Drugs for Mood Disorders

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<tr>
<td></td>
<td>NE</td>
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<tr>
<td>Tricyclic (TCA)</td>
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<tr>
<td>Imipramine</td>
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<td>Desipramine</td>
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<tr>
<td>Nortriptyline</td>
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<td>Venlafaxine</td>
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<td>Maprotiline</td>
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<td>Amitriptyline</td>
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NSR

Thioridazine – +++ – – – – – –

Sertraline – +++ – – – – – –

Paroxetine – +++ – – – – – –

Nefazodone – ++ – – – – – –

Trazodone – ++ – – – – – –

Vilazodone – ++ – – – – – –

Other

Trazodone – – – – – – – –

Venlafaxine – +++ – – – – – –

Egypazipine – – – – – – – –

Mirtazapine – – – – – – – –

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 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)

1. IMIPRamine (Tofranil) - prototype drug.
2. DESIMPramine (Norpramin) - demethylated derivative of imipramine.
3. Trimipramine (Surmontil).
5. AMITryptiline (Elavil).
6. NORTriptyline (Pamelor).
7. Protriptyline (Vivactil) - T4's 3-5 days!
8. DOPIBUtamine (Benzekan).

“Second generation” heterocyclic antidepressants (actions similar to imipramine, but slightly different pharmacokinetics).

9. AMOXAPine.


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 T4's (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

1. TCAs block serotonin, norepinephrine, and dopamine reuptake into presynaptic neurons (→ increased concentrations of monoamines in synaptic cleft); this mechanism is questionable because:
   - TCAs potent in blocking reuptake often do not correlate with clinical antidepressant effect.
   - Reuptake blockade occurs immediately, but antidepressant effect requires several weeks of continued treatment.

2. Prolonged (2-4 weeks) therapy leads to changes of monoamine receptor density (e.g. down-regulation of n1 receptors) in brain – this correlates with onset of antidepressant activity.

3. TCAs also block serotonergic, n-adrenergic, histamine, and muscarinic receptors – it is not known which, if any, of these accounts for therapeutic benefit.

AMPHETAMINES have some dopamine-blocking properties – advantageous in depressed patients with psychotic features, but risk of extrapyramidal side effects.

Side Effects

1. 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, phystostigmine, sodium bicarbonate (IV bolus → IV), antiarrhythmics (lidocaine, bretylium, phenytoin), diazepam (for seizures), cardiac monitoring for at least 6-8 hours.

2. Antimuscarinic effects (except MAPROXYL) very low for DESIPRAMINE (strongest for AMITRIPTYLINE) vs. other classes of antidepressants.

   – tolerance to anticholinergic properties develops within short time.

3. Arrhythmias with conduction delay (quinidine-like effect) due to catecholamine activity↑, orthostatic hypotension due to n1 blockade (AMITRIPTYLINE, DOXEPIN) - most serious problems in elderly.

4. Sedation (except DESIPRAMINE, PROTRIPTYLINE) especially during first several weeks – may be useful for agitation.

5. Weight gain.

6. PHYSICAL & PSYCHOLOGICAL dependence have been reported.

7. May unmask manic behavior in bipolar disorders (if anticholinergic agent is not being used).

8. TCAs lower seizure threshold (e.g. IMIPRAMINE at effective doses causes seizures in 0.3-0.6% patients).


10. Drug interactions:

IL MONOAMINE OXIDASE INHIBITORS (MAOIs)

1. IRONIZING - no longer used due to hepatotoxicity.

2. TRANYLCYPROMINE (PARANATE).

3. PHENELZINE (NARDIL).

4. BUCRABNATE.

5. MOCLOMEN®.

6. BIPHENYL®.

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

7. DEPRESIN (O SELERINE) RAMELON – MAO-B inhibitors for parkinsonism. see p. MAO B

   – at antidepressant doses, inhibits both isoenzymes (A and B).

   Selegeline 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).
- PRESHIELD and TRANYCYCLOMINE have mild amphetamine-like stimulant effect (release norepinephrine centrally – beneficial for patients with low psychomotor activity).

INDICATIONS

1. major depression: 
   a) unresponsive to TCAs
   b) with strong anxiety
   c) atypical depression.
2. phobic states
3. narcolepsy (MAOIs suppress REM sleep).

- use of MAOIs is limited because of complicated dietary restrictions and severe/unpredictable side effects.

SIDE EFFECTS

1. Orthostatic hypotension (due to uptake and release of "false transmitters" such as tyramine → affected ganglionic transmission). 
2. 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!

3. Weight gain.

4. 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 amines).

- 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 MAO therapy undegraded tyramine causes release of large amounts of stored catecholamines from nerve terminals → catalyze hypertensive crisis (sudden severe headache, stiff neck, profuse sweating, mydriasis, neutromuscular irritability, tachycardia, nausea, extreme hypertension, cardiac arrhythmias, stroke).

H: supportive treatment, observation in hospital for at least 1 week (to allow MAO deactivation).

- MAOIs and SSRIs should not be co-administered (risk of life-threatening "serotonin syndrome") – both drugs have washout periods of 2 weeks before administering other.

- "serotonin syndrome" - hyperpyrexia, myoclonus, rigidity, hyperthermia, shivering, confusion, hallucinations, agitation, restlessness, coma, autonomic instability (tachycardia, fast changes of BP), convulsions, diaphoresis, flushing, rhodomelalysis and death.

- MAOIs enhance action of general anesthetics, sedatives, atropine-like agents, narcotics (especially meperidine, which can result in hyperpyrexia), TCAs.

