DRUG TREATMENT OF PSYCHOSIS

Psychosis

- **Disruptive mental state with problems in distinguishing the external world from internally generated perceptions.**
- **Can occur in a number of disorders (schizophrenia, acute mania, depression, drug intoxication, dementia, delirium).**
- **Schizophrenia sub-types: Paranoid, catatonic, disorganized, undifferentiated.**

Schizophrenia

- A psychiatric chronic disorder or thought disorder affecting approximately 1 % of the population.
- Estimated 33 – 50 % of homeless suffer from schizophrenia.
- Usually emerges in adolescence or early adulthood; May begin at any age.
- Late onset form affects post-menopausal women.
- Males have earlier age on onset than females.
- The disorder is characterized by a divorcement from reality in the mind of the person and reduced ability to comprehend reality.
- It may involved visual and auditory hallucinations, delusions, intense suspicion, feelings of persecution or control by external forces (paranoia), depersonalization.

Schizophrenia Phases

- **Prodromal phase varies in duration and includes:**
  - Social withdrawal.
  - Impaired work function.
  - Deteriorating self care.
  - Peculiar behavior (e.g., food hoarding).
  - Blunted affect.
  - Unusual speech (vague or elaborate).
  - Magical thinking (clairvoyance or telepathy).
- **Active phase includes:**
  - Delusions (e.g., paranoia).
  - Disturbed thinking (incoherence).
  - Hallucinations (auditory most common).
  - Decreased affect.
  - Reduced motivation.
  - Motor disturbances (e.g., stereotypy, catatonia).

Schizophrenia Etiology

- Diagnosis based on symptoms.
- Exact etiology is unknown.
- **Rule out other disorders:**
  - Epilepsy, Porphyria.
  - Amphetamine, PCP abuse, Levodopa, Apomorphine, Phencyclidine.
- **Genetic predisposition:**
  - Chromosome 18 linked to schizophrenia.
- **Environmental factors:**
  - Higher incidence in lower socioeconomic groups;
    - Abnormalities in Neurodevelopmental & Neurochemical Neuroanatomic.
- Enlarge cerebral ventricles, Atrophy of cortical layers, Reduced volume of the basal ganglia.

Schizophrenia Diagnosis

- **Positive symptoms:**
  - Hallucinations, Delusions, Disorganization of thoughts, agitation, tension and paranoia, respond to classical antipsychotics.

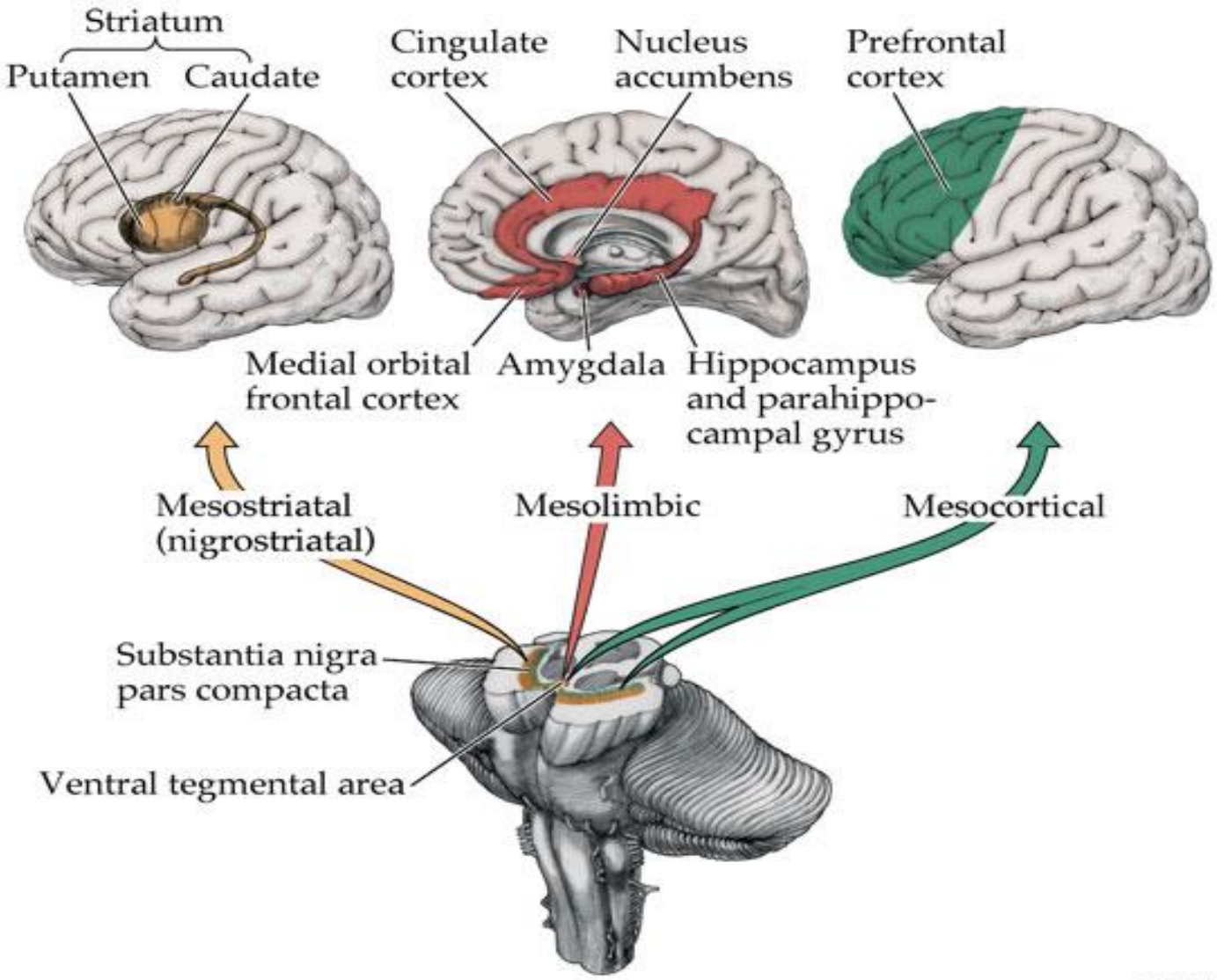
- **Negative symptoms (deficit syndrome):**
  - Dysphoria, blunt affect, speech disorder, loss of motivation, Cognitive symptoms, Dissociate thinking, Attentional impairments, poor self care, social withdrawal, Apathy, These symptoms are progressive and may respond to atypical neuroleptics.

