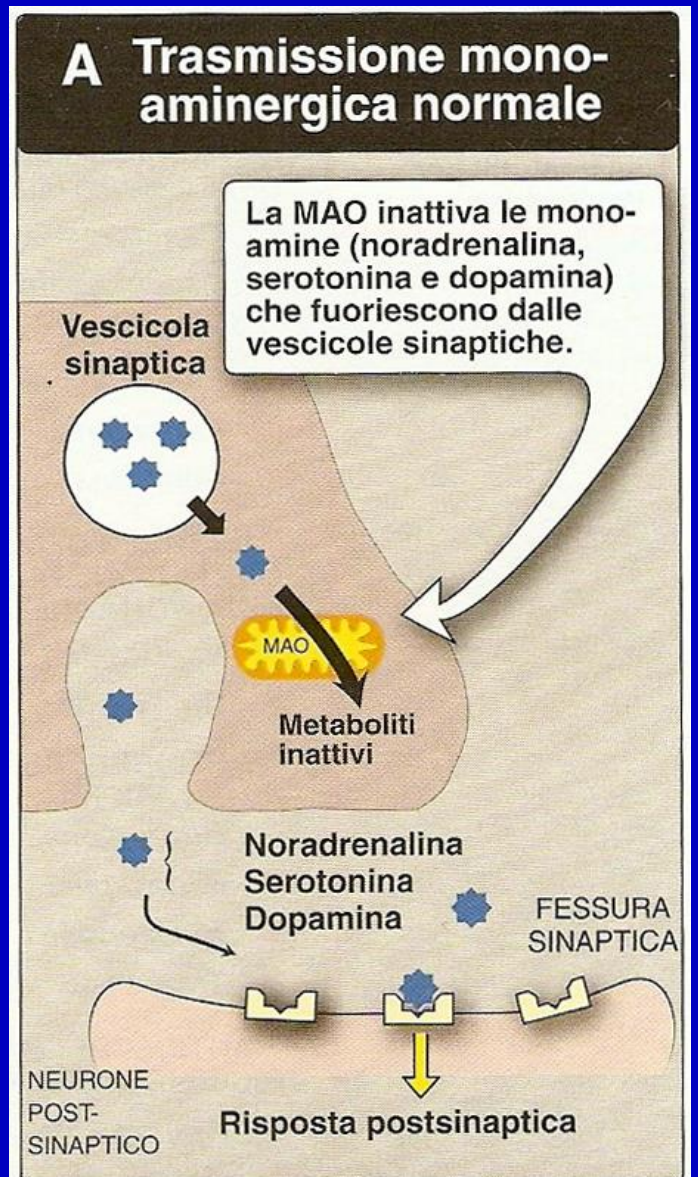
MAO inhibitors

Phenelzine
Tranylcypromine
Moclobemide

Mechanism of action of MAO inhibitors



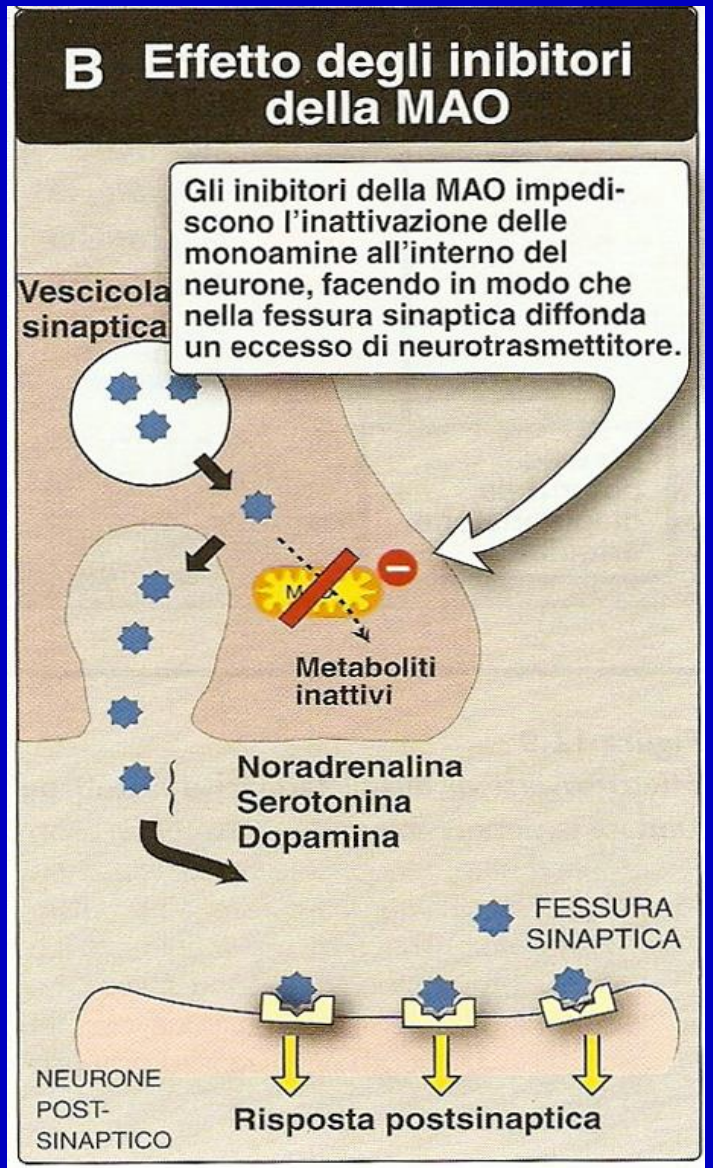


Table 47.4 Substrates and inhibitors for type A and type B monoamine oxidase

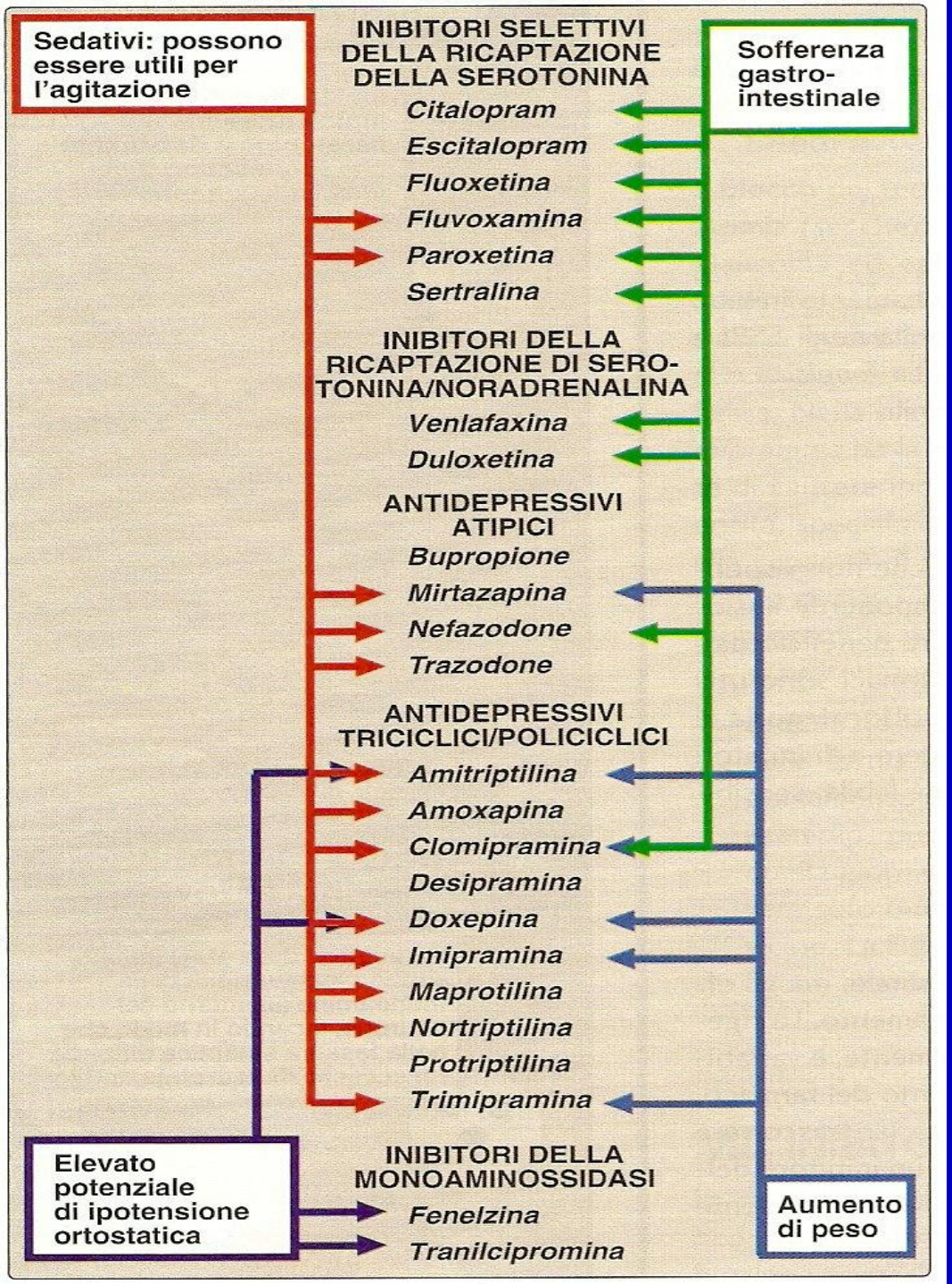
	Type A	Type B
Preferred substrates	Noradrenaline 5-Hydroxytryptamine	Dopamine Phenylethylamine Benzylamine
Non-specific substrates	Tyramine	Tyramine
Specific inhibitors	Clorgyline Moclobemide	Selegiline
Non-specific inhibitors	Pargyline Tranylcypromine Isocarboxazid	Pargyline Tranylcypromine Isocarboxazid

