Male Sexual Dysfunction: Assessment and Management Post Cancer Treatment

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Historical Background

- American Cancer Society's 2008 estimates of leading four cancer sites among men:
    1. **Prostate**
    2. Lung and Bronchus
    3. **Colon/Rectum**
    4. **Urinary Bladder**

- Increased attention to quality of life post cancer treatment by patients and national credentialing centers

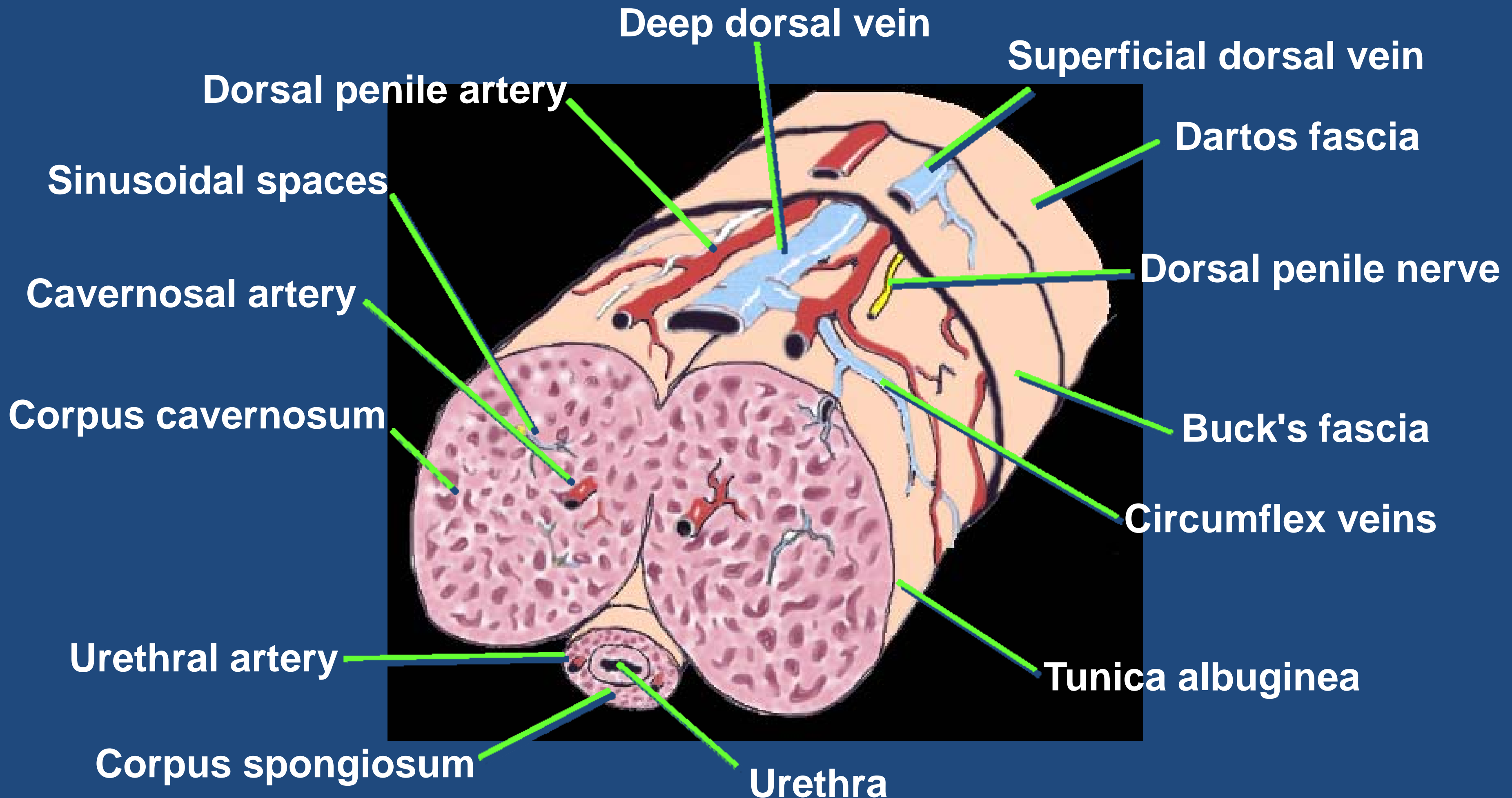
Male Sexual Dysfunction Post Cancer Care

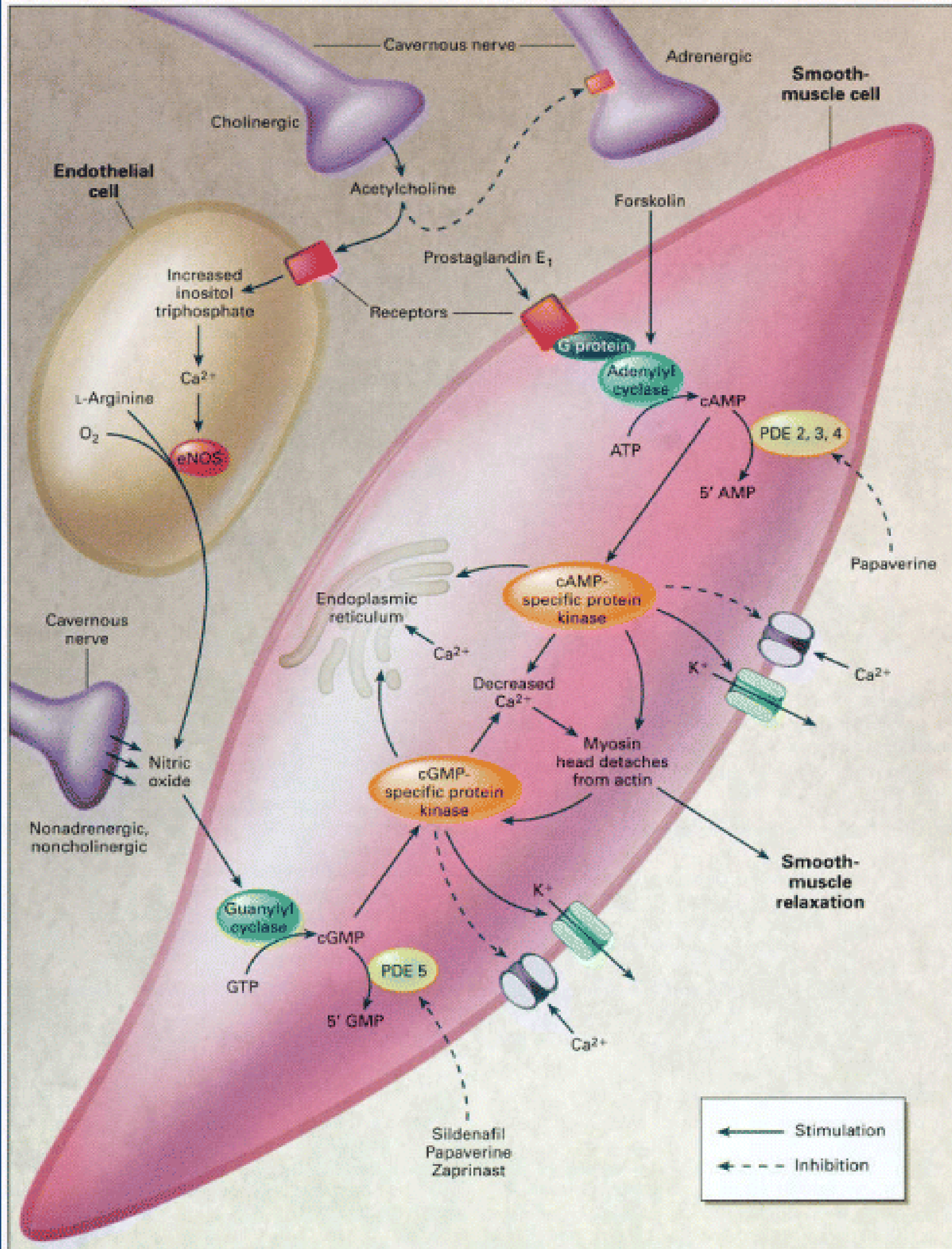
- Erectile Dysfunction
  - Organic
  - Psychogenic
  - Mixed
- Ejaculation/Orgasm disorders
  - Anejaculation/decreased volume
  - Dysorgasmia
  - Retrograde ejaculation
  - Retarded orgasm
- Incontinence
- Infertility
- Hypogonadism

