Antidepressants - Lecture 2

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There are many types of depression, but we will start by talking about Typical depression which is best treated with SSRIs

SSRIs (Serotonin-specific reuptake inhibitors)

It takes a minimum of two weeks for the drugs to have an initial effect, but their maximum efficacy is achieved after 8 weeks. This is why we don't switch the medication before the 8-week mark

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.

Withdrawal symptoms can happen with all antidepressants

- **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)

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

All of these SSRI drugs have different kinetic and dynamic levels.

- **Sertraline**, **Citalopram** and **Escitalopram** are free of drug-drug interaction (no inhibitions of CP450)

- But **Fluoxetine** and **Paroxetine** can inhibit CYP2D6 and CYP2C9 enzymes, so they are not suitable for patients with polypharmacy status (taking more than 5 drugs)

- To avoid drug-drug interaction we describe either **Citalopram** or **Escitalopram** .
- **Sertraline** causes GI upset especially in elderly that's why we don't describe it!
  So.. in elderly patients the safest drugs are **Citalopram** and **Escitalopram** (prodrugs to each other)

- **Paroxetine** has sedative effect, so it's used for depressed patients with agitation, anxiety and INSOMNIA (ladies' disease)

- **Fluoxetine** has long half life (>24 hours), so discontinuation syndrome will not happen and can be used with patients that are not responsive and do not cooperate with you!
  But if **other** drugs are stopped, discontinuation syndrome starts after 2 days.

- **Sertraline** has **neither** sleepiness effect **nor** drug-drug interaction.

- Depressed patients die early especially those with comorbidities that's why we try to treat them

- 70% will respond to SSRIs from the 100% Typical depression patients, but not all of them will fully respond (might improve partially or completely)

- SSRIs increase the incidence/thoughts/attempts of suicide in younger ages (18-25 age)

- All antidepressants are contraindicated in pregnancy for their effect on the brain of the fetus.

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 (Fluoxetine) (Will be discussed in the bipolar lecture)

Serotonin/Norepinephrine reuptake inhibitors (SNRIs) (For half of those not responding to SSRIs)

- Slightly greater efficacy than SSRIs dual effect
- Slightly fewer adverse effects than SSRIs
  - Venlafaxine → Mostly the **sexual dysfunction** as its closely related to SSRIs, insomnia and agitation are also decreased.
  - Duloxetine

- Side effects:
  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 tapering is recommended after 2 weeks of administration rather than 6 weeks of use

Also used in pain management and ADHD, widely used compared to SSRIs that are only used in panic attacks, OCD and depression.

Tricycle antidepressant (Amitriptyline)

- For the other half of those not responding to SSRIs (typical depression)
- Oldest drugs but they have the strongest activity.
- Drugs of choice in **Atypical depression** (not major depression, the patient has emotions but depressed at the same time).

- **TCAs inhibit serotonin, norepinephrine, and dopamine transporters, slowing reuptake.**
  Increase the level of all three; serotonin, NE and dopamine
- **with a resultant increase in activity.**
- **Muscarinic acetylcholine receptors, alpha-adrenoceptors, and certain histamine (H1) receptors are blocked. (mediated by the tricyclic structure)**

Side effects:

