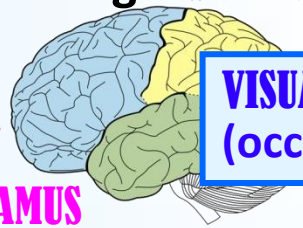
A MALE SEX ORGAN ➔ In most of the time exists in a Flaccid State

However, during a **Sexual Act** ➔ the following events occur;



FOREBRAIN
HYPOTHALAMUS
Testosterone & Others

VISUAL (occipital)

OLFACTORY (rhiencephalon)

TACTILE (thalamus)

IMAGINATIVE (limbic systems)

Loss of LIPIDO

1. Desire

DA, EN, Oxytocin, Exc. a a

Spinal Cord
Autonomc & Somatic
Cavernous & Pudendal

Erectile Dys. - IMPOTENCE

2. Arousal

+ve PNS (S2-4) / -ve SNS (T11-L2) **ERECTION / TUMESCENCE** ➔ Conduct Sexual Act

Sensory reflex
+ve SNS (T11-L2)
Emission

+ ve PNS (S2-4)
Motor
Ejection

Sensory afferents
Brain Integration
Orgasm

Ejaculatory Dys.

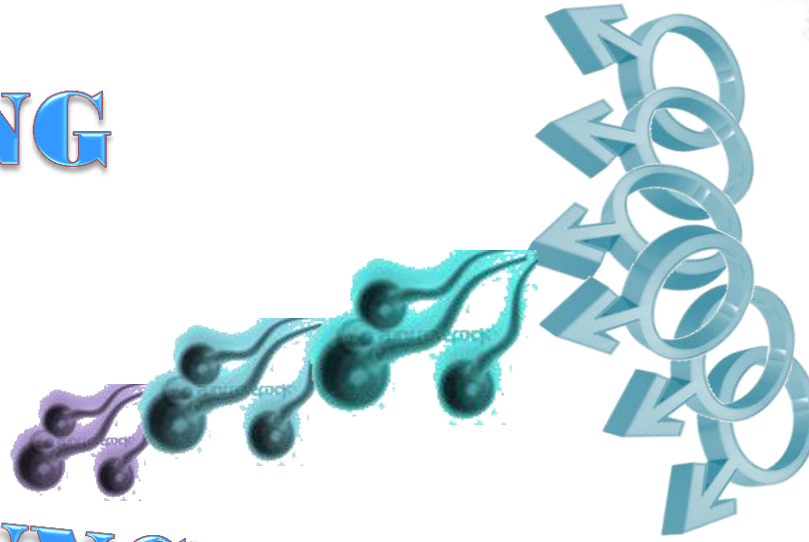
3. EJACULATION & ORGASM

PRIAPISM

+ve SNS (T11-L2) / -ve PNS (S2-4) **FLACCIDITY / DETUMESCENCE**

4. Resolution

