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
Desire or arousal

Psychological cause
Low testosterone
Insufficient dopamine
Decreased oxytocin
Medication side effects
Insomnia, OSA

Orgasm disorder

Premature ejaculation—occurs before or too soon for preference
Inhibited or delayed ejaculation
Retrograde ejaculation—ejaculate forced back into bladder

Erectile dysfunction

Psychological cause
Pornography overuse/abuse
Vascular dysfunction
Medication side effects
Neurological problem
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)$^4$

- Better genital self-image, better scores on International Index of Erectile Function (IIEF)
- 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\(^6\)
  • 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\(^7,8\)

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\(^9\)
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
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\(^\text{19}\)

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

Can also be dt limbic system damage\(^\text{21}\)
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 \(\Delta FosB\) 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
Ejaculation problems
Premature, Delayed, Retrograde
Premature

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

Most common sexual complaint by men

• Internationally 20-30% of men\textsuperscript{31}
• Probably under-reported & undertreated\textsuperscript{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)\textsuperscript{33}
PE Treatment

CBT or sex therapy
Yoga (= fluoxetine)\(^34\)
SSRIs (off-label) esp. paroxetine
Dapoxetine 30 or 60 mg (phase III trials in US)\(^35\)
  • 1\(^{st}\) 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)\(^36\)
  • Doesn’t accumulate with multiple doses\(^37\)
  • Don’t combine with MAO inhibitors, SNRIs, other SSRIs
  • Okay to use with PDE5i\(^38\)

If ED plus premature ejaculation, treat ED first (PE may not be a problem after ED treated)\(^39\)
Delayed ejaculation

Delay in, infrequency of, 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)
  • Bupropion
  • 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 helecine arteries
| Psychological                      | Depression & low libido   |
|                                  | Performance anxiety       |
|                                  | PTSD                       |
| Pornography                      | Limitless novelty (Coolidge effect) |
|                                  | Cycle of binging and craving |
|                                  | Down-regulation of dopamine & dopamine receptors |
| Neurological                     | Neurological disease (Parkinson's, AD) |
|                                  | Stroke                     |
|                                  | Damage to nerves (biking, prostate surgery) |
| Hormonal                         | Hypogonadism               |
|                                  | Thyroid dysfunction        |
|                                  | T2DM, hyperinsulinemia/IR  |
| Drugs                             | Antihypertensives          |
|                                  | SSRIs                      |
|                                  | ETOH & tobacco             |
| Vascular                          | HTN                        |
|                                  | Diabetes                   |
|                                  | Atherosclerosis            |
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}
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

Photo credit: Jason Leung
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.
Hormonal

Hypogonadism

- Minimal level testosterone necessary to maintain erectile function unknown (probably varies)\(^5^9\)
- Testosterone decreases with age & ED prevalence increases with age (50% age 50, 60% age 60, 70% age 70)\(^6^0\)

Hyperestrogenism—interdependent risk factor for ED? Increase in serum estradiol or increased estradiol-to-testosterone ratio?\(^6^1\)

Hypo or hyperprolactinemia\(^6^2,6^3\)

Hypo & hyperthyroidism—ED common\(^6^4\)

- More in hyperthyroidism\(^6^5\)

Hyperinsulinemia, IFG, T2DM—ED may be first clinical sign of metabolic disease & CVD\(^6^6\)
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\textsuperscript{67}

ED increases risk of CVD, stroke, all-cause mortality\textsuperscript{68}

ED & CVD same risk factors:
- Obesity
- HTN
- Smoking
- Physical inactivity
- Dyslipidemia
- Prediabetes, diabetes
- Standard American Diet (SAD)

ED as big a risk factor for future events as smoking & FH MI\textsuperscript{69}

Underlying mechanism for ED & CAD is endothelial dysfunction (ED = ED)\textsuperscript{70,71}

ED may be due to generalized or focal arterial disease\textsuperscript{72}

Venom-occlusive dysfunction may contribute
**Peyronie’s**

Prevalence 0.5-9% of men\(^{73-75}\)