Assessment of Sexual Dysfunction

- Medical History
- Surgical History
- Social History
  - Relationship status
  - Alcohol, recreational drugs, tobacco use
- Physical Examination
- Tests:
  - Laboratory (blood, urine)
  - Biothesiometry
  - Duplex sonogram (DUS)
  - Dynamic Infusion Cavernosometry (DIC)

Penile Anatomy: Serial Section





Cavernous nerve
Adrenergic
Smooth-muscle cell
Cholinergic
Endothelial cell
Acetylcholine
Forskolin
Prostaglandin E_1
Increased inositol triphosphate
Receptors
G protein
Adenylyl cyclase
Ca^{2+}
L-Arginine
O_2
eNOS
cAMP
ATP
PDE 2, 3, 4
5′ AMP
Papaverine
Endoplasmic reticulum
cAMP-specific protein kinase
Cavernous nerve
Ca^{2+}
K^+
Ca^{2+}
Decreased Ca^{2+}
Myosin head detaches from actin
Nitric oxide
cGMP-specific protein kinase
Nonadrenergic, noncholinergic
Smooth-muscle relaxation
K^+
Guanylyl cyclase
cGMP
PDE 5
GTP
5′ GMP
Ca^{2+}
Sildenafil
Papaverine
Zaprinast
Stimulation
Inhibition

Erectile Dysfunction (ED) is…

- … the consistent inability to achieve or maintain a penile erection sufficient for "adequate" sexual relations.

- The effects of ED interfere with[1]:
  - Man's self-esteem
  - Interpersonal relationships
  - Sense of well-being

1 Krane RJ et al, N Engl J Med 1989

Method to Evaluate ED

International Index of Erectile Dysfunction (IIEF)[1]

Questoinnaire-based, reliable self-administered symptom scales

Maxium score = 30

5 domains: (15 questions, rating 0 or 1 – 5)

- Erectile function (6 questions)
- Orgasmic function (2 questions)
- Sexual desire (2 questions)
- Intercourse satifaction (3 questions)
- Overall satifaction (2 questions)

Results:

- < 10 = severe
- 11 – 17 = moderate
- 18 – 25 = Mild
- > 26 = normal

1 Rosen RC et al 1997

Sample Questions on IIEF

- Q1: How often were you able to get an erection during sexual activity?
- Q2: When you had erections with sexual stimulation, how often were the erections firm enough for penetration?

- 0 = No Sexual Activity
- 1 = Almost never/never
- 2 = A few times (much less than half the time)
- 3 = Sometimes (about half the time)
- 4 = Most times (much more than half the time)
- 5 = Almost always/always

- Q3: When you attempted sexual intercourse, how often were you able to penetrate (enter) your partner?
- Q4: During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?

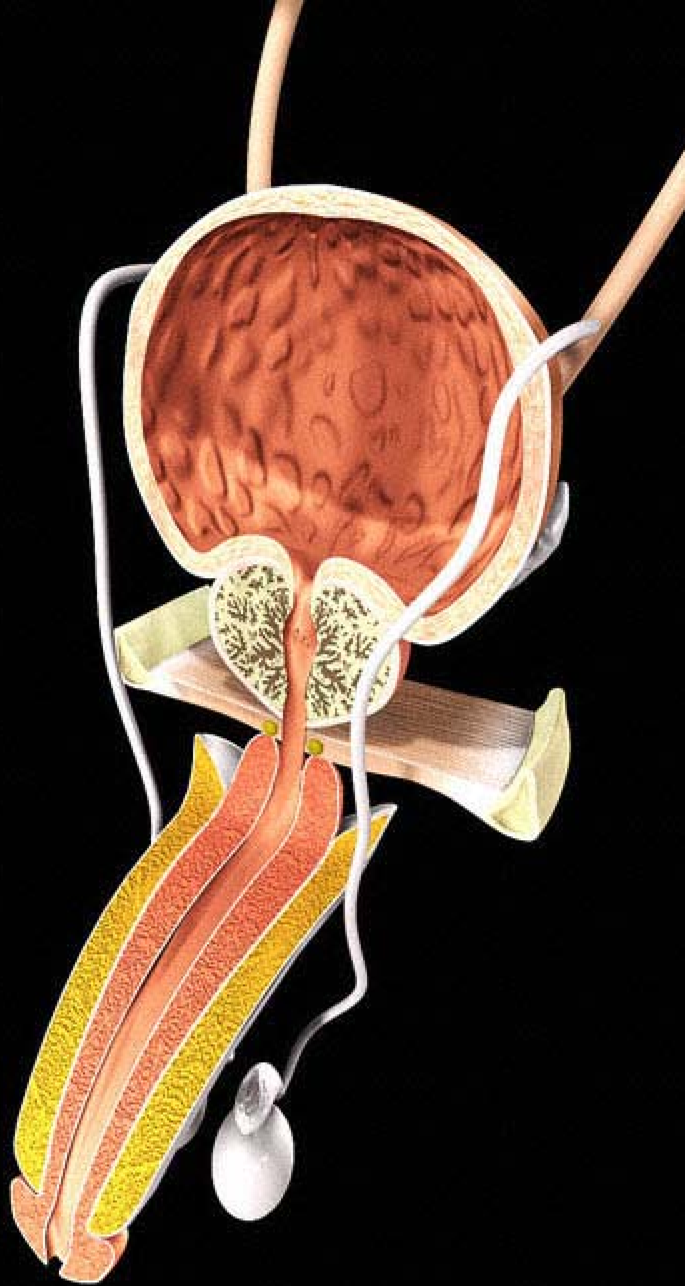
- 0 = Did not attempt intercourse
- 1 = Almost never/never
- 2 = A few times (much less than half the time)
- 3 = Sometimes (about half the time)
- 4 = Most times (much more than half the time)
- 5 = Almost always/always

- Q5: During sexual intercourse, how difficult was it to maintain your erection to complete intercourse?

