ERECTILE DYSFUNCTION

住院醫師核心課程

張嘉峰

REFERENCE

01

CAMPBELL UROLOGY 10TH EDITION

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02

CAMPBELL UROLOGY 11ST EDITION

03

AUA GUIDELINE ON ERECTILE DYSFUNCTION 2018

04

EAU GUIDELINE SEXUAL DYSFUNCTION 2018

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2019

The 2019 Male Sexual Dysfunction Guidelines have not been updated since 2018. This is the current version.

2018

For the 2018 edition of the EAU Male Sexual Dysfunction Guidelines, the Guidelines Office have transitioned to a modified GRADE methodology. For each recommendation within the guidelines there is an accompanying online strength rating form which addresses a number of key elements namely:

1. the overall quality of the evidence which exists for the recommendation;
2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact of patient values and preferences on the intervention;
6. the certainty of those patient values and preferences.

These key elements are the basis which panels use to define the strength rating of each recommendation. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence, and nature and variability of patient values and preferences. The strength of each recommendation is represented by the words ‘strong’ or ‘weak’.

CONTENTS

DEFINITION OF ED

- ✓NIH consensus: an **individual report** of consistent **inability** to **attain** and **maintain** an erection of the penis sufficient to permit satisfactory sexual intercourse
- ✓EAU guideline: ED is defined as the persistent inability to attain and maintain an erection sufficient to permit satisfactory sexual performance
- ✓AUA guideline: an impairment in the **arousal phase** of sexual response, consistent or recurrent inability to attain and/or maintain penile erection sufficient for sexual satisfaction, including satisfactory sexual performance

EVOLUTION OF ED

TABLE 27-1 Evolution in the Management of Erectile Dysfunction

	DIAGNOSTICS	TREATMENTS	GUIDES
Pre-1970	Psychosexual history	Psychosexual therapy Herbal supplements	Studies of Masters and Johnson
1970s	Medical and psychosexual history Nocturnal penile tumescence testing	Penile prosthesis surgery Penile revascularization	International Conferences on Corpus Cavernosum Revascularization
1980s	Physical examination Endocrine evaluation Penile duplex ultrasonography, DICC	Oral medications Intracavernous pharmacotherapy Vacuum device therapy	Goal-directed management
1990s	Combined intracavernous injection and stimulation	Intraurethral pharmacotherapy Oral phosphodiesterase type 5 therapy	NIH Consensus Statement Process of Care Model
2000-Present	Biomarkers of vascular health neuroimaging	? Gene therapy ? Stemcell therapy ? Tissue engineering	ICUD algorithms (patient-centered approach) AUA Practice Guidelines (evidence-based approach)

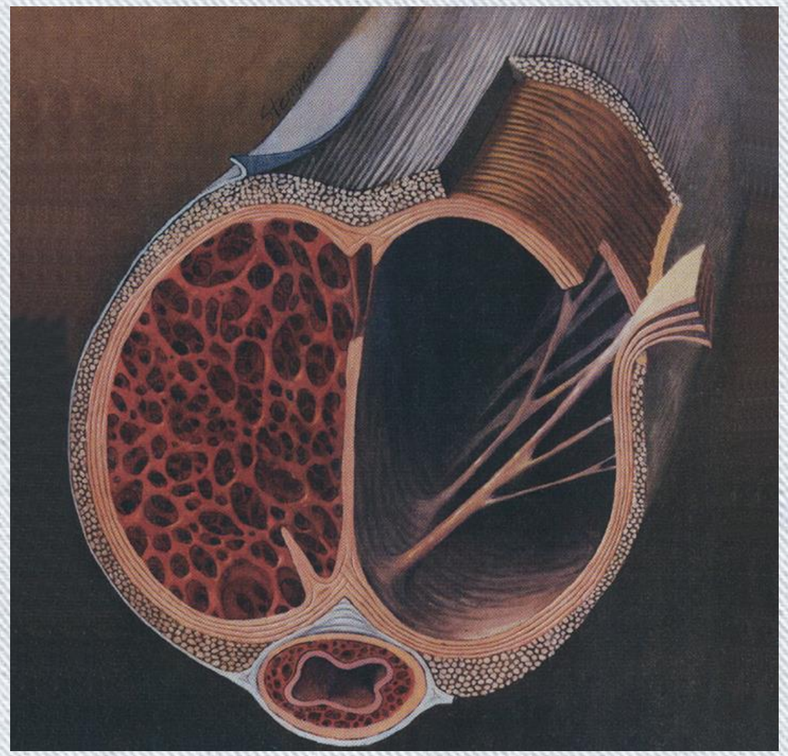
EPIDEMIOLOGY

- ✓high prevalence and incidence of ED worldwide
- ✓Massachusetts Male Aging Study (MMAS) [21] reported an overall prevalence of 52% ED in non-institutionalised men aged 40-70 years in the Boston area;
- ✓Minimal, moderate, and complete ED was 17.2%, 25.2%, and 9.6%
- ✓men seeking first medical help **for new-onset** ED, ¼ patients was younger than **40 years,**

