Guidelines on Erectile Dysfunction

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European
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of Urology

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1. BACKGROUND

1.1 Introduction

The introduction of new oral therapies has completely changed the diagnostic and therapeutic approach to erectile dysfunction (ED) (impotence). A panel of experts in this field has been established by the Guidelines Office of EAU in order to update previous published guidelines for clinical evaluation and treatment (1).

The update has been based on a review of available scientific information, as well as on current research and clinical practice in the field. Moreover, the panel has identified critical problems and knowledge gaps, setting priorities for future clinical research.

1.2 Epidemiology and risk factors

Male erectile dysfunction has been defined as the persistent inability to attain and maintain an erection sufficient to permit satisfactory sexual performance. Although ED is a benign disorder, it is related to physical and psychosocial health, and has a significant impact on the quality of life of both sufferers and their partners and families.

Recent epidemiological data have shown a high prevalence and incidence of ED worldwide. The first large-scale, community-based study, Massachusetts Male Aging Study (MMAS), reported a combined prevalence of 52% ED in non-institutionalized 40 to 70-year-old men in the Boston area (2). In this study, the individual prevalences were 17.2, 25.2 and 9.6 for minimal, moderate and complete ED, respectively. In the Cologne study (men 30-80 years old), the prevalence of ED was 19.2%, with a steep age-related increase (2.3-53.4%) (3), while the prevalence of sexual dysfunctions (not specific ED) in the National Health and Social Life Survey was 31% (4). Analysis of the longitudinal results from the MMAS study estimated that the incidence of ED was 26 new cases per 1000 men annually (5), while the incidence rates (new cases per 1000 men annually) of ED in a Brazilian (6) and in a Dutch (7) study were estimated at 65.6 (mean follow-up 2 years) and 19.2 (mean follow-up 4.2 years), respectively. Differences in these studies can be explained by the methodology design of the different surveys, the age and the socio-economic status of the populations studied.

Erection is a neurovascular phenomenon under hormonal control. It includes arterial dilatation, trabecular smooth muscle relaxation and activation of the corporeal veno-occlusive mechanism (8). Several risk factors have been identified based on our knowledge of the physiology of erection. Actually, it has become clear that ED shares common risk factors with cardiovascular disease, such as a lack of exercise, obesity, smoking, hypercholesterolaemia and the metabolic syndrome. Several lifestyle risk factors can be modified. In the MMAS, men who initiated physical activity in midlife had a 70% reduced risk for ED relative to those who remained sedentary, while in its longitudinal results, regular exercising showed a significantly lower incidence of ED over an 8-year follow up period (9). A multicentre, randomized, open-label study compared 2 years of intensive exercise and weight loss with an educational control in obese men with moderate ED (10). Significant improvements in body mass index (BMI) and physical activity scores, as well as in erectile function, were observed in the lifestyle intervention group, while those changes were highly correlated with both weight loss and activity levels. However, it should be emphasized that controlled prospective studies are necessary to determine the effects of exercise or other lifestyle changes in prevention or treatment of ED.

1.3 Managing ED: implications for everyday clinical practice

The advances in basic and clinical research in ED made during the last 15 years have led to the development of several new treatment options for ED, including new pharmacological agents for intracavernous, intraurethral, and, more recently, oral use (11-13). Reconstructive vascular surgery is associated with poor outcomes in long-term follow-up (14,15). As a result, treatment strategies have been significantly modified.

The current availability of effective and safe oral drugs for ED, together with the tremendous media interest in this condition, has resulted in an increasing number of men seeking help for ED. Many physicians without background knowledge and clinical experience of the diagnosis and treatment of ED are involved in decision-making concerning the evaluation and treatment of these men. Therefore, some men with ED may undergo little or no evaluation before treatment is initiated, or men without ED may seek treatment in order to enhance their sexual performance. In such circumstances, the underlying disease causing the symptom (i.e. ED) may remain untreated. Such observations have made the development of guidelines for the diagnosis and treatment of ED a necessity.

2. DIAGNOSIS

2.1 Basic work-up

A detailed medical and psychological history of patients and partners must always be the first step in the evaluation of ED (16,17). Although it may not often be possible to involve the partner on the first visit, an effort should be made to involve the partner during the second visit. The medical history will reveal many common disorders that are associated with ED. Pathophysiology of ED may be vasculogenic, neurogenic, hormonal, anatomical, drug-induced or psychogenic in nature (Table 1) (18).

It is important to establish a relaxed atmosphere during history-taking in order to permit questions about erectile function and other aspects of sexual history, even when men do not volunteer to describe their problem. Such an atmosphere will facilitate communication between the physician, the patient and his partner in order to explain the strategy behind the diagnostic and therapeutic approach.

Table 1: Pathophysiology of erectile dysfunction

•	**Vasculogenic**		
	-	Cardiovascular disease	
	-	Hypertension	
	-	Diabetes mellitus	
	-	Hyperlipidaemia	
	-	Smoking	
	-	Major surgery or radiotherapy (pelvis or retroperitoneum)	
•	**Neurogenic**		
	-	*Central causes*	
		-	Multiple sclerosis
		-	Multiple atrophy
		-	Parkinson's disease
		-	Tumours
		-	Stroke
		-	Disk disease
		-	Spinal cord disorders
	-	*Peripheral causes*	
		-	Diabetes mellitus
		-	Alcoholism
		-	Uraemia
		-	Polyneuropathy
		-	Surgery (pelvis or retroperitoneum)
•	**Anatomical/structural**		
	-	Peyronie's disease	
	-	Penile fracture	
	-	Congenital curvature of the penis	
	-	Micropenis	
	-	Hypospadias, epispadias	
•	**Hormonal**		
	-	Hypogonadism	
	-	Hyperprolactinemia	
	-	Hyper- and hypothyroidism	
	-	Cushing's disease	
•	**Drug-induced**		
	-	Antihypertensives (of all classes, most common by diuretics and betablockers)	
	-	Antidepressants	
	-	Antipsychotics	
	-	Antiandrogens	
	-	Antihistamines	
	-	Recreational drugs (heroin, cocaine, methadone)	
•	**Psychogenic**		
	-	Generalized type (e.g. lack of arousability and disorders of sexual intimacy)	
	-	Situational type (e.g. partner-related, performance-related issues or due to distress)	

2.1.1 *Sexual history*

The sexual history may include information about previous and current sexual relationships, current emotional status, onset and duration of the erectile problem, as well as possible previous consultations and treatments. Detailed descriptions of the quality of both erotic and morning erections, in terms of rigidity and duration, as well as arousal, ejaculation and orgasmic problems, should be made. The use of validated questionnaires, such as the International Index for Erectile Function (IIEF), may be helpful in order to assess all sexual function domains (erectile function, orgasmic function, sexual desire, ejaculation, intercourse and overall satisfaction), but also the impact of a specific treatment modality (19).

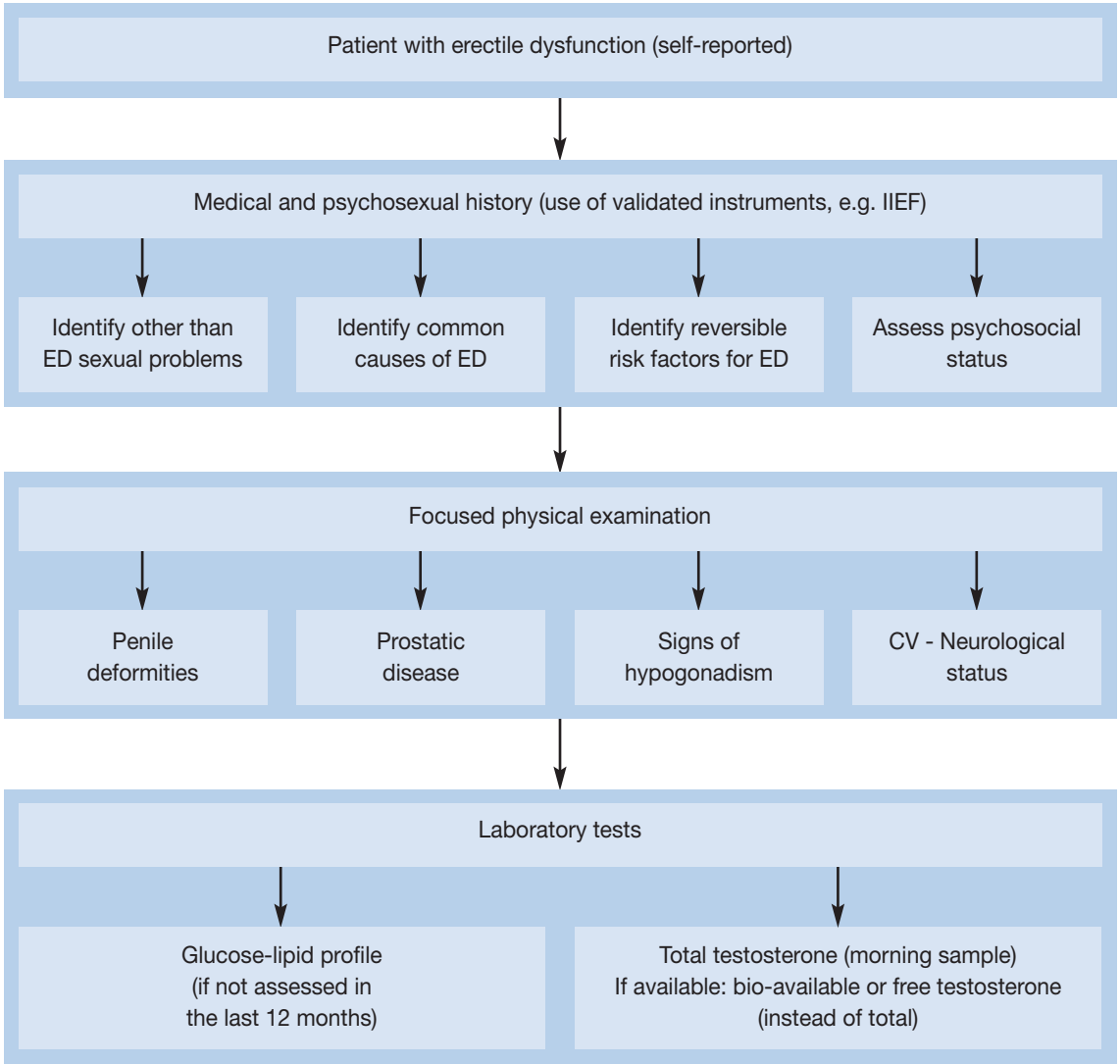
2.1.2 *Physical examination*

A focused physical examination must be performed on every patient, with particular emphasis on the genitourinary, endocrine, vascular and neurological systems (16). The physical examination may reveal unsuspected findings, such as Peyronie's disease, prostatic enlargement or cancer, as well as the signs and symptoms indicative of hypogonadism (small testes, alterations in secondary sexual characteristics, diminished sexual desire, and changes in mood) (17). A rectal examination should be performed in every patient older than 50 years. Blood pressure and heart rate should be measured if they have not been assessed in the previous 3-6 months. Particular attention must be given to patients with cardiovascular disease (see Section 2.2).