- **Illness should persist for a period of six months**

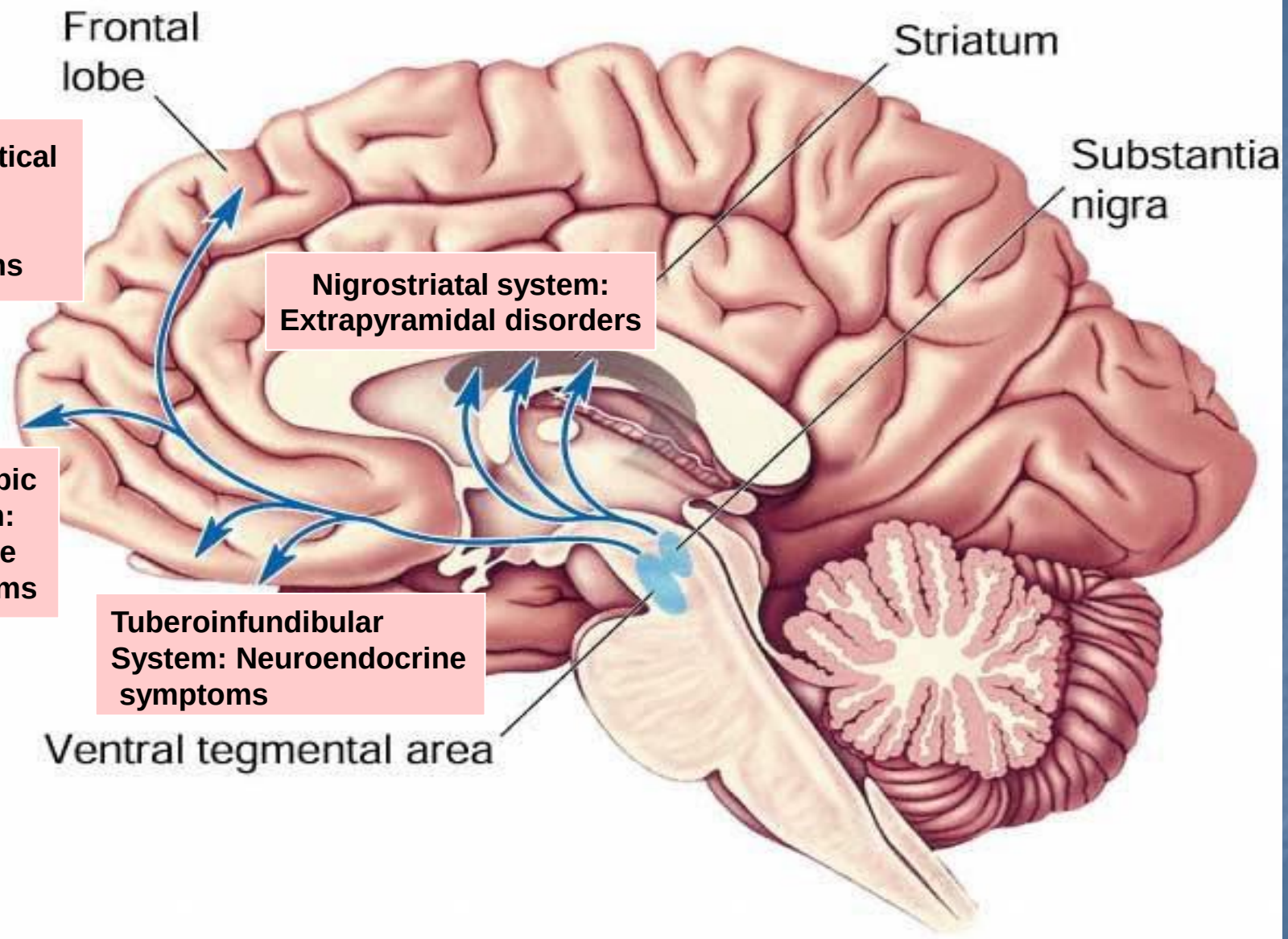
Dopamine Theory Of Schizophrenia - Excess DA

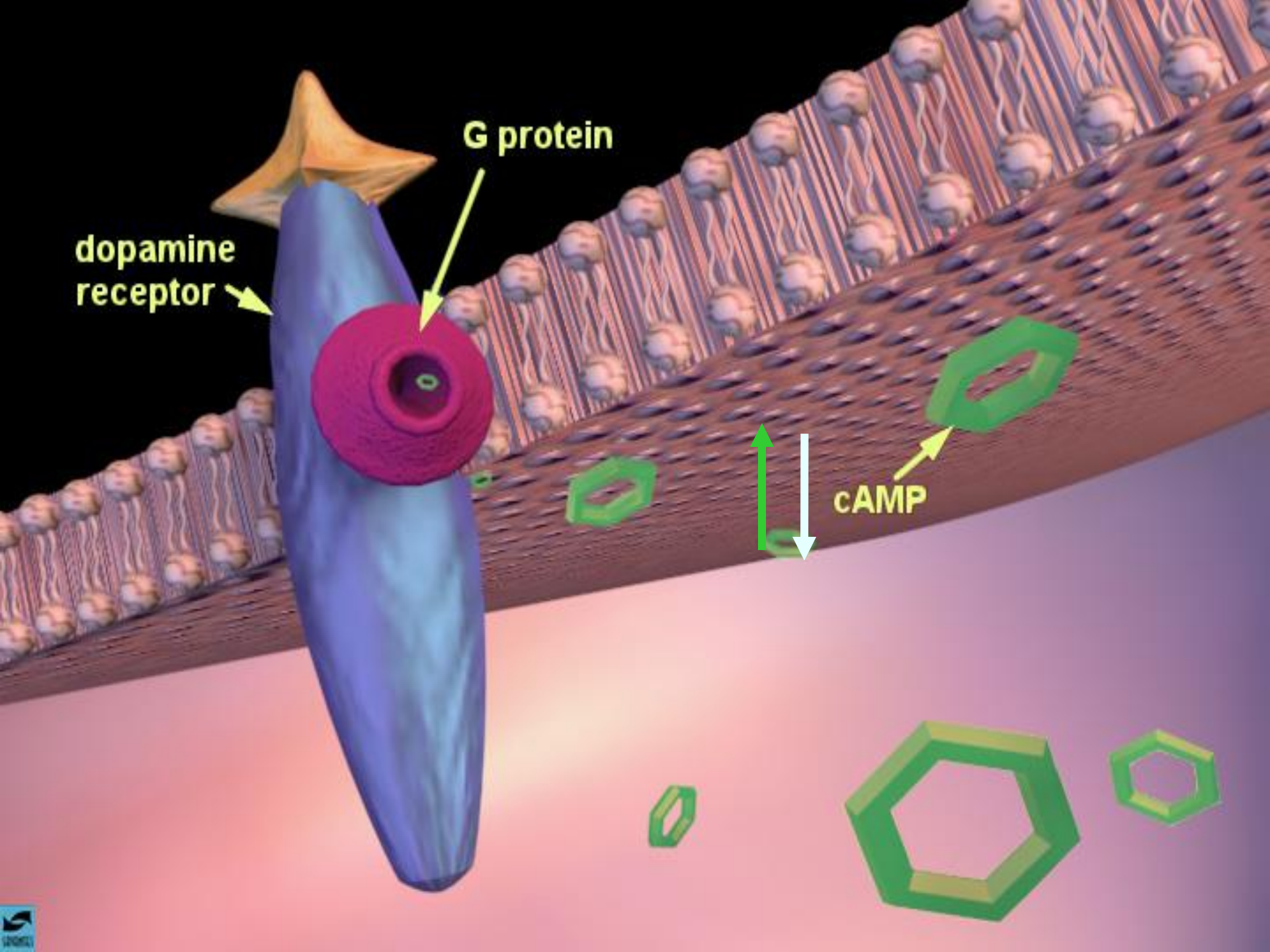
- Drugs that increase DA in the limbic system cause psychosis. (Amphetamine).
- Drugs that reduce DA in the limbic system (postsynaptic D2 antagonists) reduce psychosis (Reserpine, Chlorpromazine).
- Side effects similar to PD's (including tardive dyskinesia).
- Increased DA receptor density (Post-mortem, PET).
- Changes in amount of homovanillic acid (HVA), a DA metabolite, in plasma, urine, and CSF.