  ➔ with almost 50% of the young men complaining of severe ED

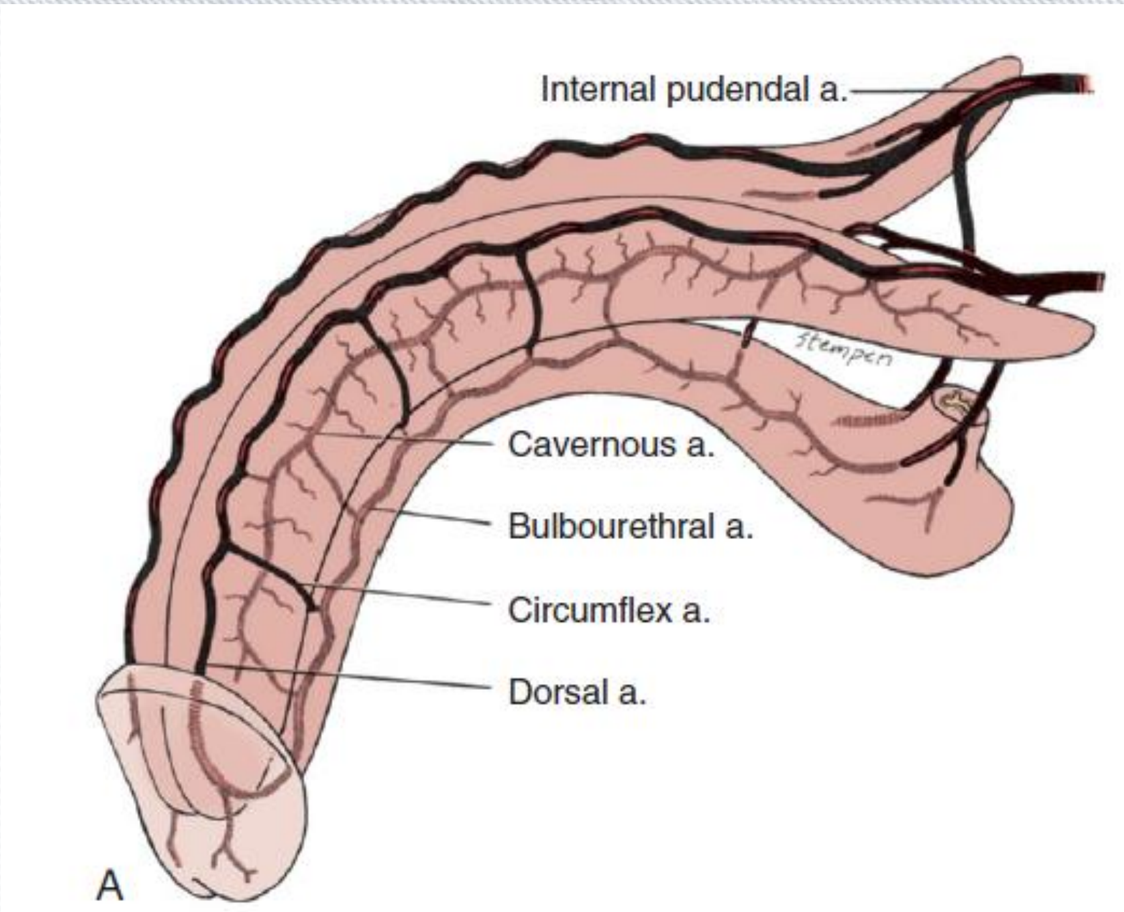
PENIS ANATOMY

TUNICA ALBUGENIA



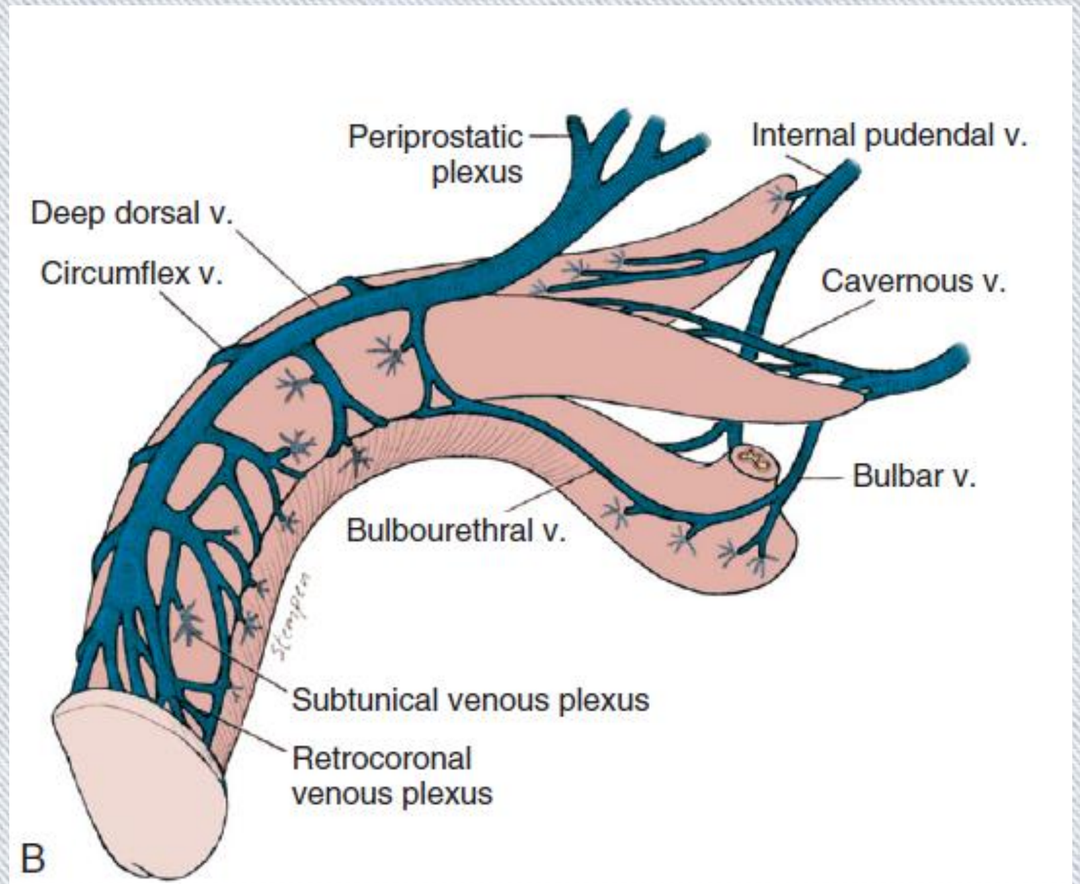
- ✓**corpora cavernosa: bilayered** structure, Inner-layer: oriented **circularly**; intracavernous pillars; Outer-layer: oriented **longitudinally**, from glans to insert into the inferior pubic rami
- ✓**corpus spongiosum:** only inner layer of tunica albugenia, nsuring a low-pressure structure during erection.

