

Anti-psychotic Drugs

Psychosis

“Illness characterized by disturbance of reality and perception, impaired cognitive functioning, and disturbances of affect or mood”

- **Positive symptoms**.....delusions / hallucinations / thought disorders / abnormal disorganized behavior / catatonia
- **Negative symptoms**.....withdrawal from social contacts / flattening of emotional responses / anhedonia / reluctance to perform everyday tasks
- **Cognitive deficit symptoms**.....deficits in cognitive functions (e.g memory, attention)

Psychosis

Pathophysiology

- Organic basis / genetic / idiopathic
- Serotonin Hypothesis
 - Hallucinogens (LSD).....5-HT receptor agonist.....5-HT_{2A} & 5-HT_{2C}
 - 5-HT_{2A} modulate release.....DA / NE / GABA / Ach / Glutamate
 - 5-HT_{2A} stimulation.....depolarization of glutamate N & NMDA rec. stability
 - 5-HT_{2C} stimulation.....inhibit DA release
 - Antipsychotics.....Blockade / Inverse agonist

Psychosis

- **Dopamine Hypothesis**
 - **Dopaminergic system effects**
 - **Mesocortical / Mesolimbic.....Behavioral effects.....Psychosis (Schizophrenia)**
 - **Nigrostriatal.....Motor control.....Extrapyramidal effects (Parkinsonism)**
 - **Tuberoinfundibular.....Endocrine effects**
 - **Medullary-periventricular.....Eating behavior**
 - **Incertohypothalamic pathway**
 - **D₁-like rec (D₅)..... increase cAMP**
 - **D₂-like rec (D₃, D₄).....decrease cAMP.....antipsychotic & extrapyramidal effects**

Psychosis

- Dopamine Hypothesis

- Drugs or conditions enhancing dopaminergic activity (level or rec.).....psychotic s/s
- Increased dopamine receptor density & dopamine levels
- Reduced cortical & hippocampal dopaminergic activity.....cognitive & negative symptoms
- Atypical Antipsychotics.....D₂ rec. blockade < 5-HT_{2A} rec. blockade

Psychosis

- **Glutamate Hypothesis**

- Phencyclidine & Ketamine.....NMDA rec. blockade.....exacerbate psychosis



- Hypofunctional NMDA rec. on GABAergic interneurons



-  GABAergic Inhibitory effect



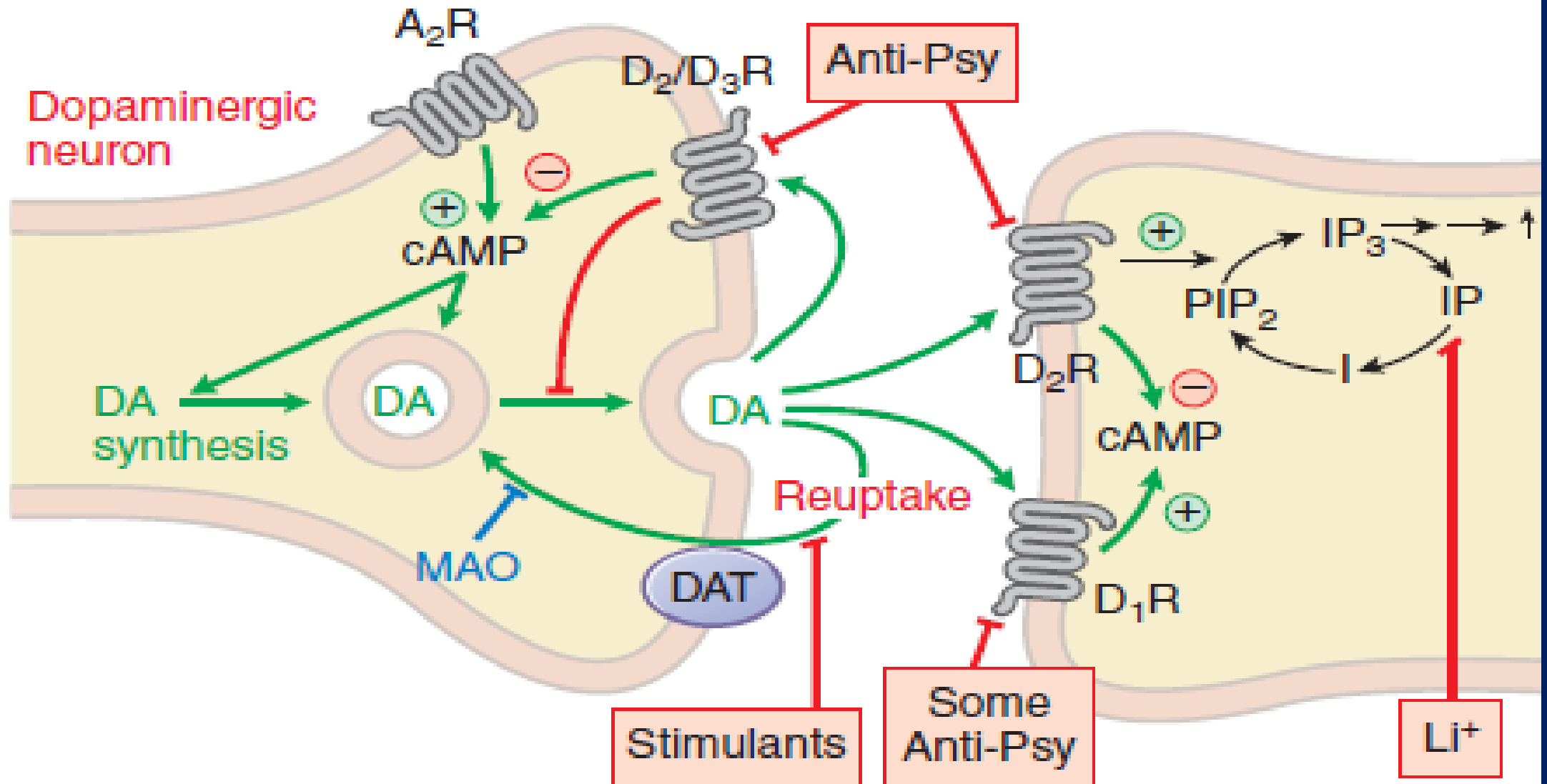
- Disinhibition of glutamatergic activity