2.1.3 *Laboratory testing*

Laboratory testing must be tailored to the patient complaints and risk factors. All patients must undergo a fasting glucose and lipid profile if not assessed in the previous 12 months. Hormonal tests must include a

Figure 1: Minimal diagnostic evaluation (basic work-up) in patients with erectile dysfunction



morning sample of total testosterone (bio-available or calculated-free testosterone is more reliable to establish the presence of hypogonadism. These tests, if available, are preferable to total testosterone.

Additional laboratory tests must be considered only in selected patients (e.g. prostate-specific antigen [PSA] for detection of prostate cancer).

Additional hormonal tests (e.g. prolactin, follicle-stimulating hormone [FSH], luteinizing hormone [LH]) must be carried out when low testosterone levels are detected. If any abnormality is observed, further investigation by referral to another specialist may be necessary (20,21). The minimal diagnostic evaluation (basic work-up) in patients with erectile dysfunction is presented in Figure 1.

2.2 Cardiovascular system and sexual activity: the patient at risk

There is a high prevalence of cardiovascular disease among patients seeking treatment for sexual dysfunction and the potential cardiac risks associated with sexual activity are well established. Furthermore, recent epidemiological studies have underscored the association between cardiovascular and metabolic risk factors and sexual dysfunction in both men and women (3,22).

The pharmacological properties of phosphodiesterase (PDE) type 5 inhibitors, including their effects on cardiac smooth muscle activity and overall cardiovascular safety, have similarly been intensively investigated. In light of these developments, a consensus conference on sexual dysfunction and cardiac risk was convened on June 4-5, 1999, in Princeton, New Jersey (23), which was updated on June 11-12, 2004 (Second conference on sexual dysfunction, *J Am Coll Cardiol*, in press). The proposed management recommendations have been adapted by the current panel.

Patients with ED initiating or resuming sexual activity can be stratified into three risk categories (Table 2). Exercise tolerance, as determined from the history, can guide the clinician in estimating the risk of sexual activity in most instances. A treatment algorithm based on cardiovascular risk profile is presented in Figure 2.

Table 2: Cardiac risk stratification

Low-risk category	Intermediate-risk category	High-risk category
Asymptomatic, < 3 risk factors for CAD (excluding gender)	≥ 3 risk factors for CAD (excluding gender)	High-risk arrhythmias
Mild, stable angina (evaluated and/or being treated)	Moderate, stable angina	Unstable or refractory angina
Uncomplicated past MI	Recent MI (> 2, < 6 weeks)	Recent MI (< 2 weeks)
LVD/CHF (NYHA class I)	LVD/CHF (NYHA class II)	LVD/CHF (NYHA class III/IV)
Post-successful coronary revascularization	Non-cardiac sequelae of atherosclerotic disease (e.g. stroke, peripheral vascular disease)	Hypertrophic obstructive and other cardiomyopathies
Controlled hypertension		Uncontrolled hypertension
Mild valvular disease		Moderate-to-severe valvular disease

CAD, coronary artery disease; CHF, congestive heart failure; LVD, left ventricular dysfunction; MI, myocardial infarction; NYHA, New York Heart Association.

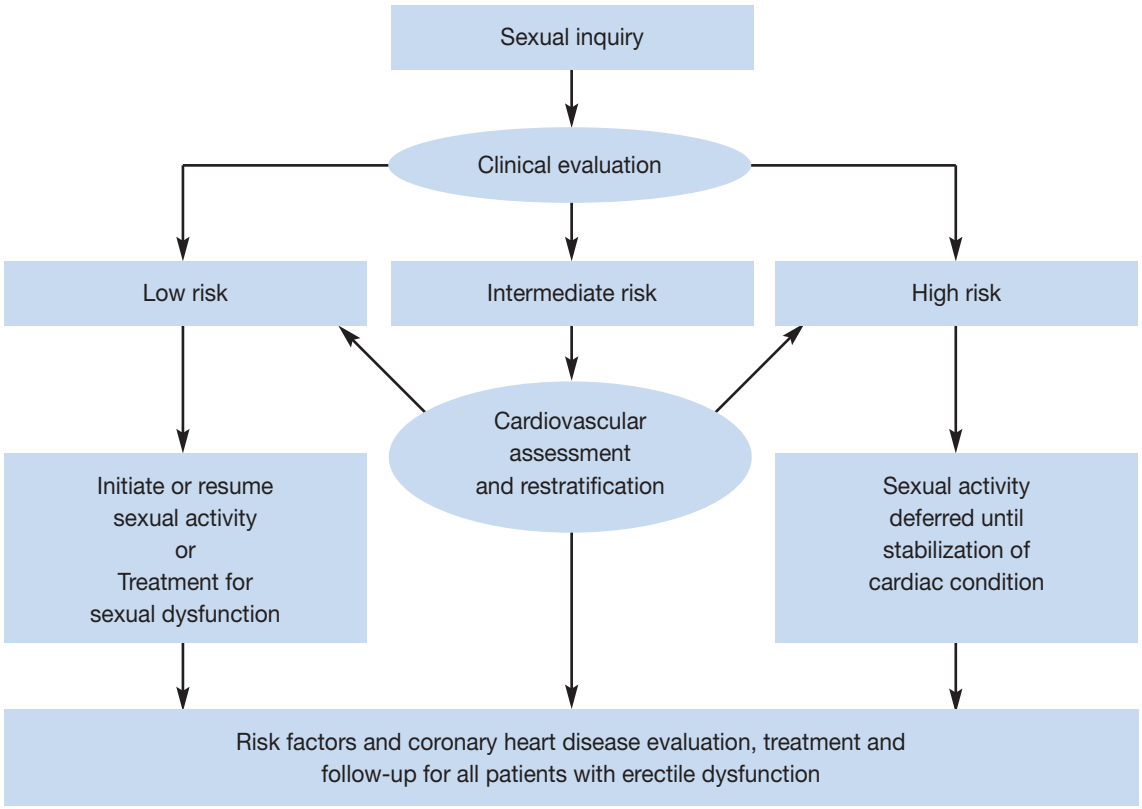
2.2.1 Low-risk category

The low-risk category includes patients who do not have any significant cardiac risk associated with sexual activity. The ability to perform exercise of modest intensity (e.g. 6 or more metabolic equivalents of energy expenditure in the resting state [METs]) without symptoms typically implies low risk. Based upon current knowledge of the exercise demands or emotional stress associated with sexual activity, no special cardiac testing or evaluation is indicated for these patients before the initiation or resumption of sexual activity or therapy for sexual dysfunction.

2.2.2 Intermediate-risk, or indeterminate-risk, category

The intermediate- or indeterminate-risk category consists of those patients whose cardiac condition is uncertain, or whose risk profile is such that further testing or evaluation is indicated before the resumption of sexual activity. Based upon the results of testing, these patients may be subsequently assigned to either the high- or low-risk group. Cardiology consultation in some cases may help the primary physician in determining the relative safety of sexual activity for the individual patient.

Figure 2: Treatment algorithm according to cardiac risk



2.2.3 High-risk category

The high-risk category consists of those patients whose cardiac condition is sufficiently severe and/or unstable that sexual activity may constitute a significant risk. Most patients are moderately to severely symptomatic. High-risk individuals should be referred for cardiac assessment and treatment. Sexual activity should be deferred until the patient's cardiac condition has been stabilized by treatment, or a decision has been made by the cardiologist and/or internist that sexual activity may be safely resumed. Under some circumstances, the patient's evaluation of risk relative to the need for sexual activity may lead to a discussion with the physician about the cardiovascular aspects of sexual activity, and the possible associated risks, and a more or less restrictive approach to resuming sexual activity.

2.3 Specialized diagnostic tests

Although the majority of patients with ED can be managed within the sexual care setting, specific diagnostic tests may be needed in certain circumstances (Table 3) and are summarized in Table 4.

2.3.1 Nocturnal penile tumescence and rigidity (NPTR)

The nocturnal penile tumescence and rigidity (NPTR) assessment should take place for at least two nights. The presence of an erectile event of at least 60% rigidity recorded on the tip of the penis, which lasts for 10 minutes or more, should be considered as indicative of a functional erectile mechanism (24).

2.3.2 Intracavernous injection test

The intracavernous injection test offers limited information regarding vascular status. A positive test is defined as a rigid erectile response (unable to bend the penis) that appears within 10 minutes after the intracavernous injection and lasts for 30 minutes (25). Such a response may indicate a functional but not necessarily normal erection, since an erection may coexist with arterial insufficiency or veno-occlusive dysfunction (26). Its clinical implication is that the patient will respond to the intracavernous injection programme. In all other cases, the test is inconclusive, and a duplex ultrasound of the penile arteries should be requested.

2.3.3 Duplex ultrasound of penile arteries

A peak systolic blood flow higher than 30 cm/sec and a resistance index higher than 0.8 are generally considered to be normal (25). There is no need to continue vascular investigation when the duplex examination is normal.

2.3.4 Arteriography and dynamic infusion cavernosometry or cavernosography

When it is abnormal, arteriography and dynamic infusion cavernosometry or cavernosography (DICC) should be performed only for patients who are considered potential candidates for vascular reconstructive surgery.

2.3.5 Psychiatric assessment

Patients with psychiatric disorders must be referred to a psychiatrist particularly interested in ED. For younger patients (< 40 years) with longstanding primary ED, psychiatric assessment may be helpful before any organic assessment is carried out.

2.3.6 Penile abnormalities

Patients with ED due to penile abnormalities, such as hypospadias, congenital curvature, or Peyronie's disease with preserved rigidity, may require surgical correction with high success rates.

2.4 Patient education - consultation and referrals

The discussion considers patient's expectations and needs, and should involve the physician, the patient and his partner. It should cover the patient's understanding of the disorder, interpretation of the diagnostic tests and a rational selection of treatment options. Patient and partner education are essential components in the management of ED (27).