- 0 = Did not attempt intercourse
- 1 = Extremely difficult
- 2 = Very difficult
- 3 = Difficult
- 4 = Slightly difficult
- 5 = Not difficult

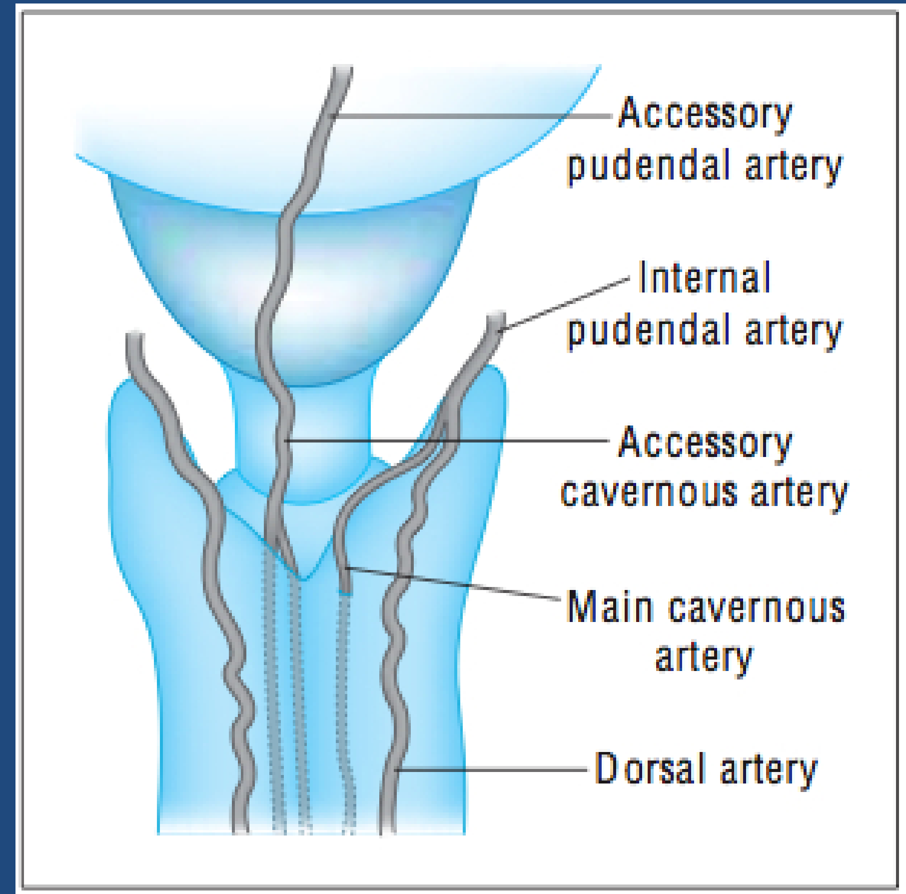
Likely Post Treatment Causes of ED

- Arteriogenic (accessory pudendal artery injury)
- Venogenic (erectile tissue damage)
- Neurogenic (cavernous nerve injury)
- Psychogenic (confidence erosion)
- Androgen Deprivation


2001 Image by Med-Art ~ http://www.med-ars.it

Accessory Pudendal Arteries

- Some men have APA as a major source of cavernosal inflow
- Most authorities believe injury to these arteries (surgery and/or radiation) plays some role in erectile dysfunction.



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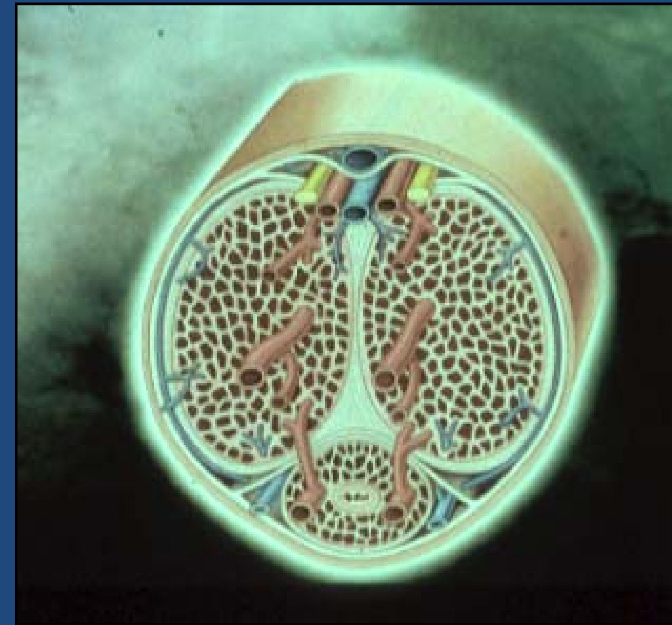


Flaccid

Erect

PO_2 = 35-40 mmHg

Increased TGF-β_1 Secretion

Collagen Production

Fibrosis and venous leak

PO_2 = 70-100 mmHg

Increased PGE Secretion

Decreased Collagen Production

Preserved erectile tissue integrity

Venous Leak

- Three crucial steps to achieve erection
  - Relaxation of trabecular smooth muscle
  - Arterial dilation
  - Venous compression
- When venous compression fails = venous leak

Mechanism of Penile Erection

Flaccid

Erect

Tunica albuginea

Subtunical venular plexus

Dorsal artery

Dorsal nerve (somatic)

