BMJ

BMJ 2014;348:g129 doi: 10.1136/bmj.g129 (Published 27 January 2014)

CLINICAL REVIEW

Erectile dysfunction

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Erectile dysfunction is defined as the inability to achieve and maintain a penile erection adequate for satisfactory sexual intercourse.[1] Increasing public awareness and the universal availability of effective oral drugs has resulted in more men seeking treatment for the problem and an increase in the number of primary care consultations and referrals to secondary care. The World Health Organization states that "Sexual health is fundamental to the physical and emotional health and wellbeing of individuals, couples and families, and to the social and economic development of communities and countries."[2] Erectile dysfunction affects the quality of life for both patients and partners and is associated with relationship difficulties.

This review aims to provide an overview of the prevalence, investigation, and management of erectile dysfunction in primary care, together with indications for referral to secondary care.

How common is erectile dysfunction?

Data from the Massachusetts Male Aging Study (MMAS), a community based, random sample prospective observational survey of non-institutionalised men aged 40-70 years, found that 52% of men reported erectile dysfunction.[3] It is a common cross cultural condition in developing and industrialised countries, but its true incidence is probably underestimated owing to embarrassment about seeking help. The MMAS study also estimated the crude incidence rate in men followed up for 8.8 years. It reported an increased incidence with age—12.4 cases per 1000 man years (95% confidence interval 9.0 to 16.9), 29.8 cases per 1000 man years (24.0 to 37.0), and 46.4 cases per 1000 man years (36.9 to 58.4) at 40-49, 50-59, and 60-69 years of age, respectively.[4]

What causes erectile dysfunction?

Erectile dysfunction may have psychogenic causes (all relevant physiological and neurovascular pathways are intact but a psychological impairment is present) or organic causes (a hormonal, neurovascular, or anatomical risk factor causes erectile dysfunction). However, in most patients both factors probably contribute to the failure to achieve an adequate erection.

Psychogenic erectile dysfunction

Psychogenic erectile dysfunction may be attributed to relationship stress, performance anxiety, or overt psychological disorders, such as depression or schizophrenia, which is further exacerbated by drugs prescribed to treat these conditions.

Organic causes of erectile dysfunction

To achieve adequate penile tumescence for successful penetrative intercourse, blood flow within the corpus cavernosum needs to increase. This requires coordination of neurovascular and biochemical pathways to allow relaxation of cavernosal smooth muscle and dilation of the cavernosal artery (figure⇓). A venous leak, which may be congenital or acquired, can also cause erectile dysfunction owing to a failure of blood remaining in the corpora.

Penile abnormalities may impair erections owing to pain or a penile deformity. These conditions include foreskin problems (phimosis, lichen sclerosus), penile curvature (congenital curvature or Peyronie's disease), and benign and malignant genital dermatoses. Fibrosis within the corpus cavernosum as a result of priapism can also cause erectile dysfunction.

Neurological disorders or spinal cord injury can inhibit the initiation and maintenance of a penile erection. Central neurological conditions often associated with erectile dysfunction include Parkinson's disease, Alzheimer's disease, multiple sclerosis, strokes, and spinal cord injury. Autonomic neuropathy, endothelial dysfunction, and microvascular disease associated with diabetes also result in erectile dysfunction. A questionnaire based cohort study found that patients with type

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Web fig 1 Shorter sexual health inventory for men
Web fig 2 Three piece inflatable penile prosthesis showing the cylinders and pump

Summary points

- Erectile dysfunction has organic and psychogenic components
- The incidence of erectile dysfunction increases with age and is a marker for endothelial dysfunction
- Changes in lifestyle can help men with erectile dysfunction and reduce cardiovascular risk factors
- First line treatment is with oral phosphodiesterase-5 inhibitors and second line treatment uses intraurethral or intracavernosal prostaglandins
- Men who do not respond to drugs have the option of penile prosthesis surgery

Sources and selection criteria

We used the keywords erectile dysfunction and impotence combined with prevalence, risks, diagnosis, treatment, and surgery to search PubMed and Medline for relevant peer reviewed original articles, meta-analyses, and reviews. We also sourced national and international guidelines and consultations. Only papers written in English were considered.

