In the name of God

Stem-cell therapy for erectile dysfunction

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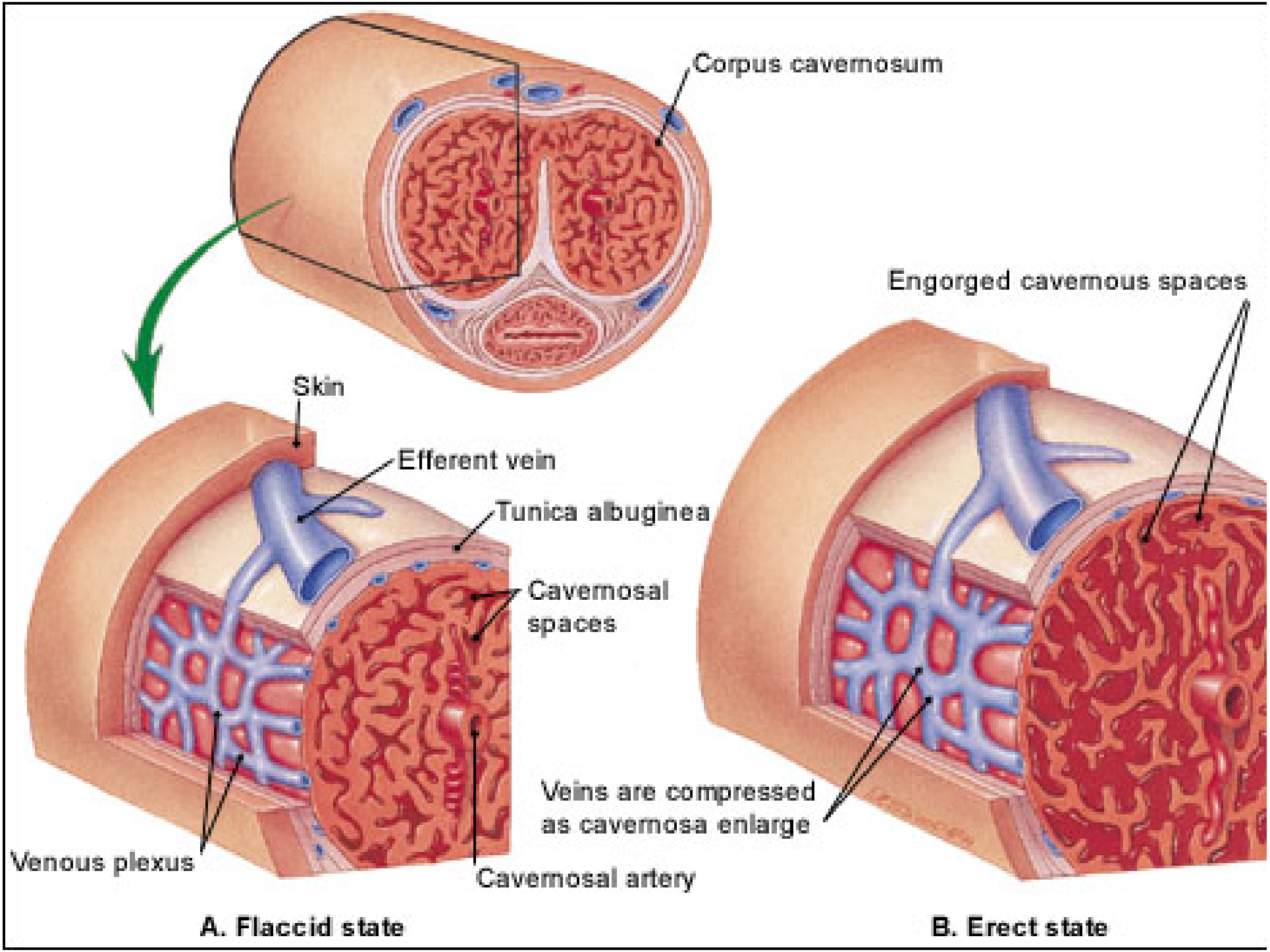
Erectile dysfunction (ED) is a common condition that refers to the inability of a male individual to attain and maintain sufficient penile erection for sexual intercourse .It is classified as organic, psychogenic or neurogenic.


