

Lecture 3

Side Effects of Drugs Used for the Treatment of the Diseases of the Central Nervous System



Psychotropic drugs, defined by the WHO as those impacting the CNS, are used to treat mental disorders such as

Schizophrenia

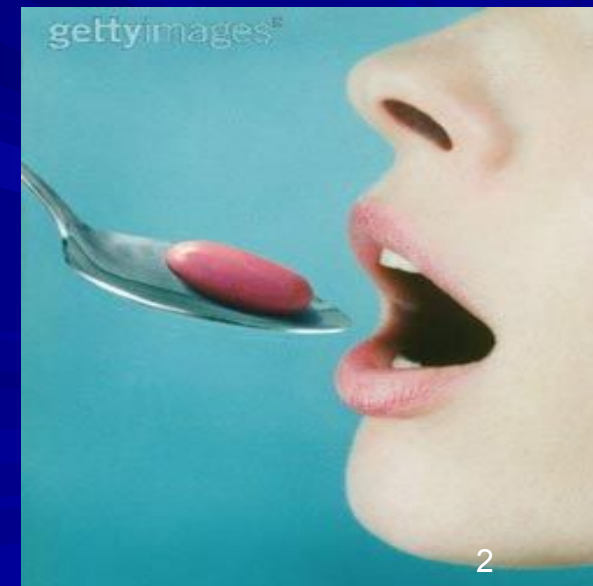
Bipolar disorder (manic-depressive psychosis – MDP)

Anxiety disorders

Attention deficit-hyperactivity disorder.

Psychotropic drugs, fall into 4 categories:

- Antipsychotics (*Neuroleptics*)
- Mood stabilizers
- Anti-anxiety drugs (*Tranquilizers*)
- Antidepressants



Common and well-documented SEs of psychotropic drugs include **Mania, Psychosis, Hallucinations, Depersonalization, Suicidal Ideation, Heart Attack, Stroke** and **Sudden Death**. The US FDA admits that probably **1-10%** of all the adverse drug effects are actually reported by patients or physicians.

Psychotropic drugs can increase the risk for **weight gain**, and therefore for **Heart Disease, Stroke** and **Diabetes**.

These include:

- **Neuroleptics**
- **Mood stabilizers**
- **Antidepressants.**

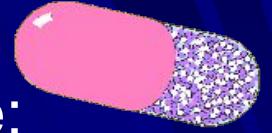
Patients need to pay close attention to their diet and activity levels.



Factors that cause increased risk of Side Effects from psychotropic drugs include:

- Decreased Kidney and Liver Function
- Concurrent Use of Other Drugs
- Taking High Doses of Drugs
- Longer Duration of Use





The more commonly used typical antipsychotics include:

Aminazine (Chlorpromazine)

Haloperidol (Haldol)

Fluphenazine (generic only)

first came on the market in the 1950s, and are used to treat both agitation and psychotic illnesses, and often have severe SE.

In the 1990's atypical antipsychotics were developed:

- Clozapine
- Sulpiride (*Eglonil*)
- Tiapride
- Risperidone

Common Side Effects of Typical Neuroleptics

- Photosensitivity - Sensitivity to the Sun, Sunburn
- Dry Mouth, Blurred Vision
- Rapid Heartbeat
- Constipation, Urinary Retention
- Sleepiness, Drowsiness
- Dizziness when changing positions
- Orthostatic Hypotension
- Skin Rashes
- Decrease in sexual interest or ability
- Menstrual problems for women

◆ Patients should sip water to relieve dry mouth and also wear sunscreen to prevent sunburns.

Typical antipsychotics cause problems with movement such as restlessness, muscle spasms, rigidity, facial grimacing and tremors.

Dystonia – acute spasm of the muscles:

- the muscles of the trunk, shoulders, and neck go into spasm, so that the head and limbs are held in unnatural positions;
- spasm of the facial muscles can prevent the patient from opening his jaws.

Parkinsonism refers to tremor and rigidity, similar to those seen in Parkinson's disease patients.