2 and type 1 diabetes had a twofold and threefold increased risk of erectile dysfunction, respectively, compared with patients without diabetes.[5] Iatrogenic injury to the cavernosal nerves during radical pelvic surgery or after external beam radiotherapy (for example, for prostate cancer) is another common risk factor.[6]

Both primary and secondary hypogonadism resulting in very low free and total testosterone values are associated with a reduction in sexual libido and erectile dysfunction. Hyperprolactinaemia (commonly related to antipsychotic drugs) inhibits the release of gonadotrophin releasing hormone, leading to hypogonadotrophic hypogonadism. Other hormonal abnormalities associated with erectile dysfunction are hyperthyroidism through increases in the sex hormone binding globulin concentration and reduced free testosterone levels.

Several commonly prescribed drugs, including antipsychotics, antidepressants, and antihypertensive, are associated with erectile dysfunction through a range of mechanisms (box 1).

Erectile dysfunction shares several common risk factors with cardiovascular disease—for example, obesity, metabolic syndrome, smoking, lack of exercise, diabetes, and hypercholesterolaemia. A Danish community based cross sectional study reported that erectile dysfunction was more prevalent in men with a body mass index (BMI) of 30 or more.[7] Another study found that men with a BMI above 25 are at a higher risk of erectile dysfunction.[8]

The common pathway linking cardiovascular disease and erectile dysfunction probably involves endothelial dysfunction and small vessel atherosclerosis, which impairs smooth muscle relaxation within the penis. This link with cardiac disease initially led to the publication of the first Princeton consensus,[9] which proposed assessing men for exercise ability to ensure that they can meet the demands of sexual activity. The second Princeton consensus stratified patients into low, intermediate, or high risk categories on the basis of the number of cardiovascular risk factors (table 1⇓).[10] Patients in the intermediate category should be offered a stress test before prescribing treatment for erectile dysfunction and high risk patients require referral to a cardiologist. Recently the third Princeton consensus defined cardiovascular risk as the risk of morbid events over a three to five year interval from the onset of erectile dysfunction in men without known cardiovascular disease.[11]

What lifestyle factors are associated with erectile dysfunction?

Cigarette smoking contributes to erectile dysfunction through the development of atherosclerosis and endothelial dysfunction. A meta-analysis of four prospective cohort studies and four case-control studies (28 586 participants) concluded that smoking was a risk factor for erectile dysfunction in current smokers (odds ratio 1.81) and ex-smokers (1.25).[12]

A population based epidemiological study using data from MMAS indicated that bicycle riding for more than three hours a week was an independent risk factor for mild to moderate erectile dysfunction (1.72).[13] The proposed pathogenesis relates to compression of the pudendal nerve and arteries while cycling.[14]

A sedentary lifestyle is also associated with a higher risk of erectile dysfunction, so patients should be advised about the benefits of regular exercise even when prescribed treatment. Results from a meta-analysis of seven studies concluded that moderate or high physical activity confers a lower risk of erectile dysfunction (odds ratio 0.63 for moderate activity and 0.42 for high activity).[15]

How should patients with erectile dysfunction be assessed in primary care?

A cross sectional study of 13 primary care practices in London found that 8.8% of 18-75 year old male attendees had an ICD-10 (international classification of diseases, 10th revision) clinical diagnosis of erectile dysfunction.[16] In addition, a postal questionnaire based study found that two thirds of general practitioners thought that sexual dysfunction was of sufficient importance for management in general practice.[17]

Clinicians should ask men with diabetes, cardiovascular disease, and lower urinary tract symptoms about erectile dysfunction. Current National Institute for Health and Care Excellence guidelines recommend assessing all men with type 2 diabetes annually for erectile dysfunction and offering treatment with the oral drug that has the lowest acquisition cost.[18]

A medical and sexual history combined with basic laboratory investigations can be performed in primary care. This will identify risk factors such as diabetes or hypogonadism and relevant lifestyle factors such as excessive alcohol, smoking, recreational drugs, and lack of regular exercise that might precipitate erectile dysfunction. The clinician can use this information to ensure appropriate referral to secondary care for more specialised investigations where necessary.

Sexual history should focus on the onset and pattern of erectile dysfunction in the current or previous sexual relationship and whether it is due to a lack of rigidity or early detumescence. In addition, ejaculatory dysfunction, penile curvature, and orgasmic dysfunction need to be identified because these conditions require an alternative treatment algorithm.

