Review Article

PHARMACOLOGICAL THERAPY OF ERECTILE DYSFUNCTION

Lt Col MK GARG ^{*}, Brig JS SAINI ^{VSM⁺}

MJAFI 2001; 57 : 47-51

KEY WORDS : Erectile dysfunction; Therapy.

Introduction

The first description of erectile dysfunction dates back to 2000 BC. Influx of air was proposed as a mechanism of erection, but Ambroise Pare gave an accurate description of penile anatomy and vascular concept of erection [1]. Sexuality is an important quality of life issue that is often overlooked. Potency has been related to male sexual function since time immemorial. Male sexual function encompasses libido (sexual desire and initiative), erection (engorgement of penis with blood), ejaculation (expulsion of semen per urethra), orgasm (subjective sensation of pleasure) and fertility. Among these decreased erectile function is the most common and distressing. Male erectile dysfunction has been defined as the persistent inability to attain and/or maintain penile erection sufficient for satisfactory sexual performance [2]. Various methods have been devised to assess erectile dysfunction, of which MMAS (Massachusetts male ageing study)[3] and IIAF (International Index of Erectile Function) [4] are widely used. The prevalence of erectile dysfunction ranges from 52% in men aged 40-70 years to greater than 95% in men over age 70 [3].

Anatomy and Physiology of Erectile Function

The penis has two corpora cavernosa, which is surrounded by a thick fibrous sheath, the tunica albuginea. The erectile tissue consists of multiple, interconnected lacunae lined by vascular epithelium. Multiple helicine arteries branch off from cavernosal artery and open directly into these lacunar spaces. Blood is drained through subtunical venules, which are compressed against thick tunica albuginea during erection and help in maintaining tumescence [5].

Erection is a vascular event under neurogenic control. Medial preoptic area and the paraventricular nucleus of hypothalamus is integration centre for sexual

drive and penile erection. Tactile, auditory, visual or imaginative stimuli elicit penile erection by increasing central parasympathetic and decreasing sympathetic outflow. Decreased penile vascular resistance with resultant increased penile blood flow is considered a primary hemodynamic event in penile erection. The process of erection and detumescence has been divided into seven phases :- Phase 0 - flaccid Phase, 1 - latent filling, 2-tumescence, 3-full erection, 4-rigid erection, 5-transition, 6-initial detumescence and 7-fast detumescence [6]. During phase 1-4 parasympathetic activity dominates whereas sympathetic activity dominates during phase 5-7. Activation of postsynaptic parasympathetic neurons (Non Adrenergic Non Cholinergic-NANC) causes release of nitric oxide, which stimulates formation of cyclic guanosine monophosphate (cGMP) level in lacunar and arterial smooth muscles by guanylate cyclase. Relaxation of lacunar vascular cells is mediated by cGMP and terminated by degradation of cGMP by phosphodiesterase type 5 [7]. Sympathetic activation leads to detumescence by endothelin mediated vasoconstriction. Prostaglandins E1, receptor for which has been demonstrated on lacunae, relaxes smooth muscle through adenylate cyclase and cAMP formation [8].

Etiological Factors

Erectile dysfunction is common, prevalence increases with age. It is caused by organic, psychological, interpersonal and pharmacological factors. Organic causes may be related to vascular, neurogenic, endocrine or local pathology (Table-1). Common disorders associated with erectile dysfunction include hypertension, diabetes mellitus, atherosclerosis, neurodegenerative disorders, pelvic surgery or trauma, chronic systemic illness and alcoholism. Psychological factors were thought to be main cause of impotence in the past. Presently erectile dysfunction is conceptualised as predominantly psychogenic or pre-

^{*}Classified Specialist (Medicine) & Endocrinology, Command Hospital (Southern Command), Pune-411040. ⁺DDMS, 11 Corps, C/O 56 APO.

