Sexual Dysfunction in Men

Causes, Diagnosis, & Treatment Options

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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

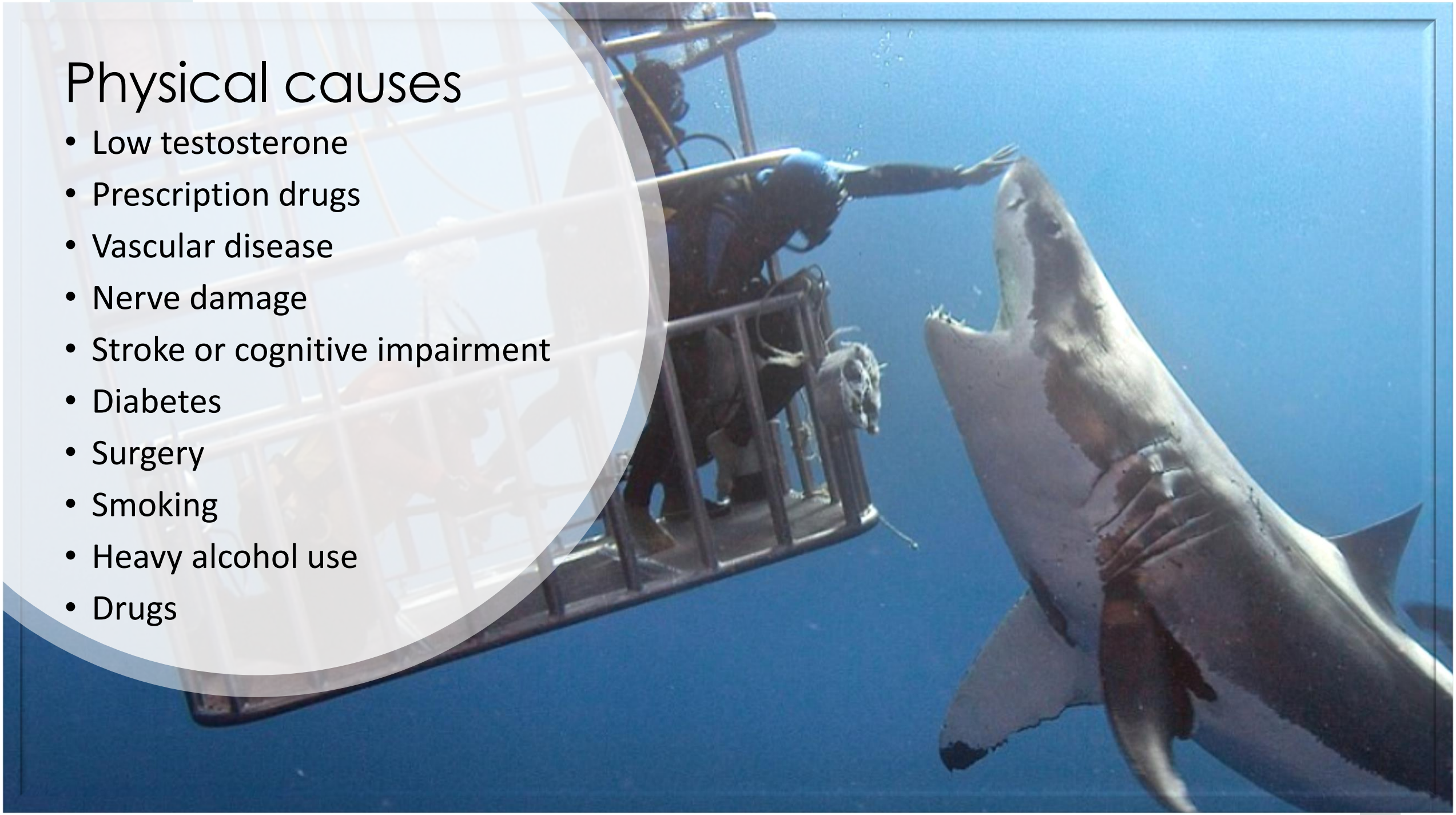
Neurological problem

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


Photo credit: Simon Matzinger

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[3]

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) (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[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

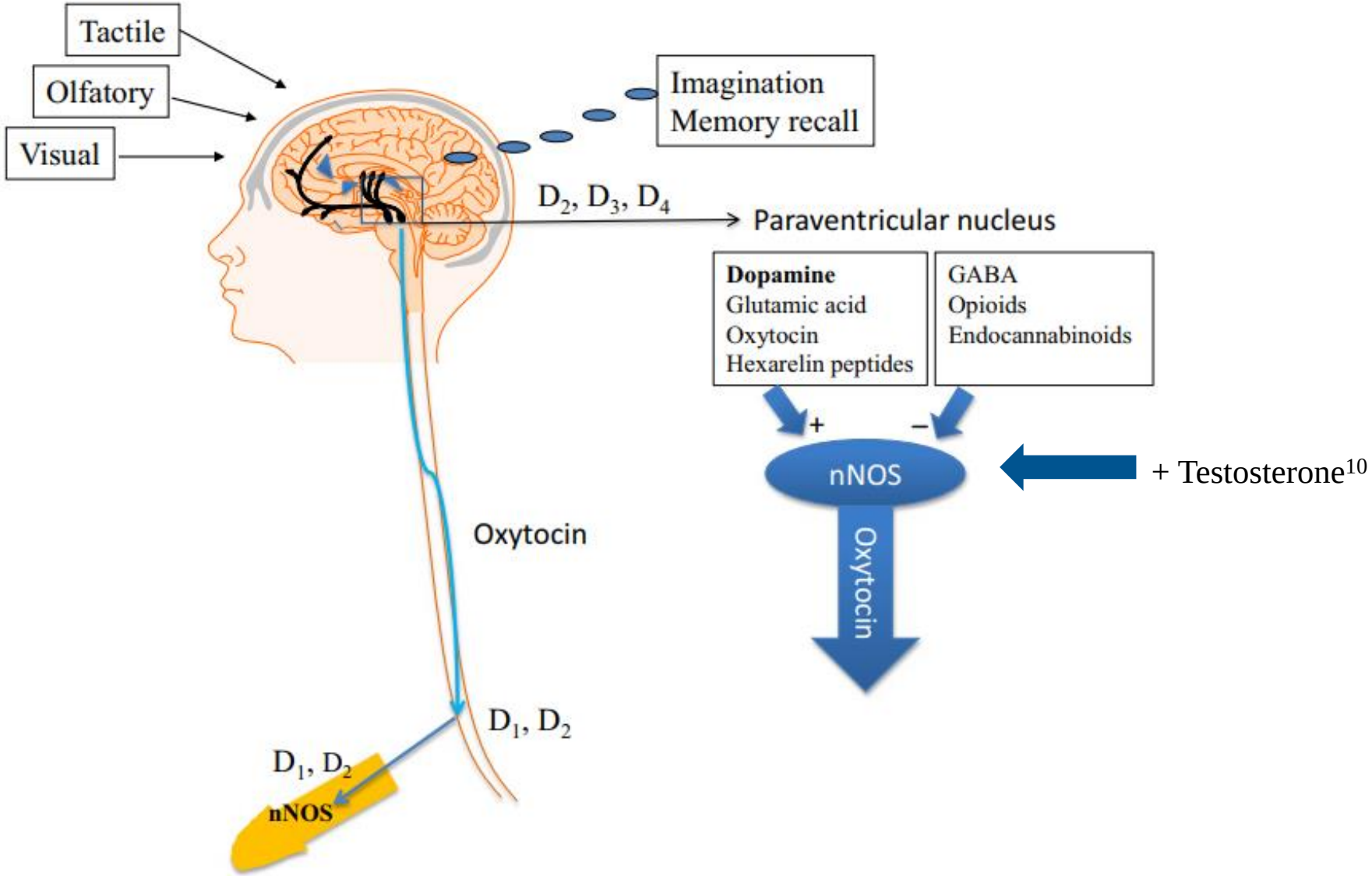
Reward-mediated behavior & reinforcement

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]



Simonsen U, et al. (2016). Modulation of dopaminergic pathways to treat erectile dysfunction. Basic Clin Pharmacol Toxicol. 119(Suppl3):63-74.

