Beyond Oral Therapies

Proactive ED Management when Oral Therapy is No Longer an Option

Preliminary OVERVIEW

Module preparation, delivery and assessment provided by an Unrestricted Educational Grant for Men’s Health from Vivus, Inc.

Utilizing the principles of professional education for relevant solutions.
The learner will be able to:

- Recognize potential patients within their practice who are at risk for erectile dysfunction (ED), based on new prevalence data, pathophysiology, and risk factors associated with ED.

- Identify a plan for tailoring the treatment of ED to patients with concomitant diabetes, cardiovascular disease, prostate cancer, or those patients who have failed or are likely to fail oral agents.

- Discuss the advantages and disadvantages of currently available therapies and be able to use them to improve the probability of success in treating patients with ED.

- List helpful strategies to improve and maintain positive patient compliance that incorporate patient needs, preferences and follow-up.

Erectile dysfunction is generally defined as a condition characterized by the inability to achieve or maintain firm erections sufficient for sexual intercourse. Although not life threatening, erectile dysfunction causes considerable suffering to very large numbers of men, and therefore, represents a significant health concern. It is estimated that over 20 million U.S. men have some degree of erectile dysfunction.

The investigation and management of erectile dysfunction has traditionally been carried out in a secondary care setting due to, in part, the invasive and somewhat empirical nature of early treatments. With the advent of new, non-invasive therapies, treatment initiation and monitoring comfortably falls within the scope of the primary health care sector. Provided the necessary educational needs can be met, the management of ED is ideally placed in primary care.
Normal erectile function requires a complex set of dynamic neural and vascular interactions. Conditions affecting either vascular or nerve function commonly affect erectile function as well. In the flaccid penis, a balance exists between blood flow in and out of the erectile bodies. Penile erection can be elicited by at least two distinct mechanisms: (1) central psychogenic and (2) reflexogenic, which interact during normal sexual activity. Psychogenic erections are initiated centrally in response to auditory, visual, olfactory or imaginary stimuli. Reflexogenic erections result from stimulation of sensory receptors on the penis that, through spinal interactions, cause somatic and parasympathetic efferent actions.

On arousal, parasympathetic and non-adrenergic non-cholinergic (NANC) nerve activity triggers a series of processes starting with the release of nitric oxide and other neurotransmitters, and ending with smooth muscle relaxation in the erectile tissues of the penis. Blood flow into the corpora cavernosa increases dramatically. The rapid filling of the cavernosal spaces compresses venules resulting in decreased venous outflow, a process often referred to as the corporeal veno-occlusive mechanism. The combination of increased inflow and decreased outflow rapidly raises intracavernosal pressure resulting in progressive penile rigidity and full erection.

Currently, first-line treatment for the majority of men with erectile dysfunction consists of oral therapy with a class of compounds know as phosphodiesterase type 5 (PDE5) inhibitors, which have be shown to help restore penile blood flow and erections in response to sexual stimulation. When a man is sexually stimulated, nitric oxide (NO) is released by nerves or endothelial cells and diffuses into smooth-muscle cells in the walls of penile arteries and spongy erectile tissue. NO stimulates the enzyme guanylate cyclase to synthesize cyclic guanosine monophosphate (cGMP) from guanosine triphosphate GTP. Increased levels of cGMP lead to decreased Ca\(^{2+}\) concentration in the smooth muscle cells of the erectile tissues, smooth muscle relaxation and ultimately increased blood flow into the penis. Concentration of cGMP is degraded by the activity of a second enzyme, PDE5, which hydrolizes cGMP to GMP. Sildenafil, Tadalafil and Vardenafil have been shown to inhibit PDE5, preventing cGMP from hydrolysis and thus amplifying the effect of pelvic nerve stimulation.

