**Assist Professor Hayder M. Al-kuraishy Lec.7**

**Erectile dysfunction** (**ED**) or **impotence** is sexual dysfunction characterized by the inability to develop or maintain an erection during sexual activity in humans. Penile erection is managed by two mechanisms: the reflex erection, and the psychogenic erection, which is achieved by erotic stimuli. The former uses the peripheral nerves and the lower parts of the spinal cord, whereas the latter uses the limbic system of the brain. In both cases, an intact neural system is required for a successful and complete erection. Stimulation of the penile shaft by the nervous system leads to the secretion of nitric oxide (NO), which causes the relaxation of smooth muscles of corpora cavernosa (the main erectile tissue of penis), and subsequently penile erection. Additionally, adequate levels of testosterone and an intact pituitary gland are required for the development of a healthy erectile system. Impotence may develop due to hormonal deficiency, disorders of the neural system, lack of adequate penile blood supply or psychological problems. Spinal cord injury causes sexual dysfunction including ED. Restriction of blood flow can arise from impaired endothelial function due to the usual causes associated with coronary artery disease, but can also be caused by prolonged exposure to bright light.

Erection is caused by vasorelaxation in the arteries and arterioles supplying the erectile tissue. This increases penile blood flow. Nitric oxide is the main mediator of erection and is released both from nitrergic nerves and from endothelium.

Erectile function is adversely affected by several therapeutic drugs (including many antipsychotic, antidepressant and antihypertensive agents). Furthermore, erectile dysfunction is common in middle-aged and older men.

Aphrodisiac drugs (i.e. a drug that stimulates libido). Alcohol 'provokes the desire but takes away the performance', and cannabis can also release inhibitions and probably does the same. **PGE**1 (**alprostadil**) is often combined with other vasodilators when given intracavernosally. It can also be given transurethrally as an alternative to injection. Adverse effects of all these drugs include priapism,. Treatment consists of aspiration of blood and, if necessary, cautious intracavernosal administration of a vasoconstrictor such as **phenylephrine**.

**PHOSPHODIESTERASE TYPE V INHIBITOSR**

**Sildenafil**, the first selective phosphodiesterase type V inhibitor, was found incidentally to influence erectile function. **Tadalafil** and **vardenafil** are also phosphodiesterase type V inhibitors licensed to treat erectile dysfunction. Tadalafil is longer acting than sildenafil. In contrast to intracavernosal vasodilators, phosphodiesterase type V inhibitors are not sufficient to cause erection independent of sexual desire, but enhance the erectile response to sexual stimulation. They have transformed the treatment of erectile dysfunction.

Phosphodiesterase V is the isoform that inactivates cGMP. Nitrergic nerves release nitric oxide (or a related nitrosothiol), which diffuses into smooth muscle cells, where it activates guanylate cyclase. The resulting increase in cytoplasmic cGMP mediates vasodilation via activation of protein kinase G Consequently, inhibition of phosphodiesterase V potentiates the effect on penile vascular smooth muscle of endothelium-derived nitric oxide and of nitrergic nerves that are activated by sexual stimulation. Other vascular beds are also affected, suggesting other possible uses, notably in pulmonary hypertension.

Tadalafil has a longer half-life than sildenafil, so can be taken longer before sexual activity. A clinically important pharmacodynamic interaction occurs with *organic nitrates*, which work through increasing cGMP and are therefore markedly potentiated by sildenafil. Consequently, concurrent nitrate use, including use of **nicorandil**, contraindicates the use of any phosphodiesterase type V inhibitor. Many of the unwanted effects of phosphodiesterase type V inhibitors are caused by vasodilation in other vascular beds; these effects include hypotension, flushing and headache. Visual disturbances have occasionally been reported and are of concern because sildenafil has some action on phosphodiesterase VI, which is present in retina and important in vision. The manufacturers advise that sildenafil should not be used in patients with hereditary retinal degenerative diseases (such as retinitis pigmentosa) because of the theoretical risk posed by this. Vardenafil is more selective for the type V isozyme than is sildenafil but is also contraindicated in patients with hereditary retinal disorders.

