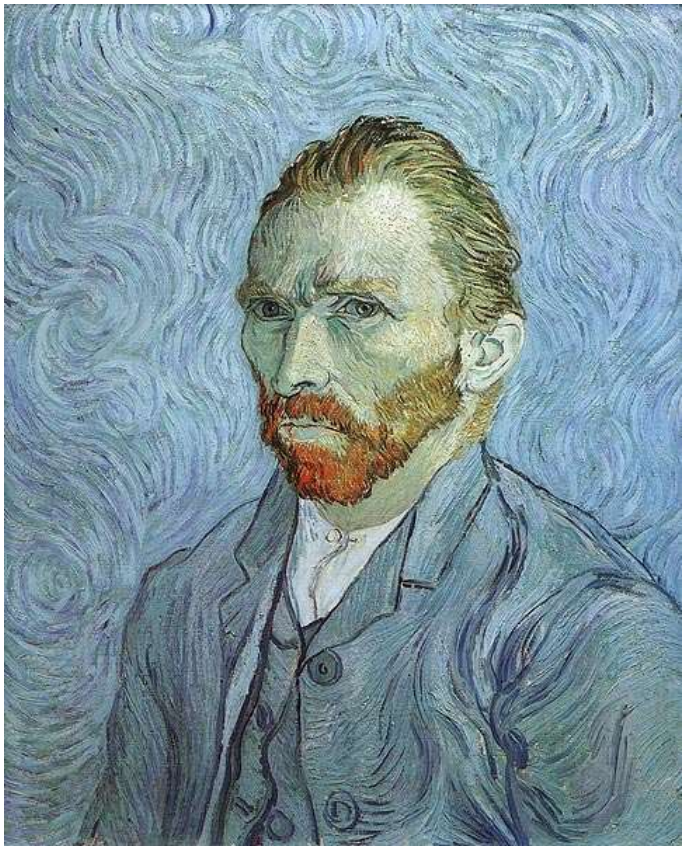
ANTIDEPRESSANT AND ANTIMANIC AGENTS



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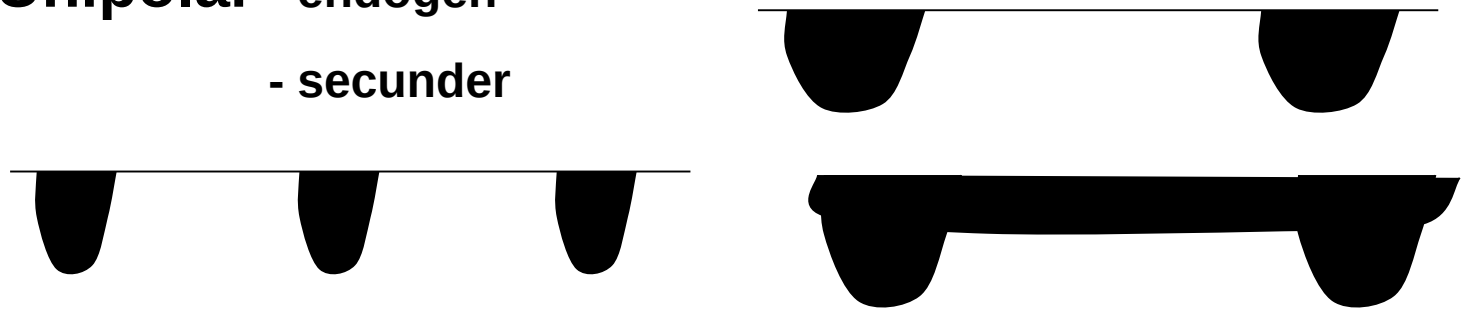
- **The most common psychiatric disorder**
- **5-6% of the population is affected**

