

Drugs for Mood Disorders

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ANTIDEPRESSANTS (S. THYMOLEPTICS)

Drug	Reuptake Inhibition			Receptor Affinity					
	NE	Serotonin	Dopamine	5-HT ₂	D ₂	H ₁	M	α ₁	α ₂
Tricyclic (TCA)									
Imipramine	++	++	-	++	-	++	++	+++	+
Amitriptyline	++	++	-	++	+	+++	+++	+++	++
Doxepin	++	++	-	++	-	+++	++	+++	++
Desipramine	+++	+	-	+	-	+	+	++	+
Nortriptyline	++	+	-	++	-	++	+	+++	+
Protriptyline	+++	+	-	++	-	++	++	++	+
Maprotiline	++	-	-	+	+	+++	+	+++	+
Amoxapine	++	+	-	+++	+	++	+	+++	+
SSRI									
Fluoxetine	-	+++	-	+	-	-	-	+	-
Sertraline	-	+++	-						
Paroxetine	-	+++	-						
Nefazodone, Trazodone	-	+	-	++					
Vilazodone									
Other									
Trazodone	-	+	-	++	-	+	-	+++	++
Venlafaxine	+++	+++	+			-	-	-	
Bupropion	+	+	+	-	-	-	-	+	-
Mirtazapine	-	-	-	+	-	+	-	-	+

- antidepressants increase concentration of different monoamines in synaptic cleft by blocking reuptake mechanisms selectively (SSRIs) or nonselectively (TCAs), or by inhibiting degradation (MAOIs).

Main mechanism of action for all antidepressants - neuronal receptor down-regulation over time (> 2 weeks) in response to enhanced neurotransmitter availability.

N.B. onset of antidepressant effects requires several weeks! (at least 2-4 weeks; full response in 4-6 weeks)

All antidepressants ≈ equally can induce / exacerbate suicidal tendencies in patients < 24 yrs old! (esp. during first 1-2 months of treatment)

- some children exhibit behavioral side effects (BSE) that include activation and disinhibition.

I. TRICYCLIC ANTIDEPRESSANTS (TCAs)

- IMIPRAMINE (TOFRANIL) - prototype drug.
- DESIPRAMINE (NORPRAMIN) - demethylated derivative of IMIPRAMINE.
- TRIMIPRAMINE (SURMONTIL)
- CLOMIPRAMINE (ANAFRANIL)
- AMITRIPTYLINE (ELAVIL)
- NORTRIPTYLINE (PAMELOR)
- PROTRIPTYLINE (VIVACTIL) - T_{1/2} 3-5 days!
- DOXEPIN (SINEQUAN)

"Second generation" heterocyclic antidepressants (actions similar to IMIPRAMINE, but slightly different pharmacokinetics):

- AMOXAPINE
- MAPROTILINE - tetracyclic drug.

Advantages of TCAs – low cost.
Disadvantages of TCAs – need to titrate dose to therapeutic level, considerable toxicity in overdose.

PHARMACOKINETICS

- TCAs are well absorbed per os.
- lipophilic - readily penetrate into CNS, long T_{1/2} (e.g. 4-17 hours for IMIPRAMINE).
- divided doses may minimize side effects, but once-daily dosing (often at bedtime) is feasible because of long half-life and sedating properties.
- variable first pass metabolism in liver → low and inconsistent bioavailability (patient's response is used to adjust dosage).
- catabolized by hepatic microsomal system and conjugated with glucuronic acid.
- NORTRIPTYLINE has well-defined therapeutic window (i.e. range of blood concentrations above and below which less than maximal clinical response occurs).

MECHANISM OF ACTION

- TCAs **block NOREPINEPHRINE and SEROTONIN reuptake** into presynaptic neuron (→ increased concentrations of monoamines in synaptic cleft); this mechanism is questionable because:
 - TCA potency in blocking reuptake often does not correlate with clinical antidepressant effect.
 - reuptake blockade occurs immediately, but antidepressant effect requires several weeks of continued treatment.
- Prolonged (2-4 week) therapy** leads to **changes of monoamine receptor densities** (e.g. down-regulation of α_1 receptors) in brain – this correlates with onset of antidepressant activity.
- TCAs also **block serotonergic, α -adrenergic, histamine, and muscarinic receptors** - it is not known which, if any, of these accounts for therapeutic benefit.

