



## A CRITICAL REVIEW ON CURRENT THERAPY FOR ERECTILE DYSFUNCTION

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### ABSTRACT

Erectile dysfunction is a sexual dysfunction characterized by the inability to develop or maintain an erection of the penis sufficient for satisfactory sexual performance. There are so many therapies are available for treating the impotence in the males. In this oral drugs sildenafil citrate (Viagra) vardenfil, tadalafil, alprostadil, phenotolamine injections are mainly inhibiting the PDE5 and enhancing the penile erection and non pharmacological therapies vaccum therapy, surgery (penile prosthesis), counseling also shows role in ED treatment, currently herbal medicines are shows prominent role in ED patients. Mainly some of herbal drugs *Ginko biloba*, *securidaca lengepedvneulata*, *citropisis articulata*, *cola acuminata*, *tribulus terrastris*, *avena sativa* etc there are nearly 32 plants are used in the sexual dysfunctions and also hormonal therapy also showing role in treating ED. This current therapy advancingly improved with safety and efficacy for ED patients.

**Key words:** Erectile dysfunction, PDE5, Sildenafil, tadalafil, vardenefil, herbal drugs.

### INTRODUCTION

Erectile dysfunction (ED) is relatively new, having replaced impotence approximately a decade ago. ED is the inability of the male to attain or maintain an erection sufficient for satisfactory sexual intercourse. (NIH consensus development panel on impotence, 1993). ED affects of men world wide with implications that go far beyond sexual activity alone. ED is assumed to be associated with advancing age, other possible concomitant risk factors include chronic diseases, such as atherosclerosis, heart diseases, hypertension, diabetes mellitus, depression and renal failure and life style factors, such as cigarette smoking and excessive alcohol consumption. (Becher E and Glinas, 2002).

An erection occurs as a hydraulic effect due to blood entering and being retained in sponge like bodies with in the penis. The male erectile response is a neurovascular event reliant on the complex interaction between neurological and vascular responses (Nehra & Moreland 2001). The process is most often initiated as a result of sexual arousal, when signals are transmitted from the brain to nerves in the pelvis. ED is indicated when an erection is consistently difficult or impossible to produce, despite arousal. ED often multiple underlying causes, some of which are treatable medical conditions. A recent male aging study showed that 52% of respondents have same degree. Of erectile dysfunction with 35% men aged 40-70 reporting. Moderate or complete impotence (Morgentaler, 1999). Erectile dysfunction tied closely as it is to cultural notions of potency, success and masculinity, can have severe psychological consequences. There is a strong culture of silence and inability to discuss the matter. In reality, it has been estimated that around 1 in 10

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men will experience recurring impotence problems at some point in their lives. (Anonymus<sup>1</sup>, 2009).

Besides treating the underlying causes and psychological consequences, now current therapy on ED is mostly based on causes, psychological consequences, diagnostic parameters. Sexual therapy are now a days using for treating the ED. In that hormonal supplying, drug therapy, vacuum therapy, surgery, counseling, exercise, herbal medicines and controversial therapies are using to treating erectile dysfunction. Numerous alternative therapies are used to improve sexual function some include inorganic elements and some medicinal plants. The earliest attempts at treating erectile dysfunction date back to muslim physicians and pharmacists in medieval Islamic world. They were the first to prescribe medication for the treatment of this erectile dysfunction (ED), and they developed sexual methods of therapy. Erectile dysfunction were being treated with tested drugs in the Islamic world since the 9<sup>th</sup> century until the 16<sup>th</sup> century by a number of muslim physicians and pharmacists. (Al Dayela & Nal-zuhair, 2006).

Dr. John R. Brinkley, initiated a boom in male impotence cures in the US in the 1920s and modern drug therapy for ED made a significant advance in 1983 by phentolamine induced erection. (Brindley, 1983). The effect that Brindley discovered established the fundamentals for the later development of specific, safe, orally, effective drug therapies.

### EPIDEMIOLOGY

Erectile dysfunction is a common and widespread health problem that affects approximately 30 million men in US (Feldmann *et al.*, 1994) and in 1995 there was an estimated projection of 152 million men world wide who experienced ED. It will rise to about 322 million men by the year 2025 (Ayta *et al.*, 1999). The ED increases with age and other concomitant conditions like causes and psychological parameters. The executive committee of this conference believes that the current prevalence data regarding ED are strong, they see a need for strengthening the incidence data. (Ajay nehra *et al.*, 2002). The Massachusetts male aging study is one of the pivotal studies on the prevalence of ED between 1987 and 1989, men between the ages of 40 and 70 years were asked to categorize their sexual health as potent or totals, moderately, or minimally important (Feldman *et al.*, 1994).

