# Antidepressants

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

Dr Malek Zihlif

# 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

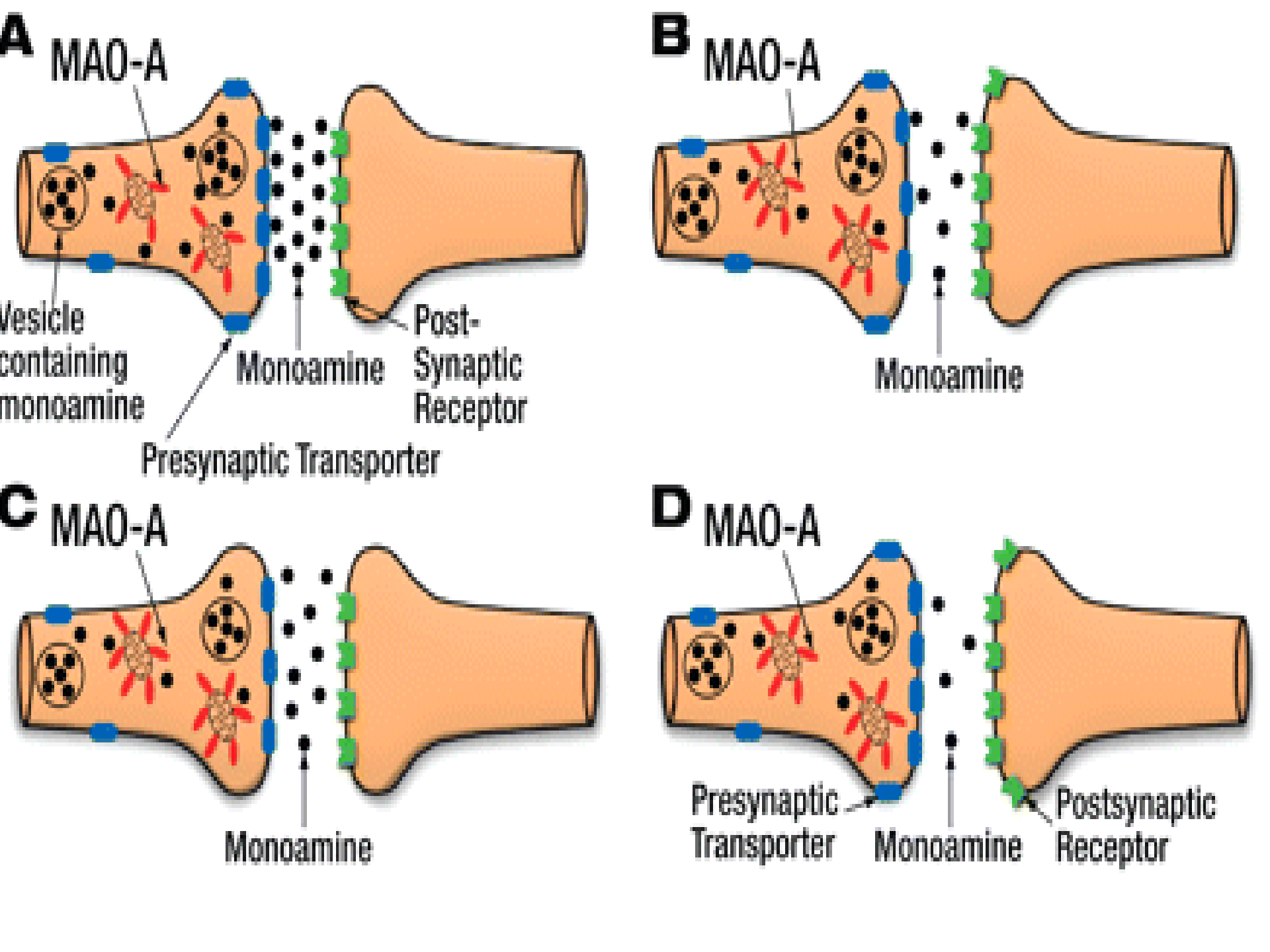
- **Depression appears to be associated with a drop in brain-derived neurotrophic factor (BDNF) levels in the cerebrospinal fluid and serum as well as with a decrease in tyrosine kinase receptor B activity**

- **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**


A
MAO-A
Vesicle containing monoamine
Monoamine
Post-Synaptic Receptor
Presynaptic Transporter
B
MAO-A
Monoamine
C
MAO-A
Monoamine
D
MAO-A
Presynaptic Transporter
Monoamine
Postsynaptic Receptor

# **Tricycle 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) Anticholinergeric 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-$HT_2$ 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 advantagous 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-$HT_2$ antagonists

