Drugs for Urologic Disorders

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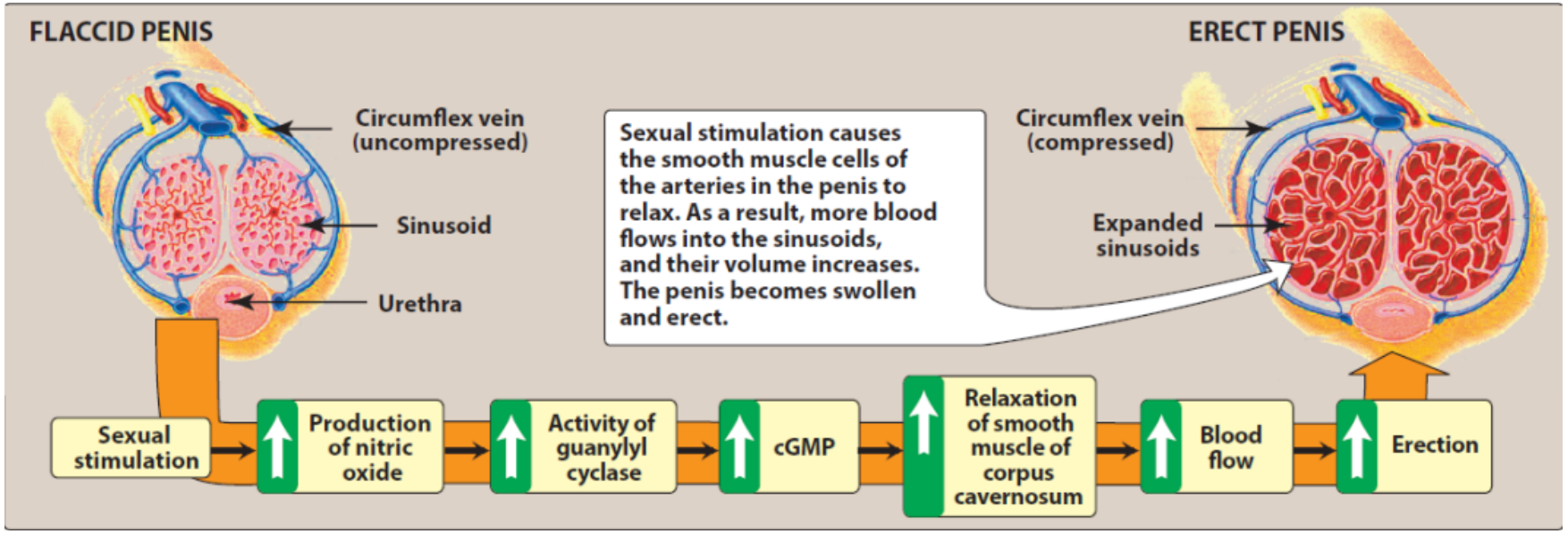
Drugs used to treat erectile dysfunction and benign prostatic hyperplasia

- Erectile dysfunction (ED) is the inability to maintain penile erection for the successful performance of sexual activity.

- ED has many physical and psychological causes, including vascular disease, diabetes, medications, depression, and sequelae to prostatic surgery.



Drugs used to treat erectile dysfunction and benign prostatic hyperplasia

- Benign prostatic hyperplasia (BPH) is nonmalignant enlargement of the prostate, which occurs naturally as men age.

- As the prostate grows in size, lower urinary tract symptoms develop, which can significantly impact a patient's quality of life.