- Hyperstimulation of cortical neuronsPsychosis

- Glycine binding on NMDA rec. – not fully saturated

PRESYNAPTIC

POSTSYNAPTIC



Anti-psychotic Drugs

CLASSIFICATION

FIRST GENERATION OR TYPICAL

- Phenothiazine Derivatives
 - Aliphatic Derivatives.....Chlorpromazine
 - Piperidine Derivatives.....Thioridazine
 - Piperazine Derivatives.....Fluphenazine
.....Perphenazine
.....Trifluoperazine
- Thioxanthene Derivatives
 - Thiothixene
- Butyrophenone Derivatives
 - Haloperidol
 - Droperidol
- Miscellaneous
 - Molindone
 - Pimozide

Anti-psychotic Drugs

CLASSIFICATION

SECOND GENERATION OR ATYPICAL

- Clozapine
- Olanzapine
- Quetiapine
- Risperidone
- Paliperidone**
- Ziprasidone
- Aripiprazole
- Loxapine
- Sertindole
- Asenapine
- Zotepine
- Cariprazine
- Brexpiprazole

GLUTAMATERGIC ANTIPSYCHOTICS (Investigational)

- Bitopertin
- Sarcoserine

Anti-psychotic Drugs

PHARMACOKINETICS

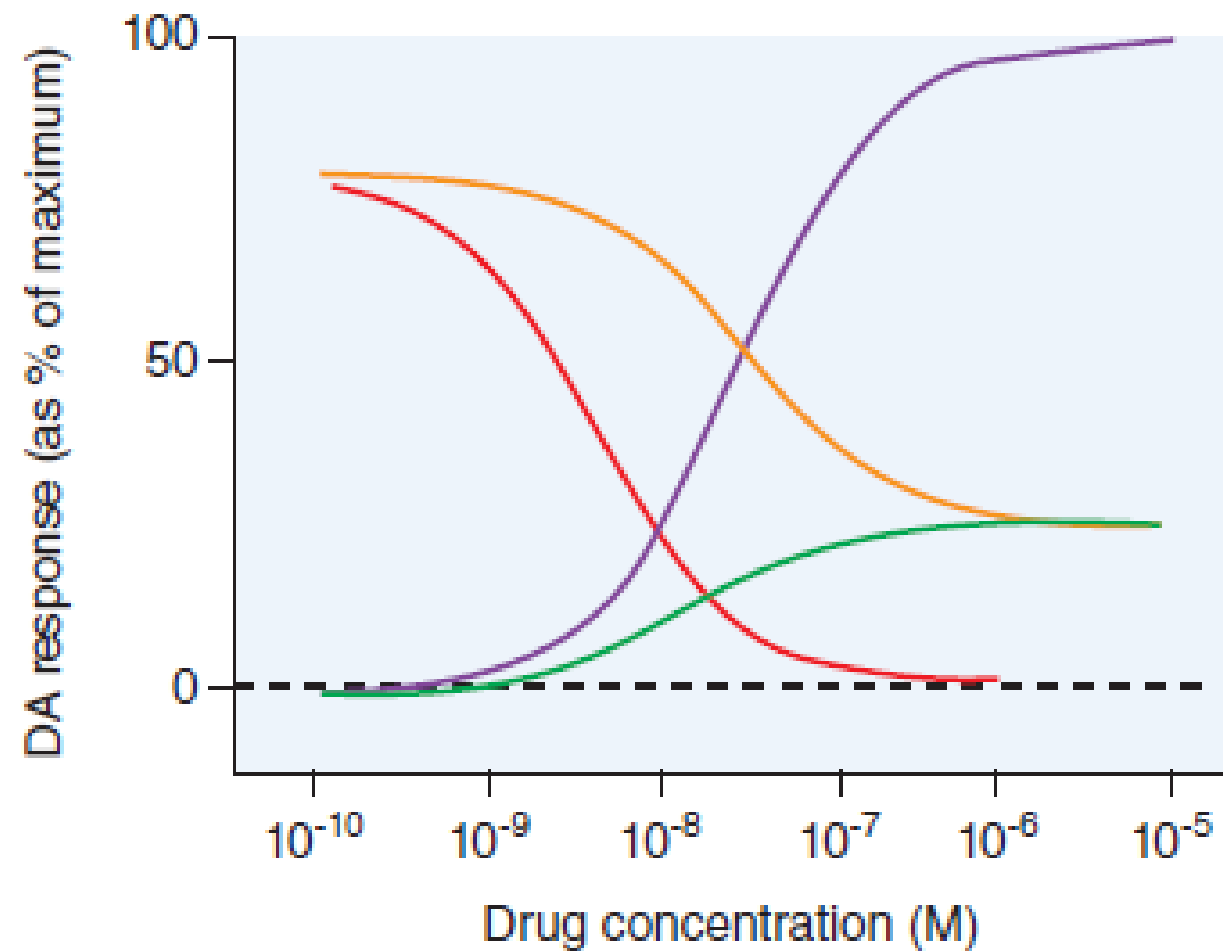
- ROA.....oral / intramuscular / slow-release depot preparation
- Parenteral & depot formulations.....Fluphenazine / Haloperidol / Risperidone / Paliperidone / Olanzapine / aripiprazole
- FPM / PPB / lipophilicity / distribution
- Metabolism.....CYP3A4 / CYP2D6 / CYP1A2
- Excretion
- $t_{1/2}$ vs DOA (receptor occupancy).....e.g. long acting injectable formulation
- Variable time for relapse (exc. Clozapine)