Dopamine Pathways



Dopamine pathways involved in schizophrenia




G protein
dopamine receptor
cAMP

Anatomic Correlates of Schizophrenia

Areas Associated with Mood and Thought Processes

Frontal cortex	**DA**
Amygdala	**DA**
Hippocampus	**DA**
Nucleus accumbens	**DA**
Limbic Cortex	**DA**

Evidence Against The Hypothesis

- Antipsychotics are only partially effective in most (70%) and ineffective for some patients.
- Phencyclidine, an NMDA receptor antagonist, produces more schizophrenia-like symptoms in non-schizophrenic subjects than DA agonists.
- Atypical antipsychotics have low affinity for D2 receptors.

Role Of Other Neurotransmitters Systems: Serotonin

- **LSD, Phencyclidine (PCP) antagonise $5HT_2$ receptor induce schizophrenia-like effects e.g. Hallucinations.**
- **Atypical antipsychotics, antagonise $5HT_2$ receptors in cortex, block 5HT inhibition of DA, so increase DA in frontal lobes improve negative symptoms.**

Role Of Other Neurotransmitters Systems: Glutamate And Glycine

- **Ketamine (hallucinogenic) blocks NMDA-type glutamate receptors.**
- **Decrease in glutamate (excitatory) in schizophrenia, associated with both positive and negative symptoms.**
- **Glycine (inhibitory), with glutamate is important for cognition.**

Role Of Other Neurotransmitters Systems: GABA

- Evidence of low levels of GABA in schizophrenia.
- Enzyme that catalyses GABA synthesis may also be deficient.
- Inadequate inhibition in frontal cortex, get loss of filtering/ selective attention.
- Cortical GABA neurons developing at birth, perinatal insult?

Schizophrenia Treatment

- Reduce psychological and social stress.
- Counseling, psychotherapy.
- **Antipsychotic drugs:**
  - Treatment of choice.
  - Relapse rates still high.
  - Low patient compliance.
- No single antipsychotic has superior efficacy compared to others for controlling positive symptoms.
- **Objectives:**
  - Clinical settings;
    - Treat active psychosis.
  - Outside the clinic;
    - Prevent relapse and maintain social interactions.

Antipsychotic Drugs

- **Typical Antipsychotics.**
- **Atypical Antipsychotics.**
- **Antipsychotic half-lives are generally long enough to permit once-a-day or twice-a-day dosing.**

Typical Antipsychotics (Neuroleptics)

- Chlorpromazine (aliphatic).
- Perfenazine (aliphatic).
- Trifluoperazine (piperazine).
- Thioridazine (piperidine).
- Fluphenazine.
- Haloperidol.
- Thiothixene.

Atypical Antipsychotics

- Moderate blockade of dopamine receptors, Stronger blockade of serotonin receptors, Risk of EPS is low.
- **Old Atypicals:**
  - Risperidone (D_2/5-HT_2 antagonist).
  - Clozapine (binds to many receptors).
- **Newer Atypicals (clozapine-like):**
  - Olanzepine, Sertindole, Loxapine, ziprasidone, Quetiapine.

Use of Antipsychotic Agents

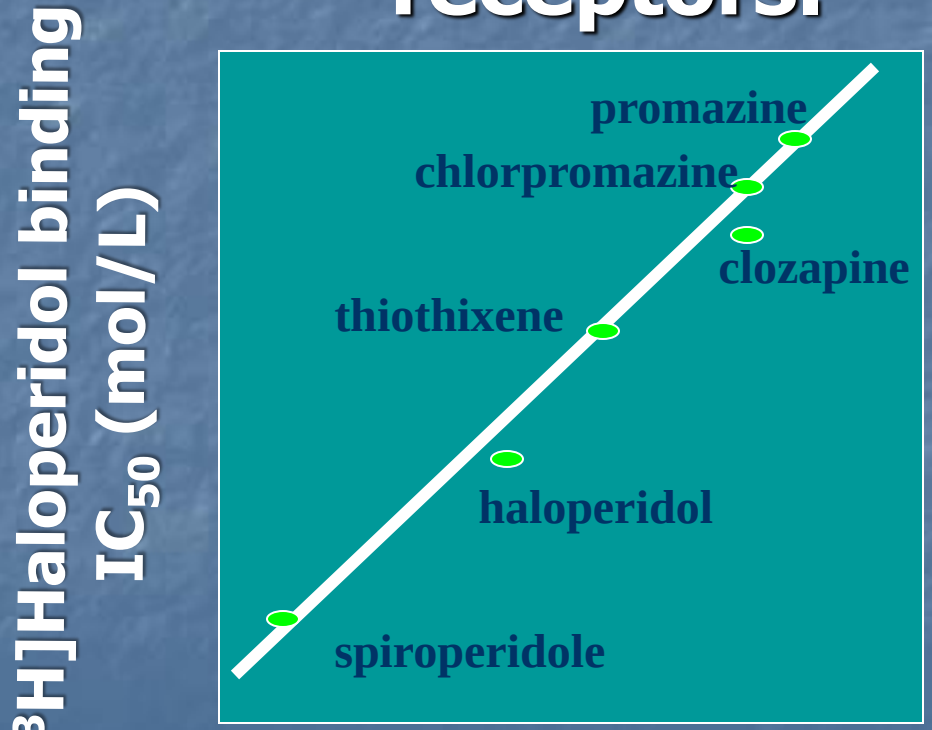
- Schizophrenia.
- Delusional disorders.
- Acute mania; Bipolar disease.
- Depressive psychosis.
- Drug-induced psychosis.
- Suppress emesis.
- Tourette's Syndrome.
- Huntington's Chorea.