Box 1 Common prescription and recreational drugs associated with erectile dysfunction

Antidepressants
- Selective serotonin reuptake inhibitors
- Monoamine oxidase inhibitors
- Tricyclic antidepressants

Antihypertensives
- β blockers
- Verapamil
- Methyldopa
- Clonidine
- Guanethidine

Cardiac drugs
- Digoxin
- Amiodarone

Diuretics
- Spironolactone
- Thiazide

Hormonal
- Antiandrogens (flutamide, cyproterone acetate)
- Luteinising hormone releasing hormone agonists (leuprorelin, goserelin)
- 5α reductase inhibitors
- Corticosteroids
- Ketoconazole

Histamine receptor 2 antagonists
- Cimetidine
- Ranitidine

Recreational drugs
- Alcohol, marijuana, cocaine

Differentiating between psychogenic and organic erectile dysfunction

Men with mainly psychogenic causes are often younger, with no identifiable medical risk factors, and they may recall a specific time when the problem began (such as relationship breakdown, start of intimacy with a new partner). Other features suggesting a psychogenic cause include nocturnal and early morning erections being generally preserved, erections being maintained during masturbation, and erections being adequate for intercourse with a different partner

Validated psychometric questionnaires such as the international index of erectile function or the shorter sexual health inventory for men (web fig 1) provide an objective assessment for several domains of sexual functioning. The questionnaires are also useful for monitoring treatment response and as a research tool.[19]

What clinical examination is necessary?

Men should undergo a penile examination to check for the penile abnormalities described above. Secondary sexual characteristics, testicular size, and testicular consistency are good indicators of whether primary hypogonadism is present. A digital rectal examination of the prostate is considered in older men with prostate symptoms or ejaculatory dysfunction.

Because erectile dysfunction may be one manifestation of generalised vascular disease and endothelial dysfunction, blood pressure, heart rate, waist circumference, and BMI should also be recorded.

What laboratory tests are needed?

Fasting serum lipid profile, fasting plasma glucose, and glycated haemoglobin are recommended as baseline tests for all new patients presenting with erectile dysfunction.[20 21] Total testosterone, luteinising hormone, and sex hormone binding globulin are measured on a blood sample taken between 8 am and 11 am. A prostate specific antigen test is recommended only if the digital rectal examination result is abnormal and the patient is over 50 years (if he is requesting screening or has risk factors for prostate cancer) or if testosterone replacement is considered.

What treatments are available in primary care?

Lifestyle modifications

Simple lifestyle measures such as regular exercise, smoking cessation, and weight loss are simple and effective options in men with these risk factors who have mild erectile dysfunction.[22] These lifestyle modifications also reduce long term cardiovascular risk and improve endothelial function so should continue after drug treatment begins.

Herbal and over the counter remedies

Although several herbal remedies have been used in parts of Asia, Africa, and some regions of Europe and North America, only three herbal remedies have published data from studies in humans—*Panax ginseng*,[23] *Butea superba*,[24] and yohimbine.[25] Clinicians have been reluctant to support herbal therapy owing

to a lack of good quality evidence from clinical studies and the lack of regulatory obligations to undertake rigorous testing for the safety and efficacy of these supplements. *Panax ginseng* contains ginsenosides which mediate both acetylcholine induced smooth muscle relaxation as well as release of nitric oxide in animal studies. Side effects at high doses include headache, restlessness, and tachycardia.[26] The active ingredient in *Butea superba* is butenin, but the mechanism of action in erectile dysfunction is unclear. Yohimbine is an alkaloid that blocks presynaptic α2 adrenoceptors in the brain and spinal cord and enhances the sexual response. Side effects at lower doses include tachycardia, blood pressure changes, hallucinations, and dizziness.

What drugs are available?

Currently, several drugs are available for treating erectile dysfunction. Oral phosphodiesterase (PDE) inhibitors are considered as first line option and can be started in primary care. Intracavernosal injections and transurethral prostaglandins are used as second line treatment options and are instituted in secondary care.

