Sexual Dysfunction in Men
Causes, Diagnosis, & Treatment Options

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AMMG: November 1, 2018
Sexual dysfunction:
Physical or psychological problems that prevents sexual satisfaction
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Psychological causes

- Performance anxiety
- Sexual trauma or PTSD
- Relationship problems
- Depression
- Feelings of guilt
- Anxiety
- Low self-confidence or self-esteem
- Stress
Physical causes

- Low testosterone
- Prescription drugs
- Vascular disease
- Nerve damage
- Stroke or cognitive impairment
- Diabetes
- Surgery
- Smoking
- Heavy alcohol use
- Drugs
Desire or arousal problem: inhibition, low libido, hypo & hypersexual desire
Expectation

Sexual frequency (2010 AARP survey of 1,670 men & women ≥ 45 yo)$^1$

- Sex at least 1 x week
  - 41% of men in 50s
  - 24% of men in 60s
  - 15% of men ≥ 70s
- 34% of men masturbate at least once a week
- 48% of single currently dating (6% of respondents) have sex at least once a week vs 36% married people (54% of respondents)
- 60% singles satisfied with their sex lives vs 52% married
- 20-30% of men & women remain sexually active into their 80s$^2$
Genital self-image & self-confidence

Kinsey study 2,500 men

- Average flaccid penis 1-4”
- Average erect penis: 5-6.5” long, 4-5” circumference
  - There was a slight underestimation of penis size compared to actual measurement

Micropenis: <2.8” in length when stretched

- 0.6% of men, caused by low testosterone at late stage of fetal development
Male Genital Self-Image Scale (MGSIS)\textsuperscript{4}

Better genital self-image, better scores on International Index of Erectile Function (IIEF) (Herbenick)

Heterosexual men had better scores than those choosing “other” for sexual orientation

>90% of men comfortable with partner viewing their genitals ~25% comfortable with medical exam

20% of men dissatisfied with penis size
Sexual desire occurs in the brain

Limbic system (amygdala, hippocampus, dentate & cingulate gyrus)

- Common to all mammals & is one of the oldest areas of the brain
- Regulates emotion & attempts to avoid pain & seek pleasure

Activation of amygdala triggers erections, sexual feelings, pleasure, & sexual memories

Sexually-pleasing visual stimuli activate amygdala & hypothalamus more in men than women\(^5\)
Sexual desire occurs in the brain

Input from amygdala travels to ventral striatum (nucleus accumbens, putamen, medial caudate nucleus)

Nucleus accumbens large concentration of dopaminergic neurons
  • Pleasure & reward area

During orgasm, mesodiencephalic transition zone activated
  • Involved in variety of rewarding behaviors
  • “Ejaculation parallels heroin rush”
  • Also rCBF increases in cerebellum (plays a role in emotional processing)
Dopamine

Synthesized in brain & kidneys

Reward-mediated behavior & reinforcement

Anticipation triggers release

Main neurotransmitter that facilitates sexual motivation, intercourse, & genital reflexes

Can trigger erections by acting on oxytocinergic neurons in the paraventricular nucleus (PVN) of hypothalamus

Activation of dopamine receptors in lumbosacral parasympathetic nerves of spinal cord facilitate erections
Oxytocin

Peptide hormone & neuropeptide made by hypothalamus, released by posterior pituitary during kissing, hugging, sexual arousal, & possibly orgasm\textsuperscript{11-13}

Attachment, bonding, mb monogamy
- Activates nucleus accumbens & ventral tegmental area (VTA)
- Intranasal oxytocin increases attractiveness of partner compared to other females\textsuperscript{14}

Promotes erections
- Oxytocin injected into PVN & VTA of male rats induces erections & increases dopamine in nucleus accumbens & PVN\textsuperscript{15,16}
Oxytocin

Regulated by other hormones & neurotransmitters

- Inhibited by endogenous opioids, GABA, endocannabinoids
- Stimulated by dopamine

Life experiences affect the methylation of the oxytocin receptor gene & its expression\(^\text{17}\)

- Social isolation reduces expression of oxytocin receptor

Plays a role in muscle regeneration\(^\text{18}\)

- Genetic lack of oxytocin causes premature sarcopenia

Photo credit: Bettina Balnis
Hypoactive sexual desire disorder (HSDD)

**Orbitofrontal cortex**

First place where olfactory & taste information converge

Large network of connections projecting to hippocampus, ventral tegmental area, & amygdala

Involved in learning, prediction, & decision making for emotional & reward-related behaviors\(^{19}\)

Increased activity in medial orbitofrontal cortex in HSDD\(^{20}\)