Table 3: Indications for specific diagnostic tests

•	Primary erectile disorder (not caused by organic disease, or psychogenic disorder)
•	Young patients with a history of pelvic or perineal trauma who could benefit from potentially curative vascular surgery
•	Patients with penile deformities (e.g. Peyronie's disease, congenital curvature) that might require surgical correction
•	Patients with complex psychiatric or psychosexual disorders
•	Patients with complex endocrine disorders
•	Specific tests may be indicated at the request of the patient or his partner
•	Medicolegal reasons (e.g. implantation of penile prosthesis, cases of sexual abuse)

Table 4: Specific diagnostic tests

•	Nocturnal penile tumescence and rigidity (NTPR) using Rigiscan®	
•	Vascular studies	
	-	Intracavernous vasoactive drug injection
	-	Duplex ultrasound of the cavernous arteries
	-	Dynamic infusion cavernosometry or cavernosography (DICC)
	-	Internal pudendal arteriography
•	Neurological studies (e.g. bulbocavernosus reflex latency, nerve conduction studies)	
•	Endocrinology studies	
•	Specialized psychodiagnostic evaluation	

3. TREATMENT

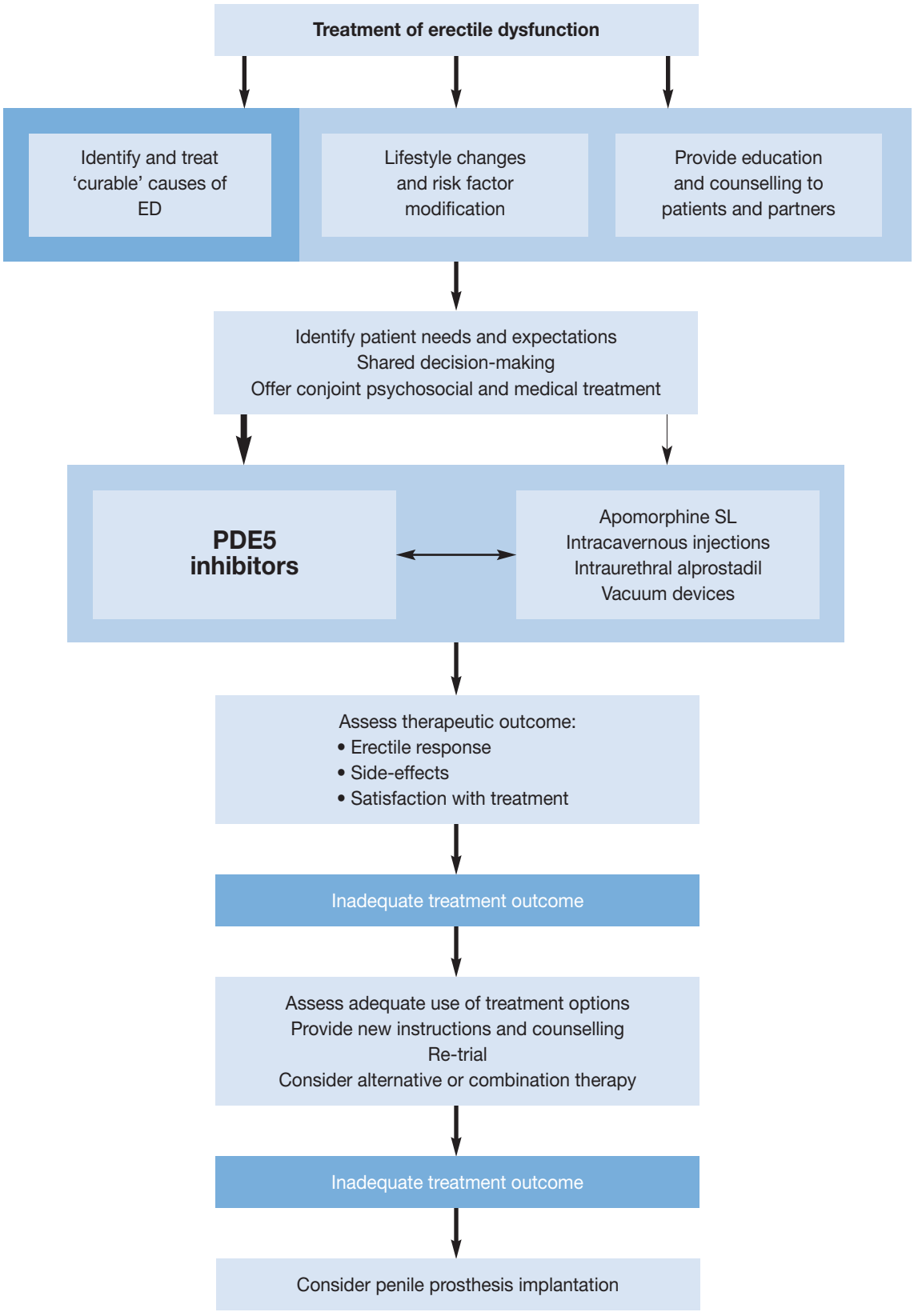
3.1 Treatment options

The primary goal in the management strategy of a patient with ED is to determine the aetiology of the disease and treat it when possible, and not to treat the symptom alone. It is clear that ED may be associated with modifiable or reversible factors, including lifestyle or drug-related factors, which may be modified prior to, or together with, the employment of specific therapeutic operations.

Erectile dysfunction can be treated successfully with current treatment options but certainly cannot be cured. The only exceptions to this rule are psychogenic erectile dysfunction, post-traumatic arteriogenic ED in young patients and hormonal causes (e.g. hypogonadism, hyperprolactinaemia), which can be potentially cured with specific treatment modalities.

The majority of men with erectile dysfunction will be treated with no cause-specific treatment options. This fact leads to a structured treatment strategy that depends on efficacy, safety, invasiveness and cost, as

Figure 3: Treatment algorithm for ED



well as patient preferences (28). In order to counsel patients properly with ED, physicians must be fully informed of all treatment options.

Besides efficacy and safety, patient and partner satisfaction, as well as other quality of life items, are important endpoints when assessing treatment options. A treatment algorithm for ED is presented in Figure 3.

3.2 Lifestyle management in ED with concomitant risk factors

The basic work-up must identify reversible risk factors for ED. Lifestyle changes and risk factor modification must precede or accompany ED treatment. These guidelines include lifestyle modification (e.g. weight loss, exercise) for ED, but also address psychosocial issues, adverse side-effects of prescription or non-prescription drugs and the presence of hypogonadism as a modifiable aetiology or comorbidity of ED.

The potential benefits of lifestyle changes may be of special relevance in individuals with ED and specific comorbid cardiovascular or metabolic diseases, such as diabetes or hypertension (9,29,30). For these men, the positive consequences of aggressive lifestyle changes may be of special benefit not only for improving erectile function, but also for improving overall cardiovascular and metabolic health. Recent studies support the potential value of lifestyle intervention, for both ED and overall health benefits (10).

Clearly, further studies are needed to expand and clarify the role of lifestyle changes in the management of ED and related cardiovascular disease (CVD). Lifestyle changes may be recommended independently or in combination with PDE5 therapy. Some studies have suggested that the therapeutic effects of PDE5 inhibitors may be enhanced if other comorbidities or risk factors are aggressively managed (31). Although suggestive, these results have yet to be confirmed in well-controlled, long-term studies. Given the success of pharmacological therapy for ED, clinicians in the future will need to provide specific evidence for the potential benefits of lifestyle change. Hopefully, further evidence for these benefits will become available in the future.

3.3 'Curable' causes of ED

3.3.1 Hormonal causes

The advice of an endocrinologist is essential for patients with hormonal abnormalities. Testosterone deficiency may be a result of primary testicular failure or may be secondary to pituitary/hypothalamic causes, including a functional pituitary tumour resulting in hyperprolactinaemia.

3.3.1.1 Testosterone replacement therapy

Testosterone replacement (intramuscular, oral or transdermal) is effective, but can only be used when other possible endocrinological causes for testicular failure have been excluded. Testosterone replacement therapy is contraindicated in men with a history of prostate carcinoma or with symptoms of prostatism. Prior to initiating testosterone replacement, a digital rectal examination (DRE) and serum PSA test should be performed. Patients receiving androgen therapy should be monitored for clinical response as well as for the development of hepatic or prostatic disease.

There is no contraindication for testosterone therapy in men with coronary artery disease (CAD) with a properly diagnosed hypogonadism and/or ED. However, caution should be exercised regarding the occasional increase in haematocrit level, especially in those with congestive heart failure. It should be mentioned that this treatment is not always effective in the management of ED associated with hypogonadism (20).

3.3.2 Post-traumatic arteriogenic ED in young patients

In young patients with pelvic or perineal trauma, a surgical penile revascularization procedure is associated with a 60-70% long-term success rate. The lesion must be demonstrated by duplex ultrasound and confirmed by penile pharmaco-arteriography. The presence of corporeal veno-occlusive dysfunction is a contraindication to revascularization and must be excluded by DICC (15). Vascular surgery for the treatment of veno-occlusive dysfunction is no longer recommended due to poor results at long-term follow-up (14).

3.3.3 Psychosexual counselling and therapy

For patients with a significant psychological problem, psychosexual therapy may be given either alone or in combination with another therapeutic approach. Psychosexual therapy takes time and has been associated with variable results (32).

3.4 First-line therapy

3.4.1 Oral pharmacotherapy

The PDE5 enzyme hydrolyzes cyclic guanosine monophosphate (cGMP) in the cavernosum tissue of the penis. Inhibition of PDE5 results in increased arterial blood flow leading to smooth muscle relaxation, vasodilatation and penile erection (33).

Three potent selective PDE5 inhibitors are currently on the market approved by the European Medicines Agency (EMEA) and the US Food and Drug Administration (FDA) with proven efficacy and safety for the treatment of ED. They are not initiators of erection but require sexual stimulation in order to facilitate an erection.

3.4.1.1 Sildenafil

Sildenafil is the first PDE5 inhibitor. More than 20 million men have been treated over a 6-year post-marketing experience. It is effective (erection with rigidity sufficient for vaginal penetration) within 30-60 minutes from administration. Its efficacy is reduced after a heavy fatty meal due to prolonged absorption. It is administered in 25, 50 and 100 mg doses. The recommended starting dose is 50 mg and should be adapted according to the patient's response and side-effects. Efficacy may be maintained for up to 12 hours (34). The pharmacokinetic data of sildenafil are presented in Table 5. Adverse events (Table 6) are generally mild in nature and self-limited by continuous use, with the drop-out rate due to adverse events similar to placebo (35).