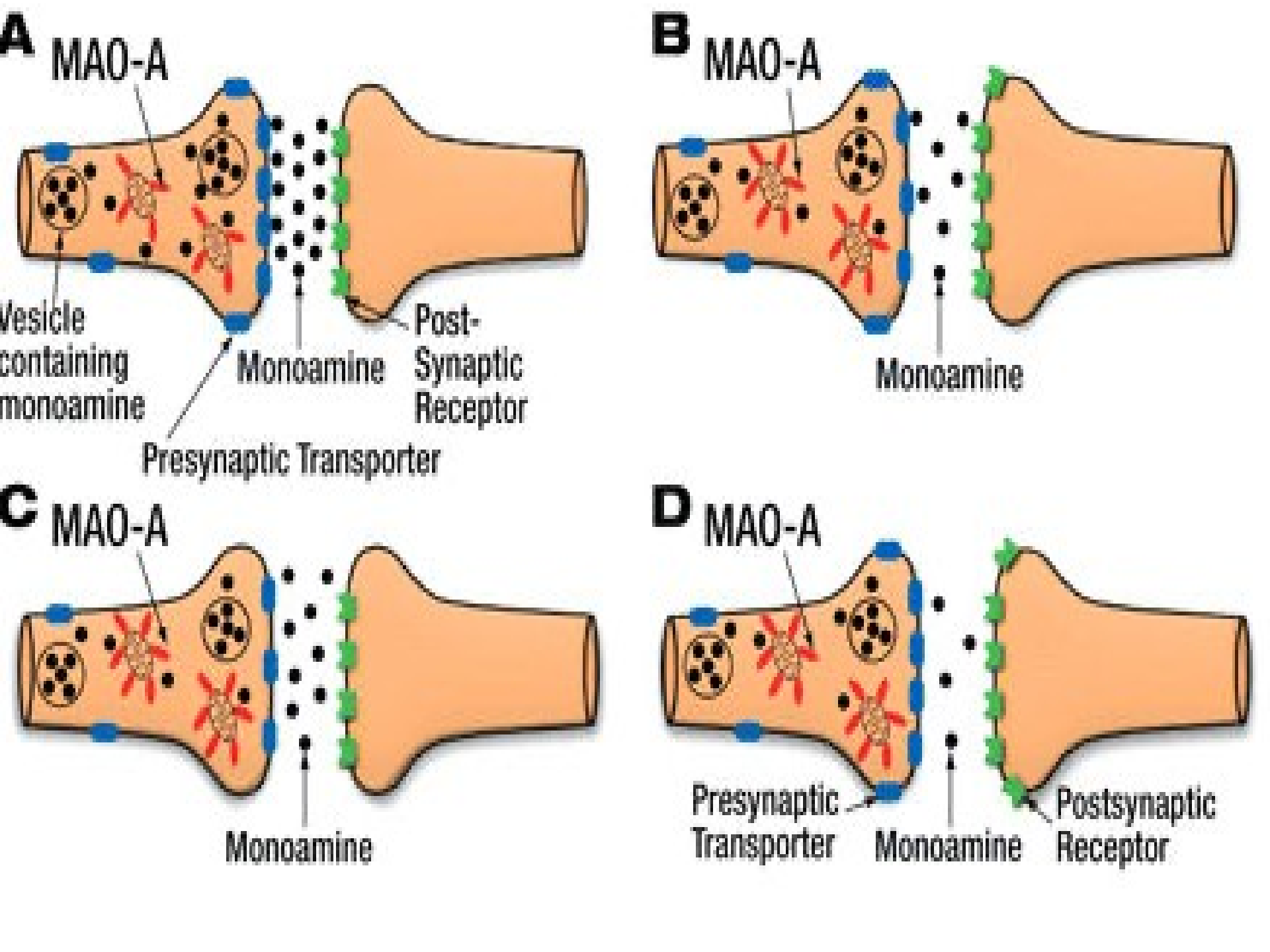
(1) drug-induced Sedation (By it's binding to H1 receptors)

(2) Orthostatic hypotension (Alpha1 receptors)

(3) Cardiac effects (Dopamine receptors)

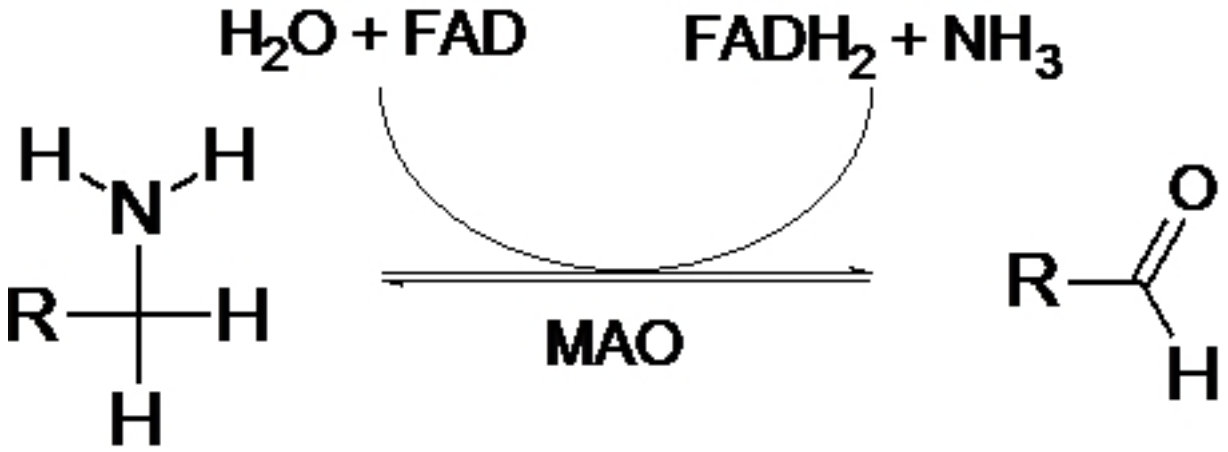
(4) Anticholinergeric effects dry mouth, constipation,blurred vision, urinary retention (Muscarinic receptors)

