

Antidepressants

The optimal use of antidepressant required a clear understanding of their mechanism of action, pharmacokinetics, potential drug interaction and the differential diagnosis of psychiatric illnesses.

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Depression

A World Health Organization (WHO) Prediction

- **Depression is currently the FOURTH most significant cause of suffering and disability worldwide**
- **and, sadly, It will be the SECOND most debilitating human condition by the year 2020.**

Chemical “Jobs”

Dopamine

- Attention
- Pleasure
- Emotions
- Reward
- Motivation
- Movement

Norepinephrine

- alertness
- Observance
- Daydreaming
- Heart/BP rates
- Stress

Serotonin

- Regulates mood
- sleep
- emesis
- sexuality
- Appetite
- impulsiveness/
aggression

Depression

- **Symptoms**
 - **Cognitive**
 - **Thoughts of hopelessness, poor confidence, negative thoughts.**
 - **Emotional**

Feeling sad, unable to feel pleasure, irritability
 - **Psychomotor/Physical**
 - **Decreased libido, energy**
 - **Sleep changes (70% less, 30% more)**
 - **Appetite changes (70 % less, 30 % more)**

Depression: Treatment

- **Antidepressant Medications**
 - **Selective serotonin reuptake inhibitor (SSRI's) are first line of treatment**
- **Psychotherapy**
 - **Usually individual psychotherapy**
 - **Cognitive behavioral therapy has most evidence for efficacy of treatment.**
- **Sometimes exercise or body awareness has been found to helpful**

Drug ⌵	Brand ⌵	Class ⌵	2007 Prescriptions (in millions) ⌵
Sertraline	Zoloft	SSRI	29.652
Escitalopram	Lexapro	SSRI	27.023
Fluoxetine	Prozac	SSRI	22.266
Bupropion	Wellbutrin	NDRI	20.184
Paroxetine	Paxil	SSRI	18.141
Venlafaxine	Effexor	SNRI	17.200
Citalopram	Celexa	SSRI	16.246
Trazodone	Desyrel	SRI	15.473
Amitriptyline	Elavil	TCA	13.462
Duloxetine	Cymbalta	SNRI	12.551
Mirtazapine	Remeron	TeCA	5.129
Nortriptyline	Pamelor	TCA	3.105
Imipramine	Tofranil	TCA	1.524

Drug name	Commercial name	Drug class	Total prescriptions
Sertraline	Zoloft	SSRI	33,409,838
Citalopram	Celexa	SSRI	27,993,635
Fluoxetine	Prozac	SSRI	24,473,994
Escitalopram	Lexapro	SSRI	23,000,456
Trazodone	Desyrel	SARI	18,786,495
Venlafaxine (all formulations)	Effexor (IR, ER, XR)	SNRI	16,110,606
Bupropion (all formulations)	Wellbutrin (IR, ER, SR, XL)	NDRI	15,792,653
Duloxetine	Cymbalta	SNRI	14,591,949
Paroxetine	Paxil	SSRI	12,979,366
Amitriptyline	Elavil	TCA	12,611,254
Venlafaxine XR	Effexor XR	SNRI	7,603,949
Bupropion XL	Wellbutrin XL	NDRI	7,317,814
Mirtazapine	Remeron	TeCA	6,308,288
Venlafaxine ER	Effexor XR	SNRI	5,526,132
Bupropion SR	Wellbutrin SR	NDRI	4,588,996
Desvenlafaxine	Pristiq	SNRI	3,412,354
Nortriptyline	Sensoval	TCA	3,210,476
Bupropion ER	Wellbutrin XL	NDRI	3,132,327
Venlafaxine	Effexor	SNRI	2,980,525
Bupropion	Wellbutrin IR	NDRI	753,516

Monoamine hypothesis of depression

- **The monoamine hypothesis grew originally out of associations between the clinical effects of various drugs that cause or alleviate symptoms of depression and their known neurochemical effects on monoaminergic transmission in the brain**
- **The monoamine hypothesis of depression suggests that depression is related to a deficiency in the amount or function of cortical and limbic serotonin (5-HT), norepinephrine (NE), and dopamine (DA)**