In pre-marketing studies, after 24 weeks of treatment in a dose-response study, improved erections were reported by 56%, 77% and 84% of men taking 25, 50 and 100 mg of sildenafil, respectively, compared with 25% of men taking placebo (11). Sildenafil statistically improved IIEF, sexual encounter profile 2 (SEP2), SEP3 and general assessment question (GAQ) and satisfaction scores.

The efficacy of sildenafil in almost every subgroup of patients with ED has been successfully established (36). In diabetic patients, 66.6% reported improved erections (GAQ) and 63% successful intercourse attempts, respectively, compared with 28.6% and 33% of men taking placebo (37). In patients after bilateral nerve-sparing radical prostatectomy, 76% responded to sildenafil (defined as successful vaginal intercourse) (38).

3.4.1.2 Tadalafil

Tadalafil is effective from 30 minutes after administration, but its peak efficacy is expected in about 2 hours' time. Efficacy is maintained for up to 36 hours (39). Its efficacy is not influenced by food. It is administered in 10 and 20 mg doses. The recommended starting dose is 10 mg and should be adapted according to the patient's response and side-effects. Pharmacokinetic data of tadalafil are presented in Table 5. Adverse events (Table 6) are generally mild in nature, self-limited by continuous use, and the drop-out rate due to adverse events is similar to placebo (40).

In pre-marketing studies, after 12 weeks of treatment and in a dose-response study, improved erections were reported by 67% and 81% of men taking 10 mg and 20 mg of tadalafil compared with 35% of men in the control placebo group (13). Tadalafil statistically improved IIEF, SEP2, SEP3 and GAQ and satisfaction scores. These results were confirmed in post-marketing studies (41).

Tadalafil also improved erections in difficult-to-treat subgroups. In diabetic patients, 64% reported improved erections (i.e. improved GAQ) compared to 25% of patients in the control group and the final IIEF erectile function domain score change was 7.3 compared to 0.1 for placebo (42). In patients after bilateral nerve-sparing radical prostatectomy, the mean percentage of successful penetration attempts was 54% and the mean percentage of successful intercourse attempts was 41%. For a subgroup with evidence of postoperative tumescence, these values were 69% and 52%, respectively. Improved erections were reported by 62% of all patients randomized to tadafil and 71% of subgroup patients randomized to tadafil (43).

3.4.1.3 Vardenafil

Vardenafil is effective after 30 minutes from administration. Its effect is reduced by a heavy fatty meal (> 57% fat). It is administered in 5, 10 and 20 mg doses. The recommended starting dose is 10 mg and should be adapted according to the patient's response and side-effects. In vitro, it is 10-fold more potent than sildenafil; however, this does not necessarily imply greater clinical efficacy (44). Pharmacokinetic data of vardenafil are presented in Table 5. Adverse events (Table 6) are generally mild in nature and self-limited by continuous use, with a drop-out rate similar to placebo (45).

In pre-marketing studies, after 12 weeks of treatment and in a dose-response study, improved erections were reported by 66%, 76% and 80% of men taking 5 mg, 10 mg and 20 mg of vardenafil, respectively, compared with 30% of men taking placebo (46). Vardenafil statistically improved IIEF, SEP2, SEP3 and GAQ and satisfaction scores. Efficacy is confirmed in post-marketing studies (47).

Vardenafil has also improved erections in difficult-to-treat subgroups. In diabetic patients, 72% reported improved erections (i.e. improved GAQ) compared to 13% of patients taking placebo and the final IIEF erectile function domain score was 19 compared to 12.6 for placebo (48). In patients after bilateral nerve-sparing radical prostatectomy, the average intercourse success rate per patient receiving 20 mg vardenafil was 74% in men with mild to moderate ED and 28% in men with severe ED, compared to 49% and 4% for placebo, respectively. Positive GAQ responses were reported by 71.1% of patients (49).

3.4.1.4 Choice or preference between the different PDE5 inhibitors

To date, no data are available from double- or triple-blind multicentre studies comparing the efficacy and/or the preference for sildenafil, tadalafil and vardenafil. Patients should be informed about the effects (short- or long-acting) and possible disadvantages of each drug, as well as on how to use the drug. The frequency of intercourse (occasional use or regular therapy, 3-4 times weekly) and personal experience will determine the drug of choice. Before being considered to be non-effective and replaced by another PDE5 inhibitor, each drug should be administered at least four times.

Table 5: Summary of the key pharmacokinetic data for the three PDE5 inhibitors (fasted state, higher recommended dose, data from EMEA statements on product characteristics)

Parameter	Sildenafil 100 mg	Tadalafil 20mg	Vardenafil 20 mg
Cmax	560 µg/L	378 µg/L	18.7 µg/L
Tmax	0.8 – 1 h	2 h	0.9 h
$T_{1/2}$	2.6 – 3.7 h	17.5	3.9 h
AUC	1685 µg.h/L	8066 µg.h/L	56.8 µg.h/L
Protein binding	96%	94%	94%
Bioavailability	41%	NA	15%

Cmax: maximal concentration, Tmax: time to maximum plasma concentration;
$T_{1/2}$: plasma elimination half-time; AUC: area under curve - serum concentration time curve.

Table 6: Common adverse events of all three PDE5 inhibitors (from EMEA statements on product characteristics)

Adverse event	Sildenafil	Tadalafil	Vardenafil
Headache	12.8%	14.5%	16%
Flushing	10.4%	4.1%	12%
Dyspepsia	4.6%	12.3%	4%
Nasal congestion	1.1%	4.3%	10%
Dizziness	1.2%	2.3%	2%
Abnormal vision	1.9%		<2%
Back pain		6.5%	
Myalgia		5.7%	

3.4.1.5 Safety issues for PDE5 inhibitors

Cardiovascular safety

Clinical trial results and post-marketing data of sildenafil, tadalafil and vardenafil demonstrated no increase in myocardial infarction rates in patients that received these agents, as part of either double-blind, placebo-controlled trials or open-label studies, or compared to expected rates in age-matched populations of men. None of the PDE5 inhibitors were found to adversely affect total exercise time or time to ischaemia during exercise testing in men with stable angina (50-52). In fact, they may actually improve exercise tests. Sildenafil does not alter cardiac contractility, cardiac output or myocardial oxygen consumption based on evidence reviewed to date.

Nitrates are totally contraindicated with PDE5 inhibitors

Organic nitrates (e.g. nitroglycerine, isosorbide mononitrate, isosorbide dinitrate) and other nitrate preparations used to treat angina, as well as amyl nitrite or amyl nitrate ('poppers' used for recreation) are absolute contraindications with the use of PDE5 inhibitors. They result in cGMP accumulation and unpredictable falls in blood pressure and symptoms of hypotension. The duration of interaction between organic nitrates and PDE5 inhibitors is dependent upon the PDE5 inhibitor and nitrate under study.

If a PDE5 inhibitor is taken and the patient develops chest pain, nitroglycerine must withheld for at least 24 hours if sildenafil (and likely vardenafil) was used (half-life, 4 hours) and for at least 48 hours if tadalafil was used (half-life, 17.5 hours). If a patient develops angina while taking a PDE5 inhibitor, other agents may be administered instead of nitroglycerine until the appropriate time has passed. If nitroglycerine must be reintroduced following administration of a PDE5 inhibitor, the patient should receive it only after an appropriate interval has elapsed, as described above and under close medical observation.

Antihypertensive drugs
Co-administration of PDE5 inhibitors with antihypertensive agents (angiotensin converting enzyme inhibitors, angiotensin receptor blockers, calcium blockers, betablockers, diuretics) may result in small additive drops in blood pressure, which are usually minor. In general, the adverse event profile of the PDE5 inhibitor is not worsened by a background of antihypertensive medicines, even when the patient is on multiple antihypertensive agents.

Alpha blocker interactions
All PDE5 inhibitors appear to have some interaction with alpha blockers, which under some conditions may result in orthostatic hypotension. Sildenafil labelling currently describes a precaution advising that 50 or 100 mg (not 25 mg) of sildenafil should not be taken within a 4-hour window of an alpha blocker. In the USA, vardenafil is absolutely contraindicated with alpha blockers. However, the co-administration of vardenafil with tamsulosin is not associated with clinical significant hypotension (53). Tadalafil is contraindicated in patients taking alpha blockers, except for tamsulosin 0.4 mg (54). These interactions are more pronounced when PDE5 inhibitors are given to healthy volunteers not previously taking alpha blockers. Additional studies with other PDE5 inhibitors and other alpha blockers (e.g. alfuzosin OD) or mixed alpha/beta blockers (e.g. carvedilol, labetalol) are needed to improve understanding of the interaction between these two classes of agents.

Dosage adjustments
Certain drugs can inhibit the metabolic breakdown of PDE5 inhibitors (by inhibiting the CYP3A4 pathway), such as ketoconazole, itraconazole, erythromycin, clarithromycin and HIV protease inhibitors (ritonavir, saquinavir). Such agents may increase blood levels of PDE5 inhibitors and may require lower doses of PDE5 inhibitors. On the other hand, other agents, such as rifampin, phenobarbital, phenytoin and carbamazepine, may induce CYP3A4 and enhance the breakdown of PDE5 inhibitors, so that higher doses of PDE5 inhibitors are required. Severe kidney or hepatic dysfunction may require dose adjustments or warnings.

3.4.1.6 Apomorphine sublingual
Apomorphine is a centrally acting drug (dopamine agonist, mainly D2) that improves erectile function by enhancing the natural central erectile signals that normally occur during sexual stimulation (55,56). It is administered sublingually on demand in 2 or 3 mg doses. Apomorphine has been approved for erectile dysfunction treatment in several countries but not in the USA.

Efficacy rates (erections sufficient for intercourse) range from 28.5% to 55% (57-59). Due to rapid absorption, 71% of erections are achieved within 20 minutes. The most common adverse events are nausea (7%), headache (6.8%) and dizziness (4.4%) (58). These events are generally mild in nature and self-limited (60). Severe events, such as syncope, are extremely rare (< 0.2%) (61). Apomorphine is not contraindicated in patients taking nitrates or antihypertensive drugs of all classes and it does not affect vital signs (62). There was no marked improvement in sexual desire but a slight improvement in orgasmic function was noticed (63).