* The penile blood vessel contain PDE-5 enzyme.
* Sexual stimulation ↑ penile NO → ↑ guanylcyclase → ↑ cGMP → ↓ intracellular Ca+ → penile vasodilatation → erection, but PDE-5 remove the cGMP, so PDE-5 inhibitor ↑ cGMP and ↑ erection.
* **PDE-5 inhibitors are:**
1. **Sildenafil (viagra):**
* Rapid acting (within 30 min.) short duration (4 hours).
* Its absorption ↓ by food, mainly fatty food.
* Cause color vision disturbance due to PDE-6 inhibition in retina cause blue vision.
1. **Tadalafil (Cialis):**
* Slow acting, long duration (36 hours).
* Not affected by food.
* Not cause color vision disturbance, because it not inhibit PDE-6

All these drugs ☺**NEED SEXUAL STIMULATION**

* NO-donor → organic nitrate and Ca+ channel blocker ↑ penile blood flow and erection.
* **Vardenafil:**
	+ Effective after 30 minutes.
	+ Useful in subgroups which are difficult to treat.
	+ Its effect is reduced by a fatty meal but it has less interaction with food. A rapidly absorbed orodispersible preparation has now been made available which is more rapdily absorbed.
* **Avanafil:**
	+ Effective after 30 minutes.
	+ High selection for phosphodiesterase inhibition minimises the risk of side-effects.
	+ Effect may be delayed when administered with food but can be taken with or without food.

**Sulfoaildenafil** (natural viagra )is structural analog of sildenafil (Viagra), a phosphodiesterase type 5 inhibitor,has been found as an adulterant in a variety of supplements which are sold as "natural" or "herbal" sexual enhancement products.

***Panax ginseng* (“red ginseng”)** has solid research behind it. Researchers [reviewed seven studies](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2561113/) of red ginseng and ED in 2008. Dosages ranged from 600 to 1,000 mg three times daily. They concluded there was “suggestive evidence for the effectiveness of red ginseng in the treatment of erectile dysfunction.” One small [study](http://nutraxin.com.tr/pdf/RhodiolaRosea/Rhodiola_02.pdf) also indicated *Rhodiola rosea* may be helpful. Twenty-six out of 35 men were given 150 to 200 mg a day for three months. They experienced substantially improved sexual function.

Dehydroepiandrosterone (DHEA) is a natural hormone produced by the adrenal glands. It can be converted to both estrogen and testosterone in the body. Scientists make the dietary supplement from wild yam and soy.

**L-arginine** is an amino acid naturally present in the body. It helps make nitric oxide. Nitric oxide relaxes blood vessels to facilitate a successful erection.

**Bromocriptine** also has a sexuality-enhancing effect, though it is not commonly sold for that purpose. Nevertheless, there is little doubt that in many people, bromocriptine will support sexual response. The reason why the drug is not specifically sold as impotence or frigidity medication: a sufficient number of studies to achieve FDA approval for the purpose of sexual enhancement have not been conducted. Bromocriptine, on the other hand, works on the brain, making a person more receptive for sexual stimulation and creating a frame of mind for more powerful orgasms. Both effects are a logical consequence of the way, bromocriptine is traditionally used… to lower levels of the hormone prolactin, and to increase levels of the neurotransmitter dopamine.
High levels of prolactin are generally associated with a decreased sex drive. So, by lowering levels of prolactin, especially when they are high, bromocriptine increases the interest in sex.

**Yohimbine** blocks the pre- and post-synaptic α2 receptors. Blockade of post-synaptic α2 receptors causes only minor corpus cavernosum smooth muscle relaxation, due to the fact that the majority of adrenoceptors in the corpus cavernosum are of the α1 type. Blockade of pre-synaptic α2 receptors facilitates the release of several neurotransmitters in the central and peripheral nervous system — thus in the corpus cavernosum — such as nitric oxide and norepinephrine. Whereas nitric oxide released in the corpus cavernosum is the major vasodilator contributing to the erectile process, norepinephrine is the major vasoconstrictor through stimulation of α1 receptors on the corpus cavernosum smooth muscle. Under physiologic conditions, however, nitric oxide attenuates norepinephrine vasoconstriction.