Oxytocin

Peptide hormone & neuropeptide made by hypothalamus, released by posterior pituitary during kissing, hugging, sexual arousal, & possibly orgasm[11-13]

Attachment, bonding, mb monogamy

- Activates nucleus accumbens & ventral tegmental area (VTA)
- Intranasal oxytocin increases attractiveness of partner compared to other females[14]

Promotes erections

- Oxytocin injected into PVN & VTA of male rats induces erections & increases dopamine in nucleus accumbens & PVN[15,16]

Hippocampus whitei

Photo credit: Pat Morris

Oxytocin

Regulated by other hormones & neurotransmitters

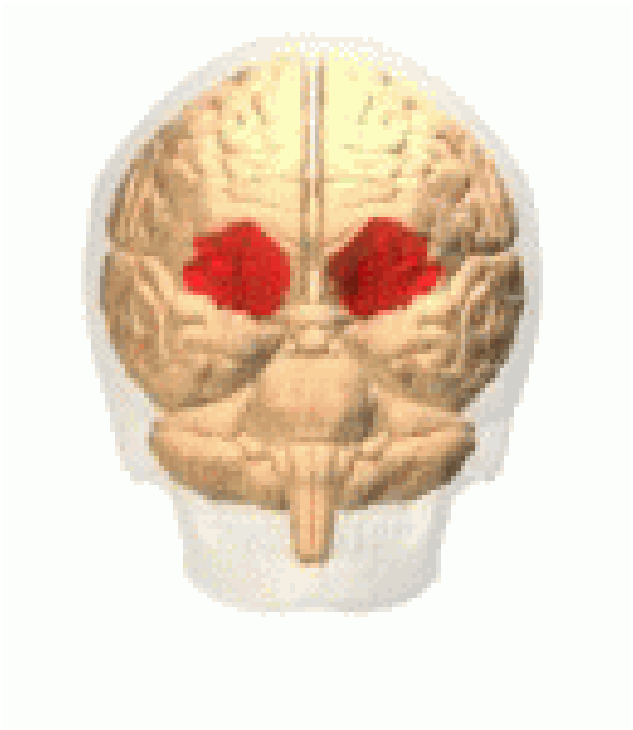
- Inhibited by endogenous opiods, GABA, endocannabinoids
- Stimulated by dopamine

Life experiences affect the methylation of the oxytocin receptor gene & its expression[17]

- Social isolation reduces expression of oxytocin receptor

Plays a role in muscle regeneration[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[19]

Increased activity in medial orbitofrontal cortex in HSDD[20]

Can also be dt limbic system damage[21]

Photo credit: Linus Nylund

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[22,23]

Causes (lifelong, situational, acquired): [24]

- Gender identity or sexual orientation
- Paraphilia (“abnormal” sexual desires)
- Trauma
- Difficulty in new or long-term relationship
- Testosterone deficiency
- Neurotransmitter imbalance[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

Photo credit: Pietro Jeng

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[26]
  - Injury to prefrontal cortex
  - Temporal lobe epilepsy[27]

Photo credit: Kyaw Tun

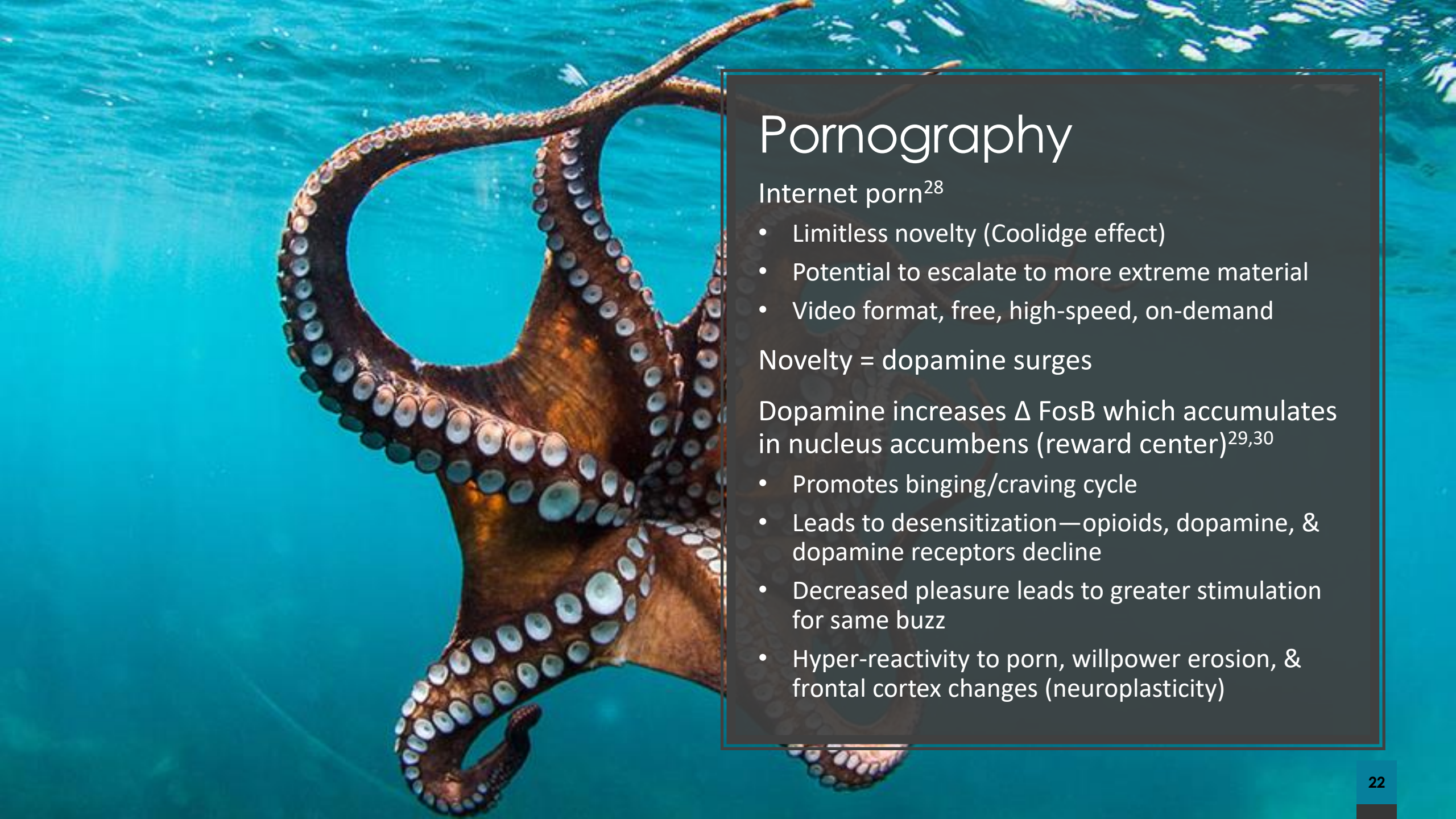

Photo credit: Pratik Mehta

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

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[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)[34]

SSRIs (off-label) esp. paroxetine

Dapoxetine 30 or 60 mg (phase III trials in US)[35]

- 1st 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]

Photo credit: Fabrizio Frigeni

Delayed ejaculation

Delay in ejaculation or infrequency or absence of ejaculation ≥75% of occasions for ≥ 6 mos

Least studied & understood male sexual dysfct[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[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 [42]

Photo credit: Jong Marshes

Delayed ejaculation treatment

Masturbation retraining

CBT

Penile vibratory stimulation (vibrators)

Testosterone therapy (low T assoc w/DE, high T assoc w/PE[43]

- 60 mg topical T to axillar for 4 mos ineffective[44]

Medications (all off-label)[45]

- Amantadine, cabergoline, apomorphine (dopamine agonists)
- Buproprion
- Cyproheptadine (serotonin & histamine antagonist)