Sinusoidal spaces

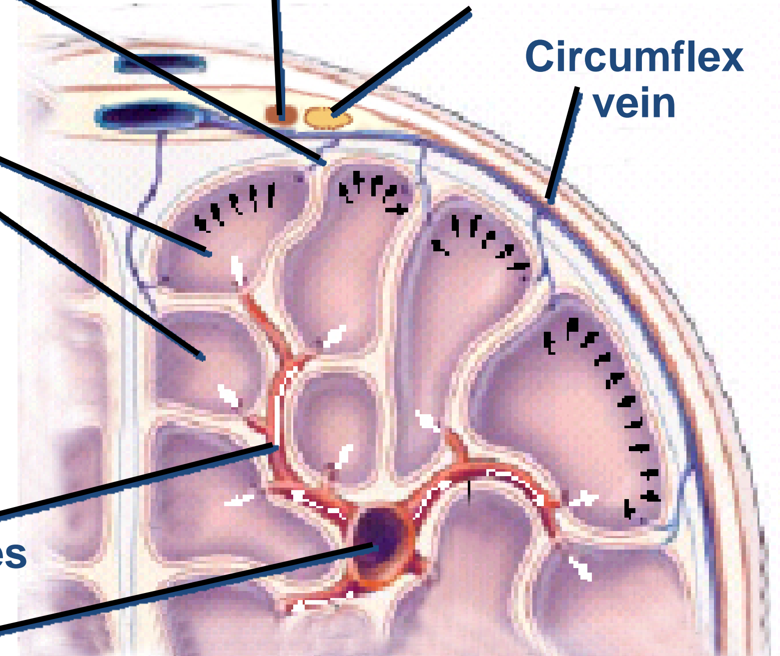
Circumflex vein

Corpora cavernosa

Trabecular smooth muscle

Helicine arteries

Cavernous artery



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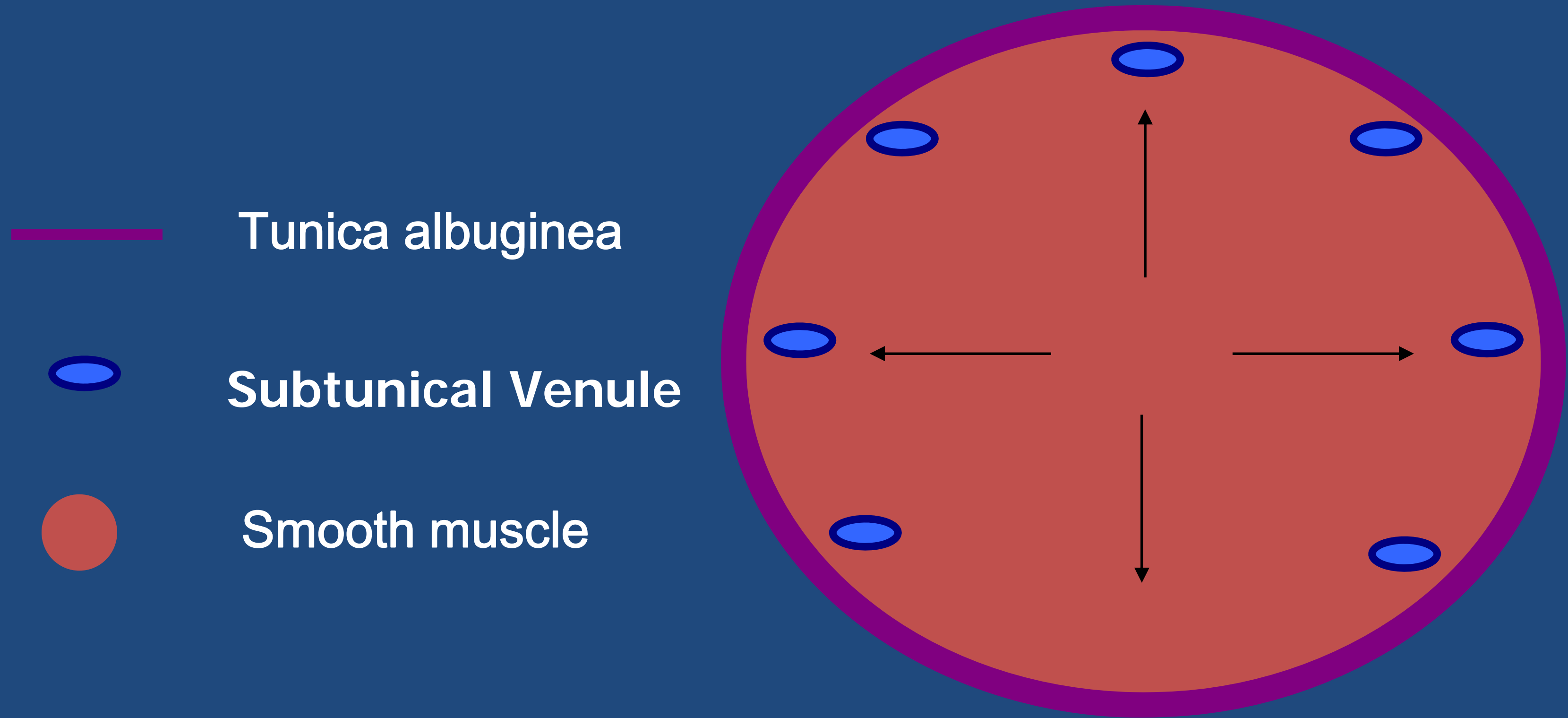
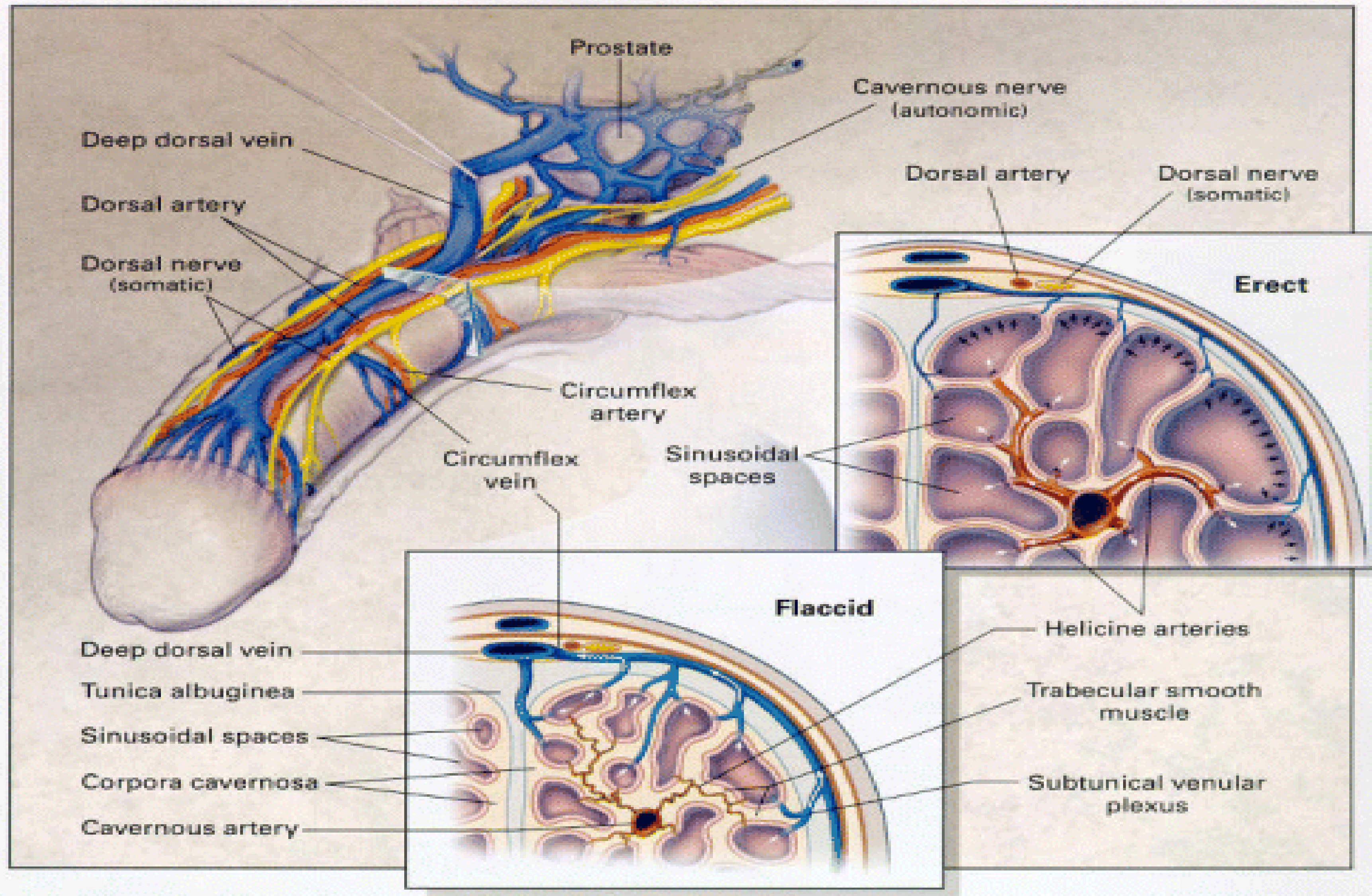
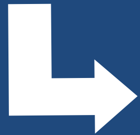


