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Erectile Dysfunction

Clinical Policy Bulletins | Medical Clinical Policy Bulletins

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Policy

Please see amendment for Pennsylvania Medicaid at the end of this CPB.

Aetna considers the diagnosis and treatment of erectile dysfunction (ED; impotence) medically necessary according to the criteria outlined below.

I. Diagnosis

Aetna considers the following diagnostic workup of erectile dysfunction medically necessary:

- Comprehensive history and physical examination (including medical and sexual history and psychosocial evaluation)
- Duplexscan (Doppler and ultrasound) in conjunction with intracorporeal papaverine
- Dynamic infusion cavernosometry and cavernosography only for members who are to undergo re-vascularization procedures and meet medical necessity criteria for penile re-vascularization (see below)
- Pharmacological response test for erectile dysfunction (using vasoactive drugs, e.g., papaverine HCl, phentolamine mesylate, prostaglandin E1)
- Pudendal arteriography (angiography) only for members who are to undergo penile re-vascularization and meet the medical necessity criteria for penile revascularization (see below).

Policy History

Last Review

12/26/2019

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Next Review: 01/09/2020

Review History

Definitions

Additional Information

Clinical Policy Bulletin Notes

Aetna considers the following laboratory tests medically necessary for the diagnosis of erectile dysfunction:

- Biothesiometry (Note: biothesiometry is considered an integral part of the comprehensive history and physical examination)
- Blood glucose
- Complete blood count
- Creatinine
- Hepatic panel
- Lipid profile
- Prostate specific antigen
- Serum testosterone

  Tests for evaluation of pituitary dysfunction (e.g., measurement of luteinizing hormone, follicle-stimulating hormone, and prolactin levels) if serum testosterone level is below normal

- Thyroid function studies
- Urinalysis.

Note: Routine nocturnal penile tumescence (NPT) and/or rigidity testing has no proven value. Nocturnal penile tumescence testing using the postage stamp test or the snap gauge test is rarely medically necessary; it is considered medically necessary where clinical evaluation, including history and physical examination, is unable to distinguish psychogenic from organic impotence and any identified medical factors have been corrected. Nocturnal penile tumescence testing using the RigiScan is considered medically necessary only where NPT testing is indicated, and the results of postage stamp or snap gauge testing are equivocal or inconclusive.

Aetna considers the following workup/laboratory tests for the diagnosis of erectile dysfunction experimental and investigational because their effectiveness has not been established:

- Angiotensin-converting enzyme insertion/deletion polymorphism testing (for determining erectile dysfunction susceptibility)
- Cavermap cavernous nerves electrical stimulation with penile plethysmography (also referred to as cavernosal nerve mapping). This policy is based upon an assessment by the Centers for Medicare and Medicaid Services (CMS, 2006)
- Corpora cavernosal electromyography

- Dorsal nerve conduction latencies
- Endothelial nitric oxide synthase polymorphism (4 VNTR, G894T, and T786C) testing for estimating risk of erectile dysfunction
- Evoked potential measurements (including stimulus evoked response for measurement of bulbocavernosus reflex latency)
- Iron binding capacity
- Measurement of serum melatonin levels
- Penile plethysmography
- Prostatic acid phosphatase
- Shear wave elastography
- The use of serum biomarkers (e.g., E-selectin, endothelial progenitor cells, endothelial micro-particles, homocysteine, interleukin-10, malondialdehyde, nitric oxide, and ratio of tumor necrosis factor-alpha to IL-10) for the development and/or progression of ED.

II. Treatments

Aetna considers the following therapies for the treatment of erectile dysfunction medically necessary:

A. Injectable Medications

Aetna considers self-administered injectable medications for the treatment of erectile dysfunction medically necessary.* Medically necessary self-administered medications for erectile dysfunction include:

1. Injections into the corpus cavernosa to cause an erection (papaverine, alprostadil, phentolamine) and,
2. Medicated Urethral System for Erection (MUSE) method of treatment for erectile dysfunction that involves inserting medication through a small catheter into the urethra.

Titrating doses of injectable impotence medications that are administered in a physician's office and the accompanying office visits are considered medically necessary. This includes in office titrating doses of papaverine, alprostadil (prostaglandin E1 or Caverject) and phentolamine. Except for phentolamine, which is not generally used alone, these drugs can be used alone or in combination. The drug MUSE, a pellet from of alprostadil, is also used as an alternative to alprostadil injections.

Diagnostic injections of impotence medications by the treating physician are also considered medically necessary.

*Note: Coverage of injectable medications is subject to the terms of the member's benefit plan. Please check benefit plan descriptions for details.

B. Oral and Transdermal Medications

Aetna considers exogenous testosterone replacement therapy, including transdermal preparations, experimental and investigational for the treatment of non-hypogonadal impotence because its effectiveness in non-hypogonadal impotence has not been established. (See CPB 0345 - Implantable Hormone Pellets (../300_399/0345.html).)

Aetna considers topical cream or gel containing vasodilators, such as verapamil cream, experimental and investigational for the treatment of erectile dysfunction because their effectiveness for this indication has not been established.

Note: Many Aetna pharmacy benefit plans exclude coverage of drugs for lifestyle enhancement or performance. Please check benefit plan descriptions for details. Under these plans, sildenafil citrate (Viagra), vardenafil hydrochloride (Levitra) and tadalafil (Cialis) are covered only when required by state regulation or when a plan sponsor has elected an optional rider under the pharmacy plan, or, for indemnity or PPO plans without a separate pharmacy benefit, when the plan sponsor has added optional coverage under the medical plan.

C. External Devices

Aetna considers the external penile vacuum pump device medically necessary durable medical equipment (DME) when it is prescribed by a physician as an alternative to other therapies for erectile dysfunction. External penile pumps are considered experimental and investigational for other indications including for the prevention of erectile dysfunction following prostatectomy because their effectiveness for these indications has not been established.

D. Implantable Devices

Aetna considers implantation of semi-rigid penile prostheses or inflatable penile prostheses (implantable penile pumps) medically necessary for members with documented physiologic erectile dysfunction when ***all*** of the following criteria are

met

1. Absence of active alcohol or substance abuse; ***and***
2. Absence of drug-induced impotence related to: anabolic steroids, anticholinergics, antidepressants, antipsychotics or central nervous system depressants; ***and***
3. Absence of untreated depression or psychiatric illness; ***and***
4. Nonsurgical methods have proven ineffective or are contraindicated; ***and***
5. Normal prolactin and thyroid hormone levels; ***and***
6. Normal serum testosterone levels (low testosterone suggests treatable endocrine cause of impotence); ***and***
7. History of organic disease including any one or more of the following:

    a. Documented injury to perineum/genitalia; ***or***
    b. Major pelvic trauma affecting bladder and/or anal and/or erection control; ***or***
    c. Major vascular surgery involving aorta or femoral blood vessels; ***or***
    d. Neurological disease (eg, diabetic neuropathy); ***or***
    e. Peyronie's disease; ***or***
    f. Renal failure; ***or***
    g. Secondary to spinal cord injury; ***or***
    h. Status-post prostate, bladder, bowel or spinal surgery; ***or***
    i. Vascular insufficiency or venous incompetence documented by dynamic infusion cavernosometry and cavernosography (DICC); ***or***
    j. Venous leak of the penis.

Removal of a penile implant is considered medically necessary for infected prosthesis, intractable pain, mechanical failure, or urinary obstruction.

Reimplantation of a penile implant is considered medically necessary for persons who meet medical necessity criteria above for a penile implant and whose prior prosthesis was removed for medically necessary indications.

Implantable penile prostheses are considered experimental and investigational for other indications because their effectiveness for indications other than the one listed above has not been established.

Note: Some traditional medical plans exclude coverage of charges for the treatment of sexual dysfunction. Under these plans, procedures for treatment of impotence would be excluded from coverage. Please check benefit plan descriptions.

E. Surgical Re-Vascularization

Aetna considers penile re-vascularization for vasculogenic erectile dysfunction medically necessary only in men less than 55 years old who meet all of the following criteria:

1. A focal blockage of arterial inflow is demonstrated by duplex Doppler ultrasonography or arteriography; ***and***
2. Diagnostic work-up reveals normal corporeal venous function; ***and***
3. Member is not actively smoking; ***and***
4. Member is not diabetic and has no evidence of systemic vascular occlusive disease; ***and***
5. The erectile dysfunction is the direct result of an arterial injury caused by blunt trauma to the pelvis and/or perineum.

Penile re-vascularization is considered experimental and investigational for other indications because its effectiveness for indications other than the one listed above has not been established. Consistent with clinical guidelines of the American Urological Association, Aetna considers arterial reconstructive procedures, dorsal vein arterialization procedures, or penile venous occlusive surgery (e.g., venous ligation, dorsal vein ligation) in men with erectile dysfunction secondary to arteriosclerotic occlusive disease experimental and investigational because such procedures have not been proven to be effective.

F. Experimental and Investigational Treatments for Erectile Dysfunction

Aetna considers the following treatments experimental and investigational for erectile dysfunction because their effectiveness has not been established:

1. Acupuncture
2. Acoustical wave therapy (Alpha Wave SwissWave Protocol)
3. Botulinum toxin
4. Epalrestat
5. Extracorporeal shock wave therapy (ESWT)
6. Gene therapy
7. Percutaneous electrostimulation of the perineum
8. Statins
9. Stem cell therapy (including adipose-derived stem cells and mesenchymal stem cells)

10. Tacrolimus.

G. Peyronie's Disease

1. Plaque Excisions and Venous Graft Patching

   Aetna considers surgical correction of Peyronie's disease (e.g., plaque excisions and venous graft patching, tunica plication, Nesbit tuck procedure) medically necessary for the treatment of members with Peyronie's disease for 12 or more months with significant morbidity who have failed conservative medical treatment. Surgical correction of Peyronie's disease is considered experimental and investigational when criteria are not met.