ARTERIES

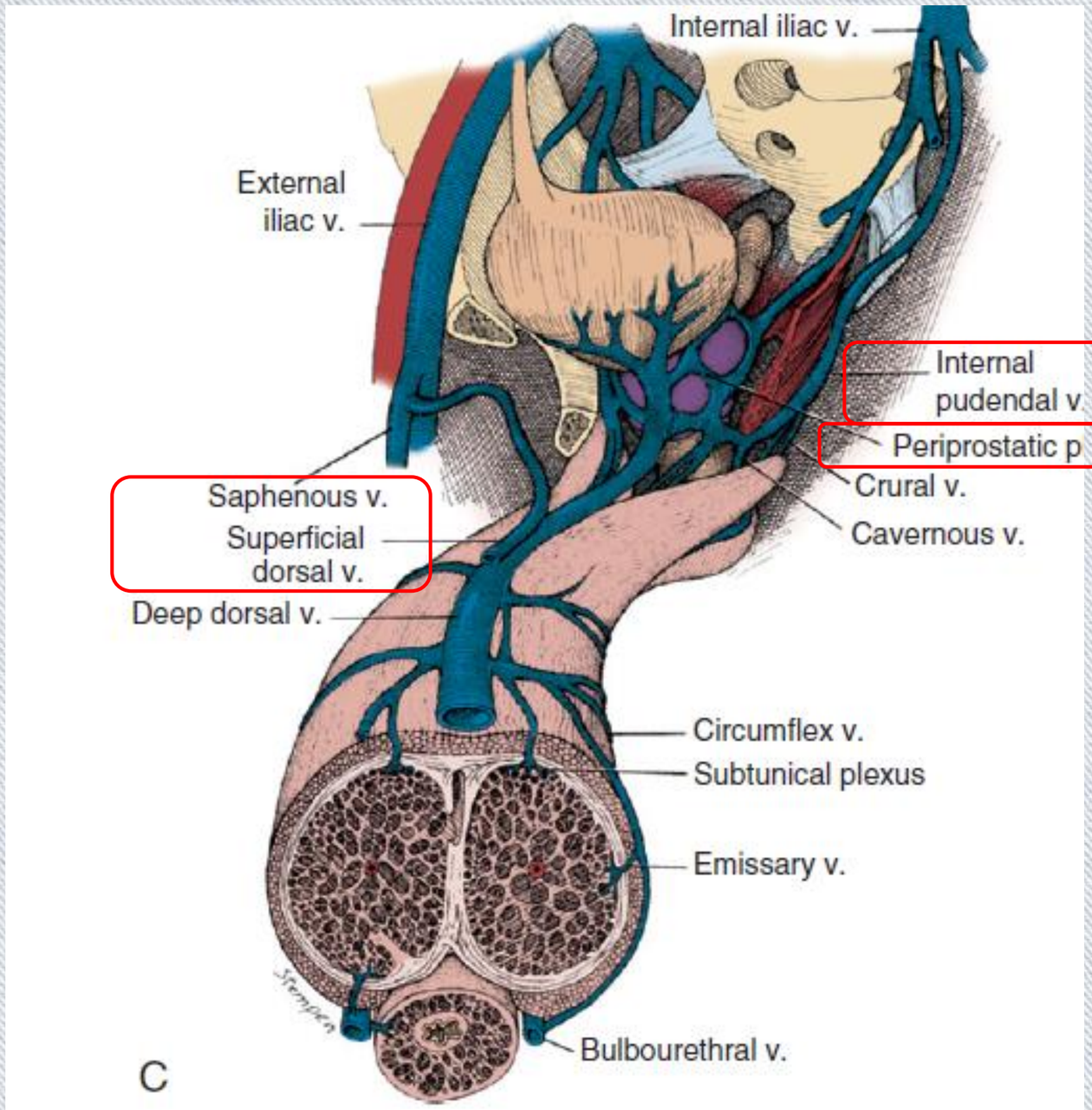


- ✓The source of penile blood is usually the **internal pudendal artery**, a branch of **the internal iliac artery**
- ✓In many instances, however, **accessory arteries** exist, arising from the external iliac, obturator, and vesical and femoral arteries, and they may in some men constitute the dominant or only arterial supply to the corpus cavernosum