Concurrent ED, treat with PDE5i

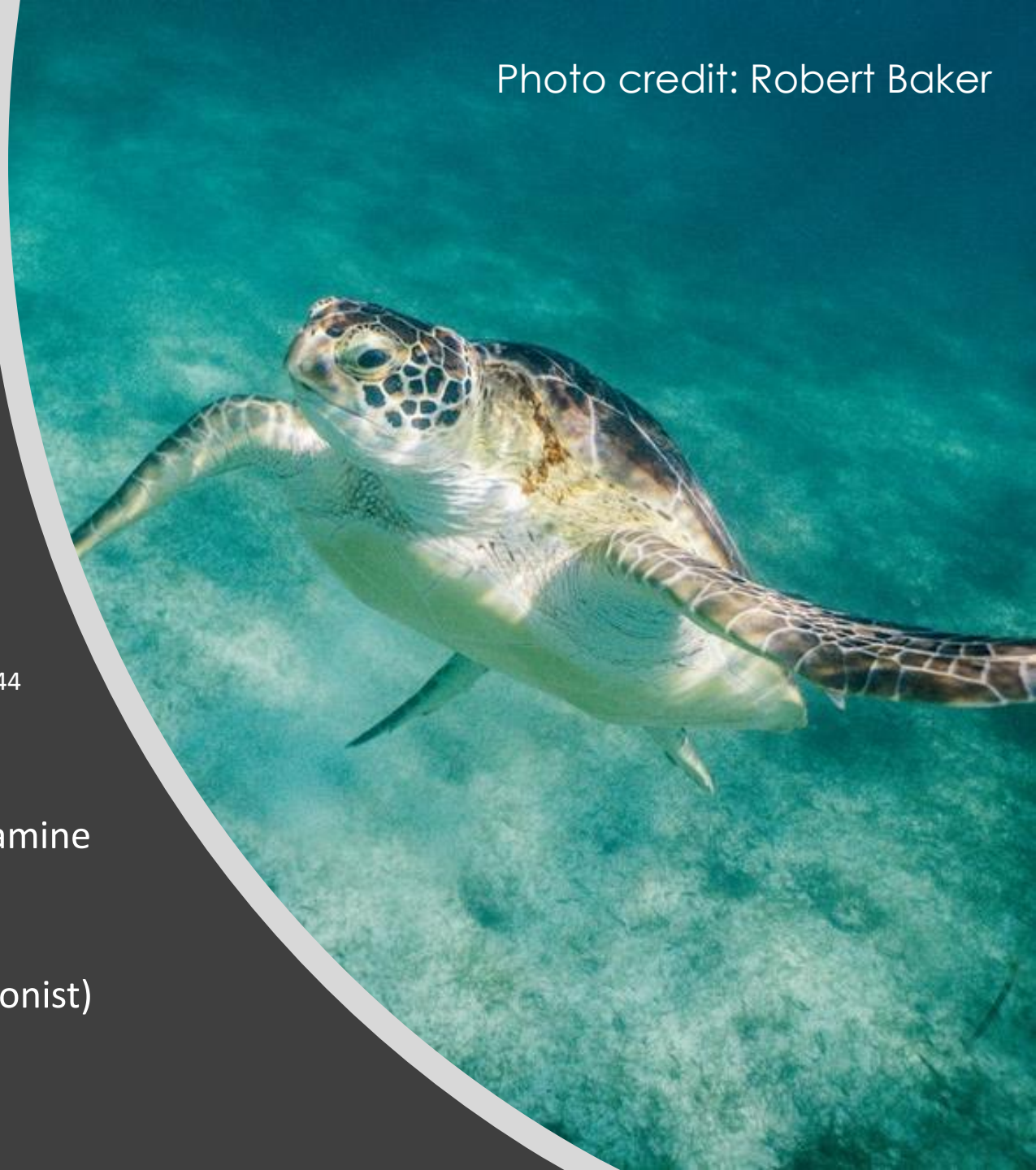


Photo credit: Robert Baker

Retrograde

Reduced ejaculation or dry orgasms

Causes:[46]

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

Medications

- Alpha-adrenergic blockers
- Psychotropics

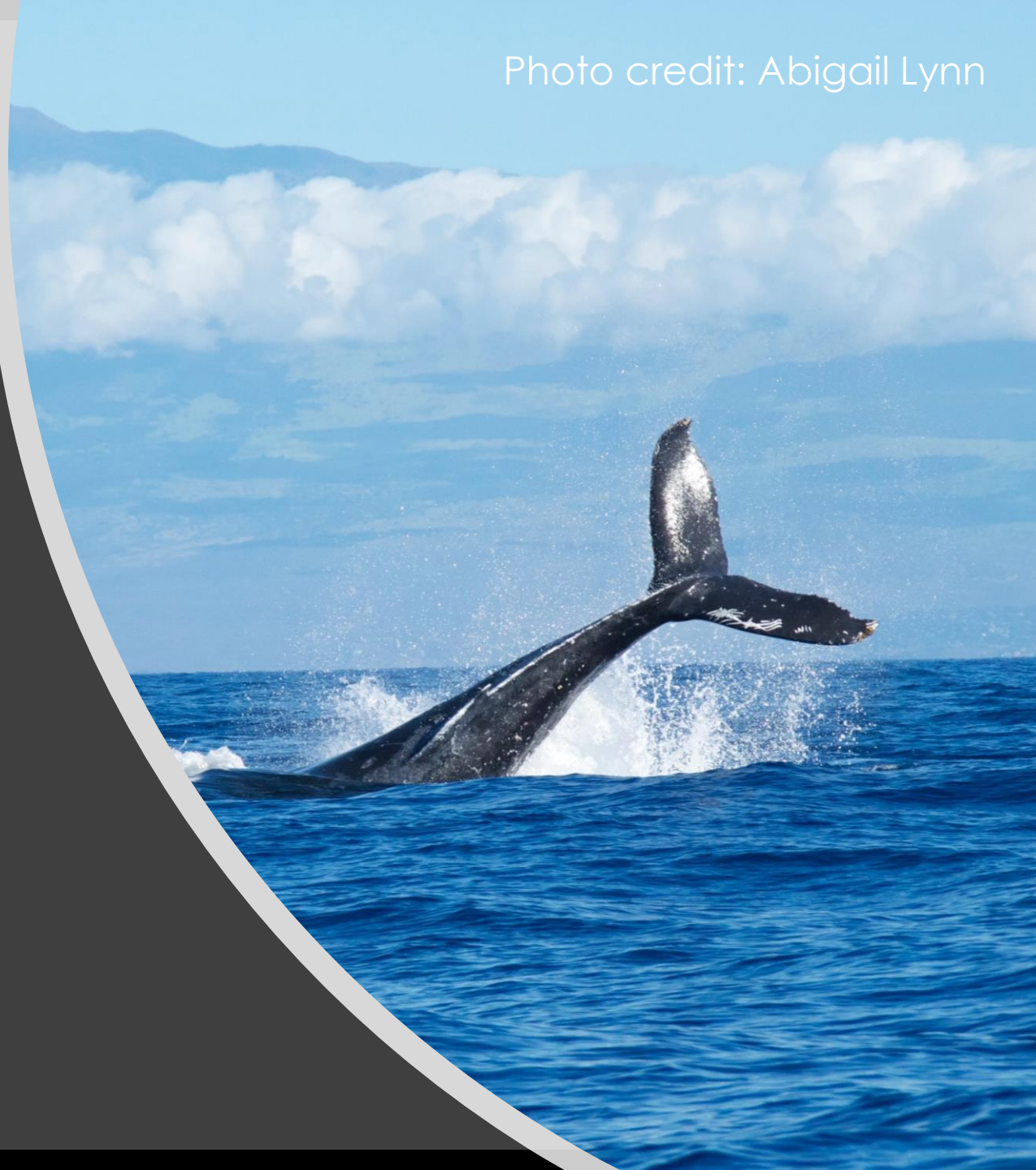
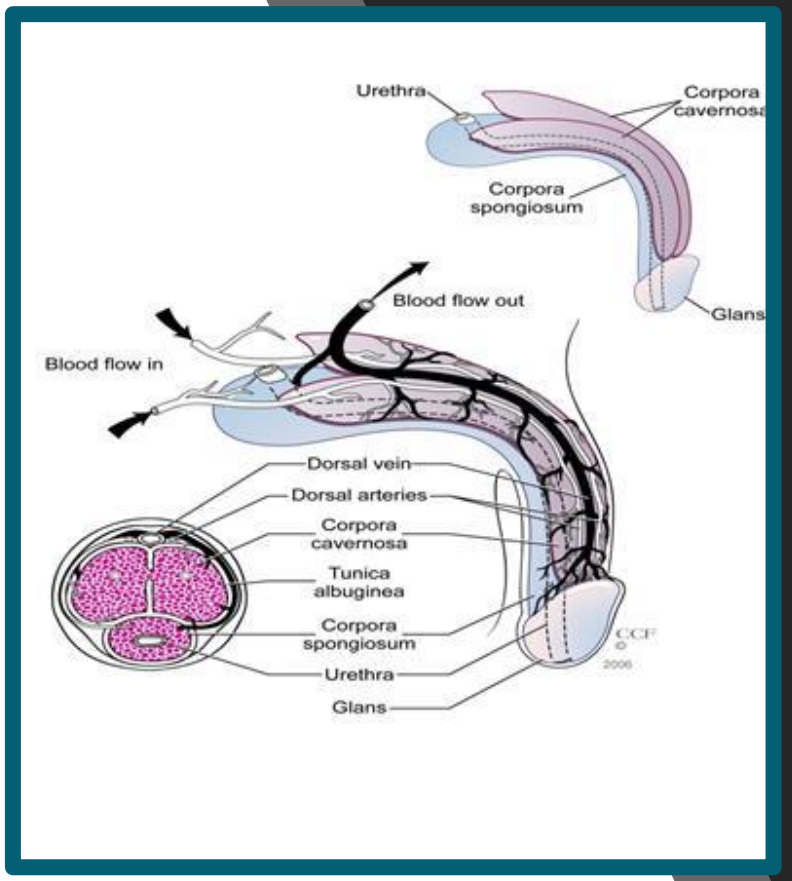