Drugs used to treat erectile dysfunction

A. Phosphodiesterase-5 (PDE-5) inhibitors

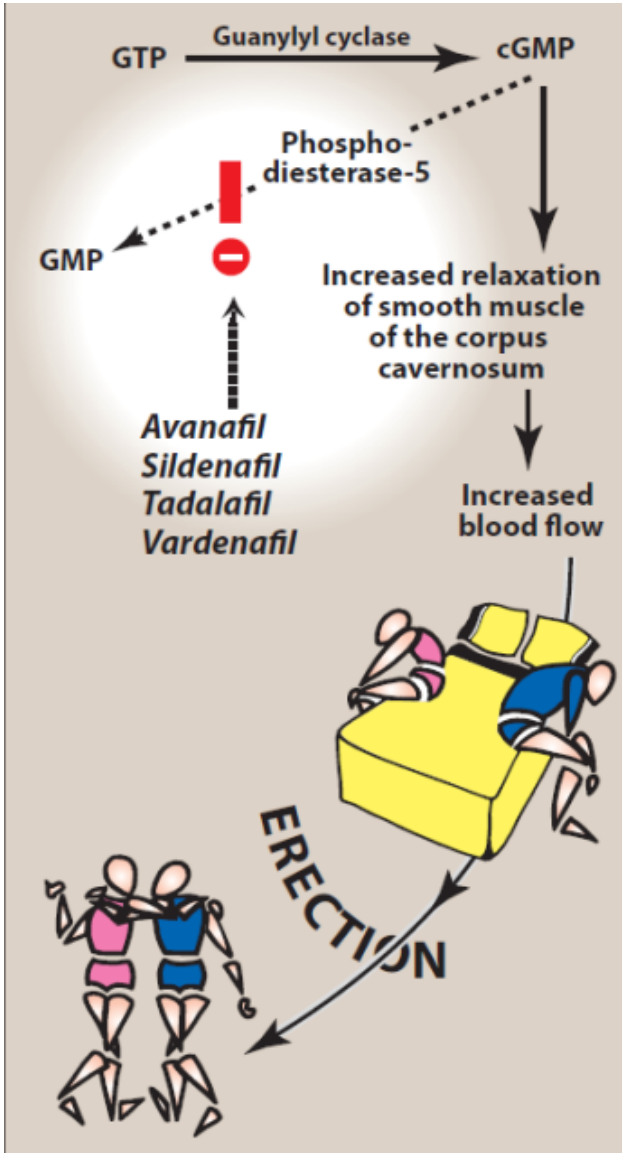
- **Sildenafil, vardenafil, tadalafil, and avanafil** are equally effective in treating ED, and the adverse effect profiles of the drugs are similar.

- However, these agents differ in the duration of action and the effects of food on drug absorption.

- **Mechanism of action:** Sexual stimulation results in smooth muscle relaxation of the corpus cavernosum, increasing the inflow of blood. The mediator of this response is nitric oxide (NO). NO activates guanylyl cyclase, which forms cyclic guanosine monophosphate (cGMP) from guanosine triphosphate. cGMP produces smooth muscle relaxation through a reduction in the intracellular Ca^{2+} concentration.

- The duration of action of cyclic nucleotides is controlled by the action of phosphodiesterase (PDE). Sildenafil, vardenafil, tadalafil, and avanafil inhibit PDE-5, the isozyme responsible for degradation of cGMP in the corpus cavernosum.

- The action of PDE-5 inhibitors is to increase the flow of blood into the corpus cavernosum at any given level of sexual stimulation. At recommended doses, PDE-5 inhibitors have no effect in the absence of sexual stimulation.



Drugs used to treat erectile dysfunction

A. Phosphodiesterase-5 (PDE-5) inhibitors

- **Pharmacokinetics:** **Sildenafil and vardenafil** should be taken approximately 1 hour prior to anticipated sexual activity, with erectile enhancement observed for up to 4 hours after administration. The absorption of both drugs is delayed by consumption of a high-fat meal.

- **Vardenafil** is also available in an orally disintegrating tablet (ODT) formulation, which is not affected by a high-fat meal.

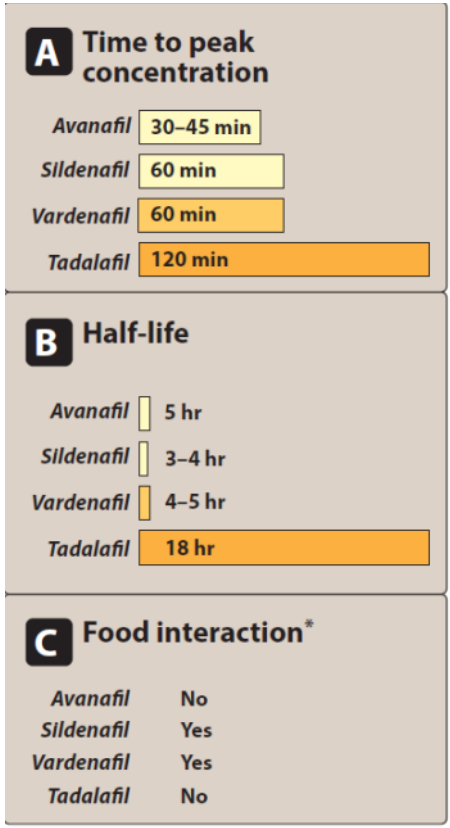
- **Tadalafil** has a slower onset of action than **sildenafil and vardenafil**, but a significantly longer half-life of approximately 18 hours.

- Furthermore, the absorption of **tadalafil** is not clinically influenced by food.