Can also be dt limbic system damage\(^{21}\)
Hypoactive sexual desire disorder (HSDD)

Persistent or recurrent deficient or absent sexual/erotic thoughts or fantasies & low or absent desire for sexual activity

Causes distress or impairs man’s life or interpersonal relationships

Not attributable to another psychiatric disorder, substance use (drugs or medications), or medical conditions
HSDD prevalence & causes

15% of men (National Health & Social Life Survey), up to 40% older men\textsuperscript{22,23}

Causes (lifelong, situational, acquired): \textsuperscript{24}

- Gender identity or sexual orientation
- Paraphilia ("abnormal" sexual desires)
- Trauma
- Difficulty in new or long-term relationship
- Testosterone deficiency
- Neurotransmitter imbalance\textsuperscript{25}

Photo credit: Vlad Tcompalov
Hypersexual disorder

Recurrent, intense sexual fantasies, urges, & behavior ≥ 6 months w/ ≥ 4 of the following:

• Excessive time spent fantasizing about sex, planning for & engaging in sexual behavior

• Repetitively engaging in
  • Sexual fantasies, urges, & behavior in response to dysphoric mood states (e.g., anxiety, depression, boredom)
  • Sexual fantasies, urges, and behavior in response to stress
  • Sexual behavior while disregarding the risk for physical or emotional harm to self or others

• Unsuccessful efforts to control or reduce these sexual fantasies, urges, & behavior
Hypersexual disorder

“Sex addiction” dx controversial

Similar to other addictions—addicts crave euphoria from sex & use it to escape from unpleasant or painful emotions (a form of self-medicating)

Cycle of indulging, feeling guilt and remorse, desire to change, giving into craving

Causes & risk factors:

- Childhood or prior sexual abuse
- Co-occurring psychiatric disorder (impulse control, BPD, bipolar disorder, anxiety)
- Co-occurring substance abuse/addiction
- Brain injury
  - Limbic or temporal lobe injury
  - Bilat damage to hypothalamus
  - Injury to prefrontal cortex
  - Temporal lobe epilepsy

Photo credit: Kyaw Tun
Coolidge Effect

Coined by Frank Beach, psychologist & founder of behavioral endocrinology

President Coolidge and his wife were individually shown around a farm. When Mrs. Coolidge came to the chicken yard she noticed a rooster who mated repeatedly & asked how often it happened. When told “dozens of times each day” she said, “Tell that to the President when he comes by.”

Upon being told, the President asked, "Same hen every time?" The reply was, "Oh, no, Mr. President, a different hen every time." President: "Tell that to Mrs. Coolidge."

Definition: males exhibit renewed sexual interest if introduced to different receptive sexual partners. Possible evolutionary benefit so a male can fertilize multiple females.
Pornography

Internet porn$^{28}$
- Limitless novelty (Coolidge effect)
- Potential to escalate to more extreme material
- Video format, free, high-speed, on-demand

Novelty = dopamine surges

Dopamine increases Δ FosB which accumulates in nucleus accumbens (reward center)$^{29,30}$
- Promotes binging/craving cycle
- Leads to desensitization—opioids, dopamine, & dopamine receptors decline
- Decreased pleasure leads to greater stimulation for same buzz
- Hyper-reactivity to porn, willpower erosion, & frontal cortex changes (neuroplasticity)
Most common Rxs that inhibit libido

TCAs: amitriptyline, doxepin, imipramine, nortriptyline
SSRIs: fluoxetine, sertraline, paroxetine, citalopram, escitalopram
Diuretics: spironolactone, thiazides
α-adrenergic blockers: terazosin, prazosin
β-blockers: propranolol, metoprolol, carvedilol
Hormone blockers: Lupron, Zoladex

Photo credit: Jared Poledna
Ejaculation problems
Premature, Delayed, Retrograde
Premature

Ejaculation prior to or soon after vaginal penetration with inability to delay ejaculation & negative consequences (e.g., distress, avoidance of sexual intimacy)

Most common sexual complaint by men

• Internationally 20-30% of men\(^{31}\)
• Probably under-reported & undertreated\(^{32}\)

Occasional PE is normal. Ave time from beginning of intercourse to ejaculation is 5 min.