Not all ED has the same pathogenesis, and not all patients with ED respond to the same therapy. Patients who cannot generate nitric oxide due to surgical trauma, neuropathy, or other nerve damage may not benefit from PDE-5 inhibitors. The trauma caused by nerve-sparing prostatectomies results in a temporary loss of conduction along the nerve. This absence of functional innervation (neurapraxia) within the erectile tissues prevents the release of nitric oxide from non-adrenergic non-cholinergic manufacture of cyclic GMP within the copora cavernosa. Without cyclic GMP, PDE-5 inhibitors cannot effectively enhance an
erection. Similarly, patients with long-standing diabetes and accompanying neuropathy may also be non-responsive to oral agents.

PDE5 inhibitors are also contraindicated in patients taking any nitrates. ED patients with active coronary ischemia not taking nitrates, patients with a history of congestive heart failure or those patients using drugs such as erythromycin, cimetidine, or ketoconazole which interact with the cytochrome P450 3A4 enzyme will not have a high degree of success with oral therapy. Patients with retinal disease or those patients on a multidrug, antihypertensive program will have limited success.

For these patients there are alternative therapies available, many of which can be easily initiated by PCPs or GPs. A discussion of these therapies is presented in the following sections.
Evaluation and Treatment of Erectile Dysfunction in Men With Diabetes Mellitus, Jayant Dey et al., Mayo Clinic Proceedings. 2002; 77:276-282

Figure 1. Evaluation and management of erectile dysfunction (ED) in diabetic men.

*Hemoglobin A thyrotropin, and AM total testosterone levels. Testosterone deficiency should be further evaluated by measuring luteinizing hormone, follicle-stimulating hormone, and prolactin levels to elucidate a specific etiology. (Bioavailable testosterone should be considered in men >50 years or body mass index >30kg/m2.)
†Phosphodiesterase inhibitors or others.
‡Androgen replacement and oral ED therapy are often initiated simultaneously in men with hypogonadism.
§Perform follow-up and reassessment.
Alternative Therapies

There are advantages and disadvantages of each of the treatment options for ED:

- Intraurethral alprostadil MUSE®
- Vacuum erection devices
- Constriction band therapy
- Intracavernosal injection (ICI) therapy
- Penile Implants

**Intraurethral Alprostadil  MUSE**

MUSE is a drug delivery system that can be administered by the patient to deliver a medicated pellet directly into the urethra of the penis where the medication is absorbed for local action. Local drug delivery is based on the concept that a high degree of safety and efficacy can be provided by delivering the medicine to the area of the body where the medicine is needed. Alprostadil, the active ingredient in MUSE, is chemically identical to prostaglandin E1, a naturally occurring substance that causes blood vessels to dilate.

**Advantages**

- High safety
- Local therapy; No systemic side effects
- Intraurethral therapy is effective in a large percentage of patients⁴
- Intraurethral therapy mimics the natural physiology of erection by relaxing smooth tissue in the penis
- This treatment method restores erection without surgery and associated complications
- Treatment does not affect sensation, ejaculation, or fertility.
- Erection occurs in 5-10 minutes; allows for spontaneity
- May be administered up to twice daily
- No drug-drug interactions reported
- 30 second to 10 minute half-life resulting in minimized systemic exposure to the drug and corresponding low opportunity for drug-drug interactions
- No significant risk of priapism or prolonged erection
- No fibrosis
- Preliminary observations show that patients who have failed oral or ICI therapy might respond to transurethral therapy
- Minimally invasive; Less invasive than the needle
- May be used in combination with sildenafil when alprostadil and sildenafil monotherapies fail
- 1-800 phone line for one-on-one physician and patient consultation and direction
- No medical waste disposal – applicator to regular household trash.
- Currently 75-80% of prescriptions are covered by medical plan

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⁴ Approximately 50% of patients with predominantly severe ED and 50% of those experiencing sildenafil failures have been successful with intraurethral alprostadil MUSE.
Disadvantages
- Transient penile burning 32%; reduced pain with 4 or more administrations as been reported
- Initial apprehension to applicator
- Dizziness – 3%
- Fainting - .4%
- Patients with poor manual dexterity, poor vision, or severe obesity may not be able to accurately administer drug
- Investment of time in teaching patients proper administration technique

Vacuum erection devices

Vacuum devices enhance venous engorgement thereby helping to achieve and maintain erection.