The prevalences pertain, as do those in the present report compared to women, men are 88% who had been sexually active during the last 12 months. The greatest proportions of sexually active women 92-95% and men 92% were found among the 25-49 years olds,

and lower proportions were evident for the 18-24 years old women 87% and men 85% the focus of report is to describe the extent to which different sexual disabilities.

### ETIOLOGY

There are various and often multiple underlying causes. Some of which are treatable medical conditions. The most important organic causes are cardiovascular disease and diabetes, neurological problems (for example, trauma from prostatectomy surgery), hormonal insufficiencies (hypogonadism) and drug side effects. ED mainly based on various causes as psychogenic, organic (hormonal, vascular, drug induced, or neurogenic) or mixed psychogenic and organic. (Goldstein *et al.*, 1998). Up to 80% of ED cases have an organic origin. The most common cause of ED is vascular disease in this coronary artery disease, peripheral vascular disease, hypertension, diabetes mellitus and psychogenic, neurogenic and multifactorial factors like aging, end-stage renal disease pelvic trauma. Some drugs induced the ED mainly  $\beta$ -blockers, calcium channel blockers, alcohol, antidepressant, anti psychotic cimetidine, antiandrogens etc. Artherosclerosis is the most common cause of vasculogenic ED. Chronic tobacco use is a major risk factor for the development of vasculogenic ED because of its effects on the vascular endothelium (Kendirchi *et al.*, 2005).

Additionally chronic illness, depression, and lack of a sexual partners are all prevalent in this age population. Some sorts of surgery like radiation therapy, surgery of the colon, prostate, bladder, or rectum may damage the nerves and blood vessels involved in erection. Prostate and bladder cancer surgery often require removing tissue and nerves surrounding a tumor which increases the risk for impotence convarnosal disorders like peyronie's diseases and ED causes mainly hormonal deficiency pituitary gland tumor, abnormally high levels of the penis. Neurogenic disorders like spinal cord and brain injuries, nerve disorders such as parkinson's disease, alzheimer's diseases, multiple sclerosis, and stroke some evidence suggests that smaller penis size is associated with erectile dysfunction (Awwad *et al.*, 2005).

### PATHOPHYSIOLOGY

Most basic and clinical studies of ED have shown the condition to be caused by a variety of psychological and organic factors. Many of these factors have a direct effect on the central and peripheral mechanism of action of erectile function. In this five synergistic systems of penile erection are cyclic guanosine monophosphate, cyclic adenosine monophosphate, protein kinases and potassium channels, (Ajay Nehra *et al.*, 2002).

Generally penile erection is managed by two different mechanisms. The first is the reflex erection, it is achieved by directly touching the penile shaft. The second is the psychogenic erection, it is achieved by erotic or emotional stimuli. Atrophy owing to loss of  $\alpha$ -1 expression in smooth muscle, and increased connective tissue synthesis, due to TGF  $\beta$ , result in decreased compliance of cavernosal tissue (Acci *et al.*, 2000). Both these changes reduce with the gap junctions and  $K^+$  channels in cavernosal smooth muscle that are necessary for coordinated relaxation of cavernosal tissue (Christ GI, 1995) in peripheral mechanisms of the penis mainly the signals from the central nervous system influence the balance between the contract and relaxant factors that leads to stimulation of penile shaft (Moreland, 1998) and secretion of nitric oxide (NO), (Vickers and Satyanarayan, 2002) which causes the relaxation of smooth muscles of corpora cavernosa and subsequently penile erection will occur and additionally adequate levels of testosterone and an intact pituitary gland are required for the development of a healthy erectile system.  $\alpha$ , melanocyte, melanocortin receptor, serotonin 5-HT<sub>2c</sub> receptors stimulation are good therapeutic alternatives in the treatment of ED (Ajay Nehra *et al.*, 2002).

In the normal erection impotence may develop due to hormonal deficiency, disorders of the neural system, lack of adequate penile blood supply or psychological problems. And some diabetic patients apoptosis owing to loss of BCL-2 expression in smooth muscle, and increase connective tissue synthesis, due to TGF  $\beta$ , result in decreased compliance of cavernosal tissue. (Acici *et al.*, 2000, Dahiya *et al.*, 1999). These changes reduce or interfere with the gap junctions and K channels in cavernosal smooth muscle that are necessary for coordinated relaxation of cavernosal tissue (Vickers *et al.*, 2002).