Causes: psychological, environmental, endocrine, neurobiological, possibly genetic (5-HT1 receptor polymorphism)\(^{33}\)
PE Treatment

CBT or sex therapy

Yoga (= fluoxetine)\textsuperscript{34}

SSRIs (off-label) esp. paroxetine

Dapoxetine 30 or 60 mg (phase III trials in US)\textsuperscript{35}

- 1\textsuperscript{st} drug specifically developed for PE
- Serotonin, dopamine, NE reuptake inhibitor
- Can be used “on demand” – peaks in 60 min
- Mean half-life 1.4 hrs (vs 21 h-4 d with other SSRIs)\textsuperscript{36}
- Doesn’t accumulate with multiple doses\textsuperscript{37}
- Don’t combine with MAO inhibitors, SNRIs, other SSRIs
- Okay to use with PDE5i\textsuperscript{38}

If ED plus premature ejaculation, treat ED first (PE may not be a problem after ED treated)\textsuperscript{39}
Delay in ejaculation or infrequency or absence of ejaculation ≥75% of occasions for ≥ 6 mos

Least studied & understood male sexual dysfct\textsuperscript{40}

Can be lifelong (primary) or acquired (secondary)

Prevalence 1-4%

Increases with age—3% of men in their 40s, 43% of men in their 70s\textsuperscript{41}

Causes:

• Psychological
• Neurological damage (stroke, MS, spinal cord injury)
• DM
• Endocrine (hypogonadism, hyperprolactinemia)
• Chronic prostatitis/chronic pelvic pain syndrome
• PC, BPH/LUTS surgery
• Medications (SSRIs, tamsulosin, finasteride, spironolactone)
• Heavy ETOH & marijuana use \textsuperscript{42}
Delayed ejaculation treatment

Masturbation retraining

CBT

Penile vibratory stimulation (vibrators)

Testosterone therapy (low T assoc w/DE, high T assoc w/PE\textsuperscript{43}
  - 60 mg topical T to axillar for 4 mos ineffective\textsuperscript{44}

Medications (all off-label)\textsuperscript{45}
  - Amantadine, cabergoline, apomorphine (dopamine agonists)
  - Buproprion
  - Cyproheptadine (serotonin & histamine antagonist)

Concurrent ED, treat with PDE5i
Retrograde

Reduced ejaculation or dry orgasms

Causes:

• Congenital
• Prostate surgery (TURP)
• Bladder neck damage
• Spinal cord injuries

Medications

• Alpha-adrenergic blockers
• Psychotropics
Erectile dysfunction
Erectile physiology

Sexual stimulation → parasympathetic nerves release Ach → endothelial cells release NO → cGMP

Smooth muscle relaxation in arteries/arterioles of corpus cavernosa & spongiosum → rapid filling & expansion of sinusoidal system

Blood trapped in corpus caverona by occlusion of venous plexuses & tunica albuginea

Full erection intercavernous pressure 100 mmHg. Ischiocavernosus muscles compress blood-filled cavernosa. Perineal muscles contract causing final rigidity.

Ejaculation—vascular inflow & outflow temporarily cease & penile intracavernous pressure reaches several hundred mmHg

Erectile neurotransmitter release stops, PDE enzymes break down cGMP, SNS discharge during ejaculation → detumescence.
Nerves

Autonomic (sympathetic & parasympathetic) and somatic (sensory & motor)

- Sympathetic (T11-L2): anti-erectile; control ejaculation & detumescence
- Parasympathetic (S2-S4): pro-erectile

Sympathetic & parasympathetic nerves merge to form cavernous nerves, which enter the corpora cavernosa, corpus spongiosum, and glans penis—regulate blood flow during erection

Pudendal nerve:

- Somatic sensory to entire pelvis
- Motor: all sphincters, pelvic floor, rigidity muscles
Vascular System

Internal pudendal arteries provide blood flow to the penis

Bulbourethral artery passes through the deep penile (Buck) fascia—supplies the bulb of the penis & penile (spongy) urethra

Dorsal artery travels between the dorsal nerve & deep dorsal vein & gives off circumflex branches that accompany the circumflex veins—terminal branches are in the glans

Deep penile (cavernosal) artery enters the corpus cavernosum at the crus and runs the length of the penile shaft—supply helcine arteries
# ED causes & contributing factors

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Depression & Anxiety

Mild-to-moderate depression plus ED—when ED improves with treatment, depression may improve\textsuperscript{47}

Performance anxiety—first described by Masters & Johnson in 1970\textsuperscript{48}

PTSD & hyperactive amygdala:

- ED in 85% of veterans w/PTSD vs 22% of veterans w/o PTSD\textsuperscript{49}

Psychogenic ED Dx: erectile function normal with masturbation, with a different partner, or with different stimuli.

- Nocturnal or morning erections often normal.
- Often abrupt onset or associated w/stress (e.g., job loss, death of relative, financial problems)
Porn-induced ED

2002 meta-analysis of ED studies reported consistent rates of 2% in men under 40.\textsuperscript{50}

This was before Internet “porn tube sites” which appeared in 2006.