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\(^{76}\)

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

Nothing—natural course over 12 mos\textsuperscript{77}
- 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\textsuperscript{78}

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

Coenzyme Q10 (300 mg)\textsuperscript{79}

Intralesional verapamil injection\textsuperscript{80-85}
  \begin{itemize}
  \item Younger age and larger baseline curvature may respond better\textsuperscript{84}
  \item Possibly better diluted (10 mg verapamil/20 mL)
  \end{itemize}

L-carnitine (2 g/d) plus intralesional verapamil (10 mg x 10 wks)\textsuperscript{86}

Interferon injections\textsuperscript{87}

Vacuum pump\textsuperscript{88}

Extracorporeal shock wave therapy (ESWT)\textsuperscript{89,90}
  \begin{itemize}
  \item Improves pain, but may not improve curvature or plaque size
  \item Possibly better with 5 mg daily tadalafil\textsuperscript{91}
  \end{itemize}

PRP or stem cell intercavernosal injections\textsuperscript{92}
Ineffective treatments

- Vitamin E (mb combined with verapamil, topical diclofenac, antioxidants)\(^9\)
- Colchicine\(^9\)
- 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 (IIEF-15): 15 questions, validated in 32 languages\(^95\)
  - IIEF-5: 5 questions\(^96\)
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<td>2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration (entering your partner)?</td>
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<td>3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?</td>
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<td>4. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?</td>
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<td>5. When you attempted sexual intercourse, how often was it satisfactory for you?</td>
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Add the numbers corresponding to questions 1–5. TOTAL:

The Sexual Health Inventory for Men further classifies ED severity with the following breakpoints:
1–7 severe ED  8–11 moderate ED  12–16 mild to moderate ED  17–21 mild ED
<table>
<thead>
<tr>
<th>Over the past six months:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 How do you rate your <strong>confidence</strong> that you could get and keep an erection?</td>
</tr>
<tr>
<td>2 When you had erections with sexual stimulation, how often were your erections hard enough for penetration?</td>
</tr>
<tr>
<td>3 During sexual intercourse, <strong>how often</strong> were you able to maintain your erection after you had penetrated (entered) your partner?</td>
</tr>
<tr>
<td>4 During sexual intercourse, <strong>how difficult</strong> was it to maintain your erection to completion of intercourse?</td>
</tr>
<tr>
<td>5 When you attempted sexual intercourse, <strong>how often</strong> was it satisfactory for you?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Very low</th>
<th>Low</th>
<th>Moderate</th>
<th>High</th>
<th>Very high</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Almost never/never</td>
<td>A few times (much less than half the time)</td>
<td>Sometimes (about half the time)</td>
<td>Most times (much more than half the time)</td>
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</tr>
<tr>
<td>Extremely difficult</td>
<td>Very difficult</td>
<td>Difficult</td>
<td>Slightly difficult</td>
<td>Not difficult</td>
</tr>
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<td>Almost never/never</td>
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</tr>
</tbody>
</table>

* The IIEF-5 score is the sum of the ordinal responses to the five items; thus, the score can range from 5 to 25.
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. (no recalling of porn).
   - Compare quality of erection & 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 ED in #2, then you have porn-induced ED.
   - If #2 is strong, but you have trouble with a real partner, then you have anxiety-induced ED.
   - If you have problems during #1 & 2, may be severe porn-induced ED or an organic problem.

www.yourbrainonporn.com/how-do-i-know-if-my-ed-porn-related-test

Photo credit: David Clode
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. Decreasing sexual arousal w/sexual partner(s)
8. Losing erection while attempting penetration
9. Inability to maintain erection or ejaculate with oral sex
Treatment

Tolle causam
Treat whole person
Mental & physical health

Photo credit: David Clode

CBT
EMDR
Sex addicts anonymous (SA)
Diet
Exercise
Weight loss
Treating Porn-induced low libido or ED