VEINS

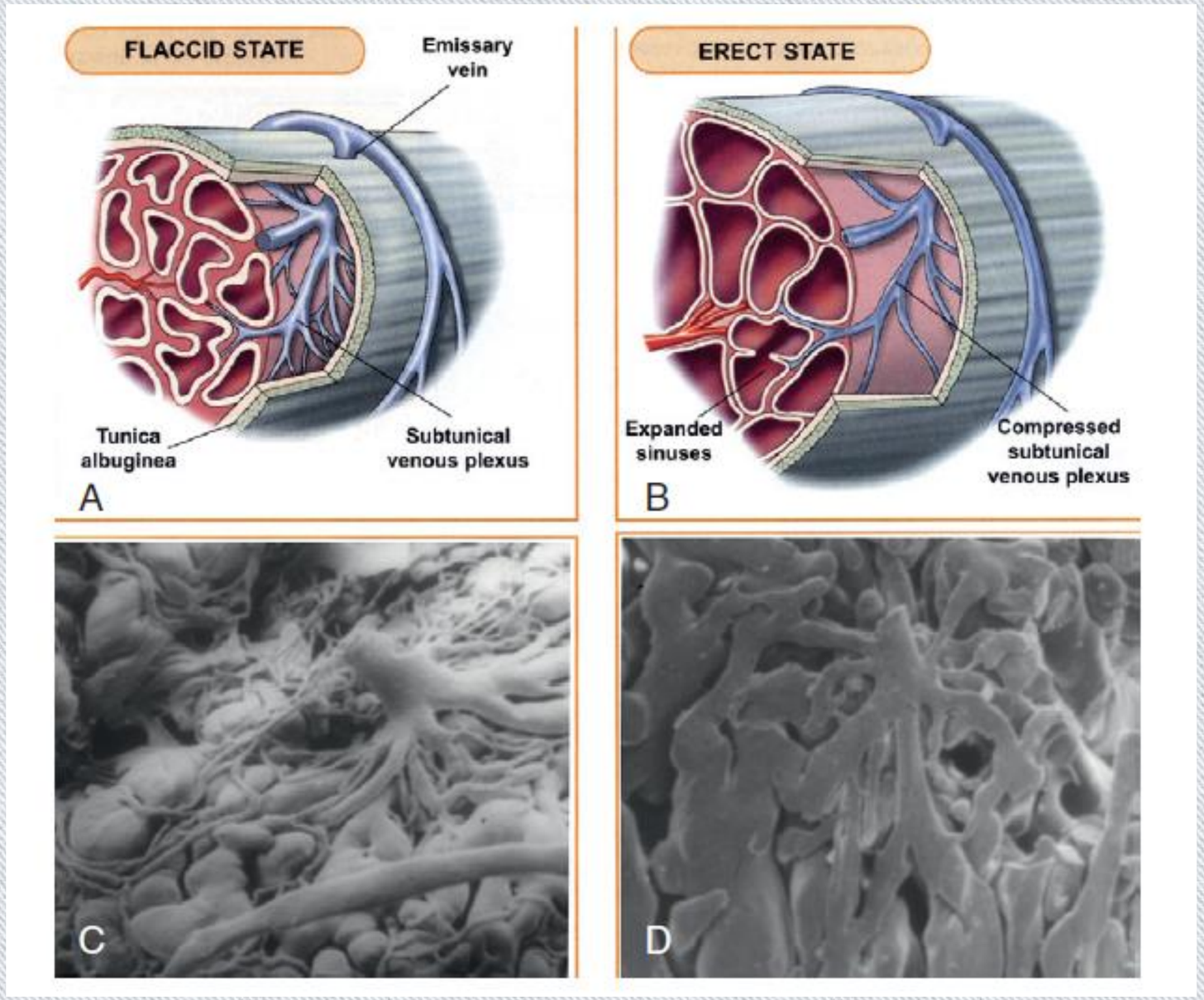


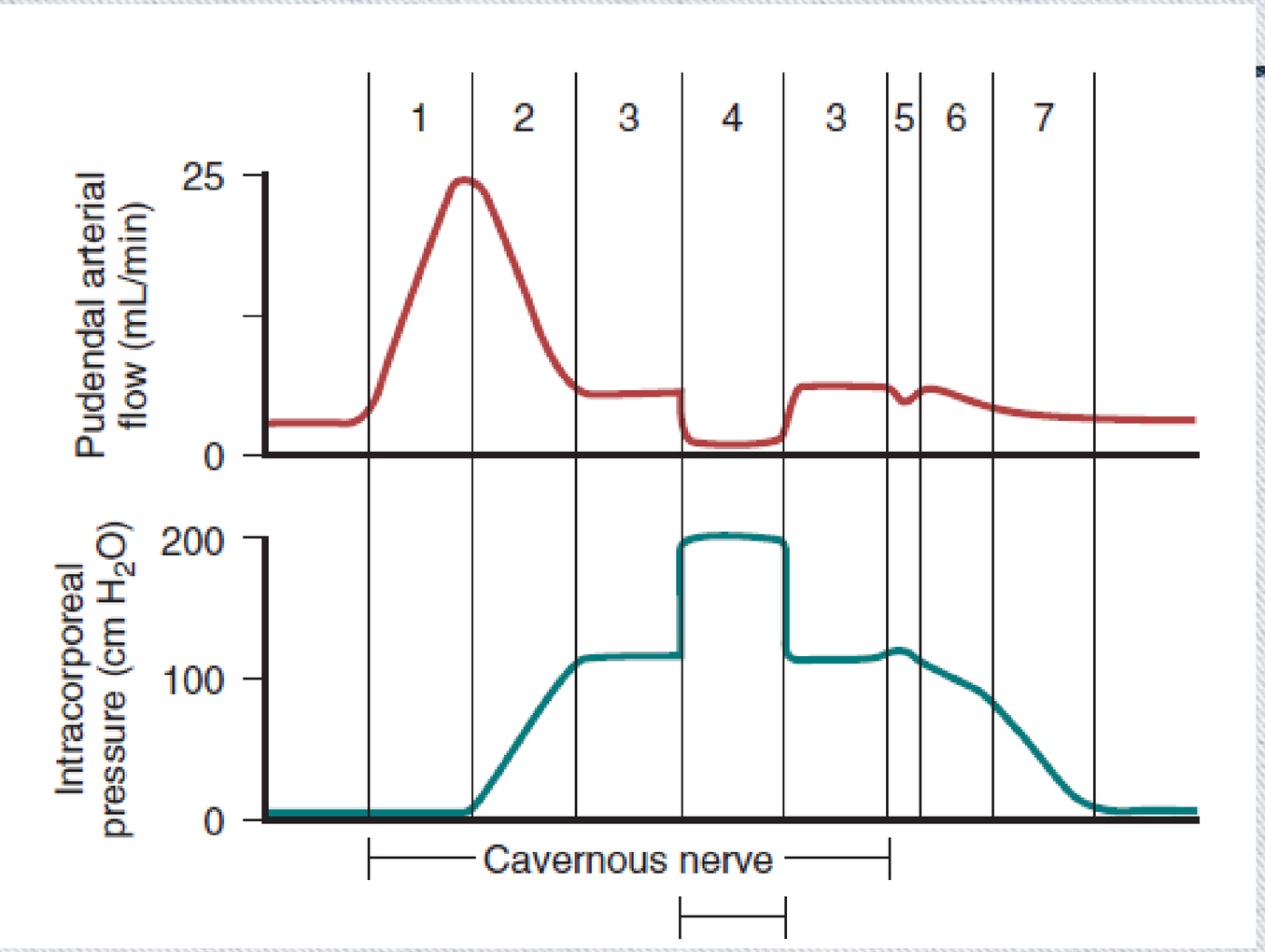
- ✓The venous drainage from the three corpora originates in tiny venules leading **from the peripheral sinusoids immediately beneath the tunica albuginea.**
- ✓These venules travel in the trabeculae between the tunica and the peripheral sinusoids to form the subtunical venous plexus before exiting as the emissary veins


Internal iliac v.
External iliac v.
Internal pudendal v.
Periprostatic p
Crural v.
Cavernous v.
Saphenous v.
Superficial dorsal v.
Deep dorsal v.
Circumflex v.
Subtunical plexus
Emissary v.
Bulbourethral v.
C

HEMODYNAMICS AND MECHANISM OF ERECTION AND DETUMESCENCE

- ✓ Sexual stimulation triggers release of **neurotransmitters** from **the cavernous nerve terminals**.
- ✓ This results **in relaxation of these smooth muscles** and the following events
- ✓ (1**) dilation of the arterioles and arteries** by increased blood flow in both the diastolic and systolic phases;
- ✓ (2) trapping of the incoming blood by the **expanding sinusoids**;
- ✓ (3) **compression of the subtunical venous plexuses** between the tunica albuginea and the peripheral sinusoids, reducing venous outflow;
- ✓ (4) **stretching of the tunica to its capacity**, which occludes the emissary and further decreases venous outflow to a minimum;
- ✓ (5**) an increase in PO2** (to about 90 mm Hg) and **intracavernous pressure** (around 100 mm Hg),
- ✓ (6) contraction of the ischiocavernosus muscles (rigid erection phase).


FLACCID STATE
Emissary vein
Tunica albuginea
Subtunical venous plexus
A
ERECT STATE
Expanded sinuses
Compressed subtunical venous plexus
B
C
D



0, flaccid; 1, latent; 2, tumescence; 3, full erection; 4, rigid erection; 5, **initial detumescence**; 6, **slow** detumescence; 7, **fast** detumescence

NEUROANATOMY AND NEUROPHYSIOLOGY OF PENILE ERECTION SPINAL CENTERS AND PERIPHERAL PATHWAYS

AUTONOMIC PATHWAYS.

- ✓The sympathetic pathway originates from the **T11 to L2 spinal segments** and passes through the **white rami to the sympathetic chain** ganglia.
- ✓parasympathetic pathway arises from neurons in the **intermediolateral cell columns** of the **S 2.3.4 segments**.
- ✓to the pelvic plexus, where they are joined by the sympathetic nerves from the superior **hypogastric plexus**.
- ✓**sacral parasympathetic input is responsible for tumescence**
- ✓ **thoracolumbar sympathetic pathway is responsible for detumescence**

CNS

- ✓(1) a perceptual-cognitive component that **recognizes the visual stimuli as sexual** and is performed in the **bilateral inferior temporal cortices**;
- ✓(2) an **emotional/ motivational** component **that processes sensory information** with motivational states and is performed in the **right insula, right inferior frontal cortex, and left cingulate cortex (paralimbic areas);** and
- ✓(3) a physiologic component that **coordinates the endocrine and autonomic functions** and is performed in the left **anterior cingulate cortex.**

- ✓ **Reflexogenic erection** is produced by **tactile stimulation of the genital organs**.
- ✓The impulses reach the **spinal erection centers**; some then **follow the ascending tract**, resulting in sensory perception,
- ✓while others **activate the autonomic nuclei to send** messages **via the cavernous nerves to the penis to induce erection**.
- ✓This type of erection is **preserved in patients with upper spinal cord injury**.
- ✓**Nocturnal erection** occurs mostly during **rapid-eye-movement (REM) sleep**.
- ✓PET scanning of humans in REM sleep shows **increased activity** in **the pontine area, the amygdalae, and the anterior cingulate gyrus** but **decreased activity in the prefrontal and parietal cortex.**