2. Extracorporeal Shock Wave Therapy
   Aetna considers ESWT experimental and investigational for Peyronie's disease because of a lack of evidence from prospective randomized controlled clinical studies of the effectiveness of ESWT for this indication.

3. Interferon Alpha

   For interferon alpha for Peyronie's disease, see C
   PB 0404 - Interferons (../400_499/0404.html).

4. Verapamil Iontophoresis or Nicardipine/Verapamil Intra-Lesional Injection

   Aetna considers iontophoresis or intra-lesional injection of nicardipine or verapamil experimental and investigational for Peyronie's disease because of a lack of evidence from prospective randomized controlled clinical studies of the effectiveness of this approach for this indication.

5. Testosterone Injection

   Aetna considers testosterone injection experimental and investigational for Peyronie's disease because of a lack of evidence from prospective randomized controlled clinical studies of the effectiveness of this approach for this indication.

6. Xiaflex - Initiation

Aetna considers Xiaflex (collagenase Clostridium histolyticum) for the treatment of Peyronie's disease medically necessary when the following criteria are met: Also see CPB 0800 - Dupuytren's Contracture Treatments (../800_899/0800.html).

a. The member has stable Peyronie's disease without clinical changes (e.g., worsening curvature) for at least three months; ***and***
b. The member has a palpable plaque and curvature deformity of at least 30 degrees and less than 90 degrees prior to initiating Xiaflex therapy; ***and***
c. The member has intact erectile function (with or without medication); ***and***
d. The member is 18 years of age or older; ***and***
e. The member will receive a maximum of one treatment course with a maximum of 8 injections total, including any injections the member has received for any previous treatment.

7. Xiaflex - Continuation of Therapy

Aetna considers continuation of Xiaflex (collagenase Clostridium histolyticum) for the treatment of Peyronie's disease medically necessary when ***all*** of the following criteria are met:

a. The member meets all initial selection criteria; ***and***
b. The member has curvature deformity of at least 15 degrees at the time of the continuation request; ***and***
c. The member has received less than 8 injections total, including any injections the member has received for any previous treatment.

Dosing Recommendations

Peyronie's Disease

Collagenase clostridium histolyticum is available as Xiaflex for intralesional injection as single-use glass vials containing 0.9 mg of collagenase clostridium histolyticum as a sterile, lyophilized powder for reconstitution. Sterile diluent for reconstitution is also provided in a single-use glass vial.

- Xiaflex should be administered by a healthcare provider experienced in the treatment of male urological diseases.

- A treatment cycle consists of two Xiaflex injection procedures and a penile modeling procedure.
- Recommended to inject 0.58 mg Xiaflex into the target plaque of a flaccid penis once on each of 2 days, 1 to 3 days apart, according to the injection procedure.
- Perform a penile modeling procedure 1 to 3 days after the second injection of each treatment cycle.
- For each plaque causing the curvature deformity, up to 4 treatment cycles may be administered. Each treatment cycle may be repeated at approximately 6-week intervals. If the curvature deformity is less than 15 degrees after the first, second or third treatment cycle, or if further treatment is not clinically indicated, then subsequent treatment cycles should not be administered.

Source: Endo Pharmaceuticals, 2018

Background

This policy is supported by guidelines from the American Urological Association (Monatague et al, 2005; Monatague et al, 2006).

Researchers have been examining less invasive alternatives to surgery for Peyronie's disease. A number of studies have examined the effectiveness of transdermal administration of verapamil as a treatment for Peyronie's disease. One study found a non-significant improvement in penile curvature with transdermal administration of verapamil (Greenfield et al, 2007). Greenfield et al (2007) stated that while surgery remains the gold standard of therapy to correct the acquired curvature of Peyronie's disease, the search for a less invasive therapy continues. Transdermal drug delivery was proposed to be superior to oral or injection therapy because it bypasses hepatic metabolism and minimizes the pain of injection. After electromotive drug administration with verapamil tunica albuginea specimens were demonstrated to contain detectable levels of the drug. Due to varying success with verapamil as injectable therapy for Peyronie's disease, these researchers performed a double-blind, placebo controlled trial to determine the effectiveness of verapamil delivered through electromotive drug administration. A total of 42 men with Peyronie's disease volunteered to participate in this study, which was approved by the authors' institutional review board. A genito-urinary examination was performed on all patients, including plaque location, stretched penile length, objective measurement of curvature after papaverine injection and duplex ultrasound. Each subject was randomized to receive 10 mg verapamil in 4 cc saline or 4 cc saline via electromotive drug administration. A Mini-Physionizer (Physion, Mirandola, Italy) device was used at a power of 2.4 mA for 20 minutes. Treatments

were performed 2 times weekly for 3 months. After 3 months each patient was re-evaluated with physical examination and duplex ultrasound by a technician blinded to the treatment received. A modified erectile dysfunction index of treatment satisfaction questionnaire was also completed by each patient. A total of 23 patients were randomized to the verapamil treatment group (group 1) and 19 were randomized to the saline group (group 2). There were no significant differences between patient groups with respect to patient age, disease duration or pretreatment curvature. In group 1, 15 patients (65 %) had measured improvement (mean 9.1 degrees, range 5 to 30), 5 (22 %) had no change and in 3 (13 %) the condition worsened. In group 2, 11 patients (58 %) had measured improvement (mean 7.6 degrees, range 5 to 30), 7 (37 %) showed no change and in 1 (5 %) the condition worsened. To better evaluate effectiveness the total number of patients experiencing significant improvement (20 degrees or greater) was calculated and compared. Seven patients (30 %) in group 1 and 4 (21 %) in group 2 achieved this criterion. The authors found that, although a greater percent of patients treated with verapamil in the electromotive drug administration protocol had a measured decrease in curvature, the results were not statistically significant. The authors stated that further research is needed to determine whether electric current may have a role in the treatment of Peyronie's disease as well as if verapamil delivered via electromotive drug administration may have a role as effective treatment.

Cabello Benavente et al (2005) reported on a small, uncontrolled study of the effects of transdermal iontophoresis with verapamil and dexamethasone in patients with early Peyronie's disease, finding effects on pain, but limited effects on curvature. These researchers treated 10 patients with Peyronie's disease of less than 1 year of evolution twice-weekly during 6 consecutive weeks using iontophoresis with a Miniphysionizer dispositive. This device generates a 2-mA electric current during 20 mins that triggers the transdermal penetration of medication. In every session dexamethasone 8 mg and verapamil 5 mg were administered inside a small self-adhesive receptacle on the penile skin overlying the fibrosis plaque. To evaluate the efficacy, penile curvature was measured by Kelami's test, while the plaque size was assessed by penile ultrasound. Other parameters like pain, erectile function and ability for vaginal intercourse were recorded using questionnaires. Safety parameters were also assessed during treatment. No improvement or progression in penile curvature was evidenced in any of the patients. The hardness of the plaque was reduced in 5 patients, becoming impalpable in 2 of them. Decrease in plaque volume was observed by penile ultrasound in 6. Pain improved in 8 patients, disappearing in 6 of them. One patient recovered his erectile function at the end of the treatment; whereas 3 referred that their ability for intercourse enhanced while 2 reported that treatment improved their sexual life in general. These researchers didn't record any significantly side effects, except for a transitory and slight dermal redness on the site of electrode placement. The authors concluded that transdermal iontophoresis had an effect on pain control in early

stages of Peyronie's disease, but efficacy in reducing penile curvature seems to be limited. They stated that controlled clinical trials are needed, and perhaps reviewing indications in order to obtain more relevant clinical effects.

Shirazi et al (2009) assessed the effect of intra-lesional verapamil on the treatment of Peyronie's disease. This randomized study involved 80 patients. First, they were divided into 2 groups -- the 1st group (case: 40 patients) received intra-lesional verapamil and the 2nd group (control: 40 patients) local saline injection. They were followed about 24 weeks and evaluated for the size of plaques, plaque softening, reduction of pain and amelioration of penile deformity and erectile dysfunction (ED) (estimated by the International Index of Erectile Function) before and after treatment. Reduction of plaque size was seen in 17.5 % of the case group and 12.8 % of the control group ($p = 0.755$). Pain was reduced in 30 % of the case group and 28.2 % of the control group ($p = 0.99$). Curvature was decreased in 17.5 % of the case group and 23.1 % the control group ($p = 0.586$). Plaque softening was seen in 30 % of the case group compared with 25.6 % improvement in the control group ($p = 0.803$). Also these investigators found 5 % and 2.6 % improvement in sexual dysfunction in the case and control groups, respectively ($p = 0.985$). The authors concluded that although in some studies verapamil has been found to be effective in the treatment of Peyronie's disease, these researchers did not find any improvement in comparison with the control group. They stated that larger scale studies are warranted to assess the effect of this drug on the treatment of Peyronie's disease.

Heidari et al (2010) evaluated the effect of intra-lesional injection of verapamil in Peyronie's plaque with confirmed lesion. This randomized clinical trial was performed between March 2005 and March 2006 on 16 patients with Peyronie's disease. Performing a comprehensive physical examination, the genitalia of the patients were checked to confirm the diagnosis and reject other sexual disorders. Besides, parameters such as penis curving, lesion size were measured. Then, based on the 10-point visual analog scale, sexual satisfaction of patients and their wives were recorded in a questionnaire. Patients got intra-lesional verapamil every 14 days and were treated for 6 months. After that, the parameters were assessed and data collected was analyzed using paired t-test. P-value < 0.05 was considered statistically significant. On average, lesion size and penis curving decreased 30 %. Almost 20 % of patients and their wives were satisfied with the outcome of the treatment. No significant side effect was seen during the treatment. The authors concluded that injection of calcium channel blockers are effective for treatment of the Peyronie's disease; however, more studies with more patients are needed.