Cavernous Nerves

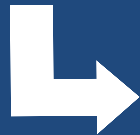


Evolution Of ED Therapy

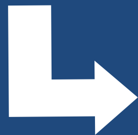
1960'S
Sex therapy



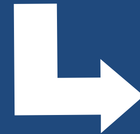
1970's
Penile Prosthetics



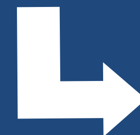
1980's
Penile injection therapy



1997
MUSE™



1998
Viagra™



PDE5I
Transdermal Tx
Injection Tx

Management of ED

- Modify reversible causes
  - Medication change or discontinuation
  - Lifestyle modification
- First-line therapy
  - Oral agents
  - Vacuum erection device
  - Individual/couples therapy
- Second-line therapy
  - Intracavernosal Injections
  - Intraurethral suppository
- Third-line therapy
  - Surgical prosthesis
  - Vascular surgery

PDE5 Inhibitors

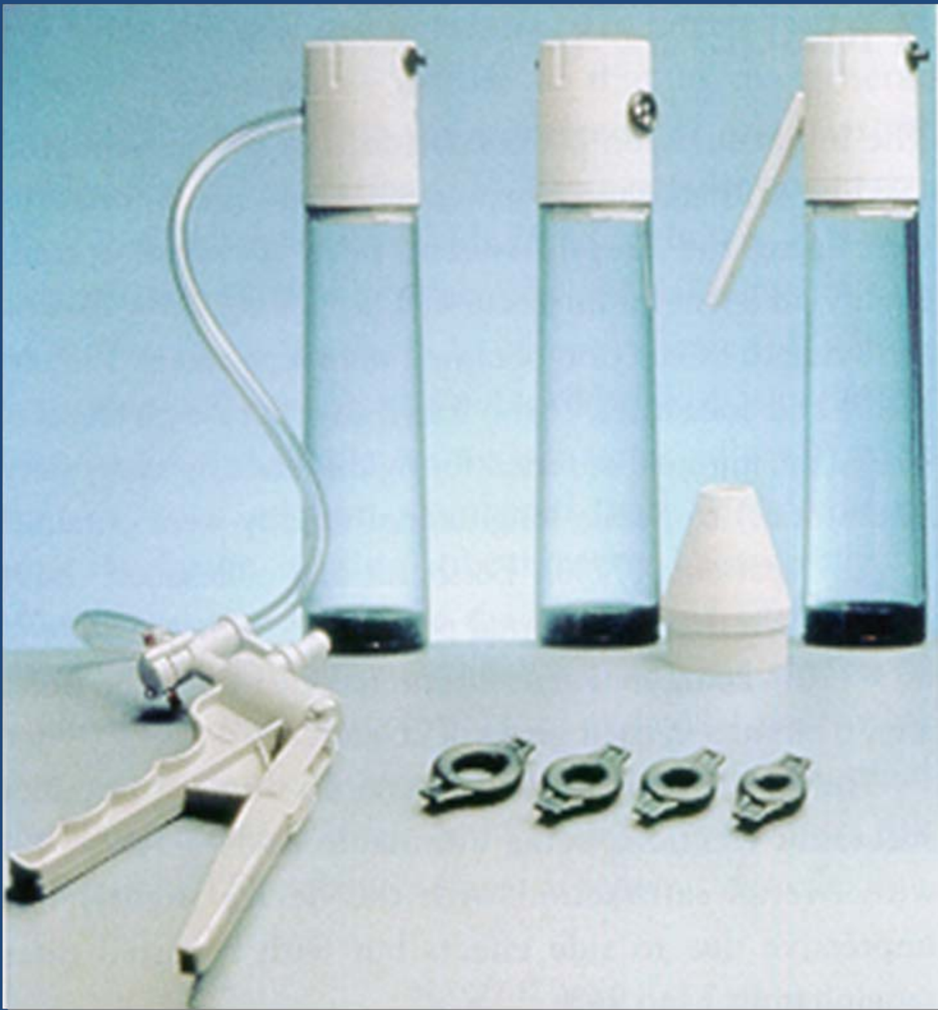
- Nitric oxide dependent mechanism
- Success in patients depends on
  - Time of trial
  - Degree of neuron sparing (surgery/radiation)
  - Responsiveness of CCSM
- Post-RP evolution of response
  20% @3 months
  50% @ 12 months
  Slightly higher @ 18 months

Hong S et al et al, IJIR 1999; Zippe C et al, Urology, 52:963, 1998

Correct PDE5 Inhibitor Use

- Take one hour prior to sexual activity
- Take on empty stomach
- Avoid taking when tired or under stress
- Must be engaged in sexual activity (partner or masturbatory)
- Contraindicated:
  - Unstable angina requiring nitroglycerine use (Nitrolingual®, Imdur®)
  - History of hypotension
  - History retinitis pigmentosa

Vacuum Erectile Device (VED)



- Mechanical or battery operated
- Placed over penis
- Vacuum created drawing venous blood into penis
- Tension ring placed at base of penis to hold in the blood

Intracavernosal Injection (ICI) Therapy

- Involves direct injection of papaverine, phentolamine, and alprostadil separately or in combination into the corpus cavernosum

- Utilized when oral agents not effective

- Results in inhibition of PDE5, leading to increased cAMP and cGMP in penile erectile tissue.