DRUGS AFFECTING



ERECTILE DYSFUNCTION

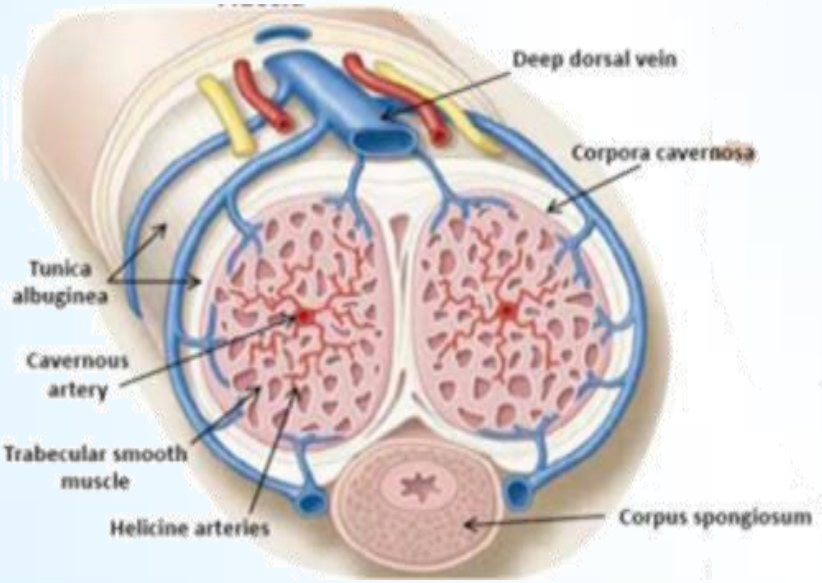
DRUGS AFFECTING ERECTILE DYSFUNCTION

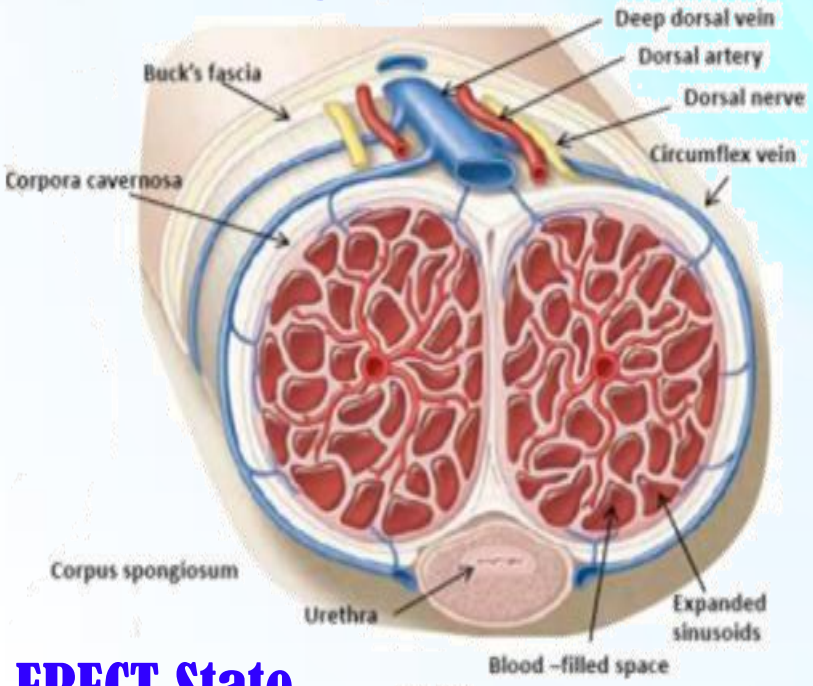
ILOs

By the end of this lecture you will be able to:

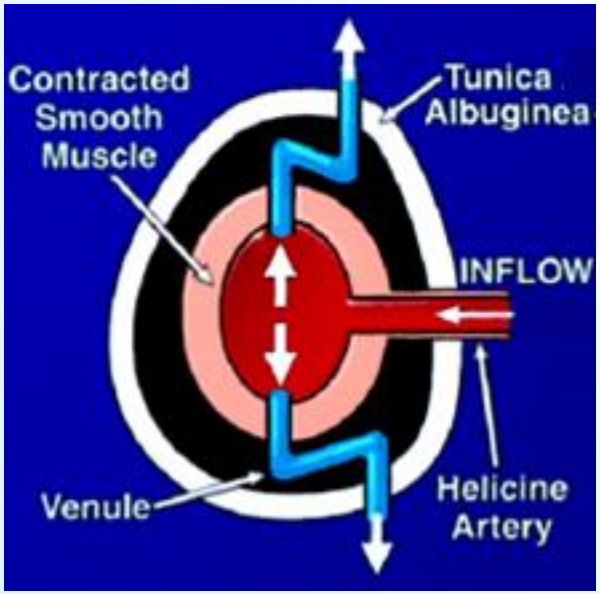
- Revise the haemodynamic changes inducing normal erection
- Interpret its different molecular control mechanisms
- Define erectile dysfunction [ED] and enumerate its varied risks
- List drugs inducing ED and reflect on some underlying mechanisms
- Correlate drugs used in treatment of ED to the etiopathogenesis
- Classify oral 1st line therapy relevent to; Mechanism / Utility / ADRs
- Compare the pharmacological difference of PDE_5 inhibitors
- Study the transurethral, intracavernous or topical 2nd line therapies; Mechanism / Utility / ADRs
- Enumerate lines of treatment of priapism