Early studies suggested a potential benefit on neurogenic ED (NED) from percutaneous electrostimulation of the perineum, although additional studies are needed. Shafik et al (2008) examined the hypothesis that percutaneous perineal stimulation evokes erection in patients with NED. Percutaneous electro-stimulation of the perineum (PESP) with synchronous intra-

corporeal pressure (ICP) recording was performed in 28 healthy volunteers (age of 36.3 +/- 7.4 years) and 18 patients (age of 36.6 +/- 6.8 years) with complete NED. Current was delivered in a sine wave summation fashion. Average maximal voltages and number of stimulations delivered per session were 15 to 18 volts and 15 to 25 stimulations, respectively. Percutaneous perineal electro-stimulation of healthy volunteers resulted in an increase in ICP ($p < 0.0001$), which returned to the basal value upon cessation of stimulation. The latent period recorded was 2.5 +/- 0.2 seconds. Results were reproducible on repeated PESP in the same subject but with an increase of the latent period. Patients with NED recorded an ICP increase that was lower ($p < 0.05$) and a latent period that was longer ($p < 0.0001$) than those of healthy volunteers. The authors concluded that PESP resulted in ICP increase in the healthy volunteers and patients with NED. The ICP was significantly higher and latent period shorter in the healthy volunteers than in patients with NED. They noted that PESP may be of value in the treatment of patients with NED, provided that further studies are carried out to reproduce these results.

There is reliable evidence that oral phosphodiesterase-5 (PDE-5) inhibitors (e.g., sildenafil, vardenafil, tadalafil, mirodenafil, and udenafil) improve erectile functioning in men with ED. However, there is a lack of reliable evidence of the efficacy of hormonal treatments and the value of hormone testing for ED.

The American College of Physicians (ACP) developed guidelines on hormonal testing and pharmacological treatments of ED (Qaseem et al, 2009). Current drug therapies include PDE-5 inhibitors as well as hormonal treatment. The ACP recommended (i) clinicians initiate therapy with a PDE-5 inhibitor in men who seek treatment for erectile dysfunction and who do not have a contra-indication to PDE-5 inhibitor use, and (ii) clinicians base the choice of a specific PDE-5 inhibitor on the individual preferences of men with erectile dysfunction, including ease of use, cost of medication, and adverse effects profile. The ACP did not recommend for or against routine use of hormonal blood tests or hormonal treatment in the management of patients with ED.

In a systematic review and meta-analysis, Tsertsvadze and colleagues (2009) evaluated the efficacy and harms of oral PDE-5 inhibitors and hormonal treatments for ED and assessed the effect of measuring serum hormone levels on treatment outcomes for ED. The authors concluded that oral PDE-5 inhibitors improved erectile functioning and had similar safety and efficacy profiles. However, results on the efficacy of hormonal treatments and the value of hormone testing in men with ED were inconclusive. The authors selected randomized, controlled trials (RCTs) of oral PDE-5 inhibitors and hormonal treatment for ED, and observational studies reporting measurement of serum hormone levels, prevalence of hormonal abnormalities, or both in men with ED. Two independent reviewers abstracted data on study,

participant, and treatment characteristics; efficacy and harms outcomes; and prevalence of hormonal abnormalities. Data, primarily from short-term trials (less than or equal to 12 weeks), indicate that PDE-5 inhibitors were more effective than placebo in improving sexual intercourse success (69.0 % versus 35.0 %). The proportion of men with improved erections was significantly greater among those treated with PDE-5 inhibitors (range of 67.0 % to 89.0 %) than with placebo (range of 27.0 % to 35.0 %). The PDE-5 inhibitors were associated with increased risk for any adverse events compared with placebo (e.g., relative risk with sildenafil, 1.72 [95 % confidence interval (CI): 1.53 to 1.93]). In 4 head-to-head RCTs comparing sildenafil, vardenafil, and tadalafil, improvement of ED and adverse events did not differ among treatments. Results from 15 RCTs evaluating hormonal treatment of ED were inconsistent on whether treatment improved outcomes. Evidence was insufficient regarding whether men with ED had a higher prevalence of hypo-gonadism than men without ED.

There is insufficient evidence of the effectiveness of acupuncture for the treatment of ED. In a systematic review, Lee et al (2009) found insufficient evidence for the use of acupuncture in the treatment of ED. Systematic searches were conducted in 15 electronic databases, with no language restrictions. Hand-searches included conference proceedings and the authors' files. All clinical studies of acupuncture as a treatment for ED were considered for inclusion, and their methodological quality was assessed using the Jadad score. Of the 4 studies included, 1 RCT showed beneficial effects of acupuncture compared with sham acupuncture in terms of response rate, while another RCT found no effects of acupuncture. The remaining 2 studies were uncontrolled clinical trials. Collectively, these data showed that RCTs of acupuncture for ED are feasible but scarce. Most investigations had methodological flaws (e.g., inadequate study design, poor reporting of results, small sample size, and publication without appropriate peer review process). The authors concluded that the evidence is insufficient to suggest that acupuncture is an effective intervention for treating ED. They stated that further research is needed to examine if there are specific benefits of acupuncture for men with ED.

There is emerging interest in the use of adipose-derived stem cells for treatment of Peyronie's disease. Adipose-derived stem cells (ADSCs) are a somatic stem cell population contained in fat tissue that possess the ability for self-renewal, differentiation into one or more phenotypes, and functional regeneration of damaged tissue, which may benefit the recovery of erectile function. Lin et al (2009) reviewed available evidence concerning ADSCs availability, differentiation into functional cells, and the potential of these cells for the treatment of ED. These researchers examined data from 1964 to 2008 that were associated with the definition, characterization, differentiation, and application of ADSCs, as well as other kinds of stem cells for stem cell-based therapies of erectile dysfunction. They noted that ADSCs are para-vascularly localized in the adipose tissue. Under specific induction medium conditions, these cells differentiated into neuron-like cells, smooth muscle cells, and endothelium in vitro. The

insulin-like growth factor/insulin-like growth factor receptor pathway participates in neuronal differentiation while the fibroblast growth factor 2 pathway is involved in endothelium differentiation. In a preliminary in vivo experiment, the ADSCs functionally recovered the damaged erectile function. However, the underlying mechanism needs to be further examined. The authors concluded that ADSCs are a potential source for stem cell-based therapies, which imply the possibility of an effective clinical therapy for ED in the near future.

Other treatments for ED include inflatable penile prostheses, and vacuum erectile devices, and vascular surgery. Hellstrom and colleagues (2010) provided state-of-the-art knowledge regarding the treatment of ED by implant, mechanical device, and vascular surgery, representing the opinions of 7 experts from 5 countries developed in a consensus process over a 2-year period. The inflatable penile prosthesis (IPP) is indicated for the treatment of patients with organic ED after failure or rejection of other treatment options. Comparisons between the IPP and other forms of ED therapy generally reveal a higher satisfaction rate in men with ED who chose the prosthesis. Organic ED responds well to vacuum erection device (VED) therapy, especially among men with a sub-optimal response to intra-cavernosal pharmacotherapy. After radical prostatectomy, VED therapy combined with PDE-5 therapy improved sexual satisfaction in patients dissatisfied with VED alone. Penile re-vascularization surgery seems most successful in young men with absence of venous leakage and isolated stenosis of the internal pudendal artery following perineal or pelvic trauma. Currently, surgery to limit venous leakage is not recommended. The authors stated that more research is needed in the area of re-vascularization surgery, in particular, venous outflow surgery.

Hilz and Marthol (2003) stated that neurogenic, particularly autonomic disorders, frequently contribute to the etiology and pathophysiology of ED. Parasympathetic and sympathetic outflow mediates erection. Non-cholinergic, non-adrenergic neurotransmitters induce activation of cyclic monophosphates, leading to relaxation of smooth muscles of the corpora cavernosa and by this to tumescence and rigidity, i.e., erection. The diagnosis of neurologic causes of ED requires a detailed history and neurologic examination. Conventional neurophysiological procedures evaluate the function of rapidly conducting, thickly myelinated nerve fibers only. Therefore, techniques such as sphincter ani externus electromyography, latency measurements of the pudendal nerve or bulbocavernosus reflex studies frequently do not contribute to the diagnostic process. The evaluation of small nerve fibers that are essential for erection, for example by means of psychophysical quantitative thermo-testing, might improve the diagnosis of neurogenic causes of ED. In addition, the assessment of heart rate variability at rest, during metronomic breathing, Valsalva maneuver, and active standing might be helpful to identify an autonomic neuropathy as the cause of ED.