1. Eliminate porn, porn substitutes, & recalling porn (all artificial sexual stimulation)
2. Rewire sexual arousal to real people

How long will it take?
• 2 mos for men >50 (older guys didn’t start on Internet porn when young & brain most vulnerable to addiction)
• 2-5 mos younger men

May experience withdrawal symptoms:
• Mood swings
• Anxiety including panic attacks
• Agitation/irritability
• “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 & recover erectile function.
Diet

Beets, leafy greens high in nitrates convert to nitrites. Increase NO & endothelial function, lower BP\textsuperscript{97-99}

Pomegranate seeds, juice decrease ox & glyc LDL & reduce IMT.\textsuperscript{100,101} Improve NO & lower inflammation & BP\textsuperscript{102, 103}

Flavonoids from berries improve endothelial function\textsuperscript{104}

HFCS & soft drinks increase metabolic syndrome, atherosclerosis, DM, & ED\textsuperscript{105}

Advanced glycation end products (AGEs) contribute to DM, CVD, ED\textsuperscript{106-108}

- Highest AGEs: bacon, fast food hamburgers, hot dogs, cheese, pizza, fried food (esp meat, chicken, potatoes)

Salt impairs vasodilation & endothelial function\textsuperscript{109, 110}

4 clinical trials show MedDiet & lifestyle influence sexual function\textsuperscript{111}

MedDiet in diabetic men delays sexual dysfct & lowers inflammation\textsuperscript{112}
Exercise

Improves:\textsuperscript{113-118}
\begin{itemize}
  \item Visceral fat loss
  \item Endothelial function
  \item BP
  \item Inflammation
  \item Insulin sensitivity
  \item Lipoproteins
\end{itemize}

Increases endothelial progenitor cells (EPCs)\textsuperscript{119}

Improves ED\textsuperscript{120}

Photo credit: David Clode
Lose the fat

Fat tissue secretes >35 adipokines—nearly all promote inflammation, insulin resistance, & vascular disease\textsuperscript{121,122}

Weight loss improves erectile function\textsuperscript{123}

- Nutritional counseling & exercise advice
- Monthly meetings 1\textsuperscript{st} year; bimonthly second year
- Goal: 10% weight loss; outcome 15% weight loss
- Increase activity ~ 3 hours per week
- Ave 33 lbs in 2 yrs
- Decreased IL-6, CRP

Photo credit: Flip Nicklin, National Geographic
Physical & manual therapy

Physical therapy
Penis pump

Photo credit: David Clode
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)¹²⁴

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)
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

Herbs
Amino acids
Yohimbe  
(\textit{Pausinystalia yohimbe})

Evergreen native to central Africa
  - Bark contains 3 alkaloids: yohimbine (most active), rauwolscine, & corynanthine

Effective for ED\textsuperscript{126-129}

My help with delayed/inability to ejaculate\textsuperscript{130}

Dosage: 15-30 mg, up to 100 mg qd
  - Onset 10-15 min; half life 35 min
  - S/E: GI, tachycardia, HTN, anxiety

OTC brands not reliable
  - 49 most popular brands—0 to 12.1 mg yohimbine/serving\textsuperscript{131}
    - 19 brands no rauwolscine & corynanthine
    - 11 brands listed a specific quantity of yohimbine on the label--most were inaccurate
    - 2 brands accurate quantity of yohimbine & listed S/E
**Tribulus terrestris**

Grows in Europe, Asia, Africa, & Middle East

Root & fruit used in Chinese & Ayurvedic medicine

Doesn’t raise testosterone (IV in primates does)\(^{132-135}\)

May improve libido

May increase NO & improve erectile function (rats, rabbits)\(^{136,137}\)

One human RCT (500 mg Tribulus terrestris, standardized to furostanol saponins, not less than 112.5 mg, TID pc): improved libido, ED, intercourse satisfaction, orgasmic function. No adverse effects.\(^{138}\)
**Eurycoma longifolia**  
(Malasian ginseng, Tongkat Ali)