Akathisia - a state of agitation, distress, and restlessness .

Tardive dyskinesia is a movement disorder consisting of involuntary constant movements esp. of the lower face,
Tongue Protrusion,
Facial Grimacing,
Lip Smacking.

- Every year, an estimated **5%** of people taking typical antipsychotics get **TD** that can range from mild to severe.
- The condition happens to fewer people who take the new, atypical antipsychotics, but some people may still get **TD**.
- These symptoms also occur occasionally with the newer, atypical antipsychotic drugs, but far less often than with the older medications.

Clozapine is considered the most effective antipsychotic for patients with schizophrenia who haven't responded to other medications.

- It treats psychotic symptoms, hallucinations, and breaks with reality, such as when a person believes he or she is the president.

But **clozapine** can cause a serious problem:

- A decreased production of leucocytes, **agranulocytosis**, which can lead to infections.

Monitoring of blood work is necessary for patients taking clozapine every week or two.

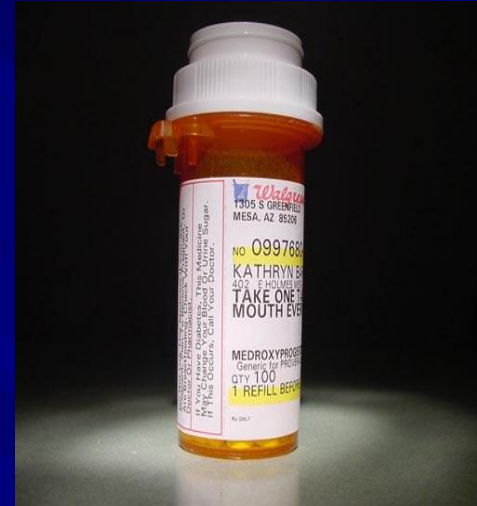
Other atypical antipsychotics such as

Sulpiride (Eglonil), **Tiapride**, **Risperidone** are effective, and none cause agranulocytosis. 9

Atypical Antipsychotics Cause:



Weight Gain
High Cholesterol
Diabetes.



- ◆ Patients' weight, glucose and lipid levels should be monitored regularly while taking an atypical antipsychotic.

Make Time for Physical Activity

- To lose weight or prevent weight gain, patients are recommended to plan to do at least 60 min of moderate to vigorous intensity exercise on most days,
- Find an activity that causes to breathe a little heavier and makes the HR quicken and pick smth they enjoy, because people are more likely to stick with it if they are having fun.
- A brisk walk at a pace of ~3–4 miles / hour is considered moderate intensity activity for the average person.



2001: *The Journal of Toxicology* reported that the ingestion of a single tablet of **Clozapine**, **Olanzapine** (*Zyprexa*) and **Risperidone** may cause significant toxicity in a toddler.

Ataxia (involuntary muscular movement), confusions, EPS (extrapyramidal symptoms), coma and respiratory arrest have been reported following ingestion of 100 mg of **Clozapine** in toddlers.



2005: Researchers published a study in

The New England Journal of Medicine that compared the older neuroleptics with several newer ones. Far from proving effectiveness, of the **1,493 patients who participated**

- **74%** discontinued taking antipsychotics before the end of their treatment due to inefficacy, intolerable SE or other reasons.
- **64%** of the patients stopped taking **Zyprexa** after 18 months of taking - commonly because it caused sleepiness, weight gain or neurological symptoms like stiffness and tremors.



The Malignant Neuroleptic Syndrome

Purulent Melting of Muscles accompanied by

- Pain in muscles,
- Hyperthermia,
- Stupor



can end fatally in the absence of intensive countermeasures.

Lithium preparations *Lithium carbonate* (Li_2CO_3) and *Lithium oxybutyrate* are often referred to as antimanic drugs, and *mood-stabilizers* - can cause side effects:

- Loss of coordination, Excessive thirst, Frequent urination,
- Blackouts, Changes in vision,
- Slurred speech, heartbeat, itching, rash,
- Seizures
- Hallucinations (seeing things or hearing voices that do not exist)
- Swelling of the eyes, face, lips, tongue, throat, hands, feet, ankles, or lower legs.

