“The penis does not obey the order of its master, who tries to erect or shrink it at will. Instead, the penis erects freely while its master is asleep. The penis must be said to have its own mind, by any stretch of the imagination.”

—Leonardo da Vinci

**Major Influences**

- Psychological
- Neural
- Vascular
- Hormonal

**Penile Innervation**

- Autonomic:
  - Sympathetic: T₁₁ – L₂
  - Parasympathetic: S₂ – S₄
- Detumescence
- Tumescence
- Pelvic plexus
- pudendal
- cavernous nerves
- Somatic sensory
- Penile receptors
- Dorsal nerve
- Motor
- Onuf's nucleus (S₂–S₄)
- Pudendal nerve
Neurotransmitters

- NO (nitric oxide)
- Acetylcholine
- PGE\textsubscript{1} (prostaglandin E)
- VIP (vasoactive peptide)
- CGRP (calcitonin gene-related peptide)

Arterial Blood Supply to the Penis

- Dorsal artery
- Cavernous artery
- Common penile artery
- Bulbourethral artery

The Corporal Veno-Occlusive Mechanism

- Tunica albuginea:
  - Outer longitudinal layer
  - Inner circular layer
  - Emissary vein
  - Circumflex vein
  - Helicine arteriole
  - Trabeculae
  - Sinusoids

Compressed Venules Against the Tunica Albuginea with Resultant Venous Outflow Blockade

- NO = nitric oxide
- NANC = nonadrenergic, noncholinergic neurons
- PDE5 = phosphodiesterase type 5

Erection
- Increased arterial inflow
- Increased storage, sinusoids
- Increased intracorporeal pressure
- Decreased venous outflow
- Ischiocavernosus muscle

ED Definition
- The consistent or recurrent inability of a man to achieve or maintain an erection sufficient for satisfactory sexual intercourse
- Duration: >3 months

Prevalence
- Numbers vary greatly
  - ED definition
  - Methodology
  - Cultural, racial difference of study cohorts
- Prevalence INCREASES with age
- Approx. 1 in 5 men in the US

Risk Factors
- Sexual Dysfunction
  - Poor General Health
  - Diabetes
    - IDDM worse
  - Cardiovascular Disease
  - Ψ Disorder
  - Socio-economic status
- Erectile Dysfunction
  - Tobacco Use
  - Obesity
  - Hypogonadism
  - Diabetes
  - Chronic Disease
  - Medications
  - Concomitant GU Dx

Risk Factors Diagram
Psychogenic ED
- Generalized
  - Generalized Unresponsiveness
  - Generalized Inhibition
    - Direct inhibition, Cortical Level
- Situational
  - Partner-related
    - Conflict/Stress
  - Performance-related
    - Anxiety (performance or otherwise)
  - Psychogenic Distress
    - Depression
      - MMAS – 90% ED with severe depression
    - Conflict

Causes of Organic ED
- Vascular
- Diabetes
- Medication
- Pelvic Surgery, Radiation, or Trauma
- Neurological Causes
- Endocrine Problems
- Other

Neurogenic ED
- Brain
  - Parkinson’s
    - Imbalance of dopaminergic pathways
    - CVA of thalamus
- Spinal cord
  - Injury
    - Neurogenic versus Psychogenic
    - Multiple Sclerosis
- Cavernous nerves
  - Surgery – GU and Colorectal Procedures
  - Diabetes - Neuropathy

Hormonal ED
- Androgens
  - CNS effects
- Hypogonadism
- Hyper- and Hypo-thyroidism
- Hyperprolactinemia

Hypogonadism
- Low testosterone is a risk factor for ED
- The causal relationship between the two is not strong
  - As a community we overestimate the ability of T to fix/reverse ED
  - Supplementing T leads to increases in libido, sexual acts and nocturnal erections
    - Sexually stimulated erections are androgen independent
  - However, replacing T in the hypogonadal population may increase response to PDE5 inhibitors