Peripheral HAEMODYNAMIC CHANGES inducing ERECTION

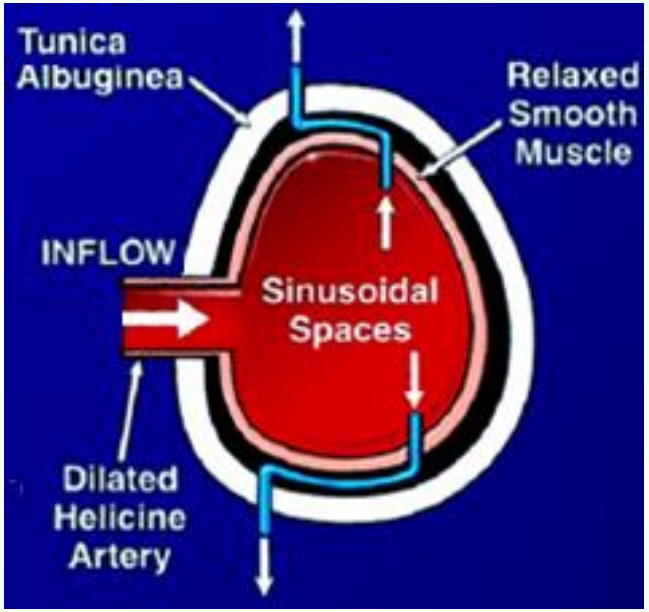


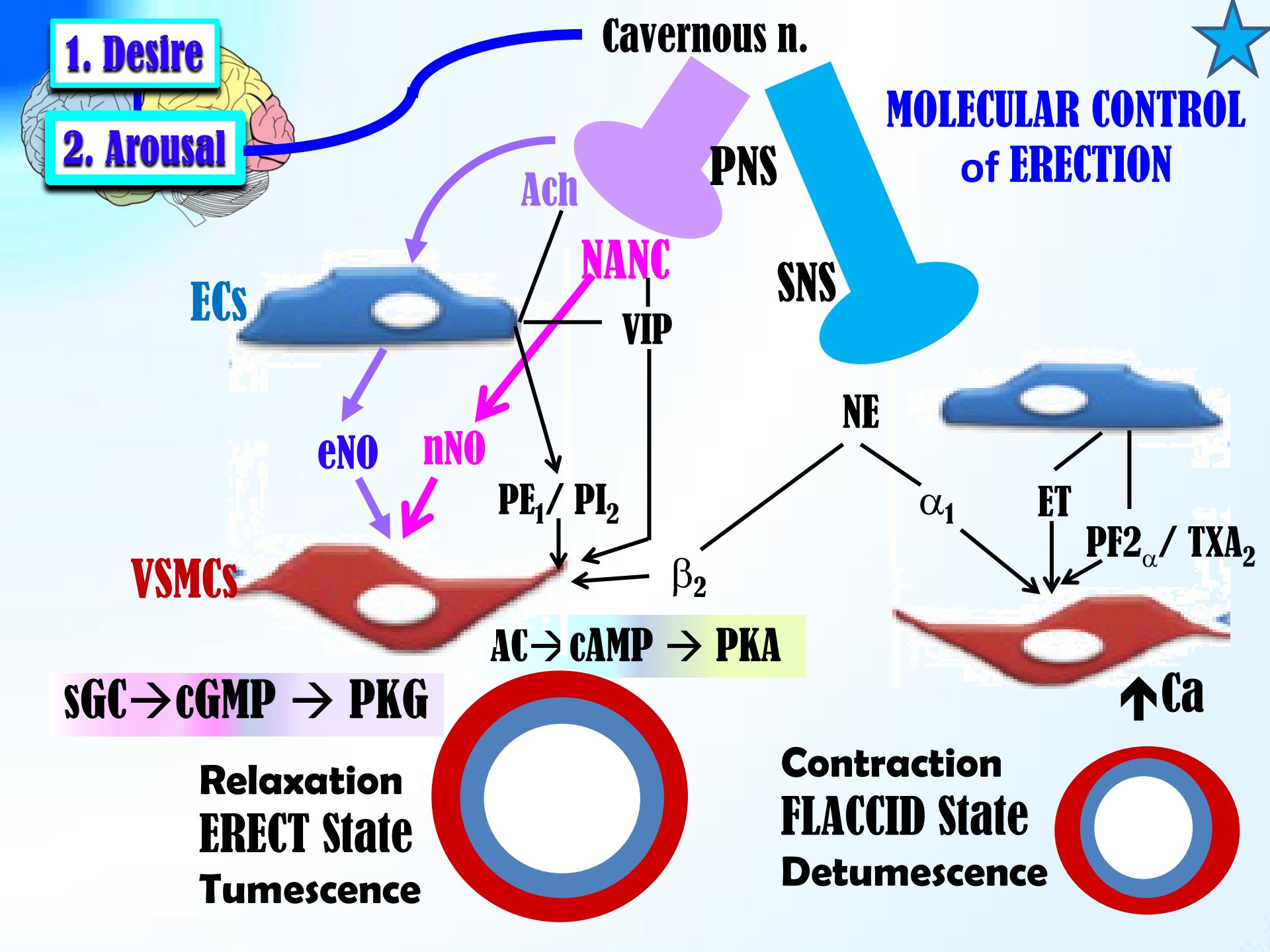


FLACCID State



ERECT State



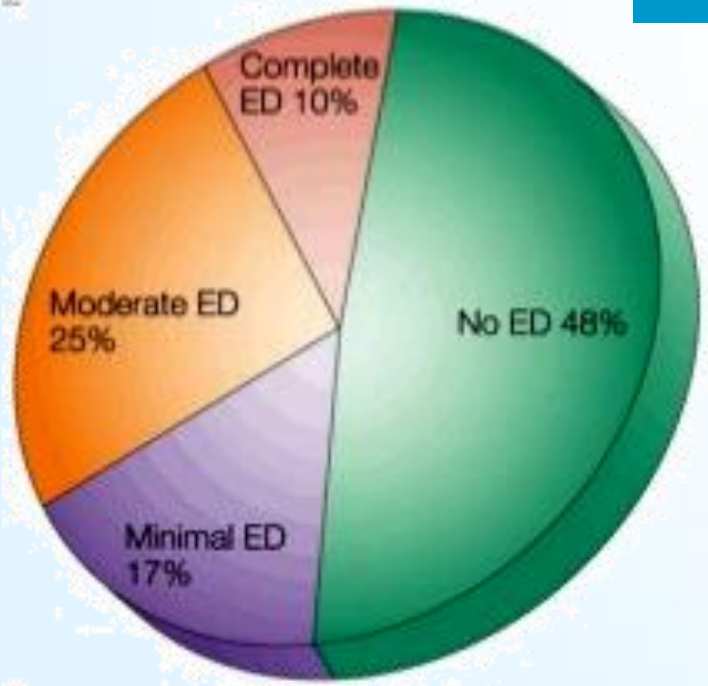

1. Desire
2. Arousal
Cavernous n.
MOLECULAR CONTROL of ERECTION
PNS
SNS
Ach
NANC
ECs
VIP
eNO
nNO
NE
PE1/ PI2
α1
ET
PF2α/ TXA2
VSMCs
β2
AC→ cAMP → PKA
sGC→cGMP → PKG
↑Ca
Relaxation
ERECT State
Tumescence
Contraction
FLACCID State
Detumescence