Medications

- Papaverine
- Phentolamine
- Alprostadil (Caverject®, Edex®)
- Compounded multi-agent mixtures (Bimix, Trimix, Super Trimix)

Papaverine

- Vasodilator
- Smooth muscle spasmolytic producing a generalized smooth muscle relaxation
- Muscle relaxation occurs due to inhibition of phosphodiesterases in a non-specific fashion increasing cAMP

Phentolamine

- Non-selective α-adrenoceptor blocker
- Completely blocks α-adrenergic receptors to produce brief antagonism of circulating epinephrine and norepinephrine
- Used in combination with papaverine or papaverine and alprostadil

Alprostadil (PGE1)

- Prostaglandin E1
- Causes vasodilation by means of direct effect on vascular smooth muscle
- Relaxes trabecular smooth muscle by dilation of cavernosal arteries promoting arterial flow and blood entrapment within the lacunar spaces of the penis

MSKCC Compounded Mixtures

- **Bimix**
  - Papaverine 30mg/ml
  - Phentolamine 1mg/ml
- **Trimix**
  - Papaverine 30mg/ml
  - Phentolamine 1mg/ml
  - PGE1 10mcg/ml
- **Super Trimix**
  - Papaverine 30mg/ml
  - Phentolamine 2mg/ml (**check this**)
  - PGE1 20mcg/ml

Contraindications

- Obese abdomen
- History vaso-vagal response
- Dexterity problems
- Uncontrolled hypertension
- Concurrent use of MAO Inhibitors

Contraindications

- Predisposition to priapism due to hematologic disorders (e.g., sickle cell anemia, multiple myeloma, leukemia)
- Penile prosthesis
- Sexual activity is inadvisable or contraindicated

Training

- Scheduled for two sessions
- Provided verbal and written instructions
- First session: injected with Trimix 5 units to assess response (i.e., rigidity & duration)
- Second session: self-injection taught (dose adjusted according to response at first session)

Training

- Injection supplies:
  - Vial of medication
  - Syringe (29 gauge, ½”needle, 50 unit/0.5cc)
  - Alcohol swabs
  - Sharps container
- Instructed on drawing medication from multi-dose vial
- Taught to rotate injection sites

Training

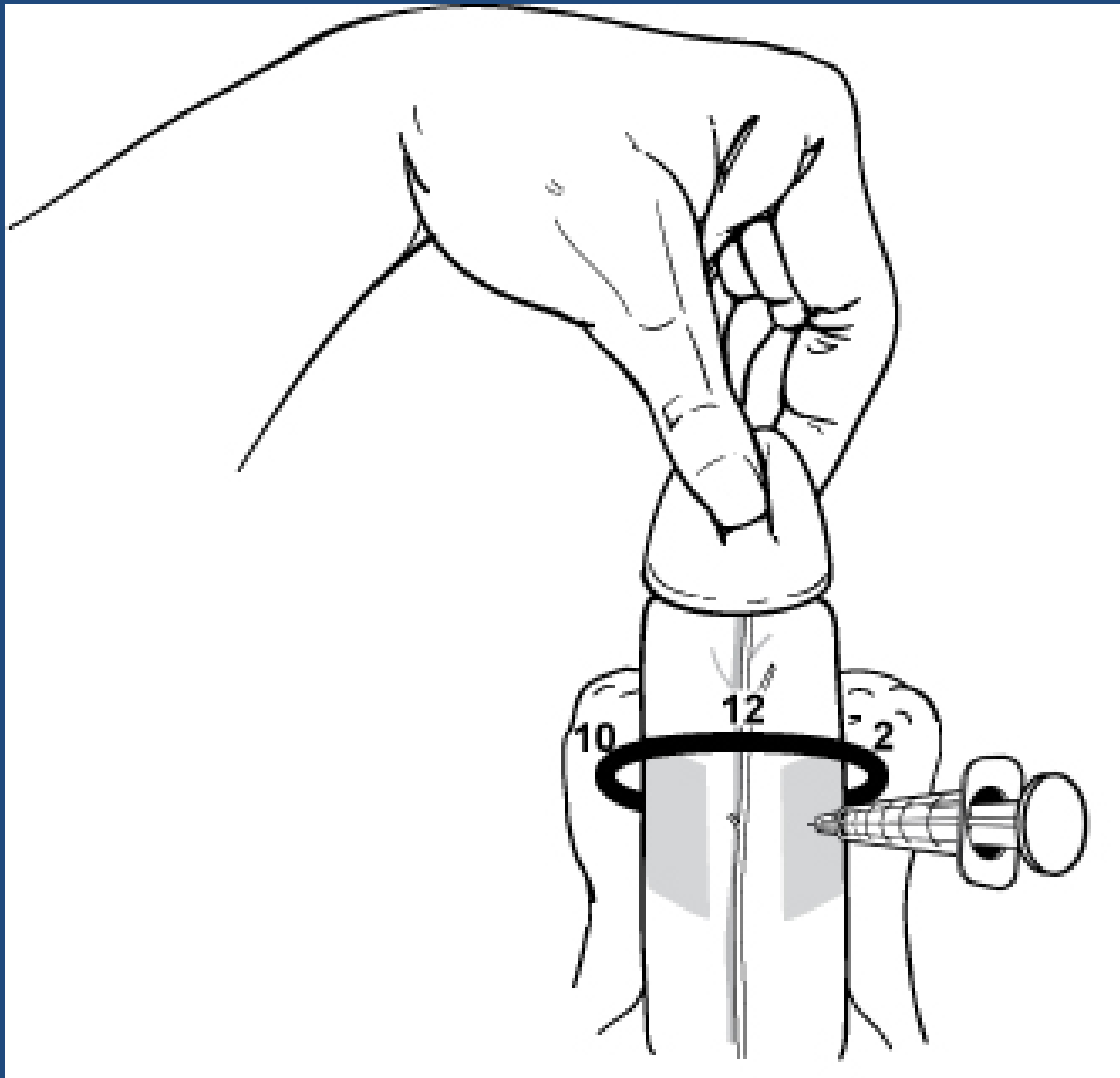
- Preparation of penis and choice of injection site

- Divide penis into two parts:
  - Area proximal to mid-point of shaft
  - Area distal to mid-point of shaft