Anti-psychotic Drugs

PHARMACODYNAMICS

Mechanism of Action

- Most of typical & some atypical.....**D₂ rec. antagonist**
- Most of atypical & some typical.....**5-HT_{2A} rec. antagonist**
- Relative rec. affinity / blockade
- Extrapyramidal effects.....80% D₂ rec. occupancy
- **Neuroleptic**.....high incidence of EPS
- **D₁ & D₃ / 5-HT / α -adrenergic / muscarinic / H₁ histamine rec.....additional & side effects**
- Clozapine & Olanzapine.....5-HT_{2A} rec. antagonist
- Aripiprazole.....partial agonist of D₂ & **5-HT_{1A} rec.** / Antagonist of 5-HT_{2A} rec.
- Cariprazine..... Antagonist of D₂ & 5-HT_{2A} rec. / Partial agonist of **D₃ rec.**
- **Glutamatergic Antipsychotics** (Bitopertin & Sarcoserine).....GlyT1 inhibitors



100 nM dopamine



+ aripiprazole

100 nM dopamine



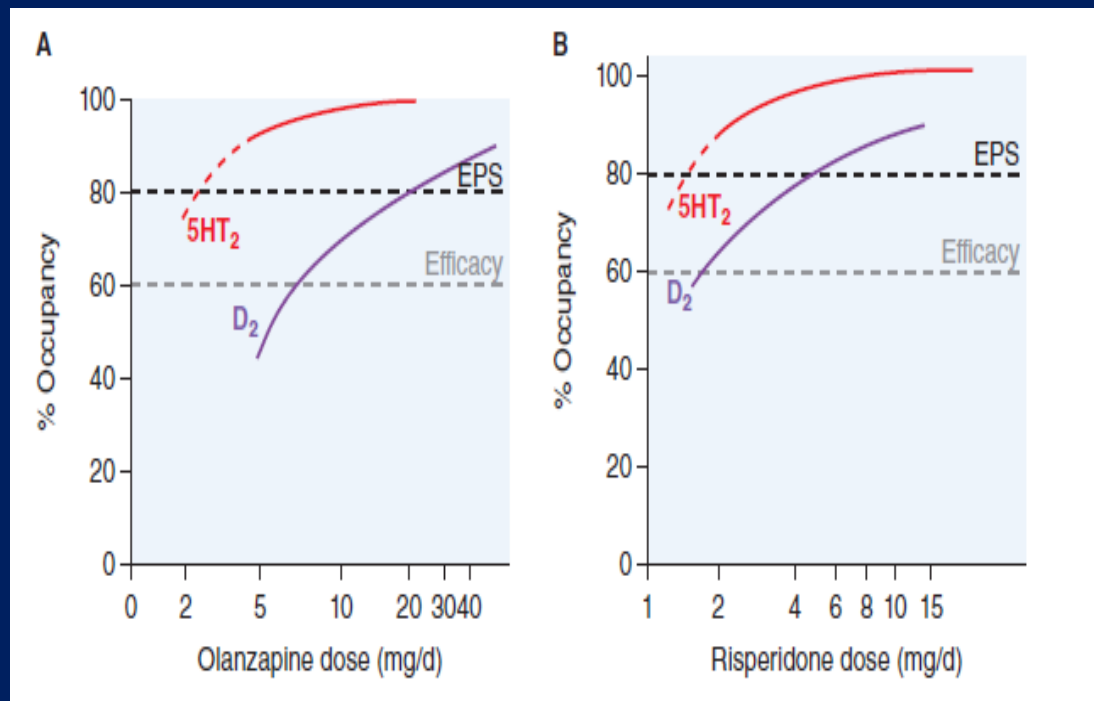
+ haloperidol

dopamine



aripiprazole





Chlorpromazine: α_1 = 5-HT_{2A} > D₂ > D₁

Haloperidol: D₂ > α_1 > D₄ > 5-HT_{2A} > D₁ > H₁

Clozapine: D₄ = α_1 > 5-HT_{2A} > D₂ = D₁

Olanzapine: 5-HT_{2A} > H₁ > D₄ > D₂ > α_1 > D₁

Aripiprazole: D₂ = 5-HT_{2A} > D₄ > α_1 = H₁ >> D₁

Quetiapine: H₁ > α_1 > M_{1,3} > D₂ > 5-HT_{2A}

Anti-psychotic Drugs

PHARMACOLOGICAL EFFECTS

Psychological Effects

- Nonpsychotic.....unpleasant subjective effects & impaired performance
- Akathisia, sleepiness, restlessness, autonomic effects
- Psychotic.....Improved behavior, performance & cognition
- Extrapyramidal effects.....mild to severe
- Sleep promoting effect.....low dose (esp. quetiapine)

Electroencephalographic (EEG) Effects

- EEG frequencies & amplitude.....slowing (focal or unilateral) / increased synchronization
- Decrease seizure threshold.....seizure-like EEG pattern.....caution in epileptic patient

Anti-psychotic Drugs

PHARMACOLOGICAL EFFECTS

Endocrine Effects

- Tuberoinfundibular.....Endocrine effects
- Typical, risperidone & paliperidone.....Increased prolactin.....S/E
- Atypical.....minimal effect.....prolactin & EPS

Cardiovascular Effects

- Phenothiazines.....Decreased BP (postural), PVR, stroke vol.....Increased HR
- Thioridazine.....QT interval / abnormal configuration of ST segment & T wave
.....torsades de pointes.....second line drug
- Atypical (sertindole, ziprasidone, quetiapine).....QT interval prolongation
- Atypical.....Metabolic syndrome with increased risk of CAD, stroke, HTN

TABLE 29–2 Adverse pharmacologic effects of antipsychotic drugs.

Type	Manifestations	Mechanism