Patients should visit the doctor regularly to check the levels of lithium in the blood, and make sure the kidneys and the thyroid are working normally.

Anxiolytics *Diazepam (Valium), Chlordiazepoxide, Nozepam, Lorazepam* et al. tend to cause:

- Drowsiness
- Memory difficulties, Amnesia
- Decreased attention
- Excessive Sedation
- Confusion, Dizziness
- Orthostatic Hypotension
- Dry mouth, blurred vision
- ↑ Intraocular pressure
- Addiction and Intractable Dependence



A higher intake of BZDs was associated with an **increase** in **fractures** and thus with more serious consequences of **falls** which jeopardize these patients' safety.

Abrupt cessation can lead to severe withdrawal symptoms, including convulsions in some patients.

The withdrawal from drugs like

VALIUM (a brand of **DIAZEPAM**)

is more prolonged and often more difficult

than withdrawal from **HEROIN !**

Short-term treatment and a long tapering period is recommended to limit these risks.



Zolpidem is a non-benzodiazepine hypnotic prescribed often for insomnia.

2008: The Australian Therapeutic Goods Administration imposed a boxed warning in the product information for medicines containing **Zolpidem** (*Stilnox*).

The boxed warning stated:

“**Zolpidem** may be associated with potentially dangerous complex sleep-related behaviors which may include sleep walking, sleep driving and other bizarre behaviors.”

Antidepressants work on neurotransmitters such as **serotonin**, **noradrenaline**, and **dopamine**, that affect the mood and emotional responses.

Tricyclic antidepressants:

Imizine (*Imipramine*)

Amitriptyline

The most popular types of antidepressants - SSRI:

Fluoxetine (*Prozac*)

Fluvoxamine

Sertraline (*Zoloft*)

Paroxetine

Selective NORADRENALINE reuptake inhibitors:

Maprotiline

Desipramine

MAO inhibitors:

1. Non-selective:

Nialamide

Ttransamine (*Trancylpromine*)

2. Selective **MAO A** inhibitors:

Moclobemide (*Aurorix*)

Pirazidole (*Pirlindole*)