ERECTILE DYSFUNCTION

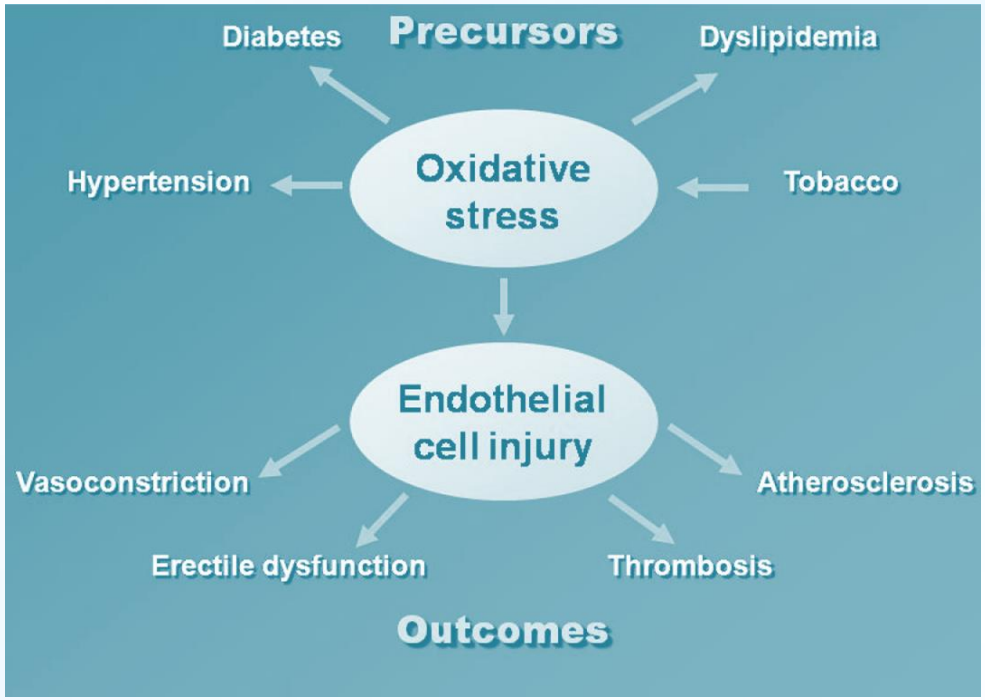
Persistent or recurrent inability to attain (acquire) & maintain (sustain) an erection (rigidity) sufficient for satisfactory sexual performance

"Impotent" is reserved for those men who experience erectile failure during attempted intercourse more than 75 % of the time.

Prevalence



Endothelial Dysfunction → Commonest Cause



I.M.P.O.T.E.N.C.E

For details see: Siroky, Mike B. *Handbook of Urology* 2003

Inflammatory	Prostatitis, urethritis
Mechanical	Peyronie's Disease, chordee
Psychological	Depression, performance anxiety, stress, relationship difficulties
Occlusive vascular	Art: Hypertension, smoking, hyperlipidemia, DM., peripheral vascular disease Ven: venous occlusion due to anatomical or degenerative changes
Trauma	Pelvic fracture, SC inj, penile trauma
Endocrine	Hypogonadism, hyperprolactinemia, hypo + hyperthyroidism
Neurologic	Parkinsons, multiple sclerosis, spina bifida, pelvic surgery, peripheral neuropathy
Chemical	Anti-HTN, anti-arrhythmics, antidepressants, anxiolytics, anti-androgens, anticonvulsants, alcohol, marijuana, anti-parkonson drugs, LHRH analogues
Extra factors	Prostatectomy, old age, CRF, cirrhosis

DRUGS ADVERSLY CAUSING ED

Drug Class	Specific drug examples
Beta-blockers Calcium-channel blockers Alpha-adrenergic agonists Cardiac glycosides	propranolol, metoprolol, atenolol verapamil, nifedipine clonidine digoxin
Thiazide diuretics Aldosterone antagonists	hydrochlorothiazide spironolactone
Fibric acid derivatives	gemfibrozil, clofibrate
Selective serotonin reuptake inhibitors Tricyclic antidepressants Other antidepressants	fluoxetine, sertraline, paroxetine, citalopram amitriptyline, desipramine, nortiptyline lithium
Benzodiazepines	lorazepam, alprazolam, diazepam
Histamine (H_2) receptor antagonists	ranitidine, cimetidine
Butyrophenones and phenothiazines	haloperidol, prochlorperazine, chlorpromazine
Hydantoin anticonvulsants	phenytoin
Cytotoxic agents	cyclophosphamide, methotrexate
Recreational drugs	alcohol, cocaine, marijuana

DRUGS ADVERSLY CAUSING ED

Centrally Acting Drugs

DA>NE promote arousal / 5HT action on $5HT_2$ →↓DA release →↓ arousal

Most ADDs→ ↓ 5HT uptake;

non-selectively as TCAs

selectively as SSRIs

↑ 5HT in synapse act on $5HT_2$

Peripherally; antagonize NO actions / ↓ genital sensation→ Delay ejaculation

Treat Premature Ejaculation

- Anti-psychotic drugs → DA antagonist + hyperprolact. → ↓ arousal
- Anti-epileptic drugs (phenytoin) → have GABA effect
  →antagonize Exc. a.a. → ↑ sedation → ↓ arousal.

Centrally acting anti-hypertensives

- Methyl dopa, Reserpine !!! → ↓ arousal
- Clonidine → arousal centrally / Vasoconstriction peripherally !!!