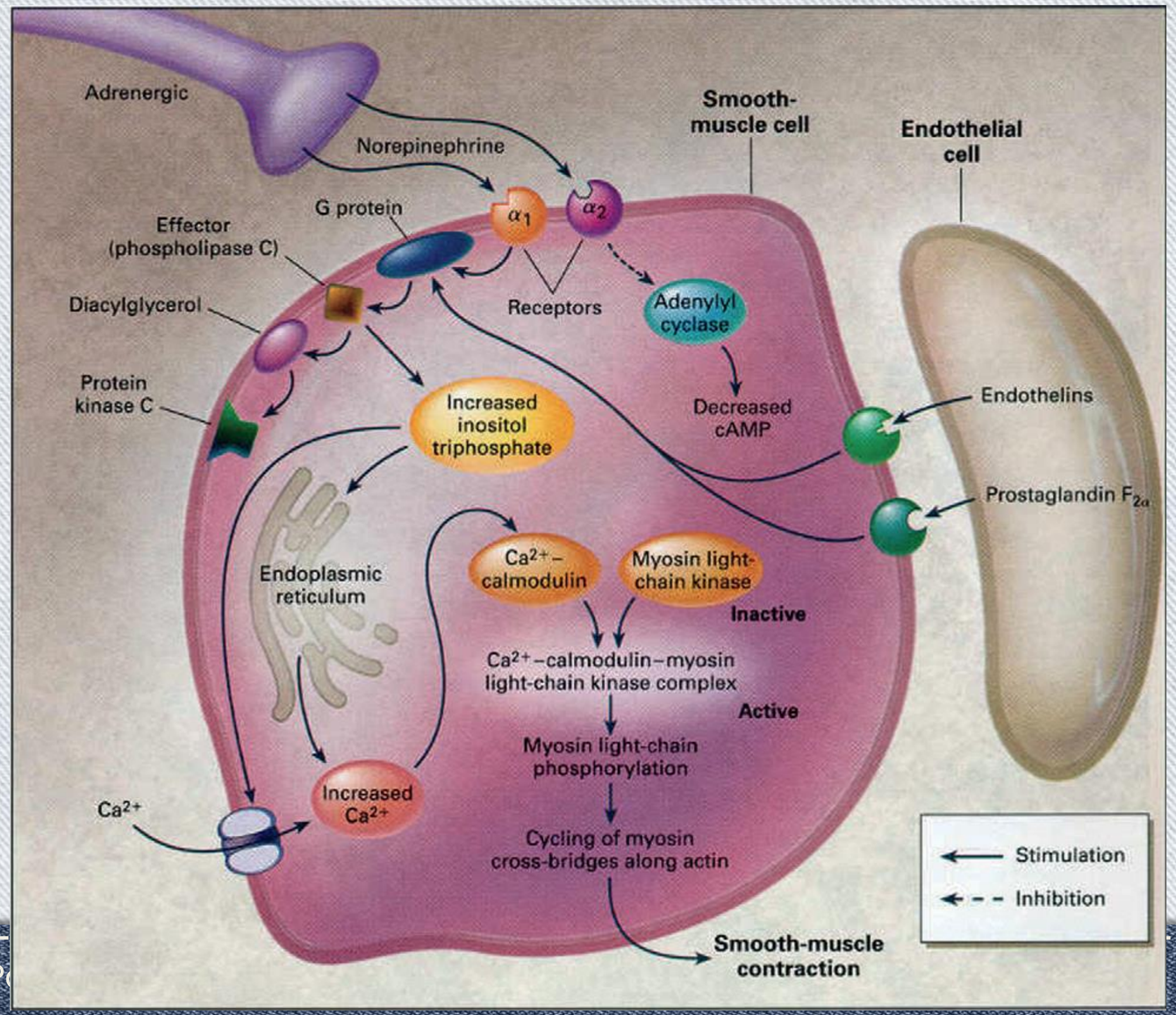
NEUROTRANSMITTERS

- ✓ **norepinephrine** has generally been accepted as the principal neurotransmitter to control penile **flaccidity** and **detumescence**
- ✓ **NO** released from **nonadrenergic/noncholinergic (NANC)** neurotransmission and **from the endothelium** is the principal neurotransmitter mediating penile **erection**
- ✓ **Acetylcholine** is not the predominant neurotransmitter, it does contribute **indirectly to penile erection** by **presynaptic inhibition of adrenergic neurons** and **stimulation of NO release from endothelial cells**
- ✓ (dopamine, norepinephrine,5- hydroxytestosterone [5-HT], and oxytocin) and neural hormones (oxytocin, prolactin) have been implicated in regulation of sexual function.
- ✓ It is suggested that **dopaminergic and adrenergic receptors** may **promote sexual function** and **5-HT receptors inhibit it**

SMOOTH MUSCLE PHYSIOLOGY

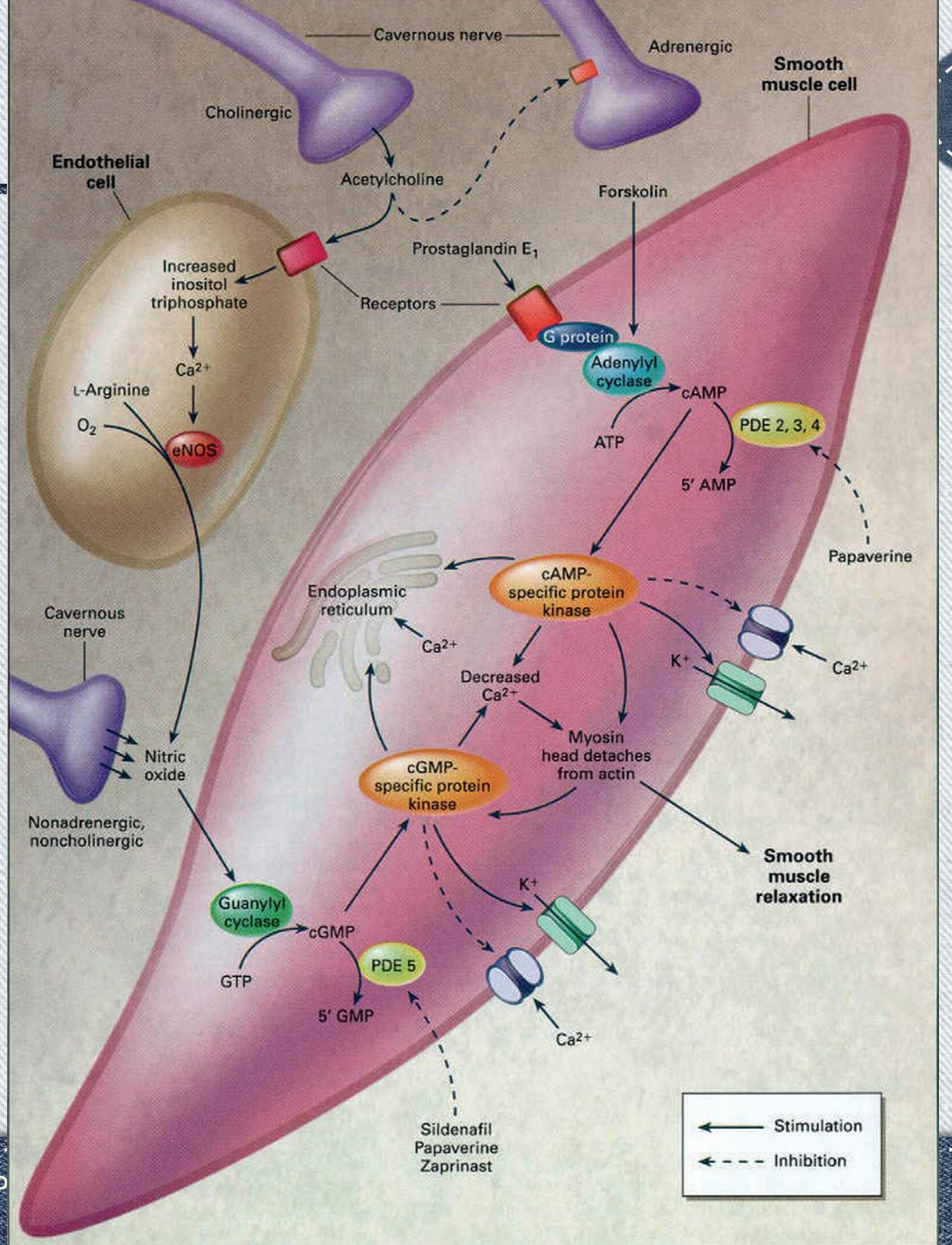
smooth muscle contraction

✓Adrenergic nerve ➔ NE ➔ G protein ➔ increase inositol triphosphate ➔ ca2+ influx ➔ myosin phosphorylation ➔ smooth muscle contraction