Photo credit: Abigail Lynn

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 → detumesence.

Nerves

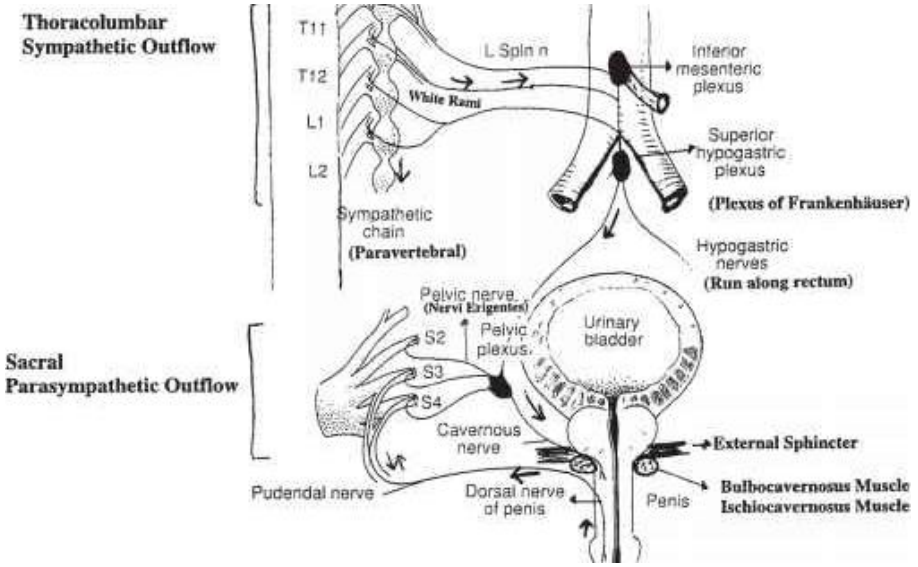
Autonomic (sympathetic & parasympathetic) and somatic (sensory & motor)

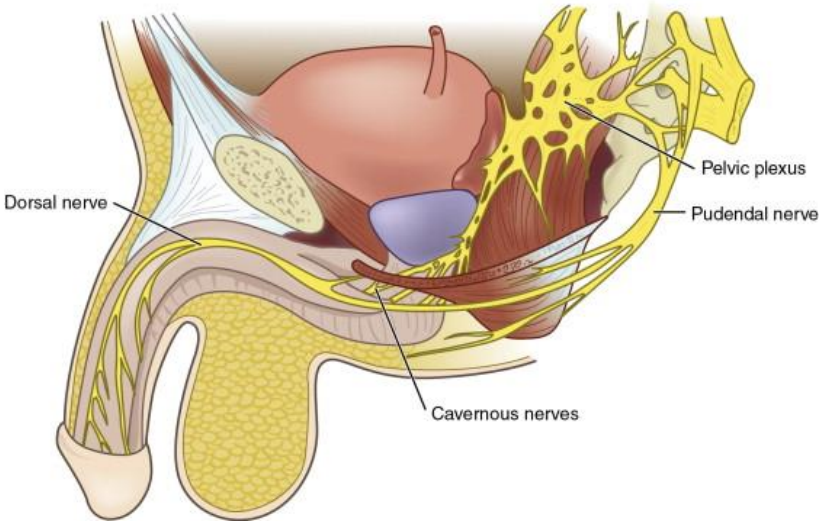
- Sympathetic (T11-L2): anti-erectile; control ejaculation & detumescense
- Parasympathetic (S2-S4): pro-erectile

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





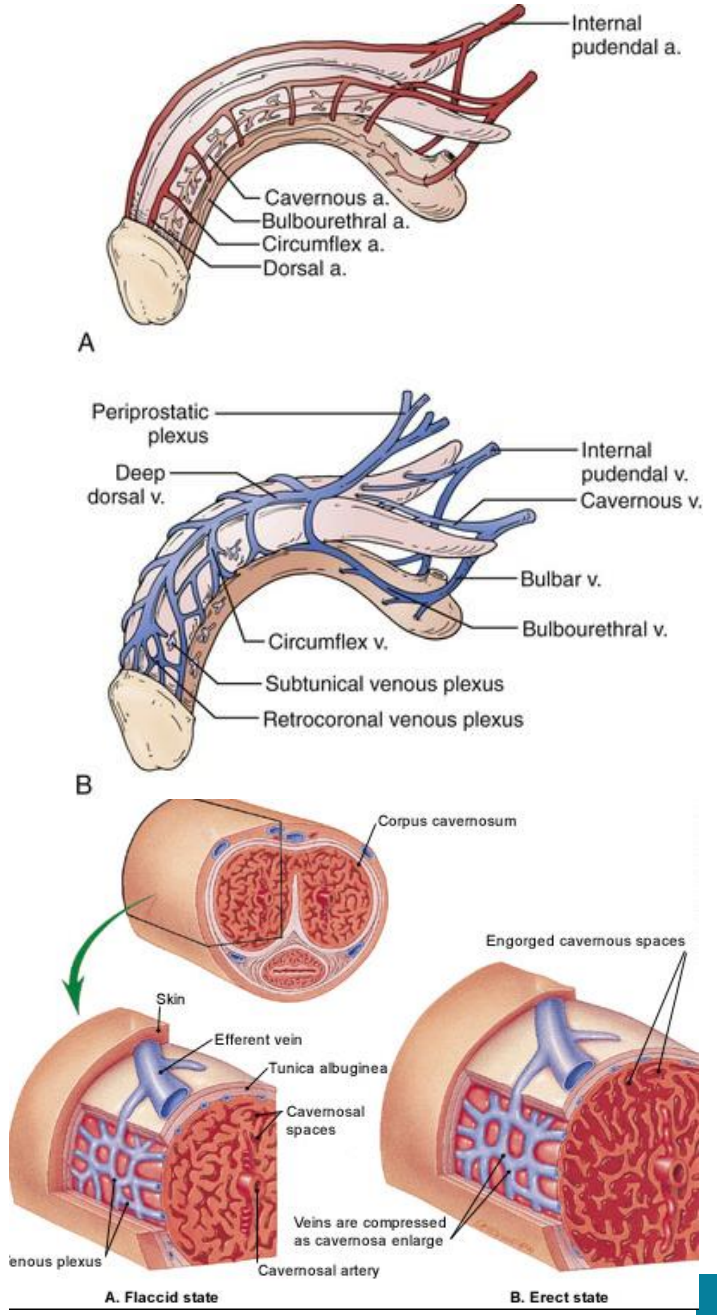
Vascular System

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

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[47]