dominantly organic. However about less than 30% patients with erectile function can be attributed to psychological factors particularly depression [9] and chronic anxiety. Interpersonal concerns can be extremely important in the genesis of erectile dysfunction eg. anger, inhibition, marital disharmony, environment etc. Erectile dysfunction has been reported with wide variety of drugs particularly antihypertensives, antianginal and antipsychotics. Antiandrogens, digitalis, ranitidine and ketoconazole reduce androgen availability. Alcoholism is associated with high prevalence of erectile dysfunction due to hypogonadism with feminization, neuropathy and vascular disease. Cigarette smoking is a risk factor for atherosclerosis and erectile dysfunction. Nicotine has inhibitory effect on corporeal blood flow.

TABLE 1
Common organic causes of erectile dysfunction

I. Systemic disorders	Atherosclerosis
	Hypertension
	Diabetes mellitus
	Renal failure
	Hyperlipidemia
	Aortoiliac obstruction
	Peripheral vascular disease
II. Neurogenic	Veno-occlusive incompetence
	Cerebrovascular stroke
	Parkinsonism
	Multiple sclerosis
	Diabetes mellitus
	Epilepsy
	Alcoholism
III. Endocrine	Primary or secondary hypogonadism
	Hyperprolactinaemia
	Diabetes mellitus
	Cushing's syndrome
	Hypothyroidism
IV. Local	Hyperthyroidism
	Peyronie disease
	Penile trauma
	Hypo/Epispadiasis
	Penile carcinoma
	Pelvic surgery or radiation
	Pudendal nerve trauma (Bicycle Rider's Palsy)
V. Medications	Antihypertensives : (Beta blockers, Spironolactone, Clonidine, Thiazide, Ganglions blockers, Methyldopa)
	Antidepressants : (Tricyclics, MAO Inhibitors, Lithium, SSRI)
	Antipsychotics : (Phenothiazines)
	Antiandrogens : (Estrogen, Flutamide, 5- α Reductase inhibitors)
	Sedatives : (Benzodiazepines)
	Opiates
	Alcohol
	Tobacco
VI. Substance abuse	

MAO - Monoamine oxidase inhibitors, SSRI - Selective serotonin reuptake inhibitors

Approach to Erectile Dysfunction :

History and physical examination usually leads to probable cause of erectile dysfunction i.e. hypertension, diabetes mellitus, coronary artery disease indicating presence of generalised atherosclerosis, systemic illness, local fibrosis (Peyronie's disease), pelvic surgery or drugs. Many young patients may not complain of erectile dysfunction due to social inhibition. They usually complain of vague ill health and weakness. Evasiveness to give detail nature of illness should lead to suspicion of underlying sexual disorder. Direct questioning usually helps to elucidate exact nature of these problems. Nocturnal penile tumescence (NPT) can be assessed by stamp test, snap gauze test or Rigiscan portable NPT monitor. However usefulness of NPT to exclude organic cause is under scrutiny [10]. Hormonal assessment (LH, FSH, and Testosterone) is required where endocrinal cause is suspected. Neurological testing including autonomic function test can be assessed in a case with neurological disease. Integrity of arterial supply can be evaluated non-invasively by penile brachial blood pressure index, and duplex ultrasonographic assessment. Various invasive tests should be done at a specialised centre when patient is willing for further invasive therapy. Invasive evaluation includes intracorporeal injection of papaverine or papaverine-phenolamine, and penile arteriography. Venous insufficiency can be suggested by failure of erection inspite of good arterial flow assessed by duplex scanning following intracorporeal injection. Cavernosonography and cavernosometry are valuable for the identification of veno-occlusive incompetence. Details of each test [1] will be out of scope of this review.

Pharmacotherapy of Erectile Dysfunction

Treatment of erectile dysfunction is based on clinical evaluation and primary treatment of medical condition. Emotional factors should not be underestimated, hence *life style modification* (regular exercise, healthy diet and behavioural changes) is essential. Sex therapy technique may allow improvement of sexual attitudes. Behavioural changes may include elimination of alcohol, smoking, arranging appropriate time and environment, and encouraging intimacy, mutual pleasuring, experimentation and communication. Change or decrease in the dose of drug with adverse effect on erectile function may have beneficial effect. Advantages and disadvantages of various pharmacological and nonpharmacological modes of treatment are given in (Table-2).

