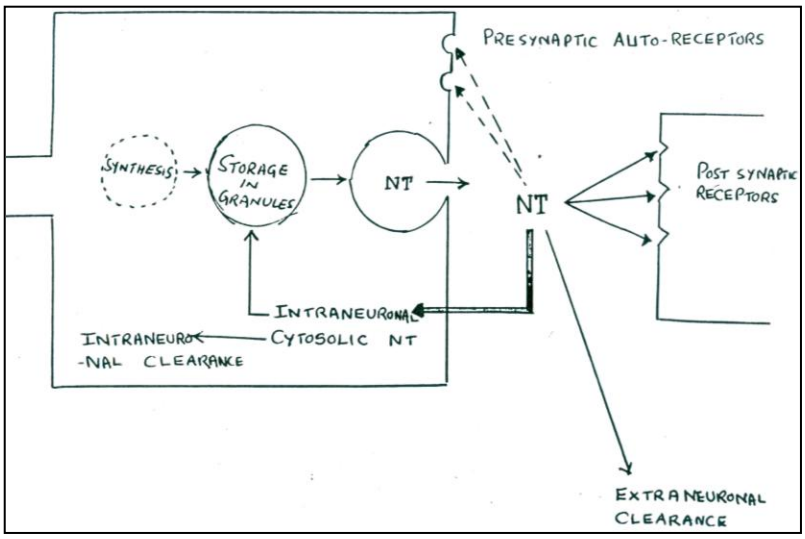
Unit VIII – Problem 11 – Pharmacology: Affective Disorders

- **Drugs acting on CNS:**
  - They are not like drugs acting on the heart or kidney where you understand the patho-physiology of the disease. In addition, there are animal models in which you can replicate and you can objectively measure things such as blood pressure or urine output… etc.
  - On the other hand, the patho-physiology of mood disorders is poorly understood and there are no objective measures (how am I going to measure how happy you are?!). In addition, you can't replicate complex human emotions in animals.
- **Notice that biological psychiatry emerged in 1962 (before that, most of psychiatrists used to treat these diseases as if it is a conflict between super-ego and ego… etc).**
- **Neuroleptics**: these are drugs which produce emotional quieting. This term is replaced now by (anti-psychotics).
- **WHO classification of drugs acting on CNS:**
  - **Anasthetics**: drugs inducing a temporary state characterized with one or more of the following: analgesia, paralysis, amnesia and unconsciousness.
  - **Analgesics**: group of drugs used to achieve analgesia (relief from pain).
  - **Anxiolytics/ sedative-hypnotics** (these were explained in details in problem 10).
  - **Antipsychotics**: class of psychiatric medication primarily used to manage psychosis (including delusions, hallucinations or disordered thought) which are seen in particular in schizophrenia and bipolar disorder.
  - **Antidepressants**: drugs used for treatment of major depressive disorders and other conditions.
  - **Psychomotor stimulants**: psychoactic drugs that induce temporary improvements in either mental or physical functions or both.
  - **Psychotomimetics**: drugs with actions which mimic the symptoms of psychosis.
    Note: all of the previous drugs are used as therapeutic drugs except for psychotomimetics which are considered as substance abuse.
- **Drugs acting on CNS are also classified according to their different approaches:**
  - **Chemical basis**: benzodiazepines, phenothiazines… etc
  - **Biochemical targets in which drugs are going to act**: monoamine oxidase inhibitors (MAOIs), selective serotonine reuptake inhibitors (SSRIs)… etc
  - **Behavioral effects (what is the effect which is produced?):** antipsychotic, antidepressant, antianxiety… etc
  - **Undefinable categories**: nootropic drugs (drugs used to treat dementia), atypical antipsychotics… etc
- **Evolution of monoaminergic hypothesis:**
  - **In 1960's, Schildkraut introduced the biogenic amine hypothesis** → based on discovering that reserpine which was used at that time as an antihypertensive drug lead to development of depression in patients. Notice that reserpine is depeleting monoamines. Therefore, he supposed that monoamines are associated with mood and behavior (these monoamines include: noreepinephrine, serotonin and dopamine).
  - **In 1980's, neurotransmitter dysregulation hypothesis was introduced**. They noticed that antidepressant usually takes 2-3 weeks to show its effect although levels of monoamines will be corrected within 24 hours of administrating the drug! This latent period is required for the dysregulation of receptor to be corrected.
  - **In 1990's, signal transduction impairment hypothesis was introduced.**
  - **In 2000, altered gene expression hypothesis was introduced**. Main focus was on transporter gene which is required for monoamines to cross the membrane of neurons.
  - **Nowadays, brain-derived neurotropic factors are studied.**
- **Psycho-neuro-immuno-endocrine model:**
  - Depressed people have suppressed immune system.