Monoamine hypothesis of depression

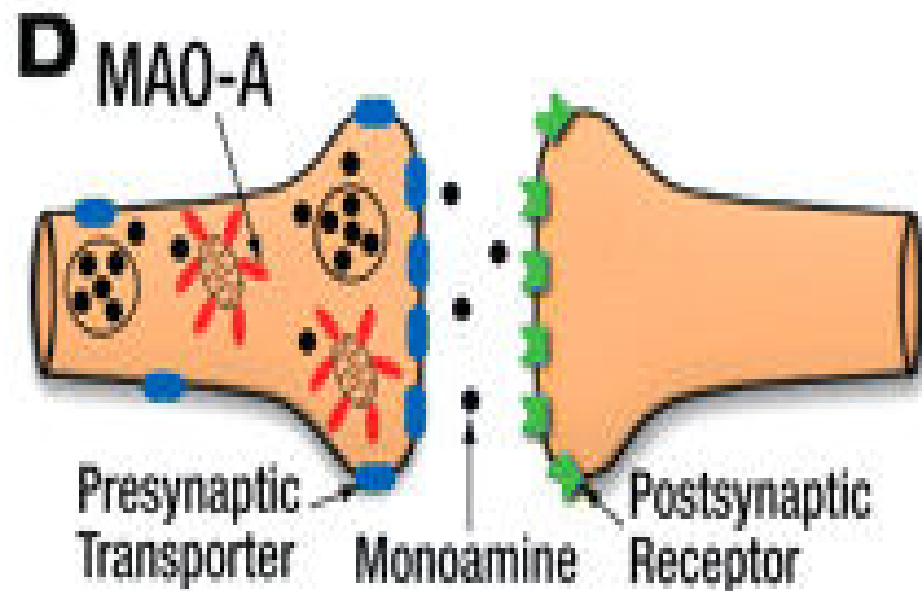
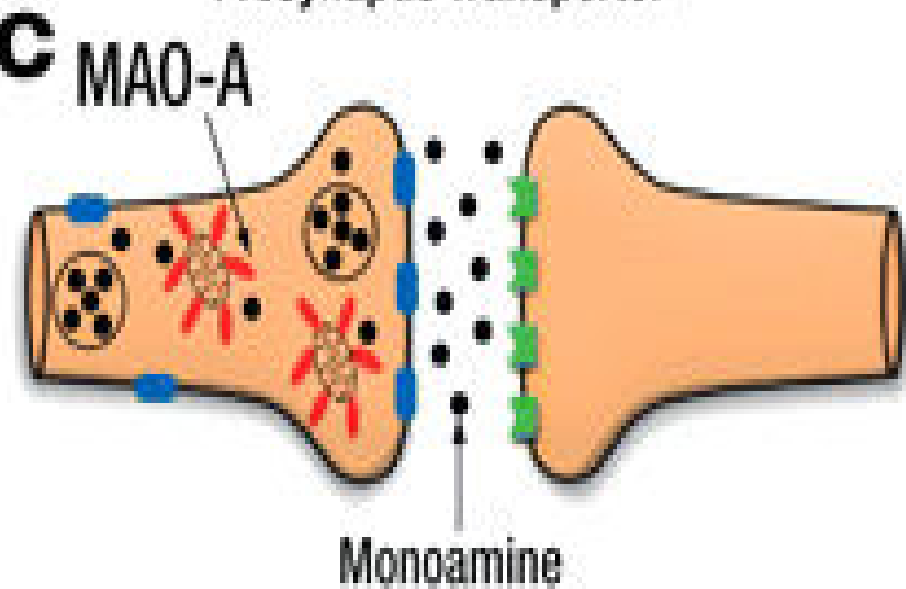
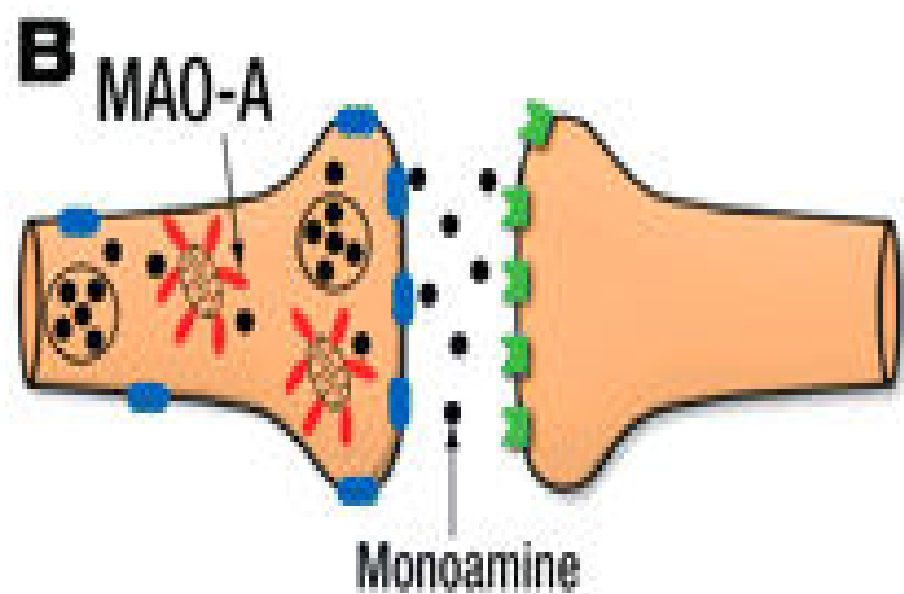
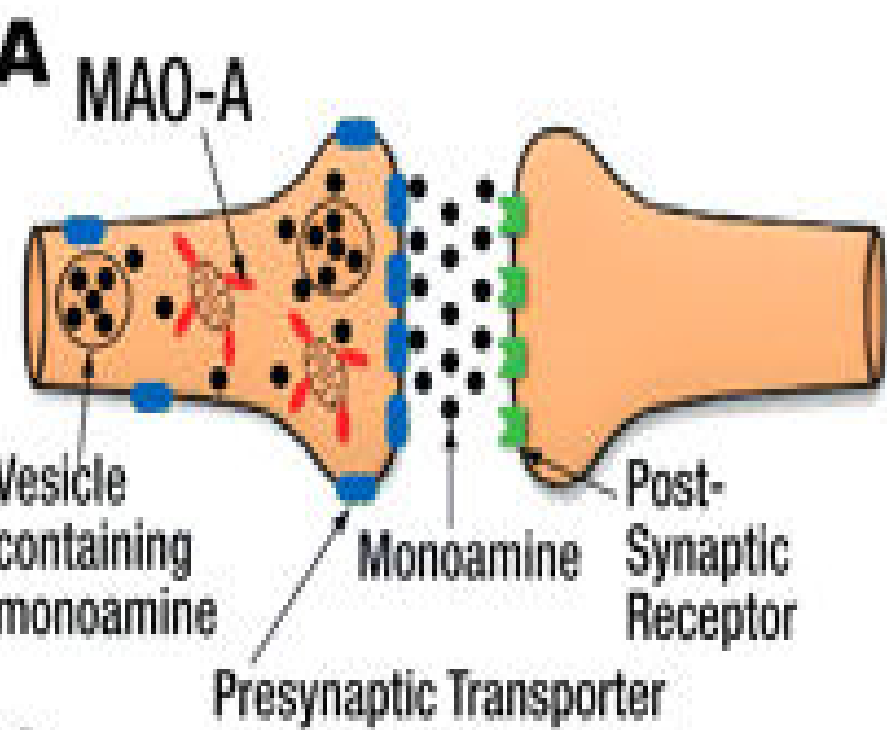
- **The chronic activation of monoamine receptors by antidepressants appears to increase in BDNF transcription**
- **One of the weaknesses of the monoamine hypothesis is the fact that amine levels increase immediately with antidepressant use, but maximum beneficial effects of antidepressants are not seen for many weeks**
- **The time required to synthesize neurotrophic factors has been proposed as an explanation for this delay of antidepressant effects**