Advantages
- They are non-invasive; do not require either injections or surgery.
- They are widely considered safe and have no significant side effects.
- There is a little or no discomfort or pain.
- There is only a one-time cost. Once the device is purchased, there is minimal further expense such as lubricants and new bands.
- The cost is usually covered by insurance.
- There are a variety of models to choose from.
- They are entirely mechanical, which is seen as an advantage by physicians who don’t want some patients taking additional medication.
- Vacuum device representatives have been established an excellent rapport with the doctors by providing in-service programs.
- No Rx required

Disadvantages
- The initial impression of these devices is intimidating due to their large size.
- Many patients complain that the device is cumbersome and difficult to use.
- There is a lack of spontaneity, because of the cumbersome nature of the devices.
- They are not discreet and require an understanding partner.
- They are messy; patients must coat the penis with lubricant before attaching the device.
- The erection is unnatural, because the penis is only erect beyond the constriction band and because the constriction band often causes the penis to become cold and discolored.
- Some patients experience accidental bruising of the penis.
- Patients cannot leave the constriction ring on for longer than 30 minutes, due to diminished blood flow to the penis.
- Some patients complain of lack of sensation due to the tightness of the constriction band.
- Partners occasionally complain that during intercourse the band hits the clitoris, causing partner discomfort.
- The devices are ineffective in patients with severe vascular disease.
- There is very little clinical data on long-term efficacy and safety.
- Lack of glans sensitivity
Constriction band therapy

Although constriction bands are an integral part of vacuum device therapy, they may also be used alone in the treatment of erectile dysfunction. The bands slow venous outflow from the penis (venous leak). Venous leak is thought to be caused by abnormal penile vasculature that will not allow the storage of blood necessary to fill the penis and cause erection. Bands, i.e. ACTIS®, prevent the outflow by mechanical constriction and may be all a patients needs for ED treatment. Constriction band therapy is the least invasive treatment for ED, including oral therapies. In addition, therapies that increase arterial inflow, such as MUSE or PDE5 drugs, may help in combination with band therapy.

Advantages
- Least invasive of all ED therapies, including oral agents.
- Over-the-counter
- Inexpensive
- Safe
- No systemic side effects
- May be safely used in combination with other ED therapies

Disadvantages
- Does not improve arterial inflow
- Will not help those patients who have not erectile function and cannot achieve an erection on their own
- Low image (sex shop image)

Intracavernosal injection (ICI) therapy

Vasoactive compounds, including phentolamine, papaverine, moxisylate and alprostadil, have been injected into the corpora cavernosa in order to produce erection.

Advantages
- Injection therapy is effective in a large percentage of patients.
- Self-injection therapy mimics the natural physiology of erection by relaxing smooth tissue in penis.
- This treatment method restores erection without surgery and associated complications.
- Injections do not affect sensation, ejaculation, or fertility.
- More spontaneity is possible than with vacuum devices.
- This method can be somewhat discreet, since an injection can be given privately before the initiation of sexual activity.

Disadvantages
- Most patients are uncomfortable with needle injections.
- The injection technique can be difficult and requires training. This usually necessitates both initial instruction as well as follow-up visits to ensure proper technique.
- With Caverject, a great deal of time may be spent adjusting the exact dosage required to achieve an adequate erection in each patient (doses can vary by increments as small as 0.1 cc.).
- Following each administration, the patient must compress the injection site for three to five minutes to minimize bleeding.
- Patients with poor manual dexterity, poor vision, or severe obesity may not be able to accurately inject themselves.
- Patients with heart disease, previous strokes, liver disorders, or blood disorders may be at risk from the medication used.
- Potential side effects include lingering pain at the injection site, dizziness, infection, penile pain and burning, development of scar tissue (which commonly results in loss of sensation and may affect the ability of the erectile tissue to expand), and the possibility of prolonged erections or priapism, which can permanently damage penile tissue. Studies of alprostadil suggest that prolonged erections or priapism can occur more often when the drug is injected than when delivered via transurethral administration.
- Reconstituted injectable products require refrigeration. They lose potency very quickly at room temperature. Caverject does not require refrigeration in the powdered form, but must be reconstituted before use.
- Traveling with syringes can be an issue. Patients must carry their prescription with them to prove the need for the syringes.
- Injection therapy can only be used up to three times a week and never more than once in the same day due to potential scarring or fibrosis.
- The cost of injection therapy may not be covered by insurance.
- The dropout rate for injection therapy over 12 months is about 60% or higher due to a decline in patient motivation to continue injecting themselves, as well as side effects (primarily fibrosis).
- Investment of time in teaching patients proper administration technique
- Syringes require medical waste hazard material disposal. Must be discarded properly; not in regular household trash.