ED much more common in younger men now

- 2012 Swiss study: 30% of men 18-24 yo\textsuperscript{51}
- 2013 Italian study: 25% of men <40 yo\textsuperscript{52}
- 2014 Canadian study: 25% of men 16-21 yo\textsuperscript{53}

See “The Great Porn Experiment” – Ted Talk, Gary Wilson
Neurogenic

10% to 19% of all causes of ED\textsuperscript{54}

- MS, Parkinson’s
- Diabetes (also vascular)
- Stroke
- Surgery (radical prostatectomy: 18-24 mos dt cavernous nerve neuropraxia)
- Spinal cord injury
- Long-distance cycling?
  - Compression of pudendal nerve & blood vessels b/n saddle & pubic symphysis decreases blood flow & oxygen to penis\textsuperscript{55,56}
  - ED mb temporary
  - Swimmers & runners same ED as cyclists\textsuperscript{57}
  - Cyclists higher urethral strictures
Spinal Cord Injuries

WWII soldiers with severe or complete cervical or thoracic spinal cord injuries—still able to achieve complete erections

- Physical penile stimulation sends sensory signals via the pudendal nerve to sacral nerves.
- Incoming signals activate connector nerve cells (interneurons) to stimulate nearby parasympathetic neurons.
- These neurons then transmit signals from the sacral spine to the penile blood vessels.
- As long as this reflex arc remains intact, an erection is possible.

Photo credit: Samuel Zeller
Hormonal

Hypogonadism

• Minimal level testosterone necessary to maintain erectile function unknown (probably varies)\textsuperscript{59}
• Testosterone decreases with age & ED prevalence increases with age (50% age 50, 60% age 60, 70% age 70)\textsuperscript{60}

Hyperestrogenism—interdependent risk factor for ED?
Increase in serum estradiol or increased estradiol-to-testosterone ratio?\textsuperscript{61}

Hypo or hyperprolactinemia\textsuperscript{62,63}

Hypo & hyperthyroidism—ED common\textsuperscript{64}

• More in hyperthyroidism\textsuperscript{65}

Hyperinsulinemia, IFG, T2DM—ED may be first clinical sign of metabolic disease & CVD\textsuperscript{66}
Medication side effects

Alpha-adrenergic blockers: tamsulosin (Flomax)
Beta-blockers: carvedilol, atenolol, metoprolol
H2 receptor blockers: cimetidine (Tagamet), ranitidine (Zantac), Pepcid
Diuretics: HCTZ, spironolactone, triamterine
CNS depressants: alprazolam, diazepam, codeine
CNS stimulants: cocaine, amphetamines (Ritalin, Adderall)
Diuretics, such as furosemide (Lasix), spironolactone
SSRIs
Synthetic hormones: Lupron (Eligard)
Vascular dysfunction

- Erectile dysfunction—harbinger of systemic disease?
- ED & CVD share same risk factors
- ED may be due to generalized or focal arterial disease (e.g., pudendal artery)
- Veno-occlusive dysfunction may contribute
Peyronie’s

Prevalence 0.5-9% of men (Stuntz, Mulhall)

Risk factors: age, DM, smoking, genetics (20% of PD have Dupuytren’s)

Tunica albuginea is mainly collagen with 5% elastin—allows penis to expand & lengthen during erection

Trauma or micro trauma to tunica albuginea combined with abnormal wound healing causes fibrotic nodules/plaques to form

May cause ED dt scar preventing full expansion of corpus cavernosa and compression of veins, allowing venous leakage

- 32-80% also have ED

Penile curvature may make penetration difficult
Treatment—FDA approved

Nothing—natural course over 12 mos (Mulhall)
  • Nearly all complete pain resolution
  • Curvature:
    • 12% improve
    • 40% remain stable
    • 48% worsen

Collegenase clostridium histolyticum (Xiaflex)—only FDA-approved, non-surgical treatment
  • MOA: selectively binds collagen, unravels fibril structure of plaques, breaks peptide bonds
  • After 52 weeks, 33-35% change in erect penile curvature compared with 18-22% in placebo

Plaque excision, esp when curvature >60° or w/severe narrowing (“hinging”) or plaque is large or calcified
Possibly effective treatments

- Coenzyme Q10 (300 mg) (Safarinejad MR)
- Verapamil (Russell, Rehman)
- L-carnitine (2 g/d) plus intralesional verapamil (10 mg/week)
- Interferon injections (Hellstrom)
- Vacuum pump (Raheem)
- ECSW (possibly better with 5 mg daily tadalafil) Palmieri
- Stem-cells (rat model)
Ineffective treatments

