

Intracavernosal Penile (ICP) Injections

Nelson Vergel



This information is not a recommendation nor is it intended to provide direction regarding diagnoses, treatments, or potential outcomes. Any interpretation of this information is the opinion of Clinic Optimizers and should be used by the prescriber at his/her discretion.



Intracavernosal Penile (ICP) Injections

Clinical Management Booklet

This information is not a recommendation nor is it intended to provide direction regarding diagnoses, treatments, or potential outcomes. Any interpretation of this information is the opinion of Clinic Optimizers and should be used by the prescriber at his/her discretion.

Intracavernosal Penile Injections

- Tri-Mix is a mixture of Papaverine, Phentolamine, and Prostaglandin
- Only offered by compounding pharmacies
- More effective in smaller doses than if these compounds were used individually
- 503B Outsourcing Facilities who specialize in ED offer numerous strengths and combinations that include aprostadil
- **Lyophilized** version preferred for longer shelf-life (lower cost to the patient)



Lyophilization, also known as freeze-drying, is a process used for preserving biological material by removing the water from the sample, which involves first freezing the sample and then drying it, under a vacuum, at very low temperatures. Lyophilized samples may be stored much longer than untreated samples

ED Treatment Options

- Oral medications – Phosphodiesterase Type 5 Inhibitors (PDE-5): Viagra (sildenafil), Levitra (vardenafil), Cialis (tadalafil), and Stendra (avanafil).
- Urethral suppositories (MUSE)
- Injection therapy - Caverject, Trimix, Bimix, Quadmix
- Vacuum constriction device
- Surgery (implant)
- Sex therapy

ED Medication Profiles

Medication	Viagra (sildenafil)	Levitra (vardenafil)	Cialis (tadalafil)	Stendra (avanafil)
Type	PDE-5 Inhibitor	PDE-5 Inhibitor	PDE-5 Inhibitor	PDE-5 Inhibitor
Dose	25-100 mg	5-20 mg	5-20 mg	50-200 mg
Peak Time	1 hour	42-54 minutes	2 hours	15-30 minutes
Gone from body	8-12 hours	8-12 hours	36 hours	8-12 hours
Contra-indicated	Nitrates	Nitrates	Nitrates	Nitrates
FDA Approval	3/29/98	8/20/03	2/02/04	4/1/12
Effects of eating and drinking	No food or drink 1-2 hours before	Not effected by food or alcohol	Not effected by food or alcohol	Not effected by food or alcohol
Side Effects	Headache, flushing, nasal congestion, abnormal vision, heartburn, bloodshot eyes	Headache, flushing, nasal congestion, abnormal vision, heartburn, bloodshot eyes	Headache, flushing, nasal congestion, heartburn, bloodshot eyes, backache, leg cramps	Headache, flushing, nasal congestion, heartburn, bloodshot eyes, backache, leg cramps
Other	For many patients the key negatives are shorter half-life (than Cialis) and less effective when taken with fatty meal.	Greater selectivity (and thus usually fewer side effects) than Cialis. Slower to take effect when taken with fatty meal.	Sid effects can linger for 3 days	Greater selectivity (and thus usually fewer side effects) than Cialis. Slower to take effect when taken with fatty meal.

38% of Men Do Not Respond Well to Oral ED Medications

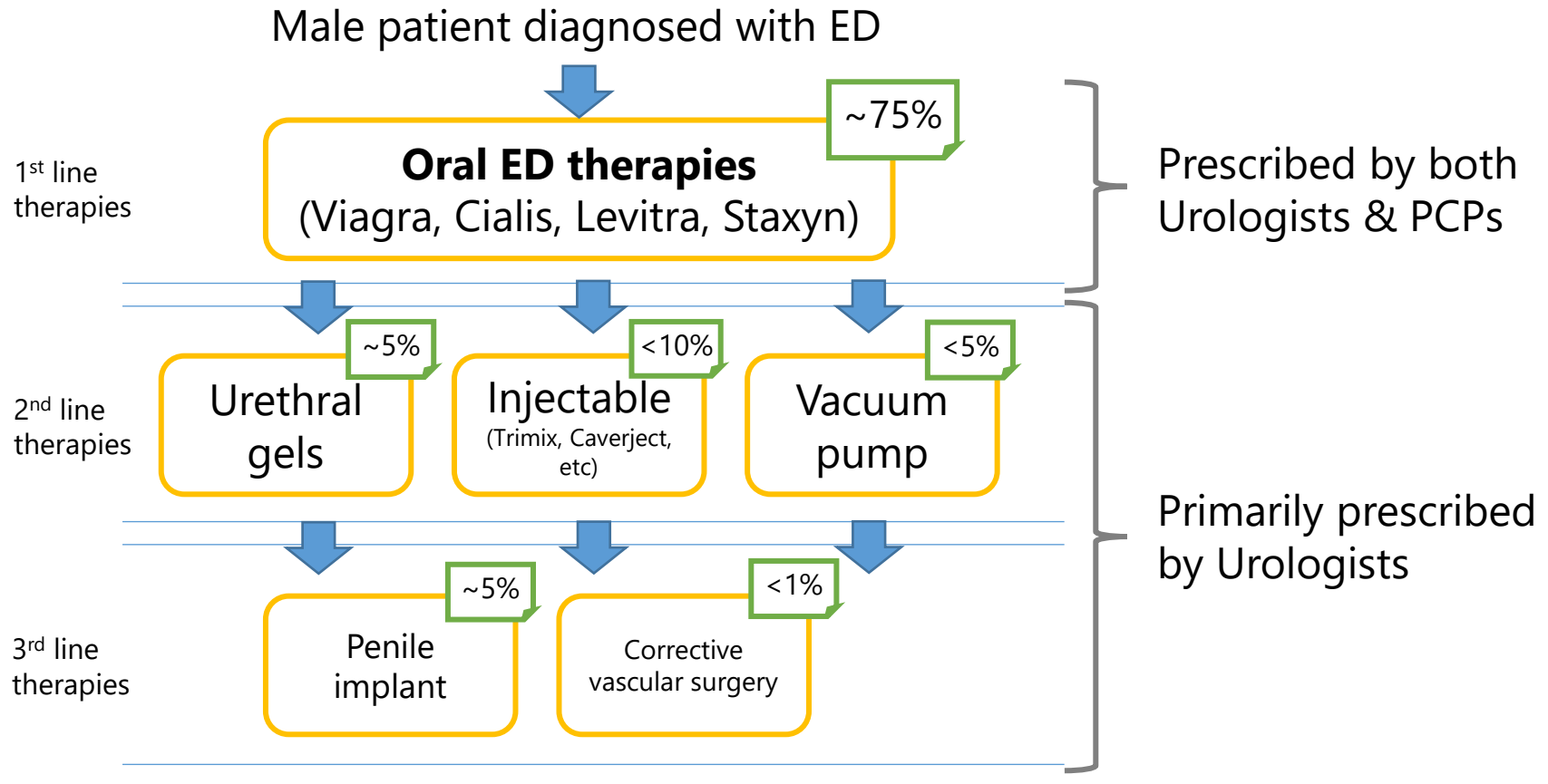
Most important considerations when starting ED medications:

Variables	Av. Rank	No. Pts	Importance Score	Importance Rank
Cure	1.57	30	2.67	1
Pleasure	2.63	40	3.35	2
Partner Satisfaction	2.04	27	3.85	3
Reproduction	2.16	19	5.80	4
Naturalness	2.13	16	6.79	5
Control	2.57	14	9.36	6
Duration	2.33	12	9.90	7
Spontaneity	2.78	9	15.75	8
Penetration	2.00	6	17.00	9
Times/wk.	2.75	8	17.53	10

Most important reasons for discontinuing ED medications:

Reasons for discontinuation (quantitative data)	%
Non-effectiveness	38.0
Erection recovery	22.3
Concerns about cardiovascular safety of PDE5	15.7
Cost	13.7
Secondary effects	12.3
Lack of sexual opportunity	11.5
Other treatments	9.3
Lack of spontaneity	8.7
Fear of drug dependence	6.0
Decreased sexual interest	5.4
Constrain/embarrassment in obtaining the drug	2.7

Current ED Treatment Approaches



Source: Adapted from American Urologic Association Treatment of ED Guidelines, emedicine.com, L.E.K. Consulting Interviews and analysis.

Penile Injection Therapy

- Smooth muscle – relaxing medication injected directly into the penis
- Insulin needle and syringe
- Drug dosage - .3 cc or less
- 5-15 minute response time
- 30 minute to 2 hour duration
- Possible side effects
 - Pain on administration
 - Prolonged erections (Priapism)
 - Hematomas (Bruising- specially in men taking aspirin and blood thinners)
 - Scarring (Poor injection technique)

Penile Injection Therapy

Caverject, Edex, Bi/Tri/Quad-Mix

- Mechanism of action: smooth muscle vasodilator
- Monotherapy (Alprostadil) (Muse) or combination of 2 (Caverject and BiMIX) or 3 agents (Papaverine + Phentolamine + Alprostadil)
- Administration: 10, 20, 40ug
- Inject directly into corporeal bodies of the penis
- Results: 70%-90%
- Dropout rates: 25%-60%
- Side effects: pain (36%), priapism (4%), fibrosis, bruising

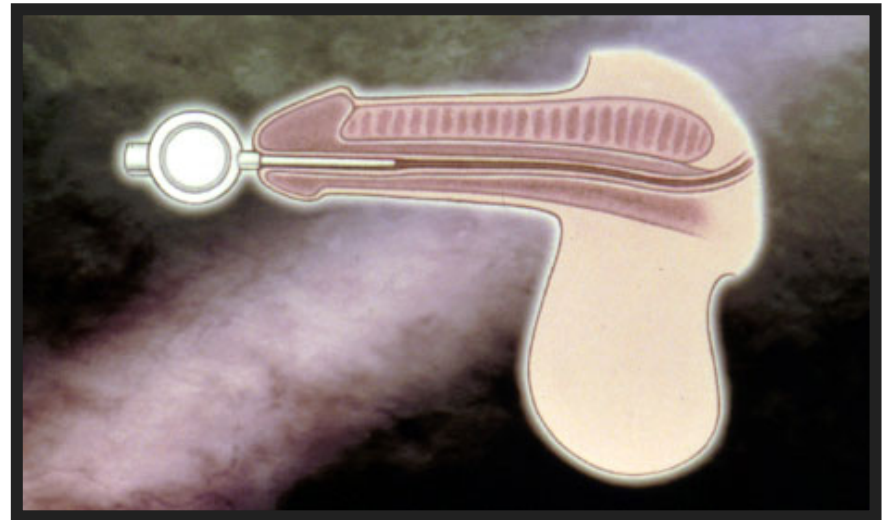
Alprostadil Brand Names

- Caverject: Direct injection of papaverine/alprostadil.
- MUSE: alprostadil alone is produced in intraurethral pellets; tiny tablets that can be inserted down into the opening of the penis with the aid of a minute insertion stick.
- “TriMix”: alprostadil+ papaverine+phentolamine

Caverject



Transurethral Medication: MUSE



ED Rx Price Comparison

Medication	Cost Per Dose
Viagra 100mg/Generic	\$13.70/\$11.20
MUSE 1000µg	\$48.53
Intraurethral Gel (Muse) 250/0.3/0.2	\$24.98***
Caverject 20ug	\$40.56*
Tri-Mix	\$3.94**

*Caverject is a single use vial so product. Manufacturer recommends once mixed product to be discarded regardless what dose is used

** Tri-Mix dose used here is 40 units (0.4ml). In a 10ml vial a person would get 24 doses

***Need to order 6 doses to get this price

ICP Formulation Components

- **Papaverine** is a smooth muscle relaxant and vasodilator. Experiments carried out in dogs display papaverine's ability to decrease the resistance to arterial inflow while also increasing the resistance to venous outflow
- **Phentolamine** is classified as an Alpha-Adrenoceptor Antagonist. Noradrenaline effects the smooth muscle tone of the penile tissues by keeping the corpora cavernosa in a contracted state.
- **Prostaglandin E1 (Alprostadil)** binds with PGE receptors, and the resultant relaxation response in the smooth muscle is mediated by cAMP.

Long-term Stability of Trimix

- Alprostadil (Prostaglandin E1) is the least stable of the drug components at room temperature and under refrigeration.
- About 8% alprostadil loss occurred in five days at room temperature; under refrigeration losses of about 6% and 11% occurred after 1 and 2 months, respectively.
- Frozen at -20 deg C and -70 deg C, less than 5% loss of any of the drug components occurred in 6 months.
- A beyond-use date of 6 months when stored frozen at -20 deg C and 1 month when stored refrigerated at 4 deg C is appropriate for batches of the injection that have passed sterility testing.
- Room temperature exposure should be limited, and the vial should be returned to refrigeration as soon as possible.

Trissel LA, Zhang Y. Long-term stability of trimix: a three-drug injection used to treat erectile dysfunction. Int J Pharm Compd. 2004;8(3):231-235.