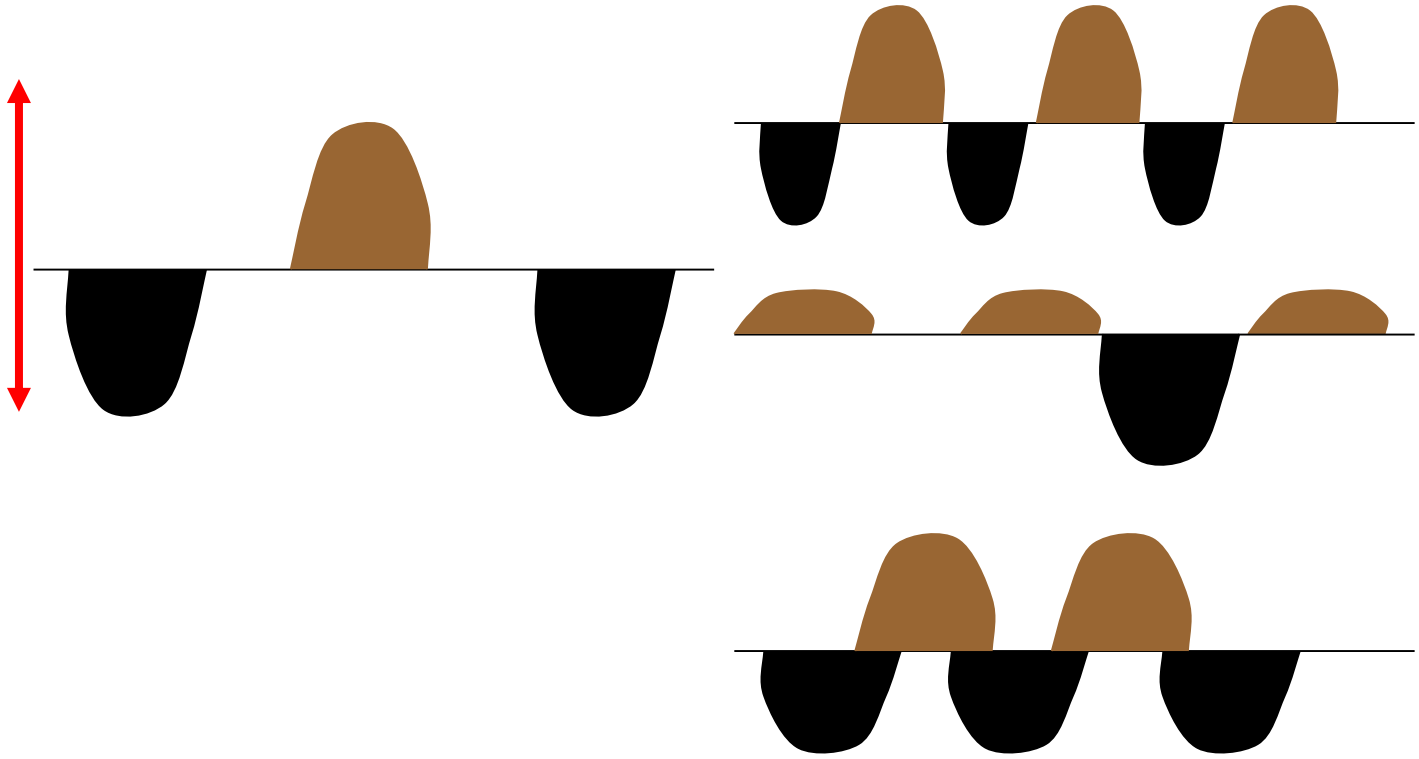
1). Unipolar - endogen

- secunder



2). Bipolar

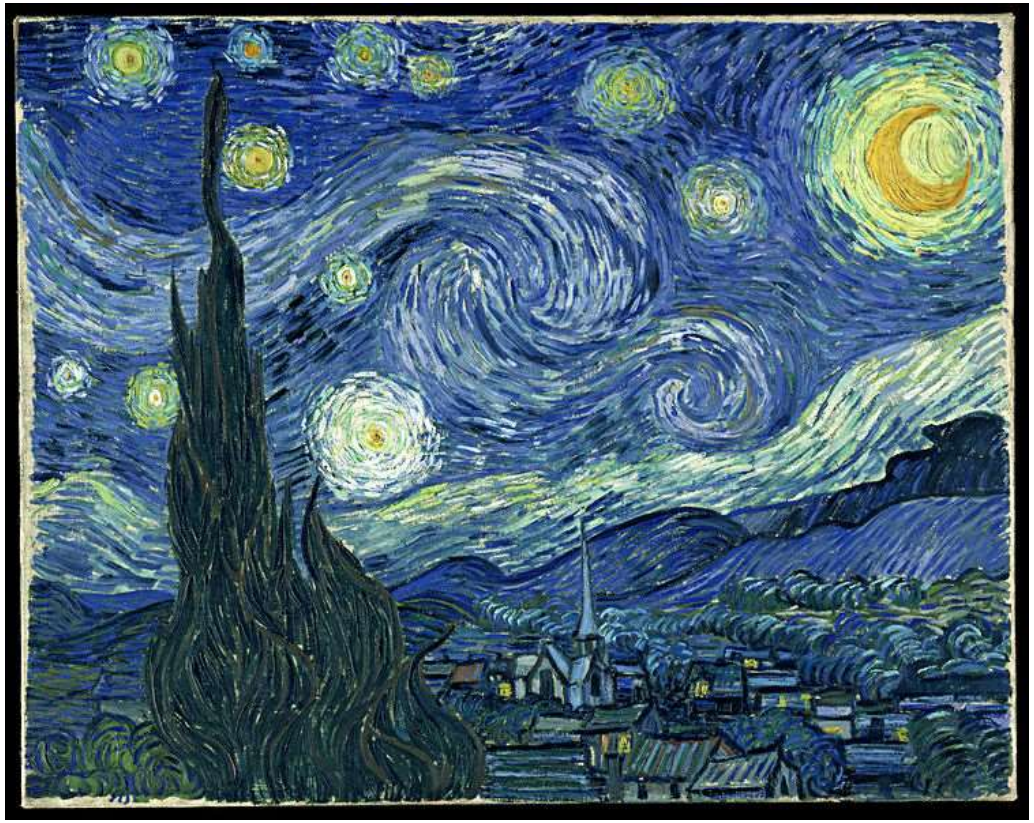
Mania
Hypomania
Euthymia
Dysthymia
Depression



Symptoms of depression

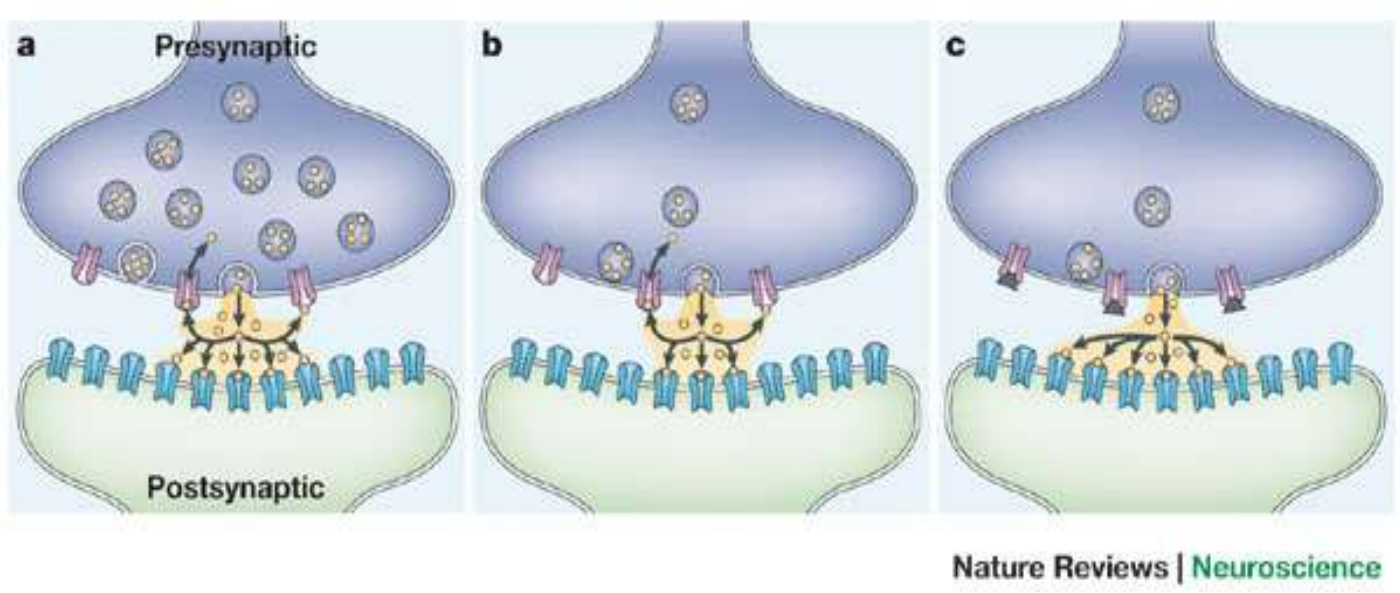
- marked lack of feeling joy
- pessimism
- feeling of worthlessness or exaggerated consciousness of guilt
- decrease of ability to concentrate
- decision making problems
- insomnia or sleepiness, fatigue
- returning thoughts in relation to death and suicide
- loss of apetite