Monoamine oxidase inhibitors (MAOI)

- Main examples are phenelzine, tranylcypromine, isocarboxazid and moclobemide.
- For many years superseded by tricyclic antidepressants (TCA), mainly because of drug and food interactions; currently undergoing a revival.
- Action is long lasting (weeks) because of irreversible inhibition of MAO. Moclobemide has a short duration of action. Reversible binding
- Main side-effects: postural hypotension (sympathetic block); atropine-like effects (as with TCA); weight gain; CNS stimulation, causing restlessness, insomnia; liver damage (rare).
- Acute overdose causes CNS stimulation, sometimes convulsions.
- May cause severe hypertensive response to tyramine-containing foods ('cheese reaction'); this does not occur with moclobemide.
- MAOI should not be given simultaneously with TCA or 5-HT reuptake inhibitors (SSRI).
- Interact with many drugs (e.g. pethidine, causing hyperpyrexia and hypotension.)

Major interactions with other drugs

Antidepressivo	Interazioni pericolose	Interazioni di modesta rilevanza
IMAO	amfetamine, TCA, atomoxetina, β_2-agonisti, brimonidina, bupropione, buspirone, carbamazepina, ciproeptadina, cocaina, destrometorfano, dopamina e dopaminomimetici, droperidolo, efedrina, entacapone, fenfluramina, iperico, levodopa, litio, mazindol, meperidina, metildopa, metilfenidato, morfina, nefazodone, nefopam, sibutramina, SSRI, tolcapone, tramadolo, triptani	antidiabetici, barbiturici
TCA	analgesici oppiacei,anestetici generali alogenati, antiaritmici di classe I e III, SSRI, antiipertensivi, antimicotici imidazolici, antipsicotici, antivirali, chinolonici, antibiotici macrolidici, cotrimossazolo, IMAO, linezolid, octreotide, primidone, rifampicina, simpaticomimetici, triptani, alcool	clonidina, alfametildopa, ansiolitici, ipnotici, β_2-agonisti, anticoagulanti orali, antiepilettici, antimuscarinici, primidone, β-bloccanti, calcio-antagonisti, cannabinoidi, carbamazepina, cimetidina, iperico, miorilassanti, nitroderivati
SSRI	analgesici oppiacei, desfenfluramina, destrometorfano, droperidolo, IMAO, iperico, sibutramina, tramadolo, trazodone, triptofano, triptani	alcool, anestetici, antiaritmici, anticoagulanti orali, antiepilettici, antipsicotici (escluso il droperidolo), anti-H2, barbiturici, β-bloccanti, bupropione, buspirone, cannabinoidi, ciproeptadina, clozapina, litio, teofillina, TCA