Classification of Conventional Antipsychotics

- Low potency — chlorpromazine.
- Medium potency.
- High potency — haloperidol.
- Potency refers to size of dose needed to elicit a given response, not the ability to relieve symptoms.
- Low, medium and high potency drugs while having the same ability to relieve symptoms, have different side effects.

Neuroleptics Effects

- **Correlations between therapeutic potency and affinity for binding D2 receptors.**



Neuroleptics Effects (Cont)

The acute effects of antipsychotics do not explain why their therapeutic effects are not evident until 4-8 weeks of treatment.

Blockade of Presynaptic

D_2 receptors

⇓

Short term/Compensatory effects:

- ⇑ **Firing rate and activity of nigrostriatal and mesolimbic DA neurons.**
- ⇑ **DA synthesis, DA metabolism, DA release.**

Neuroleptics Effects (Cont)

Postsynaptic Effects
Depolarization Blockade

Inactivation of nigrostriatal and mesolimbic DA neurons.

↓

Receptor Supersensitivity

Traditional Antipsychotics

- Antagonise dopamine D_2 receptors in limbic system (positive symptoms) and striatum (extrapyramidal side-effects).
- Vary in potency (ability to block receptors), need 60-75% block for clinical effectiveness.
- Approximately one-third of patients with schizophrenia fail to respond.
- **Antipsychotics reverse hyperkinetic behaviors (increased locomotion and stereotyped behavior):**
  - Blockade of D_2 receptors in limbic areas.
- **Limited efficacy against:**
  - Negative symptoms.
  - Affective symptoms.
  - Cognitive deficits.
- High proportion of patients relapse.

Typical Antipsychotics

- Include phenothiazines and nonphenothiazines.
- Can be broken down into three smaller classifications:
- Aliphatics → Sedation and anticholinergic effects – Prototype – chlorpromazine.
- Piperazines → Extrapyramidal reactions - fluphenazine decanoate.
- Piperidines → Sedation - mesoridazine & thioridazine.

Typical Antipsychotics (Cont)

- **Nonphenothiazine antipsychotics can be divided into several drug classes:**
- **Butrophenones – haloperidol.**
- **Dibenzoxazepines - loxapine succinate.**
- **Dihydroindolones – molindone.**
- **Diphenylbutylpiperidines – pimozide.**
- **Thioxanthenes – thiothixine.**

Antipsychotic/Neuroleptics (Cont)

Clinical Problems with antipsychotic drugs include:

1) Failure to control negative effect.
2) **Significant toxicity:**
   a) Parkinson-like symptoms.
   b) Tardive Dyskinesia (10-30%).
   c) Autonomic effects.
   d) Endocrine effects.
   e) Cardiac effects.
3) Poor Concentration.

Conventional Antipsychotic Agents—Side Effects

Receptor type	Consequence of blocking
D2 Dopaminergic	EPS; Prolactin release
H1 Histamine	Sedation
Muscarinic cholinergic	Dry mouth, blurred vision, urinary retention, constipation, tachycardia
Alpha1- Adrenergic	Orthostatic hypotension, Reflex tachycardia
5-HT2-Serotoninergic	Weight gain

Antipsychotics; Cardiovascular Effects

- **α_1-Adrenergic antagonism:**
  - Orthostatic hypotension, reflex tachycardia, sexual dysfunction, priapism, miosis (pupil constriction).
  - Thioridazine, clozapine and chlorpromazine have the highest α_1 receptor affinity.
  - Haloperidol, olanzapine, and trifluoperazine have lower α_1 receptor affinity.
  - Thioridazine can produce ventricular arrhythmias and death;

    - Prolonged QT and PR intervals.

Antipsychotics; Endocrine Effects

- **Antipsychotics prevent DA inhibition of prolactin release from pituitary.**
- **Blockade of D2 receptors in lactotrophs:**

  ➔ Hyperprolactinemia

  Enlarged breasts in males, suppresses hypothalamic function, lactation (galactorrhea) amenorrhea or irregular menses, osteoporosis, infertility in women, impotence in men.

Antipsychotics; Anticholinergic Effects

- **Dry mouth, urinary retention, constipation, blurred vision (mydriasis), sinus tachycardia, confusion, memory impairment, impaired cognition, delirium, constipation, decreased sweating, glaucoma.**
- **Clozapine, Chlorpromazine,Thioridazine.**