Symptoms of mania



- hyperactivity
- increased self confidence
- excitement, impulsivity
- aggression, diminished need for sleep
- increased communicative competence
- grandiose ideas/plans

Pathophysiology



Schildkraut: - depression-deficiency of monoamin transmission (mania - overactivated)

- ***RESERPIN* – blocks the uptake of biogenic amines into the storage vesicles (depression developed in 50% of the patients)**

Pathophysiology

PRO

effective drugs

- **MAO-inhibitors**

→ increased monoamines (MAs) in storage vesicles

- **TCA- inhibit the reuptake of MA → increased MAs in the synaptic cleft**

- **α_2 – antagonists → increase the release of MAs**

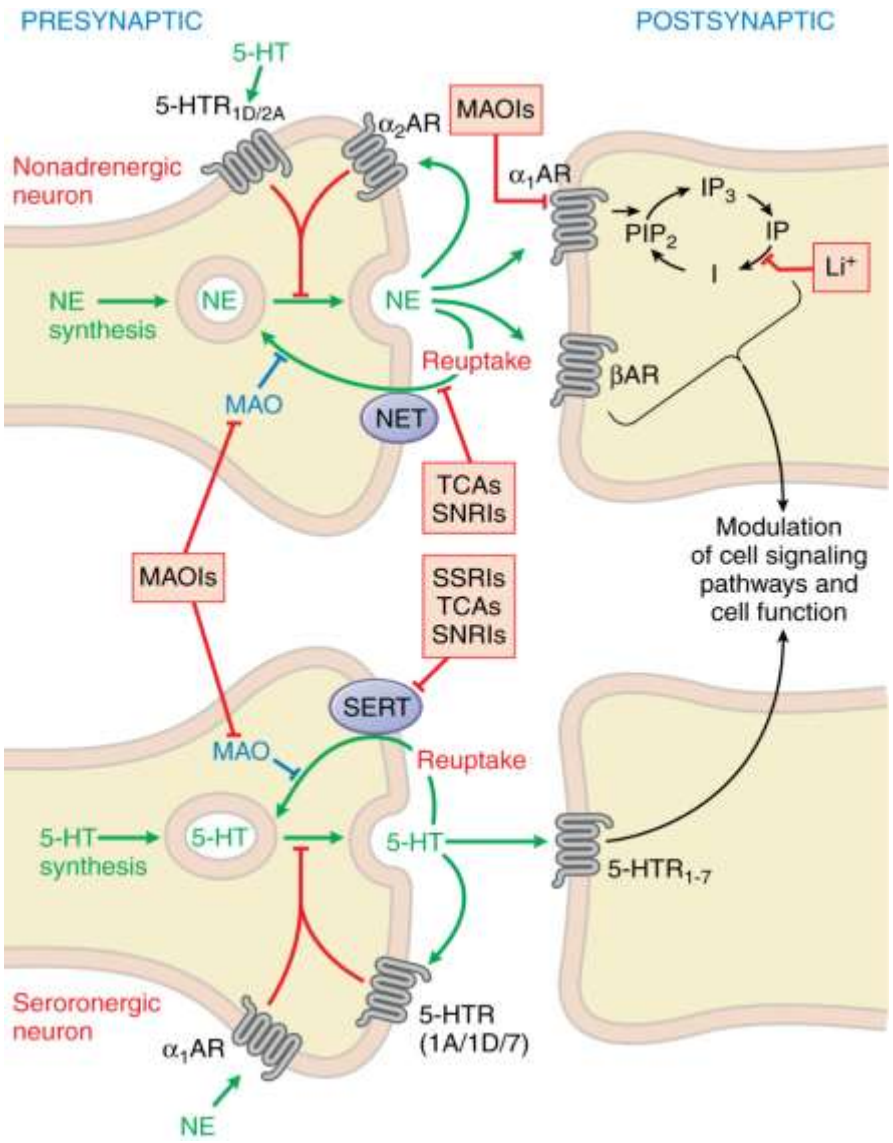
CONTRA

- **pharmacologic effect develops immediately**

- **relief of symptoms takes min. 2-3 weeks**

ADAPTIVE CHANGES

desensitization and decreased number of α_2, β and 5-HT_2 receptors



The Pharmacological Basis of Therapeutics. Goodman & Gilman's. 12th Edition

Adaptive receptorial sensitivity changes

(2-3 weeks)

Chronic antidepressant treatment

↓

5-HT_{1A}, 5-HT_{7}, 5-HT_{1D} ,

5-HT_{2A} , α_2 ↓


Van Gogh
-Will Fan-

Classification:

1. NET-I / SERT-I /receptor antagonists

1.1. NET-I /SERT-I
- **1.1.1. tricyclics (TCA) – imipramine, amitriptylline, etc. (NET/SERT-I)**
- **1.1.2. tetracyclics: maprotiline, amoxapine (NET-I)**

1.2. SSRI – fluoxetine, paroxetine, fluvoxamine, citalopram, sertraline

1.3. (s)SNRI – venlafaxine, desvenlafaxine, duloxetine

1.4. (s)NRI – reboxetine, atomoxetine

1.5. NDAI – bupropion

2.1. SERT-I & 5HT-R antag.