Comparative studies clearly show that apomorphine is associated with significantly lower efficacy and satisfaction rates than sildenafil (64,65). The most significant strength of apomorphine is its safety profile (66). Even in pre-marketing studies apomorphine improves erectile function, intercourse and overall satisfaction domains of the IIEF, significantly better than placebo. Its use is limited to patients with mild to moderate erectile dysfunction or psychogenic causes due to reduced efficacy rates. It may also be a first-line treatment in patients with certain contraindications for the use of PDE5 inhibitors, such as the use of nitrates.

3.4.1.7 Other oral agents
Several other drugs have been used in the treatment of ED with various mechanisms of action (67). Yohimbine is a centrally and peripherally active α_2 adrenergic antagonist used as an aphrodisiac for almost a century. Delequamine is a more specific and selective α_2-adrenergic antagonist than yohimbine. Trazodone is a serotonin reuptake inhibitor (antidepressant) that has been associated with prolonged erections and priapism. It is also a non-selective α-adrenergic antagonist in the corporal smooth muscle cells. L-arginine is a nitric oxide donor and nalmefene/naltrexone is an opioid-receptor antagonist. Red Korea ginseng is a formulation with a currently unknown mechanism of action (though it may possibly act as a nitric oxide donor). Limaprost is an alprostadil derivative for oral use. Finally, an oral formulation of phentolamine (non-selective α-adrenergic antagonist) underwent phase III clinical trials (68).

Results from randomized studies showed that the efficacy of yohimbine and trazodone is similar to placebo in patients with organic causes of ED (69,70). Studies on oral phentolamine showed efficacy rates (erections sufficient for intercourse) of about 50% (68). Possible carcinogenesis in animal models stopped further development of the drug. Efficacy data on Red Korea ginseng show that it may have a role in treatment of ED (71). There are no efficacy data on all other drugs. Today, there is no place for these drugs in the treatment of ED.

3.5 Topical pharmacotherapy

Several vasoactive drugs (2% nitroglycerine, 15-20% papaverine gel and 2% minoxidil solution or gel) have been used for topical application to the penis. In order to overcome the poor drug absorption through the thick and dense tunica albuginea, several drug absorption enhancers have been developed for combination with vasoactive drugs (72). A combination (Topiglan™) of alprostadil gel 1% with 5% SEPA® (enhancer of absorption) resulted in an erection sufficient for vaginal penetration in 38.9% of patients compared with 6.9% of patients who received placebo (73). Adverse events include skin and glans erythema, burning sensation, allergic reactions and side-effects in the partner (hypotension, headache) due to absorption from the vagina. No topical therapy has been approved and their role in the treatment of ED is currently unknown.

3.6 Vacuum constriction devices

Vacuum constriction devices (VCD) provide passive engorgement of the corpora cavernosa in conjunction with a constrictor ring placed at the base of the penis to retain blood within the corpora. Thus, erections with these devices are not normal since they do not use physiological erection pathways. Efficacy, in terms of erections satisfactory for intercourse, is as high as 90%, regardless of the cause of ED and satisfaction rates range between 27% and 94% (74). Men with a motivated, interested and understanding partner report the highest satisfaction rates. Long-term use of VCDs drops to 50-64% after 2 years (75). Most men who discontinue use of VCDs do so within 3 months.

Common adverse events include pain, inability to ejaculate, petechiae, bruising and numbness (30% of patients). These are the most common adverse events found in less than 30% of patients (76). Serious adverse events (skin necrosis) can be avoided if patients remove the constriction ring within 30 minutes. VCD are contraindicated in patients with bleeding disorders or on anticoagulant therapy.

VCDs are generally not accepted by younger patients. However, they may be the treatment of choice in well-informed older patients with infrequent sexual intercourses and the presence of comorbidities that demand a non-invasive, drug-free management of ED.

3.7 Second-line therapy

Patients not responding to oral drugs may be offered intracavernous injections with high success rates of 85% (77).

3.7.1 Intracavernous injections

3.7.1.1 Alprostadil

Intracavernous administration of vasoactive drugs was the first medical treatment for ED more than 20 years ago (78).

Alprostadil (Caverject™, Edex/Viridal™) is the first and only drug approved for intracavernous ED treatment (79). It is the more efficacious monotherapy for intracavernous treatment in 5-40 µg doses. The erection appears after 5-15 minutes and lasts according to the dose injected. An office-training programme (one or two visits) is required for the patient to learn the correct injection process. In cases of limited manual dexterity, the technique may be taught to their partners. The use of an automatic special pen that avoids a view of the needle can resolve the fear of the penile puncture and can simplify the technique.

Efficacy rates for intracavernous alprostadil of more than 70% have been found in general ED populations, as well as in patient subgroups (e.g. diabetes or cardiovascular disease), with reported sexual activity after 94% of the injections and satisfaction rates of 87-93.5% in patients and 86-90.3% in partners (80,81).

Complications of intracavernous alprostadil include penile pain (50% of patients, after 11% of injections), prolonged erections (5%), priapism (1%) and fibrosis (2%) (79,82). Pain is usually self-limited after prolonged use. It can be alleviated with the addition of sodium bicarbonate or local anaesthetic (83,84). Fibrosis requires temporary discontinuation of the injection programme for several months. Systemic side-effects are uncommon. The most common is mild hypotension especially when using higher doses.

Contraindications include men with a history of hypersensitivity to alprostadil, men at risk of priapism and men with bleeding disorders.

Despite these favourable data, intracavernous pharmacotherapy is associated with high drop-out rates and limited compliance. Drop-out rates of 40.7-68% have been described (85,86), with most patients who discontinue treatment doing so within the first 2-3 months. In a comparative study, alprostadil monotherapy had the lowest discontinuation rates (27.5%) compared to overall drug combinations (37.6%), with an attrition rate after the first months of therapy of 10% per year (87). Reasons for discontinuation included desire for a permanent modality of therapy (29%), lack of a suitable partner (26%), poor response (23%), especially in the early drop-out rate, fear of needles (23%), fear of complications (22%) and lack of spontaneity (21%) (86,88). Careful counselling of patients during the office-training phase as well as close follow-up is important in addressing patient withdrawal from an intracavernous injection programme.

Today, intracavernous pharmacotherapy is considered a second-line treatment. Patients not responding to oral drugs may be offered intracavernous injections with high success rates of 85% (77,89).

Most long-term injection users can switch to sildenafil despite underlying pathophysiology (90,91). However, almost one-third of long-term intracavernous injections users who subsequently responded also to sildenafil preferred to continue with an intracavernous injection programme (92,93).

Action to be taken with prolonged erection

After 4 hours of erection, patients are advised to consult the doctor to avoid any damage to the intracavernous muscle, which would provoke permanent impotence. A 19-gauge needle is used to aspirate blood and thereby decrease intracavernous pressure. This simple method is usually sufficient to make the penis flaccid.

However, if the penis becomes rigid again after this, phenylephrine intracavernous injection is required, starting at a dose of 200 µg every 5 minutes and increasing to 500 µg if necessary. The risk of having a prolonged erection during following subsequent injections cannot be predicted. When this problem occurs, the dose is usually reduced for the next injection.

3.7.1.2 Combination therapy

The rationale for combination treatment is to take advantage of different modes of action as well as to alleviate side-effects by using lower doses of each individual drug.

Papaverine (20-80 mg) was the first oral drug used for intracavernous injections. It is not used today as monotherapy due to a higher incidence of adverse events.

Phentolamine is another drug that has been used in combinations augmenting efficacy although alone it has a poor erectile response.

Sparse data in the literature support the use of other drugs, such as vasoactive intestinal peptide (VIP), nitric oxide (NO) donors (linsidomine), forskolin, potassium channel openers, moxisylyte or calcitonin gene-related peptide (CGRP), mostly in combinations with the main drugs (94,95). Most of the combinations are not standardized and some drugs have limited availability worldwide.

The combinations of papaverine (7.5-45 mg) plus phentolamine (0.25-1.5 mg), and of papaverine (8-16 mg), phentolamine (0.2-0.4 mg) plus alprostadil (10-20 µg), have been widely used with better efficacy rates (especially the latter), although they have never received approval for the treatment of ED (96,97). The combination regimen of papaverine, phentolamine and alprostadil was associated with the highest efficacy rates reaching 92% (97,98), with similar complications to alprostadil. The incidence of penile pain is lower (due to lower doses of alprostadil). However, fibrosis is more common (5-10%) when papaverine is used (depending on total dose), and mild hepatotoxicity has been reported with papaverine (99).

Despite high efficacy rates, 5-10% of patients will not respond to combination intracavernous injections. The combination of sildenafil with intracavernous injection of the triple combination solution may salvage as many as 31% of patients not responding to the triple combination alone (100). However, combination therapy was associated with an incidence of adverse effects in 33% of patients, including dizziness in 20% of patients.

This strategy can be considered in carefully selected patients before proceeding to implantation of a penile prosthesis.

3.7.1.3 Intraurethral alprostadil

A specific formulation of alprostadil (125-1000 µg) in a medicated pellet (MUSE™) has been approved for use in erectile dysfunction patients (101). A vascular interaction exists between the urethra and the corpora cavernosa that permits drug transfer between these structures (102). Erections sufficient for intercourse were achieved in 30-65.9% of patients (101,103,104). In clinical practice, only the higher doses (500 and 1000 µg) were encountered and consistency rates were low (105). The application of a constriction ring at the root of the penis (ACTIS™) may improve efficacy (106).

The most common adverse events are local pain (29-41%) and dizziness (1.9-14%). Penile fibrosis and priapism are very rare (< 1%). Urethral bleeding (5%) and urinary tract infections (0.2%) are adverse events related to the mode of administration (78).

Efficacy rates are significantly lower than intracavernous pharmacotherapy (107). Intraurethral pharmacotherapy is a second-line therapy, providing an alternative to intracavernous injections in patients who prefer a less invasive, but less efficacious, treatment.

3.8 Third-line therapy

3.8.1 Penile prosthesis

The surgical implantation of a penile prosthesis may be considered in patients who fail pharmacotherapy or who prefer a permanent solution to their problem. Two types of prosthesis exist: malleable (semi-rigid) and inflatable (two- or three-piece).

Most patients prefer the three-piece inflatable devices due to the more ‘natural’ erections obtained. However, the two-piece inflatable prosthesis can be a reliable option with fewer mechanical complications and

a simpler implantation technique. A semi-rigid prosthesis provides a constantly rigid penis and can be a choice in older patients with infrequent sexual intercourse (108). The inflatable prosthesis is much more expensive. In several countries, patients are reimbursed for the cost of the prosthesis, but an organic cause has to be determined for the ED and the patient has to undergo a complete impotence assessment.