- Chinese review of 11 RCTs & pilot trials: improved ED, semen volume, libido, & testosterone\(^{139}\)
- Mild increase in libido (8-10%)\(^{140}\)
- May increase testosterone, especially free T\(^{141,142}\)
- Improves ED\(^{143,144}\)
- Lowers cortisol & increases testosterone in stressed subjects & athletes\(^{145}\)
- Increases muscle strength\(^{142}\)
- Water root extract safe at high doses & long-term
- Dosage: 200-300 mg QD or BID, patented form 22% eurypeptides & 40% glycosaponins
**Epimedium**
(Horny goat weed)

Farmers noted that goats & sheep became amorous after eating the weed

>60 species from Berberidaceae family

Icariin, assumed active ingredient--prenylated flavonoid

Improves erectile function (rats)\textsuperscript{146}

PDE5 inhibitor\textsuperscript{147,148}

May increase NO\textsuperscript{149,150}

Dosage 900-1,500 mg qd
L-arginine & L-citrulline

L-arginine conditionally essential AA (if arginase enzyme increased, DM, renal failure\textsuperscript{151,152}

- Used by enterocytes of intestine, liver, or converted into L-citrulline or L-ornithine
- 6 g PO absorption \~68\%; 10 g absorption \~20\%\textsuperscript{153,154}
- L-citrulline \rightarrow arginine in kidneys & \rightarrow absorption\textsuperscript{155}

When converted to citrulline, NO is byproduct

- Citrulline may increase plasma arginine > arginine supplementation\textsuperscript{156}

May improve ED—5,000 mg (esp if low urinary NOx)\textsuperscript{157}

- Increased ADMA inhibits eNOS. L-arginine supplementation may re-establish L-arginine:ADMA ratio to improve NO production/endothelial function.\textsuperscript{158}

More effective for ED combined w/yohimbine or pycnogenol (pine bark of \textit{Pinus pinaster})\textsuperscript{159-161}

S/E: Herpes activation & unsafe with recent MI (9g QD increased mortality)\textsuperscript{162}
Boosting Dopamine

Exercise\textsuperscript{163,164}

• Exercise requiring learning new skill better than sustained exercise for increasing synaptic connections\textsuperscript{165-167}

Meditation—increases theta activity correlated w/increased dopamine release\textsuperscript{168}

AA precursors & cofactors to increase dopamine synthesis

• Amino acid precursors (L-phenylalanine → L-tyrosine → L-dopa → dopamine → NE → epinephrine)
• Cofactors for production (tetrahydrobiopterine or BH\textsubscript{4}, iron, B6)
• \textit{Mucuna pruriens} improves sexual behavior in diabetic rats\textsuperscript{169}
• Hypersexuality is S/E dopamine agonists (pramipexole & ropinirole)\textsuperscript{170}
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 & Greenstone (subsidiary of Pfizer) marketing generic since 12/2017)
- Vardenafil (Levitra®) – Bayer, 2003 (patent expires Oct. 31, 2018)
- 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 $\rightarrow$ 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).\(^{171}\)

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

No head-to-head trials. Differences in onset, duration of action, & S/E/

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 & vardenafil)

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®)

Derived from morphine—doesn’t contain morphine or bind 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

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 S/E. Can combine w/sildenafil or tadalafil.