- **2.1.1. trazodone – 5HT reuptake inhibitor, $5HT_{2A}$ antagonist**
- **2.1.2. vilazodone – 5HT reuptake inhibitor, $5HT_{1A}$ partial agonist**

2.2. Receptor antag. & NET-I – mirtazapine (α_2 & $5HT_{2A/C}$ & $5HT_3$ & H_1 antag.)

3. MAOI

4. Tianeptine (AMPA receptor modulator)

5. $5HT_{2C}$ antag. & $MT_{1/2}$ agon. – agomelatine

1.1. REUPTAKE INHIBITORS

1.1.1. Tricyclic antidepressants (TCA)

inhibit the reuptake of NE and 5-HT

imipramine, amitriptyline, clomipramine

1.1.2. Tetracyclic antidepressants

inhibits mainly the NE reuptake

maprotiline

Adverse effects

H_1 antagonism - sedation, dizziness, confusion
- weight gain

α_1 blockade - dizziness, orthostatic hypotension, reflex tachycardia,

Anticholinergic - dry mouth, constipation, urinary retention, blurred vision

- confusion, impaired cognitive functions

***Ventricular arrhythmias*: blockade of HERG type K^+ channels in the heart**

Pharmacokinetics

Long elimination half life, $t_{1/2}$=25-35 óra

Interactions

- Potentiate the effect of alcohol – respiratory depression

- Together with MAO inhibitors → **Serotonin Syndrome** (hyperpyrexia, seizures, coma)

Indications

- **depression**
- **panic disorders - IMIPRAMINE, CLOMIPRAMINE**
- **Nocturnal enuresis (nighttime urinary incontinance)**
- **neuropathic pain: AMITRIPTYLINE, CLOMIPRAMINE**
- **migraine profilaxis: AMITRIPTYLINE**

1.1. REUPTAKE INHIBITORS

1.2. *SSRI* *(selective serotonine reuptake inhibitors)*

selective inhibition of 5-HT reuptake

fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram

Adverse effects

Lack of TCA like adverse effects!