Other anti-hypertensives

- β_2 blockers → -ve vasodilating β_2 + potentiate α_1 effect
- **Thiazide diuretics** → ↓ spinal reflex controlling erection + ↓ arousal

↓ Desire ← **Anti-androgens**

- **Finasteride** → α reductase inhibitor → **irreversible erectile dysfunction**
- **Cyproterone acetate** → synthetic steroidal antiandrogen
- **Cimetidine** (high doses) / **Ketoconazole** / **Spironolactone** → hyper-prolactinemia + gynecomastia
- **Estrogen-containing medications**

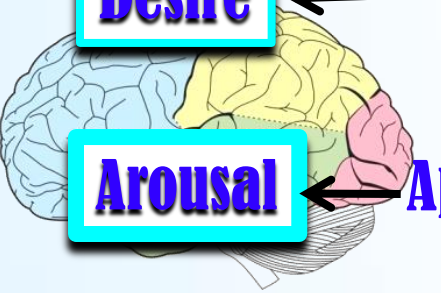
Habituating Agents

- **Cigarette smoking** → vasoconstriction + penile venous leakage
- **Alcohol** [small amounts]→↑ desire +↓ anxiety + vasodilatation
- Alcohol [big amounts]→↑ sedation+ ↓ desire
- Chronic alcoholism→ hypogonadism + polyneuropathy

DRUGS TREATING ED

CENTRALLY

- Desire ← Androgens
- Arousal ← Apomorphine



PERIPHERALLY

ORAL

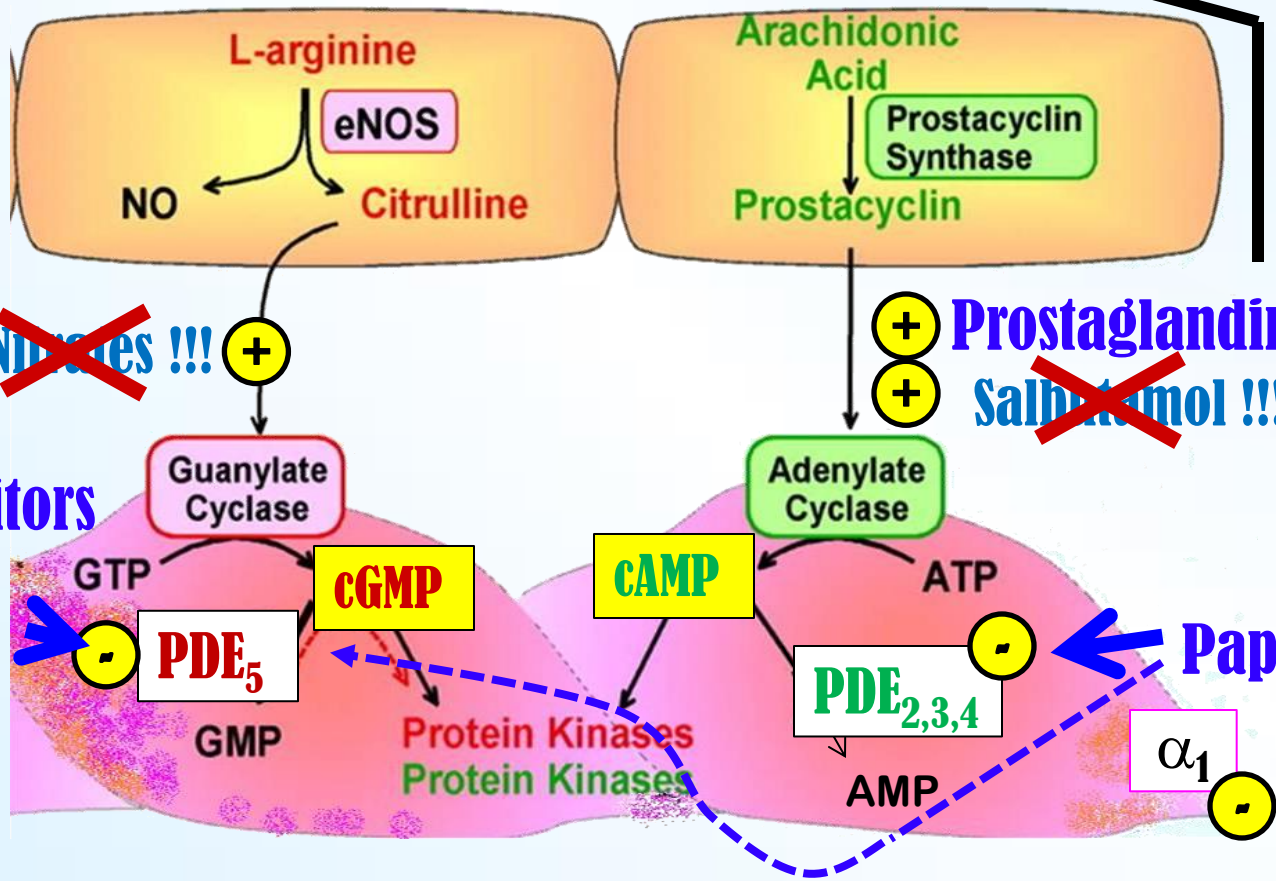
- ~~Nitrates~~ !!! (+)
- PDE$_5$ Inhibitors
  - Sildenafil
  - Vardenafil
  - Tadalafil
  - Avanafil

Transurethral

- (+) Prostaglandin Analogues
- (+) ~~Salbutamol~~ !!!

Intracavernosal Inj.