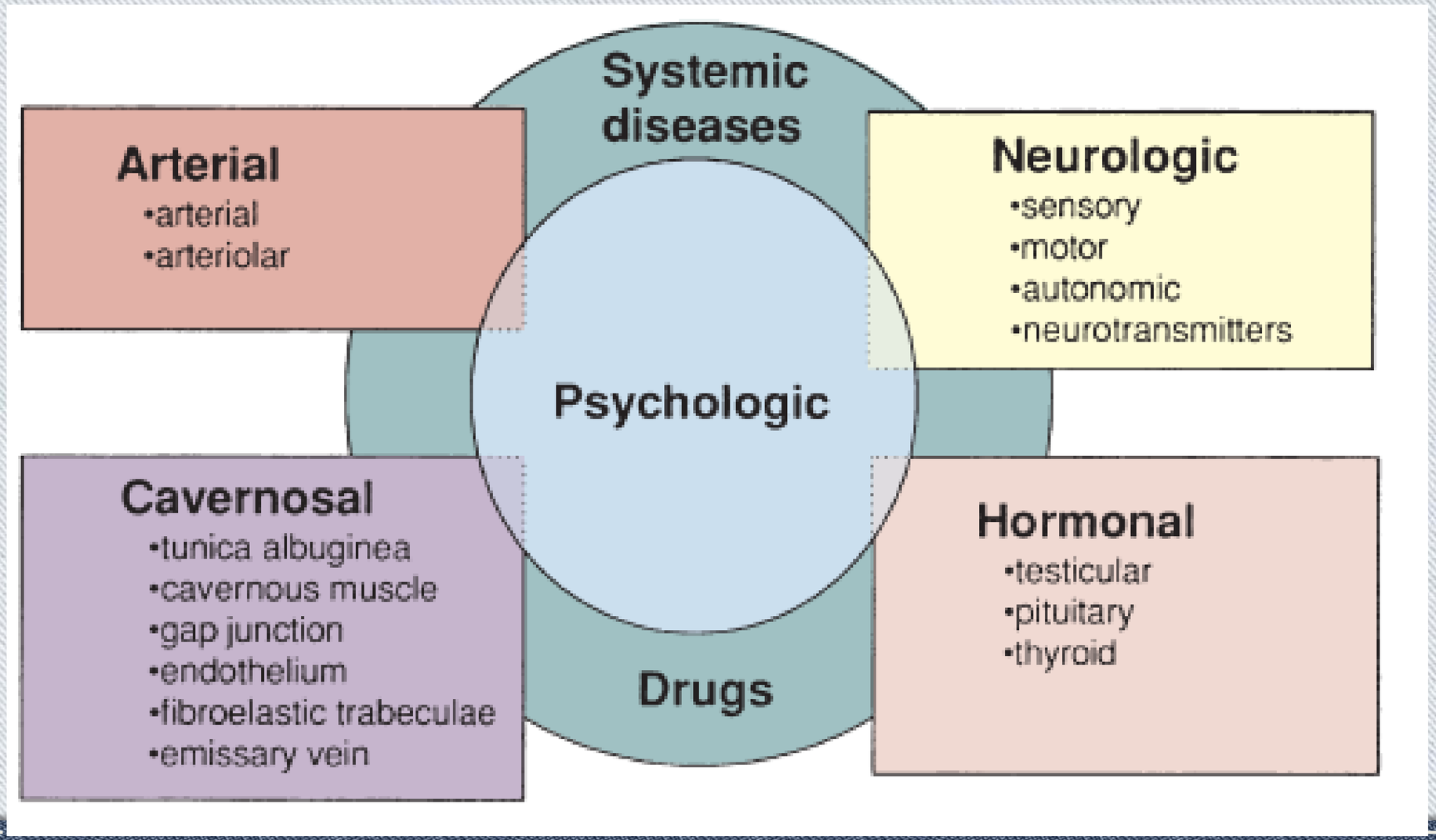


smooth muscle relaxation

- ✓**NO** from **noadrenergic-noncholinergic nerve** ➔ GTP-> cGMP ➔ decrease Ca2+ ➔ smooth muscle relaxation
- ◆PDE5 block cGMP to 5'GMP ➔ increase cGMP
- ✓Prostaglandin E1 ➔ ATP -> cAMP ➔ decrease Ca2+ ➔ smooth muscle relaxation
- ◆PDE 2.3.4 block cAMP to 5'AMP ➔ increase cAMP
- ✓Cholinergic nerve stimulation endothelial cells ➔ eNOS +O2 ➔ release NO



CLASSIFICATION AND ETIOLOGY OF ED



- ✓Systemic
- ✓Psychologic
- ✓Drug
- ✓Arterial
- ✓Cavernosal
- ✓Neurologic
- ✓Hormonal

RISK FACTORS

- ✓general health status, diabetes mellitus, cardiovascular disease, concurrence of other genitourinary disease, psychiatric/psychological disorders, other chronic diseases, and sociodemographic conditions.
- ✓**low socioeconomic** status category had **a greater** than twofold increase in risk of ED

ENDOCRINOLOGIC

Testosterone and DHT

Hyperprolactinemia

ED may also be associated with hyperthyroidism and hypothyroidism.

VASCULAR AND STRUCTURAL CHANGES LEADING TO ERECTILE DYSFUNCTION

TABLE 26-10 Vascular and Structural Changes Leading to Erectile Dysfunction

PENILE STRUCTURE	CHANGES IN ERECTILE DYSFUNCTION
Cavernous artery	Increased vascular resistance, narrow lumen
Smooth muscle	Increased tone (hypertonicity) Decreases muscle content Alteration of potassium channels and gap junctions
Erectile tissue	Fibrosis Impaired veno-occlusive mechanism
Endothelium	Impaired endothelium-dependent relaxation
Tunica albuginea	Alteration of elastic and collagen fibers
Neurotransmitters	Decreased nNOS, eNOS

eNOS, endothelial nitric oxide synthase; nNOS, neuronal nitric oxide synthase.