Performance anxiety—first described by Masters & Johnson in 1970[48]

PTSD & hyperactive amygdala:

- ED in 85% of veterans w/PTSD vs 22% of veterans w/o PTSD[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)

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

Porn-induced ED

2002 meta-analysis of ED studies reported consistent rates of 2% in men under 40.[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[51]
- 2013 Italian study: 25% of men <40 yo[52]
- 2014 Canadian study: 25% of men 16-21 yo[53]

Photo credit: Masaaki Komori

Photo credit: Jason Leung

Neurogenic

10% to 19% of all causes of ED[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[55,56]
  - ED mb temporary
  - Swimmers & runners same ED as cyclists[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[58]

- 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


Photo credit: David Clode

Hormonal

Hypogonadism

- Minimal level testosterone necessary to maintain erectile function unknown (probably varies)[59]
- Testosterone decreases with age & ED prevalence increases with age (50% age 50, 60% age 60, 70% age 70)[60]

Hyperestrogenism—interdependent risk factor for ED? Increase in serum estradiol or increased estradiol-to-testosterone ratio?[61]

Hypo or hyperprolactinemia[62,63]

Hypo & hyperthyroidism—ED common[64]

- More in hyperthyroidism[65]

Hyperinsulinemia, IFG, T2DM—ED may be first clinical sign of metabolic disease & CVD[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)

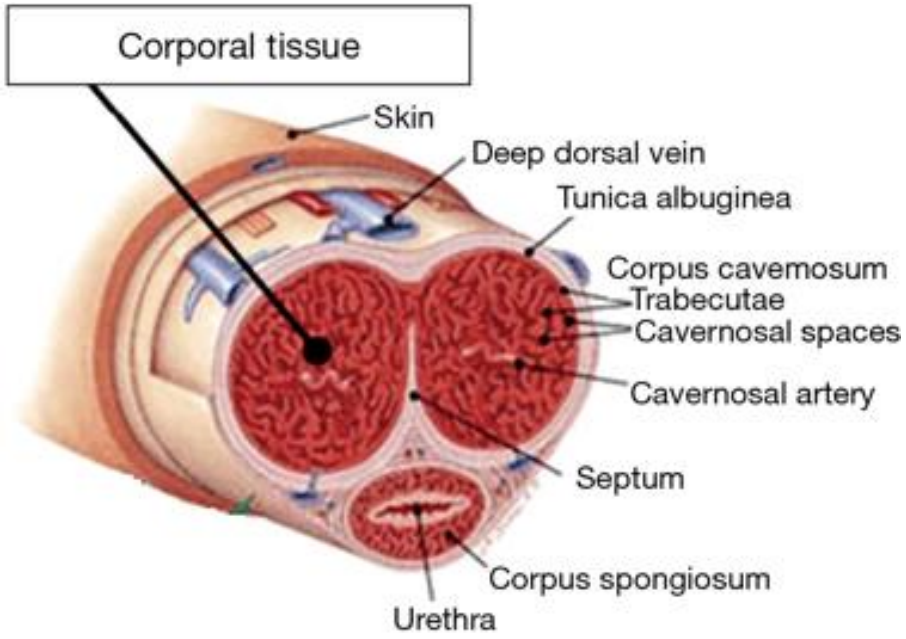
Tunica albuginea is mainly collagen with 5% elastin—allows penis to expand & lengthen during erection

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


Photo credit: David Clode

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

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. 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

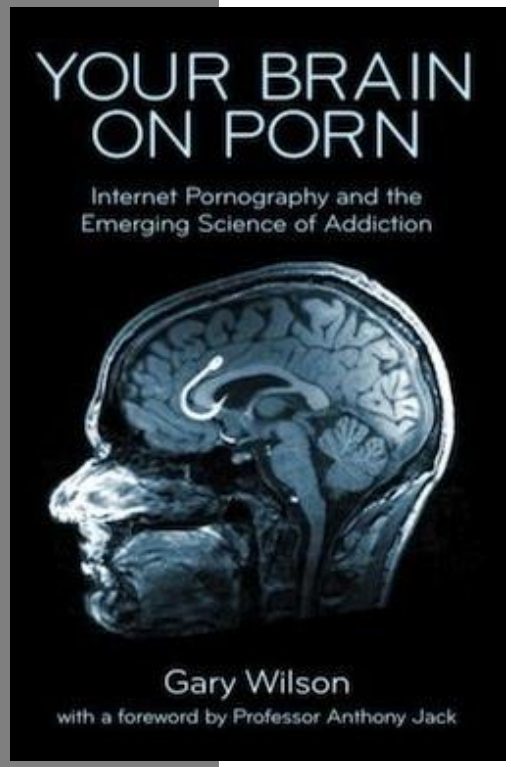
Sex addicts anonymous (SA)

Diet

Exercise

Weight loss

Treating Porn-induced low libido or ED



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?

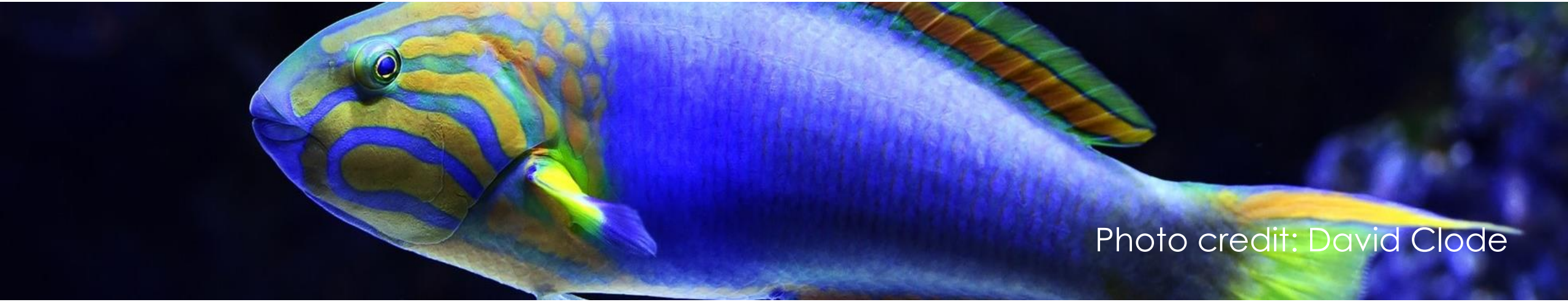
- 2 mos for older men >50 (older guys didn't start on Internet porn when young and brain most vulnerable to addiction)
- 2-5 mos younger men

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.