Side effects of antidepressants

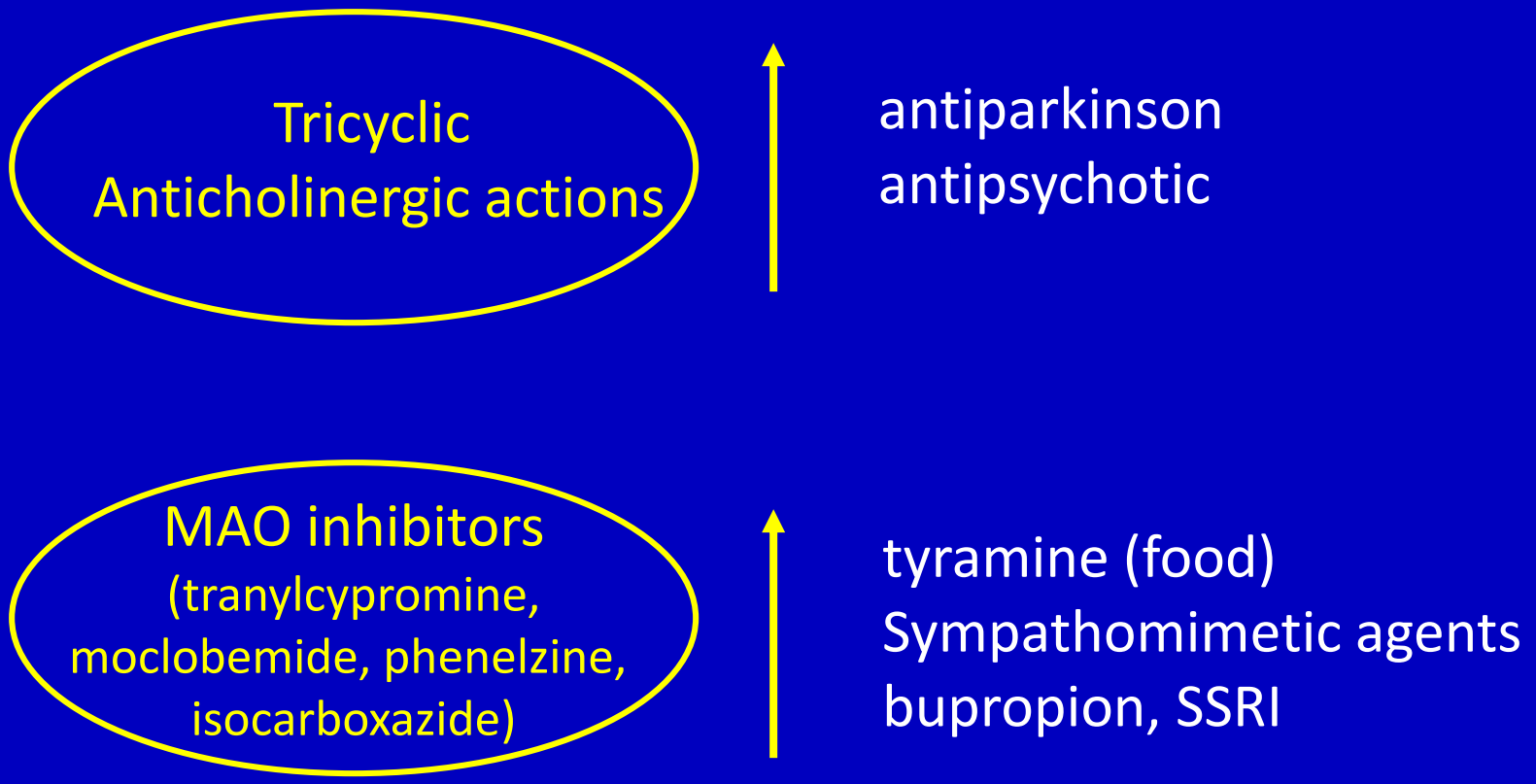
	SSRIs (Selective serotonin reuptake inhibitors)	TCAs (Tricyclic antidepre-ssants)	MAOIs (Monomine oxidase inhibitors)
Onset of action	slow	slow	slow
Initial exacerbation of anxiety	+/-	+/-	-
Therapeutic tolerance	-	-	-
Withdrawal	+	+	+
Abuse potential	-	-	-
Interactions with ethanol	+	+	++
Dietary restrictions	-	-	+++
Sedation	-	++	-
Overdose risks	-	++	++

MAO-Is and SSRI

SEROTONIN SYNDROME

- **At least three of the following symptoms must be present following dose increase of a compound acting by elevating serotonergic function or following its association with other drugs:**
  - **Agitation**
  - **Behavioural abnormatilites (confusion, hypomania)**
  - **Hypertension, tachycardia**
  - **Myoclonus**
  - **Hyperreflexia**
  - **Excessive sweating**
  - **Shivering**
  - **Tremors**
  - **Diarrhea**
  - **Lack of coordination**
  - **Fever**

Interaction between MAO-Is, tricyclic and other drugs



Citocrome P450 (CYP)

fluvoxamine	↓	CYP1A2	↑ β antagonist, caffeine, specific antipsychotic, tricyclic antidepressant
fluoxetine fluvoxamine	↓	CYP2C9	↑ carbamazepine
fluvoxamine	↓	CYP2C19	↑ barbiturate, imipramine, propranolol, phenitoine
paroxetine fluoxetine sertraline	↓	CYP2D6	↑ β antagonist, specific antipsychotic, tricyclic antidepressant
fluvoxamine nefazodone	↓	CYP3A3/4	↑ benzodiazepine, carbamazepine, antidepressant, antibiotic

Increase or reduction of antidepressant effects:

✓ **Plasma proteins**

- The binding between TCA and plasma proteins is decreased due to competition with: fenitoina, fenilbutazone, aspirina, aminopirina, scopolamina, fenotiazine

✓ Microsomal **Enzymes CYP**

- Barbiturates, antiepileptics (carbamazepina), smoking, induce CYP enzymes
- SSRI competes with the metabolism of TCA and inhibits CYP (higher plasma concentration of TCA)
- Slow and ultra-rapid metabolizer (prodrugs)