AMOXAPINE has some **dopamine-blocking properties** - advantage in depressed patients with psychotic features, but risk of extrapyramidal side effects.

INDICATIONS

- major depression** (TCAs were standard drug treatment for several decades).
 - some **panic disorders**
 - bed-wetting** in children > 6 years (**IMIPRAMINE** - causes contraction of internal sphincter of bladder).
 - chronic pain, neuralgia.**
 - sleep apnea (PROTRIPTYLINE).**
- TCAs elevate mood, improve mental alertness, increase physical activity, reduce morbid preoccupation.
 - onset of mood-elevation is slow (requires 2-4 weeks); **initial treatment period** is typically 4-8 weeks → **dosage is gradually reduced** unless relapse occurs.
 - TCAs do not produce CNS stimulation or mood elevation in normal individuals (may produce sleepiness).
 - TCAs can be used for prolonged treatment without loss of effectiveness.
 - all TCAs have similar therapeutic efficacy (patients who do not respond to one TCA may benefit from different drug in TCA group).

SIDE EFFECTS

TCAs have disadvantage that they affect neurochemical systems not essential for antidepressant efficacy.

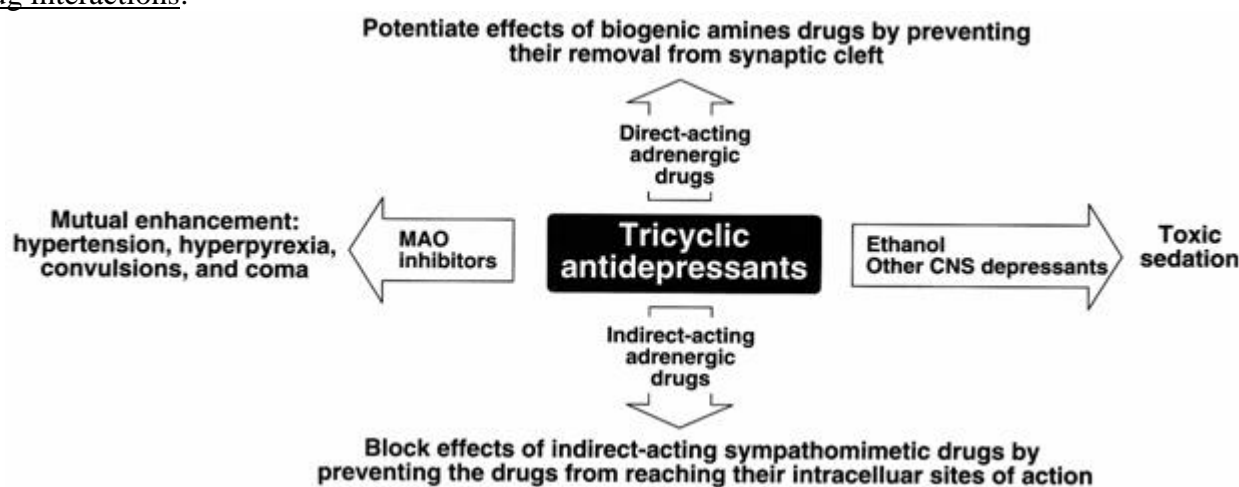
- Narrow therapeutic index** (e.g. 5-6 times maximal daily dose of IMIPRAMINE can be lethal) - suicidal patients should be given only limited quantities of these drugs!

TCAs are one of most common causes of drug-related death in USA!

Acute poisoning: anticholinergic toxicity, seizures, drowsiness, coma, **lethal ventricular arrhythmias** (QTc prolongation is first sign).