Corpus cavernosum
Skin
Efferent vein
Tunica albuginea
Cavernosal spaces
Venous plexus
Cavernosal artery
A. Flaccid state
Engorged cavernous spaces
Veins are compressed as cavernosa enlarge
B. Erect state

- Over the past years, ED as a public health problem .
- High incidence and an increasing prevalence worldwide
- Approximately 52% men aged 40–70 years suffered from ED .

- Disorders linked to ED :diabetes mellitus, metabolic syndrome, cardiovascular diseases, hypertension, age, lower education , obesity, depression, spinal injuries , smoking, Parkinson's diseas , radical prostatectomy e , pelvic nerve injury , side effects due to drug medication and alterations in hormone levels such as testosterone

- The majority of these disorders are associated with endothelial dysfunction, which is linked to the severity of ED as the corpora cavernosa vascular homeostasis is mainly regulated by the vascular endothelium .

Evaluation of Men with ED
Basic evaluation

- **Medical History**
- **Cardiovascular history**
- **Endocrine history**
- **Sexual history/questionnaire**

Evaluation of Men with ED

- **Sexual history**

- **Questionnaire(IIEF) or direct inquiry**
- **Use terminology with which the patient is comfortable**
- **Begin with nonspecific questions**
- **Gradual or abrupt onset**
- **Presence or absence of morning and nocturnal erections**
- **Medication history**

Evaluation of Men with ED
Sexual History(cont)

- **Presence or absence of erection with masturbation**
- **Premature ejaculation**
- **Retarded ejaculation**
- **Painful intercourse**
- **Anorgasmia**
- **Decreased Libido**

Evaluation of Men with ED

Differentiating Psychogenic from Organic ED

Organic ED:

- Gradual deterioration
- Decrease in morning erections and nocturnal erections
- No erections with masturbation
- Presence of co-morbid conditions

Psychogenic ED

- Often sudden onset
- Younger patient (<40)
- Preservation of morning erections and nocturnal erections
- Achieve erection with masturbation
- May be partner-specific

Evaluation of Men with ED
Physical Examination

- **Blood pressure**
- **Examine penis (Peyronie's disease)**
- **Determine size and consistency of testes**
- **Digital rectal exam**
- **Focused vascular exam/peripheral pulses**
- **Focused neurologic exam**

Laboratory testing

- **must be tailored to the patient complaints and risk factors. All patients must undergo a**
- **fasting glucose**
- **lipid profile.**
- **Testosterone**
- **Men<50: Only if low libido**

- **Men>50: Routinely**

((prolactin – FSH- LH)

- **when low testosterone levels are detected.**
- **Thyroid function,, Liver function, Creatinine**

PSA in men >50 years

Specialized diagnostic tests

- Nocturnal penile tumescence and rigidity (NPTR)
- Intracavernous injection test
- Duplex ultrasound of penile arteries
- Arteriography and dynamic infusion cavernosometry or cavernosography (DICC)
- Psychiatric assessment

Treatment

- Patients with ED should see a mental health professional as adjunctive therapy

- Therapeutic options lifestyle changes or oral medications, to more invasive treatments such as vacuum constriction devices, intraurethral and intracorporeal injection, and surgically implanted penile prostheses.
- Most international clinical guidelines suggest the use of oral phosphodiesterase type 5 inhibitors (PDE5-Is) as firstline therapy for ED because of their excellent efficacy and safety profiles.
- 30–35% of ED patients are not responsive to PDE5-Is . PDE5-Is only provide temporary symptom relief and rarely address the underlying etiology of a patient's ED.

Treatment of ED

- **Lifestyle changes**
- **Oral agents**
- **Penile injection**
- **Urethral suppositories**
- **External vacuum devices**
- **Topical cream**
- **Surgical intervention**

Nonpharmacologic Treatment

Lifestyle changes:

- **Reduce fat and cholesterol in diet**
- **Eliminate alcohol consumption**
- **Eliminate tobacco use and substance abuse**
- **Weight loss if appropriate**
- **Regular exercise**

Treatment Modalities

1st	Oral	-Counselling
2nd	Injection Vacuum Intraurethral	- Counselling
3rd	Surgery	- Counselling