- Anatomical landmarks reviewed

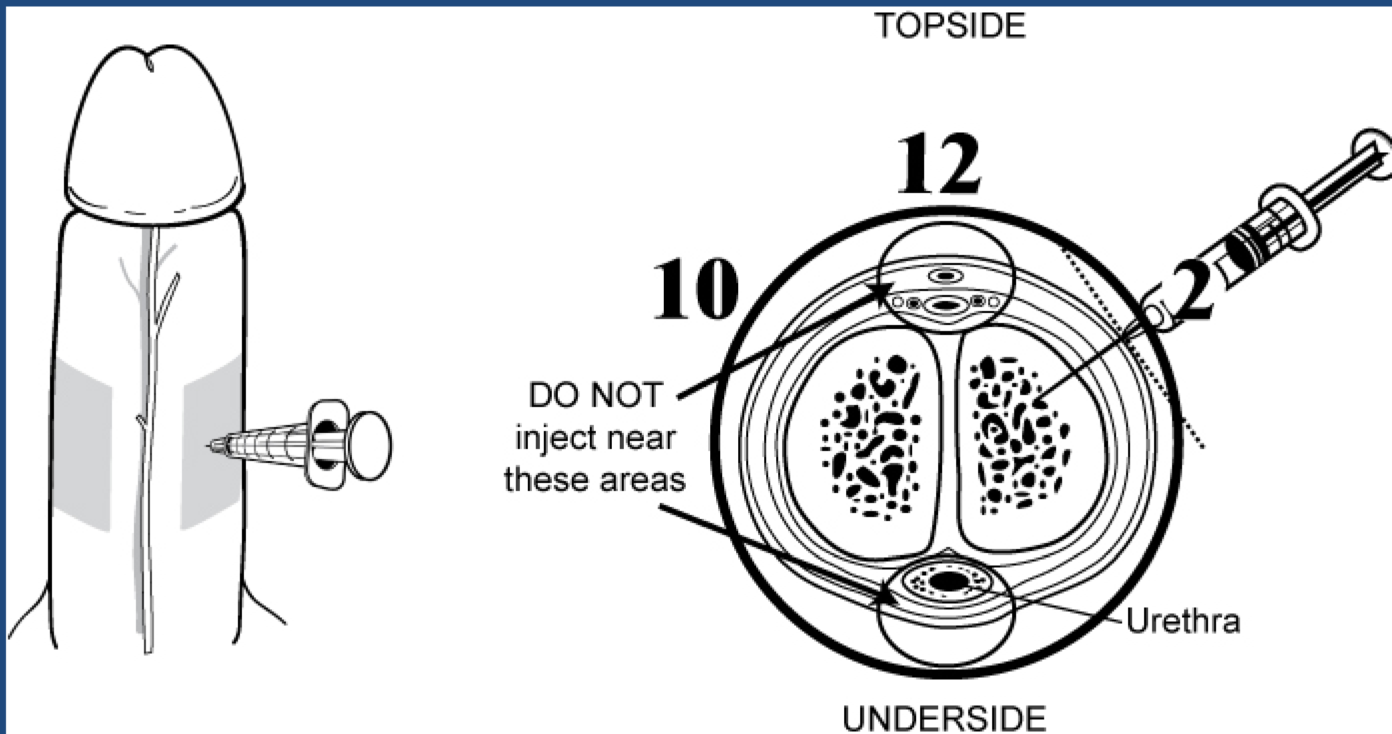
Training

- Patient grasps glans with less dominant hand (must retract foreskin if uncircumcised) and gently stretches penis
- Area to be injected located and swabbed with alcohol wipe
- Holding needle as dart or pen position toward area to be injected


12
10
2

Training

- Instructed to angle needle at 10 o'clock or 2 o'clock position on shaft directly behind midline



Responses

- Patient informed may experience warm sensation within 3-5 minutes followed by "stretching", "tight", or "heavy" non-painful sensation along shaft

- Rigidity should occur within 10-20 minutes with minimal stimulation

Responses

- Erection scale used to grade response

  0 = no erection

  6 = erection just firm enough for penetration

  8-10 = Satisfactory for sexual intercourse

  10 = 100% erect

Complications

- Poor or no response:
  - Majority due to technique leading to subcutaneous or intra-tunical injection
    - Plunger pressed as needle inserted
    - Needle pulled out as plunger pressed
    - Accidental release of penis as injecting
    - Needle rolls against tunica when inserting
    - Injected at base of penis
  - Vial of medication exposed to heat or light

Complications

- Adverse Reactions:
  - Priapism
  - Penile pain (Lane, et al., 2005)
  - Hematoma or ecchymosis at injection site
  - Penile rash or edema
  - Fibrosis

Priapism

- Instructed to take 4 tablets of pseudophedrine (Sudafed®) 30mg if erection 6 or firmer > two hours
- Erection remains ≥ 6/10 at third hour after pseudophedrine, patient contacts office
- By fourth hour, at Emergency Department for intracavernosal injection of phenylephrine (Neo-Synephrine®)
- If unresponsive to phenylephrine will need to aspirate blood

Monitoring

- Contacts office reporting result after first home injection for titration instructions
- Injects 2-3x/week regardless of sexual activity
- If poor or no response cannot repeat for 24 hrs
- No PDE5 Inhibitor within 18-24 hours of ICI

Monitoring

- May take 3-4 weeks injecting 2-3x/week to reach appropriate dose
- Continues nightly low dose PDE5 Inhibitor on nights when not injecting for first year post surgery or RT
- Follow-up scheduled four months or sooner for additional teaching session if required

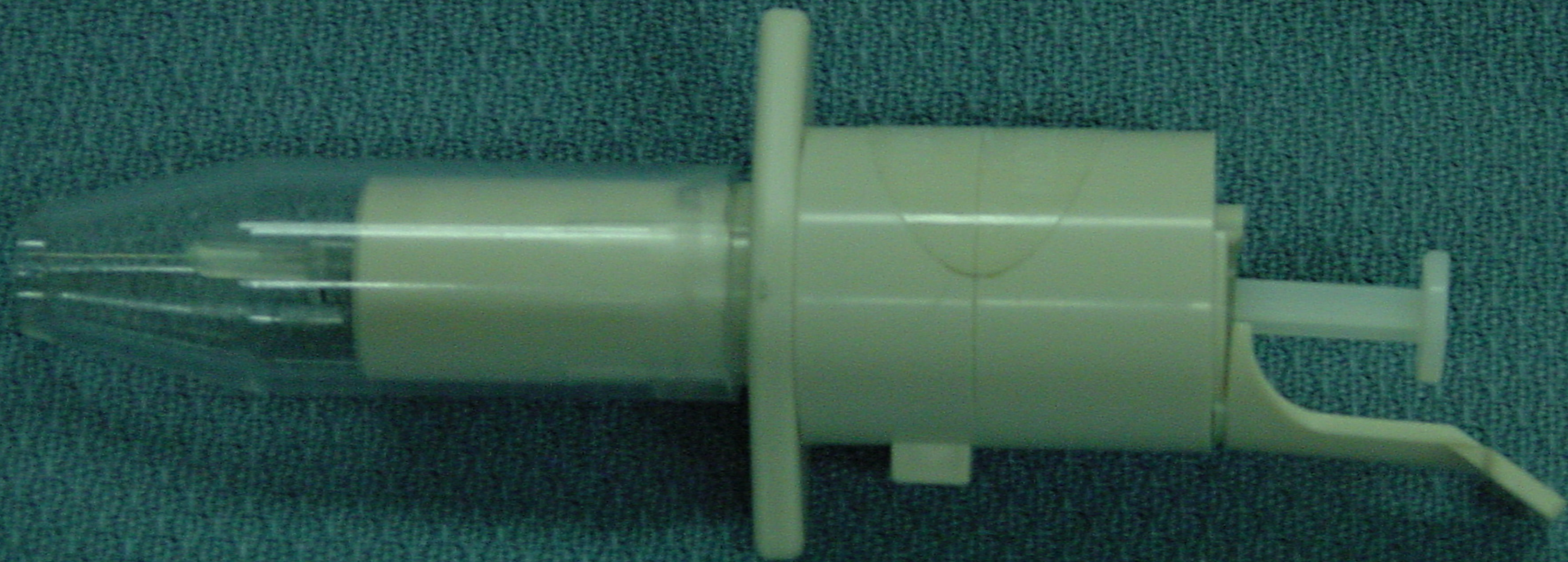
Patient Drop-out

- 30-80% at 3-5 yrs
- Realistic expectations
- Patient/partner education
- Reasons:
  - Cost
  - Failure
  - Needle-phobia
  - Adverse effects
  - Change in patient goals
  - Partner issues

Althof et al. J Sex Mar Ther, 15:121-129;
Sundaram et al, Urology. 49: 932, 1997;
Mulhall et al, J Urol. 158: 1752, 1999