## CLINICAL MANIFESTATIONS AND DIAGNOSIS

### Physical Examination

The physical examination should include a careful testicular examination to assess testicular size, asymmetries, presence of hernias, or varicoceles. Additionally, a digital rectal examination to assess the prostatic size, consistency and presence of nodules is warranted. Penile inspection and palpation should be performed, with special attention to possible fibrotic plaques. Palpation and auscultation of femoral arteries for possible bruits is another important part of the examination (Rakel & Bope, 2009).

### Medical Diagnosis

Erectile dysfunction diagnosis mainly some blood tests are generally done to exclude underlying disease, such as diabetes, hypogonadism and

prolactinoma. Impotence is also related to generally poor physical health, poor dietary habits, obesity, and most specially cardiovascular disease such as coronary artery disease and peripheral vascular disease.

### Clinical Tests used to Diagnose ED

Duplex ultrasound, Penile nerves function, Nocturnal penile tumescence (NPT), Penile biothesiometry, Penile Angiogram, Dynamic Infusion Cavrosometry, Corpus Cavrosometry, (Dawson and Whitefield, 1996) Digital Subtraction Angiography, Magnetic resonance angiography (MRA). This clinical tests are available for diagnose ED.

### CLINICAL MANAGEMENT

Today there are many effective therapies for the treatment of ED. First-line therapies include oral pharmacotherapy and psychosexual therapy-second line therapies include intra urethral and intracavernosal administration of vasoactive drugs, vacuum devices and penile prostheses. Vacuum devices can be used as first-line therapy.

### Pharmacological therapy

ED can in many cases be treated by drugs taken orally, injected or as penile suppositories. These drugs increase the efficacy of NO, which dilates the blood vessels of corpora cavernosa. Oral drugs or suppositories less effective compare to injections into the erectile tissue of the penile shaft are extremely effective but occasionally cause priapism. The first oral medication for the treatment of ED was sildenafil citrate (Viagra). Since then, oral agents have become the preferred mode of treatments by patients in surveys world wide. There are three oral agents that inhibit PDE5 currently on the market. Those are sildenafil citrates (Viagra), vardenfil (levitra), Tadalafil (Cialis). These drugs inhibiting PDE5, which maintains intracavernosal levels of cGMP, subsequently producing vasodilation and penile erection.

### SILDENAFIL CITRATE (VIAGRA)

Sildenafil citrate (Viagra) is a selective and potent inhibitor of cyclic guanosine monophosphate (PDE5) that enhances penile erection to sexual stimulation by the predominant enzyme that metabolized cGMP in the corpus cavernosum (Boolell *et al.*, 1996). Since its introduction in 1998, sildenafil has gained world wide acceptance as the first-line treatment of erectile dysfunction of organic, psychogenic or mixed etiology (Goldstein *et al.*, 1998).

After oral administration the drug is rapidly absorbed (Muirhead *et al.*, 1996), with an appropriate duration of therapeutic activity that is convenient for most couples (Eardley *et al.*, 1997).

Sildenafil significantly improves the ability to achieve and maintain erections and successfully engage in sexual intercourse (Sadovsky *et al.*, 2001). Sildenafil is safe and efficacy in special subsets of patients, including those with concomitant type-1 or type-2 diabetes treated

hypertension depression, end-stage renal disease maintained with hemodialysis or spinal cord injury (Rendell *et al.*, 1999).

#### **Vardenafil (Levitra)**

Vardenafil (Levitra) is a highly potent inhibitor of PDE5. (Ajay Nehra *et al.*, 2002). It was approved for use in the United States in late 2003. It is a more selective PDE5 inhibitor than sildenafil citrate (Viagra). The absorption of vardenafil (Levitra) is delayed by a fatty content of more than 30% in a male. (Rakel & Bope, 2009). The half life of vardenafil (Levitra) is 4.4 to 4.8 hours, the first trial using the agent included 580 patients, excluding patients with spinal cord injury, radical prostatectomy, hypogonadism, thyrotoxicosis (Vickess *et al.*, 2002).

#### **TADALAFIL (CIALIS)**

Tadalafil (Cialis) is a selective inhibitor of PDE5 with a long half-life (Corbin & Francis, 2002). It has half life of 17.5 hours. The clinical onset of action occurs in less than 1 hour. There is no interaction between food and alcohol on the absorption of the drug. (Rakel & Bope, 2009). Tadalafil associated with an improvement in depressive symptoms and quality of life is men with a diagnosis of mild to moderate depression according to a structured rating interview for DSM-IV (Seidman *et al.*, 2001).