TABLE 2

Advantage and disadvantage of various forms of therapy for erectile dysfunction

Therapy	Advantage	Disadvantage
Oral therapy : Sildenafil		
	Effective Fewer side effects	Not useful in arterial disease, and local causes Causes headache, flushing, visual disturbances Drug abuse Requires external stimuli
Transurethral Alprostadil		
	Effective in ~ 40% Minimally invasive	Not useful in arterial disease Penile pain, urethral trauma, hypotension, syncope Contraindicated in IHD, CVA Requires applicator
Intracorporeal injection : Papavarine or Alprostadil		
	Effective Moderately invasive No external stimuli	Not useful in arterial disease Injection technique Hematoma, Pain, Fibrosis, Hypotension, Syncope Priapism Contraindicated in IHD, CVA, Anticoagulants
Vacuum devices		
	Safe Successful Minimum side effects	Technique dependent Cumbersome Costly

Oral Pharmacotherapy

Sildenafil : Sildenafil (Viagra) is a potent and competitive inhibitor of the type V cGMP specific phosphodiesterase, predominant isoenzyme in the human corpus cavernosum and eye. It decreases catabolism of cGMP, which enhances relaxation of the cavernosal smooth muscle, increases blood flow leading to increased intracavernosal pressure and penile rigidity. Sildenafil restores natural erectile response to various sexual stimuli but does not causes erection in the absence of stimuli. It is given in the dose of 50-100 mg orally. It is rapidly absorbed and maximum plasma levels are achieved in about one hour after oral administration. It has mean half-life of three to five hours [11]. Boolell et al[12] first reported its effectiveness in a double blind, placebo controlled, four way cross over trial in erectile dysfunction of psychogenic origin in twelve patients. They reported achievement of rigidity of 80% in 10 of 12 patients compared with 2 of 12 receiving placebo therapy. However the drug was effective for the duration of two hours only after its intake. Hence the drug should ideally be given an hour before anticipation of sexual activity. Goldstein et al [13] have demonstrated its effectiveness in men with erectile dysfunction of diverse causes e.g. organic, psychological and mixed. Sildenafil improved erectile function, orgasmic function and intercourse satisfaction. However only 70%

of all sexual attempts were successful in sexual intercourse compared to 22% in placebo group. It had no effect on sexual desire as expected from its mechanism of action. This drug is well tolerated. Its main side effects are headache, flushing, dyspepsia, pelvic musculo-skeletal pain, rhinitis and visual disturbances. Insufficient response is observed in about 2-3% patients. This drug was approved in USA by FDA on 27 March 99. Since then it has been marketed in various countries.

Yohimbine : Yohimbine is an indole alkaloid with α 2 adrenergic blocking properties. It is believed to exert beneficial effect on erectile activity by central mechanisms on the nervous system. It is used in doses of 6-10 mg three times a day. Morales et al [14] initially reported a sustained improvement in erectile dysfunction in 26% of 23 men, however its effect was not more than a placebo response reported in above studies. Potential side effects include mild blood pressure elevation, palpitations, tremors, nervousness, and irritability.

Trazodone : This antidepressant has facilitatory actions on central serotonin and dopamine pathways and adrenoceptor antagonistic effects at the level of the erectile tissue. A dose range of 50-200 mg (commonly 100 mg at bedtime) should be used. Its effect should be evaluated after about a month of therapy. It is effective in about 60% of patients, hence constitutes one of first line therapy in the treatment of erectile dysfunction [15]. It can be combined with yohimbine, which probably has synergistic effect [16]. Potential side effects are drowsiness, irritability, and rarely priapism has been reported.