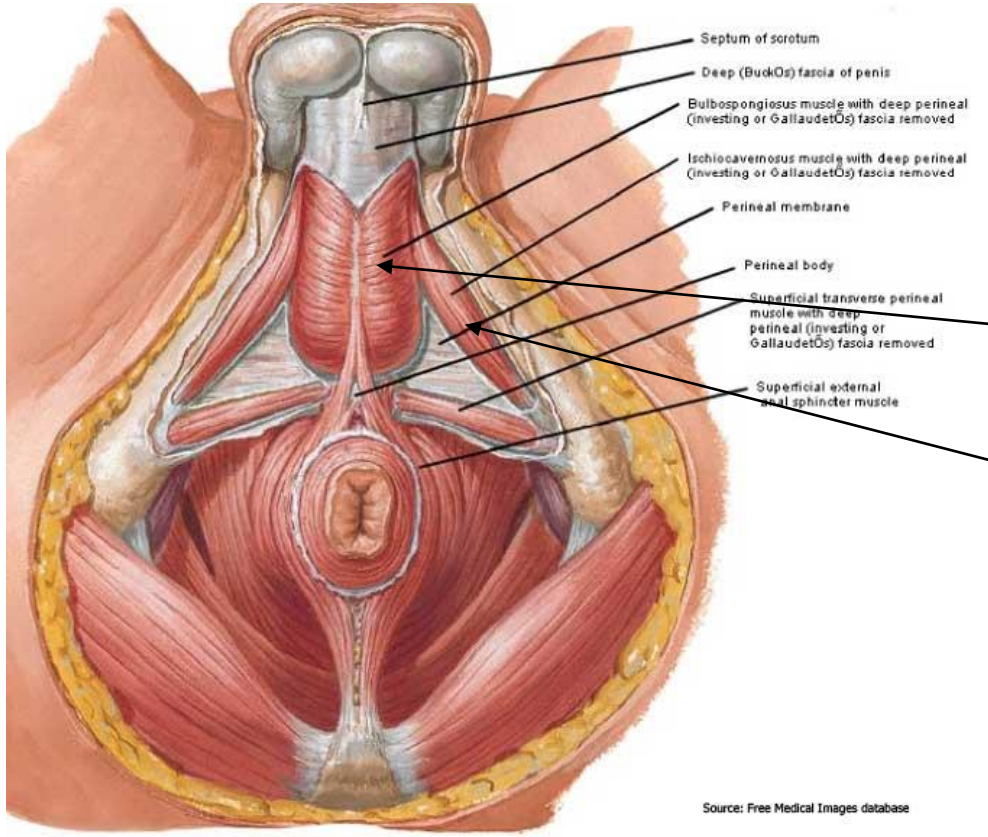
Physical & manual therapy



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)

Arnold Kegel, MD, 1894-1981

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, consectetuer adipiscing elit.

CBT

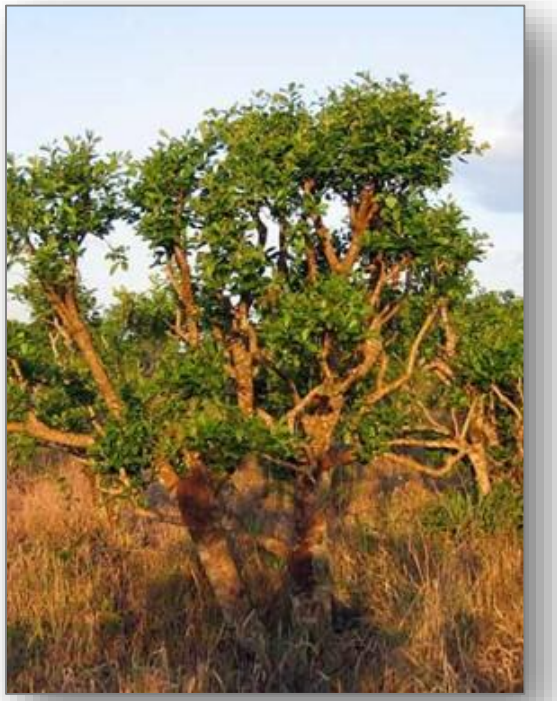
EMDR

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



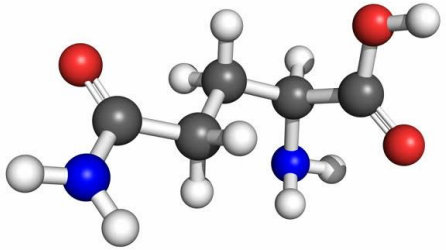
Carey MP, Johnson BT. Effectiveness of yohimbine in the treatment of erectile disorder: four meta-analytic integrations. *Arch Sex Behav*. 1996; 25: 341-360.

Ernst E, Pittler MH. Yohimbine for erectile dysfunction: a systematic review and meta-analysis of randomized clinical trials. *J Urol*. 1998; 159: 433-436.

Cohen P, et al. Pharmaceutical quantities of yohimbine found in dietary supplements in the USA. *Drug Test Anal*. 2016;8(3-4):357–369.

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



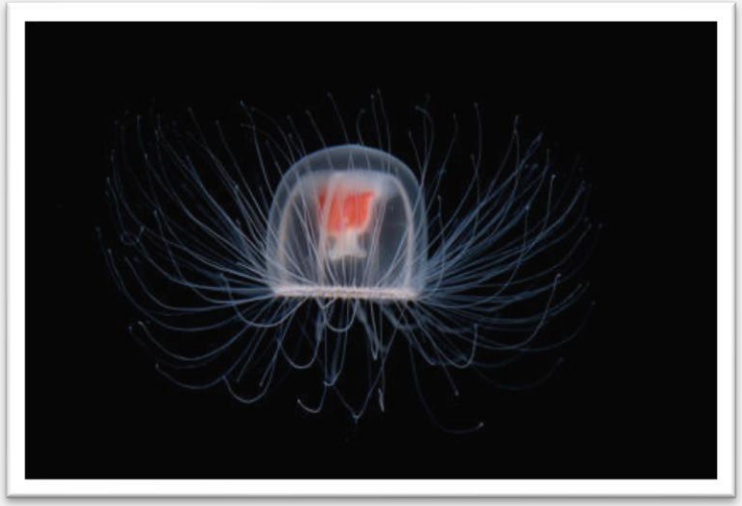
Stanislavov R, Nikolova V. Treatment of erectile dysfunction with pycnogenol and *L-arginine*. *J Sex Marital Ther*. 2003;29(3):207-13.

- 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.

Chen J, et al. Effect of oral administration of high-dose nitric oxide donor L-arginine in men with organic erectile dysfunction: results of a double-blind, randomized, placebo-controlled study. *BJU Int*. 1999;83(3):269-73.

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 BH_4, iron, B6)
  - Release and binding to receptors on postsynaptic cell
  - Removal or degradation
  - Relationship