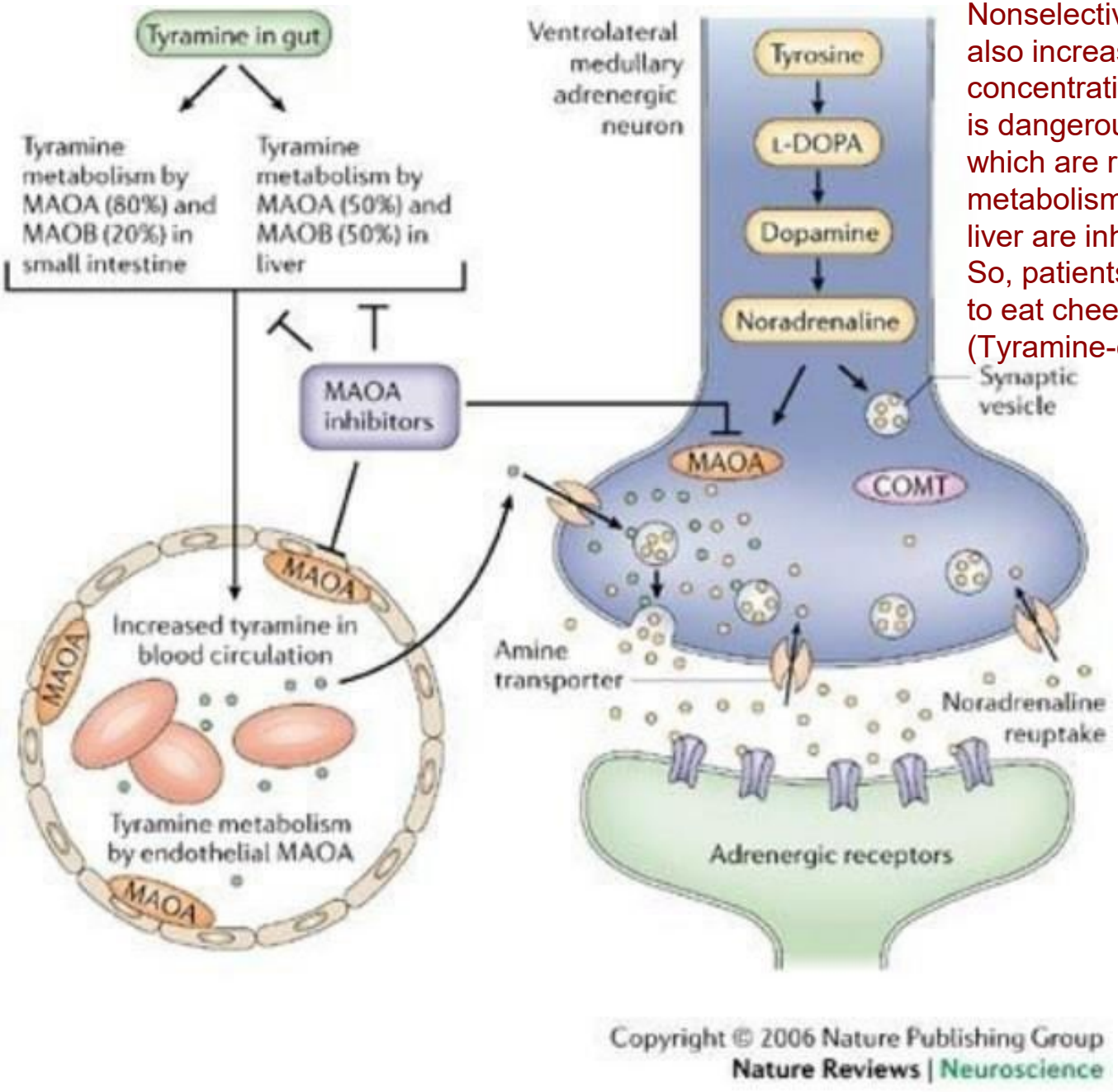
- These drugs have been replaced, because their binding everywhere leads to many side effects.


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

MONOAMINE OXIDASE (MAO) AND DEPRESSION (For atypical depression, they're better than and replace TCAs)

- 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





Nonselective MAOI drugs will also increase tyramine concentration in the blood which is dangerous! As MAO(A+B) which are responsible for the metabolism of tyramine in the liver are inhibited by these drugs. So, patients on MAOI are told not to eat cheese/ drink beer (Tyramine-containing food)

Monoamine oxidase inhibitors (MAOI)

- Drugs of choice for Atypical depression
- **Inhibition of intra-neuronal degradation of serotonin and norepinephrine causes an increase in extracellular amine levels.**
- **Phenelzine is a none selective,** Patient should avoid tyramine-containing food like cheese and beer
- Moclobemide is a reversible and selective inhibitor of MAO-A **Selegiline is a selective for MAO-B (Only increase dopamine)**

Phenelzine and **Moclobemide** are used as antidepressant drugs
Selegiline is only used as antiParkinson drug.

- **Side effects:**

Blood pressure problems, Dietary requirements, Weight gain, Insomnia, Edema.