Prosthesis implantation has one of the highest satisfaction rates (70-87%) among treatment options for ED based on appropriate consultation (109,110).

The two main complications of penile prosthesis implantation are mechanical failures and infection. Several technical modifications of the most commonly used three-piece prosthesis (AMS 700CX/CXM™ and Mentor Alpha I™) resulted in mechanical failure rates of less than 5% in the long-term (5-year follow-up) (111,112). Careful surgical technique with proper antibiotic prophylaxis against gram-positive and gram-negative bacteria reduced infections rates to 2-3% (113). The infection rate may be further reduced (to 1%) with the implantation of an antibiotic-impregnated prosthesis (AMS Inhibizone™) or hydrophilic-coated prosthesis (Mentor Titan™) (114,115).

Although diabetes is considered to be one of the main risk factors for infection, current data do not support this fact (108). Infections, as well as erosions, are significantly higher (9%) in patients with spinal cord injuries (9%) (116). Infection requires removal of the prosthesis, antibiotic administration and reimplantation after 6-12 months. However, a salvage therapy with removal and reimplantation at the same time, after copious irrigation of the corpora with multi-drug solutions, is associated with 82% success rates (117).

4. CONCLUSION

A great deal of progress has been made in the pharmacological treatment of ED. Modern treatment of ED has been revolutionized by the worldwide availability of the three PDE5 inhibitors (sildenafil, tadalafil, vardenafil) for oral use, which are associated with high efficacy and safety rates, even in difficult-to-treat populations (e.g. diabetes mellitus, radical prostatectomy). Patients should be encouraged to try all three PDE5 inhibitors and to develop their own opinions. They will choose the compound perceived by them to have the best efficacy, as well as considering other features such as time of onset, duration of action, window of opportunity and their own individual experience with side-effects.

Treatment options for patients not responding to oral drugs (or contraindicated) include intracavernous injections, intraurethral alprostadil, vacuum constriction devices and implantation of penile prosthesis.

It must be emphasized that the physician should warn the patient that sexual intercourse is considered to be a vigorous physical activity, which increases heart rate as well as cardiac work. Physicians should assess the cardiac fitness of patients prior to treating ED.

Any successful pharmacological treatment for erectile failure demands a degree of integrity of the penile mechanisms of erection. Further studies of individual agents and synergistic activity of available substances are underway. The search for the ideal pharmacological therapy for erectile failure aims at fulfilling the following characteristics: good efficacy, easy administration, freedom from toxicity and side-effects, with a rapid onset and a possible long-acting effect.

5. REFERENCES

1. Wespes E, Amar E, Hatzichristou DG, Montorsi F, Pryor J, Vardi Y. EAU guidelines on erectile dysfunction. Update March 2004. Eur Urol 2002;41:1-5. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11999460
2. Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ, McKinlay JB. Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. J Urol 1994;151:54-61. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=8254833
3. Braun M, Wassmer G, Klotz T, Reifenrath B, Mathers M, Engelmann U. Epidemiology of erectile dysfunction: results of the 'Cologne Male Survey'. Int J Impot Res 2000;12:305-311. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11416833
4. Laumann EO, Paik A, Rosen RC. Sexual dysfunction in the United States: prevalence and predictors. JAMA 1999;281:537-544. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10022110
5. Johannes CB, Araujo AB, Feldman HA, Derby CA, Kleinman KP, McKinlay JB. Incidence of erectile dysfunction in men 40 to 69 years old: longitudinal results from the Massachusetts male aging study [see comments]. J Urol 2000;163:460-463. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10647654
6. Moreira ED Jr, Lbo CF, Diament A, Nicolosi A, Glasser DB. Incidence of erectile dysfunction in men 40 to 69 years old: results from a population-based cohort study in Brazil. Urology 2003;61:431-436. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12597962
7. Schouten BW, Bosch JL, Bernsen RM, Blanker MH, Thomas S, Bohnen AM. Incidence rates of erectile dysfunction in the Dutch general population. Effects of definition, clinical relevance and duration of follow-up in the Krimpen Study. Int J Impot Res 2005 Jan-Feb;17(1):58-62. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15510192
8. Lue TF, Tanagho EA. Physiology of erection and pharmacological management of impotence. J Urol 1987;137:829-836. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=3553617
9. Derby CA, Mohr BA, Goldstein I, Feldman HA, Johannes CB, McKinlay JB. Modifiable risk factors and erectile dysfunction: can lifestyle changes modify risk? Urology 2000;56:302-306. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10925098
10. Esposito K, Giugliano F, Di Palo C, Giugliano G, Marfella R, D'Andrea F, D'Armiento M, Giugliano D. Effect of lifestyle changes on erectile dysfunction in obese men: a randomized controlled trial. JAMA 2004;291:2978-2984. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15213209
11. Goldstein I, Lue TF, Padma-Nathan H, Rosen RC, Steers WD, Wicker PA. Oral sildenafil in the treatment of erectile dysfunction. Sildenafil Study Group N Engl J Med 1998;338:1397-1404. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=9580646
12. Hellstrom WJ, Gittelman M, Karlin G, Segerson T, Thibonnier M, Taylor T, Padma-Nathan H; Vardenafil Study Group. Sustained efficacy and tolerability of vardenafil, a highly potent selective phosphodiesterase type 5 inhibitor, in men with erectile dysfunction: results of a randomized, double-blind, 26-week placebo-controlled pivotal trial. Urology 2003;61:8-14. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12657355

13. Brock GB, McMahon CG, Chen KK, Costigan T, Shen W, Watkins V, Anglin G, Whitaker S. Efficacy and safety of tadalafil for the treatment of erectile dysfunction: results of integrated analyses. J Urol 2002;168:1332-1336. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12352386
14. Wespes E, Schulman C. Venous impotence: pathophysiology, diagnosis and treatment. J Urol 1993;149:1238-1245. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=8479008
15. Rao DS, Donatucci CF. Vasculogenic impotence. Arterial and venous surgery. Urol Clin North Am 2001;28:309-319. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11402583
16. Davis-Joseph B, Tiefer L, Melman A. Accuracy of the initial history and physical examination to establish the etiology of erectile dysfunction. Urology 1995;45:498-502. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=7879338
17. Hatzichristou D, Hatzimouratidis K, Bekas M, Apostolidis A, Tzortzis V, Yannakoyorgos K. Diagnostic steps in the evaluation of patients with erectile dysfunction. J Urol 2002;168:615-620. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12131320
18. Lewis RW. Epidemiology of erectile dysfunction. Urol Clin North Am 2001;28:209-216, vii. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11402575
19. Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, Mishra A. The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. Urology 1997; 49:822-830. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=9187685
20. Morales A, Heaton JP. Hormonal erectile dysfunction. Evaluation and management. Urol Clin North Am 2001;28:279-288. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11402581
21. Lue TF, Giuliano F, Montorsi F, Rosen RC, Andersson K-E, Althof S et al. Summary of the Recommendations on Sexual Dysfunctions in Men. J Sexual Medicine 2004;1:6-23.
22. Laumann EO, Paik A, Rosen RC. The epidemiology of erectile dysfunction: results from the National Health and Social Life Survey. Int J Impot Res 1999;11 (Suppl 1):S60-64. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10554933
23. DeBusk R, Drory Y, Goldstein I, Jackson G, Kaul S, Kimmel SE, Kostis JB, Kloner RA, Lakin M, Meston CM, Mittleman M, Muller JE, Padma-Nathan H, Rosen RC, Stein RA, Zusman R. Management of sexual dysfunction in patients with cardiovascular disease: recommendations of the Princeton Consensus Panel. Am J Cardiol 2000;86:62F-68F. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10899282
24. Hatzichristou DG, Hatzimouratidis K, Ioannides E, Yannakoyorgos K, Dimitriadis G, Kalinderis A. Nocturnal penile tumescence and rigidity monitoring in young potent volunteers: reproducibility, evaluation criteria and the effect of sexual intercourse. J Urol 1998;159:1921-1926. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=9598488
25. Meuleman EJ, Diemont WL. Investigation of erectile dysfunction. Diagnostic testing for vascular factors in erectile dysfunction. Urol Clin North Am 1995;22:803-819. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=7483130
26. Hatzichristou DG, Hatzimouratidis K, Apostolidis A, Ioannidis E, Yannakoyorgos K, Kalinderis A. Hemodynamic characterization of a functional erection. Arterial and corporeal veno-occlusive function in patients with a positive intracavernosal injection test. Eur Urol 1999;36:60-67. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10364657

27. Rosen RC, Leiblum SR, Spector IP. Psychologically based treatment for male erectile disorder: a cognitive-interpersonal model. J Sex Marital Ther 1994;20:67-85. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=8035472
28. Hatzichristou D, Rosen RC, Broderick G, Clayton A, Cuzin B, Derogatis L et al. Clinical evaluation and management strategy for sexual dysfunction in men and women. J Sexual Medicine 2004;1:49-57.
29. Moyad MA, Barada JH, Lue TF, Mulhall JP, Goldstein I, Fawzy A. Prevention and treatment of erectile dysfunction using lifestyle changes and dietary supplements: what works and what is worthless, part II. Urol Clin North Am 2004;31:259-273. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15123406
30. Moyad MA, Barada JH, Lue TF, Mulhall JP, Goldstein I, Fawzy A. Prevention and treatment of erectile dysfunction using lifestyle changes and dietary supplements: what works and what is worthless, part I. Urol Clin North Am 2004;31:249-257. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15123405
31. Guay AT. Optimizing response to phosphodiesterase therapy: impact of risk-factor management. J Androl 2003;24:S59-62. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14581497
32. Rosen RC. Psychogenic erectile dysfunction. Classification and management. Urol Clin North Am 2001;28:269-278. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11402580
33. Lue TF. Erectile dysfunction. N Engl J Med 2000;342:1802-1813. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10853004
34. Moncada I, Jara J, Subira D, Castano I, Hernandez C. Efficacy of sildenafil citrate at 12 hours after dosing: re-exploring the therapeutic window. Eur Urol 2004;46:357-360; discussion 60-61. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15306108
35. Langtry HD, Markham A. Sildenafil: a review of its use in erectile dysfunction. Drugs 1999;57:967-89. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10400408
36. Padma-Nathan H, Giuliano F. Oral drug therapy for erectile dysfunction. Urol Clin North Am 2001;28:321-334. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11402584
37. Stuckey BG, Jadzinsky MN, Murphy LJ, Montorsi F, Kadioglu A, Fraige F et al. Sildenafil citrate for treatment of erectile dysfunction in men with type 1 diabetes: results of a randomized controlled trial. Diabetes Care 2003;26:279-284. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12547849
38. Raina R, Lakin MM, Agarwal A, Mascha E, Montague DK, Klein E, Zippe CD. Efficacy and factors associated with successful outcome of sildenafil citrate use for erectile dysfunction after radical prostatectomy. Urology 2004;63:960-966. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15134989
39. Porst H, Padma-Nathan H, Giuliano F, Anglin G, Varanese L, Rosen R. Efficacy of tadalafil for the treatment of erectile dysfunction at 24 and 36 hours after dosing: a randomized controlled trial. Urology 2003;62:121-125; discussion 125-126. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12837435
40. Curran M, Keating G. Tadalafil. Drugs 2003;63:2203-2212; discussion 2213-2214. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14498756