ERECTILE DYSFUNCTION

PDE5 Inhibitors

- Sildenafil (Viagra)
- Taldafil (Cialis)
- Vardenafil (Levitra)

Oral agents

PDE 5 Inhibitors

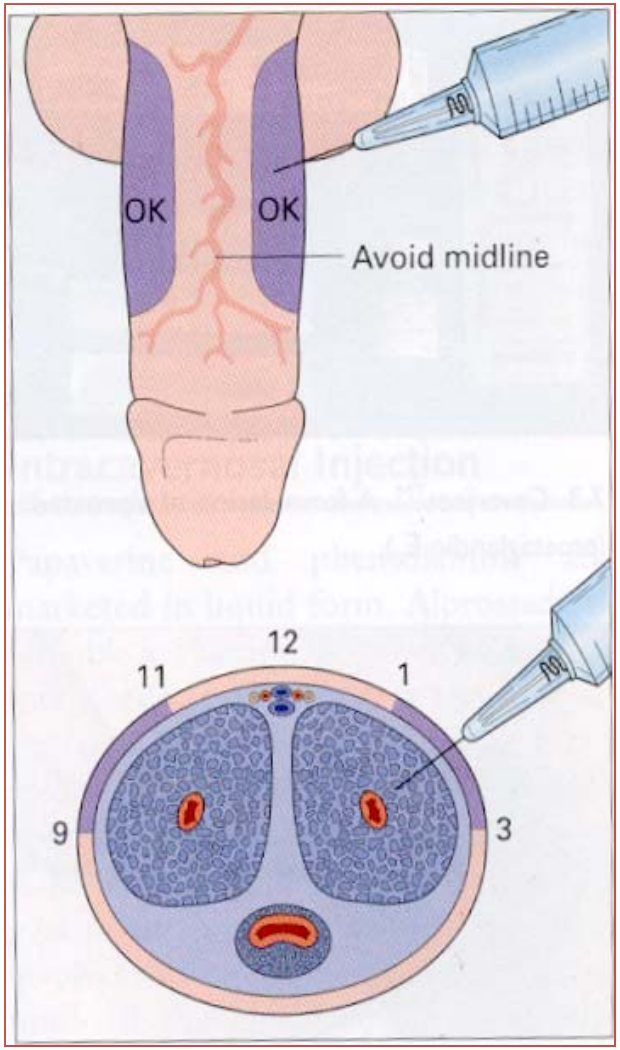
- **Enhance and potentiate corporal smooth muscle relaxation**
- **Active sexual stimulation necessary**
- **1 hour prior to planned intercourse**
- **Effective 70 - 90%**
- **Intact neurovascular bundle necessary**

Sildenafil

- **Brand name: Viagra**
- **25, 50, 100 mg**
- **Take 1 hour before sexual activity; effects last for up to 4 hours**
- **Absorption may be delayed by high-fat meal**
- **Side effects: headache, flushing, dyspepsia**
- **Contraindication: use of nitrates**

Tadalafil

- **Brand name: Cialis**
- **5, 10, 20 mg**
- **Improves erectile function for up to 36 hours**
- **Can be taken with food but limit alcohol consumption**
- **Side effects: headache, dyspepsia, back pain, myalgia**
- **Contraindications: use of nitrates, alpha blockers (except tamsulosin)**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OK
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12
11
1
9
3

Intracavernous Pharmacotherapy

- **Patients that are not responding to oral drugs may be offered intracavernous injections.**
- **Papaverine and alprostadil are the main drugs used for intracavernous treatment.**

Alprostadil Brand Names

- **Caverject: Direct injection of papaverine/alprostadil.**
- **MUSE: alprostadil is produced in intraurethral pellets; tiny tablets that can be inserted down into the opening of the penis with the aid of a minute insertion stick.**
- **Befar, Alprox, and Topiglan: topical cream of alprostadil, currently available only in Asia.**
- **"Triple Mix": prostaglandin E1 (PGE1), papaverine/phentolamineThis tri-mix has an extremely high rate of efficacy at 92%**

Alprostadil (MUSE, Caverject, Befar)