MAO A – Noradrenaline

Serotonin

MAO B – Dopamine,

Phenylethylamine,

Tyramine

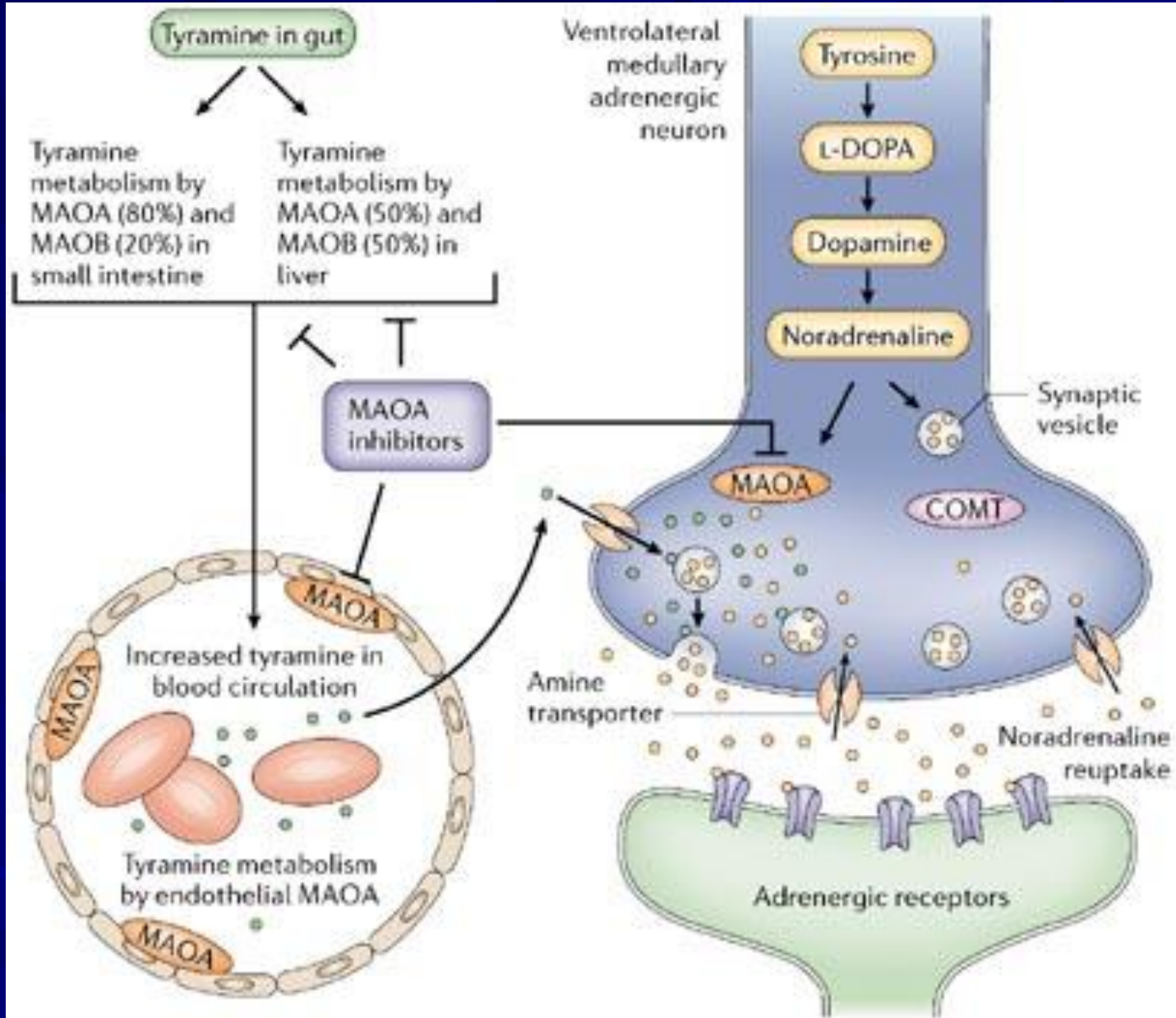
Tricyclic antidepressants can cause SE such as:

- Dry mouth, constipation, bladder problems
- Memory loss, Blurred vision
- Sexual problems, Drowsiness