Erections 10-25 minutes after use firm enough for penetration in ~50% vs ~ 30 baseline

S/E: nausea, headaches, dizziness. Caution with antiemetics such as Zofran dt hypotension & possible LOC
Testosterone

• 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 (alprostadil)\textsuperscript{175,176}

97.6% effective with bi, tri, quadmix\textsuperscript{177}

Options:

- Prostaglandin E1 (compounded alprostadil or FDA Caverject Impulse\textsuperscript{®}, Edex\textsuperscript{®})—pain 48.5%
- Bimix (phentolamine, papaverine)—no E1
- Trimix (PGE1, phentolamine, papaverine)—pain 2.9%
- Quadmix (PGE1, phentolamine, papaverine, atropine)—pain 0%

See excellent Medscape article: Intracavernosal Injection Algorithm by Jeffrey A. Albaugh: http://www.medscape.com/viewarticle/551563_1
Intercavernosal injections

PGE1: 10, 20, or 40 mcg/mL N saline

Bi-Mix (per mL N saline):
- Phentolamine 0.5, 1, 2, or 3 mg
- Papaverine 30 mg

Trimix (per mL N saline)
- PGE1 5, 8.3, or 10 mcg
- Phentolamine 0.5, 0.83, or 1.0 mg
- Papaverine 15, 22.5, or 30 mg

Quad-mix (per mL N saline)
- PGE1 10, 20, or 60 mcg
- Phentolamine 1 or 2 mg
- Papaverine 30 mg
- Atropine 0.15 mg

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

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.

Risk of Peyronie’s & priapism—ER if >3 hour erection
Low-intensity extracorporeal shockwave therapy

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

High energy sound waves, not electrical shocks

When acoustic wave reaches the speed of sound, air cannot easily move out of the way—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 microcavitation

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

Originated in 1990s. Ultrasound induced angiogenesis in rat wounds—increased expression of vascular endothelial growth factor (VEGF)\textsuperscript{178}

MOA for ED: promotes regeneration of penile nNOS-positive nerves, endothelium, & smooth muscle by recruiting endogenous mesenchymal stem cells.\textsuperscript{179}

Also may activate local penile progenitor cells\textsuperscript{180}

Not currently FDA-approved for ED (off-label use)
First ED efficacy study\textsuperscript{181}

2010, Israel

20 men, non-responders to PDE5-I, ave age 56

2 sessions per week for 3 weeks

LI-ESW to the penile shaft and crura at 5 different sites

Results: improvement in erectile function, duration of erections, & penile rigidity at 1 month; sustained at 6 months

Significant increases in IIEF-ED domain scores in all men
RCTs in PDE5i responders

2012, Vardi et al\textsuperscript{182}
67 men, all PDE5i responders
After 1 mo PDE5i-washout, 12 sessions of LI-ESW or sham treatment
Erectile function & penile hemodynamics assessed before 1st treatment & after final treatment
~50% treated men able to achieve erections firm enough for penetration & had improved penile blood flow.
No adverse effects

2015, Srini et al\textsuperscript{183}
135 men, all DPE5i responders
1 mo PDE5i washout
12 sessions vs sham treatment
F/U 1, 3, 6, 9, 12 mos
78% at 1 mo, 71% at 5 mos initially unable to achieve erections firm enough for penetration able to do so. None in placebo group.
Very high dropout rate (58% sham, 42% treatment arm) at 12 mos
No adverse effects
PDE5i non-responders may become responders

2012, Gruenwald et al\textsuperscript{184}

Open-label single-arm prospective study

29 men, all PDE5i non-responders

2 treatments per week x 3 weeks; repeated after 3-week no-treatment interval (12 total treatment)

15,000 pulses, 120 shocks/min

ED improved slightly at 1 mo. PDE5i given at that time. 72% able to achieve erections firm enough for penetration at second month

2016, Kitrey et al\textsuperscript{185}

RCT

58 men, all PDE5i non-responders

12 sessions, 15,000 pulses, 120 shocks/min vs sham treatment

54.1% of treatment group able to achieve erections firm enough for penetration (EHS score) at 1 mo using PDE5i; 40.5% improved IIEF-EF score

0% improved in sham group
Open-label trial, PDE5i non-responders, 1 y f/u

Vascular risk factors: DM, HTN, dyslipidemia, CAD

50 men, considered non-responders if correct dosage of PDE5i, correction of risk factors & testosterone level, improved sexual stimuli, proper diet training

Ave age 64.8 yrs, ED duration ave ~ 6 yrs

14,400 shockwaves over 4 weeks

Success = improvement in Erection Hardness Score (EHS), ED severity (IIEF-EF), Sexual Encounter Profile (“Penis hard but not enough for penetration & hard enough for penetration but not completely hard”), Global Assessment Question (GAQ) “Has tx improved quality of your erections?”