Buproprion

- It doesn't cause serotonin syndrome when given with other antidepressants that's why we can combine it with any other drugs. (It doesn't increase serotonin)

► Good for use as an augmenting agent

► Mechanism of action likely reuptake inhibition of dopamine and norepinephrine (NDRI)

► No weight gain, sexual side effects , sedation or cardiac interactions

► Low induction of mania (because serotonin is not involved)

► Does not treat anxiety unlike many other antidepressants and can actually cause anxiety, agitation and insomnia

The doctor stopped here
Good luck ♥

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

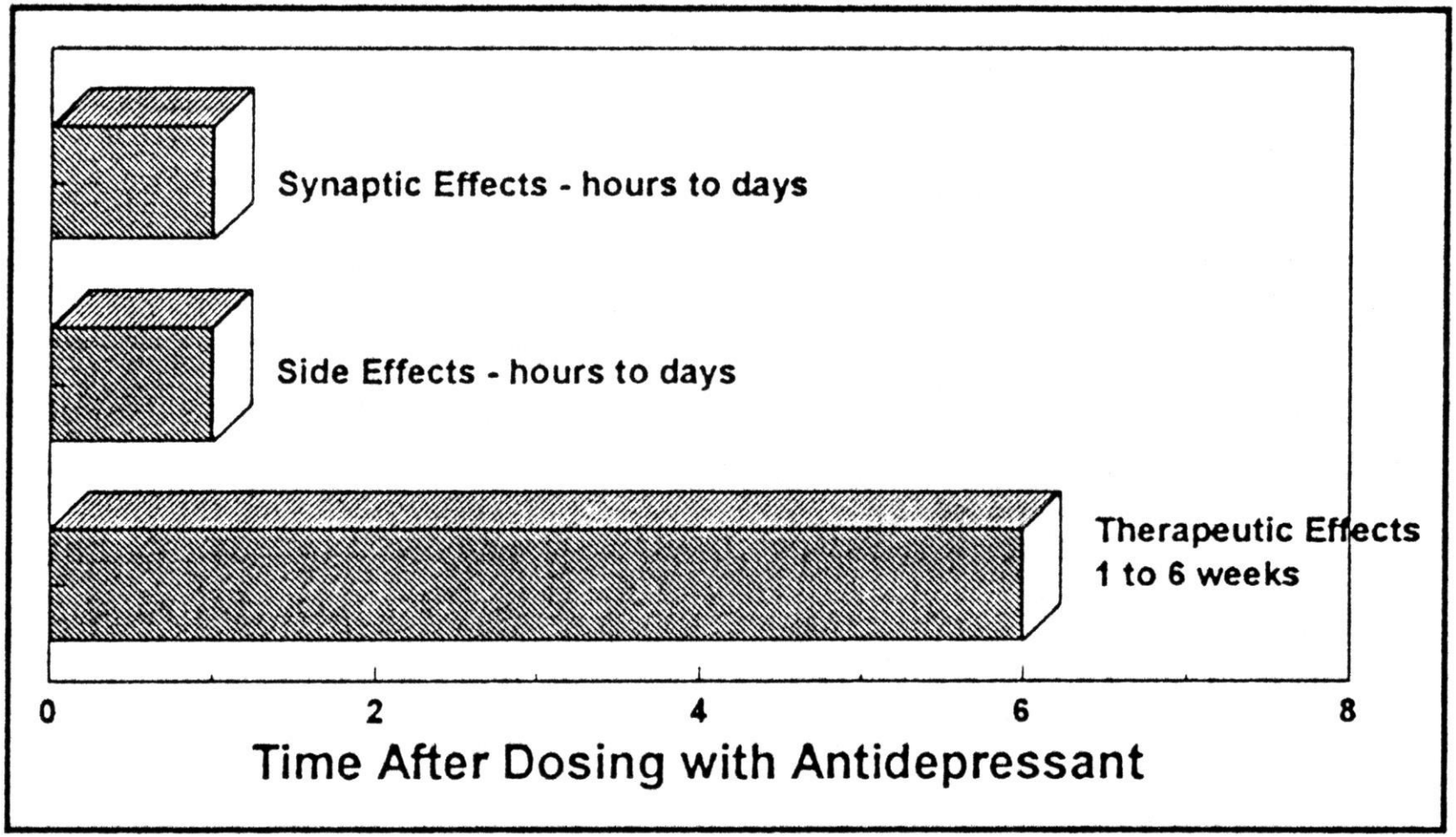
- Low doses of trazodone (50-100 mg) have been used widely both alone and concurrently with SSRIs or SNRIs to treat insomnia

5-HT_2 antagonists

1) Sedation : necessitates dosing at bedtime

2) Dose-related GIT SEs

1) weight gain (mirtazapine)



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.