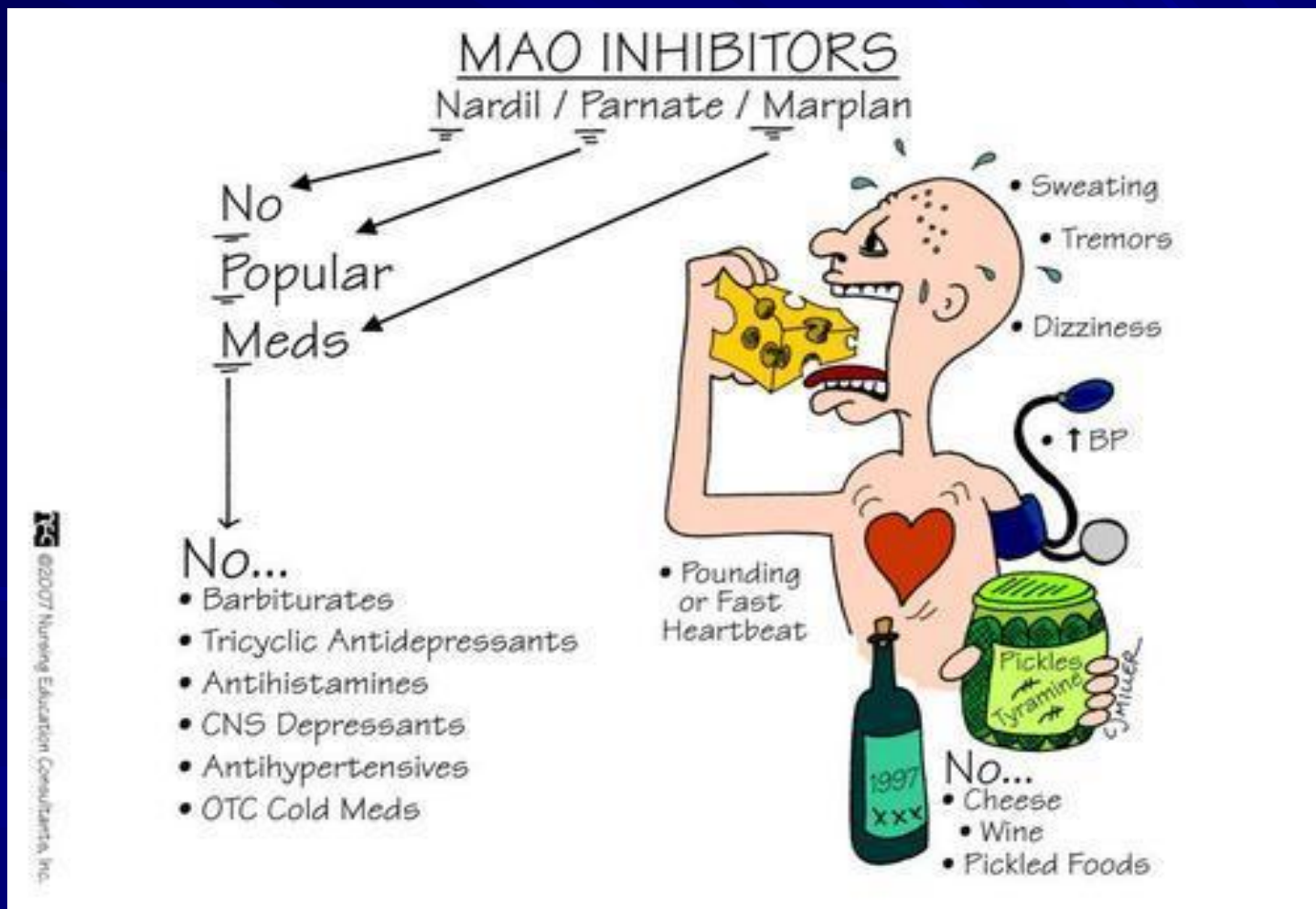


The SE associated with **SSRIs** and **SNRIs** include:

- an increase in suicidal thoughts
- Mania - a state of excitation with reduced sleep and increased energy
- Dizziness, insomnia or drowsiness;
- Diarrhea, nausea;
- Restlessness and Agitation (feeling jittery);
- Sexual dysfunction



- Patients taking **MAOIs** should avoid food containing **tyramine** as the combination of **MAOIs** and **tyramine** can lead to **increased BP**, potentially causing **stroke** or **cardiac arrhythmias**.
- An MAOI **Skin Patch** has recently been developed and may help reduce some of these risks.



- The medication should be taken **in the RIGHT DOSE for the right amount of time**. It can take 3 or 4 weeks until the medicine takes effect.
- It's important to give the body time to adjust to the change.
- If a medication does not work, it is helpful to be open to trying another one.
- If a person with difficult-to-treat depression does not get better with a first medication, chances of getting better increase when the person try a new one or added a second medication to his or her treatment.
- People don't get addicted, or "hooked," on the medications, but stopping them abruptly can cause withdrawal symptoms.



Carbamazepine induces the drug metabolizing enzymes in the liver, and the enhanced hepatic *P-450* system activity increases the metabolism of other drugs such as:

Anticoagulants

Oestrogens

Glucocorticoides

Cardiac glycosides.