- Alprostadil is a vasoactive prostaglandin E1.
- It is more effective when used in combination with phentolamine and papaverine; this is considered a tri-mix combination therapy.
- alprostadil is normally administered by itself.. It also has an almost immediate onset of action
- 80% successful
- Side Effects:
- penile pain, prolonged erections,
- priapism, and fibrosis

VACUUM ERECTION DEVICES (VED

- Negative pressure on the penis draws blood into the penis ⟶ erection
- Constriction band at base of penis to maintain erection
- 2 - 10' to produce erection
- Band in place no more than 30' Effective in 95% of men
- need for personal instruction in use

INTRA-URETHRAL PELLETS
PROSTAGLANDIN E1 (MUSE)

- Easy administration
- Patient education required
- Onset of response ~20'
- Erection lasting 30 - 60'
- 50 - 60% successful
- SIDE EFFECTS
- Local pain, urethral burning Minor urethral bleeding

SURGICAL TREATMENT

- Last resort treatment option, no returning to other options
- Two types of prosthesis exist: malleable (semi-rigid) and inflatable (two- or three-piece).

Penile Prosthesis

Indications:

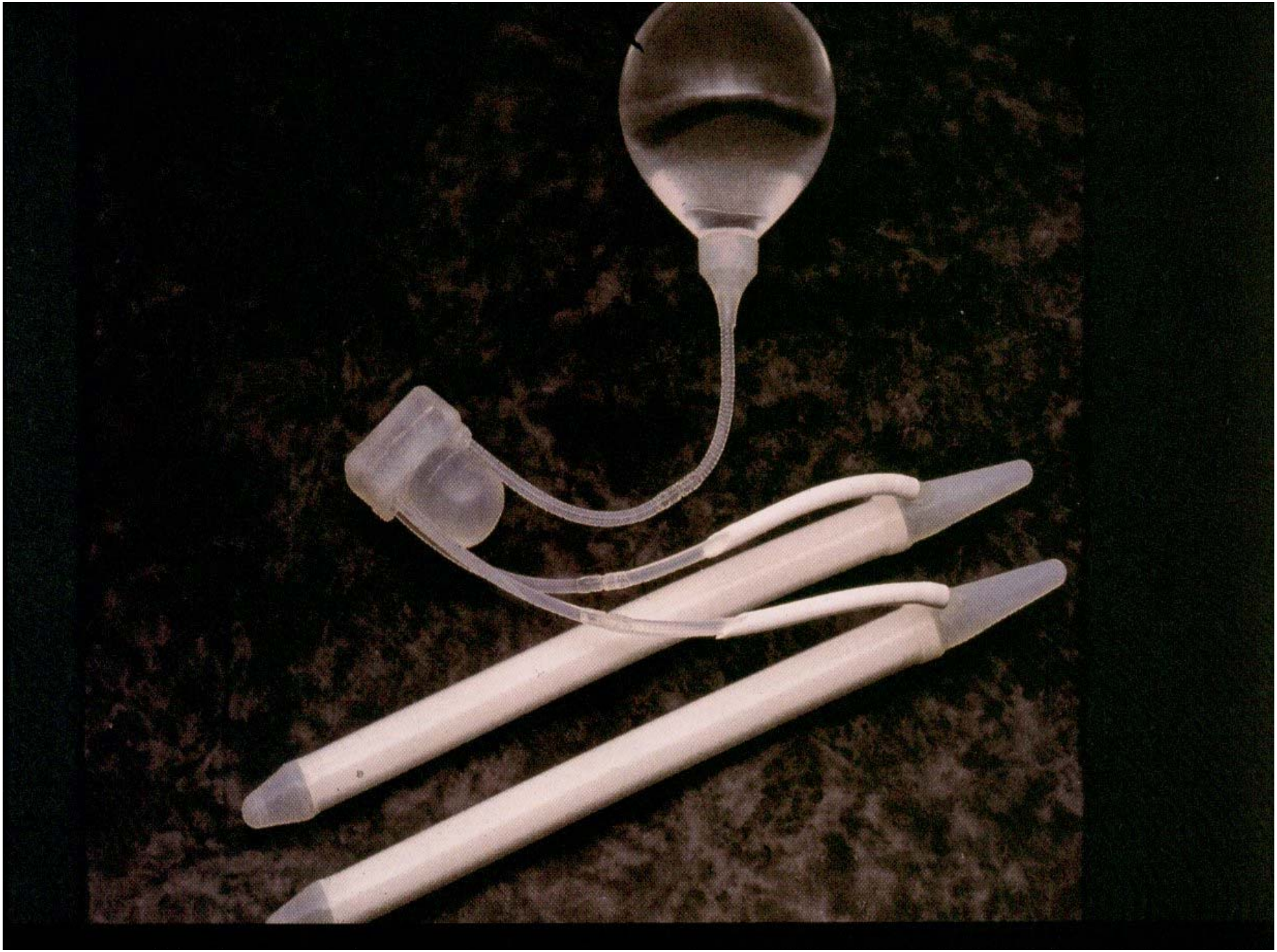
- **Patients who have failed other therapies**
- **Peyronie's disease**
- **Severe vasculogenic disease**