Autonomic nervous system	Loss of accommodation, dry mouth, difficulty urinating, constipation	Muscarinic cholinergic blockade
	Orthostatic hypotension, impotence, failure to ejaculate	α -Adrenoceptor blockade
Central nervous system	Parkinson's syndrome, akathisia, dystonias	Dopamine-receptor blockade
	Tardive dyskinesia	Supersensitivity of dopamine receptors
	Toxic-confusional state	Muscarinic blockade
Endocrine system	Amenorrhea-galactorrhea, infertility, impotence	Dopamine-receptor blockade resulting in hyperprolactinemia
Other	Weight gain	Possibly combined H ₁ and 5-HT ₂ blockade

Anti-psychotic Drugs

Therapeutic Uses

Psychiatric Indications

- **Schizophrenia**
 - Catatonic form.....BZD (I/V).....antipsychotics
 - Negative symptoms.....atypical
 - Refractory case.....Clozapine / olanzapine.....6 months
 - Reduce suicidal tendency.....Clozapine
- **Schizoaffective disorders**
 - Antipsychotics / antidepressants / Lithium / Valproic acid

Anti-psychotic Drugs

Therapeutic Uses

Psychiatric Indications

- Schizophrenia
- Schizoaffective disorders
- Bipolar affective disorder
 - Manic phase
 - Antipsychotics / Lithium / Valproic acid / BZD (e.g. Lorazepam, clonazepam)
 - Depressive phase.....Psychotic depression
 - Antipsychotics (aripiprazole / quetiapine / clozapine) with antidepressants (fluoxetine)
 - More effective in manic phase

Anti-psychotic Drugs

Therapeutic Uses

Psychiatric Indications

- Agitation
 - Schizophrenia / Bipolar affective disorder / delirious or post surgical patients
 - Haloperidol / ziprasidone / aripiprazole.....I/M
- Unipolar depression.....Adjunctive use with antidepressants
- Non-maniac excited states.....BZD / Antipsychotics
- Alzheimer's disease.....disturbed behavior
- Tourette's syndrome

Anti-psychotic Drugs

Therapeutic Uses

Non-psychiatric Indications

- **Antiemetic**.....typical (exc. Thioridazine).....D₂ rec. antagonist.....Prochlorperazine
- **Relief of Pruritus**.....phenothiazines.....H₁ rec. antagonist
- **Preoperative sedative**.....promethazine(Phenergan)
- **Neuroleptanesthesia**.....Droperidol + Fentanyl + Nitrous oxide

Anti-psychotic Drugs

Therapeutic Uses

Choice of Drug and Dosage

- Differences in efficacy / adverse effects
- Oral / Parenteral & depot formulations (LAI)
- Titration to an effective dose.....broad TI
- Patient characteristics
- Patient past response.....Switching of drugs
- Cost-effectiveness.....generic forms.....aripiprazole