H: activated charcoal, gastric lavage, PHYSOSTIGMINE, SODIUM BICARBONATE (IV bolus → IVI), antiarrhythmics (LIDOCAINE, BRETYLIUM, PHENYTOIN), DIAZEPAM (for seizures), cardiac monitoring for at least 6-8 hours.

- Antimuscarinic effects** (except **MAPROTILINE**; very low for **DESIPRAMINE**) (strongest for **AMITRIPTYLINE**)! vs. other classes of antidepressants
 - tolerance to anticholinergic properties develops within short time.
- Arrhythmias** with conduction delay (quinidine-like effect) due to catecholamine activity↑, **orthostatic hypotension** due to α_1 blockade (**AMITRIPTYLINE, DOXEPIN**) - most serious problems in elderly!
- Sedation** (except **DESIPRAMINE, PROTRIPTYLINE**) especially during first several weeks – may be useful for agitation.
- Weight gain.**
- PHYSICAL & PSYCHOLOGICAL dependence** have been reported.
- May **unmask manic behavior** in bipolar disorders (if antimanic agent is not being used).
- TCAs lower **seizure** threshold (e.g. IMIPRAMINE at effective doses causes seizures for 0.3-0.6% patients).
- Dyspareunia (AMOXAPINE).**
- Drug interactions:

**II. MONOAMINE OXIDASE INHIBITORS (MAOIs)**

- IPRONIAZID** - no longer used due to hepatotoxicity.
- TRANLYCYPROMINE (PARNATE)**
- PHENELZINE (NARDIL)**
- ISOCARBOXAZID**
- MOCLOBEMIDE***
- BEFLOXATONE***

*MAO-A selective and reversible MAOIs; not yet available in US

- DEPRENYL** (s. **SELEGILINE**), **RASAGILINE** - MAO-B inhibitors for parkinsonism. see p. Mov10 >>
 - at antidepressant doses, inhibits both isoenzymes (A and B).
 - Selegiline *skin patch* (EMSAM[®]) is FDA approved for major depression; at lowest strength (6 mg delivered over 24 h) can be used without dietary restrictions needed for MAOIs!

PHARMACOKINETICS

- MAOIs are rapidly well absorbed per os.

MECHANISM OF ACTION

Mitochondrial enzyme MAO functions as "safety valve" to oxidatively deaminate and inactivate any excess neurotransmitter molecules (norepinephrine, dopamine, serotonin) that may leak out of synaptic vesicles when neuron is at rest.

MAO-A - **norepinephrine, serotonin** catabolism (important for depression).

MAO-B - dopamine catabolism (important for Parkinson disease).

- MAOIs **irreversibly inactivate MAO** (both MAO-A and MAO-B) → *neurotransmitter molecules* accumulate within presynaptic neuron and *leak into synaptic space* → activation of NOREPINEPHRINE and SEROTONIN receptors.
- although MAO is fully inhibited after several days of treatment, *antidepressant action is delayed several weeks* (i.e. onset of mood-elevation is slow - requires 2-4 weeks).
- enzyme regeneration** occurs several weeks after drug termination (when switching antidepressant agents, allow minimum of 2 weeks delay after MAOIs termination).
- PHENELZINE** and **TRANLYCPROMINE** have mild **amphetamine-like stimulant effect** (release norepinephrine centrally - beneficial for patients with low psychomotor activity).