41. Montorsi F, Verheyden B, Meuleman E, Junemann KP, Moncada I, Valiquette L, Casabe A, Pacheco C, Denne J, Knight J, Segal S, Watkins VS. Long-term safety and tolerability of tadalafil in the treatment of erectile dysfunction. Eur Urol 2004;45:339-344; discussion 344-345. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15036680
42. Saenz de Tejada I, Anglin G, Knight JR, Emmick JT. Effects of tadalafil on erectile dysfunction in men with diabetes. Diabetes Care 2002;25:2159-164. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12453954
43. Montorsi F, Nathan HP, McCullough A, Brock GB, Broderick G, Ahuja S, Whitaker S, Hoover A, Novack D, Murphy A, Varanese L. Tadalafil in the treatment of erectile dysfunction following bilateral nerve sparing radical retropubic prostatectomy: a randomized, double-blind, placebo controlled trial. J Urol 2004;172:1036-1041. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15311032
44. Bischoff E, Schneider K. A conscious-rabbit model to study vardenafil hydrochloride and other agents that influence penile erection. Int J Impot Res 2001;13:230-235. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11494080
45. Keating GM, Scott LJ. Vardenafil: a review of its use in erectile dysfunction. Drugs 2003;63:2673-2703. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14636086
46. Porst H, Rosen R, Padma-Nathan H, Goldstein I, Giuliano F, Ulbrich E, Bandel T. The efficacy and tolerability of vardenafil, a new, oral, selective phosphodiesterase type 5 inhibitor, in patients with erectile dysfunction: the first at-home clinical trial. Int J Impot Res 2001;13:192-199. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11494074
47. Potempa AJ, Ulbrich E, Bernard I, Beneke M. Efficacy of vardenafil in men with erectile dysfunction: a flexible-dose community practice study. Eur Urol 2004;46:73-79. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15183550
48. Goldstein I, Young JM, Fischer J, Bangerter K, Segerson T, Taylor T. Vardenafil, a new phosphodiesterase type 5 inhibitor, in the treatment of erectile dysfunction in men with diabetes: a multicentre double-blind placebo-controlled fixed-dose study. Diabetes Care 2003;26:777-783. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12610037
49. Brock G, Nehra A, Lipshultz LI, Karlin GS, Gleave M, Seger M, Padma-Nathan H. Safety and efficacy of vardenafil for the treatment of men with erectile dysfunction after radical retropubic prostatectomy. J Urol 2003;170:1278-1283. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14501741
50. Kloner RA. Novel phosphodiesterase type 5 inhibitors: assessing hemodynamic effects and safety parameters. Clin Cardiol 2004;27:I20-25. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15115192
51. Thadani U, Smith W, Nash S, Bittar N, Glasser S, Narayan P, Stein RA, Larkin S, Mazzu A, Tota R, Pomerantz K, Sundaresan P. The effect of vardenafil, a potent and highly selective phosphodiesterase-5 inhibitor for the treatment of erectile dysfunction, on the cardiovascular response to exercise in patients with coronary artery disease. J Am Coll Cardiol 2002;40:2006-2012. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12475462
52. Vardi Y, Bulus M, Reisner S, Nassar S, Aboud L, Sprecher E, Gruenwald I. Effects of sildenafil citrate (Viagra) on hemodynamic parameters during exercise testing and occurrence of ventricular arrhythmias in patients with erectile dysfunction and cardiovascular disease. Eur Urol 2003;43:544-551. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12706001

53. Auerbach SM, Gittelman M, Mazzu A, Cihon F, Sundaresan P, White WB. Simultaneous administration of vardenafil and tamsulosin does not induce clinically significant hypotension in patients with benign prostatic hyperplasia. Urology 2004;64:998-1003; discussion 1004. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15533493
54. Kloner RA, Jackson G, Emmick JT, Mitchell MI, Bedding A, Warner MR, Pereira A. Interaction between the phosphodiesterase 5 inhibitor, tadalafil and 2 alpha-blockers, doxazosin and tamsulosin in healthy normotensive men. J Urol 2004;172:1935-1940. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15540759
55. Hagemann JH, Berding G, Bergh S, Sleep DJ, Knapp WH, Jonas U, Stief CG. Effects of visual sexual stimuli and apomorphine SL on cerebral activity in men with erectile dysfunction. Eur Urol 2003;43:412-420. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12667723
56. Montorsi F, Perani D, Anchisi D, Salonia A, Scifo P, Rigiroli P, Deho F, De Vito ML, Heaton J, Rigatti P, Fazio F. Brain activation patterns during video sexual stimulation following the administration of apomorphine: results of a placebo-controlled study. Eur Urol 2003;43:405-411. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12667722
57. Heaton JP. Apomorphine: an update of clinical trial results. Int J Impot Res 2000;12(Suppl 4):S67-73. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11035390
58. Dula E, Bukofzer S, Perdok R, George M. Double-blind, crossover comparison of 3 mg apomorphine SL with placebo and with 4 mg apomorphine SL in male erectile dysfunction. Eur Urol 2001; 39:558-553; discussion 564. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11464037
59. Martinez R, Puigvert A, Pomerol JM, Rodriguez-Villalba R. Clinical experience with apomorphine hydrochloride: the first 107 patients. J Urol 2003;170:2352-2355. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14634414
60. Buvat J, Montorsi F. Safety and tolerability of apomorphine SL in patients with erectile dysfunction. BJU Int 2001;88 (Suppl 3):30-35. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11578277
61. Bukofzer S, Livesey N. Safety and tolerability of apomorphine SL (Uprima). Int J Impot Res 2001;13 (Suppl 3):S40-44. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11477491
62. Fagan TC, Buttler S, Marbury T, Taylor A, Edmonds A. Cardiovascular safety of sublingual apomorphine in patients on stable doses of oral antihypertensive agents and nitrates. Am J Cardiol 2001;88:760-766. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11589843
63. Kongkanand A, Opanuraks J, Tantiwongse K, Choeypunt N, Tantiwong A, Amornvejsukit T. Evaluating dose regimens of apomorphine, an open-label study. Int J Impot Res 2003;15 (Suppl 2):S10-12. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12825098
64. Eardley I, Wright P, MacDonagh R, Hole J, Edwards A. An open-label, randomized, flexible-dose, crossover study to assess the comparative efficacy and safety of sildenafil citrate and apomorphine hydrochloride in men with erectile dysfunction. BJU Int 2004;93:1271-1275. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15180621
65. Perimenis P, Gyftopoulos K, Giannitsas K, Markou SA, Tsota I, Chrysanthopoulou A, Athanasopoulos A, Barbalias G. A comparative, crossover study of the efficacy and safety of sildenafil and apomorphine in men with evidence of arteriogenic erectile dysfunction. Int J Impot Res 2004;16:2-7. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14963464

66. Montorsi F. Tolerability and safety of apomorphine SL (Ixense (TM)). Int J Impot Res 2003;15 (Suppl 2):S7-9.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12825097
67. Padma-Nathan H, Christ G, Adaikan G, Becher E, Brock G, Carrier S et al. Pharmacotherapy for erectile dysfunction. J Sexual Medicine 2004;1:128-140.
68. Goldstein I. Oral phentolamine: an alpha-1, alpha-2 adrenergic antagonist for the treatment of erectile dysfunction. Int J Impot Res 2000;12 (Suppl 1):S75-80.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10845768
69. Teloken C, Rhoden EL, Sogari P, Dambros M, Souto CA. Therapeutic effects of high dose yohimbine hydrochloride on organic erectile dysfunction. J Urol 1998;159:122-124.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=9400452
70. Costabile RA, Spevak M. Oral trazodone is not effective therapy for erectile dysfunction: a double-blind, placebo controlled trial. J Urol 1999;161:1819-1822.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10332444
71. Hong B, Ji YH, Hong JH, Nam KY, Ahn TY. A double-blind crossover study evaluating the efficacy of korean red ginseng in patients with erectile dysfunction: a preliminary report. J Urol 2002;168:2070-2073.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12394711
72. Montorsi F, Salonia A, Zanoni M, Pompa P, Cestari A, Guazzoni G, Barbieri L, Rigatti P. Current status of local penile therapy. Int J Impot Res 2002;14(Suppl 1):S70-81.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11850739
73. Goldstein I, Payton TR, Schechter PJ. A double-blind, placebo-controlled, efficacy and safety study of topical gel formulation of 1% alprostadil (Topiglan) for the in-office treatment of erectile dysfunction. Urology 2001;57:301-305.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11182341
74. Levine LA, Dimitriou RJ. Vacuum constriction and external erection devices in erectile dysfunction. Urol Clin North Am 2001;28:335-41, ix-x.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11402585
75. Cookson MS, Nadig PW. Long-term results with vacuum constriction device. J Urol 1993;149:290-294.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=8426404
76. Lewis RW, Witherington R. External vacuum therapy for erectile dysfunction: use and results. World J Urol 1997;15:78-82.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=9066099
77. Shabsigh R, Padma-Nathan H, Gittleman M, McMurray J, Kaufman J, Goldstein I. Intracavernous alprostadil alfadex (EDEX/VIRIDAL) is effective and safe in patients with erectile dysfunction after failing sildenafil (Viagra). Urology 2000;55:477-480.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10736486
78. Leungwattanakij S, Flynn V Jr, Hellstrom WJ. Intracavernosal injection and intraurethral therapy for erectile dysfunction. Urol Clin North Am 2001;28:343-354.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11402586
79. Linet OI, Ogrinc FG. Efficacy and safety of intracavernosal alprostadil in men with erectile dysfunction. N Engl J Med 1996;334:873-877.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=8596569
80. Porst H. The rationale for prostaglandin E1 in erectile failure: a survey of worldwide experience. J Urol 1996;155:802-815.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=8583582