DRUG-INDUCED

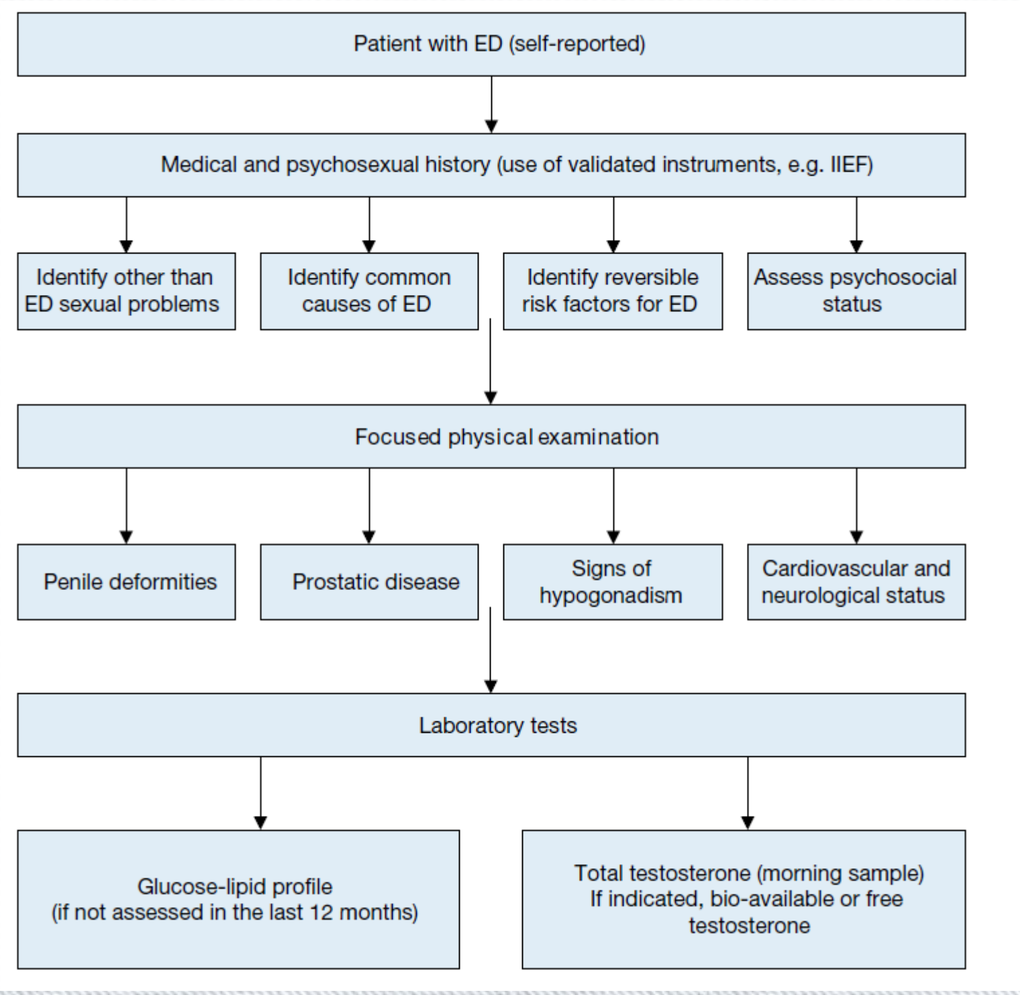
- ✓ Antihypertensive Agents.
- ✓ Diuretics. carbonic anhydrase inhibitors that alkalinize cells and cause vasodilation.
- ✓ Aldosterone Receptor Antagonist.
- ✓ Psychotropic Medication. Anxiolytics. Antidepressants.
- ✓ Digoxin.
- ✓ Statins. (?)
- ✓ Histamine H2 Receptor Antagonists.
- ✓ Opiates.
- ✓ Antiretroviral Agents.
- ✓ Tobacco.
- ✓ Alcohol. small amounts improves erection and sexual drive because of its vasodilatory effect and suppression of anxiety; however, large amounts can cause central sedation, decreased libido, and transient ED

TABLE 26-12 Drug-Induced Erectile Dysfunction and Suggested Alternatives

CLASS	KNOWN TO CAUSE ERECTILE DYSFUNCTION	SUGGESTED ALTERNATIVES
Antihypertensives	Thiazide diuretics General β blockers	α-Blockers Calcium channel blockers Specific β-blockers Angiotensin-converting enzyme inhibitors Angiotensin II receptor antagonists
Psychotropics	Antipsychotics Antidepressants Anxiolytics	Newer anxiolytics (bupropion, buspirone)
Antiandrogen	Androgen receptor antagonists Luteinizing hormone–releasing hormone agonists 5α-Reductase inhibitors	
Opiates		
Antiretroviral agents		
Tobacco		Quit smoking
Alcohol	Large amount	Small amount

AGENT	EFFECT	MECHANISM
Diuretics	ED (twice as common as placebo)	Unknown
β-Blocker (nonselective)	ED	Prejunctional α_2-receptor inhibition
β_1-Blocker (selective)	None	
α_1-Blocker	Decreases ED rate but may cause retrograde ejaculation	Failure of sympathetically induced closure of internal sphincter and proximal urethra during ejaculation
α_2-Blocker	ED	Inhibition of central α_2 receptor
Angiotensin-converting enzyme inhibitor	None	
Angiotensin II receptor blocker	Decreases ED rate	
Calcium channel blocker	None	

EVALUATION OF ED



PE: penis deformities, prostate disease, sign of hypogonadism, cadiac vascular or nuerologic disease signs

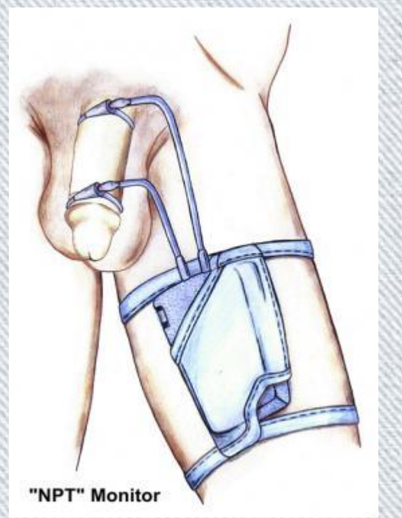
Laboratory test: glucose and lipid profile and testosterone