Malleable Prosthesis

- **Easy for patient and partner to use**
- **Few mechanical parts**
- **Same-day surgery usually possible**
- **Least expensive type of prosthesis**

Three-Piece Inflatable Prosthesis

- **Most closely approximates the feel of a natural erection**
- **Cylinders expand in girth**
- **Some cylinders have the potential to expand in length**
- **When inflated, it feels more firm and more full than other prosthetic erections**
- **When deflated, it feels softer and more flaccid with better conceal ability than with other prosthetic devices**



- Thus, unmet needs in the treatment for ED have prompted the development of novel minimally invasive therapeutic modalities, including stem-cell (SC) therapy.

Rat ED models

- Bochinski et al.first reported in 2004 the injection of ESC into rat ED models with cavernous nerve injury (CNI).

- In 2017, Hou et al. performed a meta-analysis of 20 studies that used a total of 248 rats .
- The results showed that ADSC therapy can regenerate damaged cavernous tissues.
  Subgroup analysis also suggested that ADSC modified growth factors such as nerve growth factor, vascular endothelial growth factor, hepatocyte growth factor, and neurotrophic factors such as brain-derived neurotrophic factor,which significantly improved erectile function compared with ADSC alone.

Because of these promising preclinical data, clinical translation of SC therapy for ED has emerged in recent years

Table 1 A summary of completed phase I and II clinical trials with published results of SCs therapy for ED.

Publication	Disease	Study type	Cells used	Outcomes
Bahk et al. [26]	Diabetic ED	Single blind	Allogeneic hUCB-SC 1.5×10^7 cells	No adverse events. Improved subjective outcomes
Levy et al. [24]	Peyronie's disease	Open label Nonrandomized Single center	PM-MSCs Not quantified	No adverse effect. Statistically significant increases in PSV. 7/10 plaques disappeared completely at 3 m
Lander et al. [25]	Peyronie's disease	Pilot study	SVF combined with penile shock-wave treatment Not quantified	Subjective improvement in curvature and plaque size. 7/11 patients reported improvement in erectile function.
Levy et al. [27]	Chronic organic ED	Open label, nonrandomized, single center	PM-MSC Not quantified	3/8 patients reported injection site irritation. Significant increases in PSV.
Yiou et al. [29]	ED post-RP	INSTIN clinical trial first stagenonrandomized, dose-escalation, phase I/II pilot	Autologous BM-MNCs 2×10^9 cells. 1×10^9 cells. 2×10^8 cells. 2×10^7 cells.	No serious side effects. Mild pain and hemoglobin decrease after aspiration. Significant improvement of IIEF-15 and EHS. Greater improvement with the higher doses
Yiou et al. [28]	ED post-RP	INSTIN clinical trial Second stage Phase I/II pilot	Autologous BM-MNCs 1×10^9 cells.	No adverse effect. Significant improvements in EF-15 and erectile function after 6 m.
Demour et al. [31]	Diabetic ED	Open label Phase I Single arm Single center	2 consecutive autologous BM-MSC, one at baseline, the second at day-30. 30×10^6 cells	No significant adverse effects. Significant improvement of IIEF-15 and EHS
Haahr et al. [30]	ED post-RP	Open label, nonrandomized Single arm single center phase 1	SVF and ADRC. 2.2×10^7/50 µL	No serious adverse events. 8/15 (53%) patients in the continent group reported improved erectile function. No improvements in the incontinent group.
Protogerou et al. [32]	Organic ED	Phase 1, Open label Single center, pilot study	Group A: $38.9 \pm 14.4 \times 10^6$ ADMSC in combination with 2.2 ± 0.3 mL of PL ($1708 \pm 76 \times 10^6$ PLTs) Group B: 2.3 ± 0.4 mL of PL ($1693 \pm 52 \times 10^6$ PLTs)	No severe adverse reactions Improved erectile function No statistically significant difference between group A and B

Table 2 A table of registered completed or ongoing trials without full published results.