Neurotrophic Hypothesis

- Depression appears to be associated with a drop in brain-derived neurotrophic factor (BDNF) levels in the cerebrospinal fluid and serum as well as with a decrease in tyrosine kinase receptor B activity
- BDNF is thought to exert its influence on neuronal survival and growth effects by activating the tyrosine kinase receptor B in both neurons and glia

Neurotrophic Hypothesis

- **Animal and human studies indicate that stress and pain are associated with a drop in BDNF levels and that this loss of neurotrophic support contributes to atrophic structural changes in the hippocampus and perhaps other areas such as the medial frontal cortex and anterior cingulate**
- **Studies suggest that major depression is associated with substantial loss of volume in the hippocampus, anterior cingulate and medial orbital frontal cortex**



Tricyclic antidepressant (Amitriptyline)

- TCAs inhibit serotonin, norepinephrine, and dopamine transporters, slowing reuptake.
- with a resultant increase in activity.
- Muscarinic acetylcholine receptors, alpha-adrenoceptors, and certain histamine (H1) receptors are blocked.

Side effects:

- (1) drug-induced Sedation
- (2) Orthostatic hypotension
- (2) Cardiac effects
- (3) Anticholinergic effects dry mouth, constipation, blurred vision, urinary retention

SSRIs (Serotonin-specific reuptake inhibitors)

inhibits the reuptake of serotonin without seriously effecting the reuptake of dopamine & norepinephrine.

- Most common side effects include GI upset, sexual dysfunction (30%+!), anxiety, restlessness, nervousness, insomnia, fatigue or sedation, dizziness**
- Can develop a discontinuation syndrome with agitation, nausea, disequilibrium and dysphoria**

SSRI/SNRI Discontinuation Syndrome in **Adults**

F.I.N.I.S.H.

- **F**lu-like symptoms: fatigue, muscle aches, headache, diarrhea
- **I**nsomnia: vivid or disturbing dreams
- **N**ausea
- **I**mbalance: gait instability, dizziness, lightheadedness, vertigo
- **S**ensory disturbance: paresthesia, “electric shock” sensation, visual disturbance
- **H**yperarousal: anxiety, agitation
- **Onset:** 24-72 hours + **Resolution:** 1-14 days
- **Incidence:** ~ 20 - 40 % (who have been treated at least 6 weeks)

Why there are many of them

Paroxetine: Sedating properties (dose at night) offers good initial relief from anxiety and insomnia

Significant CYP2D6 inhibition

Sertraline: Increased number of GI adverse drug reactions

Fluoxetine Secondary to long half life, less Discontinuation Syndrome

Significant P450 interactions so this may not be a good choice in pts already on a number of meds

Initial activation may increase anxiety and insomnia

More likely to induce mania than some of the other SSRIs

Serotonin/Norepinephrine reuptake inhibitors (SNRIs)

- Slightly greater efficacy than SSRIs
 - Slightly fewer adverse effects than SSRIs
 - Venlafaxine
 - Duloxetine
1. Can cause a 10-15 mmHG dose dependent increase in diastolic BP.
 2. May cause significant nausea,
 3. Can cause a bad discontinuation syndrome, and taper recommended after 2 weeks of administration

5-HT₂ antagonists

- Agents: Nefazodone, Trazodone, mirtazapine.
- Inhibition of 5-HT_{2A} receptors in both animal and human studies is associated with substantial antianxiety, antipsychotic, and antidepressant effects
- Nefazodone is a weak inhibitor of both SERT and NET, whereas trazodone is also a weak but selective inhibitor of SERT