- Vitamin E (possibly effective when combined with colchicine (Castro)
- Tamoxifen
- Carnitine
- Serrapeptase and nattokinase
Diagnosis

Labs
Imaging
Questionnaires
Desire, Orgasm, ED

Take a good history

- Psychosocial issues (expectations, stressors, relationship)
- Health conditions (neurological issues, metabolic syndrome, DM, HTN, CVD, liver or kidney disease)
- Smoking
- ETOH & other drug use
- Medications

Questionnaires:

- Health Inventory (SHIM): 5 questions
- The International Index of Erectile Function (IIEF-5): 15 questions, validated in 32 languages
Workup

✓ Lab work: CBC, CMP, lipid panel, insulin, HbA1c, total & free testosterone, LH, estradiol, TSH, free T4, free T3, possibly prolactin, DHEA-S, cortisol

✓ PE: BP, evidence of CVD (peripheral vascular disease, carotid bruit, JVD), waist circumference, liver enlargement, penile & testicular exam, pelvic floor muscle strength

✓ Imaging (reserved for potentially surgical intervention)
  • Duplex doppler ultrasound
  • Penile arteriography (injecting dye to see blood flow in penile arteries)
  • Magnetic resonance imaging (MRI)
Porn Induced ED?

Porn vs anxiety-related ED:

1. On one occasion masturbate to your favorite porn (or simply recall it).

2. On another masturbate with no porn/porn fantasy. That is, no recalling of porn.

• Compare quality of erection & the time it took to orgasm. A healthy young man should have no trouble attaining a full erection & reaching orgasm without porn or porn fantasy.

• If you have a strong erection in #1, but erectile dysfunction in #2, then you have porn-induced ED.

• If #2 is strong and solid, but you have trouble with a real partner, then you have anxiety-induced ED.

• If you have problems during #1 & 2, you may have severe porn-induced ED or an organic problem.

www.yourbrainonporn.com/how-do-i-know-if-my-ed-porn-related-test
Other symptoms associated with porn dependency or addiction

1. Delayed ejaculation
2. Greater sexual excitement w/porn than w/partner
3. Decreased penile sensitivity
4. Ejaculating when only partly erect or getting totally erect only with ejaculation
5. Needing to fantasize to maintain erection or interest with sexual partner
6. Losing interest in earlier genres of porn
7. Declining sexual arousal w/sexual partner(s)
8. Losing erection while attempting penetration
9. Inability to maintain erection or ejaculate with oral sex
Treatment
Mental & physical health

CBT
EMDR
Sex addicts anonymous (SA)
Diet
Exercise
Weight loss

Photo credit: David Clode
1. Eliminate porn, porn substitutes, and recalling the porn, i.e., eliminate all artificial sexual stimulation.

2. Rewire sexual arousal to real people.

How long will it take?

- 2 mos for older men >50 (older guys didn’t start on Internet porn when young and brain most vulnerable to addiction)
- 2-5 mos younger men

May experience withdrawal symptoms:

- Mood swings
- Anxiety including panic attacks
- Agitation
- “Flatline”—little or no libido

Prepare to confront deniers. Many men don’t believe internet porn has caused their ED until they stop using it and recover erectile function.
Physical & manual therapy

Physical therapy
Penis pump
Improve pelvic floor muscle tone/strength

Maintenance of erection (not done by NO alone)

Get weaker with age

Pelvic floor therapy improves ED (up to 75% of men may improve or resolve ED sx in 6 mos) (Dorey)

Retract penis & lift scrotum (bulbocavernosus & ischiocavernosus muscle function)

1. Maximum contraction: 3 x lying, 3 x sitting, 3 x standing BID

2. Tighten pelvic floor muscles strongly after voiding urine

Also cured dribbling in 66% of men
Kegel exercise

• Stop urine midstream several times during urination. These are the muscles you’ll use.
• Perform Kegel holding for 5 seconds, 10-20 times, 3 x day
• Breathe and relax (no clenching buttocks or other muscles or holding breath)
Vacuum constriction device (penis pump)

Geddins Osbon developed a “youth equivalent device” in 1960s. He personally used the device for more than 20 years without failure. First VCD device (Erecaid) FDA approved in 1982.

3 parts: vacuum cylinder, battery or manually operated pump, & constriction rings. Directions:
1. Place correct constriction ring over the open end of vacuum cylinder.
2. Apply water-soluble lubricant to base of penis & place vacuum cylinder over penis.
3. Generate negative pressure (100–225 mmHg) by hand or battery-operated pump to create an erection.
4. Move constriction ring onto the base of the penis to maintain erection. Do not leave on > 30 min dt risk of ischemia.
Supplements

Lorem ipsum dolor sit amet, consectetur adipiscing elit.