Status	Study director/contact	Interventions	Locations
Completed in 2018 full results awaited	Chungsu Kim	Mesenchymal stem cell phase 1	Korea
Completed in 2018 full results awaited	Abdallah Awidi Sophia Al-Adwan	Wharton Jelly Mesenchymal stem cells, phase 1	Jordan
Completed in 2019 full results awaited	Abdallah Awidi Sophia Al-Adwan	Wharton Jelly Mesenchymal stem cells phase 1 and phase 2	Jordan
Completed in 2018 full results awaited	Jacob Rajfer	CaverStem	Los Angeles
Completed in 2017 full results awaited	Mark H Berman	Administration of autologous adipose-derived SVF	Rancho Mirage, CA
Completed in 2016 full results awaited	Andrey A Pulin, Mikhail E Chalyy	Intracavernosal administration of autologous ADRC phase 1 and phase 2	Moscow
Not yet recruiting	Rabih EL OSTA	Autologous bone marrow derived Mesenchymal Stem Cells phase 1	France
Recruiting estimated completion: 2022	Chungsu Kim	Follow-up	Korean
Recruiting estimated completion: 2020	Jianwu Dai	NeuroRegen scaffold/BMMCs transplantation NeuroRegen scaffold/HUC-MSCs transplantation phase 1 and phase 2	Nanjing, China
Recruiting estimated completion: 2020	Jianwu Dai	HUC-MSCs Injectable Collagen Scaffold + HUC-MSCs phase 1	Nanjing, China
Recruiting estimated completion: 2029	Dr Ayn O'Reilly David L Greene	Amniotic and umbilical cord tissue procedure phase 1	Multiple locations in the USA
Recruiting estimated completion: 2022	Jibing Chen	Very small embryonic-like stem cell (VSEL) phase 1 and phase 2	China, Guangdong
Unknown	Saleh Binsaleh	liposuction for retrieval of own stem cells from fat cells phase 2	Saudi Arabia
Unknown	Khaled A Gadalla	Adipose tissue stem cell injection	Egypt
Ongoing	Odense Universitets Hospital	Stromal vascular fraction phase 1	Denmark

Side Effects

1. Overall, there were no side effects reported.
2. Mild postoperative pain at the bone marrow aspiration site
3. No cases of priapism.
4. Microbial growth was noted in the samples taken from three patients but without any clinical side effects.
   A decrease in hemoglobulin was noted due to the aspiration of the cells but no blood transfusion was needed.
5. There were no increases in PSA values nor changes in the digital rectal examination in the patients post-treatment.
6. Haahr et al.reported only mild effects on the injection site (transient redness and swelling, scrotal and penile hematomas) or from the liposuction site; all of them recovered spontaneously.
   no side effects in two years of follow up regarding nervous, cardiovascular, respiratory and gastro-intestinal systems.

Conclusions

Preclinical research in animal models has generated excitement for the use of SC as a potentially curative treatment for ED.

The primary mechanism proposed is paracrine effects, while possible engraftment and cellular differentiation are potential auxiliary mechanisms.

Less than 100 patients have been reported to receive SC injections so far, future large-scale clinical trials with controls are necessary to assess the safety and efficacy of SC therapy for patients with ED.

Future Implementation and Perspectives

Questions need to be answered such as:

which is the ideal stem cell for the treatment of ED?

What is the optimal dose?

Should we use expanded cultured cells or SVF from the adipose tissue?

Should we combine expanded cells with PLP to get the best of the two treatments?

Most importantly, should we use a patient's own stem cells or instead should we use cells from a younger, healthier donor?

THE END