Arteriogenic ED
- Atherosclerosis/atherosclerosis
- Trauma
  - Long distance cycling
- Hypertension
- Hyperlipidemia
- Nicotine
- Diabetes
- Radiation
Among men with CAD, ED correlates with CAD severity (single vs multi vessel disease)

- Men with CAD and ED
  - ED preceded CAD symptoms in 93% of cases
  - Time interval between onset of ED and CAD 2-3 years
  - Onset of ED was self-reported

Cavernous/Venogenic ED
- Trauma/Penile Fracture
- Peyronie’s Disease
- Aging
- DM2
- Shunting procedures

Peyronie’s Disease
- Affects up to 5% of men in the US
- Disordered scar formation and wound healing
- Associated with microfracture of the tunica albuginea
- 20-30% of men may experience ED due to venous leak at the site of injury
- May be associated with Dupuytren’s contracture of the hand
- Many treatment options available including penile stretch devices, intrallesional injections and surgical correction of curvature and/or ED

Diabetes Mellitus
- Prevalence of ED is three times more common in diabetic men
- Occurs at an earlier age
- Risk increases with DM duration
  - Risk increases further with diabetic neuropathy
- ED in diabetic men
  - Associated with 14x greater risk of silent MI
  - Increased risk of cardiovascular morbidity and mortality

Hypertension
- Independent risk factor of ED
- ED not related to blood flow issue
  - Biochemical changes and endothelial dysfunction related to HTN more likely

Aging
- Largest risk factor for ED
- Aging leads to corporal fibrosis and inability for smooth muscle to relax
- What’s normal??
  - Decreased Turgor
  - Increased Refractory Time
  - Decrease Ejaculate Volume and Force
- Is ED a normal part of aging???
Metabolic Syndrome

- Risk of ED doubled
- ED related to change in androgen balance and inflammatory state, and endothelial dysfunction
- Obesity is also an independent risk factor for ED

Medication Induced ED

- Antihypertensives
- Antipsychotics
- Antidepressants
- Anti androgens
  - 5α-reductase inhibitors
- Central sympatholytics
- Tranquilizers
- Alcohol

<table>
<thead>
<tr>
<th>AGENT</th>
<th>EFFECT</th>
<th>MECHANISM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics</td>
<td>ED (twice as placebo)</td>
<td>Unknown</td>
</tr>
<tr>
<td>β blocker (nonselective)</td>
<td>ED</td>
<td>Prejunctional α₁ receptor inhibition</td>
</tr>
<tr>
<td>α₁ blocker</td>
<td>Decreases ED</td>
<td>Failure of sympathetic induced closure of internal sphincter and proximal urethra during ejaculation</td>
</tr>
<tr>
<td>α₂ blocker</td>
<td>ED</td>
<td>Inhibition of central α₁ receptor</td>
</tr>
</tbody>
</table>

Antipsychotics

- 40-70% of people on antipsychotics have ED
- ED related underlying psychopathology, no direct causal link between antipsychotic medication and ED

Anti Depressants

- Cochrane Review (SSRIs)
- 15 randomized trials assessing ED related to antidepressant use
  - Adding a PDE5 inhibitor or bupropion mitigates ED
  - May also change medications
  - Paroxetine has high risk of ED, citalopram has a low risk
  - Mirtazapine, an analogue of mianserin, may also have less of an ED risk

Anti Androgens

- Downregulate and/or block androgen receptors in CNS
  - Leads to sexual dysfunction
- 5α reductase inhibitors prevent T to DHT conversion
  - Up to 5% experience sexual dysfunction with 5 mg
  - 1 mg doses (propecia) should not cause sexual dysfunction
  - ??? Permanent sexual dysfunction
- AR blockers & LHRH agonist/antagonists
  - ED and sexual dysfunction in most if not all men

Noteworthy Substances
- Digoxin
- Statins
  - ED related to underlying pathology, not statin
  - Atorvastatin may have positive effects
- Cimetidine
- Tobacco
  - 20 pack years
- Alcohol
  - Moderated use improves erectile function
  - Uncontrolled use acts as a sedative
    - Transient ED
    - Decreased libido