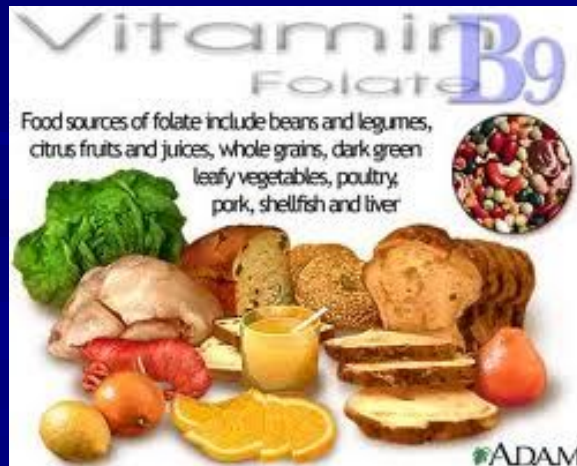
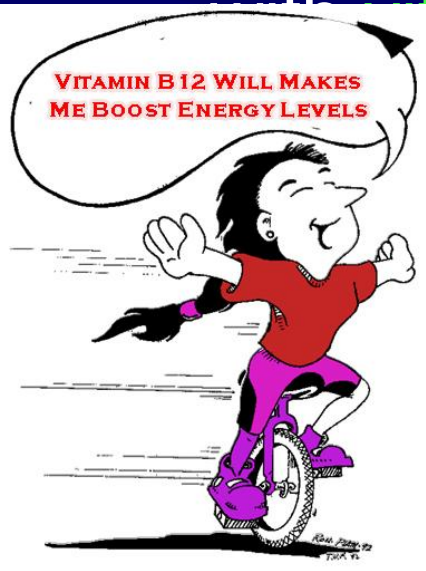
Adverse effects:

- ◆ Diplopia, ataxia, unsteadiness, drowsiness,
- ◆ Fluid retention, rashes, photosensitivity, hepatitis,
- ◆ Leukopenia, agranulocytosis, aplastic anaemia
- ◆ Lupus like syndrome
- ◆ Sluggishness, both mental and physical
- ◆ Serious liver toxicity.

Anyone being treated with *carbamazepine* should have frequent liver function tests.

Diphenin (*Phenytoin, Hydantoin*) – may cause:

- ❖ Depression of the CNS
- ❖ Nystagmus and ataxia
- ❖ Nausea, vomiting
- ❖ **Gingival hyperplasia** - because the drug interferes with **Folic Acid** metabolism
- ❖ **Megaloblastic anemia** - because the drug interferes with **Vitamin B₁₂** metabolism



Valproic acid may cause:

- Damage to the liver or pancreas
- Changes in weight
- Nausea, Vomiting, Stomach pain
- Anorexia, Loss of appetite
- Increase in **TESTOSTERONE** levels in teenage girls and lead to **polycystic ovarian syndrome (PCOS)**.



PCOS is a disease that can affect fertility and

make the menstrual cycle become irregular, but symptoms tend to go away after the drug is stopped.

It also may cause birth defects in women who are pregnant.



Valproic acid
Lamotrigine
Carbamazepine
Oxcarbazepine

and other anticonvulsant have
an FDA warning.

The warning states that their use may
increase the risk of **Suicidal Thoughts**

and Behaviors.



- People taking anticonvulsant medications for MDP or other illnesses should be closely monitored for new or worsening symptoms of depression, suicidal thoughts or behavior, or any

Side Effects of Anti- Parkinsonian Drugs

I. Activating Dopaminergic influences:

1. Precursors of Dopamine:

Levodopa

Sinemet (*Nakom*)

Madopar

2. D-receptor Agonists:

Bromocriptine

Pergolide

Cabergolin

3. MAO B Inhibitors:

Deprenil (*Selegeline*)

II. Inhibiting Glutamatergic influences:

Amantadine

III. Inhibiting Cholinergic

influences:

Cyclodol

Benztropine

Tropacine

Side Effects of Anti- Parkinsonian Drugs

- Low blood pressure upon standing
- Orthostatic hypotension
- Nausea (generally mild and transient)
- Ankle swelling
- Confusion , Hallucinations and Delusions
- Daytime sleepiness

Management: Discontinuing drugs

- Hydration
- Arising slowly, especially after a meal
- Sitting down if light headed
- Medications to raise BP



Thank You for
Attention!