CBT
EMDR
12 step program
Yohimbe (Pausinystalia Yohimbe)

Evergreen native to central Africa

- Bark contains 3 alkaloids: yohimbine (most active), rauwolscine, & corynanthine
- 2 meta-analyses show effectiveness over placebo.
- Onset 10-15 min; half life 35 min
- Study of 49 most popular brands—quantity of yohimbine per recommended serving was 0 to 12.1 mg.
  - 19 brands no rauwolscine and corynanthine, suggesting that the yohimbine was either from highly processed plant extract or synthetic in origin.
  - 11 brands listed a specific quantity of yohimbine on the label; most were inaccurate.
  - S/E: GI, tachycardia, HTN, anxiety


L-arginine

- 40 men with ED, age 25-45
  - 1.7 g L-arginine x 1 mo—5% experienced normal erection
  - L-arginine plus 40 mg pycnogenol (pine bark extract) bid x 1 mo—80% normal erection
  - Above and increased pycnogenol tid—92.5% normal erection

- 50 men with ED, RCT placebo-controlled trial
  - 5,000 mg/d L-arginine po x 6 weeks
  - Plasma and urine nitrite and nitrate (stable metabolites of nitric oxide) measured at 3 & 6 weeks
  - 31% treatment arm and 11% placebo had improvement in sexual function. Treatment arm that improved had low urinary NOx that doubled at end of study
  - Hemodynamics of the corpus cavernosum were not affected by oral L-arginine at the dosage used.


Boosting Dopamine

• >100 neurotransmitters & neuropeptides in brain

• Neurotransmitters altered via:
  • Synthesis & packaging in presynaptic neuron
    • Amino acid precursors (L-phenylalanine→L-tyrosine→L-dopa→dopamine→NE→epinephrine)
    • Cofactors for production (tetrahydrobiopterine or BH₄, iron, B₆)
  • Release and binding to receptors on postsynaptic cell
  • Removal or degradation
  • Relationship
Boosting Dopamine

• Exercise (Sutoo, Robinson)
  • Exercise requiring learning new skill better than sustained exercise for increasing synaptic connections (studies in rats but mb good for PD) (Black, Garcia, Kleim)

• Meditation
  • Increased theta activity correlated with increased dopamine release (Kjaer)
Medications & hormones

SSRIs for premature ejaculation (dapoxetine under FDA review)
Testosterone
Oxytocin
PDE5i
Apomorphine
Intercavernosal injections
Phosphodiesterase 5 Inhibitors (PDE5i)

- Sildenafil (Viagra®) – Pfizer, 1998 (patent expires 04/2020 but Teva & others marketed generic in 12/2017)
- Vardenafil (Levitra®) – Bayer, GlaxoSmithKline, 2003
- Tadalafil (Cialis®) – Eli Lilly, 2003
- Avanofil (Stendra®) – Vivus, 2012
- Lodenafil (Hellavu—not FDA-approved)
- Udenafil (not FDA-approved)
- Miradenafil (Mvix—not FDA approved)
Mechanism of Action

1. Sexual arousal > NO release in corpus cavernosum & spongiosum
2. cGMP produced from GTP accumulates
3. Causes smooth muscle relaxation leading to an erection
4. PDE5i prevent cGMP breakdown, increasing NO activity

PDE5i have different selectivities for PDE isozymes (11 identified).

- PDE6 enzyme in the retina transfers light into nerve impulses. Inhibition of this enzyme causes color perception disturbances.
- Vardenafil 3x, sildenafil 7x, tadalafil 700x more selective for PDE5 than for PDE6.
PDE5i Comparison

No head-to-head trials. Differences in onset, duration of action, & side effects.

Sildenafil onset 30-60 min; half-life 4 hrs; duration 12 hrs (don’t use within 4 hrs tamsulosin)

Tadalafil onset 60-120 min; half-life 17.5 hrs; duration 36 hrs

Vardenafil onset 30-60 min; half-life 4 hours; duration 10 hrs

Avanafil onset 15-30 min; half-life 3 hrs; duration 6 hrs

Hepatic metabolism via CYP3 A4
Side effects

Headache (10%-20%)
Flushing (5%-15%)
Dyspepsia (4%-12%)
Nasal congestion (1%-10%)
Dizziness (2%-5%)
Priapism (rare)

Vision abnormalities (6%)—“chromatopsia” dt PDE6 retinal phototransduction enzyme, more common with sildenafil & vardenafi)