**Apomorphine** hydrochloride was a therapy used in the treatment of erectile dysfunction . It is its mode of stimulating dopamine in the brain which is believed to enhance the sexual response. It was found to be of poor efficacy. Erections in men are generally classified into two categories: Reflexogenic erections, that is erections triggered by physical stimulus, and Psychogenic erections, which are triggered by sexual fantasies, thoughts and looking at things which are sexually stimulating. Psychogenic erections are generally gradually lost in men somewhere between the ages of 45 and 65. Apomorphine has been shown to restore Psychogenic erections in men who are otherwise unable to achieve them.

**Papaverine** has also been demonstrated to be a selective phosphodiesterase inhibitor for the PDE10A subtype found mainly in the striatum of the brain. When administered chronically to mice, it produced motor and cognitive deficits and increased anxiety, but conversely may produce an antipsychotic effect. Papaverine when injected in penile tissue causes direct smooth muscle relaxation and consequent filling of the corpus cavernosum with blood resulting in erection. A topical gel is also available for ED treatment.

# Sexual motivation and hormones

**Testosterone**appears to be a major contributing factor to sexual motivation in male. The elimination of testosterone in adulthood has been shown to reduce sexual motivation in male. Male humans who had their testicular function suppressed with a GnRH anatagonist displayed decreases in sexual desire. Testosterone levels in males have been shown to vary according to the ovulating state of females. Males who were exposed to scents of ovulating women recorded a higher testosterone level than males who were exposed to scents of non-ovulating women.

**Estrogen and progesterone** typically regulate motivation to engage in sexual behaviour for females. Estrogens have been shown to correlate positively with increases in female sexual motivation, and progesterone has been associated with decreases in female sexual motivation. Menopause is associated with a rapid decline of estrogen, as well as a steady rate of decline of androgens. The decline of estrogen and androgen levels is believed to account for the lowered levels of sexual desire and motivation in postmenopausal women.

**Oxytocin and vasopressin** are implicated in regulating both male and female sexual motivation. Oxytocin is released at orgasm and is associated with both sexual pleasure and the formation of emotional bonds. Based on the pleasure model of sexual motivation, the increased sexual pleasure that occurs following oxytocin release may encourage motivation to engage in future sexual activities. Emotional closeness can be an especially strong predictor of sexual motivation in females and insufficient oxytocin release may subsequently diminish sexual arousal and motivation in females.

High levels of vasopressin can lead to decreases in sexual motivation for females. A link between vasopressin release and aggression has been observed in females, which may impair female sexual arousal and sexual motivation by leading to feelings of neglect and hostility toward a sexual partner. In males, vasopressin is involved in the arousal phase. Vasopressin levels have been shown to increase during erectile response in male sexual arousal, and decrease back to baseline following ejaculation. The increase of vasopressin during erectile response may be directly associated with increased motivation to engage in sexual behaviour.

**Frigidity**

Frigidity: Failure of a female to respond to sexual stimulus; or failure of a female to achieve an orgasm (anorgasmia), also called **Female sexual arousal disorder** (**FSAD**). These factors include both psychological and physical factors. Psychologically, possible causes of the disorder include the impact of childhood and adolescence experiences and current events - both within the individual and within the current relationship.

**Flibanserin** is an agonist at postsynaptic serotonin (5HT) 5HT1a receptors and an antagonist at 5HT2 receptors; the binding appears preferential for prefrontal cortex (PFC) pyramidal neurons that regulate monoamine release. Thus, flibanserin dosing results in increased release of dopamine (DA) and norepinephrine (NE) in the PFC. Flibanserin is also associated with decreased release of 5HT in the PFC, nucleus accumbens, and hypothalamus, but not hippocampus. Whereas DA and NE putatively increase sexual desire and arousal and 5HT inhibits sexual desire and arousal, this pharmacodynamic profile may explain the suggested benefits of the drug in women with hypoactive sexual desire disorder (HSDD). Flibanserin was originally developed as an antidepressant with a potentially rapid onset of action it was effective in some but not all animal models of depression.

**Estrogen therapy.**  improvs vaginal tone and elasticity, increasing vaginal blood flow and enhancing lubrication.

**Androgen therapy.**  Testosterone plays a role in healthy sexual function in women as well as men, although women have much lower amounts of testosterone.Androgen therapy for sexual dysfunction is controversial. Some studies show a benefit for women who have low testosterone levels and develop sexual dysfunction.

**Phosphodiesterase inhibitors** not work on females