Auto-injectors

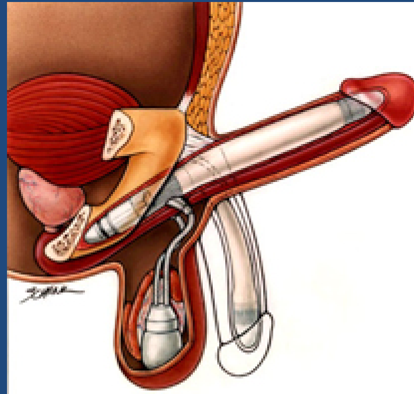
- Experience in other conditions supports use (eg., Epipen®, diabetes)
- Primary purpose to reduce anxiety
- Absence of evidence-based analyses
- Use based on personal preference
- Needle-less injectors



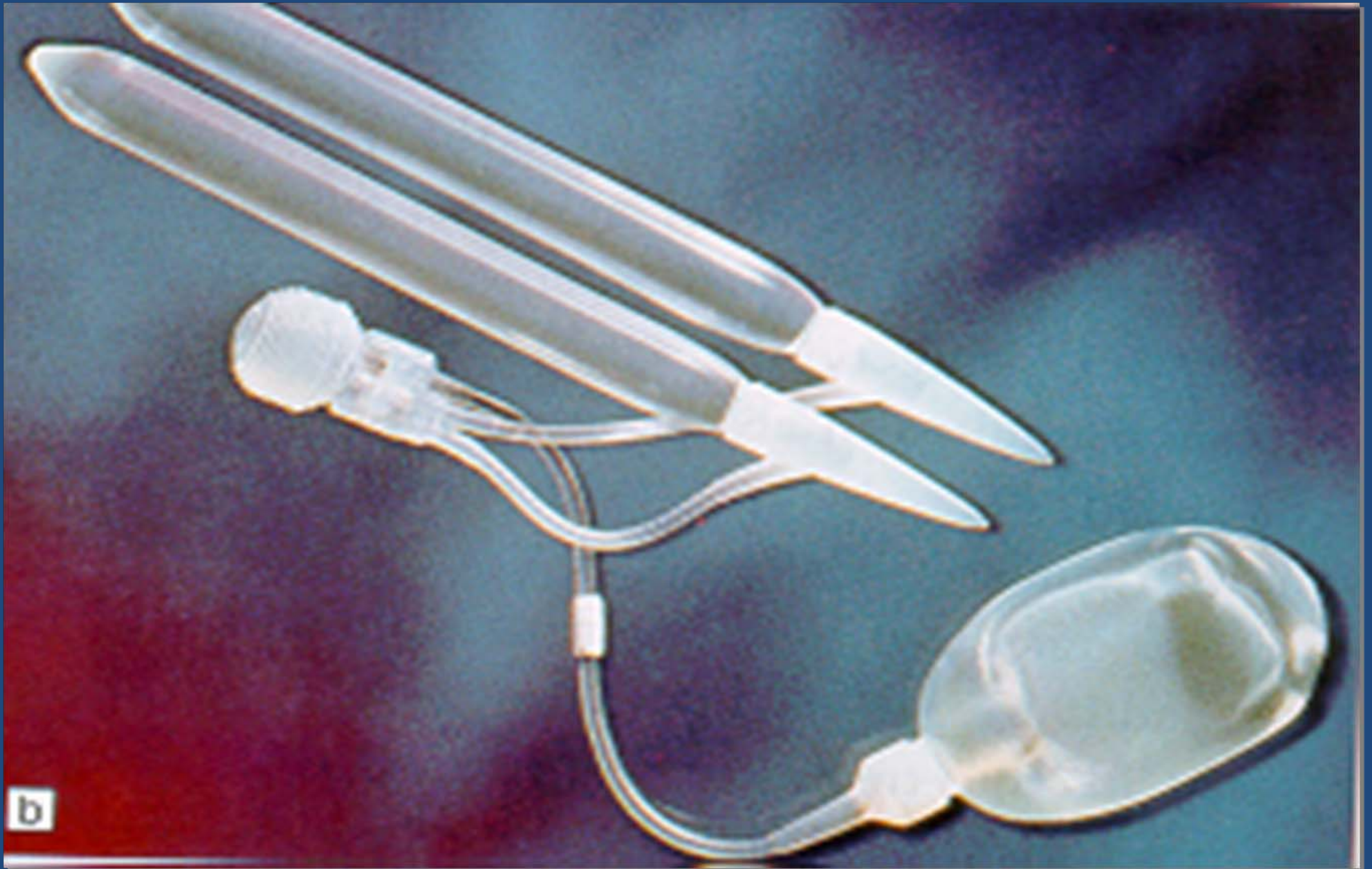
Penile Prosthesis

- Utilized in patients who have failed drug therapy or patient burn-out with therapies
- Advantages:
  - Generates a 100% rigid erection
  - 5-15 seconds to generate erection
- Disadvantages:
  - Invasive surgical procedure
  - Risk of infection (2-3%)
  - Mechanical breakdown (15% first 10 years)
- Implant types:
  - Mechanical
  - Inflatable
    - Two piece
    - Three piece

Penile Prosthesis 2-Piece Implant



Penile Prosthesis 3-Piece Implant



Ejaculation Disorders

- Anejaculation or decreased volume
- Dysorgasmia (painful erections)
  - Tamsulosin HCL (0.4mg)
  - Alfuzosin (10mg)
  - Patient education regarding side effects of α-blockers
- Retrograde ejaculation
- Retarded orgasm
  - Neuropathy (chemotherapy/radiation)

Incontinence

- Common after radical pelvic surgery
- Fear of urine loss with foreplay/intercourse
- Patient and partner distress
- Treatments:
  - Kegel exercises
  - Condoms
  - Penile constriction loop
  - Artifical urinary sphincter

Infertility

- Effects of chemotherapy, radiation, and/or surgery
- Counsel patients regarding sperm preservation
  - Sperm banking
  - Electro-ejaculation
- Interventions post-treatment
  - Testicular tissue extraction
  - Androgen replacement

Hypogonadism

- Testosterone
  - Major sex hormone in adult male
  - Produced predominantly by testicles (small amount by adrenal glands)
- Failure of testicles to produce testosterone
- Failure of pituitary to secrete enough LH to stimulate cells in testicles
- Surgery (Orchiectomy)
- Chemotherapy, total body irradiation (bone marrow and stem cell transplants)

Hypogonadism

- Reduction in general well-being
- Decrease in sexual drive (libido)
- Increased fatigability
- Loss of energy
- Depression
- Erectile problems
- Osteopenia/osteoporosis
  - Axial Bone Densitometry Scan
  - Androgen replacement

Hypogonadism

- Androgen Replacement
  - Testosterone
    - Patches
    - Topical Gels
    - Intramuscular injections
  - Clomiphene citrate (25mg QOD)
- Laboratory blood work
- Repeat Axial DEXA Scan

Summary

- Important to counsel patients pre and post cancer treatment
- Early intervention and initiative to assess and manage patient can be key to post treatment satisfaction
- Refer to the Male Sexual and Reproductive Medicine Program

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