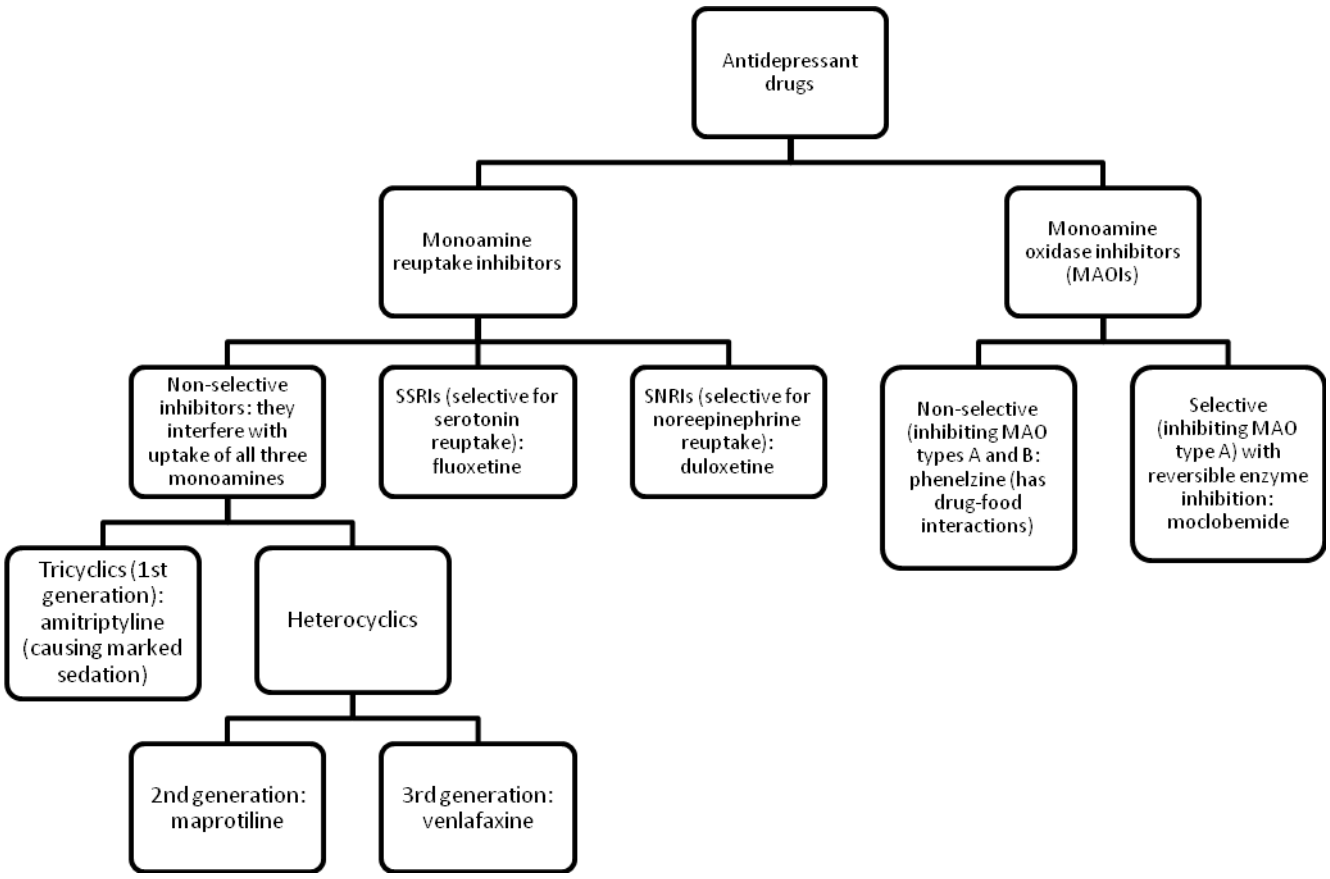
- When someone is depressed, endocrine axes are altered (hypothalamo-pituitary axis and thyroid axis mainly).