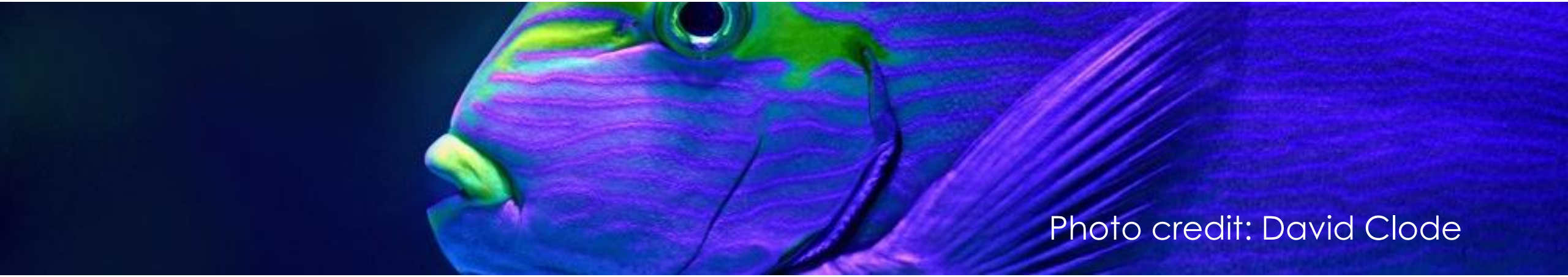


Turritopsis dohrnii

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

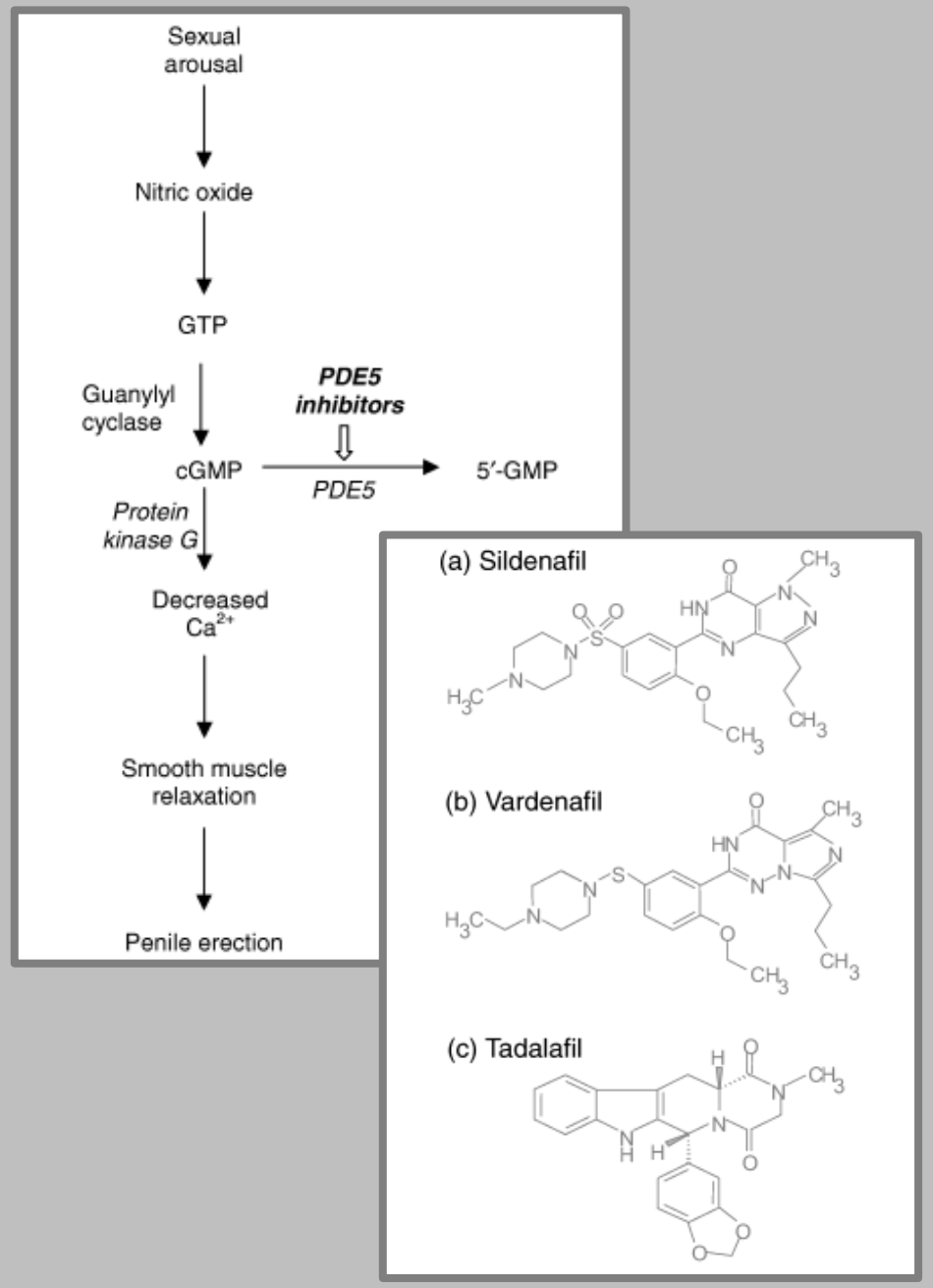
PDE5i

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 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, & 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

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, papaeverine, E1, with or without atropine

E1-Alprostadiol Rx: Caverject Impulse®, Edex®—0.25 mcg with additional 0.25 mcg if ineffective. Wait 24 hours and increase by 5-10 m to 40 mcg.

May be painful, ineffective, & expensive

Can use Bimix, Trimix, Quadmix

Painful & expensiveTrimix (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:

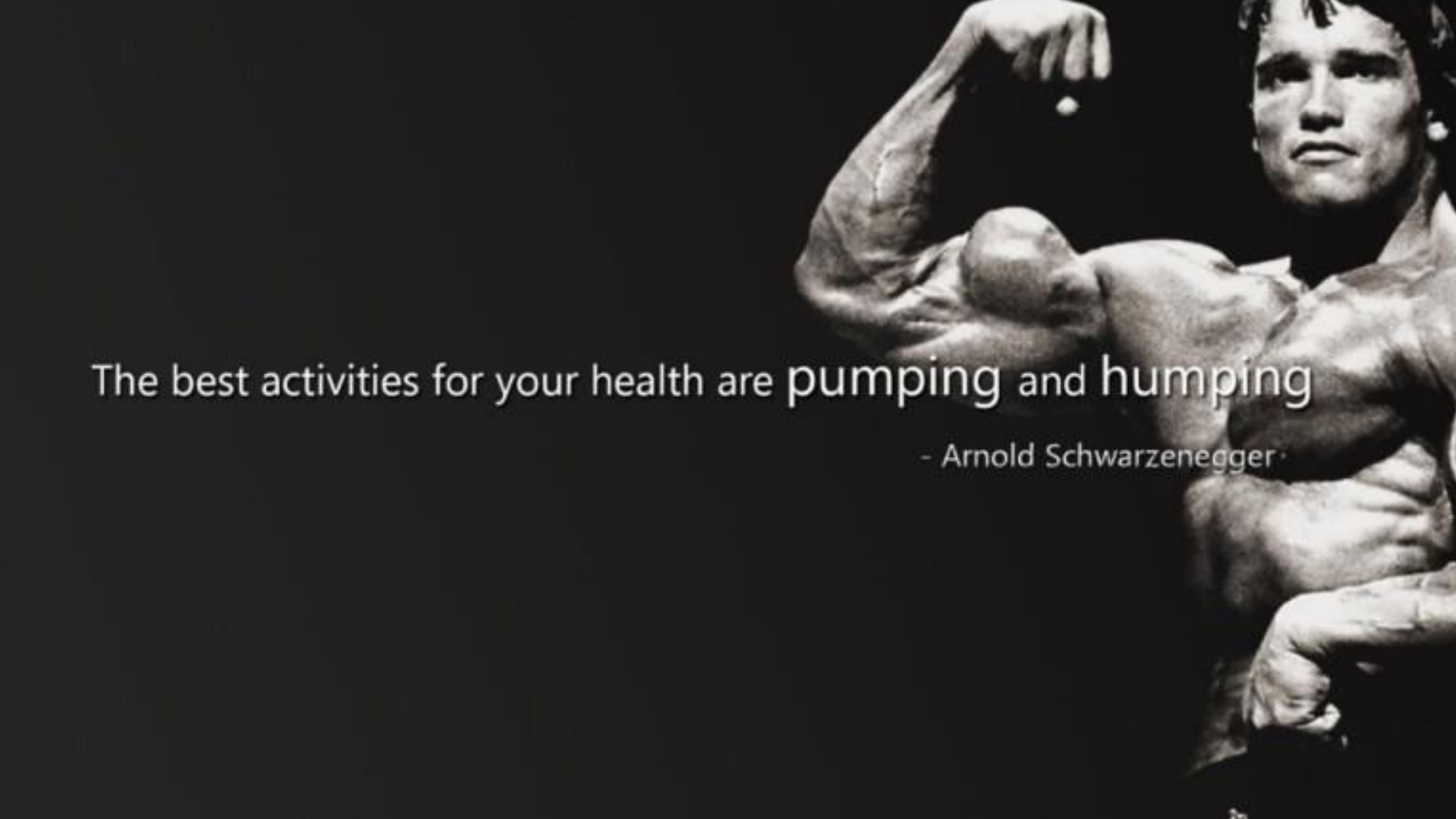
- No history ED age <55: 0.1-0.2 ml
- History of ED or age ≥ 55: 0.3 ml
- Increase by 0.1-0.3 ml if needed

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: Intracavernosol Injection Algorithm by Jeffrey A. Albaugh: http://www.medscape.com/viewarticle/551563_1