Drug Combinations

- Antidepressants / BZD / Lithium / Valproic acid / ECT

Adverse effects

**Neurological
effects**

**Metabolic & Endocrine
effects**

**Neurolept malignant
syndrome**

**ANTI
PSYCHOTIC
AGENTS**

Cardiac Toxicity

Behavioural effects

Autonomic nervous system

Adverse Effects

- **Neurological Effects**

- **Extrapyramidal reactions**

- Parkinson's syndrome, akathisia, acute dystonic reactions
 - Antimuscarinics / antihistamines (diphenhydramine)

- **Tardive dyskinesia**

- Abnormal choreoathetoid movements
 - Relative cholinergic deficiency secondary to supersensitivity of DA rec. in caudate-putamen
 - Typical (20 – 40%) / Risperidone & paliperidone
 - Early detection.....reversal
 - **Management**
 - Dose reduction / switching to atypical (quetiapine or clozapine)
 - Withdrawal of drugs with antimuscarinic effect (TCAs, antimuscarinics for PD)
 - Diazepam

- **Seizures**

- Chlorpromazine / clozapine
 - Anticonvulsants

Adverse effects

**Neurological
effects**

**Metabolic & Endocrine
effects**

**Neurolept malignant
syndrome**

**ANTI
PSYCHOTIC
AGENTS**

Cardiac Toxicity

Behavioural effects

Autonomic nervous system

Adverse Effects

- **Neuroleptic Malignant Syndrome**

- Life threatening extrapyramidal syndrome

- **Pathophysiology**

- Extreme sensitivity to DA rec. blockade.....excessive rapid DA rec. blockade

- **Symptoms & Signs**

- Marked muscular rigidity (lead pipe rigidity) / hyperthermia / tachycardia / HTN / Autonomic instability / tachypnea / altered mental status (delirium, confusion)

- **Biochemical**

- Leukocytosis / elevated muscle-type creatine kinase

- **Management**

- Antiparkinsonism drugs, muscle relaxant (BZD / Dantrolene)
- General measures / cooling measures
- Switching to atypical antipsychotics

Adverse effects

**Neurological
effects**

**Metabolic & Endocrine
effects**

**Neurolept malignant
syndrome**

**ANTI
PSYCHOTIC
AGENTS**

Cardiac Toxicity

Behavioural effects

Autonomic nervous system

Adverse Effects

• Behavioral Effects

- Typical.....dosage timings
- Pseudo-depression.....drug-induced akinesia (t/m antiparkinsonism drugs) / high dose
- Confusional state.....antimuscarinic effects

• Autonomic Nervous System Effects

- Urinary retention, constipation etc.....antimuscarinic effect
- Postural hypotension, impaired ejaculation..... α -adrenergic blockade

• Cardiac Toxicity

- Thioridazine.....T wave changesvent. Arrhythmias, torsades de pointes, cardiac conduction block, sudden death.....Combination (antimuscarinics, tricyclic antidepressants).....caution
- Ziprasidone.....QT prolongation.....Combination.....Thioridazine, Pimozide, Antiarrhythmics (1A / 3)
- Clozapine.....myocarditis

Adverse effects

**Neurological
effects**

**Metabolic & Endocrine
effects**

**Neurolept malignant
syndrome**

**ANTI
PSYCHOTIC
AGENTS**

Cardiac Toxicity

Behavioural effects

Autonomic nervous system

Adverse Effects

- **Metabolic and Endocrine Effects**

- Weight gain & Hyperlipidemia.....clozapine / olanzapine..... caution
- Hyperglycemia.....insulin resistance.....DM (clozapine / olanzapine)
- Diabetic ketoacidosis
- Risperidone / paliperidone / aripiprazole (less)..... Ziprasidone (least).....Wt & Lipids
- Risk of atherosclerotic cardiovascular diseases
- Monitoring.....physical / biochemical (BSF, HbA_{1c}, lipid profile)
- **Hyperprolactinemia**
 - Females.....amenorrhea / galactorrhea / infertility / osteoporosis
 - Males.....loss of libido / impotence / infertility
 - Atypical.....Aripiprazole

Adverse Effects

- **Toxic or Allergic Reactions**

- Agranulocytosis.....clozapine (1-2%).....6–18 wks.....monitoring (weekly – 6m/ 3 wks)
- Cholestatic jaundice / skin eruptions

- **Ocular Complications**

- Deposits in cornea & lens.....chlorpromazine
- Deposits in retina.....thioridazine.....browning of vision.....retinitis pigmentosa

- **Dysmorphogenesis**.....teratogenic risk.....neurodevelopment (NT)

- **Overdosage**

- Thioridazine / mesoridazine
- Drowsiness, miosis, agitation, convulsions, hypotension, vent. arrhythmias, hypothermia, coma
- ABCD treatment.....airway, breathing, circulation, definitive t/m