5. Overdosage: agitation, headache, hallucinations, convulsions, hypotenison / hypertension.

H: supportive treatment, observation in hospital for at least 1 week (to allow MAO deactivation).

III. SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs)

1. FLUOXETINE (PROZAC) – prototype drug: most widely prescribed antidepressant in USA!
2. PAROXETINE (PAXIL).
3. FLUVAXADINE (LUFOX).
4. SERTRALINE (ZELDOF).
5. CITALOPRAM (CELEXA) – racemic mixture of S-enantiomer (100-fold more active) and R-enantiomer (almost inactive and perhaps linked to some side effects).
6. ESITIALDIPRAM (LEXAPRO) – S-enantiomer of CITALOPRAM.
7. TRAZODONE (DEZYPRE).
8. NEFEDIPRAM (STIVORO).
9. VILAZODON (VIBRITRO).

SSRIs* are not suitable for use by persons < 18 years for treatment of “depressive illness” – because of risk of suicidality.

*except FLUOXETINE

PHARMACOKINETICS

- Long* T½s - can be taken once daily, usually in morning (because of potential sleep disruption).
  e.g. FLUOXETINE: T½ > 10 days (3-30 days for its active metabolite MOLYDOXETINE).
  *except TRAZODONE and NEFEDIPRAM - short T½s (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.

DRUGS FOR MOOD DISORDERS

PsY15 (3)
Mechanism of Action:  
- selectively inhibit serotonin reuptake vs. TCAs - nonspecifically inhibit uptake of serotonin and norepinephrine + block muscarinic, H₂, α-adrenergic receptors.
- NEURITICIN, TRIAZODINE potentially & selectively block 5-HT₂ receptors & only moderately inhibit serotonin reuptake - therefore they are called serotonin modulators (instead of SSRIs).

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*.

Serotonin 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-HT₃ receptors (PAROXETINE, FLUOXETINE, serotonine 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.


3. Tremors.
- 4. Loss of libido, delayed ejaculation (men), anorgasmia (women) – due to stimulation of 5-HT₃ receptors (serotonin modulator: block 5-HT₃ receptors – do not produce sexual dysfunction†).

5. Priapism (TRIADZINE).
- 6. Drug interactions:
  - SSRIs & MAOI or SSRI and tricyclic concurrent use is contraindicated (risk of life-threatening "serotonin syndrome") – see above).
  - FLUOXETINE is (as other SSRIs) potent inhibitor of cytochrome P-450 Ioenzyme* responsible for elimination of TCAs, neuroleptics, some antiarthirhymics, β-adrenergic antagonists.
  - ≈ 7% of white population lack this P-450 enzyme – metabolize FLUOXETINE very slowly.
  - N.B. each SSRI drug inhibits isozymes (such as ZD6 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 MELD.
- 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 (Efexor):  
- selective serotonin-norepinephrine reuptake inhibitor (SNRI); also weakly inhibits dopamine reuptake.
  - may be effective in treatment resistant depression.
  - avoid abrupt stopping (↔ withdrawal).
  - high doses cause sustained diastolic hypertension.

DESVLENAXINE (Pristin®) – major active metabolite of venlafaxine.

DULoxetine (Cymbalta) – potent effective serotonin-norepinephrine reuptake inhibitor (SNRI); also weakly inhibits dopamine reuptake.
- no significant affinity for dopaminergic, adrenergic, cholinergic or histaminergic receptors.
- FDA approved for chronic musculoskeletal pain (including discomfort from osteoarthritis and chronic lower back pain), diabetic peripheral neuropathy, fibromyalgia
  - may cause slight BP increase.
  - do not abruptly discontinue.

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
MIPTAZAPINE (Remeron) - norepinephrine-serotonin modulator.
1) HELITROPA (MODAFINIL) is increased release of norepinephrine and serotonin.
2) potent antagonist at postsynaptic 5-HT₃, 5-HT₂; and H₁ receptors.
- analog of MANBRANN (antidepressant that has been available in Europe).
- side effects – antihistaminic (weight gain, strong sedation*), antiinflammatory (dizziness, dry mouth, constipation).
- alternative for patients who do not respond to SSRIs.
*superior to SSRI in depression associated with severe insomnia and anxiety.
**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.

**SIDE EFFECTS**
- non-sedative, euphoriant or depressant.
- no noticeable effect on normal individuals.
- not sedative, euphoriant or depressant.

**MODE OF ACTION**
- Lithium decreases cellular concentration of inositol triphosphate (IP3; PIP2); also influences serotonin and/or NE reuptake.

**PHARMACOKINETICS**
- well absorbed orally.
- secreted into breast milk.
- T1/2: 20-36 hours - could be administered 1x/day (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.
- excrusted by kidney (90% of lithium is reabsorbed in proximal tubule; this is increased by hypothyroidism - decreased renal clearance) or excessive sweating.
- 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- 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 adenyl cyclase → polyuria, excessive thirst (nephrogenic diabetes insipidus).

Drink plenty of fluids to prevent dehydration!

- chronic use interferes with thyroid synthesis → thyroid enlargement (due to higher thyroxine synthesis).
- use during early pregnancy → cardiovascular anomalies (e.g. Eptstein's anomaly).
- drug interactions: NSAIDs (except sulindac) and thiazides reduce lithium clearance!
- urination (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 IV/PO - 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.

**BIBLIOGRAPHY** for ch. “Psychiatry” - follow this LINK. ---