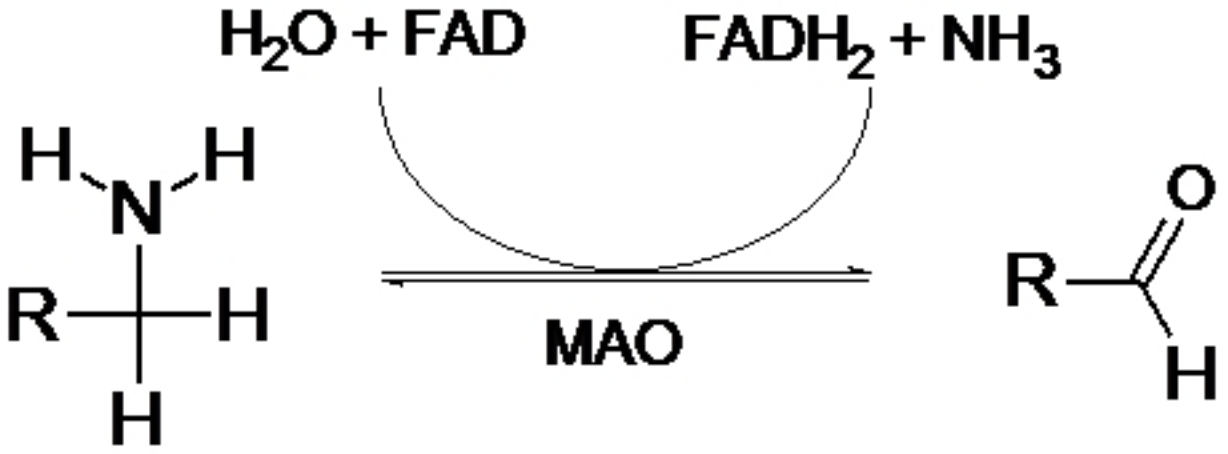
1) Sedation : necessitates dosing at bedtime

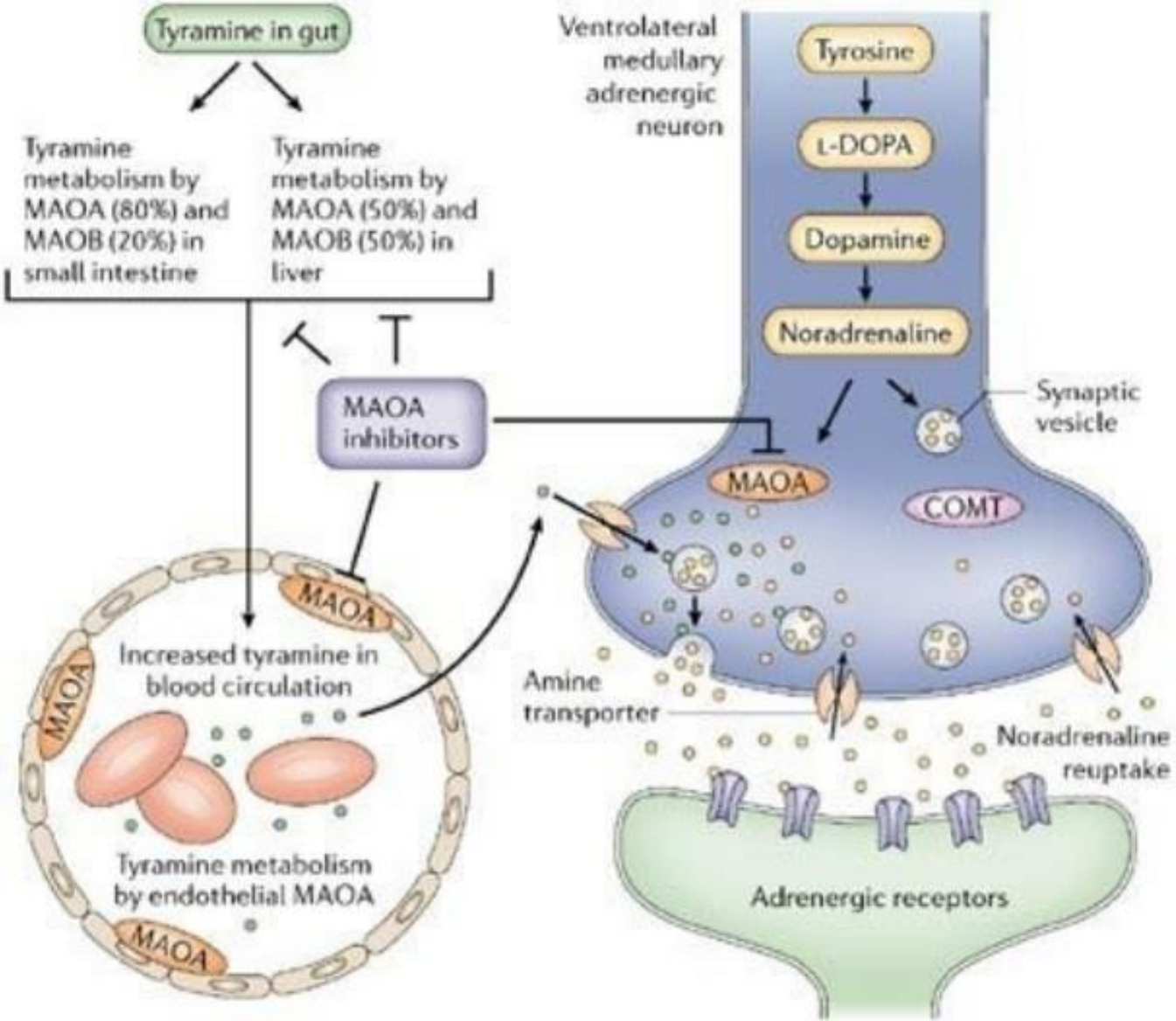
2) Dose-related GIT SEs

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.**
- **Phenelzine 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.**