Interaction between antidepressants and alcohol

Acute Alcohol

Antidepressants enhance sedative action of alcohol

Increased duration of action of antidepressants

Chronic Alcohol

Increased elimination of antidepressants

Hypericum perforatum, St John's wort

Hyperforin

Mechanisms of action

Inhibition of MAO, inhibition reuptake 5HT, NA, DA, GABA, Glu

Collateral mechanisms

Substrate glycoprotein P and induces activity (intestine, kidney, liver, testicles, brain, blood)

Induction of CYP3A4 e CPY1A2

Interactions

ciclosporina

digossina

teofillina

indinavir

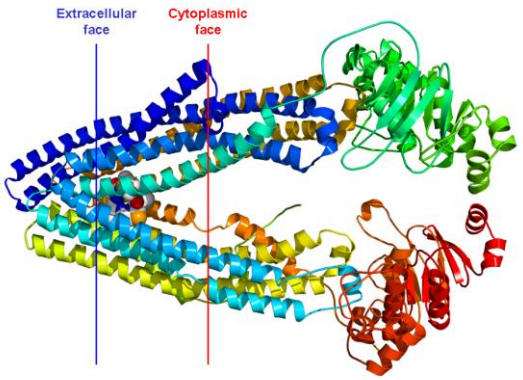
warfarina

amitriptilina

contraccettivi

paroxetina

Glycoprotein P (PGP)



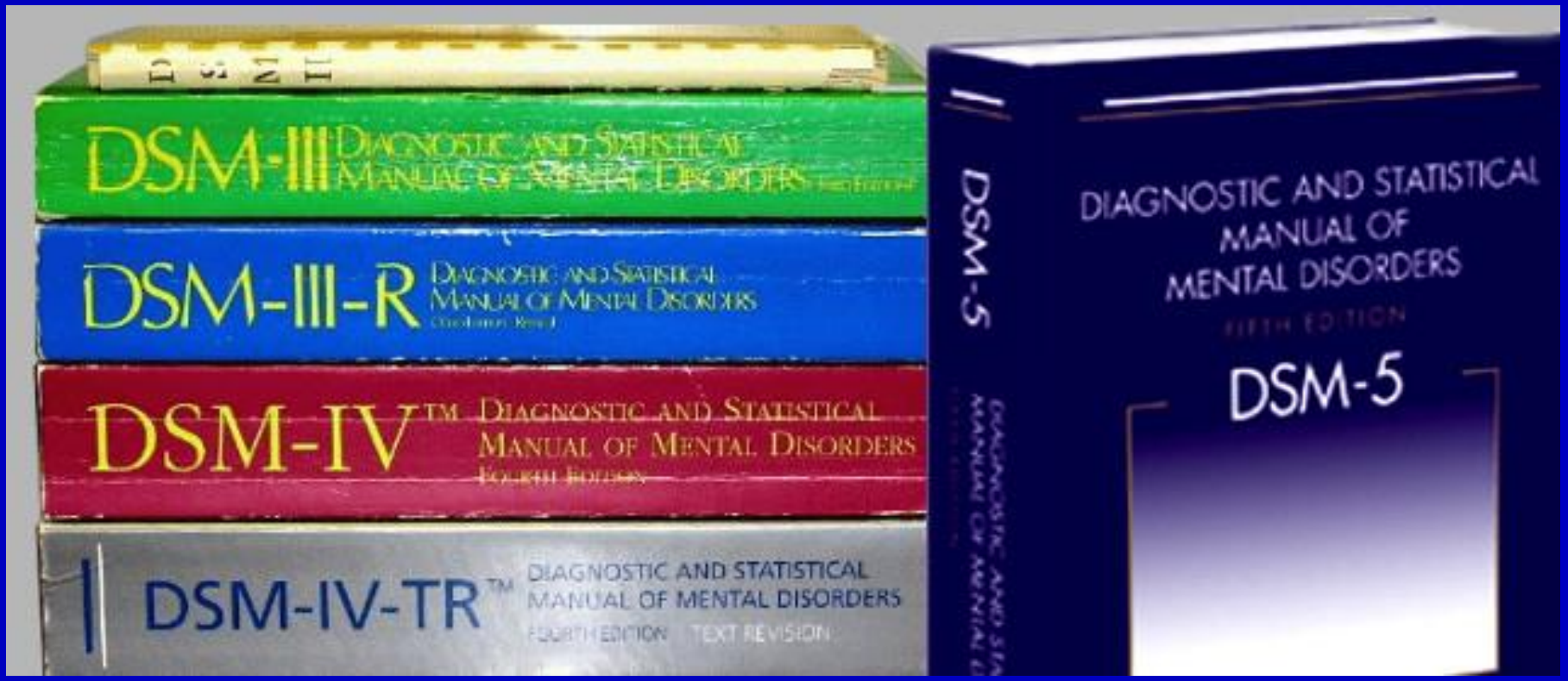
- **Limitation of drug absorption:** transfer of the drug from the enterocytes to the intestinal lumen and elimination of the drug with the faeces