Hamdan and Al-Matubsi (2009) noted that ED etiology is multi-factorial, including endocrine, neurological, vascular, systemic disease, local penile disorders, nutrition, psychogenic factors, and drug-related. This study was performed to compare the relevant comprehensive biochemical parameters as well as the clinical characteristics in diabetic ED and healthy control subjects and to assess the occurrence of penile neuropathy in diabetic patients and thus the relationship between ED and diabetes. A total of 56 patients accepted to undergo assessment for penile vasculature using intracavernosal injection and color Doppler ultrasonography. Of the 56 diabetic patients, 38 patients were found with normal blood flow and thus they were considered as the diabetic-ED group, whereas, ED diabetic patients with an arteriogenic component were excluded. These patients with an age range between 17 and 58 years, complaining of ED, with duration of diabetic illness ranging from 2 to 15 years. The control group comprised of 30 healthy subject aged between 19 and 55 years. Peripheral venous levels of testosterone, prolactin, follicle stimulating hormone (FSH), luteinizing hormone (LH), thyroid stimulating hormone (TSH), malondialdehyde and glycosylated hemoglobin (HbA(1)c) were obtained in all subjects. Valsalva maneuver and neurophysiological tests were also determined. Testosterone, prolactin, FSH, LH, and TSH hormones of the diabetic patients were not significantly different from those of the control group. Diabetic patients with ED have higher HbA(1)c and oxidative stress levels while the R-R ratio was significantly decreased. Bulbocavernosus reflex latency was significantly prolonged, whereas its amplitude, the conduction velocity and amplitude of dorsal nerve of penis were significantly reduced in the diabetic patients. The authors concluded that although ED is a multi-factorial disorder, yet, the present study revealed that in ED patients without arteriogenic ED a neurogenic component is present. Furthermore, the complex effect of the Valsalva maneuver on cardiovascular function is the basis of its usefulness as a measure of autonomic function. Thus, it can be of value in the diagnosis of ED although these hypotheses require follow-up in a large study cohort.

Lin et al (2012) noted that current therapeutic options for ED are less effective for patients having cavernous nerve (CN) injury or diabetes mellitus-related ED. These 2 types of ED are thus the main focus of past and current stem cell (SC) therapy studies. In a total of 16 studies so far, rats were exclusively used as disease models and SCs were mostly derived from bone marrow, adipose tissue, or skeletal muscle. For tracking, SCs were labeled with LacZ, green fluorescent protein, 4',6-diamidino-2-phenylindole, DiI, bromodeoxyuridine, or 5-ethynyl-2-deoxyuridine, some of which might have led to data misinterpretation. Stem cell transplantation was done exclusively by intra-cavernous (IC) injection, which has been recently shown to have systemic effects. Functional assessment was done exclusively by measuring increases of IC pressure during electro-stimulation of CN. Histological assessment usually focused on endothelial, smooth muscle, and CN contents in the penis. In general, favorable outcomes have been obtained in all trials so far, although whether SCs had differentiated into specific cell lineages remains controversial. Recent studies have shown that intra-cavernously injected SCs rapidly

escaped the penis and homed into bone marrow. This could perhaps explain why intra-cavernously injected SCs had systemic anti-diabetic effects and prolonged anti-ED effects. The authors stated that these hypotheses and the differentiation-versus-paracrine debate require further investigation.

In an open-label, single-arm, prospective study, Gruenwald and colleagues (2012) noted that low-intensity extracorporeal shock wave therapy (LI-ESWT) has been reported as an effective treatment in men with mild and moderate ED. These investigators determined the effectiveness of LI-ESWT in severe ED patients who were poor responders to PDE-5 inhibitor (PDE5i) therapy. Patients with an erection hardness score (EHS) less than or equal to 2 at baseline were included in this study. The protocol comprised 2 treatment sessions per week for 3 weeks, which were repeated after a 3-week no-treatment interval. Patients were followed at 1 month (FU1), and only then an active PDE5i medication was provided for an additional month until final follow-up visit (FU2). At each treatment session, LI-ESWT was applied on the penile shaft and crus at 5 different anatomical sites (300 shocks, 0.09 mJ/mm(2) intensity at 120 shocks/min). Each subject underwent a full baseline assessment of erectile function using validated questionnaires and objective penile hemodynamic testing before and after LI-ESWT. Outcome measures used were changes in the International Index of Erectile Function-erectile function domain (IIEF-ED) scores, the EHS measurement, and the 3 parameters of penile hemodynamics and endothelial function. A total of 29 men (mean age of 61.3 years) completed the study. Their mean IIEF-ED scores increased from 8.8 +/- 1 (baseline) to 12.3 +/- 1 at FU1 ($p = 0.035$). At FU2 (on active PDE5i treatment), their IIEF-ED further increased to 18.8 +/- 1 ($p < 0.0001$), and 72.4 % ($p < 0.0001$) reached an EHS of greater than or equal to 3 (allowing full sexual intercourse). A significant improvement ($p = 0.0001$) in penile hemodynamics was detected after treatment and this improvement significantly correlated with increases in the IIEF-ED ($p < 0.05$). No noteworthy adverse events were reported. The authors concluded that penile LI-ESWT is a new modality that has the potential to treat a subgroup of severe ED patients. Moreover, they stated that these preliminary data need to be confirmed by multi-center sham control studies in a larger group of ED patients with long-term follow-up.

Zhang et al (2013) stated that several studies have reported the influence of the insertion/deletion (I/D) polymorphism in the angiotensin-converting enzyme (ACE) gene on ED susceptibility, but the results remain controversial. These investigators performed a meta-analysis using data published to derive a more precise estimation of the relationship,. A total of 6 case-control studies, including 1,039 cases and 927 controls, were selected. The pooled odds ratios (ORs) and respective 95 % CIs were calculated by comparing the carriers of D-allele with the wild homozygotes (ID + DD versus II). Comparisons of other genetic models were also performed (ID + II versus DD, DD versus II, DI versus II and D versus I). In the overall analysis, no significant association between the polymorphism and ED risk was observed (OR = 1.07, 95

% CI: 0.84 to 1.37, p = 0.575 for ID + DD versus II). In the subgroup analysis by ethnic, no significant association was detected among Asian, Latino and European for the comparison of ID + DD versus II (Asian: OR = 1.27, 95 % CI: 0.89 to 1.81; Latino: OR = 0.76, 95 % CI: 0.46 to 1.27; European: OR = 1.06, 95 % CI: 0.67 to 1.66). Results from other comparative genetic models also indicated the lack of associations between this polymorphism and ED risk. The authors concluded that this meta-analysis indicated that the ACE I/D polymorphism might not contribute to the risk of ED.

Xu and colleagues (2013) evaluated the effect of continuous positive airway pressure (CPAP) on ED in patients with obstructive sleep apnea syndrome (OSAS). These investigators searched Cochrane Library, PubMed, China Academic Journal Full-Text Database, Chinese Biomedical Literature Database, Wanfang Resource Database and Chinese Journal Full-Text Database for clinical trials on the effect of CPAP on ED in OSAS patients. They identified the trials according to inclusion and exclusion criteria, evaluated their quality, and then extracted valid data for meta-analysis. These researchers included 4 articles, 3 in English and 1 in Chinese, involving 77 cases of OSAS with ED. Meta-analysis revealed no statistically significant heterogeneity among different studies (p = 0.80; I2 = 0 %), and therefore the fixed effect model was used for the analysis, which showed a significant increase in the IIEF-5 score after CPAP treatment (WMD = 4.19, 95 % CI: 3.01 to 5.36, p < 0.001). The authors concluded that the existing evidence from clinical trials showed that the CPAP therapy can significantly improve ED in OSAS patients. Moreover, they stated that its effectiveness has to be verified by RCTs of higher quality and larger sample size.

In a placebo-controlled, prospective, randomized, single-blind clinical trial, Hatzichristodoulou and colleagues (2013) examined the effectiveness of ESWT in the treatment of patients with Peyronie's disease. Subjects (n = 102) were randomly assigned (n = 51) to each group (ESWT or placebo). All patients were given 6 weekly treatments. Patients in the ESWT-group received 2,000 shock waves per session, using the Piezoson 100 lithotripter (Richard Wolf, Knittlingen, Germany). Patients in the placebo-group were treated with interposition of a plastic membrane, which prevented any transmission of shock waves. Primary end-point was decrease of pain between baseline and after 4 weeks follow-up. Secondary end-points were changes in deviation, plaque size, and sexual function. Pain was assessed by a visual analog scale (VAS). Deviation was measured by a goniometer after artificial erection using Alprostadil (Viridal®, Schwarz Pharma, Monheim, Germany). Plaque size was measured with a ruler and sexual function assessed by a scale regarding the ability to perform sexual intercourse. Overall, only 45 patients experienced pain at baseline. In the subgroup analysis of these patients, pain decreased in 17/20 (85.0 %) patients in the ESWT group and 12/25 (48.0 %) patients in the placebo group (p = 0.013, relative risk [RR] = 0.29, 95 % CI: 0.09 to 0.87). Penile deviation was not reduced by ESWT (p = 0.66) but worsened in 20/50 (40 %) and 12/49 (24.5 %) patients of

the ESWT and placebo-group, respectively (p = 0.133). Plaque size reduction was not different between the 2 groups (p = 0.33). Additional, plaque size increased in 5 patients (10.9 %) of the ESWT group only. An improvement in sexual function could not be verified (p = 0.126, RR = 0.46). The authors concluded that despite some potential benefit of ESWT in regard to pain reduction, it should be emphasized that pain usually resolves spontaneously with time. Moreover, they stated that given this and the fact that deviation may worsen with ESWT, this treatment cannot be recommended.

Jordan et al (2014) stated that Peyronie's disease (PD) is often physically and psychologically devastating for patients, and the goal of treatment is to improve symptoms and sexual function without adding treatment-related morbidity. The potential for treatment-related morbidity after more invasive interventions (e.g. surgery) creates a need for effective minimally invasive treatments. These investigators examined the available literature using levels of evidence to determine the reported support for each treatment. Most available minimally invasive treatments lack critical support for effectiveness due to the absence of RCTs or non-significant results after RCTs. Iontophoresis, oral therapies (e.g., vitamin E, potassium para-aminobenzoate, tamoxifen, carnitine, and colchicine), ESWT, and intra-lesional injection with verapamil or nicardipine have shown mixed or negative results. Treatments that have decreased penile curvature deformity in Level 1 or Level 2 evidence-based, placebo-controlled studies include intra-lesional injection with interferon α-2b or collagenase clostridium histolyticum.