- Papaverine (-) PDE$_{2,3,4}$
- α_1 (-) Phentolamine



SELECTIVE PDE_5 Inhibitors

Mechanism

ORAL

- Sildenafil
- Vardenafil
- Tadalafil
- Avanafil

Inhibit PDE_5 ➜ prevent breakdown of cGMP ➜ pertain vasodilatation ➜ erection.

They do not affect the lipido, so sexual stimulation is essential to a successful

Pharmacodynamic action relevant to PDE_5 inhibition ▶

Indication
Side effects

- VSMCs of Erectile Tissue of Penis
- Other VSMCs (lung, brain….) / heart
- Other non-VSMCs (prostate, bladder, seminal vesicle, GIT….)
- Platelets
- Other tissues; testis, sk. muscles, liver, kidney, pancreas, …..

Indications

- Erectile dysfunction; 1st line therapy. All types have similar efficacy

	Sildenafil	Vardenafil	Tadalafil
% Efficacy	74-84	73-83	72-81

- Pulmonary hypertension
- BPH & premature ejaculation
- Others; CHF, Raynaud's disease, IBS…..etc

Selectivity on PDE_5 is not absolute and vary with each drug

- Can partially act on PDE targeting cGMP (6, 11, 9, 1) ★
- In higher doses it can act on PDE targeting cAMP (2,3,4, 10,…) ★

PDE 1 ★	Heart, brain, lung, smooth muscle	IHD / AMI
PDE 2 ★	Adrenal gland, heart, lung, liver, platelets	
PDE 3 ★	Heart, lung, liver, platelets, adipose tissue, inflammatory cells	
PDE 4 ★	Sertoli cells, kidney, brain, liver, lung, inflammatory cells	
PDE 5 ★	Lung, platelets, vascular smooth muscle, heart	Headache/Flush nasal congestion
PDE 6 ★	Photoreceptor	Altered VISION
PDE 7 ★	Skeletal muscle, heart, kidney, brain, pancreas, T lymphocytes	
PDE 8 ★	Testes, eye, liver, skeletal muscle, heart, kidney, ovary, brain, T lymphocyte	
PDE 9 ★	Kidney, liver, lung, brain, possibly heart	
PDE 10 ★	Testes, brain	
PDE 11 ★	Skeletal muscle, prostate, kidney, liver, pituitary and salivary glands, testes	Back Pain

Sildenafil 10-fold selective
Vardenafil 16-fold selective
Tadalafil >200-fold selective

Give variability in ADRs

ADRs

Common ADRs	Sildenafil	Vardenafil	Tadalafil
Headache %	14	10	15
Flushing %	12	11	3
Nasal	Congestion	Rhinitis	Congestion
Dyspepsia %	7	3	15
Abnormal vision %	> 4	< 2	
Myalgia & Back pain %	-	-	5
Sperm functions	-	-	↓?
Q-T prolongation	-	↑	-

Major less common ADRs

1. IHD & AMI > patients on big dose or on nirates
2. Hypotension > patients on α-blockers than other antihypertensives
3. Bleeding; epistaxsis…..etc.
4. Priapism; if erection lasts longer than 4 hours ➜ emergency situation

Major rare ADRs

1. Ischemic Optic Neuropathy; can cause sudden loss of vision
2. Hearing loss

Pharmacokinetic profile difference of PDE5 inhibitors

Absorption; Fatty food interferes with Sildenafil & Vardenafil absorption
→ so taken on empty stomach / at least 2 hr.s after food
Tadalafil & [Avanafil] are not affected by food

Metabolism; All by hepatic CYT3A4; Tadalafil > the rest thus;
↑ADRs with enzyme inhibitors; erythro & clarithromycin, ketoconazole, cimetidine, tacrolimus, fluvoxamine, amiodarone…etc.
↓ efficacy with enzyme inducers; rifampicin, carbamazipine, phenytoin

Administration

All drugs are given only once a day	Sildenafil	Vardenafil	Tadalafil
Dosage (mg)	50-100	10-20	10-20
Time of administration before intercourse (hrs.)	1	1	1-12
Onset of action (min)	30-60	30-60	<30-45
Duration of action (hrs.)	4	4-5	36

NB. Avanafil has the advantage of been given 30 min before intercourse
Tadalafil must be given every 72 hrs if used with enzyme inhibitors

Contraindications

- Hypersensitivity to drug
- Patients with history of AMI / stroke / fatal arrhythmias <6 month
- Nitrates→ total contraindication / ? PDEIs in small dose + spacing at least 24hrs (48 hrs with *Tadalafil*) for fear of developing IHD/AMI due to severe hypotension *(see detailed mechanism in antianginal drugs)*

Precautions

- With α blockers [except tamsulosin] →orthostatic hypotension
- With hepato/renal insufficiency
- With Pyronie's disease
- With bleeding tendencies [leukemia's, hemophilia, Vit K deficiency, antiphospholipid syndrome,…etc]
- With *quinidine, procainamide, amiodarone* (class I & III antiarhtmics) (Vardenafil)
- Dose adjustment; *when using drugs that have interaction on hepatic liver microsomal enzymes i.e inhibitors or inducers.*
- Retinitis pigmentosa

ORAL

Testosterone

- Given to those with hypogonadism or hyperprolactenemia
- Given for promotion of desire.