Oral PDE inhibitors

Oral PDE inhibitors are a convenient, efficacious, and widely available treatment option for erectile dysfunction. They are contraindicated in patients taking nitrates, in patients in whom vasodilatation or sexual activity is inadvisable, and in those with a history of non-arteritic optic neuropathy. PDE inhibitors should be used with caution in patients with renal or hepatic impairment, recent stroke, myocardial infarction, or unstable angina and in those taking α blockers for lower urinary tract symptoms. These drugs inhibit type 5 PDE within the cavernosal smooth muscle and prevent the breakdown of cyclic guanosine monophosphate (cGMP) to GMP. Nitric oxide mediated smooth muscle relaxation is therefore facilitated in both the corpus cavernosum and cavernosal arteries (fig 1). Although several oral PDE-5 inhibitors are marketed globally, they all have the same mechanism of action but differ in their half life and potency (table 2⇓). The most common side effects seen with sildenafil include headache, flushing, dyspepsia, and rhinitis. The adverse effects with tadalafil and vardenafil are similar to sildenafil, although tadalafil is associated with a higher incidence of back pain and myalgia.[27]

Patients who are eligible for an NHS prescription include those with specific medical conditions (box 2) and those with severe distress associated with impotence, although this last category of patients require referral to secondary care. Patients are instructed to take phosphodiesterase-5 inhibitors one hour before intercourse. To ensure efficacy and reduce side effects, simultaneous sexual stimulation is required and grapefruit juice should be avoided to prevent unpredictable pharmacokinetics. Patients are advised not to take more than one dose of sildenafil or vardenafil a day. Owing to the longer half life of tadalafil, it may still have an effect after 36 hours.

How effective are PDE-5 inhibitors?

Results from multicentre clinical trials suggest that the three main PDE-5 inhibitors (sildenafil, tadalafil, and vardenafil) are effective in a wide range of patient groups. One early study (a 24 week dose-response study) that investigated the efficacy and safety of sildenafil when used "as needed" before sexual activity found that 69% of sexual attempts were successful in the sildenafil group compared with 22% in the placebo group.[28] A meta-analysis of 14 studies showed that sildenafil, tadalafil, and vardenafil are an effective treatment for erectile dysfunction compared with placebo, with a 7-10 point increase in the international index of erectile function.[29] No published double or triple blinded multicentre studies have compared the efficacy of or patients' preference for the three PDE-5 inhibitors. However, an open label multicentre preference study comparing sildenafil with tadalafil showed that although both treatments were effective, 71% of men preferred to continue with tadalafil.[30]

When should testosterone replacement be considered?

Circulating free testosterone modulates penile erection at several levels—within the brain, neural pathways, pelvic plexus, and the corpus cavernosum, where it regulates neuronal nitric oxide synthase. Importantly, testosterone replacement is licensed for use only in men with hypogonadism, which is defined as a clinical syndrome caused by androgen deficiency that may adversely affect multiple organ functions and quality of life. Hypogonadism can be caused by testicular failure (primary) or disruption of the hypothalamic-pituitary-gonadal axis (secondary). Men must be referred for specialist assessment before testosterone replacement is initiated. Men started on testosterone replacement require monitoring of prostate specific antigen, full blood count, and liver function tests annually. However, the role of treatment combining a PDE-5 inhibitor and testosterone in men with hypogonadism is still unclear. A recent systematic review that analysed molecular studies, observational studies, and randomised controlled trials related to erectile dysfunction and hypogonadism over the past 20 years proposed that PDE-5 inhibitors should be used as first line treatment.[31]

What treatments are available in secondary care?

PDE-5 inhibitors offer a convenient first line treatment option. Subsequent failure to gain an erection, especially in difficult treatment groups such as patients with diabetes or those who have had radical prostatectomy, requires referral to secondary care. Box 3 lists reasons for such referral.