- **Active drug elimination:** a) drug transfer from proximal tubule cells to the tubular lumen and drug elimination in urine; b) drug transfer from hepatocytes to bile

- **Limitation of drug distribution to tissues:** a) drug transfer from the endothelial tissue of the testis and brain to the blood capillaries; b) drug transfer from fetal tissue or capillaries to the syncytium trophloblast on the maternal side of the placenta and from there to the maternal blood; c) drug transfer from lymphocytes (eg CD4 +) to the blood

Bipolar disorder

-Maniac episodes followed by depression (1% of population)
- Significant genetic component (10-15%)
- Young, adult and older people can be affected


DSM-III
DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS
DSM-III-R
DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS
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Bipolar I Disorder

Diagnostic Criteria

For a diagnosis of bipolar I disorder, it is necessary to meet the following criteria for a manic episode. The manic episode may have been preceded by and may be followed by hypomanic or major depressive episodes.

Manic Episode

A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased goal-directed activity or energy, lasting at least 1 week and present most of the day, nearly every day (or any duration if hospitalization is necessary).

B. During the period of mood disturbance and increased energy or activity, three (or more) of the following symptoms (four if the mood is only irritable) are present to a significant degree and represent a noticeable change from usual behavior:

1. Inflated self-esteem or grandiosity.
2. Decreased need for sleep (e.g., feels rested after only 3 hours of sleep).
3. More talkative than usual or pressure to keep talking.
4. Flight of ideas or subjective experience that thoughts are racing.
5. Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed.
6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation (i.e., purposeless non-goal-directed activity).
7. Excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).

C. The mood disturbance is sufficiently severe to cause marked impairment in social or occupational functioning or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.

D. The episode is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication, other treatment) or to another medical condition.

Note: A full manic episode that emerges during antidepressant treatment (e.g., medication, electroconvulsive therapy) but persists at a fully syndromal level beyond the physiological effect of that treatment is sufficient evidence for a manic episode and, therefore, a bipolar I diagnosis.

Lithium mechanisms of actions

(Chronic treatment)

Therapeutic doses:
0,5-1 mmol/L
1,5 mmol/L (toxic)

Simil – Na+
No pump Na+/K+

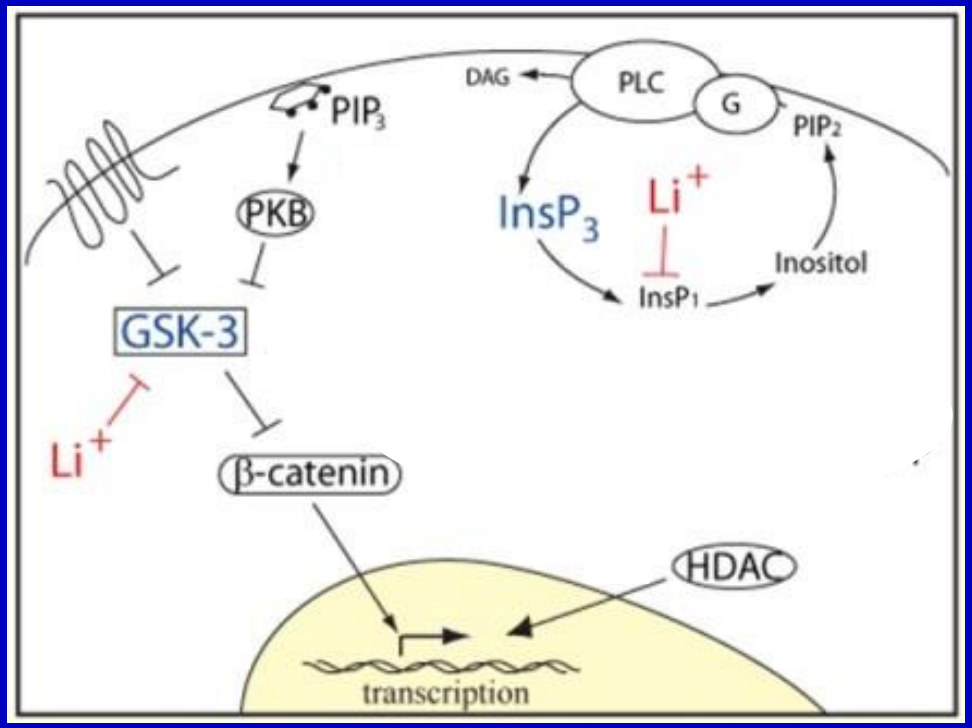
Inhibition hydrolysis of IP

Inhibition kinases
Glycogen synthase

Inhibition cAMP
PKC

Mechanism of action of Li^+

Glycogen Synthase Kinase (GSK3)