GU/GI related
- Prostate related
  - BPH associated with ED
    - Treatment of BPH medically may improve ED and vice versa
      - Cialis 5 mg daily
  - Prostatectomy
    - Erectile recovery 50% over two years
  - Penile rehabilitation
  - TURP
    - Bipolar versus monopolar
- Abdomino Perineal Resection
  - Damage to pelvic plexus

Clinical Approach
- Goal-directed approach
  - Ascertain goals of patient, and then formulate plan
- Partner involvement
- CV risk assessment
  - High risk – unstable angina, arrhythmia, uncontrolled HTN, recent MI
- Specialty referral
  - Cardiology, endocrinology, urology, vascular medicine and psychologist
  - Follow-up care

History
- Sexual history
- SEP questions
- IIEF forms
- General health
  - Medical
  - Surgical
- Medications
- Smoking history
- Social history
- Psychological assessment

Physical
- BP, pulses
- Thyroid
- Testes
  - Size, masses
- Neurological exam
- Penis
- Prostate

Duplex Ultrasound
- Relatively non-invasive, inexpensive
- Dynamic information
- Requires induced erection
  - PSV and EDV
    - Assess arterial inflow, venous outflow and anatomic abnormality/variation
- Operator dependent
Unnecessary Studies
- Penile plethysmography
- Cavernosometry
- Penile Angiography (unless young man with trauma)
- Smooth muscle content studies
- Penile MRI

Laboratory Studies
- CBC
- BMP
- LFTs
- Testosterone (HPG axis if suspicion of hypogonadism)
- Lipid panel (for CV risk assessment and need for statins)

Treatment of ED
- Goal directed approach
- Lifestyle Modifications
- Medication Change
- PDE5 Inhibitors
  - Intracavernosal Injection
  - Penile Pump
  - MUSE
  - Low intensity SWT
  - Penile revascularization
  - Penile prosthesis

Lifestyle Modifications
- Is ED reversible or preventable???
  - Yes ------- Maybe
- Tobacco Use
  - Yes more than no
- Exercise
  - Yes for sedentary individuals
- Obesity
  - Yes for obese men with moderate ED
  - Mediterranean diet for men with MetS
- Bicycle Riding
  - Changing bicycle saddle to no-nose

Risk Factor Treatment
- Hormonal Therapy
  - T replacement
    - Will more likely assist in arousal
    - Inconsistent evidence for monotherapy
  - Prolactin and thyroid disorders
    - Also inconsistent evidence for monotherapy
- Medication change
- Psychosexual treatment
PDE5 Inhibitors

- **Sildenafil** - First PDE 5 inhibitor in widespread use (1998)
  - Revolutionized ED treatment
- **Vardenafil** (Levitra) and **Tadalafil** (Cialis) released on the market in 2003
- **Vardenafil HCL** (Staxyn) orally disintegrating tablet
- **Avanafil** (Stendra) released in 2012
- All PDE 5 inhibitors are similar

### Comparison of Three PDE5 Inhibitors Currently Available in the United States

<table>
<thead>
<tr>
<th>Sildenafil</th>
<th>Vardenafil</th>
<th>Tadalafil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset (hrs)</td>
<td>1</td>
<td>0.5-1</td>
</tr>
<tr>
<td>Peak (hrs)</td>
<td>2</td>
<td>0.5-1</td>
</tr>
<tr>
<td>Half-life (hr)</td>
<td>3-4</td>
<td>6-7</td>
</tr>
<tr>
<td>Availability</td>
<td>Oral</td>
<td>Oral</td>
</tr>
<tr>
<td>Side effects</td>
<td>No headache, Priapism, Headache, Nausea</td>
<td>No headache, Priapism, Headache, Nausea</td>
</tr>
<tr>
<td>Dosage</td>
<td>25, 50, 100 mg</td>
<td>10, 20, 40 mg</td>
</tr>
<tr>
<td>Precipitated, nausea, vomiting, diarrhea</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Backache, headache</td>
<td>Rare</td>
<td>Rare</td>
</tr>
<tr>
<td>Fainting, rhinitis</td>
<td>Rare</td>
<td>Rare</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Cardiovascular with antidiabetes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Cardiovascular with diabetes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

