Unit VIII – Problem 1 – Pharmacology: Drugs for Erectile Dysfunction

- **Erectile dysfunction is a more appropriate term to be used instead of impotence because:**
  - A person might not be interested in sex (psychologically).
  - A person cannot achieve erection (organic).
- **Male sexual response cycle (associated with the autonomic nervous system).**
  - **Libido**: it is the trigger for sexual performance (hormonal, CNS).
  - **Erection of the penis**: this is achieved by parasympathetic nervous system through M-receptors.
  - **Ejaculation**: this is achieved by sympathetic nervous system through α_1-receptors.
  - **Orgasm**: CNS.
  - **Resolution (vascular)**: in which a male will not be responsive to other sexual stimuli.
    Note: the cycle is similar in females except that erection occurs to the clitoris combined with vaginal lubrication.
- **Common sexual dysfunctions:**

Male	Female
Lack/ decreased libido (libido is under the control of androgens in both males & females. In females it is under the control of adrenal androgens that is why their libido will not be affected even after menopause).	**Lack/ decreased libido**
Erectile dysfunction	**Lack of vaginal lubrication** (transudation process from the vagina itself. Lack of lubrication is known as dyspareunia → leading to a painful intercourse).
Ejaculatory dysfunctions which include: failure, retrograde (ejaculation into the bladder) or premature (in which ejaculation occurs in less than 60 seconds after introducing the penis inside the vagina).	-
Lack of orgasm	**Lack of orgasm** known as anorgasmia (females have no refractory period that is why they can have multiple orgasms at the same time)

- **Pharmacotheraputic approaches to sexual dysfunctions:**
  - **Psycho-pharmacological** (limited success with this approach): enhancing the libido.
  - **Neuro-pharmacological**: elicit spontaneous erections (through neural mechanism).
  - **Vascular-pharmacological** (the most successful approach): elicit erection with vasodilators.
- **Erectile dysfunction in male:**
  - **Occurring in**: middle-age & elderly.
  - **Due to**: psychogenic (30%), organic (35%), or both (35%).
    Note: if a male can have erections during sleep, then his problem is psychological (not vascular).
  - **Iatrogenic causes** of erectile dysfunction are common so a full history of the patient is important to be taken because some medications might be the cause.
  - It is affecting the quality of life.
- **Sildenafil (Viagra):**
  - **It is a phosphodiesterase inhibitor of isoenzyme type-5.**
    Notes:
    - ✓ Caffeine is a phosphodiesterase inhibitor affecting neuronal isoenzymes.

- ✓ Isoenzyme type-5 is present specifically in corpora cavernosa of the penis. Inhibiting it will have minimal effects on other tissue which have other types of isoenzymes.

- The response to this drug is enhanced by arousal (foreplay).
- Strength and maintenance of erection is less than in normal men but better than placebo.
- **Mechanism of action:**
  - ✓ Penile vasodilation occurs due to the release of NO from endothelial cells of capillaries → NO will stimulate the enzyme guanylyl cyclase which will convert GTP into cGMP → normally, cGMP will be converted to GMP by the enzyme phosphodiesterase-5 (this is the enzyme which will be inhibited by the drug and thus maintaining the level of cGMP and erection will be sustained).
- **Kinetics:**
  - ✓ C_{max}: 1 hour after taking the drug.
  - ✓ $t_{½}$: 3-5 hours.
  - ✓ Dose: 25-100 mg (the median dose is 50mg and it is better to start with the lowest dose).
- **Adverse reactions:**
  - ✓ Common: headache (due to dilation of meningeal blood vessels), flushing (due to vasodilation in the skin) and dyspepsia (due to relaxation of lower esophageal sphincter which will lead to acid reflux).
  - ✓ Chronic (with long-term use of the drug): visual disturbances (blue halo).
  - ✓ Rare: retinal vein thrombosis.
- **Contraindications:**
  - ✓ If the patient is using other nitrovasodilators → because this will produce severe hypotension that will lead to activation of sympathetic nervous system and eventually resulting in myocardial infarction (MI).
  - ✓ If the patient is taking P_{450} inhibitors.
  - ✓ Interaction happens with alcohol.
- **A comparison between sildenafil, tadalafil and vardenafil:**

	Sildenafil	Tadalafil	Vardenafil
Oral bioavailability (PDEIs have poor absorption with fatty food & they must be taken on an empty stomach)	Medium	**Excellent**	Good
Time of onset	45-60 min	**15-30 min (FAST)**	30-60 min
Duration of effect	< 8 hrs	**24 hrs (LONGEST)**	< 10 hrs
Biotransformation	Cytochrome P_{450}		

- **Other vasodilators for erectile dysfunction:**
  - **Intracavernous self-injection or intraurethral application of the following:**
    - ✓ α1 adrenoceptor blockers (phentolamine).
    - ✓ Prostaglandin E1 (alprostadil).
- **Iatrogenic sexual dysfunction in male:**
  - Antiandrogens (androgen receptor blocker; 5-α reductase inhibitors).
  - **Antihypertensive** (thiazides, beta blockers and methyldopa)
  - **Psychotropics** (antipsychotics, antidepressants and lithium).
  - Sympatholytics (α1 blockers → which will interfere with the process of ejaculation).
  - Antihistamines:
    - ✓ H1 blockers are anticholinergic → inhibiting erection.
    - ✓ H2 blockers are antiadrenergic → inhibiting ejaculation.