5-HT₂ antagonists- Clinical uses

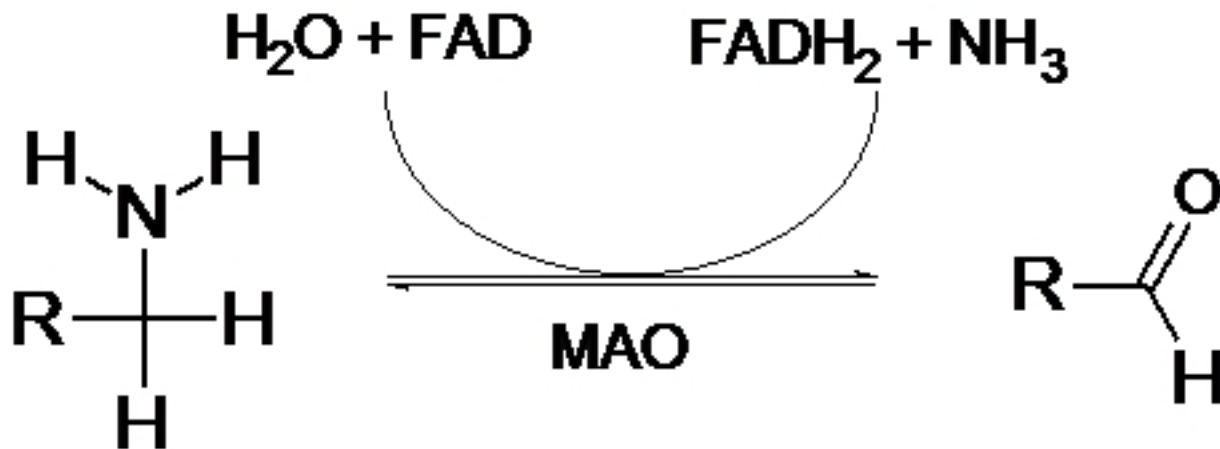
- **Depression:** Mirtazapine can be advantageous in patients with depression having sleep difficulties
- Low doses of trazodone (50-100 mg) have been used widely both alone and concurrently with SSRIs or SNRIs to treat insomnia