Apomorphine

- A dopamine agonist on D_2 receptors. *(n. paraventricularis)*
- Activates arousal centrally; Erectogenic + Little promotion of desire
- Given sublingual / Acts quickly.
- Not FDA approved / Weaker than PDE_5 Is
- Given in mild-moderate cases / psychogenic / PDE_5 Is contraindication
- ADRs: nausea, headache, and dizziness but safe with nitrate

Oral phentolamine → α_1 blocker / debatable efficacy

Yohimbine → Central and periphral α_2 agonist → Aphrodetic + Erectogenic but low efficacy and many CV side effects

Trazodone → Antidepressant, a 5HT reuptake inhibitor → priapism

Korean Ginseng → Questionable / may be a NO donner.

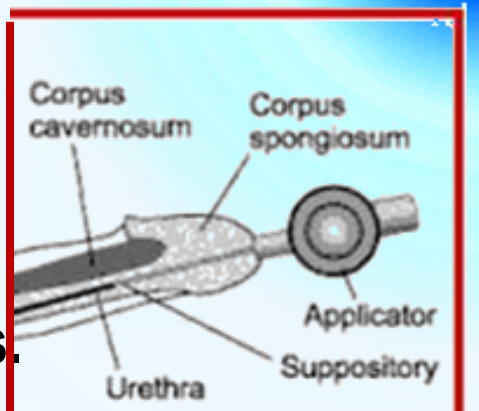
Alprostadil; PG E1 → ↑cAMP (MUSE)

TRANSURETHRALORAL

Synthetic + more stable

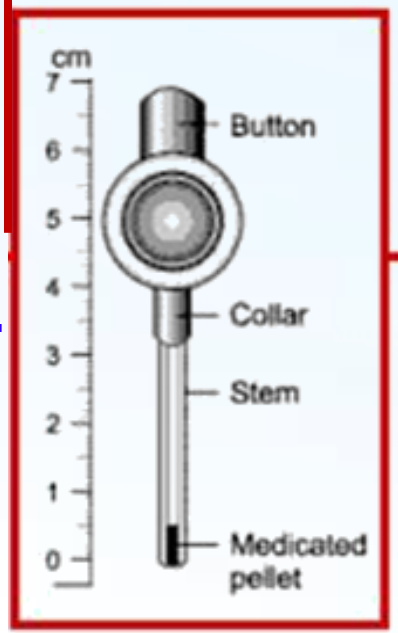
Applied by a special applicator into penile urethra & acts on corpora cavernousa →Erection

- Low - Intermediate Efficacy
- Minimal systemic effects / Rarity of drug interactions.



ADRs

- Variable penile pain
- Urethral bleeding / Urethral tract infection
- Vasovagal reflex / Hypotension
- Priapism or Fibrosis →rare



Topical

20% Papaverine; ↑cAMP + cGMP
2% Minoxidil; NO donner + K channel opener
2% Nitroglycerine
+ a drug absorption enhancers

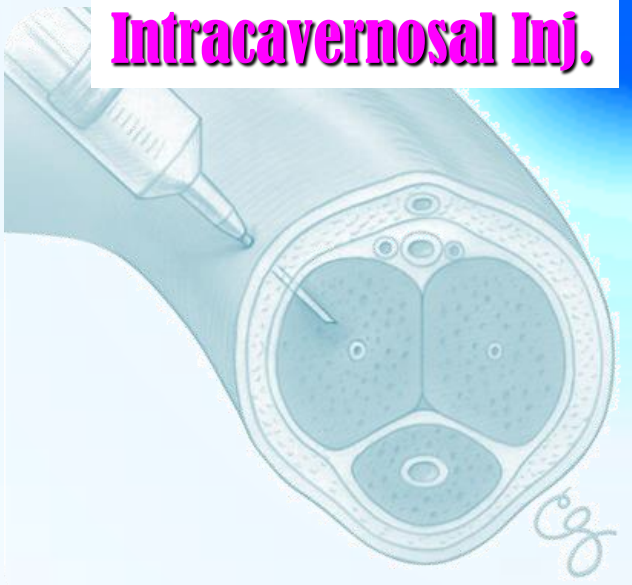
Low efficacy / No FDA approval

Female Partner can develop → hypotension, headache → vaginal absorption.

Intracavernosal Inj.

1. Alprostadil; PG E1 → ↑cAMP

Needs training → Erection → after 5-15 min
lasts according to dose injected →
May develop fear of self injury / Discontinuation