**Penile implants**

Consideration may be given to surgical intervention when other forms of treatment for ED have failed. There are a variety of implantable prostheses available.

**Advantages**
- Spontaneity is possible, because these implants become part of the patient and there is no need to plan ahead for sexual activity.
- With the inflatable models, the patient can control how long an erection lasts.
- The inflatable models are discreet and appear normal in public settings such as locker rooms, as well as with partners. This is especially an advantage for single men without a consistent partner.
- Significant clinical data is available on the procedure and its results.
- There are several different models to choose from.
Disadvantages
- This is a major surgery with all its associated drawbacks;
- Complications during surgery are possible, including complications with anesthesia.
- Postoperative pain requiring narcotics may last up to four weeks.
- A recovery time of four to six weeks is required before the patient can resume normal physical or sexual activity.
- Potential complications following the procedure include infection and mechanical failure.
- Erections after the implant procedure are usually not as wide or as long as the patient’s pre-ED erections.
- Depending on the model chosen, the erection may be permanent, which can be uncomfortable and embarrassing.
- The procedure is irreversible, since the penile tissue is permanently damaged or removed.
- The lifespan of the implant is usually eight to ten years. After this time, surgery may be required again to replace the device
- The procedure is very expensive and may not be covered by the patient’s insurance.
- Penile sensation, ability to ejaculate, and ability to reach orgasm are affected by implants.
- Lack of glans sensitivity
Combination Therapy for Patients Failing Monotherapy

Recent independent studies indicate combination therapy of MUSE® and VIAGRA® may be an option for patients who have experienced a suboptimal response from oral sildenafil or intraurethral alprostadil alone, and do not want to attempt more invasive forms of therapy such as penile injections.

Smooth muscle relaxation of the erectile tissues of the penis occurs when nerve stimulation leads to increased levels of cyclic nucleotides (cAMP and cGMP) in the smooth muscle cells. Although these two cyclic nucleotide second messengers respond to different stimuli, their effects are similar and there is a significant level of “cross-talk” between them, so that increases in cGMP typically result in increases in cAMP as well. Intraurethral alprostadil and sildenafil promote erections by stimulating different pathways within the corporeal smooth muscle. Alprostadil is a synthetic compound identical to prostaglandin E1. It causes direct stimulation of cAMP synthesis by the cavernosal smooth muscle cells. This increase in cAMP leads to smooth muscle relaxation, which stimulates increased blood flow and initiates the erection.1 Sildenafil, a PDE5 inhibitor, inhibits the breakdown of cGMP, which results in high levels of this second messenger in response to stimulation, thereby enhancing smooth muscle relaxation and erection.2

Two independent studies evaluated patient response to maximal doses of intraurethral alprostadil and oral sildenafil alone. Patients who were not satisfied with their erection following monotherapy underwent combination therapy of 100mg of Viagra and 500mcg of MUSE. The patients administered the medications as regularly directed; Viagra 1 to 1-1/2 hrs before anticipated intimacy and MUSE 10 minutes before.