Drug Interactions

- Antimuscarinics / α -adrenergic blockers / antihistaminics

Anti-psychotic Drugs

Typical vs Atypical Antipsychotics

- Chemistry
- Mechanism of Action.....differences in receptor binding / affinity
- Therapeutic Efficacy.....e.g. Atypical.....negative symptoms
- Adverse Effects.....Atypical
 - Less adverse effects: extrapyramidal, anticholinergic, endocrine effects, etc
 - Better tolerated
 - More patients compliance due to less untoward effects
- Cost-effectiveness.....Atypical

Mood-stabilizing Drugs

Bipolar Disorders

- Manic-depressive illness
- Manic phase / Depressive phase / Mixed symptoms / cognitive impairment
- Variable episodes.....mania / depression.....cycling of mood swings
- Risk of suicide

Pathophysiology

- Unknown.....strong familial component.....genetic
- Catecholamine-related activity.....Dopamine / NE / Glutamate

Treatment.....Mood-stabilizing Drugs

- Lithium
- Anticonvulsants.....Carbamazepine / Valproic acid / Lamotrigine / Gabapentin Oxcarbazepine
- Antipsychotics.....Aripiprazole / Chlorpromazine / Olanzapine / Quetiapine / Risperidone / Ziprasidone
- Olanzapine with Fluoxetine

Lithium

- Mood-stabilizing Drug

Pharmacokinetics

- Absorption.....complete
- Target plasma conc.....0.6 – 1.4 mEq/L
- Distribution.....total body water
- PPB & Metabolism.....None
- $t_{1/2}$20 - 24 hrs
- Excretion.....PCT (80% - reabs).....compete Na^+ Li^+ retention by Na^+ loss
(e.g. diuretics)
- Feces / sweat / saliva / tears / breast milk

Lithium

Pharmacodynamics

Mechanism of Action

1. Effect on Electrolytes & Ion Transport
2. Effect on Signal Transduction
3. Effect on Gene Expression & Regulation

1. Effect on Electrolytes & Ion Transport

- Develops small gradient across cell membrane
- Substitute for Na^+
- Not substrate for $\text{Na}^+ - \text{K}^+$ pump / $\text{Na}^+ - \text{Ca}^{++}$ exchanger

2. Effect on Signal Transduction

a. Effect on Receptor-G protein interaction

- Uncoupling of receptors from G protein
- Vasopressin (ADH) receptors / TSH receptors