5-HT_2 receptor stimulation

anxiety (begin of the treatment), insomnia, loss of libido, delayed orgasm

5-HT_3 receptor stimulation

nausea, vomit, GI problems, diarrhea, headache

SEROTONIN SYNDROME

- **SSRI + MAO- inhibitors → increased 5-HT level**
- **Symptoms: muscle rigidity, cramps, hyperthermia, hypertension**
- **Attention! – when we switch the drug *FLUOXETIN* – elimination requires 4-6 weeks**

Pharmacokinetcs

- ***FLUOXETIN*** **long duration of action (active metabolite: NORFLUOXETINE, $t_{1/2}$=7-9 days)**

- ***PAROXETINE, SERTRALINE*****, shorter duration of action ($t_{1/2}$=25-35 hours)**

INDICATIONS

- **Depression (1st choice drugs)**
- **Anxiety disorders, OCD**
- **Eating disorders: bulimia nervosa, but not anorexia**
- **premenstrual dysphoric disorder**

ATYPICAL OR NEWER REUPTAKE INHIBITORS

1.3. SNRI (selective 5-HT and NE reuptake inhibitors)

venlafaxine **– common use**

- 2× day, $t_{1/2}$=5-11 h

duloxetine

1.4. NRI (selective NE reuptake inhibitor)

reboxetine

ATYPICAL OR NEWER REUPTAKE INHIBITORS

1.5. DA and NE reuptake inhibitor

***bupropion* – contraindicated in epilepsy (might cause seizures)**

ATYPICAL OR NEWER REUPTAKE INHIBITORS

2.1.1. 5-HT reuptake inhibitor and 5-HT$_{2A}$ receptor antagonist: *trazodone*

2.1.2. 5-HT reuptake inhibitors and 5-HT$_{1A}$ receptor partial agonist: *vilazodone*

2.2. α_2 and 5-HT$_{2,(3)}$ antagonist *mirtazapine*

5-HT$_2$ inhibition: anxiolytic, sedative effect, better sleeping, does not modulate libido

5-HT$_3$ inhibition: antiemetic effect

4. Tianeptin

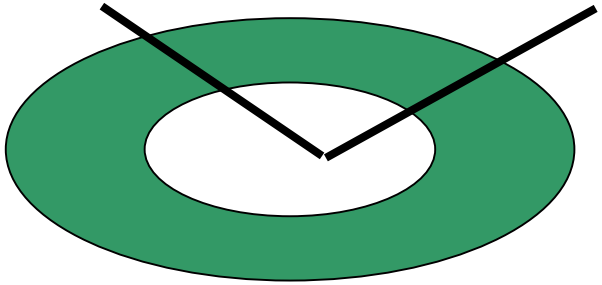
- not fully known mechanism of action, it might modulate AMPA receptors, has significant *anxiolytic* effect

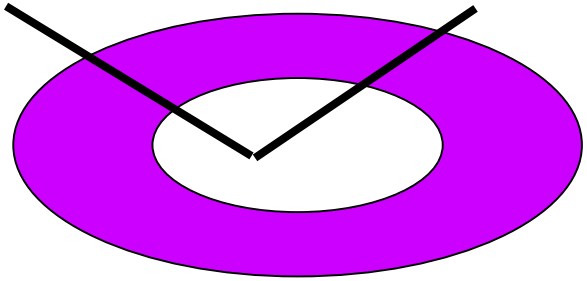
- Indication: to treat depression and anxiety during alcohol withdrawal syndrome

3. MONOAMINO-OXIDASE INHIBITORS

norepinephrine **dopamine**

serotonin **tiramine** **fenilethylamine**





MAO-A ***MAO-B***

GI- tract
nerve endings

platelets
glial cells

CLORGYLIN

SELEGILIN

MOCLOBEMID

3. MONOAMINO-OXIDASE INHIBITORS

non- selective irreversible MAO inhibitors

depression (very severe cases)

phenelzine

selective reversible MAO-A inhibitors (RIMA)

depression

moclobemid

selective irreversible MAO-B inhibitors

Parkinson disease

selegiline

Adverse effects

- **„cheese reaction" – dietary restrictions (primarily in case of irreversible MAOIs)**
- **insomnia, agitation**
- **sexual disturbances**

- **INTERACTIONS:**

  1) increase the effect of sympathomimetics;

  ***2) Serotonin Syndrome* given together with TCA or SSRI;**

  3) with Pethidin-respiratory depression, seizures

- **INDICATIONS: depression, social phobias**

- **THERAPY: *MOCLOBEMID*, 2-3×/day, start with small dose and gradual increase**

THERAPEUTICAL GIUDELINE

- **SSRI, 1st choice**
- **Monotherapy, if it is possible (cumulating adverse effects)**
- **Therapeutical effect: min. 2-4 weeks**