60% positive response
RCT with 6 mo f/u

2015, Olsen et al

112 men

5 sessions over 5 weeks

At 10 weeks, placebo received active tx

57% active group able to have intercourse without medication

At 6 mos, 19% active group, 23% active placebo group still able to have intercourse without medication (~20% “penile rehabilitation”?)
RCT with 12 mo f/u\textsuperscript{188, 189}

2017, 2018 Fojecki et al, Danish hospital

126 men, ave age 65

5 session over 5 weeks or sham

After 4 week break, both groups received 5 treatments over 5 weeks (so initial treatment group got 10 sessions over 14 weeks vs 5 sessions in sham)

Success based on IIEF-EF score of at least 5 points: 38.3\% in sham group vs 37.9\% in ESWT group

2 cycles (10 sessions) of LI-ESWT not superior to 1 cycle (5 sessions) at 6 & 12 mo f/u:
Open-label, 2 yr f/u

2018, Kitrey et al

156 men

1 mo, treatment successful in 63.5%

2 yr effective in 53.5%

Severe ED had earlier failure

All patients with DM and severe ED lost effect

Mild ED without DM, 76% preserved effectiveness
RCT for Peyronie’s, 2009\textsuperscript{191}

100 men with Peyronie’s < 12 mos

4 weekly treatments, 2000 shock waves

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 worse in the placebo group
RCT for Peyronie’s, 2012

100 men with Peyronie’s < 12 mos

4 weekly treatments, 2000 shock waves with or without tadalafil 5 mg po qd

12 weeks:
- Both groups decreased plaque size & curvature (not statistically significant)
- Both groups improved erections & quality of life scores
- Better erections with tadalafil

24 weeks: curvature degree further decreased in both groups. Plaque size stable in ESWT group with further, slight decrease in ESWT + tadalafil
Review of published literature on MOA of LI-ESWT & efficacy

Results:

• MOA likely neovascularization

• 60-75% of PDE5i responders could achieve erections firm enough for penetration without medication

• 72% of PDE5i non-responders become responders
Meta-analysis, 2017

14 studies, 7 RCTs 2005-2015

833 men

Improvement in ED and erectile hardness scores lasting at least 3 mos

Mild-moderate ED better effect than severe ED or comorbidities

Energy flux density, number of shock wavers, duration of treatment closely related to outcome
Meta-analysis, 2018

7 RCTs that used IIEF-EF score

602 men, ave age 60.7 yrs

Ave f/u 19.8 weeks

Statistically significant improvement

Significant between-group differences for total treatment shocks per patient
PRP & stem cell

Theory
Animal studies
Limited human pilot trials
No human RCTs
Platelets from anticoagulated blood spun in centrifuge—concentrated 3-5 x

Contain more than 300 bioactive proteins/growth factors\textsuperscript{196,197}

- PDGF, TGF-β, VEGF, EGF, IGF-1, FGF, chemokines, immune mediators
- Also contains fibrin, fibronectin, vitronectin, & thrombospondin—adhesion proteins

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

May improve tissue healing, nerve & blood vessel regeneration\textsuperscript{198,199}

Success based on platelet concentration, volume of PRP delivered, extent of tissue damage/dysfunction, overall condition of patient

Penile vasculature—most endothelial-rich region of the body

Blood flow in flaccid penis slower compared to systemic circulation, allowing for better retention
Nerve repair

Group I: sham operation

Groups 2 & 3: bilat cavernous nerve (CN) injury. Received PRP or N saline injection in corpus cavernosum