Lithium

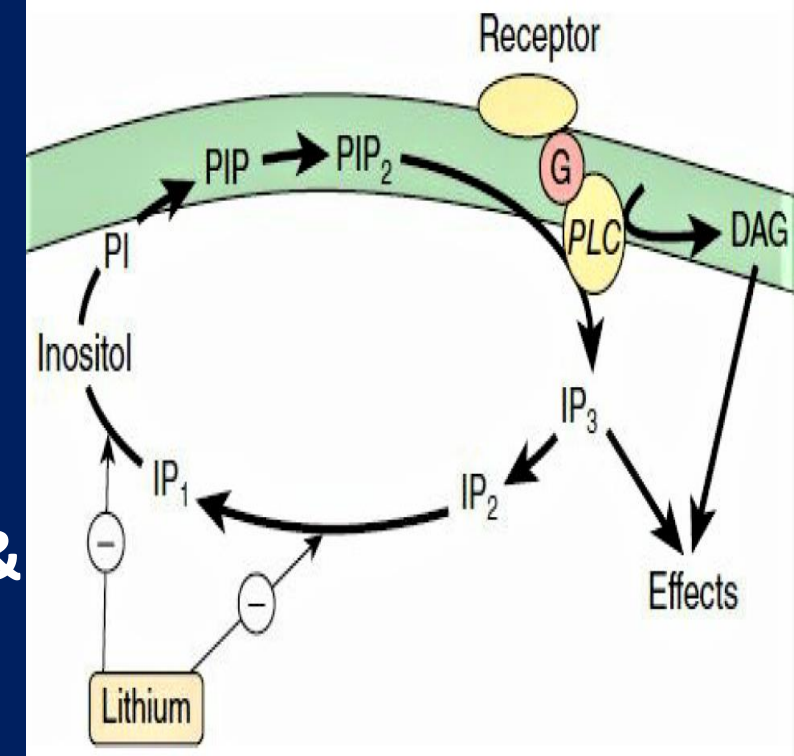
b. Effect on Second Messenger Systems

• Phosphatidylinositol Pathway

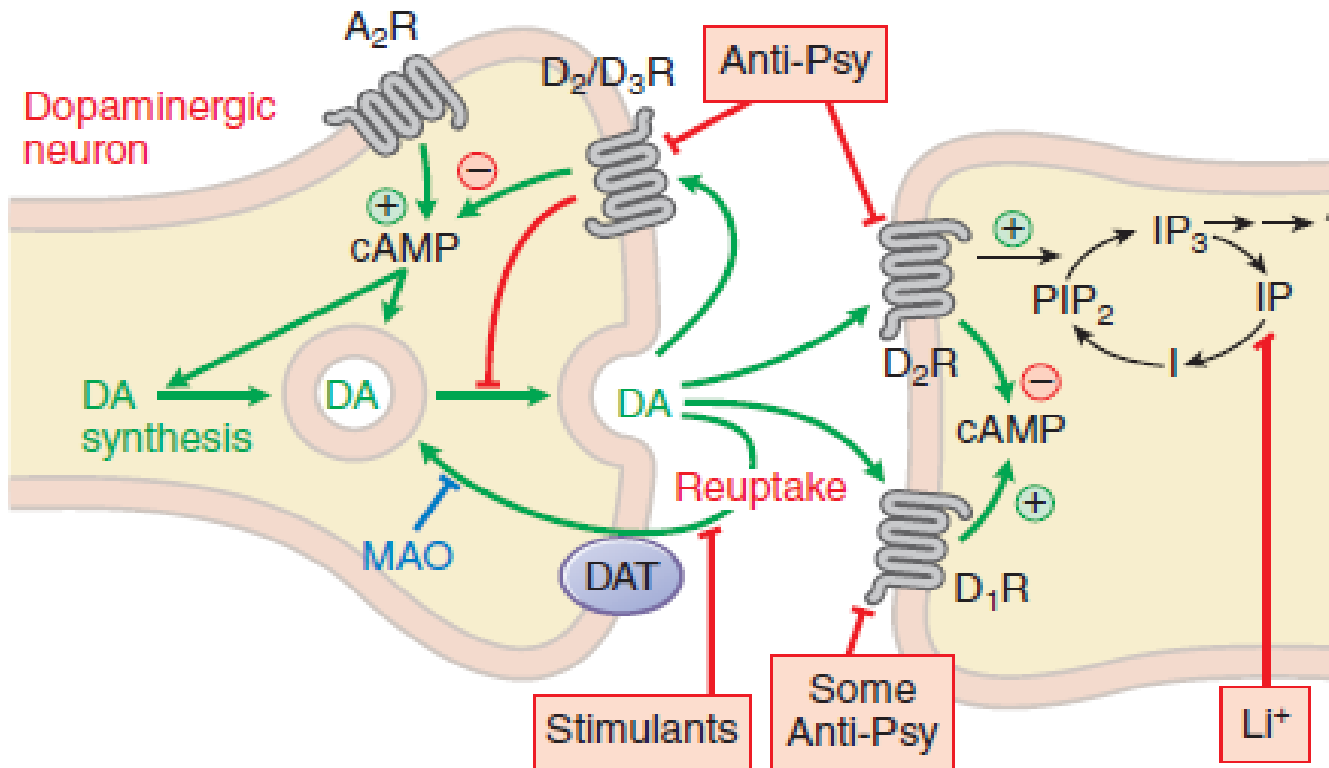
- Phosphatidylinositol (PI).....membrane lipid
- Recycling of membrane phosphoinositides**
- Inhibits **Inositol polyphosphate 1-phosphatase** & **Inositol monophosphatase**
- Decrease cerebral inositol levels
- Mania.....over-activity of the neurotransmitters pathways
- Diminished effects of neurotransmitters involving IP_3 -DAG pathway
 - Valproic acid & Carbamazepine.....Inositol depletion