Cai et al (2014) evaluated the effect of statins for ED. These investigators performed a systematic review of the literature using the Cochrane Library, Embase and PubMed from the inception of each database to June 2013. Only RCTs comparing treatment for ED with statins were identified. Placebo RCTs with the IIEF as the outcome measure were eligible for meta-analysis. A total of 7 RCTs including 2 statins with a total of 586 patients strictly met selection criteria for systematic review and 5 of them qualified for the meta-analysis. A meta-analysis using a random effects model showed that statins were associated with a significant increase in IIEF-5 scores (mean difference (MD): 3.27; 95 % CI:1.51 to 5.02; p < 0.01) and an overall improvement of lipid profiles including total cholesterol (MD: -1.08; 95 % CI: -1.68 to -0.48; p < 0.01), low-density lipoprotein (LDL) cholesterol (MD: -1.43; 95 % CI: -2.07 to -0.79; p < 0.01), high-density lipoprotein (HDL) cholesterol (MD: 0.24; 95 % CI: 0.13 to 0.35; p < 0.01) and triglycerides (TGs) (MD: -0.55; 95 % CI: -0.61 to -0.48; p < 0.01). The authors concluded that the findings of this study revealed positive consequences of these lipid-lowering drugs on erectile function, especially for non-responders to PDE5is. However, it has been reported that statin therapy may reduce levels of testosterone and aggravate symptoms of ED. They stated that larger, well-designed RCTs are needed to investigate the double-edged role of statins in the treatment of ED.

Furthermore, an UpToDate review on “Treatment of male sexual dysfunction” (Cunningham and Seftel, 2014) does not mention nicardipine and statins as therapeutic options.

Collagenase Clostridium Histolyticum Injection

Jordan (2008) evaluated the safety and effectiveness of intra-lesional clostridial collagenase injection therapy in a series of patients with Peyronie's disease. A total of 25 patients aged 21 to 75 years who were referred to a single institution with a well-defined Peyronie's disease plaque were treated with three intra-lesional injections of clostridial collagenase 10,000 units in a small volume (0.25 cm(3) per injection) administered over 7 to 10 days, with a repeat treatment (i.e., 3 injections of collagenase 10,000 units/25 cm(3) injection over 7 to 10 days) at 3 months. Primary efficacy measures were changes from baseline in the deviation angle and plaque size. Secondary efficacy end-points were patient responses to a Peyronie's disease questionnaire and improvement according to the investigators' global evaluation of change. The primary efficacy measures were change in deviation angle and change in plaque size. Secondary end-points were patient questionnaire responses and improvement according to the investigators' global evaluation of change. Significant decreases from baseline were achieved in the mean deviation angle at months 3 ($p = 0.0001$) and 6 ($p = 0.0012$), plaque width at months 3 ($p = 0.0052$), 6 ($p = 0.0239$), and 9 ($p = 0.0484$), and plaque length at months 3 ($p = 0.0018$) and 6 ($p = 0.0483$). More than 50 % of patients in this series considered themselves "very much improved" or "much improved" at all time-points in the study, and the drug was generally well-tolerated. The authors concluded that the benefits of intra-lesional clostridial collagenase injections in this trial lent support to prior studies supporting its use in the management of Peyronie's disease. Moreover, they noted that a double-blind, placebo-controlled study is currently under development.

In a phase IIb, double-blind, randomized, placebo-controlled study, Gelbard and colleagues (2012) examined the safety and effectiveness of collagenase Clostridium histolyticum and assessed a patient reported outcome questionnaire. A total of 147 subjects were randomized into 4 groups to receive collagenase C. histolyticum or placebo (3:1) with or without penile plaque modeling (1:1). Per treatment cycle 2 injections of collagenase C. histolyticum (0.58 mg) were given 24 to 72 hours apart. Subjects received up to 3 cycles at 6-week intervals. When designated, investigator modeling was done 24 to 72 hours after the second injection of each cycle. These researchers evaluated penile curvature by goniometer measurement, patient reported outcomes and adverse event profiles. After collagenase C. histolyticum treatment significant improvements in penile curvature (29.7 % versus 11.0 %, $p = 0.001$) and patient reported outcome symptom bother scores ($p = 0.05$) were observed compared to placebo. In modeled subjects 32.4 % improvement in penile curvature was observed in those on collagenase C. histolyticum compared to 2.5 % worsening of curvature in those on placebo ($p <$

0.001). Those treated with collagenase C. histolyticum who underwent modeling also showed improved Peyronie disease symptom bother scores (p = 0.004). In subjects without modeling there were minimal differences between the active and placebo cohorts. Most adverse events in the collagenase C. histolyticum group occurred at the injection site and were mild or moderate in severity. No treatment related serious adverse events were reported. The authors concluded that collagenase C. histolyticum treatment was well-tolerated. Moreover, they noted significant improvement in penile curvature and patient reported outcome symptom bother scores, suggesting that this may be a safe, non-surgical alternative for Peyronie disease.

Gelbard et al (2013) stated that IMPRESS (Investigation for Maximal Peyronie's Reduction Efficacy and Safety Studies) I and II examined the clinical safety and effectiveness of collagenase C. histolyticum intra-lesional injections in subjects with Peyronie disease. Co-primary outcomes in these identical phase III randomized, double-blind, placebo controlled studies included the percent change in the penile curvature abnormality and the change in the Peyronie disease questionnaire symptom bother score from baseline to 52 weeks. IMPRESS I and II examined collagenase C. histolyticum intra-lesional injections in 417 and 415 subjects, respectively, through a maximum of 4 treatment cycles, each separated by 6 weeks. Men received up to 8 injections of 0.58 mg collagenase C. histolyticum that are 2 injections per cycle separated by approximately 24 to 72 hours with the second injection of each followed 24 to 72 hours later by penile plaque modeling. Men were stratified by baseline penile curvature (30 to 60 versus 61 to 90 degrees) and randomized to collagenase C. histolyticum or placebo 2:1 in favor of the former. Post hoc meta-analysis of IMPRESS I and II data revealed that men treated with collagenase C. histolyticum showed a mean 34 % improvement in penile curvature, representing a mean ± SD -17.0 ± 14.8 degree change per subject, compared with a mean 18.2 % improvement in placebo treated men, representing a mean -9.3 ± 13.6 degree change per subject (p <0.0001). The mean change in Peyronie disease symptom bother score was significantly improved in treated men versus men on placebo (-2.8 ± 3.8 versus -1.8 ± 3.5, p = 0.0037). Three serious adverse events (corporeal rupture) were surgically repaired. The authors concluded that IMPRESS I and II supported the clinical safety and effectiveness of collagenase C. histolyticum for the physical and psychological aspects of Peyronie disease.

On December 6, 2013, the FDA approved a new use for Xiaflex (collagenase clostridium histolyticum) as the first FDA-approved medicine for the treatment of Peyronie’s disease. A treatment course for Peyronie’s disease consists of a maximum of 4 treatment cycles. Each treatment cycle consists of 2 Xiaflex injection procedures (in which Xiaflex is injected directly into the collagen-containing structure of the penis) and 1 penile modeling procedure performed by the health care professional. The safety and effectiveness of Xiaflex for the treatment of Peyronie’s disease were established in 2 randomized double-blind, placebo-controlled studies in 832 men with Peyronie’s disease with penile curvature deformity of at least 30 degrees.

Participants were given up to 4 treatment cycles of Xiaflex or placebo and were then followed 52 weeks. Xiaflex treatment significantly reduced penile curvature deformity and related bothersome effects compared with placebo. The most common adverse reactions associated with use of Xiaflex for Peyronie's disease include penile hematoma, penile swelling and penile pain.

According to the FDA, when prescribed for the treatment of Peyronie's disease, Xiaflex is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) because of the risks of serious adverse reactions, including penile fracture (rupture of one of the penile bodies within the penile shaft, also known as corporal rupture) and other serious penile injury. Xiaflex for the treatment of Peyronie's disease should be administered by a health care professional who is experienced in the treatment of male urological diseases. The REMS requires participating health care professionals to be certified within the program by enrolling and completing training in the administration of Xiaflex treatment for Peyronie's disease. The REMS also requires health care facilities to be certified within the program and ensure that Xiaflex is dispensed only for use by certified health care professionals.

Nitric Oxide Synthase Polymorphisms

Liu and colleagues (2015) stated that ED is a frequent disorder in men and has a serious impact on the quality of the patient's life. Recent studies have examined the relationship between endothelial nitric oxide synthase (eNOS) polymorphisms and ED. However, the results remain inconclusive. The present study aimed to offer an actual view of estimating the correlation between eNOS polymorphisms and ED. These investigators performed a meta-analysis to estimate the association between eNOS polymorphisms and ED risk. Databases employed for data mining until December 1, 2014 included PubMed, Web of Science, and the Chinese National Knowledge Infrastructure. Two study investigators independently conducted a literature search and data extraction. Odds ratios with 95 % CIs for the risk were calculated by using a random effects model or fixed effects model. A total of 20 studies in 13 publications increased ED risk in allele contrast, dominant, heterozygote, and homozygote models (allele contrast: OR = 1.514, 95 % CI were included in the meta-analysis. In the overall comparison, the eNOS G984T polymorphism was associated with an [CI]: 1.019 to 2.248). For 4 VNTR polymorphisms, the overall analysis showed a significant association between homozygote comparison and recessive genetic model (homozygote comparison: OR = 1.917, CI: 1.073 to 3.424). The eNOS T786C polymorphism increased ED risk in allele contrast, homozygote, and recessive models (allele contrast: OR = 1.588, CI: 1.316 to 1.915). Significant heterogeneity was mainly observed in studies on the G894T polymorphism. No publication bias was detected in all of the variants. The authors concluded that the eNOS polymorphisms G894T, 4 VNTR, and T786C were

associated with an increased risk for ED. However, they stated that these results are still preliminary; further studies based on different confounders and using a large population size should be conducted to generate more accurate and reliable conclusions.