INDICATIONS

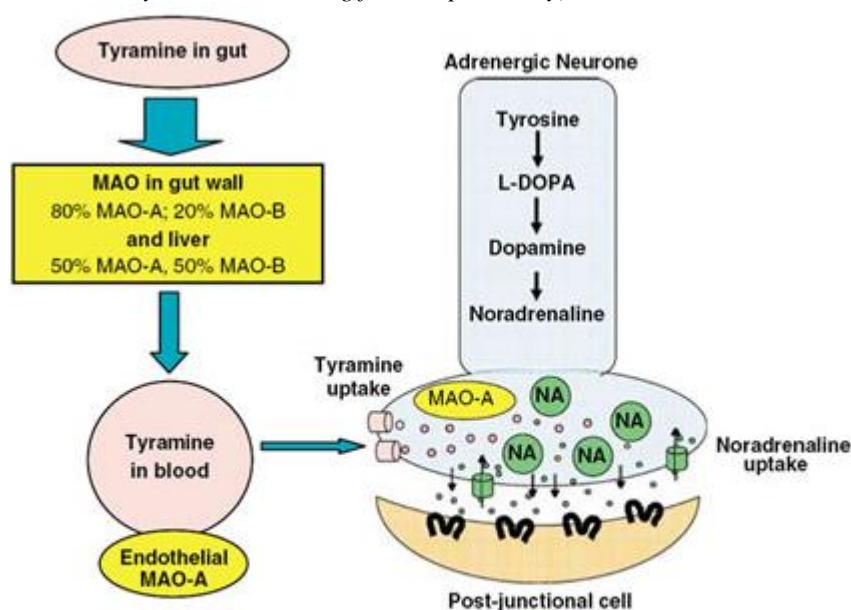
- major depression:**
 - unresponsive to TCAs
 - with strong anxiety
 - atypical depression.
 - phobic states**
 - narcolepsy** (MAOIs suppress REM sleep).
- use of MAOIs is limited because of *complicated dietary restrictions* and *severe / unpredictable side effects*.

SIDE EFFECTS

- Orthostatic hypotension** (due to uptake and release of "false transmitters" such as tyramine → affected ganglionic transmission).
- MAOIs cause **odd mixtures of sedation and stimulation** (insomnia, daytime sedation, aberrant changes in sleep-wake cycle, suppression of REM sleep).
N.B. MAOIs are usually **taken in morning** to minimize sleep disruption!
- Weight gain.**
- MAOIs also inhibit oxidases that catalyze oxidative deamination of drugs and potentially toxic substances → high incidence of drug-drug and drug-food interactions (esp. with sympathomimetic / serotonergic agents).
 - tyramine** (in aged cheeses, chicken liver, "live" beer, red wines, soybeans, air dried and fermented meats, pickled herring) is normally inactivated by MAO in gut; under MAOIs therapy undegraded tyramine causes release of large amounts of stored catecholamines from nerve terminals → cataclysmic **hypertensive crisis** (sudden severe headache, stiff neck, profuse sweating, mydriasis, neuromuscular irritability, tachycardia, nausea, extreme hypertension, cardiac arrhythmias, stroke);

H: **PHENTOLAMINE, SODIUM NITROPRUSSIDE**; for less severe cases - **CHLORPROMAZINE, PRAZOSIN**.

*Patients can carry 25-mg tablets of CHLORPROMAZINE and, as soon as signs of hypertensive reaction occur, take 1-2 tablets as they head for nearest ED.
MAOIs are dangerous in patients with suicidal tendencies (purposeful consumption of tyramine-containing foods is possibility).*



Cardiovascular effects of tyramine are potentiated by irreversible inhibitors of MAO. Normally, dietary tyramine is inactivated by the MAO-A in the gut wall, liver, vascular endothelial cells and lung. Uptake of tyramine by adrenergic neurons initiates the release of noradrenaline, which accounts for the sympathomimetic effects of tyramine.

- MAOIs and SSRIs should not be co-administered (risk of life-threatening "**serotonin syndrome**"*) - both drugs require **washout periods of 2 weeks** before administering other.
 - * "**serotonin syndrome**" - hyperpyrexia, myoclonus, rigidity, hyperreflexia, shivering, confusion, hallucinations, agitation, restlessness, coma, autonomic instability (tachycardia, fast changes of BP), nausea, diarrhea, diaphoresis, flushing, rhabdomyolysis and death.
 - MAOIs enhance action of general anesthetics, sedatives, atropine-like agents, narcotics (especially meperidine, which can result in hyperpyrexia), TCAs.
- Overdosage:** agitation, headache, hallucinations, convulsions, hypotension / hypertension.
H: supportive treatment, observation in hospital for at least 1 week (to allow MAO enzyme regeneration).

III. SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs)

- FLUOXETINE** (PROZAC) – prototype drug; most widely prescribed antidepressant in USA!
- PAROXETINE** (PAXIL)
- FLUVOXAMINE** (LUVOX)
- SERTRALINE** (ZOLOFT)
- CITALOPRAM** (CELEXA) – racemic mixture of **S-enantiomer** (100-fold more active) and **R-enantiomer** (almost inactive and perhaps linked to some side effects).
- ESCITALOPRAM** (LEXAPRO) – **S-enantiomer** of CITALOPRAM.
- TRAZODONE** (DESYREL)
- NEFAZODONE** (SERZONE)
- VILAZODONE** (VIIBRYD)

SSRIs* are not suitable for use by persons < 18 years for treatment of "depressive illness" – because of ↑risk of suicidality. *except FLUOXETINE

PHARMACOKINETICS

- long* $T_{1/2}$ - can be taken **once daily**, usually in **morning** (because of potential sleep disruption).
e.g. FLUOXETINE $T_{1/2}$ is 1-10 days (3-30 days for its active metabolite NORFLUOXETINE).
*except TRAZODONE and NEFAZODONE - short $T_{1/2}$ (necessitating multiple daily dosing).
- SSRIs are rapidly well absorbed per os (steady state is achieved after several weeks of treatment).
- for most patients, treatment can be initiated at target dose and once-daily dosing.

MECHANISM OF ACTION

- **selectively inhibit SEROTONIN reuptake;**

vs. TCAs - nonselectively inhibit uptake of NOREPINEPHRINE and SEROTONIN + block muscarinic, H₁, α-adrenergic receptors.

- **NEFAZODONE, TRAZODONE** potently & selectively block 5-HT₂ receptors and only moderately inhibit SEROTONIN reuptake – therefore they are called **serotonin modulators** (instead of SSRI).

INDICATIONS

- 1) **depression** (SSRIs are as effective as TCAs); onset of action is within 1-3 weeks (sooner for ESCITALOPRAM).
SSRIs are first-line drugs for depression!
- 2) bulimia nervosa, anorexia nervosa
- 3) obsessive-compulsive disorder
- 4) panic disorder
- 5) pain associated with diabetic neuropathy
- 6) premenstrual syndrome

SIDE EFFECTS

SSRIs are free of most of troubling side effects of TCAs (anticholinergic effects, orthostatic hypotension, weight gain)! – SSRIs are preferred antidepressants by non-specialists who write most of prescriptions for antidepressant drugs.

Failure to tolerate one SSRI drug does not preclude trial of another SSRI!

1. **Sedation** – due to stimulation of 5-HT₁ receptors (**PAROXETINE, FLUVOXAMINE**, serotonin modulators* – may be useful for agitation); or **insomnia & anxiety** – due to stimulation of 5-HT₂ receptors (**FLUOXETINE**).

*serotonin modulators do not suppress REM sleep and produce restful sleep – commonly are used as sleep aid rather than as antidepressants.

FLUOXETINE is most stimulating SSRI, **PAROXETINE** is most sedating SSRI

2. **Nausea, anorexia, weight loss** – due to stimulation of 5-HT₃ receptors.
3. **Tremors.**
4. **Loss of libido, delayed ejaculation** (men), **anorgasmia** (women) – due to stimulation of 5-HT₂ receptors (serotonin modulators block 5-HT₂ receptors – do not produce sexual dysfunction!).
5. **Priapism** (**TRAZODONE**).
6. **Drug interactions:**
 - **SSRI and MAOI** or **SSRI and triptan** concurrent use is contraindicated (risk of life-threatening “**serotonin syndrome**” – see above >>).
 - **FLUOXETINE** is (as are other SSRIs) potent inhibitor of **cytochrome P-450 isoenzyme*** responsible for elimination of TCAs, neuroleptics, some antiarrhythmics, β-adrenergic antagonists.
* ≈ 7% of white population lack this P-450 enzyme - metabolize FLUOXETINE very slowly.
N.B. each SSRI drug inhibits isoforms (such as 2D6 or 2C19) to different degrees - to avoid particular drug interaction, clinicians may choose one SSRI over another
7. **Overdoses** (**high therapeutic index** - safer than TCAs!) do not cause cardiac arrhythmias but can cause **seizures**.
8. **Pregnancy concerns:**
 - SSRIs used after 20th week of pregnancy increase 6-fold risk of **persistent pulmonary hypertension** (PPHN).
 - **PAROXETINE** (used during 1st trimester) slightly increases risk of major **congenital malformations** (particularly heart defects) - pregnancy category D.