4 weeks, electrostimulation of CN & histological exam of CN & penis

PRP increased number of myelinated axons & improved erectile function\textsuperscript{200}
Humans, PRP ED & PD

17 men, urology department, Wake Forest Baptist Medical Center, NC from 2012-2017

- 4 ED
- 11 PD
- 1 PD & ED
- 4 PD
- 1 female w/SUI

PRP activated with calcium chloride, 4-9 mL PRP per treatment

PD patients, erection induced with alprostadil & injection directly into plaques

ED improved (IIEF-5 score ave +4.14 points)

PD: 80% improved degree of curvature

Adverse effects: mild bruising and pain, no complications at f/u (mean 15.5 mos)
Human trial, PRP in PD

13 men, ave age 57.5 y
8 had curvature angles >50°
4 injections PRP + hyaluronic acid over 2 mos
F/U 9.3 mos average, 77% (10/13) improved with mean 30 ° decrease in curvature
53% decreased plaque density
Adverse effects: one hematoma, resolved
Human trial ED

9 men, 34-66 yo, ave age 56

12 mos 2015-2016 Midwest
Urological Group in Italy

PRP tx added to medication &
vacuum therapy

IIEF 15.6 to 19.9
(mild/moderate ED to mild ED)

No side effects
Bone marrow mononuclear cells

Includes hematopoietic cells such as lymphocytes, monocytes, stem cells, progenitor cells, & mesenchymal stromal cells

Chemotactic factors in injured tissue (SDF-1α, VEGF, granulocyte colony-stimulating factor, stem cell factor) mobilize EPC from bone marrow for angiogenesis\textsuperscript{204}

Testosterone/androgens stimulate angiogenesis via VEGF & EPO production. Also improve EPC function\textsuperscript{205,206}

EPCs decreased with chronic inflammation—DM, hypercholesterolemia, obesity, CVD, smokers all have decreased EPCs\textsuperscript{207}

ED assoc with deficiency in circulating EPC\textsuperscript{208}
Meta-analysis, diabetic rats

10 studies, 302 diabetic rats

Smooth muscle, smooth muscle to collagen ratio, & endothelium content greater than controls

Increase in endothelial nitric oxide synthase (eNOS), neuronal nitric oxide synthase (nNOS), & VEGF

Beneficial effect of stem cell therapy in improving erectile function
16 rat studies

Stem cells (bone marrow, adipose tissue, skeletal muscle)

Endothelial, smooth muscle, & CN improved

Intracavernously injected SCs rapidly escaped penis & homed into bone marrow

Injected SCs have systemic antidiabetic effects & prolonged anti-ED effects
Human pilot study\textsuperscript{211}

7 men, DM2, PDE5i non-responders, mean age 69.5 yrs

Human umbilical cord blood stem cells (1.5 x 10\(^7\))

Morning erections regained in 3 men at 1 mo, 6 men by 3\(^{rd}\) mo

2/7 erections firm enough for penetration with PDE5i, maintained >6 mos

BG decreased by 2 weeks, HbA1c improved for up to 4 mos

No adverse effects (despite no immunosuppression)
Human pilot study\textsuperscript{212}

12 men, ED post-radical prostatectomy (6 -18 mos prior)

ED despite alprostadil injections, PDE5i, vacuum device

4 groups, single injection, escalating doses BM-MNC

Primary objective: safety; secondary: sexual function, penile vascularization, endothelial function, change in penile length

Results:

- 6 mo f/u: improved ED & satisfaction
- 9/12 men achieved erections firm enough for penetration w/medication
- Spontaneous erections > with higher doses
- Benefit sustained at 1 yr
- No side effects
Sexual dysfunction

**Identify type**
- Desire
- Orgasm
- ED

**Diagnosis & monitoring**
- History (include pornography use)
- Lab work
- PE
- Questionnaires (SHIM, IIEF)

**Treat cause(s) & the whole person**
- Psychological
- Physical
THANK YOU
REFERENCES

Photo credit: Greg Lecoeur, National Geographic
References


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