# Buproprion

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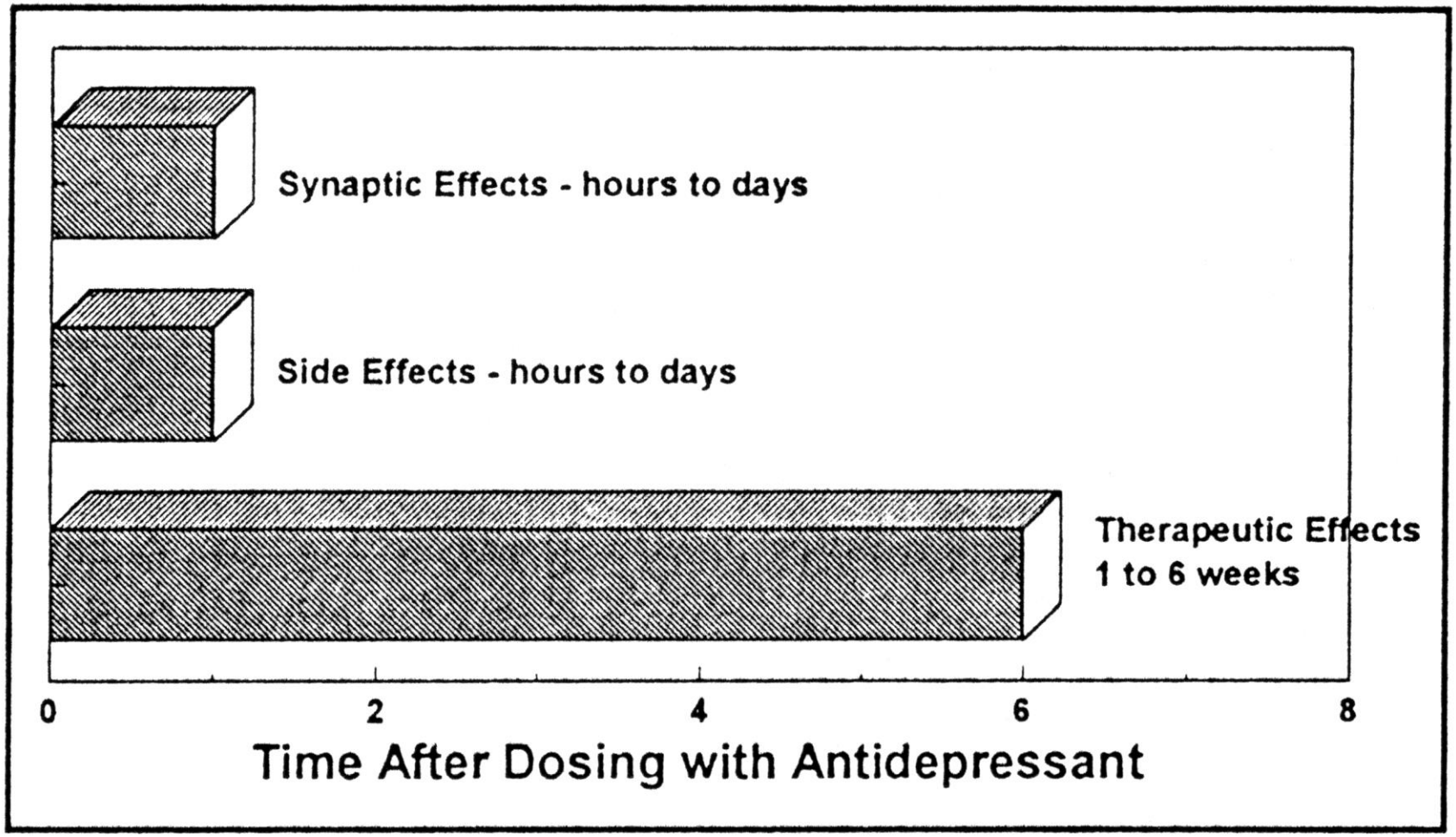
- No weight gain, sexual side effects, sedation or cardiac interactions
- Low induction of mania
- Does not treat anxiety unlike many other antidepressants and can actually cause anxiety, agitation and insomnia




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

- Following the initiation of the antideppresant dryg treatment there is generally a therapuetic 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.