- pro-apoptotic factors (p-53, Bax)

+ anti-apoptotic factors (Bcl-2)

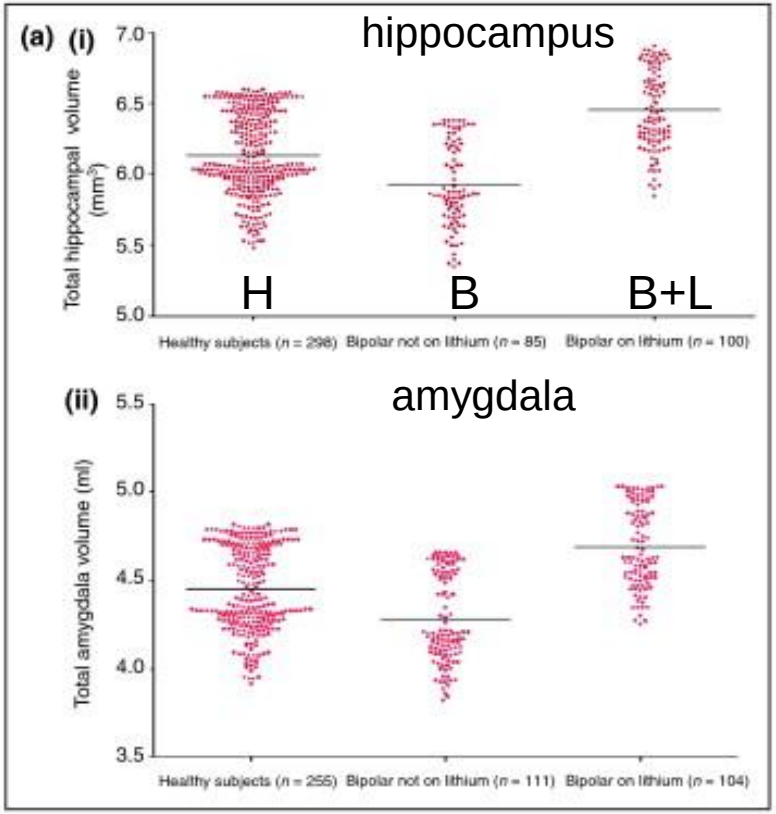
⬇ PKC activity, phospholipase A2

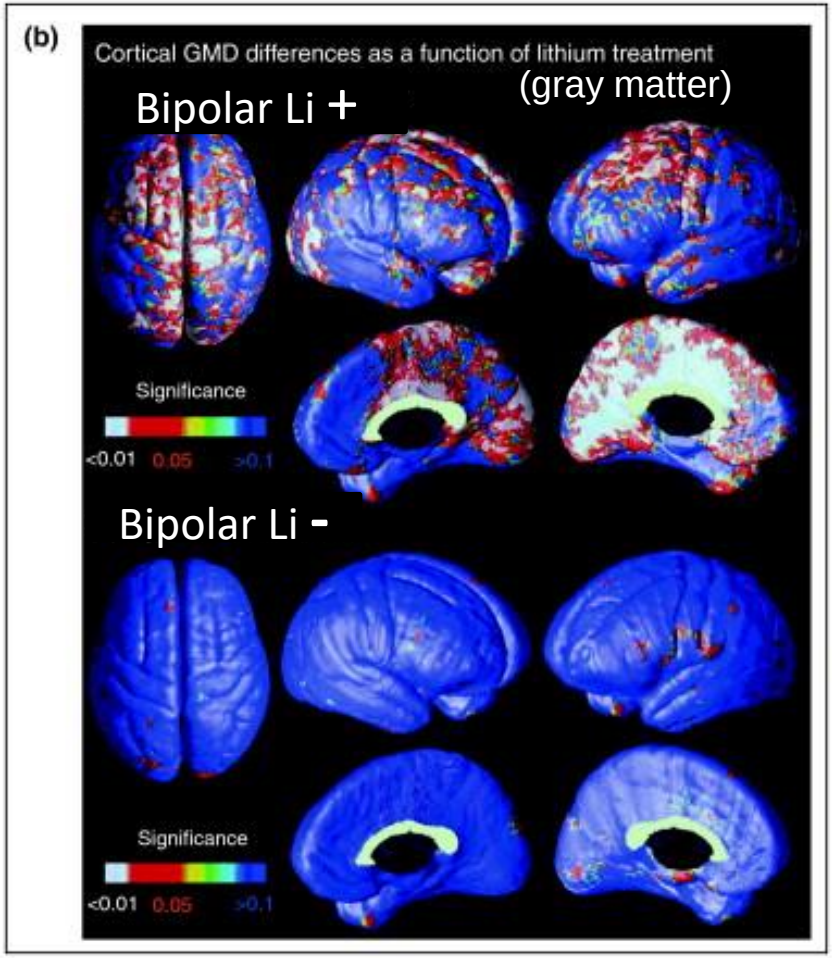
Pharmacokinetic parameters

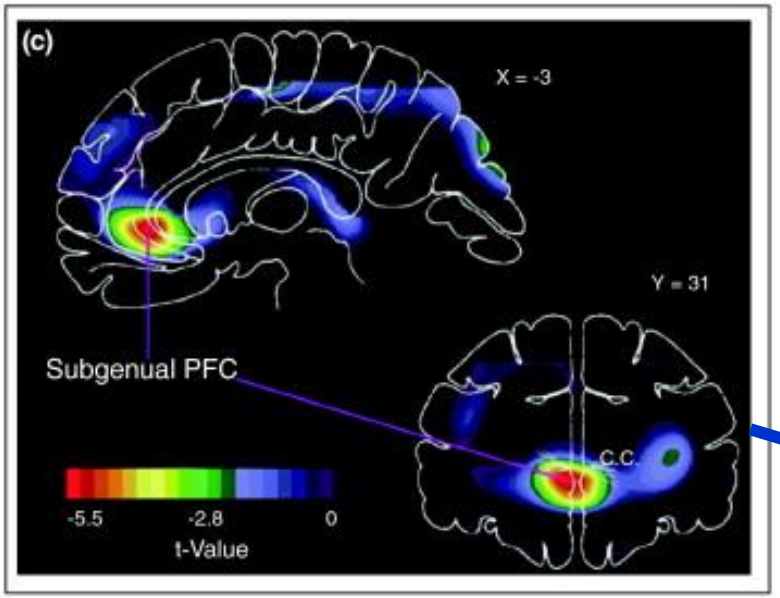
- Dose: 900-1500 mg of Lithium carbonate
- Half Life: 20-24 hrs
- Peak: 1-2 hrs
- Toxic plasma concentrations: 1,5 -3 mEq/l
- Stable concentrations: 5-6 days

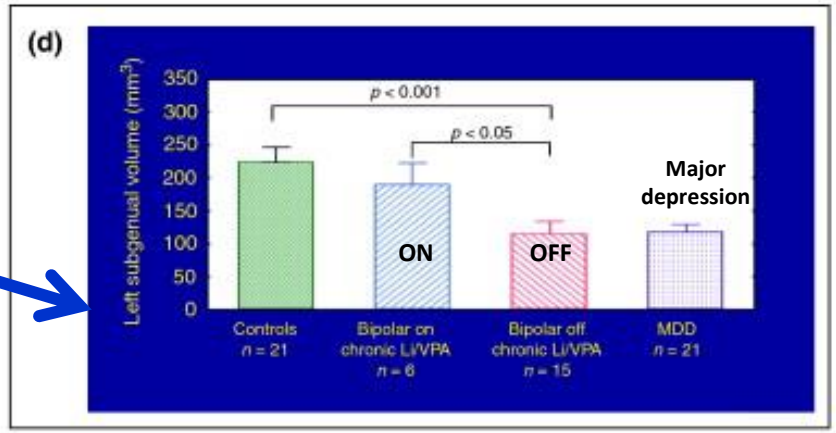
Lithium side effects

- Nausea
- vomiting
- diarrhea
- tremor → Propanolol
- Weight gain
- Confusion
- Thyroid, kidney effects → Hypothyroidism (TSH, FT4)


(a) (i)
hippocampus
Total hippocampal volume (mm³)
7.0
6.5
6.0
5.5
5.0
H
B
B+L
Healthy subjects (n = 298)
Bipolar not on lithium (n = 85)
Bipolar on lithium (n = 100)
(ii)
amygdala
Total amygdala volume (ml)
5.5
5.0
4.5
4.0
3.5
Healthy subjects (n = 255)
Bipolar not on lithium (n = 111)
Bipolar on lithium (n = 104)


(b)
Cortical GMD differences as a function of lithium treatment
(gray matter)
Bipolar Li +
Significance
<0.01
0.05
>0.1
Bipolar Li -
Significance
<0.01
0.05
>0.1


(c)
X = -3
Y = 31
Subgenual PFC
C.C.
-5.5
-2.8
0
t-Value


(d)
Left subgenual volume (mm³)
350
300
250
200
150
100
50
0
p < 0.001
p < 0.05
ON
OFF
Major depression
Controls n = 21
Bipolar on chronic Li/VPA n = 6
Bipolar off chronic Li/VPA n = 15
MDD n = 21

Carbamazepina, Valproic acid

Voltage-dependent Na^+ channels

Valproic acid

- Inositol depletion

- Increased production of Bcl-2

- Inhibition of PKC

- Activation of ERK MAP kinase

- Inhibition histone deacetylase

  transcriptions