### Instructions

- Plan Ahead
  - Viagra 1hr
  - Levitra 30-60m
  - Cialis 30-120m
  - Stendra 15-30m
- Avoid fatty foods
- Foreplay required
- Meds augment not induce erections
- Do not increase dose over maximum recommended amount
- Avoid nitrates
- No antidote to PDE5I/nitrate combination

### Common Side Effects

- Headache, Facial Flushing, Stuffy Nose, Upset Stomach, Dizziness

### Some Cautions

- With alpha-blockers: Generally, you should be stable on your alpha-blocker therapy before using an oral medication
  - May use sildenafil 25mg simultaneously or 50-100mg 4 hours later
- Should not use these medications if sex is inadvisable because of cardiovascular status
  - Past marketing data however states that medications themselves do not pre-dispose to MI
- **NAION**
- **Liver Failure**

### Penile Pump or VED

- 70% effective treatment
  - However satisfaction rates are half
- No sustainable effect on ED
- Most effective use with maintaining corporal elasticity
- Contraindicated in patients with bleeding diatheses

**Penile Erection**

- NO = nitric oxide
- NANC = nonadrenergic, noncholinergic neurons
- PDE5 = phosphodiesterase type 5

Vacuum Erection Devices

**Most Common Side Effects**
- Blocked ejaculation
- Bruising of penis
- Penile discomfort
- Penile numbness or coldness

**Most Common Reasons for Discontinuation**
- Lack of spontaneity, unnatural erections, lack of efficacy, difficult mechanics, penile bruising

Intraurethral Suppositories

**Most Common Side Effects**
- Penile pain
- Urethral pain or burning

**Most Common Reasons for Discontinuation**
- Insufficient erections, penile/urethral pain

Intraurethral Suppositories

**Alprostadil**
- Increases cAMP
- Small pellet that is inserted into the urethra
- Pellet dissolves and erection occurs
- 50% respond
  - 70% can actually have intercourse after

Intracavernosal Injection Therapy

**Many formulations**
- EDEX, Caverject (PGE1)
- Bimix (Papaverine, phentolamine)
- Trimix (PGE1, Pap, Phent)
- Quadmix

**Very successful in neurogenic population**

Penile Injection Therapy

**Some Advantages**
- Effective
- On-set of erection within 5-20 minutes

**Some Disadvantages**
- Risk of erection lasting 4 hours or more (priapism)
- Possible pain or bleeding
- Training required
- Can cause Peyronie’s disease
- Poor long-term tolerability
- Fear of sticking needle in penis
- Can be expensive

Penile Prosthetics

**Developed in 1970’s**
- Placed under general anesthetic
- Only proven successful option after medical therapy has failed

http://www.caverject.com/AboutCI.aspx, downloaded 2/15/11
Penile Implants

Long-term solution for ED

- On the market for over 40 years
- Over 300,000 implants to date
- High patient and partner satisfaction
- Entirely concealed within the body
- Provides "on demand", sustained erections that are similar to normal function

Types of Penile Implants

- 3-piece inflatable implants (pump, cylinders, reservoir)
- 2-piece inflatable implants (pump, cylinders)
- 1-piece malleable implants (cylinders)

Most Common Side Effects

- Post-operative genital pain
- Mechanical malfunction, including auto-inflation
- Infection

Most Common Reasons for Discontinuation

- Repeat surgery due to mechanical malfunction or infection

Implants are Highly Recommended

- 92% of patients would recommend to others
- 90% of partners would recommend to others

Special/Investigational Therapies

- Penile revascularization
  - Related to perineal trauma
- Angiography with stenting
  - Preliminary data promising in PDE5i non responders
- LI SWT
  - May induce neo-vascularization of cavernosal tissue and reverse ED

END

Questions???????