Beyond Trimix: Other Formulas

- A small percentage of men who do not respond completely with Trimix may be prescribed the **Super Trimix** (same concentration of papaverine as regular Trimix but double the concentration of phentolamine and prostaglandin E1) or the quad mixture (**Quad-Mix**) of phentolamine, papaverine, prostaglandin E1 and atropine.
- Others who may have pain associated with a Trimix injection use a bi mixture (**Bi-Mix**) of phentolamine and papaverine. The starting injection volume is the same for every formulation (0.05 to 0.3 mls).

ICP Indication and Formulas

BiMix: A combination of Papaverine & Phentolamine

Super BiMix: A highly concentrated version of the standard BiMix Injection

TriMix: A combination of Papaverine, Phentolamine & Prostaglandin E1

Super TriMix: A highly concentrated version of the standard TriMix Injection

QuadMix: A combination of Papaverine, Phentolamine, Prostaglandin E1 & Atropine

Super QuadMix: A highly concentrated version of the standard QuadMix Injection

ICP Indication and Formulas

ICP injection products are commonly prescribed for:

- Treatment of erectile dysfunction in males

Multiple strength combinations of ICP Injections are available:

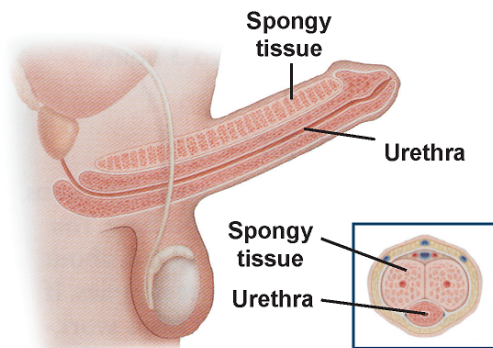
- **Bi-Mix** 5 mL vial. Papaverine HCl 30mg/mL, Phentolamine Mesylate 1mg/mL
- **Super Bi-Mix**: 5 mL vial. Papaverine HCl 30mg/mL, Phentolamine Mesylate 2mg/mL
- **Trimix**: 5 mL vial. Papaverine 30mg/mL, Phentolamine Mesylate 1mg/mL, Prostaglandin E1 10mcg/mL
- **Super Trimix**: 5 mL vial. Papaverine 30mg/mL, Phentolamine Mesylate 2mg/mL, Prostaglandin E1 20mcg/mL
- **Quad-Mix**: 5 mL vial. Papaverine HCl 30mg/mL, Phentolamine Mesylate 2mg/mL, Prostaglandin E1 20mcg/mL, Atropine Sulfate 200mcg/mL
- **Super Quadmix**: 5 mL vial. Papaverine HCl 30mg/mL, Phentolamine Mesylate 4mg/mL, Prostaglandin E1 40mcg/mL, Atropine Sulfate 400mcg/mL
- **Priapism Rx**: 2mL pre-diluted Phenylephrine HCl 0.1% (1mg/mL) vials.

ICP Dosage

- **Starting dose:** Injection of 0.05-.3 cc of reconstituted Trimix, Super Trimix or Quad-Mix solution (29-30 gauge 1½ inch) as needed before sexual activity.
- Priapism rescue: If erection lasts more than 3 hours, inject phenylephrine at 0.5mL every 5 minutes up to 2mL until detumescence (soft penis) start occurring
- **Pharmacologic Category:** Anti-erectile dysfunction preparation: vasodilator, prostaglandin, & alpha-adrenergic receptor antagonist

Anatomy of an Erection

To produce an erection, the brain, nerves, blood vessels, and hormones all have to work together. The result is extra blood flowing into the penis and staying there until after orgasm (climax). The penis is made up of spongy tissue filled with blood vessels. When stimulated, the blood vessels relax and expand. This brings more blood to the penis. The tissue swells and becomes firm enough for sex.



When There's a Problem

If the blood vessels don't expand, extra blood can't go to the tissue, so the penis stays soft. This problem is called erectile dysfunction (ED). It can make intercourse frustrating or even impossible. Emotional issues can lead to ED, but the cause is often physical. Common causes include other health problems and side effects of medications.

Injections Can Help

Medications used for self injection relax penile blood vessels. Blood can then flow freely into the penis and cause an erection. Steps for self injection are described inside this brochure.

A Satisfying Sex Life

Penile self-injection is a simple technique. But it may cause a major change in your sex life. Some men even find that self injection leads to an increase in natural erections. If you have questions or concerns about self-injection or ED, talk to your healthcare provider.



PENILE SELF-INJECTION

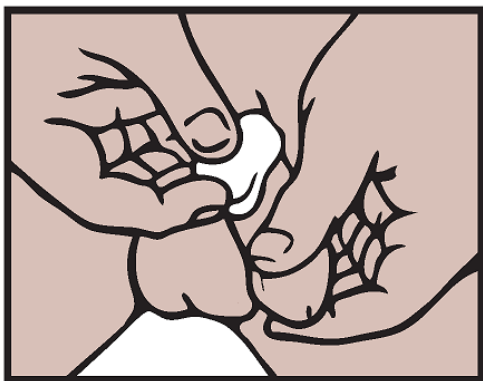


Treatment For Erectile Dysfunction

Sample Steps to Erection

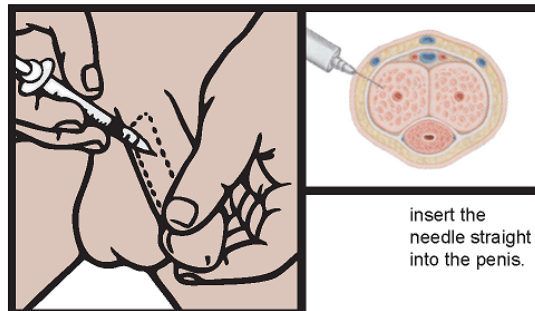
Self injection is a good option for many men with erectile dysfunction (ED). A tiny needle is used to inject medication into the penis. This helps your penis become hard and stay that way long enough for sex. Sex and orgasm will feel as good as always. You may be nervous about doing self injection at first, but with practice it will get easier. Your healthcare provider will show you how to do self injection the first time. The simple steps are outlined in this brochure.

Preparing for Injection



1. Wash your hands well with soap and water.
2. Prepare the medication (if needed).
3. Sit or stand in a comfortable position in a warm, well-lit room. If you need to, sit or stand in front of a mirror.
4. Find an injection site on one side of your penis, in a place with no visible veins. (Don't inject into the top, bottom, or head of the penis.)
5. Clean the injection site with an alcohol swab. Grasp the head of your penis firmly with your thumb and forefinger (don't just pinch the skin). Stretch the penis so the skin on the shaft is taut.