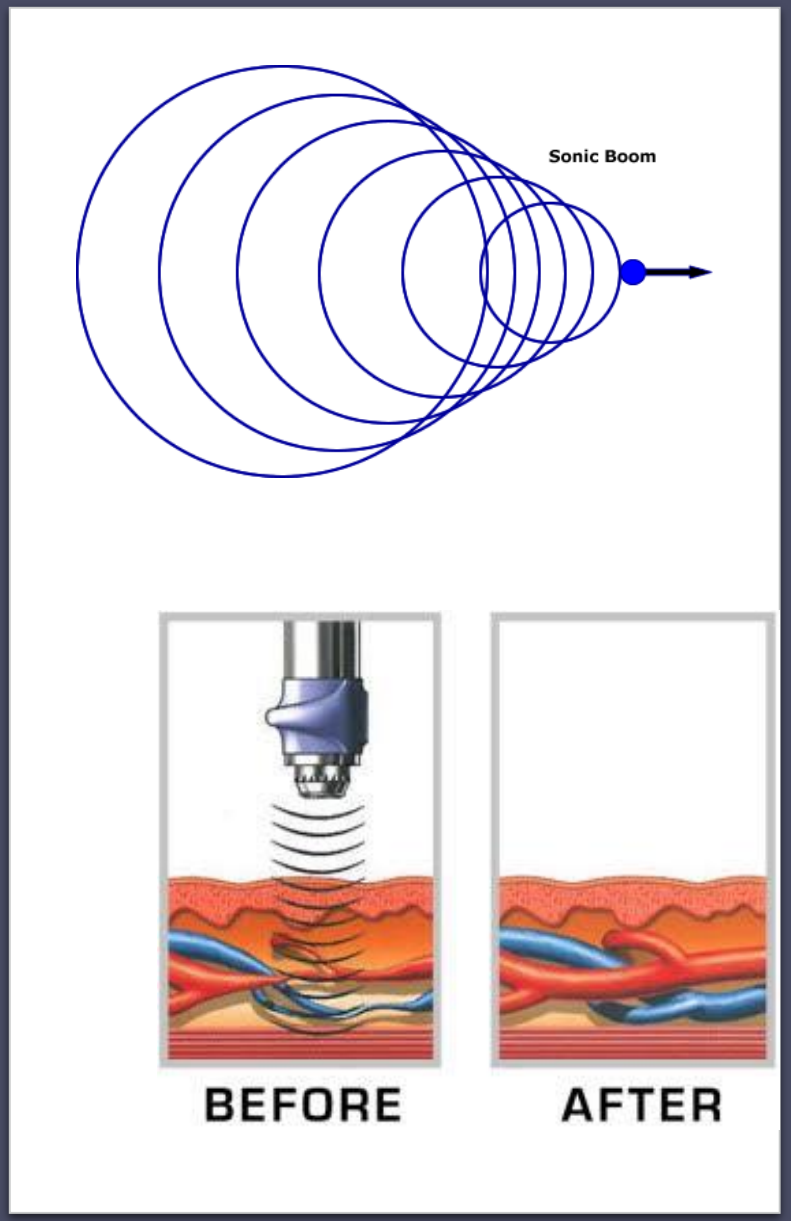

The best activities for your health are pumping and humping
- Arnold Schwarzenegger

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-ECSW 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)

Young SR, Dyson M. The effect of therapeutic ultrasound on angiogenesis. *Ultrasound Med Biol.* 1990;16(3):261-9.

Qiu X, et al. Effects of low-energy shockwave therapy on the erectile function and tissue of a diabetic rat model. *J Sex Med*. 2013;10(3):738-46.

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

Vardi Y, et al. Can low-intensity extracorporeal shockwave therapy improve erectile function? A 6-month follow-up pilot study in patients with organic erectile dysfunction. *Eur Urol*. 2010;58(2): 243–248

- 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

Vardi Y, et al. Does low intensity extracorporeal shock wave therapy have a physiological effect on erectile function? Short-term results of a randomized, double-blind, sham controlled study. *J Urol.* 2012;187(5):1769-75.

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.

Gruenwald I, et al. Low-intensity extracorporeal shock wave therapy–a novel effective treatment for erectile dysfunction in severe ED patients who respond poorly to PDE5 inhibitor therapy. *J Sex Med.*2012;9(1):259-64.

- 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.

Olsen A, et al. Can low-intensity extracorporeal shockwave therapy improve erectile dysfunction? A prospective, randomized, double-blind, placebo-controlled study. *Scand J Urol*. 2015;49(4):329-33.

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

Srini VS, et al. Low intensity extracorporeal shockwave therapy for erectile dysfunction: a study in an Indian population. *Can J Urol.* 2015;22(1):7614-22.

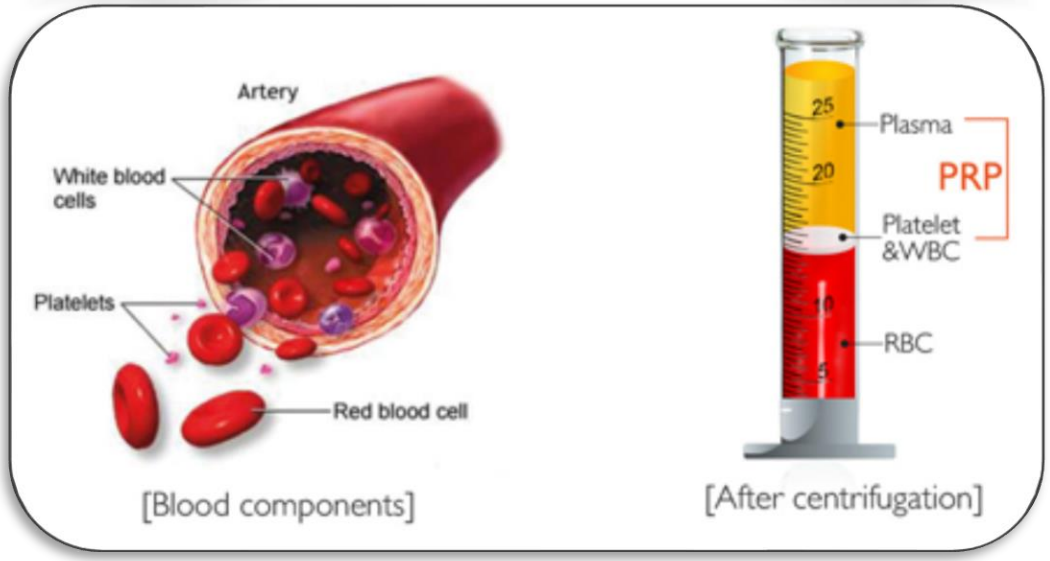
Palmieri A, et al. A first prospective, randomized, double-blind, placebo-controlled clinical trial evaluating extracorporeal shock wave therapy for the treatment of Peyronie's disease. *Eur Urol.* 2009;56(2):363-9.

PRP & stem cell

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

Ichim TE, et al. Intracavernous administration of bone marrow mononuclear cells: a new method of treating erectile dysfunction? *J Transl Med*. 2013;11:139.



PRP

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

Pavlovic V, et al. Platelet Rich Plasma: a short overview of certain bioactive components. *Open Med (Wars)*. 2016 Aug 12;11(1):242-247.

Yu W, et al. Platelet-rich plasma: a promising product for treatment of peripheral nerve regeneration after nerve injury. 2011;121(4):176-80

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

Wu CC, et al. The neuroprotective effect of platelet-rich plasma on erectile function in bilateral cavernous nerve injury rat model. *J Sex Med*. 2012;9(11):2838-48.

- 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)

Mingchao Li, et al. Stem cell therapy for diabetic erectile dysfunction in rats: a meta-analysis. PLoS One. 2016; 11(4): e0154341.

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.

Lin CS, et al. Stem cell therapy for erectile dysfunction: a critical review. *Stem Cells Dev*. 2012;21(3):345-51.

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

Banno JJ, et al. The efficacy of platelet-rich plasma for the treatment of erectile dysfunction: initial outcomes. *J Sex Med*. 2017; 14(2 Supplement):e59–e60.

- 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
- Article in Russian with no results available.

Chalyi ME, et al. The effectiveness of intracavernous autologous platelet-rich plasma in the treatment of erectile dysfunction. *Urologiia*. 2015;(4):76-9.

Identify cause(s)

Diagnosis & monitoring

Treatment options

THANK YOU

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