Intracavernosal and intraurethral prostaglandins

The synthetic prostaglandin E1 analogue alprostadil can be given as second line treatment. Alprostadil increases intracellular concentrations of cyclic AMP (cAMP), resulting in relaxation of smooth muscle. Currently, two methods of administration are available: direct intracavernosal injection of alprostadil (Caverject 2.5-20 μg) or intraurethral application of a small pellet (MUSE 250-1000 μg). In an open label flexible dosing study using intracavernosal alprostadil, 82% of men reported successful sexual intercourse.[32] The MUSE study group reported a 65.9% successful intercourse rate in a double blind placebo controlled trial of 1511 men.[33]

Vacuum erection devices

Vacuum devices can be used alone or combined with other treatments, regardless of the cause of erectile dysfunction. Complications include pain, bruising, and penile numbness, with more serious adverse events such as skin necrosis occurring if the constriction ring is left on for too long. A questionnaire based study found patient and partner satisfaction rates of 82% and 84%, respectively, with long term use.[34]

Box 2 Conditions for which patients are eligible for an NHS prescription for treatment of erectile dysfunction

- Diabetes
- Multiple sclerosis
- Parkinson's disease
- Poliomyelitis
- Prostate cancer
- Prostatectomy (radical or transurethral resection)
- Radical pelvic surgery
- Renal failure treated by dialysis or transplant
- Severe pelvic injury
- Single gene neurological disease
- Spinal cord injury
- Spina bifida

Box 3 Reasons for referral to secondary care

- Penile abnormality (phimosis, Peyronie's disease, post-priapism, penile cancer)
- Endocrinopathy (primary or secondary hypogonadism)
- Severe mental distress
- First line pharmacotherapy ineffective
- Psychogenic erectile dysfunction refractory to first line drugs
- Specialised diagnostic tests needed (for example, penile Doppler studies, nocturnal penile tumescence)
- Intermediate or high risk cardiovascular disease
- Contraindication to phosphodiesterase-5 inhibitors
- Lifelong history of erectile dysfunction

Penile prosthesis surgery

Third line treatment for erectile dysfunction involves surgery. Penile prosthesis surgery is suitable for patients with severe organic erectile dysfunction refractory to drug treatment. Two main types of prosthesis are available: a malleable prosthesis and an inflatable one (web fig 2). Complications related to the AMS inflatable prosthesis in a retrospective multicentre study include infection rates of 3.2% and device malfunction of 17.5%; 85.2% of patients were satisfied or highly satisfied with the prosthesis.[35]

What are the future treatment options for erectile dysfunction?

At the molecular level, gene therapy using a vector to transfect the corpus cavernosum with neurotrophic agents has been investigated in animal studies, although clinical studies have been lacking. Non-invasive treatment has recently focused on the effects of low intensity shock wave treatment, which is thought to promote neoangiogenesis.[36] Again, large multicentre clinical trials are awaited.

Although penile revascularisation surgery is used in selected patients with post-traumatic vasculogenic erectile dysfunction, internal pudendal artery stenting in medically refractory patients with stenosis of the artery is still in the early phases of development.[37]

MA would like to acknowledge Orchid (male cancer charity based in the UK) and the Barts and the London Charity.

Contributors: All authors conceived, planned, helped write the review, and reviewed the manuscript before submission. AM and MA performed the literature search and reviewed the literature. JK and IN helped write the manuscript. AM is guarantor.

We have read and understood the BMJ Group policy on declaration of interests and declare the following interests: AM has attended and given talks at educational meetings both in primary care and at national and international meetings related to urology, which have been supported by an educational grant or funding from Pfizer, Eli Lilly, Bayer, or American Medical Systems. Some of these have paid an honorarium for the time taken to prepare the talks and travelling expenses. There has been no contractual agreement on the educational content that is delivered and he is not on any advisory board or employed by any of these drug companies. JK has attended and given talks at educational meetings related to urology that have been supported by Pfizer, Eli Lilly, or Bayer. Some of these have paid an honorarium for the time taken to prepare the talk and travelling expenses. There has been no contractual agreement on the educational content that is delivered and he is not on any advisory board or employed by any of these drug companies.

Provenance and peer review: Not commissioned; externally peer reviewed.