IV. SELECTIVE SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITORS (SNRIs)

- safety, tolerability, and side effect profiles are similar to SSRIs, with exception that SNRIs have been associated (rarely) with sustained BP rise.

VENLAFAXINE (EFFEXOR) – **selective serotonin-norepinephrine reuptake inhibitor** (SSNRI); also weakly inhibits **dopamine** reuptake.

- may be effective in treatment resistant depression.
- avoid abrupt stopping (→ withdrawal).
- high doses cause sustained diastolic hypertension.

DESVENLAFAXINE (PRISTIQ™) – major active metabolite of VENLAFAXINE.

DULOXETINE (CYMBALTA) – potent **selective serotonin-norepinephrine reuptake inhibitor** (SSNRI); also weakly inhibits **dopamine** reuptake.

- no significant affinity for dopaminergic, adrenergic, cholinergic or histaminergic receptors.
- may cause slight BP increase.
- do not abruptly discontinue.
- FDA approved DULOXETINE to treat **chronic musculoskeletal pain** (including discomfort from osteoarthritis and chronic lower back pain).

V. DOPAMINE-NOREPINEPHRINE REUPTAKE INHIBITORS

BUPROPION (WELLBUTRIN) – weak **inhibitor of serotonin-norepinephrine-dopamine reuptake**.

- rapidly absorbed from GI tract → extensive first-pass metabolism.
- used for **major depression**.
 - significant improvement is often seen within 1 week of treatment.
 - sometimes effective in depressed patients who do not respond to TCAs.
 - least likely (of all antidepressants) to switch patient to mania.
- **BUPROPION SR** (ZYBAN) is first-line therapy in **smoking cessation**.
- does not produce sedation, orthostatic hypotension, weight gain, or sexual dysfunction!
- **contraindicated** in eating disorders, epilepsy, major head trauma (narrow therapeutic index - may produce / exacerbate **seizures**).

VI. OTHER ANTIDEPRESSANTS

MIRTAZAPINE (REMERON) - **norepinephrine-serotonin** modulator:

- 1) **presynaptic α₂-blocker** → increased release of NOREPINEPHRINE and SEROTONIN.
 - 2) potent **antagonist at postsynaptic 5-HT₂, 5-HT₃, and H₁ receptors**.
- analog of **MIANSERIN** (antidepressant that has been available in Europe).
 - **side effects** – **antihistaminic** (weight gain, **strong sedation***), **anticholinergic** (dizziness, dry mouth, constipation).
 - alternative for patients who do not respond to SSRIs.
*superior to SSRI in depression associated with severe insomnia and anxiety.

ST. JOHN'S WORT (*Hypericum perforatum*) - acts as **SSRI** (not as MAOI as previously believed).

- first-line antidepressant in many European countries.
- indication - mild-to-moderate depressive symptoms.
- dosage - 300 mg 3 times day with meals (to prevent GI upset); if no clinical response occurs after 3-6 months → use another medication.
- side effects: GI distress, phototoxicity, induces P-450 system.

BUSPIRONE (BUSPAR) - marketed as anti-anxiety medication. see p. Rx3 >>

- partial **agonist at 5-HT_{1A} receptors**; some affinity for **D₂** and **5-HT₂ receptors**.
- antidepressant effect at doses > 45 mg/d (esp. in combination with SSRIs and TCAs).

VORTIOXETINE (BRINTELLIX) - multimodal activity - two mechanisms of action: **serotonin receptor activity modulations and reuptake inhibition**.

