stabilizing action.
- ***Cardiovascular System:***
  - Chlorpromazine has complex actions on the cardiovascular system, directly affecting the heart and blood vessels and indirectly acting through CNS and autonomic reflexes.
  - Chlorpromazine and less potent antipsychotic agents, as well as reserpine, risperidone, and olanzapine, can cause **orthostatic hypotension**.
  - Partial tolerance develops after chronic use. Reflex tachycardia accompanies hypotension. Arrhythmia may occur in overdose especially with thioridazine.

Pharmacology of chlorpromazine (CPZ)

- ***Skeletal muscle:*** Neuroleptics have no effect on muscle fibers or neuromuscular transmission. They reduce certain types of spasticity : the site of action being in the basal ganglia or medulla oblongata. Spinal reflex are not affected.
- ***Kidney and Electrolyte Balance:*** Chlorpromazine may have weak diuretic effects in animals and human beings because of a **depressant action on the secretion of vasopressin** (antidiuretic hormone), **inhibition of reabsorption of water and electrolytes by a direct action on the renal tubule**, or both.

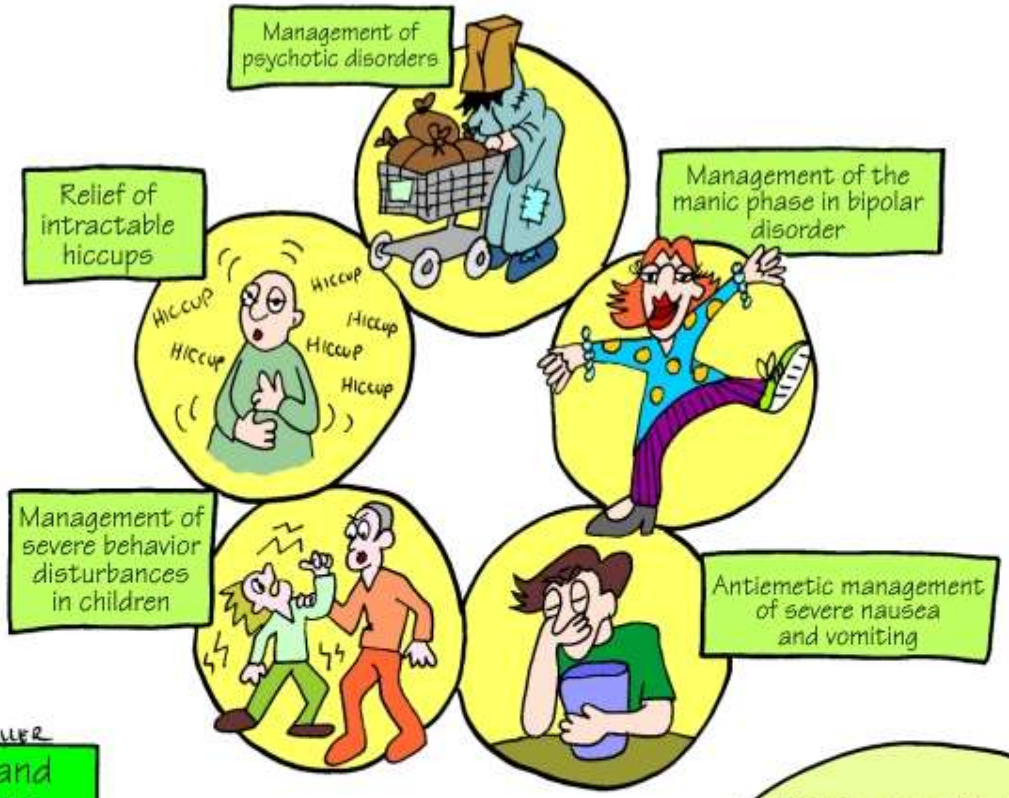
Pharmacology of chlorpromazine (CPZ)

- ***Endocrine:***
  - Neuroleptics consistently increase prolactin release by blocking the inhibitory action of DA on pituitary lactotropes. This may result in galactorrhoea and gynaecomastia. They reduce gonadotropin secretion, but amenorrhoea and infertility occur only occasionally.
  - ACTH release in response to stress is diminished- corticosteroid levels fail to increase under such circumstances. Release of GH is also reduced but this is not sufficient to cause growth retardation in children or to be beneficial in acromegaly.
  - Decreased release of ADH may result in an increase in urine volume. A direct action on kidney tubules may add to it, but Na^+ excretion is not affected.

Pharmacology of chlorpromazine (CPZ)

- **Pharmacokinetics:**
  - Some antipsychotic drugs have erratic and unpredictable patterns of absorption after oral administration.
  - Parenteral (intramuscular) administration increases the bioavailability of active drug four- to ten fold.
  - Most antipsychotic drugs are highly lipophilic, highly membrane- or protein-bound, and accumulate in the brain, lung, and other tissues with a rich blood supply.
  - They also enter the fetal circulation and breast milk. It is virtually impossible and usually not necessary to remove these agents by dialysis.
  - Volume of distribution is large 20 L/kg and metabolized in liver by CYP2D6; elimination t1/2 is variable (18-30 hr).
  - Tolerance to the sedative and hypotensive action develops within day or week.

Uses of chlorpromazine (CPZ)



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Watch for toxic and adverse reactions due to dose and blood levels which can consist of extra-pyramidal symptoms of akathisia, dystonia, Parkinsonian symptoms and tardive dyskinesia.