Apomorphine :Sublingual apomorphine [17] appears effective only in patients without neurological dysfunction. It has central dopaminergic agonistic activity. Although less likely to cause gastrointestinal upset than when given orally, it causes pronounced yawning which may have inhibitory effect on proper sexual activity. It is only an investigational drug, and is currently not available.

Other Drugs :Various forms of oral therapy have been tried with expectation of improved efficacy and patient satisfaction e.g. bethanecol, phentolamine, L-arginine, delquamine, nitroglycerine (topical therapy), minoxidil, bromocriptine and capsaicin. However efficacy of these drugs remains unproved.

Transurethral Pharmacotherapy

Transurethral Medication :Alporstadil is a synthetic compound similar to prostaglandins E₁. It increases intracellular concentration of cyclic AMP,

which is known to cause smooth muscle relaxation. Urethral submucosal veins communicate with corpus spongiosum and corpora cavernosa, hence providing potential route of drug transfer. 80% of administered drug is absorbed, while little remains in the ejaculate. Padma Nathan et al [18] evaluated effectiveness of transurethral alprostadil delivered by an applicator in the distal urethra. The onset of response was 7 minutes, maximum response was 20-25 minutes and duration to return to nonerectile state was about an hour. Only about 65% responded in clinical setting. Amongst the respondents, when drug was used at home only 60% were able to perform sexual intercourse. Hence its overall effectiveness was not more than 40%. Adverse effects reported were penile pain, hypotension, syncope, and minor urethral trauma. In view of its vascular effect this drug is unsuitable for patients with ischemic heart disease, cerebrovascular disease and local urethral disease.

Intracavernosal Pharmacotherapy

Self administration of vasoactive agents eg. papaverine, phentolamine, or alprostadil, is useful in patients with erectile dysfunction of diverse etiology but with intact vascular system. This therapy requires proper selection of patients (contraindicated in sickle cell disease, schizophrenia, severe venous incompetence, and cardiovascular disease), and patient education about self-injection. Injection is given at 10 and 2'O clock position with variation in the site of injection, which is taken not more than three times a week. Patient feels mild resistance when rigid tunica is penetrated. Twenty-seven gauge or smaller needles are used, usually with insulin syringe. Injection therapy is associated with hematoma, penile pain, urethral damage, local infection, and fibrotic changes in corpora cavernosa. Priapism occurs in about 1-5% of patients and loss of efficacy in 10% over 12 month period [19]. Systemic side effects include vasovagal syncope and hypotension.

Papavarine : Papavarine is derived from opium poppy. It increases intracellular levels of cAMP, blocks calcium channels, and increases calcium efflux from cells. Plasma half-life is 1-2 hours and it is metabolised in the liver. It is available in concentration of 30mg/ml, and used in dose of 5-60mg per injection. It is effective in 30-50% of patients. It has been used successfully in paraplegics and tetraplegics in lower doses [20].

Phentolamine :Phentolamine is a competitive alpha adrenergic receptor antagonist causing increase in corporal blood flow. It is injected in dose of 0.5-1 mg.

In combination with papavarine it has a response rate of 70% and satisfaction rate of 75% [19].

Prostaglandin E₁ :PGE₁ has been found to be more effective than papavarine in monotherapy. Overall response rate is about 70-%. It is effective in dose of 1-40µg and is commonly used in dose of 20µg. Onset of erection starts with a latency of 10 minutes and duration is about 2 hours. It has also been used with papavarine-phenotolamine combination, which is effective in 85% of patients. Combination therapy uses lower doses of individual drugs and reduces total volume of injectable solution.

Erectile dysfunction is not uncommon if specially looked for. All primary care physicians should be competent in performing basic evaluation of risk factors and discussing various therapeutic avenues available (Table-2). Initial therapy includes oral pharmacotherapy. Unresponsive patients can be offered transurethral medication. Those with persistent problem should be referred to urologist for further evaluation and education about the use of intracavernous injection therapy. Vacuum operated devices can be offered to those who are unwilling for self injection. Invasive testing should be restricted to those patients willing for invasive therapy like penile prosthesis and vascular surgery.