Dai and associates (2015) noted that the gene encoding eNOS is an interesting candidate gene for understanding the physiopathology of ED. However, an association between eNOS G894T polymorphism and ED risk is uncertain and should be updated. Therefore, a meta-analysis of the current literature was necessary to clarify this relationship. These investigators searched PubMed and China National Knowledge Infrastructure (CNKI) (last search updated on December 12, 2013) using “nitric oxide synthase”, “polymorphism or variant”, “genotype”, and “ED” as keywords. They also searched reference lists of studies corresponding to the inclusion criteria for the meta-analysis. These studies involved the total number of 1,445 ED men and 1,459 healthy control men subjects. Odds ratio and 95 % CIs were used to evaluate this relationship. Statistical analysis was performed with STATA10.0. In the overall analysis, significantly decreased associations between ED risk and eNOS G894T polymorphism were found. Moreover, in the subgroup analysis based on ethnicity, similar significant associations were detected in both Caucasians (such as GG+GT versus TT: OR 0.92, 95 % CI: 0.86 to 0.97) and Asians (such as GG+GT versus TT: OR 0.24, 95 % CI: 0.07 to 0.85). The Egger's test did not reveal the presence of a publication bias. The authors concluded that their investigations demonstrated that eNOS G894T polymorphism might protect men against ED risk. Moreover, they stated that further studies based on larger sample size and gene-environment interactions should be conducted.

Extracorporeal Shock Wave Therapy

Zou and colleagues (2017) noted that the role of LI-ESWT in ED is not clearly determined. These investigators examined the short-term safety and effectiveness of LI-ESWT for ED patients. Relevant studies were searched in Medline, Embase, Cochrane Library, China National Knowledge Infrastructure (CNKI), WANFANG and VIP databases. Effective rate in terms of IIEF-Erectile Function Domain (IIEF-EF) and EHS at about 1 month after LI-ESWT was extracted from eligible studies for meta-analysis to calculate RR of effective treatment in ED patients treated by LI-ESWT compared to those receiving sham-treatment. A total of 15 studies were included in the review, of which 4 RCTs were for meta-analysis. Effective treatment was 8.31 [95 % CI: 3.88 to 17.78] times more effective in the LI-ESWT group (n = 176) than in the sham-treatment group (n = 101) at about 1 month after the intervention in terms of EHS, while it was 2.50 (95 % CI: 0.74 to 8.45) times more in the treatment group (n = 121) than in the control group (n = 89) in terms of IIEF-EF; 9-week protocol with energy density of 0.09 mJ/mm2 and 1,500 pluses appeared to have better therapeutic effect than 5-week protocol. No significant adverse event (AE) was reported. The authors concluded that LI-ESWT, as a non-invasive

treatment, has potential short-term therapeutic effect on patients with organic ED irrespective of sensitivity to PDE5is. Moreover, they stated that owing to the limited number and quality of the studies, more large-scale, well-designed and long-term follow-up time studies are needed to confirm this analysis.

In a double-blinded, sham-controlled, randomized clinical trial, Fojecki and associates (2017) evaluated the treatment outcome of linear Li-ESWT (LLi-ESWT) for ED. Men with ED (n = 126) and a score lower than 25 points on the IIEF-EF were included. Subjects were allocated to receive LLi-ESWT once-weekly for 5 weeks or sham treatment once-weekly for 5 weeks. After a 4-week break, the 2 groups received active treatment once-weekly for 5 weeks. Subjects completed the IIEF, EHS, Sexual Quality of Life-Men, and the Erectile Dysfunction Inventory of Treatment Satisfaction at baseline, after 9 weeks, and after 18 weeks. The primary outcome measurement was an increase of at least 5 points on the IIEF-EF score. The secondary outcome measurement was an increased EHS score to at least 3 in men with a score no higher than 2 at baseline. Data were analyzed by linear and logistic regression. Mean IIEF-EF scores were 11.5 at baseline (95 % CI: 9.8 to 13.2), 13.0 after 5 sessions (95 % CI: 11.0 to 15.0), and 12.6 after 10 sessions (95 % CI: 11.0 to 14.2) in the sham group and correspondingly 10.9 (95 % CI: 9.1 to 12.7), 13.1 (95 % CI: 9.3 to 13.4), and 11.8 (95 % CI: 10.1 to 13.4) in the ESWT group. Success rates based on IIEF-EF score were 38.3 % in the sham group and 37.9 % in the ESWT group (OR = 0.95, 95 % CI: 0.4 to -2.02, p = 0.902). Success rates based on EHS score were 6.7 % in the sham group and 3.5 % in the ESWT group (OR = 0.44, 95 % CI: 0.08 to 2.61, p = 0.369). The authors concluded that no clinically relevant effect of LLi-ESWT on ED was found.

In a systematic review and meta-analysis, Man and Li (2018) evaluated the effectiveness of LI-ESWT for the treatment of ED. These researchers carried out a comprehensive search of the PubMed, Cochrane Register and Embase databases to March 2017 for RCTs reporting on patients with ED treated with LI- ESWT. The IIEF and the EHS were the most commonly used tools to evaluate the effectiveness of LI-ESWT. There were 9 studies including 637 patients from 2005 to 2017. The meta-analysis revealed that LI-ESWT could significantly improve IIEF (MD: 2.54; 95 % CI: 0.83 to 4.25; p = 0. 004) and EHS (risk difference [RD]: 0.16; 95 % CI: 0.03 to 0.28; p = 0.01)). Therapeutic efficacy could last at least 3 months (MD: 4.15; 95 % CI: 1.40 to 6.90; p = 0.003). Lower energy density (0.09mj/mm2, MD: 4.14; 95 % CI: 0.87 to 7.42; p = 0.01) increased number of pulses (3,000 pulses per treatment, MD: 5.11; 95 % CI: 3.18 to 7.05, p < 0.0001) and shorter total treatment courses (less than 6 weeks, MD: 3.73; 95 % CI: 0.54 to 6.93; p = 0.02) resulted in better therapeutic efficacy. The authors concluded that the findings of these studies suggested that LI-ESWT could significantly improve the IIEF and EHS of ED patients. Moreover, they stated that the publication of robust evidence from additional RCTs and longer-term follow-up would provide more confidence regarding use of LI-ESWT for ED patients.

Serum Biomarkers of Erectile Dysfunction

Patel and colleagues (2017) stated that ED is a common complication in patients with diabetes mellitus (DM). However, the utility of serum biomarkers as clinical surrogates for the development and/or progression of ED is unknown. These investigators summarized the current literature for serum biomarkers for ED in DM and emphasized areas for future research. Main outcome measures were human subject data demonstrating the utility of serum markers for the development and progression of ED in patients with DM. These researchers performed a systematic PubMed-Medline search in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement using Medical Subject Headings (MeSH) for articles published from January 1, 2000 through December 31, 2016 of serum biomarkers for development or progression of ED in patients with DM using erectile dysfunction [MeSH] AND (biomarkers [MeSH] or inflammation mediators [MeSH] or intercellular signaling peptides and proteins [MeSH] or cell adhesion molecules [MeSH]). A thorough review of these studies was completed. Of the 327 abstracts screened, 12 full-text studies were assessed and 1 study was excluded. A total of 11 studies assessing serum biomarkers for ED in patients with DM were included in this review. The most studied serum biomarkers for ED in men with DM included endothelial dysfunction markers such as serum E-selectin, endothelial progenitor cells, and endothelial micro-particles and specific markers of inflammation such as interleukin (IL)-10, ratio of tumor necrosis factor-alpha (TNF-α) to IL-10, and reactive oxygen species such as nitric oxide and malondialdehyde. The authors concluded that serum biomarkers for ED in men with DM are very limited. They stated that future longitudinal studies with uniform patient characteristics are needed to evaluate the potential clinical use of serum biomarkers in men with DM for the development and progression of ED.

Botulinum Toxin for the Treatment of Erectile Dysfunction

Ghanem and colleagues (2018) noted that botulinum toxin type A (BoNT-A) has been used to treat several striated and smooth muscle disorders. During the past year, human and animal studies conducted in Egypt and Canada by 2 different groups of investigators have suggested a possible role for the intra-cavernosal injection of BoNT-A in the treatment of ED. These investigators discussed BoNT-A and its current medical uses, the rationale for its new potential use in the treatment of ED, and the available evidence and concerns. They performed a literature search; and this review was based on the available studies presented at the European Society for Sexual Medicine, Sexual Medicine Society of North America, and International Society for Sexual Medicine meetings in 2016 by the 2 groups. Main outcome measures were sinusoidal diameter, penile color Doppler study, Erection Hardness Score, Sexual Health Inventory for Men questionnaire, and Sexual Encounter Profile questions 2 and 3. Two human studies conducted by the authors and 2 animal studies (1 from the authors' group and 1 from

Canada) were reviewed. These findings appeared to suggest generally favorable outcomes with the use of BoNT-A in the treatment of ED. The authors concluded that BoNT-A could be a potential therapy for ED. Moreover, they stated that in addition to the findings of the 3 pilot studies, larger multi-center trials are needed to further explore the true therapeutic efficacy and clinical safety of BoNT-A in the treatment of ED.

Acoustical Wave Therapy (Alpha Wave SwissWave Protocol)

Alpha Wave's SwissWave Protocol (acoustical wave therapy) uses a Swiss-made medical device cleared by the FDA for use on the human body as a massage device for soft tissue repair and improved blood flow, among other uses. However, there is a lack of evidence regarding the effectiveness of Alpha Wave (acoustical wave therapy) for the treatment of ED.