• Adenylyl Cyclase

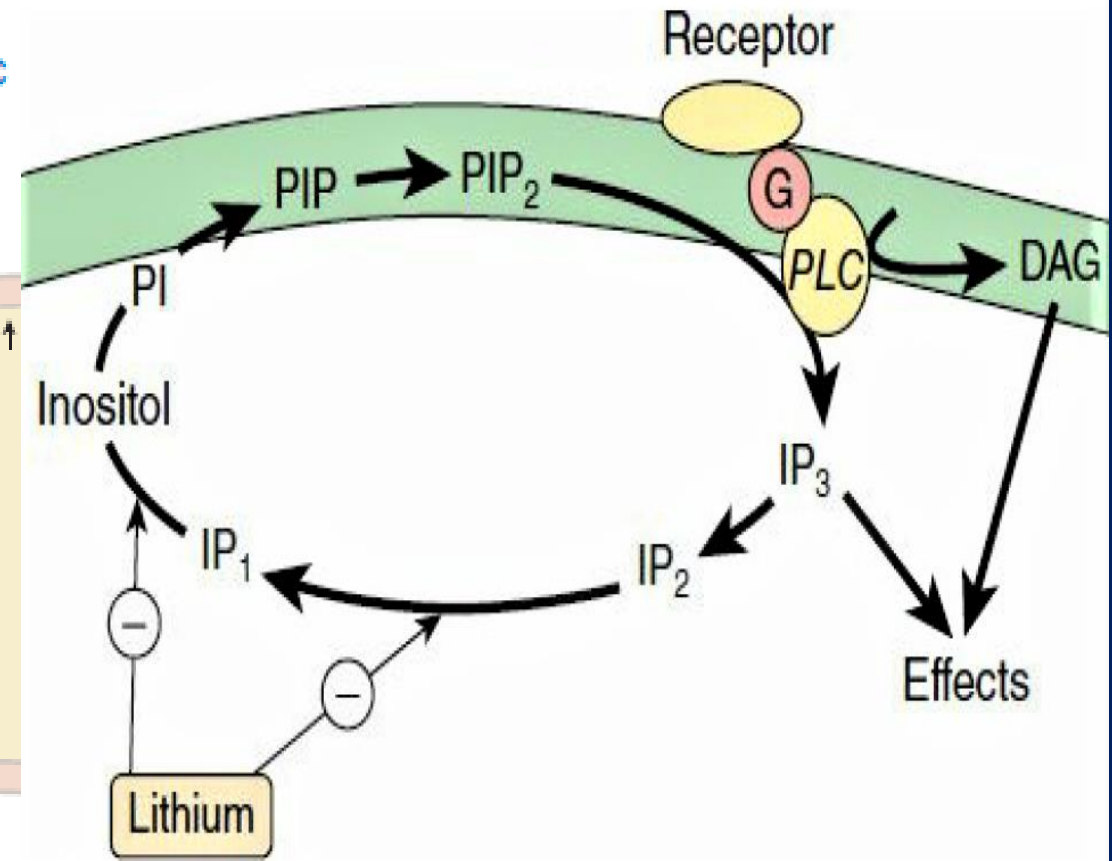
- Inhibit NE sensitive AC



PRESYNAPTIC



POSTSYNAPTIC



Lithium

c. Effect on Protein Kinases

- Decreased functioning of PK (esp. **PKC**) in brain
 - Excessive PKC activation.....behavioral dysfunction
 - Causes alteration in release of NT & hormones
 - Valproic acid

3. Effect on Gene Expression & Regulation

- Inhibit Glycogen synthase kinase-3 (**GSK-3**)
 - GSK-3 phosphorylates β -catenin.....intracellular signaling pathway
 - Increased β -catenin.....transcription factors interactions
- Alteration in gene expression & protein production
- Alteration in Synaptic & Neuronal Plasticity
- Mood Stabilization

Lithium

Therapeutic Uses

- Monitoring
- Maintenance t/m
- Bipolar Affective Disorders
- Recurrent Depression
- Schizoaffective Disorders
- Schizophrenia

Lithium

Therapeutic Uses

- **Monitoring**.....Sample (10 – 12 hrs postdose).....5 days.....desired level
- **Maintenance t/m**.....frequency / severity / pt comp./ residual damage.....0.6– 0.9 mEq/L
- **Bipolar Affective Disorders**
 - Slow onset.....supplemented.....BZD / antipsychotics.....**manic phase**
 - Combination therapy.....maintenance therapy
 - **Depressive phase**.....Antipsychotics / Bupropion / Lamotrigine / SSRIs
 - Lithium.....prevention of both phases
- **Recurrent Depression**
 - With antidepressants (e.g. imipramine)
- **Schizoaffective Disorders**
 - Schizophrenic symptoms with depression or excitement
 - With antidepressants or antipsychotics
- **Schizophrenia**
 - With antipsychotics.....refractory cases

Lithium

Adverse Effects

- Neurological & Psychiatric Effects
- Thyroid Functions
- Renal Effects
- Edema
- Cardiovascular adverse effects
- Use in Pregnancy
- Overdose

Adverse Effects

- **Neurological & Psychiatric Effects**

- Tremors.....Propranolol / Atenolol
- Neurological...Choreoathetosis, motor hyperactivity, ataxia, dysarthria, aphasia
- Psychiatric.....Mental confusion, withdrawal behavior
- Discontinuation / Monitoring

- **Thyroid Functions**

- Hypothyroidism / thyroid enlargement.....monitoring TSH (6 – 12 m)
- Uncoupling of TSH receptor for G protein

- **Renal Effects**

- **Nephrogenic Diabetes Insipidus**

Polydipsia /polyuria/ADH unresponsiveness (G-protein) /responds to Amiloride

- Decreased GFR
- Chronic interstitial nephritis
- Minimal-change glomerulopathy with nephrotic syndrome
- Avoid dehydration (increases Li^+ conc. in urine)
- Monitoring.....periodic RFTs

Adverse Effects

- **Edema**
 - Na⁺ retention
 - Weight gain
- **Cardiac Adverse Effects**
 - Bradycardia-tachycardia (sick sinus) syndrome.....C/I.....SA node suppression
 - T-wave flattening
- **Miscellaneous**
 - Weight gain.....30%
 - Transient acneiform eruptions.....temporary discontinuation
 - Folliculitis
 - Leukocytosis.....Leucopoiesis.....therapeutic application

Adverse Effects

- **Overdosage**

- Therapeutic overdose.....accumulation.....renal status / hydration / diuretics
- > 2 mEq/L.....caution
- Small ion.....dialyzed easily

- **Use in Pregnancy**

- Increased Li^+ renal clearance during pregnancy.....reversal after delivery
- Breast milk.....Lethargy, poor suck & moro reflexes, cyanosis, hepatomegaly
- Dysmorphogenesis.....cardiac (Ebstein's anomaly)

Drug Interactions

- Diuretics (thiazides).....decrease Li^+ clearance (25%).....dose adjustment
- NSAIDs (except aspirin / acetaminophen).....decrease Li^+ clearance
- Neuroleptics.....more severe EPS on combining with Li^+