Antihistaminic Effects

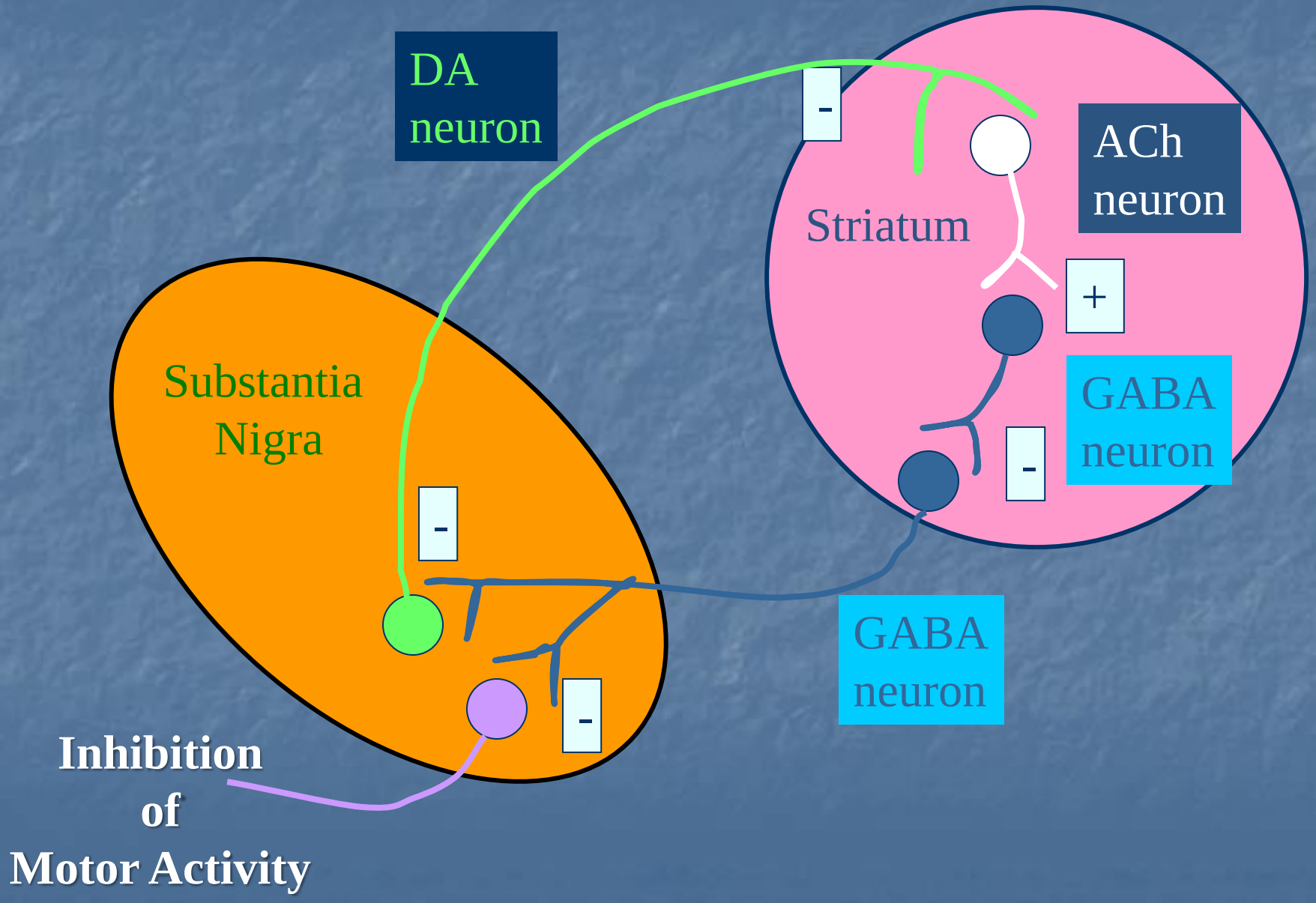
- Sedation, weight gain, confusion, disturbed concentration.
- H_1 Receptor blockade:
  - Phenothiazines and thioxanthines, Risperidone, Haloperidol & Clozapine.
  - Promethazine was one of the earliest antihistamines.

Traditional Neuroleptics Block DA Extrapyramidal (EP) System Disorders

- **Develop in 60-90% of patients, some acute and some chronic:**

1. **Acute dystonic reactions.**
2. **Akathisia.**
3. **Akinesia.**
4. **Parkinsonism.**
5. **Tardive dyskinesia.**

The Nigro-Striatal Pathway



Extrapyramidal Side Effects

- **Acute dystonia:**
  - Muscle spasms in face, neck, tongue, upward and lateral rotation of the eyes.
  - Usually occurs within 1 - 7 days of starting the drug.
  - Can be treated with anti-Parkinson's agents (e.g., benztropine) & Discontinue antipsychotic drug.
- **Akathisia:**
- Body restlessness (can't sit still), fidgeting, pacing, rocking , irritability.
- Treated with benzodiazepines, anti-Parkinson's agents or beta blockers, Reduce dosage.

Extrapyramidal Side Effects (Cont)

- **Perioral tremor:**
  - Delayed effect.
  - Similar to parkinsonism.
  - Anticholinergics effective.
- **Pseudoparkinsonism:**
- Stiffness, shuffling, mask-like face, tremor, rigidity, muscle rigidity, gait, drooling.
- **Rabbit syndrome:** Trembling of lower lip.
- **Pisa syndrome:** Leaning to one side (geriatric patients at higher risk).
- **Reduce motor activity:**
  - Blockade of dopamine receptors in basal ganglia.

Indirect Neurological Effects Tardive Dyskinesia

- Most common side effect & Usually an irreversible phenomenon.
- Smacking, licking of lips, chewing movements, rolling or protrusion of tong, jerking of fingers, ankles, toes, limbs, trunk, neck, and pelvis, choreoathetosis or dystonia.
- Develops after months or even years of treatment.
- More frequent in older patients.
- May persist after withdrawal of antipsychotic.
- Potential for increased suicide risk.
- Anti-parkinson's agents may exacerbate tardive dyskinesia.
- Can be treated with potent neuroleptic in extreme cases.
- Reduction of dose or change in medication.

Neuroleptic Malignant Syndrome

- Direct neurological effects (rare).
- Extreme Parkinson's symptoms, Due to excessively rapid blockade of postsynaptic dopamine receptors.
- Catatonia, stupor, fever, autonomic instability with altered blood pressure and heart rate, muscle rigidity, creatine kinase isozymes are usually elevated, reflecting muscle damage.
- leukocytosis and high fever associated with this syndrome may be mistaken for an infection.
- More common in men than women.
- 80% of cases occur under age 40.
- Immediately discontinue antipsychotic.
- Treated with cooling, hydration, antiparkinsonian drugs ,Dantrium, diazepam or bromocriptine have been used to lessen muscle rigidity and fever.
- Transfer to ICU and treat fever aggressively.
- Mean recovery time; 7 - 10 days.

Contraindications

- Parkinson's disease.
- Hepatic failure.
- Bone marrow depression.
- Overdose rarely fatal.