ADRs

- Pain or bleeding at injection site
- Cavernosal fibrosis
- Priapism

2. Papaverine; PG E1 → ↑cAMP + cGMP

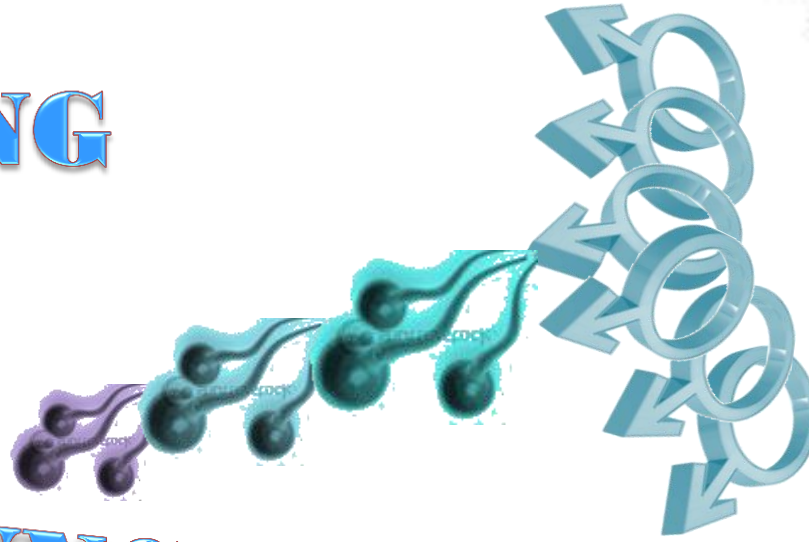
3. Phentolamine; α_1 blocker

3 combined in severe cases

Treatment of Pripism

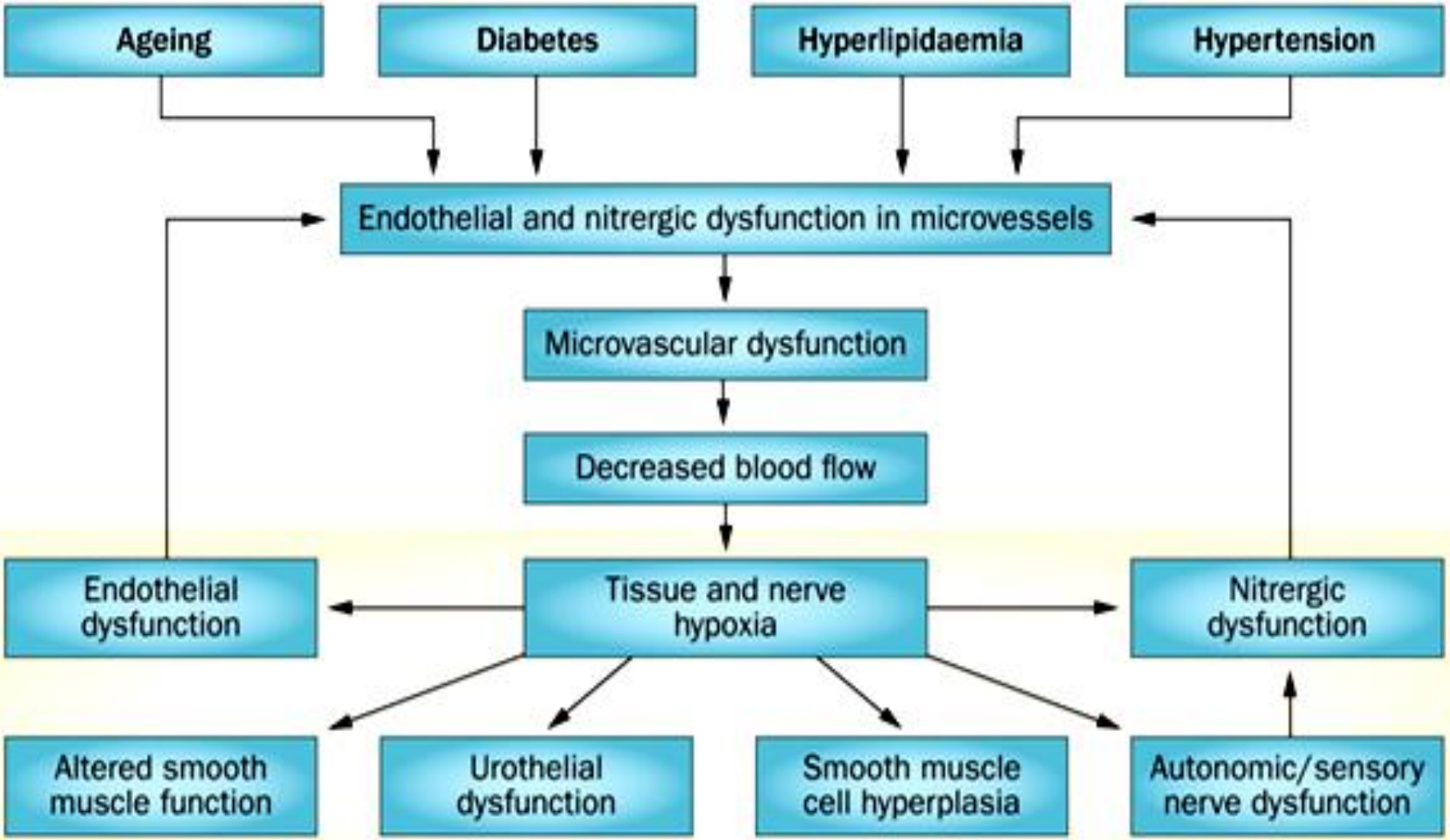
- A medical emergency
- Aspirate blood to decrease intracavernous pressure.
- Intracavernous injection of **Phenylephrine** → α_1 agonist
  → detumescence

DRUGS AFFECTING



ERECTILE DYSFUNCTION

GOOD LUCK


Ageing
Diabetes
Hyperlipidaemia
Hypertension
Endothelial and nitrergic dysfunction in microvessels
Microvascular dysfunction
Decreased blood flow
Endothelial dysfunction
Tissue and nerve hypoxia
Nitrergic dysfunction
Altered smooth muscle function
Urothelial dysfunction
Smooth muscle cell hyperplasia
Autonomic/sensory nerve dysfunction