#### **APOMORPHINE (UPRIMA)**

Apomorphine (Uprima) is a potent emetic that acts on central dopaminergic receptors. The stimulation of central dopaminergic receptors transmits excitatory signals down the spinal cord to the sacral parasympathetic nucleus, stimulating activity of the sacral nerves supplying the penis. It was been used successfully in up to 67% of patients when administered through a sublingual preparation. Subcutaneous injections of apomorphine produce almost a 100% erectile response, but nausea and vomiting are limiting factors to this mode of administration.

#### **Alprostadil (Prostaglandin E<sub>1</sub>)**

Alprostadil can be injected the penis or inserted using a special application usually just before sexual intercourse. It has an onset of action of 10-15 minutes and its effects can last over 4 hours. Alprostadil (Prostaglandin E<sub>1</sub>) mechanism mainly PGE<sub>1</sub> binds to PGE receptors and causes a relaxation response mediated by cyclic adenosine monophosphate (cAMP).

#### **PHENTOLAMINE (REGITINE)**

Phentolamine (Regitine) is an injection is used to the dysfunction. It is an  $\alpha_1$ - and  $\alpha_2$  adrenergic receptor antagonist. The mechanism of phentolamine is directly corporal smooth muscle relaxation (Brindley, 1983),

noradrenaline is the primary determinant of cavernosal smooth muscle contraction and it is released of NA induced contraction over NO-induced smooth muscle relaxation may contribute to ED. (Rakel & Bope, 2009). It having some adverse effects nasal congestion, headaches, dizziness, tachycardia, and nausea.

#### **TRAZODONE (DESYREL)**

Trazodone (Desyrel) is a serotonin reuptake inhibiting agent. Its action in ED is believed to be the result of central serotonergic and peripheral  $\alpha$ -adrenolytic activity. Side effects include drowsiness, insomnia, headaches, and weight loss.

#### **NON PHARMACOLOGICAL THERAPY**

Non pharmacological therapy mainly who do not want pharmacological intervention and they need vacuum therapy, surgery and counseling. These current therapies shows prominent role in the treatment of erectile dysfunction.

#### **Vacuum therapy**

Vacuum therapy is second line therapy. In this vacuum devices can be used as first-line therapy is couples who do not need pharmacological intervention and are not appropriate for counseling. It is working by placing the penis in a vacuum cylinder device. The device helps draw blood into the penis by applying negative pressure. A tension ring is applied at the base of the penis to help maintain the erection. This type of device is some times referred to as penis pump and may be used just prior to sexual intercourse.

#### **Surgery (Penile prosthesis)**

This surgical therapy used to be quite common before the advent of oral agents. The use of prostheses is still a suitable alternative for those who are unresponsive to less invasive treatments. Prostheses can be classified as rod, one-piece inflatable, two-piece inflatable, and three-piece inflatable which involves the insertion of artificial rods in to the pen's (ED). Patients are usually satisfied with the results of prosthetic placement.

#### **Counseling**

Counseling is often a consideration, both where a psychological cause is suspected or must be ruled out of to assist in management of any distress.

#### **Testosterone**

Testosterone provides intra penile nitrous oxide synthase (Nos), which has an important role in enhancing the production of NO' subsequent local vasodilation, and penile erection. Oral testosterone can reduce ED in some men with low levels of natural testosterone, but it is often, ineffective and may cause liver damage. (Anonyms<sup>2</sup>, 2004).

**Exercise:** Particularly aerobic exercise is an effective cheap treatment for erectile dysfunction (Anonyms<sup>1</sup>, 2009).

### Herbal therapy

Despite of all the advances in modern and orthodox medicine, traditional medicine still plays a significant role in the lives of many people erectile dysfunction, known clinically as an inability to obtain or maintain an erection. It is a medical problem affecting young as well as old men. Although a number of therapies become available in the last two decades, problems with costs, efficacy, safety and ease to administer were experienced. The therapies ranged from herbal remedies used by native healers, these drugs based on a physiological mechanisms of erection (Guirguis, 1998). The treatment of erectile dysfunction, however, can be many faceted and may involve more than one regimen (Jequier, 2000). In response to modern, sophisticated, chemical medication, there has been a renewed interest in medicinal plants in the treatment of sexual dysfunction, which are being shown to be both effective and safe (Adimoelja, 2000). Several medicinal plants have always been available and used to treat many ailments including impotence.

A number of herbal plants such as *Securidaca Longepedunculata*, *Wrightia Natelenisn*, *Rhoicissus Tridentate*, *Hypericum Perforatum*, *Serenoa Repens*, *Sabal Serrulatum*, *Ginkgo Biloba*, *Tribulus Terrestris*, *Avena Sativa* are used to treat erectile dysfunction.