SPECIALISED DIAGNOSTIC TESTS

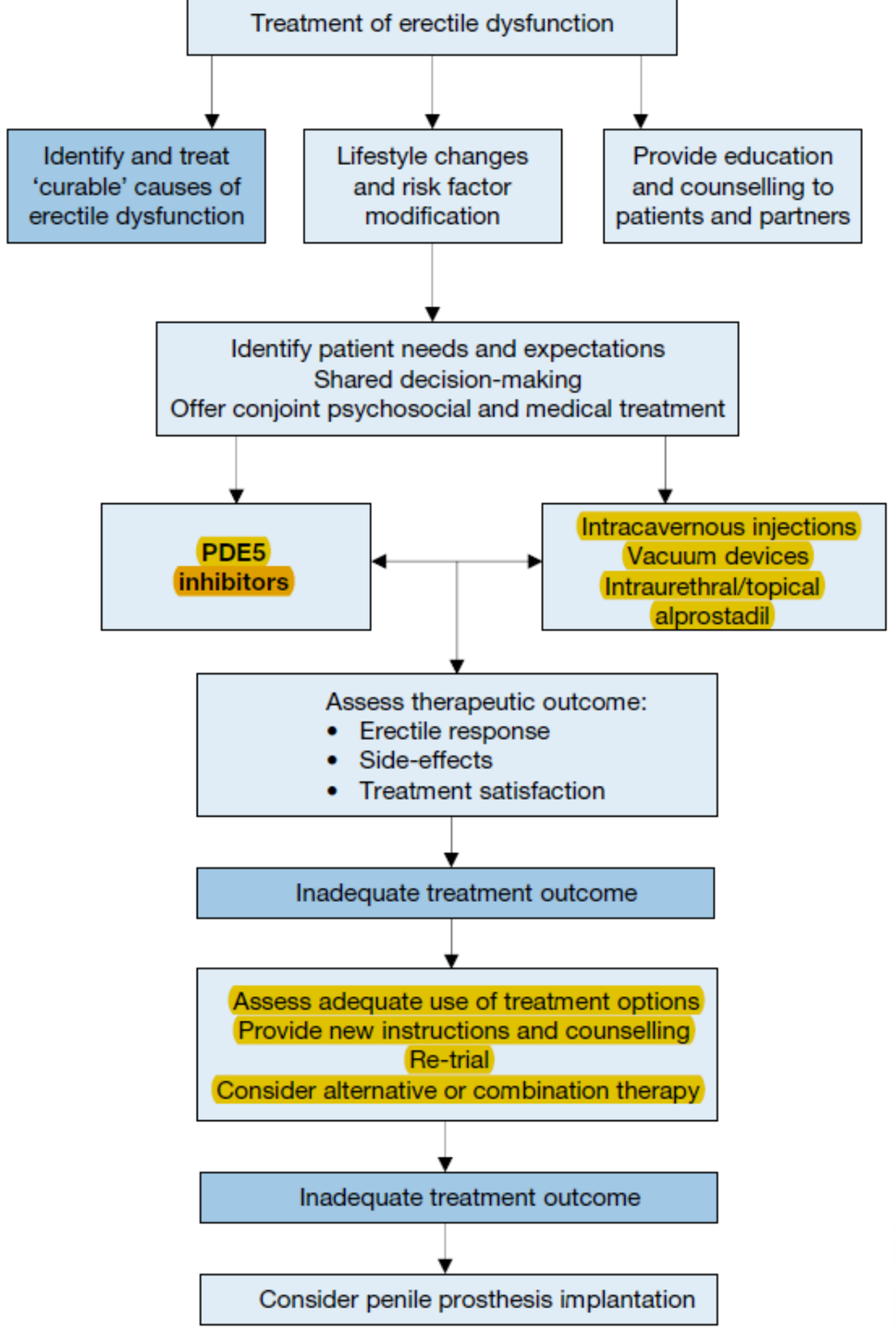
Primary ED (not caused by organic disease or psychogenic disorder).
Young patients with a history of pelvic or perineal trauma, who could benefit from potentially curative vascular surgery.
Patients with penile deformities which might require surgical correction (e.g., Peyronie's disease, congenital curvature).
Patients with complex psychiatric or psychosexual disorders.
Patients with complex endocrine disorders.
Specific tests may be indicated at the request of the patient or his partner.
Medico-legal reasons (e.g., implantation of penile prosthesis to document end stage ED, sexual abuse).

SPECIALISED DIAGNOSTIC TESTS

- ✓Nocturnal penile tumescence and rigidity test: on at least two separate nights.
- ✓Intracavernous injection test: limited information. A positive test is a rigid erectile response (unable to bend the penis) that appears within 10 min after the intracavernous injection and lasts for 30 min. Overall, the test is **inconclusive**
- ✓Duplex ultrasound of the penis: A peak systolic blood flow > 30 cm/s, an end-diastolic velocity of < 3 cm/s and a resistance index > 0.8 are
- ✓Arteriography and dynamic infusion cavernosometry or cavernosography: should be performed only in patients who are being considered for vascular reconstructive surgery
- ✓Psychiatric assessment: In younger patients (< 40 years) with long-term primary ED, psychiatric assessment may be helpful before any organic assessment is carried out



TREATMENT OF ED



Parameter	Sildenafil, 100 mg	Tadalafil, 20 mg	Vardenafil, 20 mg	Avanafil 200mg
C_{max}	560 µg/L	378 µg/L	18.7 µg/L	5.2 µg/L
T_{max} (median)	0.8-1 hours	2 hours	0.9 hours	0.5-0.75 hours
T1/2	2.6-3.7 hours	17.5 hours	3.9 hours	6-17 hours
AUC	1685 µg.h/L	8066 µg.h/L	56.8 µg.h/L	11.6 µg.h/L
Protein binding	96%	94%	94%	99%
Bioavailability	41%	NA	15%	8-10%

** Fasted state, higher recommended dose. Data adapted from EMA statements on product characteristics. C_{max}: maximal concentration, T_{max}: time-to-maximum plasma concentration; T1/2: plasma elimination halftime; AUC: area under curve or serum concentration time curve.*

Tadalafil on-demand doses of 10 and 20 mg and also an alternative daily dose of 5 mg.

- ✓Sildenafil: effective from 30-60 min after administration
- ✓ Tadalafil : effective from 30 min after administration, with peak efficacy after about 2 h.
- ✓Vardenafil: effective from 30 min after administration
- ✓Avanafil: Avanafil has a high ratio of inhibiting PDE5 as compared with other PDE subtypes allowing for the drug to be used for ED while minimising adverse effectsneeded approximately 15 to 30 minutes before sexual activity

AE OF ED MEDICATIONS

Table 6: Common adverse events of the four PDE5 inhibitors currently EMA-approved to treat ED*

Adverse event	Sildenafil	Tadalafil	Vardenafil	Avanafil 200mg
Headache	12.8%	14.5%	16%	9.3%
Flushing	10.4%	4.1%	12%	3.7%
Dyspepsia	4.6%	12.3%	4%	uncommon
Nasal congestion	1.1%	4.3%	10%	1.9%
Dizziness	1.2%	2.3%	2%	0.6%
Abnormal vision	1.9%		< 2%	none
Back pain		6.5%		< 2%
Myalgia		5.7%		< 2%

** Adapted from EMA statements on product characteristics.*

TABLE 27-7 Comparison of Four Phosphodiesterase Type 5 Inhibitors Currently Available in the United States

	SILDENAFIL	VARDENAFIL	TADALAFIL	AVANAFIL
Cmax (ng/mL)	450	20.9	378	2153
Tmax (hr)	0.8	0.7-0.9	2	0.3-0.5
Onset of action (min)	15-60	15-60	15-120	15-60
Half-life (hr)	3-5	4-5	17.5	3-5
Bioavailability	40%	15%	Not tested	30%
Fatty food	Reduced absorption	Reduced absorption	No effect	Reduced absorption
Recommended dosage	25, 50, 100 mg	5, 10, 20 mg	5, 10, 20 mg	50, 100, 200 mg
Side effects:				
Headache, dyspepsia, facial flushing	Yes	Yes	Yes	Yes
Backache, myalgia	Rare	Rare	Yes	Rare
Blurred/blue vision	Yes	Rare	Rare	No
Precaution with antiarrhythmics	No	Yes	No	No
Contraindication with nitrates	Yes	Yes	Yes	Yes

Headache: all medications

Blur or Blue vision: sildenafil

Back pain and myagia: tadalafil

Nasal congestion: vardenafil

CONTRAINDICATION AND DRUG-DRUG INTERACTION

- ✓Nitrates are contraindicated with PDE5 inhibitors
- ✓Antihypertensive drugs: Co-administration of PDE5Is with antihypertensive agents (angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, calcium blockers, β-blockers, and diuretics) may result in small additive decreases in blood pressure, which are usually minor.
- ✓α-Blocker interactions: All PDE5Is show some interaction with α-blockers, which under some conditions may result in orthostatic hypotension.
- ✓Drugs that inhibit the CYP34A pathway will inhibit the metabolic breakdown of PDE5Is, thus increasing PDE5Is blood levels

THANKS

Any Question?