MOOD STABILIZING, ANTIMANIAC DRUGS

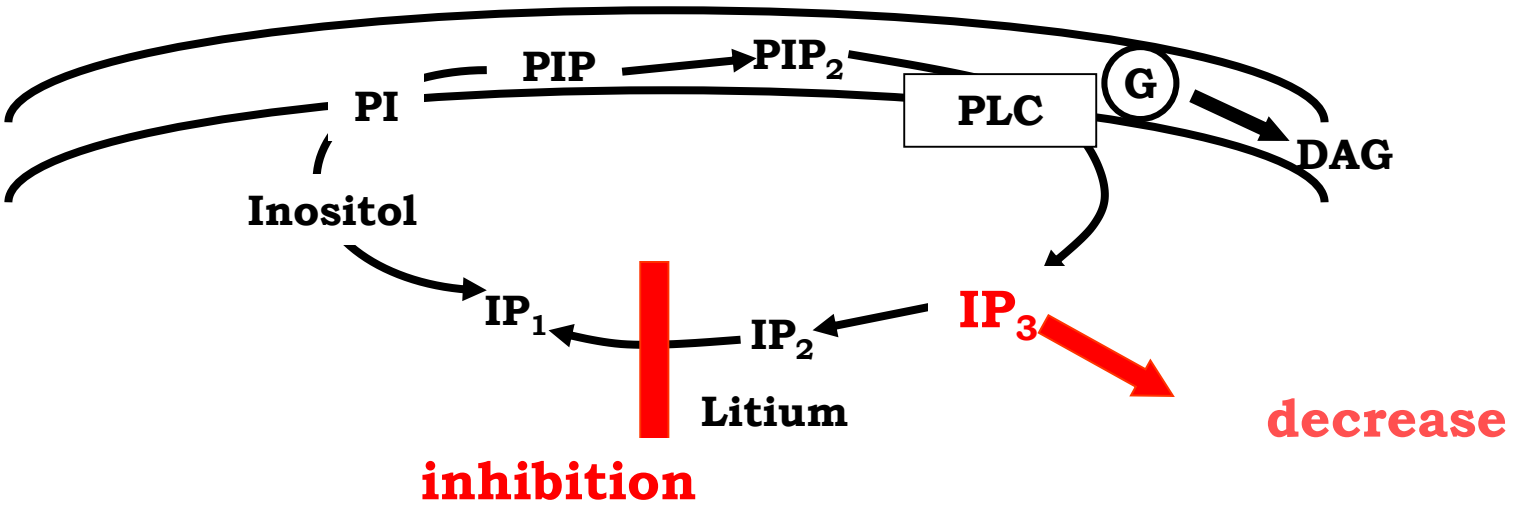
- **Lithium**: mood stabilizer, prevents the maniac phase

- **Carbamazepine, Valproate, Lamotrigine** (antiepileptics)

- Antipsychotics (Quetiapine, Olanzapine, Aripiprazole)

- BZD, high potency drugs, ex. **Clonazepam**

Lithium carbonate



Other possible mechanism of actions:

- **Influence on the Na^+ permeability**
- **inhibition of adenylate cyclase**
- **uncouple G proteins from their receptors**

PHARMACOKINETICS

- **excellent absorbtion from the gastrointestinal tract**
- **excreted unchanged by the urine**
- **half life is about 24 hours**

Serum level	**profilactic**	**0,6-1 mmol/l**
	acute maniac phase	**1,0-1,2 mmol/l**
	toxic level	**1,5-1,7 mmol/l**

Adverse effects

- **Tremor, sedation, nausea, vomit**
- **Hypothyreosis**
- **Polyuria, polydipsia - nephrogenic diabetes insipidus**
- **Terratogenic**
- **hyperactivity, seizures, coma (toxicity)**

INDICATIONS

- ***Bipolar affective disorder***

  In severe maniac phase: Li is given together with an antipsychotic. After mania is controlled, the antipsychotic drug can be discontinued.

  Li is administrated profilactically during the depressive phase of the bipolar disorder as well.

- ***Recurrent endogenous depression***

  Li potentiates the effect of antidepressants