- **Targets for antidepressant drugs:**
  - The diagram shows a synapse with a neural terminal and a post-synaptic neural membrane with receptors. There are granules in which monoamines are stored and going to be released. Most of monoamines are recycled and transported back to the cytosol through the neural membrane (monoamines can be destroyed intraneuronally or extraneuronally by different enzyme systems). Released monoamines also act on post-synaptic receptors or as autoregulators on the presynaptic-receptors.



  - **So if we want to correct the deficiency in monoamines → there are 3 possible strategies:**
    - ✓ Drugs which enhance the release of monoamines from granules. These drugs are not routinely used because they cause dependence (they have a quick response).
    - ✓ Preventing the reuptake of monoamines from the synapse (uptake inhibitors: causing accumulation). This is the main strategy used nowadays.
    - ✓ Usage of monoamine oxidase inhibitors (MAOIs). These drugs are used conservatively because they result in drug-food interactions (especially with tyramine-containing food).

- **Classification of antidepressant drugs:**



- **Notice in non-selective monoamine reuptake inhibitors, as you move from 1st generation to 3rd generation:**
  - ✓ Sedation effect decreases,.
  - ✓ Antimuscarinic action decreases.
- Also notice that side effects of antidepressants are acute at the first 2 weeks but then tolerance is developed (they are not permanent).
- **Antidepressants have long half lives** (so even if the patient misses a dose → it is not a big deal). In addition, most of these drugs have active metabolites.
- **SSRIs have strong inhibition of CYP_{450}** (so it is important to take into consideration what other drugs are taken by the patient because this can result in drug-drug interactions). **SSRIs also impair the sexual function** (but can be used as a treatment for those who suffer from premature ejaculation because it delays it). In addition, **SSRIs might increase suicidal risk** particularly in children and teenagers.
- **Patients on MAOIs should not receive pethidine.**
- **Antidepressants overdose can produce serotonin syndrome** which is characterized by malignant hyperthermia, shivering, penile erection, seizure and coma.
- **Antidepressants can cause a transition in few patients from depression to hypomania (switch phenomenon).**
- **Drug-induced depression**: important examples include methyldopa (given to a pregnancy female with pre-eclampsia), β-blockers such as (propranolol) and steroids.

- **Antidepressant drug therapy:**
  - **Dose**: as a general rule, you always start therapy with a low dose.
  - **Frequency of administration**: some prefer to divide the dose while other prefer to give the full dose at bed time (because sedation and dryness of mouth is not important when someone is sleep).
  - **Clinical response**: sleep pattern of patient improves in the first few day while mood takes a minimum of 2 weeks to be improved. Optimal response to the drug is achieved after 3 months! → then, patient will be kept on maintenance therapy for the next 6-8 months → after that, you stop treatment by tapering dosage.
    - ✓ Notice that if patient suffers from more than relapses → he must be maintained on life-long therapy.
  - **Discontinuous of antidepressants can lead to withdrawal syndrome which is worse with paroxetine and venlafaxine.**
    - ✓ All SSRIs are category-C drugs (for pregnancy) except for paroxetine which is a category-D drug.
  - **Refractory depression (patients who doesn't respond):** switch to a drug from another category but don't combine drugs!
  - **If a patient is presented with major depressive illness and suicidal tendency** → hospitalize the patient in a special ward where there is no easy access to kill himself and administer antipsychotic drugs to them (to calm them down).
- **Antidepressant treatment augmentation strategy (with SSRIs):**
  - **When a patient is not responding satisfactorily to therapy, you might give another drug (this is known as the augmentation strategy). Common augmentation strategies which are used are:**
    - ✓ Lithium.
    - ✓ Thyroxine.
    - ✓ Buspirone: useful for patient having depression and anxiety.
    - ✓ Lamotrigine.
- **Treatment of mania:**
  - **Drugs which are used to treat mania include one or combination of the following:**
    - ✓ Lithium.
    - ✓ Divalproex (it is a precursor for valproic acid).

- ✓ Atypical antipsychotics: risperidone and olanzapine.
- **If the patient is extremely agitated**: lorazepam + haloperidol.
- **If the patient has bipolar disorder**: antidepressant + mood stabilizer (lithium).

- **Pre-lithium workup:**
  - **Thyroid function**: because prolonged lithium therapy can interfere with iodine uptake in thyroid gland and lead to subclinical or clinical hypothyroidism.
  - **Renal function**: lithium can lead to nephrogenic diabetes insipidus.
  - **Pregnancy test**: lower dose of lithium is used with monitoring.