References

1. Lue TF, Boderick G. Physiology of penile erection, pathophysiology and evaluation of erectile dysfunction and priapism. In Eds:Wlsh PC, Retik AB, Vaughan ED, Wein AJ. Campbell Urology. Edition, WB Saunders Company, Philadelphia. 1998;1157-1214.
2. NIH Consensus Development Panel on Impotence. Impotence JAMA 1993;270:83-90.
3. Rosen Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ, McKinlay JB. Impotence and its medical and psychological correlates : Results of the Massachusetts male aging study. J Urol 1994;151:54-61.
4. RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, Mishra A. The International Index of Erectile Function : A multidimensional scale for assessment of erectile dysfunction. Urology 1997;49:822-30.
5. Andersson KE, Wagner G. Physiology of penile erection. Physiol Rev1995;75:191-236.
6. Aboseif SR, Lue TF. Hemodynamics of penile erection. Urol Clin N Am 1988;15:1-7.
7. Monacada S, Higgs A. The L-arginine nitric oxide pathway. N Engl J Med 1993;329:2002-12.
8. Hedlund H, Andersson KE, F vaeus M, Holmquist F, Uski T. Characterisation of contraction mediating prostanoid receptors in human penile erectile tissues. J Urol 1989;141:182-6.
9. Slag MF, Morley JE, Elson MK, Trencle DL, Nelson CJ, Nelson AE et al. Impotence in medical clinic outpatients. JAMA 1983;249:1736-40.

10. Condra M, Morales A, Surridge DHC, Owen JA, Marshall PJ, Fenemore J. The unreliability of nocturnal penile tumescence as an outcome measurement in the treatment of organic impotence. *J Urol* 1986;135:280-2.
11. Boolell M, Allen MJ, Ballard SA, Gepi-Attee S, Muirhead GJ, Naylor AM et al. Sildenafil: an orally active type 5 cyclic GMP specific phosphodiesterase inhibitor in the treatment of penile erectile dysfunction. *Int J Impot Res* 1996;47:47-52.
12. Boolell M, Gepi-Attee S, Gingell JC, Allen MJ. Sildenafil, a novel effective oral therapy for male erectile dysfunction. *Br J Urol* 1996;78:257-61.
13. Goldstein I, Lue TF, Padma-Nathan H, Rosen RC, Steers WD, Wicker PA. Oral sildenafil in the treatment of erectile dysfunction. *N Engl J Med* 1998;338:1397-404.
14. Morales A, Surridge DHC, Marshall PG, Fenemore J. Non-hormonal pharmacologic treatment of organic impotence. *J Urol* 1982;128:45-7.
15. Kurt U, Ozkarde SH, Altug U, Germiyanoglu C, Gurdal M, Erol D. The efficacy of anti-serotonergic agents in the treatment of erectile dysfunction. *J Urol* 1994;152:407-9.
16. Montorsi F, Strambi LF, Guazzoni G, Rigatti P, Pozza G, Bocciardi A et al. Effect of yohimbine-trazodone in psychogenic impotence. A randomized, double blind, placebo controlled study. *Urology* 1994;44:732-6.
17. Heaton JPW, Morales A, Adam M, Owen JA. Resolution of erectile failure after oral treatment with apomorphine. *Urology* 1995;45:200-3.
18. Padma-Nathan H, Hellstrom WJG, Kaiser F, Labasky R. Treatment of men with erectile dysfunction with transurethral alprostadil. *N Engl J Med* 1997;336:1-7.
19. Fallon B. Intracavernous injection therapy for male erectile dysfunction. *Urol Clin North Am* 1995;22:833-45.
20. Kapoor VK, Chahal AS, Jyoti SP. Intracavernous papavarine for impotence in spinal cord injured patients. *Paraplegia* 1993;31:675-80.