Atypical Antipsychotics

- Less likely to cause extrapyramidal symptoms.
- Likely to improve positive symptoms of schizophrenia.
- Improve negative symptoms of schizophrenia & cognition.
- Indicated for schizophrenic patients who are unresponsive to typical antipsychotics.

Atypical Antipsychotics; Pharmacodynamics

- Higher occupancy of 5-HT_2 vs. D_2 receptors at usual doses.
- Generally bind to D_1 and D_4 receptors (in addition to D_2).
- Affinity for 5-HT_2 vs. D_2 receptors predictive of atypical antipsychotic.
- Lower affinity for striatal D_2 receptors.
- Block histamine or adrenergic receptors (sedation, postural hypotension, anticholinergic effects).

Second Generation Antipsychotics

- **Clozapine.**
- **Risperidone.**
- **Olanzapine.**
- **Quetiapine.**
- **Ziprasidone.**

Indications for Atypical Antipsychotics

- Schizophrenia.
- Psychosis associated with depression or mania.
- Acute Agitation.
- Aggression.
- Tourette's.
- Delirium.
- Affect instability in BPD.

Clozapine

- Greater efficacy in treatment resistant.
- Antiaggressive properties, decrease suicide, smoking.
- Clozapine may be used on an every-other-day schedule in some patients.
- **Adverse effects:**
- Seizures (dose related), sedation, sialorrhea, tachycardia, weight gain, DM, myocarditis (fatality risk in first month), cardiomyopathy (2-36 mo), Orthostatic hypotension, Anticholinergic effect.
- Monitor cardiac, arrythmias, fatigue, flu-like fever, hypotension.
- **Clozapine can produce agranulocytosis in some (0.6 %) patients:**
  - CBC with differential;
    - Prior to first dose and weekly for the first 6 months.
    - Every 2 weeks after first 6 months of therapy.
- For second six months, monitor every other week.

Atypical AP: Less Severe Side Effects

- **Sedation (Antihistaminic Activity):** Clozapine>olanzapine>quetiapine>risperidone.
- **Anticholinergic:** Clozapine, Olanzapine.
- **Sialorrhea:** Clozapine.
- **Orthostasis/Tachycardia:**
  - Quetiapine, Risperidone > Olanzapine, Clozapine.
- **Dyspepsia:** Ziprasidone.
- **Headache:** Ziprasidone.

Atypical AP: Serious Side Effects

- **Agranulocytosis, seizures:** Clozapine.
- **Weight gain, diabetes, hyperlipidemia:**
  - Olanzapine = Clozapine > Quetiapine > Others.
- **Hyperprolactinemia:** Risperidone, Olanzapine.
- **QT_c prolongation:**
  - Thioridazine > Ziprasidone > Others.

Atypical AP: Dose Adjustments

	Renal Impairment	Hepatic Impairment	Elderly
Aripiprazole	-	-	-
Clozapine	-	-	-
Olanzapine	-	-	-
Quetiapine	-	↓ dose	↓ dose
Risperidone	↓ dose	↓ dose	↓ dose
Ziprasidone	Caution with injection	-	↓ dose

*Schizophrenia Therapy**

Antipsychotic agent	Decreased Incidence of EPS	↓ Effects on Prolactin Release	Treating Positive Symptoms	Treating Negative Symptoms
Clozapine	Yes	Yes	Yes?	Yes
Risperidone	Maybe	No	Maybe	No
Olanzapine	Probably	Yes	Maybe	Probably
Quetiapine	Maybe	Yes	No	No

*Relative to classical antipsychotics

Pharmacokinetic Interactions

- **Inhibitors of CYP1A2 such as Ciprofloxacin & Erythromycin increase haloperidol levels.**
- **Inducers of CYP1A2 (cigarette use) significantly lower levels of haloperidol, chlorpromazine and clozapine.**
- **Inhibitors of CYP2D6 (e.g., fluoxetine) increase clozapine levels.**
- **Inducers of CYP3A4 (e.g., carbamazepine, phenytoin) decrease haloperidol and clozapine levels.**
- **Inhibitors of CYP 3A4 (e.g., Azole antifungals, Erythromycin, Nefazodone, Fluoxetine) decrease haloperidol and clozapine levels.**

Pharmacodynamic Interactions

- Amphetamines antagonize antipsychotic effects.
- Centrally active anticholinergic drugs will worsen tardive dyskinesia.
- SSRIs can worsen extrapyramidal symptoms.
- Additive effects with sedatives.
- Additive effects with anticholinergics.
- Additive effects with antihistaminergics.
- Additive effects with α-AR blocking drugs.
- Additive effects with drugs with quinidine-like action (thioridazine).

Antipsychotic Monitoring

- **Poor correlation between plasma concentrations and therapeutic benefits.**
- **Prevalence of active metabolites complicating factor.**
- **Limited value in routine monitoring of plasma levels.**

Antipsychotic Comparing

Chlorpromazine: $\alpha_1 = 5\text{-}HT_2 = D_2 > D_1 > M \geq \alpha_2$

Haloperidol: $D_2 > D_1 = D_4 > \alpha_1 > 5\text{-}HT_2 > H_1 > M = \alpha_2$

Clozapine: $D_4 = \alpha_1 > 5\text{-}HT_2 = M > D_2 = D_1 = \alpha_2 ; H_1$

Quetiapine: $5\text{-}HT_2 = D_2 = \alpha_1 = \alpha_2 ; H_1$

Risperidone: $5\text{-}HT_2 >> \alpha_1 > H_1 \geq D_2 > \alpha_2 >> D_1$

Sertindole: $5\text{-}HT_2 > D_2 = \alpha_1$

Antipsychotic Comparing (Cont)

Drug	Clinical Potency	Ex. Py. toxicity	Sedation	Hypote.
Chlorpromaz	Low	Medium	Medium	High
Haloperidol	High	Very High	Very High	Low
Thiothixene	High	Medium	Medium	Medium
Clozapine	Medium	Very low	Low	Medium
Ziprasidone	Medium	Very Low	Low	Very low
Risperidone	High	Low	Low	Low
Olanzapine	High	Very Low	Medium	Very low
Sertindole	High	Very Low	Very low	Very Low

Tourette's Syndrome

- Neurological disorder.
- Repeated involuntary movements (tics).
- Uncontrollable vocal sounds.
- Minority of cases includes socially inappropriate phrases – coprolalia.
- Symptoms typically appear before age of 18.
- Males affected 3-4 times more often than females.
- Genetic link?
  - Family history, but no markers identified.
- Monoamine imbalance suggested by pharmacology of agents useful in treating symptoms.
- Head trauma?