Adipose-Derived Regenerative Cells (ADRC) Therapy for the Treatment of Erectile Dysfunction

In an open-label, phase-I clinical trial, Haahr and colleagues (2018) examined the safety of adipose-derived regenerative cells (ADRC) therapy in the treatment of ED. A total of 21 patients with ED after radical prostatectomy (RP), with no signs of recovery using conventional therapy, received a single intra-cavernous injection of autologous ADRC and were followed for 1 year; 6 men were incontinent, and 15 were continent at inclusion. The primary (safety of ADRC therapy) and secondary end-points (sexual function) were evaluated at 1, 3, 6, and 12 months after ADRC injection by registration of AEs and validated questionnaires using the IIEF-5 and EHS. No serious adverse events (SAEs) occurred, but 8 reversible minor events related to the liposuction were noted; 8 out of 15 (53 %) patients in the continent group reported erectile function sufficient for intercourse at 12 months. Baseline median IIEF-5 scores (6.0; inter-quartile range [IQR] 3) were unchanged 1 month after the treatment, but significantly increased after 6 to 7 (IQR 17). This effect was sustained at 12 months (median of 8; IQR 14). These researchers did not see any improvements in erectile function in the group of incontinent men or among men with ED prior to RP. The authors concluded that intra-cavernous injection of ADRC was safe in this phase-I clinical trial with a 12 month follow-up. These preliminary findings need to be further investigated in phase-II/III clinical trials.

Measurement of Serum Melatonin Levels for the Diagnosis of Erectile Dysfunction

Bozkurt and associates (2018) noted that melatonin is a hormone secreted from the pineal gland and has anti-oxidative and anti-inflammatory effects. Oxidative stress is considered as an important factor in the etiology of ED, and in many experimental models, positive results have been obtained with melatonin treatment. These investigators measured serum melatonin levels in ED patients and examined the possible relationship between ED and melatonin levels. A total

of 62 patients diagnosed with mild, moderate or severe ED according to the IIEF-5 and 22 healthy individuals were included in the study. The serum melatonin levels, anthropometric data, and other biochemical and hormonal parameters of all the subjects were recorded. Detailed anamnesis was also obtained in terms of diabetes, hypertension, cardiovascular diseases, smoking status, and alcohol use. The serum melatonin level was found 34.2 ± 13.3 ng/dL in the mild ED group, 33.3 ± 14.7 ng/dL in the moderate ED group, 34.8 ± 17.2 ng/dL in the severe ED group, and 44.6 ± 16.5 ng/dL in the control group. The serum melatonin levels were significantly lower in all ED groups compared to the control group ($p = 0.019$). There was no significant difference in the serum melatonin levels between the 3 ED groups. Diabetes, hypertension, cardiovascular diseases, smoking and alcohol use were not significantly different between the ED groups ($p > 0.05$). The authors considered that if their findings are supported by further studies with larger populations, the measurement of the serum melatonin level may have a future role in the diagnosis and treatment of ED.

The authors stated that this was the first study evaluating serum melatonin level as a causative factor in this patient group. A low serum melatonin level may result in an inadequate erection by preventing sufficient antioxidant capacity. There is a need for additional studies to determine the exact role of melatonin deficiency in ED patients. The drawbacks of this study were the absence of Doppler ultrasound findings, the lack of a treatment group and follow-up data on melatonin levels and the small sample size ($n = 62$). They stated that future studies may evaluate the association or a possible correlation between serum melatonin levels and Doppler ultrasound parameters of erectile function.

Shear Wave Elastography for the Diagnosis of Erectile Dysfunction

Cui and colleagues (2018) examined the effect of shear wave elastography (SWE) on the measurement of rigidity changes of penile erection in venogenic ED and in rigidity alterations of corpus cavernosum penis with age in normal population. The study was a prospective analysis of 81 patients referred to the department of urology with complaints of ED as well as 35 healthy volunteers; SWE was performed on the corpus cavernosum penis (CCP) in the flaccid state of healthy group. The patients were divided into venogenic ED (31 patients) and non-vascular ED (neither arterial insufficiency nor venogenic dysfunction) (36 patients) by performing color Doppler ultrasonography in association with intra-cavernous injection (ICI). SWE measurements were performed in CCP in the flaccid state, after 15 to 20 mins and 25 to 30 mins of ICI in both patients groups. Differences between groups were compared. Age was significantly negatively associated with SWE values of CCP among the 3 groups (healthy group: $r = -0.584$, $p < 0.05$; venogenic ED group: $r = -0.468$, $p < 0.05$; non-vascular ED group: $r = -0.539$, $p < 0.05$). There was no significant difference between the SWE values of the 3 groups in the flaccid state ($p > 0.05$). The mean SWE values of CCP were significantly lower in the erectile state (15 to

20 mins after ICI) compared with the flaccid state in 2 patients groups ($p < 0.05$). The mean SWE values of CCP after ICI increased with time (from 15 to 20 mins to 25 to 30 mins) in patients with venogenic ED ($p < 0.05$), while the SWE values of CCP after ICI did not statistically significantly differ with time in patients with non-vascular ED ($p > 0.05$). The authors concluded that SWE is expected to be a promising approach in terms of the etiological diagnosis of ED and the quantitative evaluation of alternations of penile structures with age.

Use of Serum Homocysteine Levels as Biomarkers for the Development and/or Progression of Erectile Dysfunction

Sansone and colleagues (2018) noted that elevated levels of serum homocysteine (Hcy) have been associated with cardiovascular diseases and endothelial dysfunction, conditions closely associated with ED. In a meta-analysis, these investigators examined serum Hcy levels in subjects with ED compared to controls in order to clarify the role of Hcy in the pathogenesis of ED. Medline, Embase, and the Cochrane Library were searched for publications investigating the possible association between ED and Hcy. Results were restricted by language, but no time restriction was applied. Standardized mean difference (SMD) was obtained by random effect models. A total of 9 studies were included in the analysis with a total of 1,320 subjects (489 subjects with ED; 831 subjects without ED). Pooled estimate was in favor of increased Hcy in subjects with ED with a SMD of 1.00, 95 % CI: 0.65 to 1.35, $p < 0.0001$. Subgroup analysis based on prevalence of diabetes showed significantly higher SMD in subjects without diabetes (1.34 (95 % CI: 1.08 to 1.60)) compared to subjects with diabetes (0.68 (95 % CI: 0.39 to 0.97), $p < 0.0025$ versus subgroup without diabetes). The authors concluded that findings from this meta-analysis suggested that increased levels of serum Hcy were more often observed in subjects with ED. They stated that based on existing literature on this topic, a causative role for hyperhomocysteinemia as an independent risk factor for ED could be postulated, although confirmation would require interventional studies aimed to decrease serum Hcy levels considering erectile function as primary outcome. These researchers stated that actually, only in rat model of hyperhomocysteinemia has been observed an improvement in erectile function after being treated with a demethylation agent. These investigators also reported significantly higher levels of Hcy in subjects without diabetes, compared to diabetic men. They noted that while one could assume that this is further proof of a multi-factorial pathogenesis for ED, it is also a clear indication that future research in this field should examine the possible association with other known risk factors such as smoking habit and obesity in order to adequately address the possible effects of different variates.

The authors stated that this study has several drawbacks, most notably the small number of studies ($n = 9$) involved and the lack of a clear definition of ED. A single study assessed presence of ED by means of a single question (“How would you describe your ability to get and

keep an erection that is adequate for satisfactory intercourse?"). The remaining studies used validated questionnaires: in detail, 4studies used the IIEF and 4 studies used the IIEF-5. However, most studies did not report separate measurements of serum Hcy based on the degree of severity of ED.

Epalrestat for the Treatment of Erectile Dysfunction

Yang and associates (2019) stated that epalrestat, an aldose reductase inhibitor (ARI), was adopted to improve the function of peripheral nerves in diabetic patients. These researchers examined if epalrestat could restore the erectile function of diabetic ED using a rat model. From June 2016, a total of 24 rats were given streptozocin (STZ) to induce the diabetic rat model, and epalrestat was administered to 10 diabetic ED (DED) rats. Intra-cavernous pressure (ICP) and mean systemic arterial pressure (MAP), levels of aldose reductase (AR), nerve growth factor (NGF), neuronal NOS (nNOS), alpha-smooth muscle antigen (α-SMA), and von Willebrand factor (vWF) in the corpus cavernosum were analyzed. These investigators discovered that epalrestat acted on cavernous tissue and partly restored erectile function; NGF and nNOS levels in the corpora were increased after treatment with epalrestat. The authors also found that the content of α-SMA-positive smooth muscle cells and vWF-positive endothelial cells in the corpora cavernosum were reduced. They concluded that epalrestat might improve erectile function by increasing the up-regulation of NGF and nNOS to restore the function of the dorsal nerve of the penis. These preliminary findings need to be further investigated.

Gene Therapy for Erectile Dysfunction

Gur and co-workers (2018) noted that ED is a common health problem in approximately 50 % of men of advanced age (40 to 70 years old). Recent attention related gene therapy to ED cases; this received much interest to further progress gene therapy for the treatment of ED. These investigators analyzed key challenges and emphasized primary areas, including mostly pre-clinical and few clinical trials, cellular target(s), and different viral vectors/nanoparticles for gene delivery in ED. While over-expression of target genes can be silenced by RNA interference (RNAi), down-regulation of these mechanisms has been implicated in ED. Although many patients with ED show high efficacy with PDE5i, this therapy is insufficient in 30 to 40 % of patients. Although several pre-clinical studies for ED treatment provided promising results, gene therapy has not shown promise in clinical practice, due to technical limitations of gene therapy to clinical translation and the ED pathogenesis. Developments in small RNA, such as siRNA, approaches for ED may lead to significant management for ED. Also, siRNA delivery into the corpus cavernosum appears to be a challenging issue and awaits further development. The

authors concluded that further investigation on several safety concerns of gene therapy, gene acquisition, preparation, and delivery are needed before any widespread application of gene therapy is used in ED.