Injecting the Medication



The injection site can be any part of the shaded area

1. Rest your penis against your inner thigh and pull it gently toward your knee. Don't twist or rotate it. This way you'll be sure to inject the medication into the spot you chose and cleaned before.
2. Hold the syringe between your thumb and fingers, like you're holding a pen. Rest your forearm on your thigh for support.
3. Insert the needle at a 90-degree angle with the shaft near the base of the penis. Do this quickly to reduce discomfort. (The needle should go in easily. If it doesn't, stop right away)
4. Move your thumb to the plunger. Press down to inject the medication, counting to 5.
5. Remove the needle and dispose of it safely.

Gaining an Erection

1. Apply pressure to the injection site for a few minutes. This prevents swelling and bruising and helps spread the medication.
2. Stand up. This may help your erection develop. Foreplay often helps, too.
3. Your penis should become firm within 10 to 20 minutes. The erection will last long enough for sex, and maybe longer.

Notes About Self-Injection

- You may feel a mild burning during injection. This is okay. But if you feel pressure or severe pain, stop the injection. There may be a problem with the injection site.
- Only inject the medication on the side of your penis. It may not work if injected elsewhere.
- To prevent scarring, inject in a different spot each time.
- Don't use this treatment if you have a bleeding disorder or any risk of infection.
- Get medical help right away if your erection lasts longer than 2 to 3 hours.

Work with Your Doctor

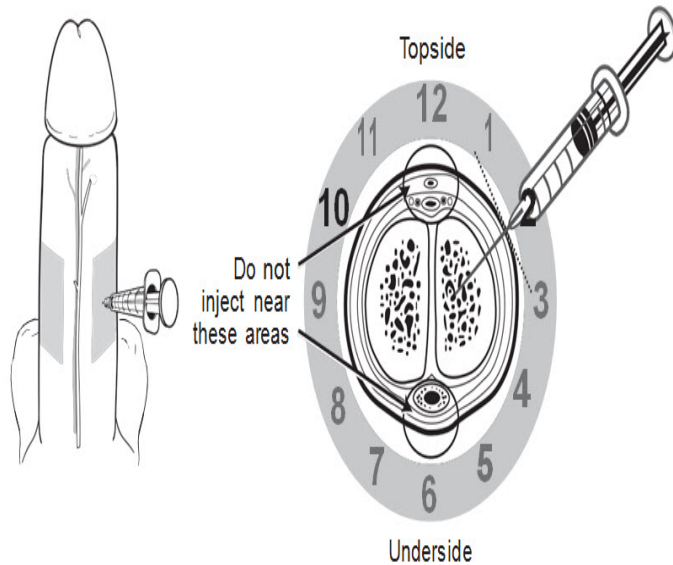
Ask how often you can safely repeat injections, as well as any other questions you have. You and your healthcare provider will talk about follow up exams and how to get supplies. If the medication doesn't work or stops working over time, tell your healthcare provider.



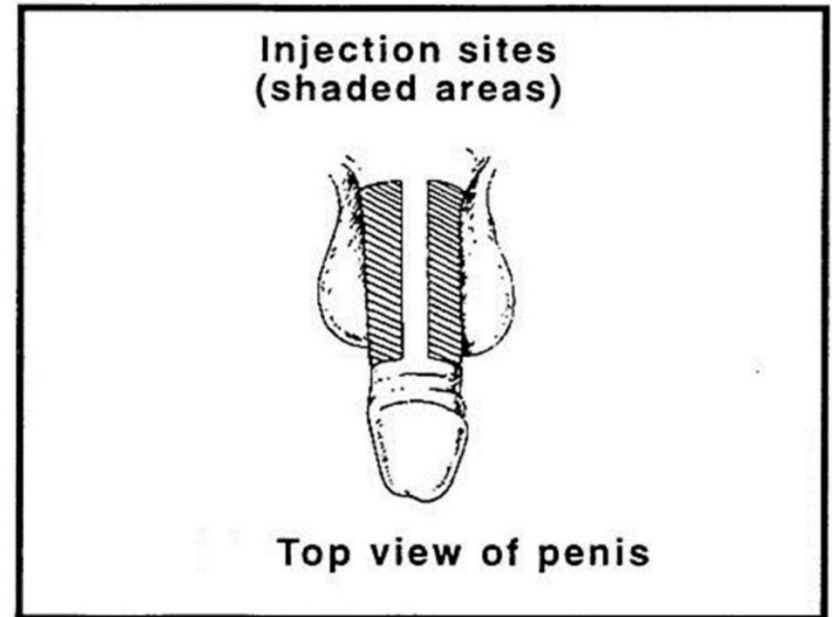
Call Your Doctor If You Have:

- An erection that lasts longer than 2 to 3 hours
- Bleeding or bruising
- Severe pain
- Scarring or curvature of the penis

ICP Injection Site



Choosing an injection site



Trimix Injection Video



[About](#) [News and Health Articles](#) [813-445-7342](#)

[Become a Patient](#)

[Patient Login](#)



[Primary
Care](#)

[Men's
Health](#)

[Women's
Health](#)

[Aesthetics](#)

[Weight
Management](#)

[IV & Injectable
Nutrition](#)

[Thyroid Therapy](#)

[Peptide Therapy](#)

If you have been prescribed Trimix or any other ICP medication, it is important to read all of the information prior to using. These medications are very powerful and, if not used correctly, they can lead to prolonged erection (severe priapism) resulting in permanent damage to the penis.

If you follow your doctor's instructions and understand the information below, then Trimix and ICP medications are very safe to use.

All Defy Medical patients prescribed Trimix and similar ICP medications will be given unlimited medical support and assistance with the administration of your medication. Our medical director and team want to ensure safety for every patient under our care. Please do not hesitate to contact the clinic for assistance with your medication.

Important Directions

1. Start small with your dosage. For Bimix, Trimix and Quadmix, we recommend starting at 0.05 ml (1/20th of a milliliter) and increasing slowly until an erection is sustained. It is much better to require an additional injection than to take too much and require medical care for priapism.
2. To prevent damage to the penis, Defy Medical requires patients to use only a 29-gauge ½ inch needle when using Trimix. Using a smaller needle increases the risk of bending the needle during injection, which will damage the tissue over time. A shorter needle will not deposit the medication deeply enough, which is why a ½ inch length is recommended.
3. Please review ALL of the following prior to use:
 - [Insert from the Pharmacy](#)
 - [Trimix Injection Directions](#)
 - [Trimix Frequently Asked Questions](#)
 - [Defy Medical's instructional video](#) (warning: this video contains nudity for the purpose of medical instruction).