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Ongoing research

Viberect Penile Vibratory Stimulation to Enhance Recovery of Erectile Function and Urinary Continence Post-Prostatectomy—Trial based at Johns Hopkins and currently recruiting

Low Intensity Extracorporeal Shock Wave Therapy for the Treatment of Erectile Dysfunction: 4 Arms. Trial using low intensity shock wave therapy based in Israel

Additional educational resources

Resources for healthcare professionals

Map of Medicine—Erectile dysfunction (http://healthguides.mapofmedicine.com/choices/map/erectile_dysfunction1.html)—Management algorithm for patients seen in primary and secondary care

British Society of Sexual Medicine. Guidelines for the management of erectile dysfunction. 2007. www.bssm.org.uk/downloads/BSSM_ED_Management_Guidelines_2007.pdf. Guidelines for the investigation and treatment of erectile dysfunction

European Association of Urology. Guidelines on male sexual dysfunction. 2013. www.uroweb.org/gls/pdf/14_Male%20Sexual%20Dysfunction_LR.pdf. Evidence based guidelines for erectile and ejaculatory dysfunction that explain the causes of erectile dysfunction and management options

Nieschlag E, Behre HM, Nieschlag S, eds. Andrology: male reproductive health and dysfunction. 3rd ed. Springer, 2009. Reference book for clinicians covering the subject of andrology in depth

Resources for patients

Sexual Advice Association (www.sda.uk.net/ed)—Advice and support for men with erectile dysfunction and their partners

NHS Choices (www.nhs.uk/conditions/Erectile-dysfunction)—Information for patients on erectile dysfunction

Patient.co.uk (www.patient.co.uk)—Information on sexual health with specific sections dedicated to erectile dysfunction

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Accepted: 31 December 2013

Cite this as: *BMJ* 2014;348:g129

Tables

Table 1| Cardiac risk stratification based on the second Princeton consensus*[10]

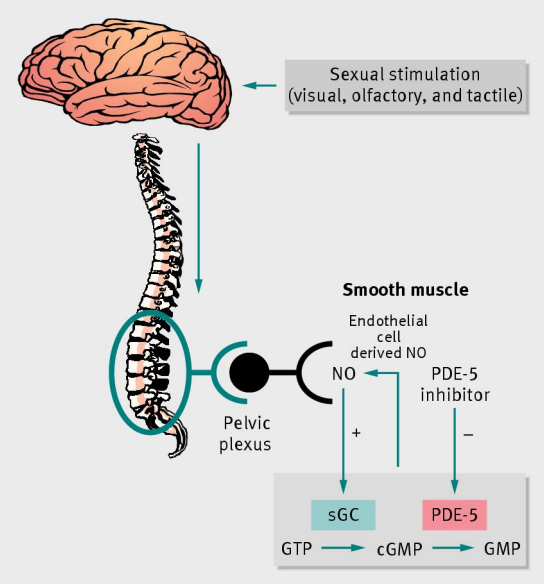
Low risk	Intermediate risk	High risk
Asymptomatic, <3 risk factors for coronary artery disease (excluding sex)	≥3 risk factors for coronary artery disease (excluding sex)	High risk arrhythmias
Mild stable angina (evaluated or being treated, or both)	Moderate stable angina	Unstable or refractory angina
Uncomplicated previous myocardial infarction	Recent myocardial infarction (>2 weeks, <6 weeks)	Recent myocardial infarction (<2 weeks)
LVD/CHF (NYHA class I)	LVD/CHF (NYHA class II)	LVD/CHF (NYHA class III/IV)
After successful coronary revascularisation	Non-cardiac sequelae of atherosclerotic disease (such as stroke, peripheral vascular disease)	Obstructive hypertrophic cardiomyopathy
Controlled hypertension	Not defined	Uncontrolled hypertension
Mild valvular disease	Not defined	Moderate to severe valvular disease, particularly aortic stenosis

*LVD/CHF= left ventricular dysfunction/congestive heart failure; NYHA=New York Heart Association.

Table 2| **Most common oral phosphodiesterase type 5 inhibitors used as first line treatment of erectile dysfunction in primary care**

Oral drugs	Dose (mg)	Time to onset (min)	Half life (h)	Duration of action (h)
Sildenafil citrate (Viagra)	25-100 on demand	30-60	4	4-8
Tadalafil (Cialis)	5 daily or 10-20 on demand	45	17.5	24-36
Vardenafil hydrochloride (Levitra)	10-20 on demand	25-40	4-5	6

Figure



Erectile dysfunction pathway illustrating the intracellular biochemical pathway and the site of action of PDE-5 inhibitors. cGMP=cyclic guanosine monophosphate; GTP=guanosine-5′-triphosphate; NO=nitric oxide; PDE-5=phosphodiesterase type 5; sGC=soluble guanylate cyclase