Treatments

- **Stress can exacerbate symptoms:**
  - **Patients should be encouraged to find ways to minimize stressful situations.**
- **Mild symptoms may be treated effectively with α_2 agonists:**
  - **Clonidine.**
  - **Guanfasine.**
- **The antipsychotics haloperidol, pimozide and risperidone are useful in treating more severe symptoms.**

Clonidine (Catapres®)

- **Absorption:**
  - Rapid and complete (~100% bioavailability).
- Distributes rapidly to CNS.
- **Adverse effects:**
  - Lethargy, drowsiness (sedation), constipation, and xerostomia.
- **Contraindications:**
  - Raynaud's syndrome (vascular disease).
  - History of depression.

Affective Disorders

- **Unipolar:**
  - One direction;
    - Depression or mania.
- **Bipolar:**
  - Alternating between depression and mania.
- **Different disorders, with different treatment approaches:**
  - Afflicts approximately 1 million patients per month.
- Bipolar patients often experience thoughts of suicide.

Mania

Core Symptoms:

- It is characterized by an elevated “high” mood.
- Talkative, go on-and-on about the things they will do.
- Increased self-esteem.
- Auditory hallucinations.
- Decrease need to sleep.
- Lack judgment, indiscrete.
- Super ME.
- Racing thoughts, distractibility, psychomotor agitation, excessive involvement in pleasurable activities.

Mood Stabilizers

- Used to treat bipolar disorder.
- Lithium-first line.
- **Anticonvulsants:** Used when lithium not tolerated or effective; Carbemazepine, valproic acid, Lamotrigine, Olzanzepine.
- **Antidepressant drugs:**
  - Reverse depression.
  - Elevate mood.
  - Exacerbate mania in bipolar patients.

Lithium

- Simple inorganic ion.
- Lithium carbonate and citrate are the drugs of choice to prevent or treat mania and bipolar disorders.
- Many drug interactions affecting blood levels.
- Discontinue with gradual taper to prevent bipolar symptoms.
- **Excreted by the kidneys:** Use with extreme caution in patient with renal impairment.
- **Sodium levels:** Sodium depletion will decrease renal excretion; drug accumulation= toxicity.
- **Narrow therapeutic margin:**
  - Frequent blood levels with initiation.
  - Periodic checks when stabilized and with changes in other drugs or dosage.
- **Plasma levels:** Lithium level must be kept Lithium level 0.4 to 1.4 mEq/L; above is toxic.

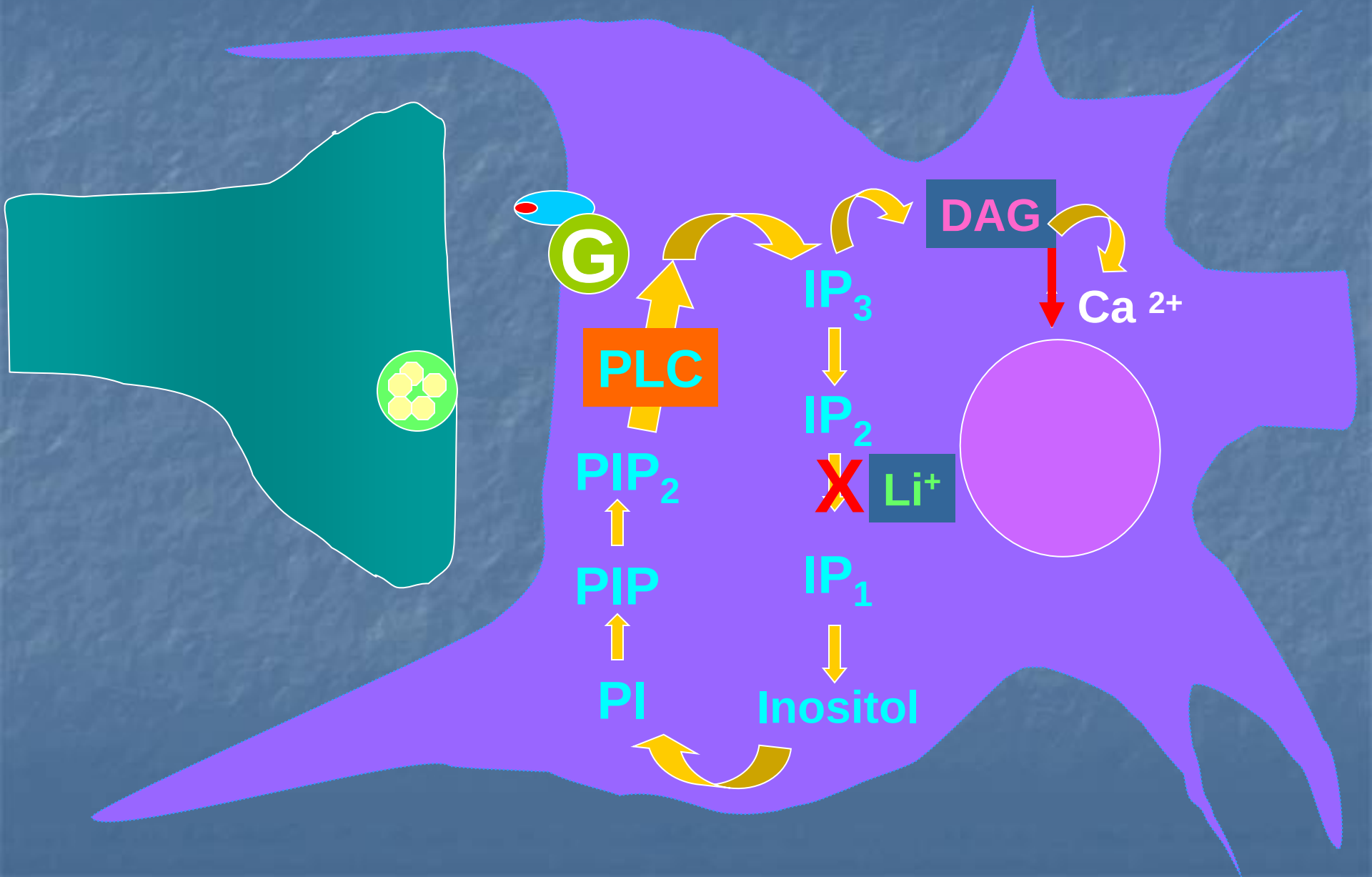
Lithium; Pharmacodynamics

- **Interferes with phosphoinositide metabolism:**
  - Inhibits inositol monophosphatases.
  - Elevates protein kinase C activity.
- Elevates glutamate reuptake.
- **Regulates cAMP production by stabilizing heterotrimeric G protein subunit association:**
  - Inactivates G_i under basal conditions.
  - Inactivates G_s under stimulated conditions.
- Blocks glycogen synthase kinase-3β.
- Decreases phosphorylation of tau protein and MAP-1B.
- Increases tau binding to microtubule proteins.
- Decreases MAP-1B binding to microtubule proteins.
- Alters cytoskeletal function (and perhaps neuroprotection).
- **Regulates catecholamine release in the CNS by:**
- Increasing norepinephrine and serotonin uptake; reducing the release of norepinephrine from the synaptic vesicles in the presynaptic neuron; inhibiting norepinephrine's action in the postsynaptic neuron.