ICP Common Questions

How is the correct dosage determined? How do I know when I have the right dose?

Dose consists of both the strength of the medication and the amount used. With the appropriate strength and amount of drug as determined by a physician (usually less than 0.5 cc), erections usually occur in 5 to 10 minutes, last for approximately 30 minutes to an hour, and become more rigid if sexual stimulation occurs.

Is sexual stimulation required for an erection? Can I use less medication if I have more stimulation?

Stimulation is not required but may speed things up a bit. You may be able to use less medication with stimulation. Masturbating right after applying pressure on the injection site may also help speed up the effect and better distribute the product throughout your penis.

Sometimes a dose that has worked fine before, produces no erection. I'm sure I injected in the right place. What happened?

You were probably in the wrong place or too deep or too shallow, or the medication had expired (lost its effectiveness).

My instructions say not to inject more than twice a week. What's the reason for not injecting every day, for example?

Injecting into the penis frequently may cause scarring.

Does the medication lose potency over time even if stored correctly?

Yes, after about six months the medication will be less effective.

Will I develop a tolerance over time requiring an increasing dose?

This occurs infrequently but if it does, your physician may have to readjust the dosage of medication.

HOW TO PREVENT PRIAPISM CAUSED BY TRIMIX AND OTHER ICPs

Priapism is an involuntary erection which lasts more than 4 hours and is unrelieved by ejaculation. This condition is a true urological emergency and early treatment allows the best chance for functional recovery. It can cause penile fibrosis, unwanted curvature (Peyronie's), and worsen ED.

- NEVER take Trimix or any ICP injection within same 24hr period as Viagra/Cialis/Levitra or other ED meds.
- Start LOW and go SLOW with your dose. Never start higher than 0.05-0.12ml (5-12 units on syringe) for the FIRST injection. Then gradually increase from there for optimal results.
- Do not inject twice within 30 minutes.

Over-The-Counter Medications for Priapism

- **Sudafed** (pseudoephedrine) is an oral decongestant available without a prescription but “behind the counter”, meaning that you have to ask the pharmacist to get it for you. Do not use other versions of Sudafed that are available on the shelf since they do not have pseudoephedrine. Chew on a 30 or 60 mg tablet with water if erection has lasted more than 2 hours. Effects should start to be noticed within 30 minutes. Be aware that this drug will disrupt your sleep or may keep you awake for hours. Having sleep aids at hand can help if you are taking Sudafed at night-time. 60mg-150mg orally.
- **Do not use Sudafed** if you have used a MAO inhibitor such as furazolidone (Furoxone), isocarboxazid (Marplan), phenelzine (Nardil), rasagiline (Azilect), selegiline (Eldepryl, Emsam, Zelapar), or tranylcypromine (Parnate) during the previous 14 days.
- **Benadryl** - chew 25mg-50mg orally

Priapism Antidote Injection

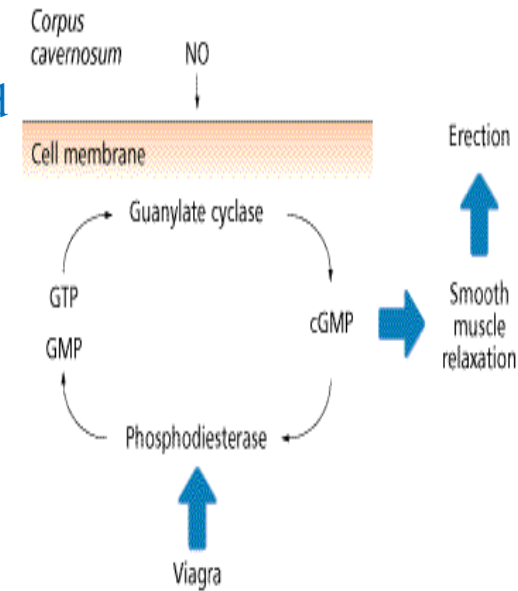
- **Compounded Phenylephrine Injection:**
potent vasoconstrictor
- 2mL pre-diluted Phenylephrine HCl 0.1% (1mg/mL) vials .
- Typical protocol is 0.5mL every 5 minutes up to 2mL until detumescence (soft penis) starts. Phenylephrine use has potential cardiovascular side-effects and it is recommended that blood pressure and pulse are monitored every 15 minutes for an hour after the injection. This is particularly important in older men with existing cardiovascular diseases.
- If these do not work and erection has been present for 4hrs and/or is painful then immediately visit the ER for treatment.



Supplemental Information

Physiological Mechanisms of Erections

- Stimulation of penile shaft by the nervous system leads to the secretion of nitric oxide (NO), causing the creation of cyclic guanosine monophosphate (cGMP) which functions to relax blood vessels (vasodilatation) so erectile tissues in the corpus cavernosa can fill with blood, and subsequently cause a penile erection.
- Phosphodiesterase type 5 (PDE5) is always present in the penis and functions to destroy cyclic GMP, causing vasoconstriction of erectile tissues and resulting in the loss of erection. In normal males, the loss of an erection occurs after orgasm and ejaculation of sperm.



An Erection Requires a Coordinated Interaction of Multiple Organ Systems

- Psychological
- Hormonal
- Vascular
- Neurologic

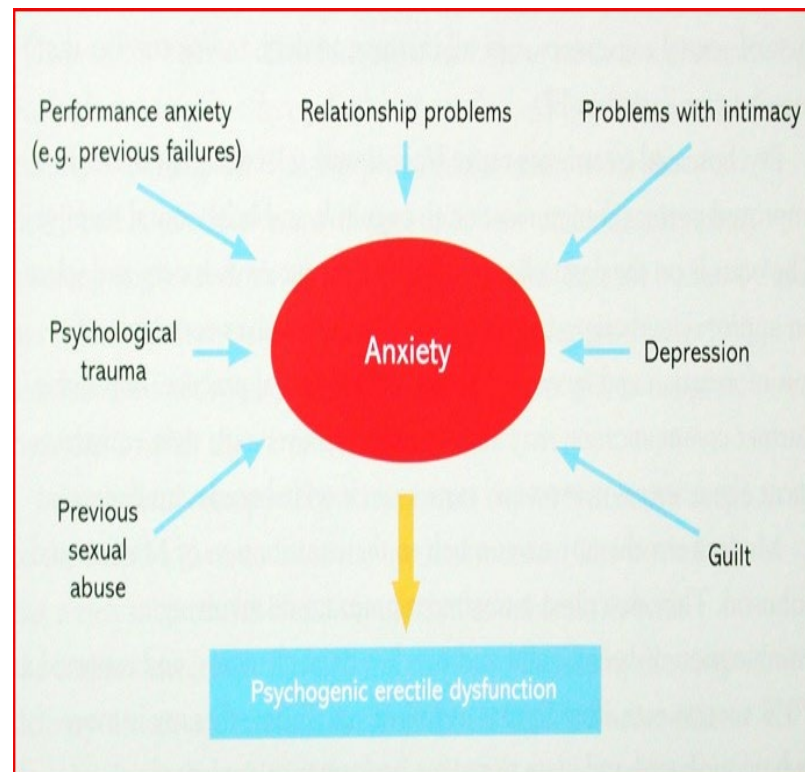
Clues Differentiating Psychogenic From Organic Causes of ED