The results of one study demonstrated 60 out of 65 patients responded successfully to the combination therapy.3 The other study showed 28 out of 28 patients who failed the monotherapies were successfully averaging 3.6 intercourses per month after 30 months of using the combination of MUSE and Viagra.4

3 Mydlo J, et al.: Initial Results Utilizing Combination Therapy for Patients with a Suboptimal Response to Either Alprostadil or Sildenafil Monotherapy. Eur Urol 2000;38:30-34
## Comparison of Agents for Erectile Dysfunction

<table>
<thead>
<tr>
<th>Drug</th>
<th>Efficacy</th>
<th>Ease of use</th>
<th>Side effects</th>
<th>Cost*</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sildenafil (Viagra)</td>
<td>Enhances erections</td>
<td>Clinically significant in mild to moderate patient profile</td>
<td>Taken orally one hour before anticipated intercourse; efficacy affected by high-fat meal</td>
<td>Headache; flushing; dyspepsia; Sinusitis; blue vision</td>
<td>$263 for 30 tablets of any size</td>
</tr>
<tr>
<td>Transurethral alprostadil (MUSE)</td>
<td>Initiates erections</td>
<td>Significantly greater than placebo; 55% effective in VIAGRA failures; consistent in all etiologies</td>
<td>Fast acting, 5-10 minutes onset of action allows for spontaneity. 1-800 telephone support. Inserted into urethra doses of 500μg or 1000μg</td>
<td>Transient penile pain 32%; reduced pain with 4 or more administrations has been reported; pain increases with dosage increase</td>
<td>$133 for box of 6; currently 80% of retail prescriptions are reimbursed.</td>
</tr>
<tr>
<td>Intracavernosal alprostadil (Caverject)</td>
<td>Initiates erections</td>
<td>Significantly greater than placebo; 80% efficacy</td>
<td>Injected via syringe into penis; inconsistent dosage</td>
<td>Penile pain; hematoma; priapism</td>
<td>$155 for box of 6 doses of 20 μg</td>
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</tbody>
</table>
Major Conditions Associated with Erectile Dysfunction are:

- **Aging**
- **Chronic Disease**
  - Heart disease
  - Hypertension
  - Lipid disorders
  - Renal failure
  - Liver disease
  - Vascular disease
- **Endocrine Abnormalities**
  - Diabetes Mellitus
  - Hypogonadism
  - Hyperprolactinemia
  - Hypothyroidism/hyperthyroidism
- **Life-Style**
  - Cigarette smoking
  - Chronic alcohol abuse
- **Medications**
  - Antihypertensive: Diuretics,
    - Sympatholytics, Beta blockers
  - Psychiatric: Antidepressants,
    - Antipsychotic, Anxiolytic
  - Antiandrogenic
  - Others: Alcohol, Ketoconazole, Niacin,
    - Phenobarbital, Phenytoin
- **Neurogenic Causes**
  - Spinal cord injury
  - Multiple sclerosis
  - Herniated disc
- **Pelvic Radiation**
- **Pelvic Trauma/Surgery**
  - Radical Prostatectomy
  - Seed therapy
- **Penile Injury/Disease**
  - Peyronie’s disease
  - Priapism
  - Anatomic abnormalities
- **Psychologic Issues**
  - Depression
  - Anxiety
  - Social stressors
- **Trauma/Injury**

The physical examination should assess the patient’s overall health. Particular attention should be given to the cardiovascular, neurologic and genitourinary systems, as these systems are directly involved with erectile function. The cardiovascular examination should include assessment of vital signs (especially blood pressure and pulse) and signs of hypertensive or ischemic heart disease. Abdominal or femoral artery bruits and asymmetric or absent lower extremity pulses are indicative of vascular disease. Skin and hair pattern evidence of vascular insufficiency should be noted. Local therapy is a highly effective treatment option when ED is caused by vascular disease, diabetes, surgery/trauma and other organic causes. Patients with predominantly organic sexual dysfunction should be informed of the various therapeutic options available so they can make an educated decision.
- Conclusion

Oral agents are first-line for most ED patients. Many patients, particularly those with complicated cases including diabetic patients and post-radical prostatectomy patients, will not respond adequately to oral agents and many others cannot use them at all. Physicians who are committed to improving the probability of success in treating their patients with ED will become expert with treatment modalities that are minimally invasive, safe and appropriate for the PCP and Specialist to prescribe. Educating patients on the proper use of the treatment modalities will provide valuable information that will maximize their options for success.