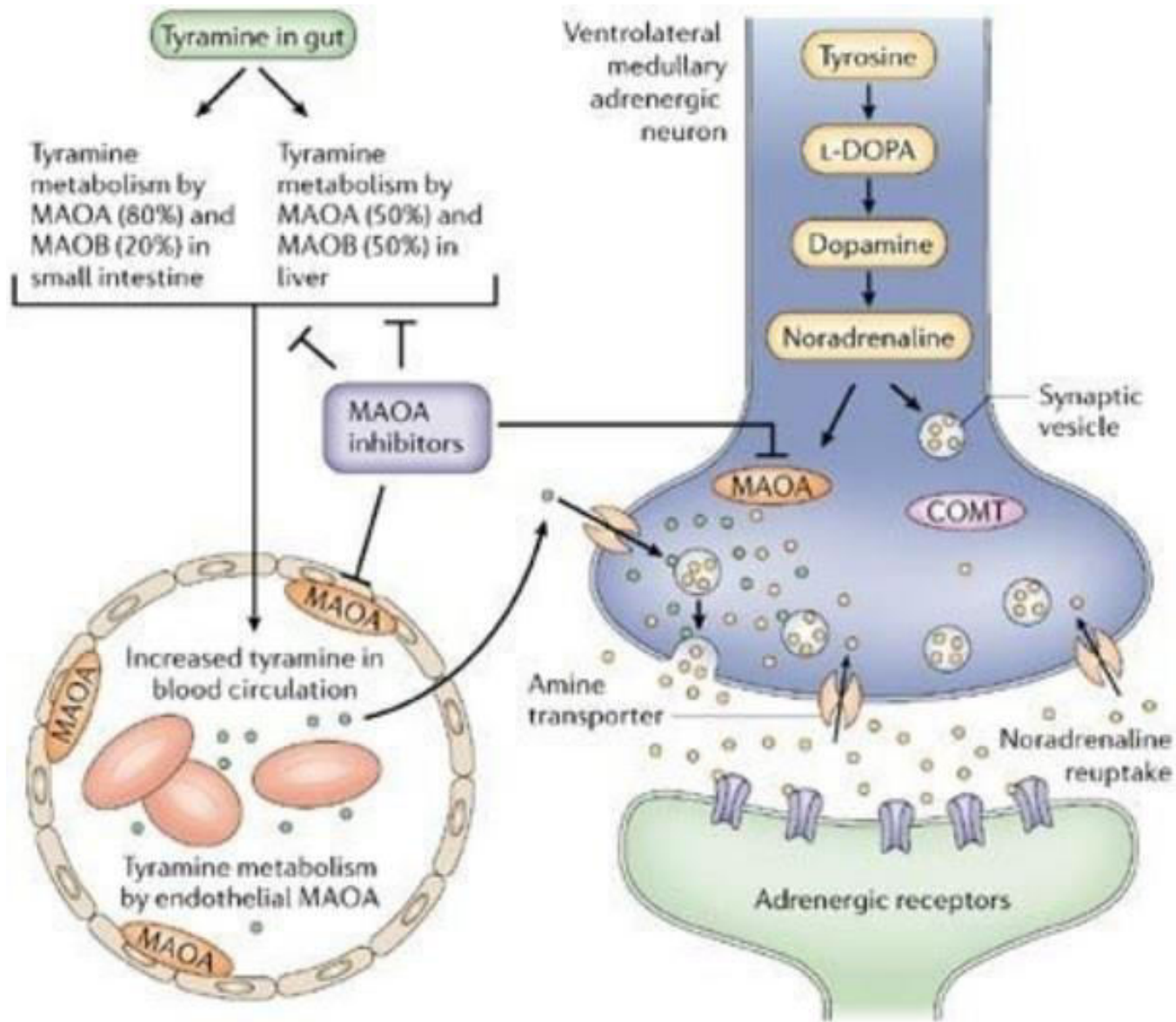
5-HT₂ antagonists

- 1) Sedation : necessitates dosing at bedtime
- 2) Dose-related GIT SEs
 - 1) weight gain (mirtazapine)

MONOAMINE OXIDASE (MAO) AND DEPRESSION

- MAO catalyze deamination of intracellular monoamines
 - MAO-A oxidizes epinephrine, norepinephrine, serotonin
 - MAO-B oxidizes phenylethylamine
 - Both oxidize dopamine nonpreferentially
- MAO transporters reuptake extracellular monoamine