MOOD STABILIZERS

LITHIUM CARBONATE

INDICATIONS

- 1) prevention (maintenance therapy) of **bipolar disorder**
- 2) treatment of acute **(hypo)manic episodes** (lithium does not work immediately but should nonetheless be started early in anticipation of maintenance use!).
- 3) as augmenting agent in combination with antidepressant for **treatment-resistant depression**.

N.B. **lithium has specific ANTISUICIDE effect!**

- therapeutic effectiveness is not evident until at least 4-10 days after institution of therapy.
- no noticeable effect on normal individuals.
- not sedative, euphoriant or depressant.

MODE OF ACTION

- *lithium* **decreases cellular concentration of inositol triphosphate (IP₃ s. PIP₂)**; also influences serotonin and/or NE reuptake.

PHARMACOKINETICS

- well absorbed orally.
- secreted into breast milk.
- T_{1/2} 20-36 hours – could be administered × 1/d (but rapid absorption from GI tract and low therapeutic index necessitate administration in 2-3 divided doses).
- start with low dose and gradually increase; it takes at least 4 days to achieve steady state.
- **serum levels** should be monitored weekly ÷ biweekly until levels are stabilized → check every 3-4 months.
- excreted by kidney (80% of lithium is reabsorbed in proximal tubule; this is increased by hyponatremia → lithium toxicity).

Salt in diet (*lithium is treated by kidney like sodium, i.e. sodium facilitates lithium excretion*): increased salt intake → reduced serum lithium levels (reduced efficacy); reduced salt intake (or excessive sweating) → increased levels (toxicity).

ADVERSE EFFECTS

Lithium salts are very toxic - **extremely low therapeutic index** (comparable to *digitalis*) - serum concentration must be carefully maintained 0.6-1.5 mEq/L (toxic effects occur at > 2.0 but may occur at levels as low as 1.0).

Majority of patients suffer side effects at therapeutic doses (although most patients classify them as mild).

- fine postural or intentional **tremor** (80%); H: **β-blocker**.
- benign **leukocytosis** often appears (obtain baseline CBC).
- **poor memory, loss of concentration, fatigue, somnolence, confusion, convulsions**.
- **hypotension** and cardiac **arrhythmias** (T-wave flattening or inversion requires no intervention).
- lithium **inhibits ADH action** on renal adenylate cyclase → polyuria, excessive thirst (**nephrogenic diabetes insipidus**).

Drink plenty of fluids to prevent dehydration!

- chronic use interferes with thyroxine synthesis → **thyroid enlargement with hypofunction** (obtain baseline TSH → monitor q6months).
- use during **early pregnancy** → **cardiovascular anomalies** (e.g. Epstein's anomaly).
- **drug interactions**: NSAIDs (except sulindac) and thiazides reduce lithium clearance!
- **intoxication** (anorexia, vomiting, diarrhea, drowsiness, muscle twitching, ataxia, slurred speech, Parkinsonian-like syndrome, seizures and coma);

N.B. **basal ganglia and cerebellum can be permanently damaged** following lithium intoxication!

- **chronic poisoning** (due to altered drug pharmacokinetics) is associated with higher morbidity & mortality than **acute intoxication**.
- treatment: **osmotic diuresis** (NaCl IVI – sodium facilitates lithium excretion!!!) **with urinary alkalizing agents** (e.g. **ACETAZOLAMIDE**) / **dialysis** (if serum level > 4.0); lithium does not bind to charcoal (but **whole GI tract irrigation** may be helpful).

CONTRAINDICATIONS

- 1) severe **cardiac conduction abnormalities** (obtain baseline ECG for individuals > 40 yrs)
- 2) **renal failure** (obtain baseline BUN, creatinine, TSH, CBC, and electrolytes)
- 3) **pregnancy**.

ANTICONVULSANTS

- **CARBAMAZEPINE, VALPROATE, LAMOTRIGINE**.

- effective as adjunct or alone in acute treatment and / or prophylaxis of manic episodes.

see p. Psy17 >>

BIBLIOGRAPHY for ch. "Psychiatry" → follow this [LINK](#) >>