Mechanism Of Action; Li^+

- Does not alter receptor numbers but alters the coupling of the receptors with their second messengers by reducing coupling of G-proteins.
- Regulation of β-AR and DAR.
- Can reduce release of NTs (5-HT) and affinity of binding to receptor.
- Inhibits breakdown of IP_2 to IP_1 (during PIP hydrolysis) => depletion of DAG and IP_3 and ↓ $[Ca^{2+}]$ in response to receptor activation (i.e. from 5-HT_2R, α_1-AR, muscarinic receptors and others).
- Alterations in adenylate cyclase and phospholipase C.

Anti-Manic Drugs



Lithium; Pharmacotherapeutics

- **Used primarily to treat acute episodes of mania and to prevent relapses of bipolar disorders.**
- **Long term prophylaxis of recurrent bipolar disorder.**
- **Other uses include: Migraine headaches; alcohol dependence; anorexia nervosa; syndrome of inappropriate ADH; and neutropenia.**
- **Helps alleviate the depressive phase of bipolar illness.**
- **Useful in refractory depression when added to SSRIs or TCAs, but not a good antidepressant alone.**

Lithium Adverse Effects

- **Gastrointestinal:** Nausea, vomiting, diarrhea.
- **CNS:** General weakness, poor coordination , poor memory, drowsiness, fatigue tremors, seizures, coma.
- **Cardiovascular:** Hypotension, cardiac arrhythmias, conduction deficits.
- **Kidney:**
  - Inhibits ADH => diuresis, Nephrogenic diabetes insipidus.
- **Endocrine:**
  - Weight gain due to ↓ thyroid function (Goiter).
- Teratogenic in first trimester of pregnancy(tricuspid valve malformation).
- **Skin disorders:** Rash, worsening of acne, psoriasis, edema, thirst, dry mouth, metallic taste.
- **Treatment:**
  - Fluids and electrolyte replacement, forced diuresis with mannitol, urinary alkalinization, hemodialysis.

Drug interactions

- Serious drug interactions with other drugs can occur because lithium has a narrow therapeutic margin of safety.
- Patients on a severe salt-restricted diet are susceptible to toxicity.
- **Plasma lithium levels are increased by:**
  - Thiazide diuretics, ACE inhibitors, NSAIDS.
- All of which decrease renal clearance of lithium.
- All neuroleptics (with the exception of clozapine), produce more severe extrapyramidal syndromes when combined with lithium.

Dosage and Monitoring

- **Li^+ has a low therapeutic index:**
  - Levels should be monitored every 2 – 3 days at first, every week for one month.
  - Later, levels can be monitored every month, then every quarter.
- **Initial doses range from 600 – 1200 mg/day of $LiCo_3$:**
  - If necessary, doses can be increased by 300 mg/day to a maximum of 2400 mg (in divided doses with meals).
- Treatment should be interrupted if patients exhibit fever, vomiting or diarrhea.
- Treatment also should be discontinued if patients will undergo surgery, have congestive heart failure, or will receive diuretics (levels of Li^+ fluctuate).
- **Maintenance levels of Li^+ range from 0.5 – 1.5 mEq/l:**
  - For treatment of bipolar illness, levels near 0.8 mEq/l are effective.
  - For treatment of acute mania, higher levels (1.0 – 1.4 mEq/l) are required.
- Toxicity is associated with levels greater than 1.5 mEq/l.

Principles Of Treatment With Lithium

- **Acute:**
- 1-2 Week latency before antimanic effects.
- Benzodiazepine or neuroleptic often added for first few weeks.
- Watch for adverse effects, esp. renal, thyroid.
- **Chronic:**
- May need to add antidepressants and/or anticonvulsants.
- Watch for adverse effects.

Other Mood Stabilizers

- **Anticonvulsants:** Sodium valproate, carbamazepine, Lamotrigine may be useful in treatment of depression in bipolar patients.
- **Benzodiazepines:** Diazepam, Clonazepam.
- **Antipsychotics:** Olanzapine approved for the treatment of acute mania.
- **Nifedeipine, Verapamil:** Mechanism of action ; NT Release?

Common Adverse Effects Of Valproate

- **CNS:** Sedation, tremor.
- **GI:** Nausea, vomiting, diarrhea.
- Coagulopathies.
- Infertility, teratogenic in pregnancy.
- **Rare:** Heptatotoxicity, pancreatitis, agranulocytosis.
- **Key drug interactions:** NSAIDS.
- Valproate is an inhibitor of P-450 enzymes.

Common Adverse Effects Of Carbamazepine

- **CNS:** Sedation, weakness, ataxia, interference with cognitive function.
- **Abnormal eye movements:** Diplopia, nystagmus.
- Skin rash, exfoliative dermatitis.
- **Hematologic:** Leucopenia, aplastic anemia.
- Cardiovascular toxicity in overdose.
- Teratogenic in pregnancy.
- higher incidence of spina bifida with carbamazepine.
- Carbamazepine is an inducer of P-450 enzymes.

Bipolar Disorder—Treatment

- **Manic phase: Initial treatment:**
  - Lithium + Benzodiazepine (Lorazepam), or.
  - Lithium + Haloperidol.
- **Manic phase: Later treatment:**
  - Lithium alone.
- **Depressive phase:**
  - Lithium + Tricyclic antidepressant (Imipramine), or.
  - Lithium + Atypical antidepressant.
  - Normalized mood.
  - Lithium.
- **Others:**
  - Carbamazepine.
  - Valproic acid.