Caused by cross-reactivity with other PDE isoenzymes esp. vascular, visceral, & pulmonary smooth muscle

High concentration of PDE5 in smooth muscle of corpora cavernosa

➢ Contraindicated with nitrates (remember Jack Nicholson in Something’s Gotta Give?)
Apomorphine

Used since 1869 for Parkinson’s (Apokyn®30 mg/3 ml—0.2-0.6 mL SC TID for hypomobility in Parkinson’s)

Derived from morphine—doesn’t contain morphine or bind to opioid receptors

High affinity for dopamine D4 receptor; moderate affinity for D2, D3, D5, & adrenergic α1D, α2B, α2C receptors.
  • RE libido & erections, probably via D2 in hypothalamus & limbic system (chen)

Marketed (Uprima®, Ixense®) in Austria, Germany, France, Italy; withdrawn from EU in 2004

Dosage: compounded 2-3 mg SL
  • As effective as 4-6 mg without SE (nausea, rarely vasovagal syncope). Can combine w/sildenafil or tadalafil in troche.

Erections 10-25 minutes after use firm enough for penetration in ~50% vs ~ 30 baseline (Altwein, Heaton)

SE: nausea, headaches, dizziness. Caution with antiemetics such as Zofran dt hypotension & possible LOC
Animal and human studies suggest that testosterone may facilitate erection by acting as vasodilator of the penile arterioles and cavernous sinusoids.

Following castration, most men have partial or complete loss of erection.

Lack of association between serum testosterone and ED.

Testosterone supplementation in hypogonadal men appears to be effective (may not help much with normal T level). Also, PDE5 inhibitors work better with adequate testosterone.
Intercavernosal injections

Introduced in 1983
Modulates endothelial function—87-93% effective (Linet)
Can be used as single agent of prostaglandin E-1 or mixture of phentolamine, papaverine, E1, with or without atropine
E1-Alprostadil Rx: Caverject Impulse®, Edex®—0.25 mcg with additional 0.25 mcg if ineffective. Wait 24 hours and increase by 5-10 mcg to 40 mcg.
May be painful, ineffective, & expensive
Can use Bimix, Trimix, Quadmix

Painful & expensive Trimix (per ml):
- Papaverine hydrochloride—30 mg
- Phentolamine—1 mg
- Alprostadil (a prostaglandin E1)—10 mcg (Bimix leaves this out)
  If ineffective, can add atropine 0.15mg/ml

Dose:
- No history ED age <55: 0.1-0.2 ml
- History of ED or age ≥ 55: 0.3 ml
- Increase by 0.1-0.3 ml if needed

Risk of priapism and Peyronie’s—ER if >3 hour erection
1 ml syringe, 27 or 30-gauge 1/2 or 5/8-inch needle.
Inject lateral shaft (10 o'clock and 2 o'clock) from base of penis to two-thirds toward glans. Avoid corpus spongiosum, urethra, glans. Rotate site.
See excellent Medscape article: Intracavernosal Injection Algorithm by Jeffrey A. Albaugh: http://www.medscape.com/viewarticle/551563_1
The best activities for your health are pumping and humping

- Arnold Schwarzenegger
Low-intensity extracorporeal shockwave therapy

What is it?
Research
Who is a good candidate?
Low-intensity extracorporeal shockwave (LI-ESW)

High energy sound waves, not electrical shocks

When moving object (or acoustic wave) reaches the speed of sound, air cannot easily move out of the way and a shock wave is formed & energy dissipates

When object moves faster than sound, resulting sound travels behind the object (sonic boom)

Shock wave travels unchanged through fluid & soft tissue until it encounters significant change in tissue structure

Pressure from shockwaves transfers to tissue causing micro cavitation

LI-ESW variables: energy flux density, total number of pulses, frequency (number of pulses per second)
LI-ESW

- Originated in 1990s using ultrasound to induce angiogenesis in rat wounds by increasing expression of vascular endothelial growth factor (VEGF)
- MOA for improving ED by promoting regeneration of nNOS-positive nerves, endothelium, and smooth muscle in the penis by recruitment of endogenous mesenchymal stem cells.
- Not currently FDA-approved for ED (off-label use)


Research

- 2010: 20 men who previously responded to PDE5-I
  - 2 sessions per week for 3 weeks
  - LI-ESW applied to the penile shaft and crura at five different nonspecific sites
  - Results: improvement in erectile function, duration of erections, & penile rigidity at 1 month; sustained at 6 months