- Of all the PDE-5 inhibitors, **avanafil** has the quickest onset of action. It should be taken 30 minutes prior to sexual activity.

- For all All PDE-5 inhibitors, dosage adjustments are recommended in patients with hepatic dysfunction.

- For patients with severe renal dysfunction, the dose of **sildenafil and tadalafil** should be reduced, and daily-dose **tadalafil and avanafil** are contraindicated in these patients.



Drugs used to treat erectile dysfunction

B. Alprostadil (synthetic prostaglandin E1 (PGE1).

- In the penile tissue, PGE1 allows for relaxation of the smooth muscle in the corpus cavernosum. Alprostadil is available as an intraurethral suppository and an injectable formulation.

- Although PDE-5 inhibitors are considered first-line therapy for the treatment of ED, alprostadil may be used for patients who are not candidates for oral therapies.

- In contrast to oral agents, alprostadil acts locally, which may reduce the occurrence of adverse effects.

- **Mechanism of action:** Alprostadil causes smooth muscle relaxation by an unknown mechanism. It is believed that alprostadil increases concentrations of cyclic AMP (cAMP) within cavernosal tissue. As a result, protein kinase is activated, allowing trabecular smooth muscle relaxation and dilation of cavernosal arteries. Increased blood flow to the erection chamber compresses venous outflow, so that blood is entrapped and erection may occur.

- **Pharmacokinetics:** The onset of action of alprostadil is 5 to 10 minutes when given as a urethral suppository and 2 to 25 minutes when administered by injection. The resulting erection may last for 30 to 60 minutes,

Drugs used to treat benign prostatic hyperplasia

A. α1-Adrenergic antagonists

- **Terazosin, doxazosin, tamsulosin, alfuzosin, and silodosin** are selective competitive blockers of the α1 receptor.

- **Mechanism of action:** **α1A** receptors are found in the prostate, **α1B** receptors are found in the prostate and vasculature, and **α1D** receptors are found in the vasculature. By blocking the α1A and α1B receptors in the prostate, the α-blockers cause prostatic smooth muscle relaxation, which leads to improved urine flow.

- **Doxazosin, terazosin, and alfuzosin** block α1A and α1B receptors, whereas **tamsulosin and silodosin** are more selective for the α1A receptor.

- Because **doxazosin, terazosin, and alfuzosin** block α1B receptors, these agents decrease peripheral vascular resistance and lower arterial blood pressure by causing relaxation of both arterial and venous smooth muscle. In contrast, **tamsulosin and silodosin** have less of an effect on blood pressure because they are more selective for the prostate-specific α1A receptor.

- In general, α-blockers cause minimal changes in cardiac output, renal blood flow, and glomerular filtration rate.

Drugs used to treat benign prostatic hyperplasia

B. 5-α reductase inhibitors

- **Finasteride and dutasteride** inhibit 5α-reductase.
- Compared to the α-blockers, which provide patients with relief from BPH symptoms within 7 to 10 days, these agents may take up to 12 months to relieve symptoms.

- **Mechanism of action:** Both finasteride and dutasteride inhibit the enzyme 5-α reductase, which is responsible for converting testosterone to the more active dihydrotestosterone (DHT). DHT is an androgen that stimulates prostate growth. By reducing DHT, the prostate shrinks and urine flow improves.

- Compared to finasteride, dutasteride is more potent and causes a greater decrease in DHT.

- In order for the 5-α reductase inhibitors to be effective, the prostate must be enlarged. Thus, it is appropriate to use a 5-α reductase inhibitor in combination with an α-blocker when the prostate is enlarged.

Comparisons of treatment for BPH

	α_1-ADRENERGIC ANTAGONISTS	5 α-REDUCTASE INHIBITORS
Decrease in prostate size	No	Yes
Peak onset	2–4 weeks	6–12 months
Decrease in PSA	No	Yes
Sexual dysfunction	+	++
Hypotensive effects	++	–
Commonly used drugs	*Tamsulosin* and *alfuzosin*	*Finasteride* and *dutasteride*

Prostate specific antigen (**PSA**) is a protease whose function is to break down the high molecular weight protein of the seminal coagulum into smaller polypeptides. This action results in the semen becoming more liquid. PSA is produced by epithelial prostatic cells, both benign and malignant.

C. Phosphodiesterase-5 inhibitor

- **Tadalafil** is the only PDE-5 inhibitor approved for the treatment of BPH.

- PDE-5 is present in the prostate and bladder. As such, inhibition of PDE-5 by tadalafil allows for vasodilation and relaxation of the smooth muscle of the prostate and bladder, which thereby improves symptoms of BPH.


Thank You!