### Securidaca Longepedunculata (Fresen)

*Securidaca Longepedunculata* (Polygalaceae) is used to treat erectile dysfunction on in vitro activity on the contraction of cavernosal smooth muscle of white New Zealand rabbits. (Rakuambo *et al.*, 2006). *Securidace*, *longepedunalata* is used as a general remedy for several other ailments such as coughs, colds, fever, sleeping sickness, venereal disease, malaria rheumatism, snake bite, tuberculosis, pneumonia (Galeffi *et al.*, 1990). Also used as contraceptive (Palgreve, 1977).

### Wrightia natalensis (stapf)

*Wrightia natalensis* (Apocyanaceae) used to treat erectile dysfunction. It is investigated in vitro activity on the contraction of corpus cavernosal smooth muscle of white New Zealand rabbits (Rakuambo *et al.*, 2006). This *wrightia* species used as dysentery, skin disease, anthelmintic and aphrodisiac (Madhava Chetty *et al.*, 2008).

### Rhoicissus tridentata

*Rhoicissus tridentata* (Vitaceae) used to treat erectile dysfunction. It is investigated in vitro activity on

the contraction of corpus cavernosal smooth muscle of white New Zealand rabbits. (Rakumbo *et al.*, 2006).

### Ginkgo Biloba

*Ginkgo Biloba* (Gingkoaceae) in also known as medientiar tree, kew tree, ginkyo, yinshing. The herb is proven the treatment of arterial erectile impotence. The *ginkgo biloba* extract showing the spontaneous and sufficient, erections after six months oval treatment. *Ginkgo biloba* main active constituents are terpenoids, steroids organic acids ascorbic, benzoic, shikimic and vanillic acid. *Ginkgo biloba* shows prevention action on corticosterone produce neuronal a trophy and cell deaths in hippocampus (Anna Walesiuk *et al.*, 2007). *Ginkgo biloba* also used in antioxidant, free radicals, covering anti-platelet (Smith *et al.*, 1996).

### Panax Ginseng (Araliaceae)

*Ginseng* has been used in the treatment of erectile dysfunction for thousands of years in China and is now used in many western countries. In the study relaxation of the smooth muscle, which is associated with erection, was observed after the application of 0.5-8.0 mg/ml of *Panax Ginseng* extracts on rabbit corpus cavernosum smooth muscle (Kim *et al.*, 1998). These extracts can facilitate the flow of blood into the penis. *Ginseng* also used in immunomodulatory, stimulant, demulsent.

### Cola Accuminata ( Colanut)

*Cola accuminata* (Sterculiaceae) fruits are widely used herbal remedies in ED and are harvested from the forest of Democratic Republic of Congo. (Maud Kamatensi-Mugisha & Hannington oryem-origa, 2005). The *cola accuminata* fruits contain about 2% catchine, caffeine (Colanine). (Hirt & Pai, 2001). The roasted seeds in Europe are used as strong stimulant, in addition to the treatment or cardiogenic, loss of appetite, anti depressant and melancholy. (Hirt & Pia, 2001).

### Mondia Whiteii (Mulondo)

*Mondia Whiteii* (Asclepiadiaceae) are used as an aphrodisiac for males and for improving female sexuality (women's Viagra) in most areas of uganda (Kematenesi-Mugisha, 2002). Particularly in urban centres and the Kampala city. To date, *Mondia whiteii* has been an old traded medicinal plant in most in Kempala. Recently the patented 'Mulondo wine' a drink flavoured by the roots of *Mondia whiteii* has hit the national and international markets (Kyamuhangire, 2004). The *mulondo* wine is also believed to be an aphrodisiac for both men and women.

### CONCLUSION

The review article focused on current therapy on erectile dysfunction. ED is the inability to attain an

erection sufficient for satisfactory sexual performance. Today there are many effective therapies for treatment of ED. In this first line therapies include oral pharmacotherapy and psycho sexual therapy. Second line therapies include intraurethral and intracavernosal administration of vasoactive drugs, vaccum devices and surgery (Penile prostheses). In the oral therapy sildenafil citrate (Viagra) and other PDE5 inhibitor drugs vardenafil, Tadalafil, Alprostadil shows major role in

treating ED. And vaccum device therapy, surgery and following counseling also useful to treatment the ED. Now a days the patients shows interest in the herbal therapy. So many herbal drugs, like *Ginkgo Biloba*, *Securidaca longepedunculata*, *Cola Accuminata*, *Citropisis Articulata* etc used in the treating of sexual dysfunctions. The herbal medicines shows prominent role is treating ED with less side effects and the patients see for current advancing therapy with safety and efficacy.

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