Tacrolimus for the Treatment of Erectile Dysfunction

Mulhall and colleagues (2018) noted that RP is associated with ED, largely mediated through cavernous nerve injury. There are robust pre-clinical data supporting a potential role for neuro-modulatory agents in this patient population. In a randomized, double-blind trial, these investigators examined tacrolimus in improving erectile function recovery rates after RP. They compared tacrolimus 2 to 3 mg daily and placebo in men undergoing RP. Patients had localized prostate cancer and excellent baseline erectile function, underwent bilateral nerve-sparing RP, and were followed-up for at least 18 months after RP. Patients received study drug for 27 weeks and completed the IIEF-erectile function domain (EFD) questionnaire at baseline and serially after surgery. Main outcome measure was the IIEF-EFD score. Data were available for 124 patients (59 tacrolimus, 65 placebo); mean age was 54.6 ± 6.2 years. No patient experienced permanent creatinine or potassium elevation. At baseline, mean EFD scores were 28.6 ± 2.1 (tacrolimus group) and 29 ± 1.5 (placebo group). By week 5, mean EFD scores had dropped to 8 ± 9.4 (tacrolimus) and 9 ± 10.7 (placebo). At 18 months, mean EFD scores were 16.0 ± 11.3 (tacrolimus) and 20.2 ± 9.0 (placebo) ($p = 0.09$). Tacrolimus failed to meet significance (hazard ratio [HR] = 0.83; $p = 0.50$), with no difference in percentage of patients achieving normal spontaneous erectile function (EFD score greater than or equal to 24); time to normalization of EFD score (greater than or equal to 24); percentage of patients capable of intercourse in response to PDE5i; and time to achieve response to PDE5i. The authors concluded that despite positive animal data, oral tacrolimus as used in this trial failed to improve erectile function after nerve sparing RP. These researchers stated that this study was limited by a high attrition rate; its strengths included a randomized, placebo controlled design, extensive patient monitoring, use of medication diaries and a validated instrument as the primary outcome measure.

CPT Codes / HCPCS Codes / ICD-10 Codes

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":

Code	Code Description
CPT codes covered if selection criteria are met:	
37788	Penile revascularization, artery, with or without vein graft
54110 - 54112	Excision of penile plaque (Peyronie disease)

Code	Code Description
54200 - 54205	Injection procedure for Peyronie disease
54230	Injection procedure for corpora cavernosography
54231	Dynamic cavernosometry, including intracavernosal injection of vasoactive drugs (e.g., papaverine, phentolamine)
54235	Injection of corpora cavernosa with pharmacologic agent(s) (e.g., papaverine, phentolamine)
54400 - 54417	Penile prosthesis procedures
74445	Corpora cavernosography, radiological supervision and interpretation
78012	Thyroid uptake, single or multiple quantitative measurement(s) (including stimulation, suppression, or discharge, when performed)
80061	Lipid panel
80076	Hepatic function panel
81000 - 81003	Urinalysis, by dip stick or tablet reagent for bilirubin, glucose, hemoglobin, ketones, leukocytes, nitrite, pH, protein, specific gravity, urobilinogen, any number of these constituents
82565	Creatinine; blood
82947	Glucose; quantitative, blood (except reagent strip)
83001 - 83002	Gonadotropin; follicle stimulating hormone (FSH), and luteinizing hormone (LH)
83727	Luteinizing releasing factor (LRH)
84146	Prolactin
84152 - 84154	Prostate specific antigen (PSA)
84402 - 84403	Testosterone; free or total
84410	Testosterone; bioavailable, direct measurement (eg, differential precipitation)
84443	Thyroid stimulating hormone (TSH)
84479	Thyroid hormone (T3 or T4) uptake or thyroid hormone binding ratio (THBR)
85025 - 85027	Blood count; complete (CBC), automated
93975 - 93976	Duplex scan of arterial inflow and venous outflow of abdominal, pelvic, scrotal contents and/or retroperitoneal organs
93980 - 93981	Duplex scan of arterial inflow and venous outflow of penile vessels
CPT codes not covered for indications listed in the CPB:	
Gene therapy - no specific code:	

Code	Code Description
0019T	Extracorporeal shock wave involving musculoskeletal system, not otherwise specified, low energy
0101T	Extracorporeal shock wave involving musculoskeletal system, not otherwise specified, high energy
11900	Injection, intralesional; up to and including 7 lesions [intra-lesional injection of nicardipin]
11901	more than 7 lesions [intra-lesional injection of nicardipin]
37790	Penile venous occlusive procedure
38240	Hematopoietic progenitor cell (HCP); allogeneic transplantation per donor
38241	autologous transplantation
38242	Allogeneic lymphocyte infusions
51792	Stimulus evoked response (e.g., measurement of bulbocavernosus reflex latency time)
54240	Penile plethysmography
54250	Nocturnal penile tumescence and/or rigidity test
64565	Percutaneous implantation of neurostimulator electrodes; neuromuscular
64580	Incision for implantation of neurostimulator electrodes; neuromuscular
64585	Revision or removal of peripheral neurostimulator electrodes
64590	Insertion or replacement of peripheral or gastric neurostimulator pulse generator or receiver, direct or inductive coupling
64595	Revision or removal of peripheral or gastric neurostimulator pulse generator or receiver
76981	Ultrasound, elastography; parenchyma (eg, organ) [shear wave]
80197	Tacrolimus
83090	Homocysteine
83550	Iron binding capacity
84066	Phosphatase, acid; prostatic
91200	Liver elastography, mechanically induced shear wave (eg, vibration), without imaging, with interpretation and report
95907 - 95913	Nerve conduction studies

Code	Code Description
95925 - 95927	Short-latency somatosensory evoked potential study, stimulation of any/all peripheral nerves or skin sites, recording from the central nervous system
97014	Application of a modality to 1 or more areas; electrical stimulation (unattended)
97032	Application of a modality to one or more areas; iontophoresis, each 15 minutes
97810 - 97814	Acupuncture
Other CPT codes related to the CPB:	
96372	Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); subcutaneous or intramuscular
HCPCS codes covered if selection criteria are met:	
C1813	Prosthesis, penile, inflatable
C2622	Prosthesis, penile, non-inflatable
J0270	Injection, alprostadil, 1.25 mcg (code may be used for Medicare when drug administered under the direct supervision of a physician, not for use when drug is self-administered)
J0275	Alprostadil urethral suppository (code may be used for Medicare when drug administered under the direct supervision of a physician, not for use when drug is self-administered)
J0775	Injection, collagenase, clostridium histolyticum, 0.01 mg
J2440	Injection, papaverine HCl, up to 60 mg
J2760	Injection, phentolamine mesylate, up to 5 mg
L7900	Male vacuum erection system
L7902	Tension ring, for vacuum erection device, any type, replacement only, each
HCPCS codes not covered for indications listed in the CPB:	
Serum biomarkers, Epalrestat - no specific code :	
J0585	Injection, onabotulinumtoxinA, 1 unit
J0586	Injection, abobotulinumtoxinA, 5 units
J0587	Injection, rimabotulinumtoxinB, 100 units
J0588	Injection, incobotulinumtoxinA, 1 unit
J0900	Injection, testosterone enanthate and estradiol valerate, up to 1 cc
J1060	Injection, testosterone cypionate and estradiol cypionate, up to 1 ml
J1070	Injection, testosterone cypionate, up to 100 mg
J1071	Injection, testosterone cypionate, 1mg

Code	Code Description
J1080	Injection, testosterone cypionate, 1cc, 200 mg
J3120	Injection, testosterone enanthate, up to 100 mg
J3121	Injection, testosterone enanthate, 1mg
J3130	Injection, testosterone enanthate, up to 200 mg
J3140	Injection, testosterone suspension, up to 50 mg
J3145	Injection, testosterone undecanoate, 1 mg
J3150	Injection, testosterone propionate, up to 100 mg
J7503	Tacrolimus, extended release, (envarsus xr), oral, 0.25 mg
J7507	Tacrolimus, immediate release, oral, 1 mg
J7508	Tacrolimus, extended release, (astagraf xl), oral, 0.1 mg
J7525	Tacrolimus, parenteral, 5 mg
J9213	Injection, interferon alpha-2A, recombinant, 3 million units
J9214	Injection, interferon alpha-2B, recombinant, 1 million units
J9215	Injection, interferon alpha-N3, (human leukocyte derived), 250,000 IU
S0090	Sildenafil citrate, 25 mg
ICD-10 codes covered if selection criteria are met:	
N48.6	Induration of penis plastica [Peyronie's disease]
N52.01 - N52.1, N52.31 - N52.39	Male erectile dysfunction [impotence of organic origin] [not covered for serum melatonin]
ICD-10 codes not covered for indications listed in the CPB:	
F12.23	Cannabis dependence with withdrawal
F12.93	Cannabis use, unspecified with withdrawal
F52.0	Hypoactive sexual desire disorder
F52.1, F52.8	Psychosexual dysfunction and other specified psychosexual dysfunctions
F52.21	Male erectile disorder [psychogenic impotence]
F52.32	Male orgasmic disorder
F52.4	Premature ejaculation
F53.3	Abuse of steroids or hormones
N52.2	Drug-induced erectile dysfunction
N52.8 - N52.9	Other and unspecified male erectile dysfunction

Code	Code Description
R37	Sexual dysfunction, unspecified

The above policy is based on the following references:

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Erectile Dysfunction

There are no amendments for Medicaid.