Psychogenic

- Sudden onset
- Situational
- Normal waking and nocturnal erections
- Normal erection with masturbation
- Relationship problems, life event
- Anxiety, fear, depression

Organic

- Gradual onset, All situations
- Reduced or absent waking and nocturnal erections
- No erection with masturbation
- Penile pain.



Erectile Dysfunction (ED) Basics

- ED is defined as the inability to achieve or maintain an erection sufficient for satisfactory sexual performance
- Prevalence increases with age, cardiovascular disease, diabetes mellitus, and hyperlipidemia.
- Diabetes is the most common cause of sexual dysfunction in men. It has been estimated that up to 50-60 % of diabetic men have erectile dysfunction.
- The primary risk factors are smoking, lack of physical exercise and obesity.
- Erectile dysfunction is strongly correlated with depressive symptoms and negatively impacts a man's quality of life.
- The U.S. pharmaceutical industry for treatment of erectile dysfunction is worth over 6 billion dollars

Prevalence of ED

- Prevalence of erectile dysfunction range from 2% to 9% in men between the ages of 40 and 49 years.
- It then increases to 20–40% in men aged 60–69 years.
- In men older than 70 years, prevalence of erectile dysfunction ranges from 50% to 100%.
- Moreover, the worldwide prevalence of erectile dysfunction has been predicted to reach 322 million cases by the year 2025.

Feldman Ha, J Urol 1994; 151:54-61

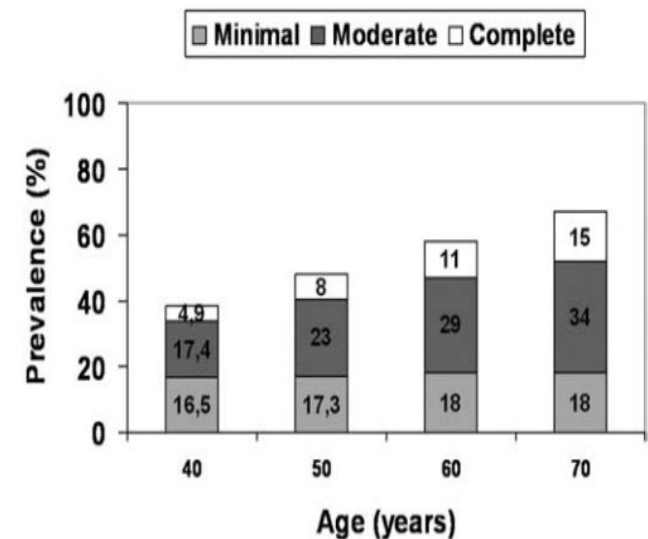
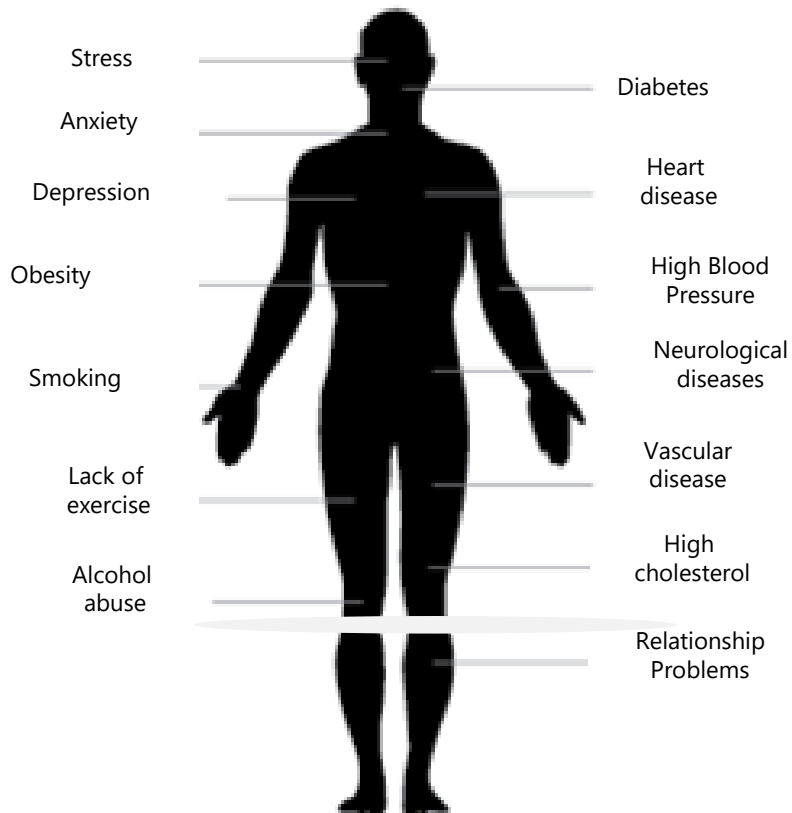


Figure 1. Prevalence and severity of erectile dysfunction in the Massachusetts Male Aging Study.

Causes of Erectile Dysfunction



Risk Factors

Risk factors	Examples
Aging	
Medication	Antihypertensives, antidepressants, digoxin, spironolactone
Lifestyle	Smoking, obesity, sedentary lifestyle, alcohol and drug abuse
Psychological disorders	Depression, performance anxiety or stress
Vascular disorders	Atherosclerosis, ischemic heart disease, peripheral vascular disease
Neurological disease	Stroke, multiple sclerosis, spinal cord injury, pelvic trauma or prostate surgery
Endocrine abnormalities	Low testosterone, high prolactin
Chronic illness	Hypertension, dyslipidemia, diabetes mellitus, cardiovascular disease, chronic renal failure, heart failure, chronic obstructive pulmonary disease

Papaverine

- A drug that causes blood vessels to expand (vasodilator); it produces an erection by allowing for increased blood flow to the penis. Papaverine interacts with adenylate cyclase resulting in increased cyclic adenosine monophosphate (cAMP) production, ultimately resulting in increased erectile capacity by relaxation of penile smooth muscle (3).
- This drug was one of the first effective therapies for erectile dysfunction administered by penile injection (4).
- Papaverine works by inhibiting phosphodiesterase nonspecifically, there are also multiple other mechanisms by which this drug acts to improve erectile capacity (5).