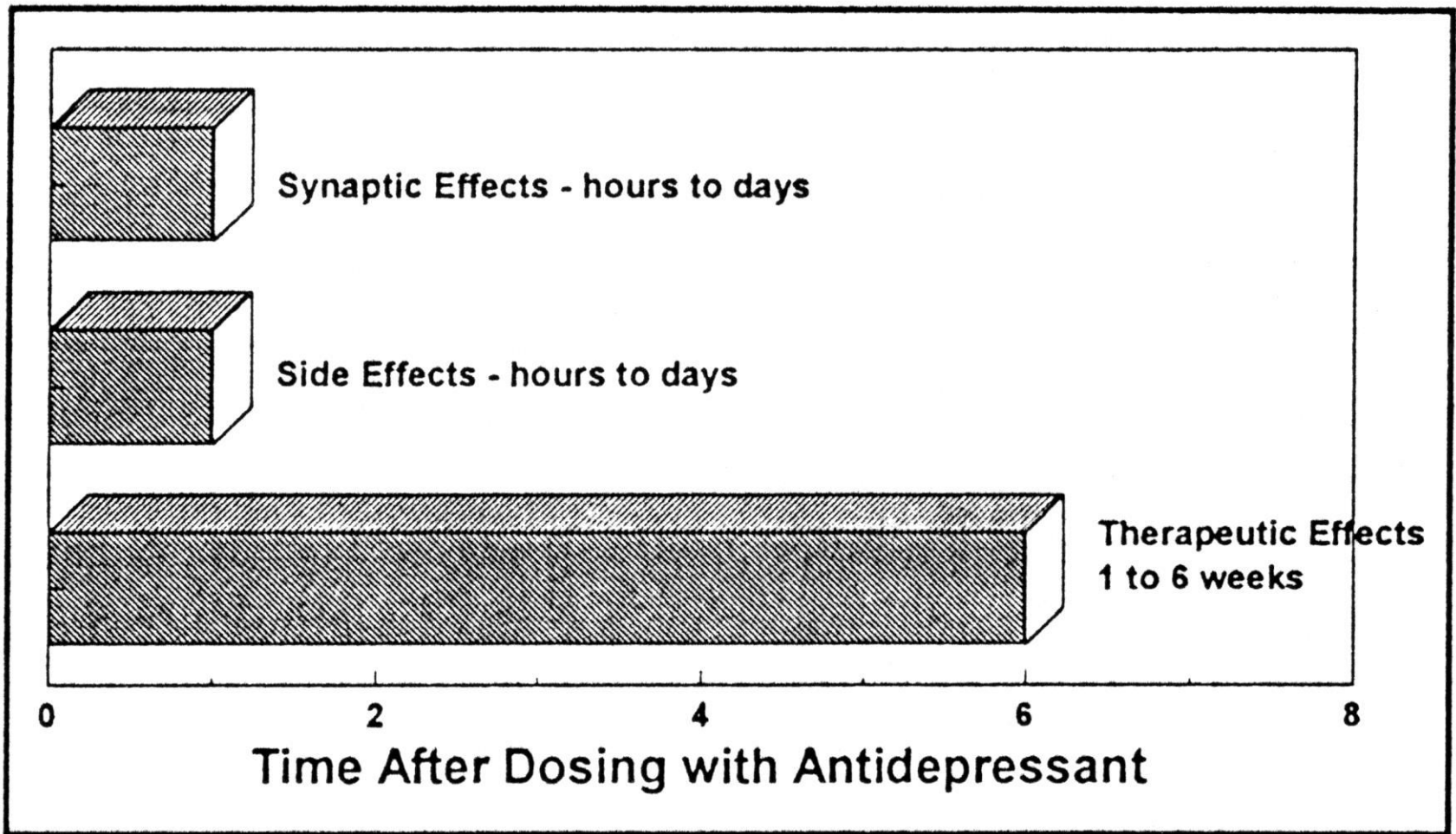


Monoamine oxidase inhibitors (MAOI)

- Inhibition of intra-neuronal degradation of serotonin and norepinephrine causes an increase in extracellular amine levels.
- Phenzelzine is a none selective
- Moclobemide is a reversible and selective inhibitor of MAO-A
- Selegiline is a selective for MAO-B
- Side effects:
Blood pressure problems, Dietary requirements, Weight gain, Insomnia, Edema.

Bupropion

- Good for use as an augmenting agent
- Mechanism of action likely reuptake inhibition of dopamine and norepinephrine
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- No weight gain, sexual side effects, sedation or cardiac interactions
- Low induction of mania
- Does not treat anxiety unlike many other antidepressants and can actually cause anxiety, agitation and insomnia



Onset of action of antidepressants. Synaptic effects and side effects of antidepressants begin before therapeutic effects are observed.

- Following the initiation of the antidepressant drug treatment there is generally a therapeutic lag lasting for 3-4 weeks.
- 8 weeks trial, then you allow to switch to another antidepressant.
- Partial response then add one another drug from different class.

- if the initial treatment was successful then 6-12 maintenance periods.
- If the patient has experience two episodes of major depression, then it is advisable to give an anti depressant life long.