- 2012 double-blind RCT: 67 men
  - Received 12 sessions of LI-ESW or sham therapy
  - Erectile function and penile hemodynamics assessed before 1st treatment and after final treatment using questionnaires and a veno-occlusive strain gauge plethysmography
  - Results: approximately 50% treated men able to achieve erections sufficient for penetration. Penile blood flow improved in treated men.
  - No adverse events or effects from treatment


Research

- 2012: open-label, single arm 29 men with severe ED patients who were poor responders to PDE5i.
  - 2 treatment sessions per week for 3 weeks, which were repeated after a 3-week no-treatment interval.
  - Follow-up at 1 month (FU1), and only then an active PDE5i medication was provided for an additional month until final follow-up visit (FU2).
  - Results: improvement in penile hemodynamics
  - No adverse effects.

- 2015: placebo-controlled RCT 112 men with ED
  - N=51 in active group; N=54 placebo group
  - 5 treatments over 5 weeks
  - Placebo group got active treatment after 10 weeks
  - 57% active group able to obtain erection firm enough for penetration without medication. After 24 weeks, 19% of active group able to have intercourse without meds
  - 9% of men in placebo group able to obtain erection without medication. Similar improvement when placebo group was treated.


Research

• 2015: placebo-controlled RCT 135 men w/ED
  ▪ All underwent a 1 month PDE5i washout period.
  ▪ N=95 active group; N=40 placebo group
  ▪ 12 sessions; followed for 1 year
  ▪ 60 men completed study; 78% men at 1 mo & 71% at 1 year who weren’t able to achieve spontaneous erections firm enough for penetration were able to do so compared to none in the placebo group
  ▪ No adverse effects

• 2009: placebo-controlled RCT 100 men with Peyronie’s >12 mo with no previous treatment
  ▪ N=50 active group; N=50 placebo group
  ▪ 4 weekly treatments
  ▪ Plaque size, penile curvature, and quality of life
  ▪ After 12 wks., pain, erectile function, & QoL improved in treatment group; stable at 24 weeks
  ▪ Plaque size and curvature degree unchanged in active group but slightly increased in placebo group
  ▪ After 24 wks., plaque size and curvature degree were worse in the placebo group


PRP & stem cell

Photo credit: Yang Miao
Platelet Rich Plasma (PRP) & Stem Cells

- Penile vasculature is the most endothelial-rich anatomical region of the body
- Blood flow in the flaccid penis is slower compared to systemic circulation, allowing for superior retention

Platelets from anticoagulated blood spun in centrifuge—concentrated 5-10 x

Contain more than 30 bioactive proteins/growth factors many of which improve tissue healing & nerve regeneration

Also contains proteins that act as cell adhesion molecules: fibrin, fibronectin and vitronectin

Concentrated platelets may be activated by calcium chloride or combined with remaining blood before injected


Rat Studies

- Male Sprague-Dawley rats
  - Group I: sham operation
  - Groups 2 & 3: bilat cavernous nerve injury receiving PRP or normal saline injection in corpus cavernosum
  - Erectile function assessed 4 weeks later by cavernous nerve electrosimulation & CNs as well as penile tissue were collected for histology
  - PRP increased number of myelinated axons and facilitated recovery of EF

- Meta-analysis 10 studies, 302 diabetic rats
  - Beneficial effect of stem cell therapy in improving erectile function
  - Smooth muscle, smooth muscle to collagen ratio, and endothelium content were greater than control group.
  - Increase in endothelial nitric oxide synthase (eNOS) and neuronal nitric oxide synthase (nNOS) and vascular endothelial growth factor (VEGF)


Stem Cell Rat Studies

- 16 rat studies
- Stem cells (bone marrow, adipose tissue, skeletal muscles)
- Intercavernous (IC) injection
- Measured IC pressure during electrostimulation of cavernous s nerve.
- Histological assessment focused on endothelial, smooth muscle, and CN contents in the penis
- Outcome good in all trials
- Recent studies have shown that intracavernously injected SCs rapidly escaped the penis and homed into bone marrow.
- This could perhaps explain why intracavernously injected SCs had systemic antidiabetic effects and prolonged anti-ED effects.

Human PRP Research

• N=9 with moderate ED (IIEF score (10-21) PRP in addition to medication & vacuum therapy

• Average Pre-PRP IIEF score 15.6 (range 12-20); 4-week post PRP IIEF score 19.9 (range 11-27)

• No adverse effects

• Russian clinical trial using PRP in men with ED with comparative effectiveness analysis of different ways of APRP administration and in combination with PDE5 inhibitors


Identify cause(s)  Diagnosis & monitoring  Treatment options
THANK YOU
References


References


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