Papaverine- 2

- The current body of medical literature has not established the predominant mechanism by which papaverine works. The multi-mechanistic manner by which this drug acts may be concentration dependent. Experimental data, performed in-vitro, displays papaverine acting to relax the penile arteries, the cavernosal sinusoids, and the penile veins (6).
- Experiments carried out in dogs display papaverine's ability to decrease the resistance to arterial inflow while also increasing the resistance to venous outflow (7).
- Papaverine's ability to decrease resistance to venous outflow has been replicated in clinical studies (8).
- A veno-occlusive mechanism may be responsible for the aforementioned findings

Biweekly intracavernous administration of papaverine for erectile dysfunction. (9)

- **Participants:** 50 patients age 40 to 70 years old
- **Administration:** intracavernosal injection at base of the penis
- **Dosage:** 60 mg papaverine in 5 ml saline every 2 weeks
- **Results:** Erection of 80% or more of normal was achieved by all but one patient, improves sexual potency

Medical treatment of impotence with papaverine and phentolamine intracavernosal injection. (10)

- **Participants:** 20 patients age 32 to 72 years old
- **Administration:** intracavernosal injection
- **Dosage:** 30 mg papaverine and phentolamine 1 mg
- **Results:** Response with erection in 20- 30 minutes, phentolamine and papaverine produced an erection sufficient for intercourse in 18 of the 20 subjects

Treatment of impotence by intrapenile injections of papaverine and phenoxybenzamine: a double blind, controlled trial. (11)

- **Participants:** 39 patients age 27 to 67 years old
- **Administration:** intracavernosal injection
- **Dosage:** 60 mg Papaverine in 10 ml saline
- **Results:** 35% full restoration of erectile capacity
65% partial restoration of erectile capacity

Evaluating erectile dysfunction: oral sildenafil versus intracavernosal injection of papaverine. (12)

- **Participants:** 39 patients age 21 to 65 years old
- **Administration:** intracavernosal injection
- **Dosage:** 30 mg papaverine
- **Results:** Papaverine improved length and circumference papaverine is effective as injection therapy for erectile dysfunction

Phentolamine

- When injected into the penis, it induces an erection by relaxing and dilating the blood vessels of the penis, as well as by elevating cardiac output.
- Phentolamine is classified as an Alpha-Adrenoceptor Antagonist. Noradrenaline effects the smooth muscle tone of the penile tissues by keeping the corpora cavernosa in a contracted state.
- By blocking the functional noradrenaline receptors, the Alpha-Adrenoceptor, erectile response can be achieved.
- Phentolamine competes with endogenous norepinephrine for the Alpha1-Adrenoceptor and Alpha2-Adrenoceptor. Phentolamine has similar binding capacities to both receptors.
- The current literature suggests that this is the main mechanism by which phentolamine exerts its physiological effects. Phentolamine also blocks 5-HT receptors, inducing the release of histamine from mast cells. Some studies also show that NOS activation could possibly be involved in another mechanism, inducing increased vasodilation (13, 14).

Phentolamine -2

- The Alpha-Adrenoceptor Antagonist of phentolamine is considered to be complex.
- The non-selective receptor blocking action interacts with adrenergic nerves in a complex fashion.
- Phentolamine action on adrenergic nerves has not been fully established.
- It is thought that there might be counteracting regulation on pre-and post-junctional nerves.
- It is not known how the counteracting regulation might affect the efficacy of phentolamine for the treatment of erectile dysfunction

Phentolamine-3

- In animal studies, penile arterial inflow resistance was decreased.
- This proves in vivo that the physiological response to phentolamine acts in a manner to achieve erectile response (7).
- However, phentolamine has not displayed a significant effect on the venous outflow from penile tissues in humans (7).
- The current body of literature has not established pharmacokinetics for phentolamine.

Phentolamine- 4

- First pass metabolism effectively reduces the efficacy in the treatment of erectile dysfunction.
- Therefore, this drug has to be administered by injection.
- The half-life of phentolamine is 30 minutes, with an effect duration of 2.5 to 4 hours (15).
- After penile injection the concentration of phentolamine in serum reaches a maximum within 20 to 30 minutes.
- After this amount of time has passed the drug rapidly is metabolized (16).

Phentolamine- 5

- Side effects of phentolamine are rare.
- However, it has been reported that orthostatic hypotension, tachycardia, arrhythmias and myocardial infarction, have occurred after penile injection.
- The mechanism to which this set of side effects occur has not been rationally deduced through scientific study.
- Phentolamine is usually added in combination with papaverine or vasoactive intestinal peptide to increase erectile response (17, 18)

Medical treatment of impotence with papaverine and phentolamine intracavernosal injection (19)

- **Participants:** 20 patients age 32 to 72 years old
- **Administration:** intracavernosal injection
- **Dosage:** 30 mg papaverine and phentolamine 1 mg
- **Results:** Response with erection in 20- 30 minutes, phentolamine and papaverine produced an erection sufficient for intercourse in 18 of the 20 subjects

Prostaglandin E1 (Alprostadil)

- A potent hormone-like substance that induces erection by relaxing the penis's blood vessels and dilating cavernosal arteries-dilation of the cavernosal arteries is accompanied by increased arterial inflow velocity and increased venous outflow resistance allowing for more blood into the penis and less blood out

Prostaglandin E1 (Alprostadil)- 2

- Prostaglandin E1 is administered intracavernosally. This drug is prescribed as a second-line treatment, after oral PDE5 inhibitors have been ineffective for treatment of erectile dysfunction (20).
- Several aspects of its effects and clinical use have been reviewed previously (21, 22).
- Currently the body of medical literature demonstrates that 40 to 70% of erectile dysfunction patients respond to treatment with prostaglandin E1.
- The failure to respond to prostaglandin E1 has not been established. The demonstration that prostaglandin E1 with S-nitrosoglutathione in combination is more effective than prostaglandin E1 alone may shed light on the lack of efficacy in some patients (23)