81. Heaton JP, Lording D, Liu SN, Litonjua AD, Guangwei L, Kim SC, Kim JJ, Zhi-Zhou S, Israr D, Niazi D, Rajatanavin R, Suyono S, Benard F, Casey R, Brock G, Belanger A. Intracavernosal alprostadil is effective for the treatment of erectile dysfunction in diabetic men. Int J Impot Res 2001;13:317-321. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11918246
82. Lakin MM, Montague DK, VanderBrug Medendorp S, Tesar L, Schover LR. Intracavernous injection therapy: analysis of results and complications. J Urol 1990;143:1138-1141. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=2342174
83. Kattan S. Double-blind randomized crossover study comparing intracorporeal prostaglandin E1 with combination of prostaglandin E1 and lidocaine in the treatment of organic impotence. Urology 1995;45:1032-1036. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=7771004
84. Moriel EZ, Rajfer J. Sodium bicarbonate alleviates penile pain induced by intracavernous injections for erectile dysfunction. J Urol 1993;149:1299-1300. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=8386779
85. Flynn RJ, Williams G. Long-term follow-up of patients with erectile dysfunction commenced on self injection with intracavernosal papaverine with or without phentolamine. Br J Urol 1996;78:628-631. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=8944522
86. Sundaram CP, Thomas W, Pryor LE, Sidi AA, Billups K, Pryor JL. Long-term follow-up of patients receiving injection therapy for erectile dysfunction. Urology 1997;49:932-935. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=9187703
87. Gupta R, Kirschen J, Barrow RC 2nd, Eid JF. Predictors of success and risk factors for attrition in the use of intracavernous injection. J Urol 1997;157:1681-1686. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=9112505
88. Vardi Y, Sprecher E, Gruenwald I. Logistic regression and survival analysis of 450 impotent patients treated with injection therapy: long-term dropout parameters. J Urol 2000;163:467-470. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10647656
89. Baniel J, Israilov S, Segenreich E, Livne PM. Comparative evaluation of treatments for erectile dysfunction in patients with prostate cancer after radical retropubic prostatectomy. BJU Int 2001;88:58-62. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11446847
90. Montorsi F, Althof SE, Sweeney M, Menchini-Fabris F, Sasso F, Giuliano F. Treatment satisfaction in patients with erectile dysfunction switching from prostaglandin E(1) intracavernosal injection therapy to oral sildenafil citrate. Int J Impot Res 2003;15:444-449. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14671665
91. Raina R, Lakin MM, Agarwal A, Ausmundson S, Montague DK, Zippe CD. Long-term intracavernous therapy responders can potentially switch to sildenafil citrate after radical prostatectomy. Urology 2004;63:532-537; discussion 538. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15028452
92. Hatzichristou DG, Apostolidis A, Tzortzis V, Ioannides E, Yannakoyorgos K, Kalinderis A. Sildenafil versus intracavernous injection therapy: efficacy and preference in patients on intracavernous injection for more than 1 year. J Urol 2000;164:1197-1200. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10992365
93. Buvat J, Lemaire A, Ratajczyk J. Acceptance, efficacy and preference of Sildenafil in patients on long term auto-intracavernosal therapy: a study with follow-up at one year. Int J Impot Res 2002;14:483-486. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12494282

94. Mulhall JP, Daller M, Traish AM, Gupta S, Park K, Salimpour P, Payton TR, Krane RJ, Goldstein I. Intracavernosal forskolin: role in management of vasculogenic impotence resistant to standard 3-agent pharmacotherapy [see comments]. J Urol 1997;158:1752-1758; discussion 1758-1759. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=9334594

95. Buvat J, Costa P, Morlier D, Lecocq B, Stegmann B, Albrecht D. Double-blind multicentre study comparing alprostadil alpha-cyclodextrin with moxisylyte chlorhydrate in patients with chronic erectile dysfunction [see comments]. J Urol 1998;159:116-119. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=9400450

96. Bechara A, Casabe A, Cheliz G, Romano S, Rey H, Fredotovich N. Comparative study of papaverine plus phentolamine versus prostaglandin E1 in erectile dysfunction [see comments]. J Urol 1997;157:2132-2134. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=9146599

97. Bennett AH, Carpenter AJ, Barada JH. An improved vasoactive drug combination for a pharmacological erection program. J Urol 1991;146:1564-1565. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=1719248

98. McMahon CG. A comparison of the response to the intracavernosal injection of papaverine and phentolamine, prostaglandin E1 and a combination of all three agents in the management of impotence. Int J Impot Res 1991;3:113-121.

99. Levine SB, Althof SE, Turner LA, Risen CB, Bodner DR, Kursh ED, Resnick MI. Side effects of self-administration of intracavernous papaverine and phentolamine for the treatment of impotence. J Urol 1989;141:54-57. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=2908954

100. McMahon CG, Samali R, Johnson H. Treatment of intracorporeal injection nonresponse with sildenafil alone or in combination with triple agent intracorporeal injection therapy. J Urol 1999;162:1992-1997; discussion 1997-1998. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10569554

101. Padma-Nathan H, Hellstrom WJ, Kaiser FE, Labasky RF, Lue TF, Nolten WE, Norwood PC, Peterson CA, Shabsigh R, Tam PY. Treatment of men with erectile dysfunction with transurethral alprostadil. Medicated Urethral System for Erection (MUSE) Study Group [see comments]. N Engl J Med 1997;336:1-7. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=8970933

102. Vardi Y, Saenz de Tejada I. Functional and radiologic evidence of vascular communication between the spongiosal and cavernosal compartments of the penis. Urology 1997;49:749-752. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=9145982

103. Guay AT, Perez JB, Velasquez E, Newton RA, Jacobson JP. Clinical experience with intraurethral alprostadil (MUSE) in the treatment of men with erectile dysfunction. A retrospective study. Medicated urethral system for erection. Eur Urol 2000;38:671-676. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11111182

104. Fulgham PF, Cochran JS, Denman JL, Feagins BA, Gross MB, Kadesky KT, Kadesky MC, Clark AR, Roehrborn CG. Disappointing initial results with transurethral alprostadil for erectile dysfunction in a urology practice setting. J Urol 1998;160:2041-2046. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=9817319

105. Mulhall JP, Jahoda AE, Ahmed A, Parker M. Analysis of the consistency of intraurethral prostaglandin E(1) (MUSE) during at-home use. Urology 2001;58:262-266. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11489714

106. Lewis RW, Weldon K, Nemo K; the MUSE-ACTIS Study Group. Combined use of transurethral alprostadil and an adjustable penile constriction band in men with erectile dysfunction: results from a multicentre trial. Int J Impot Res 1998;10:S49 (365).

107. Shabsigh R, Padma-Nathan H, Gittleman M, McMurray J, Kaufman J, Goldstein I. Intracavernous alprostadil alfadex is more efficacious, better tolerated, and preferred over intraurethral alprostadil plus optional actis: a comparative, randomized, crossover, multicentre study. Urology 2000;55:109-113. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10654905
108. Montague DK, Angermeier KW. Penile prosthesis implantation. Urol Clin North Am 2001;28:355-361, x. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11402587
109. Holloway FB, Farah RN. Intermediate term assessment of the reliability, function and patient satisfaction with the AMS700 Ultrex penile prosthesis. J Urol 1997;157:1687-1691. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=9112506
110. Tefilli MV, Dubocq F, Rajpurkar A, Gheiler EL, Tiguert R, Barton C, Li H, Dhabuwala CB. Assessment of psychosexual adjustment after insertion of inflatable penile prosthesis. Urology 1998;52:1106-1112. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=9836564
111. Wilson SK, Cleves MA, Delk JR 2nd. Comparison of mechanical reliability of original and enhanced Mentor Alpha I penile prosthesis. J Urol 1999;162:715-718. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10458350
112. Montorsi F, Rigatti P, Carmignani G, Corbu C, Campo B, Ordesi G, Breda G, Silvestre P, Giammusso B, Morgia G, Graziottin A. AMS three-piece inflatable implants for erectile dysfunction: a long-term multi-institutional study in 200 consecutive patients. Eur Urol 2000;37:50-55. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10671785
113. Goldstein I, Newman L, Baum N, Brooks M, Chaikin L, Goldberg K, McBride A, Krane RJ. Safety and efficacy outcome of mentor alpha-1 inflatable penile prosthesis implantation for impotence treatment. J Urol 1997;157:833-839. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=9072580
114. Carson CC 3rd. Efficacy of antibiotic impregnation of inflatable penile prostheses in decreasing infection in original implants. J Urol 2004;171:1611-1614. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15017233
115. Wolter CE, Hellstrom WJG. The hydrophilic-coated inflatable penile prosthesis: 1-year experience. J Sexual Medicine 2004;1:221-224.
116. Montorsi F, Deho F, Salonia A, Briganti A, Bua L, Fantini GV et al. Penile implants in the era of oral drug treatment for erectile dysfunction. BJU Int 2004;94:745-751. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15329092
117. Mulcahy JJ. Long-term experience with salvage of infected penile implants. J Urol 2000;163:481-482. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10647660

6. ABBREVIATIONS USED IN THE TEXT

This list is not comprehensive for the most common abbreviations

AUC	area under curve - serum concentration time curve
BMI	body mass index
CAD	coronary artery disease
cGMP	cyclic guanosine monophosphate
CGRP	calcitonin gene-related peptide
CHF	congestive heart failure
Cmax	maximal concentration
CVD	cardiovascular disease
DICC	dynamic infusion cavernosometry or cavernosography
DRE	digital rectal examination
ED	erectile dysfunction
EMEA	European Medicines Agency
FDA	(US) Food and Drug Administration
FSH	follicle-stimulating hormone
GAQ	General Assessment Question
IIEF	International Index for Erectile Function
LH	luteinizing hormone
LV	left ventricular dysfunction
MET	metabolic equivalent of energy expenditure in the resting state
MI	myocardial infarction
MMAS	Massachusetts Male Aging Study
NO	nitric oxide
NPTR	nocturnal penile tumescence and rigidity
NYHA	New York Heart Association
PDE	phosphodiesterase
PSA	prostate-specific antigen
SEP	sexual encounter profile
T1/2	plasma elimination half-time
Tmax	time to maximum plasma concentration
VCD	vacuum constriction devices
VIP	vasointestinal peptide