Prostaglandin E1 (Alprostadil)- 3

- Medications to activate alternative relaxant pathways in addition to by prostaglandin E1 may be necessary in patients who fail to respond to prostaglandin E1.
- Relaxation of smooth muscle is a critical component of erectile capacity. Additional agents to work in combination with prostaglandin E1 might have significant therapeutic benefits.
- Prostaglandin E1 with other erectile dysfunction medications, might have advantages in the treatment of male erectile dysfunction.
- Compounding pharmacies formulate ICP injection medications that take advantage of multi-compound synergy.
- When injected into penile tissue prostaglandin E1 is readily metabolized into other erectile promoting molecules.
- These molecules potentiate the efficacy of prostaglandin E1.
- Prostaglandin E1 has been demonstrated to alter the concentrations of noradrenalin (24), adding a secondary mechanism of action.
- However, it is still believed prostaglandin E1 primarily acts directly by increasing cAMP synthesis via EP receptor interaction, increasing muscular relaxation (25)

Prostaglandin E1 (Alprostadil)- 3

- Prostaglandin E1 has ubiquitous actions in controlling processes in many tissues.
- Known effects of prostaglandin E1 include systemic vasodilation, prevention of platelet aggregation, and ask to stimulate intestinal activity.
- Thus, prostaglandin E1 has very rarely been administered in a fashion to elicit a systemic response.
- Pharmacokinetics data is currently lacking on prostaglandin E1, the current data suggest short action duration and high rate of metabolic breakdown.
- After the first pass through the lungs 70% is metabolized (26).
- Because prostaglandin E1 is readily metabolized throughout the body, penile injection effects mainly penile tissues.
- Furthermore, this further explains the rare circulatory side effects

Prostaglandin E1 (Alprostadil)- 4

- An example of a dosage combination for Trimix is 10 micrograms of alprostadil, 500 micrograms of phentolamine and 15 mg of papaverine.
- Dosing of Trimix preparations has not been standardized.

References

- 14-Traish, A., et al., Phentolamine mesylate relaxes penile corpus cavernosum tissue by adrenergic and non-adrenergic mechanisms. *Int J Impot Res*, 1998. 10(4): p. 215-23.
- 15.-P.R., I., G. B., and B.L. . Human pharmacology of orally administered phentolamine, in *Phentolamine in Heart Failure and Other Cardiac Disorders.*, in *Proceedings of an International Workshop London, November 1975* T. S.H. and G. L.A., Editors. 1975, Hans Huber Publishers: Bern, Switzerland.
- 16.-O, H., W. U, and K. U, Systemic pharmacokinetics of papaverine and phentolamine: comparison of intravenous and intracavernous application. *Int J Impot Res*, 1990. 2 (Suppl 2): p. 247-248.
- 17.-Eardley, I., et al., Pharmacotherapy for erectile dysfunction. *J Sex Med*, 2010. 7(1 Pt 2): p. 524-40.
- 18.-Dinsmore, W.W. and M.G. Wyllie, Vasoactive intestinal polypeptide/phentolamine for intracavernosal injection in erectile dysfunction. *BJU Int*, 2008. 102(8): p. 933-7.
- 19-Dinsmore, W.W., Medical treatment of impotence with papaverine and phentolamine intracavernosal injection. *Ulster Med J*, 1990. 59(2): p. 174-6.
- 20-Albersen, M., et al., Evaluation and treatment of erectile dysfunction. *Med Clin North Am*, 2011. 95(1): p. 201-12.
- 21-Linet, O.I. and F.G. Ogrinc, Efficacy and safety of intracavernosal alprostadil in men with erectile dysfunction. The Alprostadil Study Group. *N Engl J Med*, 1996. 334(14): p. 873-7.
- 22-Porst, H., The rationale for prostaglandin E1 in erectile failure: a survey of worldwide experience. *J Urol*, 1996. 155(3): p. 802-15.
- 23-Angulo, J., et al., Rationale for the combination of PGE(1) and S-nitroso-glutathione to induce relaxation of human penile smooth muscle. *J Pharmacol Exp Ther*, 2000. 295(2): p. 586-93.
- 24.-Molderings, G.J., et al., Inhibition of noradrenaline release from the sympathetic nerves of the human saphenous vein by presynaptic histamine H3 receptors. *Naunyn Schmiedebergs Arch Pharmacol*, 1992. 346(1): p. 46-50.
- 25-Palmer, L.S., et al., Characterization of cyclic AMP accumulation in cultured human corpus cavernosum smooth muscle cells. *J Urol*, 1994. 152(4): p. 1308-14.
- 26-Golub, M., et al., Metabolism of prostaglandins A1 and E1 in man. *J Clin Invest*, 1975. 56(6)

References

- 1-Montague DK, Jarow JP, Broderick GA, et al. Chapter 1: The management of erectile dysfunction: an AUA update. J Urol 2005;174:230-9.
- 2-Leungwattanakij S, Flynn V, Hellstrom WJG. Intracavernosal injection and intraurethral therapy for erectile dysfunction. Urol Clin North Am 2001;28:343-354.
- 3-Andersson, K.E., Pharmacology of penile erection. Pharmacol Rev, 2001. 53(3): p. 417-50.
- 4-Virag, R., et al., Vasoactive intestinal polypeptide release during penile erection in man. Lancet, 1982. 2(8308): p. 1166.
- 5-K.E., A., Pharmacology of erection: agents which initiate and terminate erection. Sex Disabil 1994. 12: p. 53-79.
- 6-Kirkeby, H.J., et al., [Infusion cavernosography and erectile dysfunction]. Ugeskr Laeger, 1990. 152(24): p. 1724-6.
- 7.-Juenemann, K.P., et al., Hemodynamics of papaverine- and phentolamine-induced penile erection. J Urol, 1986. 136(1): p. 158-61.
- 8-Delcour, C., et al., The effect of papaverine on arterial and venous hemodynamics of erection. J Urol, 1987. 138(1): p. 187-9.
- 9.-Mooradian, A.D., et al., Biweekly intracavernous administration of papaverine for erectile dysfunction. West J Med, 1989. 151(5): p. 515-7.
- 10-Dinsmore, W.W., Medical treatment of impotence with papaverine and phentolamine intracavernosal injection. Ulster Med J, 1990. 59(2): p. 174-6.
- 11-Keogh, E.J., et al., Treatment of impotence by intrapenile injections of papaverine and phenoxybenzamine: a double blind, controlled trial. Aust N Z J Med, 1989. 19(2): p. 108-12.
- 12-Viswaroop, B., A. B, and G. Gopalakrishnan, Evaluating erectile dysfunction: oral sildenafil versus intracavernosal injection of papaverine. Natl Med J India, 2005. 18(6): p. 299-301.
- 13-Traish, A.M., et al., Expression of functional alpha2-adrenergic receptor subtypes in human corpus cavernosum and in cultured trabecular smooth muscle cells. Recept Signal Transduct, 1997. 7(1): p. 55-67.